Asymmetric Total Synthesis of (−)-Amphidinolide V through Effective Combinations of Catalytic Transformations

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S *Supporting Information*

ABSTRACT: An asymmetric total synthesis of (−)-amphidinolide V was accomplished. The synthesis features a base-catalyzed alkynyl silane alcoholysis/ring-closing enyne metathesis sequence for facile construction of a 1,3-diene motif. A diene RCM followed by a ring-contractive allylic transposition of cyclic silyl ethers was incorporated for the stereoselective installation of a functionalized 1,5-diene subunit. An efficient proline-mediated direct cross-aldol condensation of two advanced aldehyde intermediates was utilized for the construction of a key α,β-unsaturated epoxyaldehyde. This total synthesis demonstrates the prowess of metal-catalyzed transformations in complex molecule synthesis.

Amphidinolides belong to the structurally diverse family of secondary metabolites isolated from symbiotic dinoflagellates *Amphidinium sp.*[1] (+)-Amphidinolide V was extracted from *Amphidinium* strain Y-5 along with 14 other members of this family. The marine plankton was separated from the inside of the cell of a flatworm *Amphiscolops sp.* collected off Chatan beach, Okinawa. This scarce (0.00005% of the wet weight) natural metabolite exhibited cytotoxicity against murine lymphoma L1210 (IC$_{50}$, 3.2 μg/mL) and human epidermoid carcinoma KB cells (IC$_{50}$, 7 μg/mL) in vitro. Amphidinolide V (Scheme 1) is a 14-membered macrolactone possessing a *syn*-epoxyalcohol subunit, three isolated and two vicinal *exo*-methylene groups,

and an unsaturated side chain. The relative configurations of its four stereogenic centers (C8−C10 and C13) were deduced from ¹H−¹H coupling constants and NOESY data.[2] This assignment was later unambiguously confirmed by Fürstner et al. through the first total synthesis of (−)-amphidinolide V and its analogues.[3a] The absolute configuration was later determined by comparison of the synthetic material with an authentic sample along with structure-activity relationship studies.[3b]

One of the most distinctive structural features of amphidinolide V is its densely arrayed alkene moieties, two pairs of which are 1,3-dienes. Based on the connectivity patterns we envisioned that these 1,3-diene subunits could be effectively installed by enyne metathesis. This would allow a highly flexible approach for the synthesis of not only the natural amphidinolide V but also many congeners thereof. Herein, we describe a conceptually novel synthesis of amphidinolide V relying on several transition metal-catalyzed reactions and a proline-mediated cross-condensation of two advanced aldehyde intermediates as enabling tools.

Our strategy toward the synthesis of (−)-amphidinolide V (1) is outlined in Scheme 1. To minimize protecting group manipulations, we planned to introduce the allylic alcohol functionality after macrolactonization of *seco*-acid 2. This postlactonization-functionalization is highly meritorious considering the complications in stereoselective alkylations of epoxyaldehydes[4] or *syn*-selective reductions of epoxyketones.[5] The *seco*-acid 2 is envisaged to be accessed through a cross-aldol condensation of epoxyaldehyde 3 and donor aldehyde 4. The 1,3-diene functionality of 4 would be installed by enyne cross-metathesis (CM) between the corresponding internal alkyne and ethylene gas. The acceptor aldehyde 3, containing a siloxane moiety, could be derived from a ring contraction[6] of 8-membered silacyclodiene 5 via a Re-catalyzed allylic 1,3-transposition. The intermediate 5 would be prepared from secondary alcohol 6 and silane 7 via a metal-catalyzed silane alcoholysis followed by ring-closing metathesis (RCM). The trimethylsilyl-substituted 1,3-diene moiety of 6 could be constructed by enyne RCM with alkynylsilyl ether 8 and subsequent ring cleavage via methyllithium addition.

The preparation of enyne 8 commenced with a base-induced alcoholysis of alkynylsilane 9[7] with enantiomerically enriched homoallylic alcohol 10[8] as previously reported[9] (Scheme 2). The silyl ether 8 was converted to cyclic siloxene 11 by enyne RCM[10] with Grubbs first-generation (GI) catalyst. Ring opening of silacycle 11 with methyllithium delivered secondary alcohol 6 via

Scheme 1. Retrosynthetic Analysis
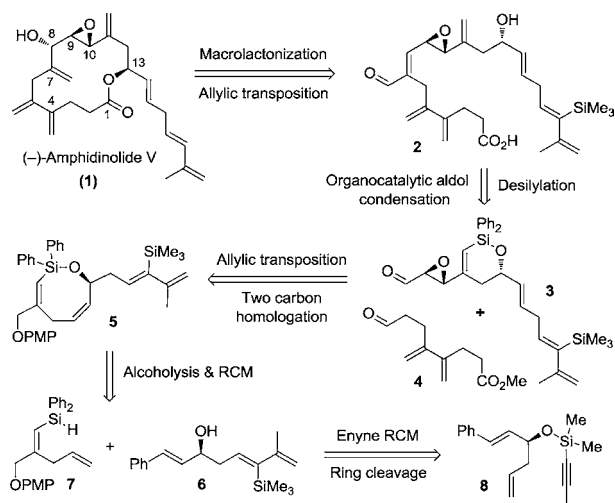
**Scheme 2. Preparation of Substrates for Allylic Transposition Precursor (5)[a]**
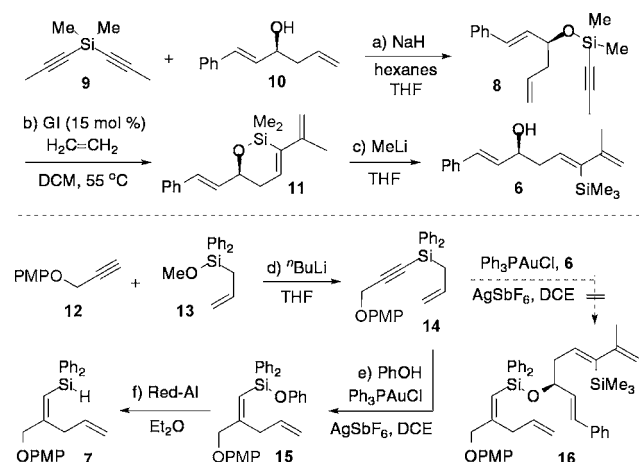
[a]Reagents and conditions: (a) NaH (10 mol %), hexanes-THF (12:1), rt, 12 h, 96%; (b) GI (15 mol %), H₂C=CH₂, DCM (0.01 M), 55 °C, 12 h, 88%; (c) MeLi, THF, −50 °C, 1.5 h, 80%; (d) n-BuLi, THF, −30 °C to rt, 5 h, 84%; (e) PhOH, Ph₃PAuCl (1 mol %), AgSbF₆ (1 mol %), DCE, rt, 10 min, 82%; (e) Red-Al (3 equiv), Et₂O, 0 °C, 0.5 h, 89%.

the concomitant unmasking of the hydroxyl group and the trimethylsilyl-substituted 1,3-diene subunit. The trimethylsilyl group plays a critical role in effectively protecting the 1,3-diene moiety from unwanted metathesis and other side reactions along the synthetic sequence. The preparation of silane counterpart 7 was initiated by the merger of lithiated p-methoxyphenyl (PMP) ether 12 and methoxysilane 13,[6] affording alkynyl allylsilane 14. Unfortunately, the initially planned gold-catalyzed intramolecular allylation[11] of 14 in the presence of allylic alcohol 6 to directly form 16 was preempted by the facile dehydration of 6 to form a conjugated tetraene under the Lewis acidic conditions. Thus, phenoxysilane 15 was prepared instead, and after several attempts, the Si−O bond in 15[12] could be efficiently reduced with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) to provide silane 7 in 89% yield.

With coupling partners 6 and 7 both in hand, we next turned to their dehydrogenative coupling (Scheme 3). After many failures, we found that silyl ether 16 could be obtained in 87% yield with a catalytic amount of (Xantphos)CuCl and a substoichiometric amount of t-BuOLi at 85 °C, a modified conditions of Ito and Sawamura.[13] RCM[14] of 16 catalyzed by Grubbs second-generation (GII) catalyst in the presence of benzoquinone[15] provided allylic 1,3-transposition[6,16] precursor 5. Importantly, the trimethylsilyl substituent of the 1,3-diene moiety directed the RCM to occur selectively with the styryl group. Under previously reported conditions[6] (Re₂O₇, Et₂O) compound 5 underwent a 1,3-allylic transposition at 0 °C delivering siloxene 17 as an inseparable mixture of E/Z-isomers (85:15). Notably, more soluble Ph₃SiOReO₃ afforded the rearranged product as a 1:1 mixture of E/Z-isomers even at lower temperatures. The PMP group of 17 was then cleaved with ammonium cerium(IV) nitrate (CAN) in the presence of 2-methyl-2-butene as a proton scavenger to give free alcohol 18 in 54% yield together with unreacted starting material.[17] Subsequent elaboration of 18 via 2-iodoxybenzoic acid (IBX)-mediated oxidation, Horner-Wadsworth-Emmons homologation, and DIBAL-H reduction followed by Sharpless asymmetric epoxidation[18] delivered epoxyalcohol 19 as an inseparable mixture of diastereomers (dr =

Scheme 3. Preparation of Acceptor Aldehyde (3)[a]
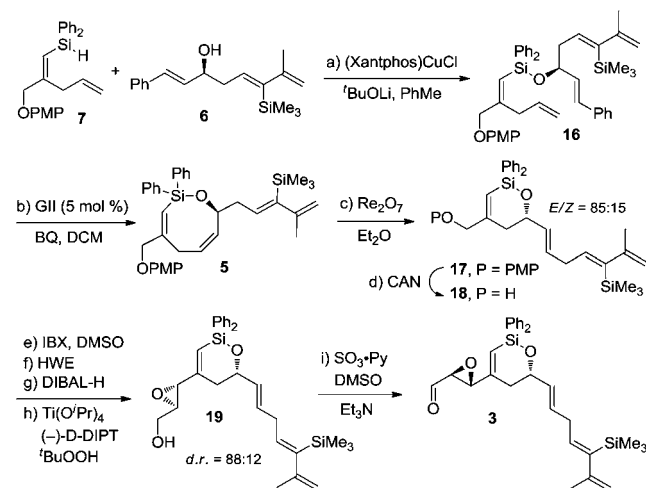
[a]Reagents and conditions: (a) (Xantphos)CuCl (5 mol %), t-BuOLi (0.7 equiv, slow addition), PhMe, 85 °C, 5.5 h, 97%; (b) GII (5 mol %), BQ (20 mol %), DCM (0.005 M), 40 °C, 12 h, 96%; (c) Re₂O₇ (10 mol %), Et₂O, 0 °C, 16 h, 85%, (E/Z = 85:15); (d) CAN (3 equiv), 2-methyl-2-butene (20 equiv), acetone-H₂O (9:1), 0 °C, 0.5 h, 54% (64% BORSM); (e) IBX, DMSO, rt, 1 h; (f) (EtO)₂P(O)-CH₂CO₂Et, NaHMDS, THF, −78 °C to 0 °C, 3 h, 79% (2 steps); (g) DIBAL-H, THF, −50 °C, 1.5 h, 91%; (h) Ti(i-PrO)₄ (10 mol %), (−)-D-DIPT (15 mol %), t-BuOOH, MS (4 Å), DCM, −20 °C, 12 h, dr = 88:12; (i) SO₃·Py, DMSO, Et₃N, DCM 10 °C, 3 h, 94% (2 steps). Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, BQ = 1,4-benzoquinone, NaHMDS = sodium bis(trimethylsilyl)amide, DIBAL-H = diisobutylaluminum hydride, (−)-D-DIPT = (−)-diisopropyl D-tartrate.

88:12). The formation of the observed diastereomers of 19 should primarily be the consequence of partial racemization[6] of 17 during the allylic transposition.[7] Oxidation of epoxyalcohol 19 was best achieved under the Parikh-Doering conditions[19] providing epoxyaldehyde 3 in 94% combined yield over two steps.

Once the aldol condensation acceptor aldehyde 3 was secured, we searched for a route to access the relatively simple donor aldehyde 4, which commenced with monosaponification of the known symmetric diester 20 (Scheme 4).[7] Treatment of 20 with 1 equiv of potassium hydroxide in MeOH-H₂O solution afforded monoacid 21 in 54% yield together with equal amounts of diacid and unreacted starting material 20, which was recycled. Acid 21

Scheme 4. Preparation of Donor Aldehyde (4)[a]
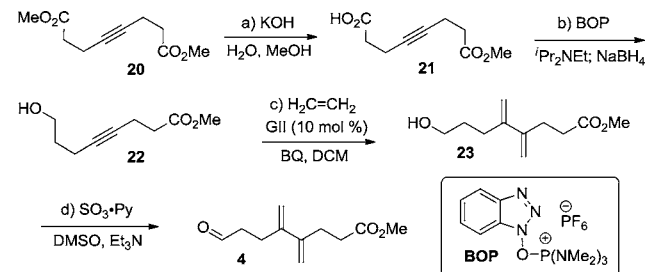
[a]Reagents and conditions: (a) KOH (1 equiv), MeOH-H₂O (2:1), 12 h, 54%, (77% BORSM); (b) BOP (1.1 equiv), i-Pr₂NEt 0.5 h, then NaBH₄, 94%; (c) H₂C=CH₂ (2 atm), GII (10 mol %), BQ (20 mol %), DCM, 50 °C, 12 h, 76%; (d) SO₃·Py, DMSO, Et₃N, DCM, 0 °C to rt, 2 h, 79%. BORSM = based on recovered starting material.

Scheme 5. Cross-Aldol Condensation and Completion of the Synthesis[a]
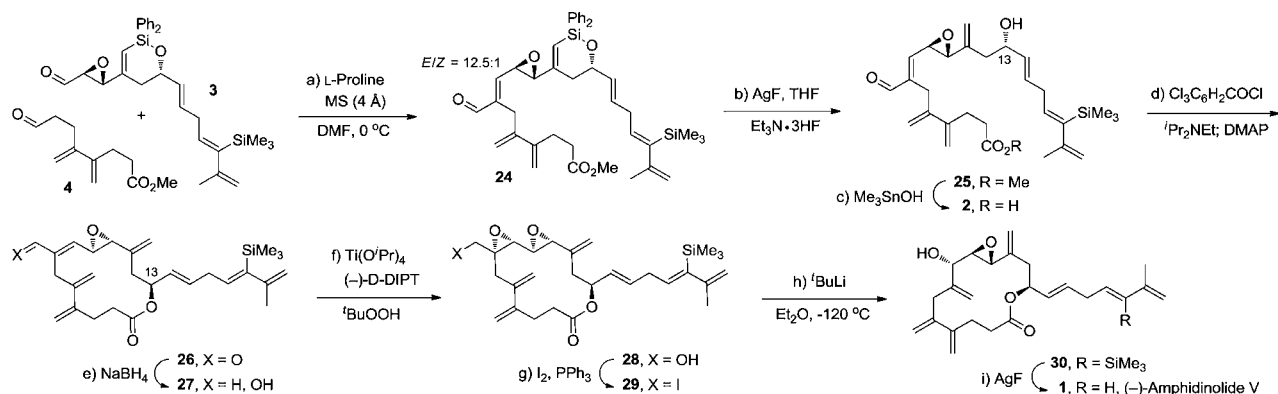
[a]Reagents and conditions: (a) L-proline (1 equiv), MS (4 Å), DMF, 0 °C, slow addition of **4** over 24 h, 66%, (E/Z = 12.5:1), 60% E; (b) AgF (4 equiv), Et$_3$N·3HF, THF, rt, 0.5 h, 77%; (c) Me$_3$SnOH (10 equiv), DCE, 100 °C, 2.5 h, quantitative; (d) Cl$_3$C$_6$H$_2$COCl, i-Pr$_2$NEt, THF, 2 h, then DMAP, PhMe (0.002 M), 61%, (50% of **26**); e) NaBH$_4$, MeOH, 0 °C, 91%; (f) Ti(i-PrO)$_4$ (10 mol %), (−)-D-DIPT (15 mol %), t-BuOOH, MS (4 Å), DCM, −20 °C, 12 h; (g) I$_2$, PPh$_3$, imidazole, DCM, rt, 1.5 h, 85% (2 steps); (h) t-BuLi, Et$_2$O (0.002 M), −120 °C, 80%, (i) AgF (5 equiv) THF-MeOH-H$_2$O (10:9:1), rt, 3 h, 62%.

was then reduced to alcohol **22** with NaBH$_4$ through its hydroxybenzotriazole ester.[20] Enyne CM[10] of **22** with ethylene in the presence of benzoquinone delivered diene **23**, which was subsequently oxidized to provide donor aldehyde **4** using the Parikh-Doering protocol.

With both the acceptor and donor aldehydes in hand, we optimized conditions for their cross-aldol condensation. Although the direct organocatalytic cross-aldol reaction of two nonequivalent aldehydes is known,[21] the direct cross-condensation to form the corresponding α,β-unsaturated aldehyde is limited to the reaction with formaldehyde.[22] It is well-known that H$_2$O plays an important role in the proline-catalyzed aldol reaction assisting hydrolysis of oxazolidinone intermediates formed in the catalytic cycle.[23,24] Aldol condensations mediated by a secondary amine proceed via Knoevenagel-Mannich-type mechanism with second-order dependence of the reaction rate on the catalyst concentration.[22b,25] Therefore, removal of H$_2$O from the reaction medium should increase the amount of iminium ion intermediate or the corresponding oxazolidinone form, thus facilitating the condensation process. Based on this reasoning, we examined the reaction between aldehydes **3** and **4** in the presence of 4 Å molecular sieves (MS) with increased loading of L-proline (Scheme 5). We found that the addition of 4 Å MS had a dramatic effect on the ratio between cross-aldol and cross-condensation products. Thus, a slow addition of donor aldehyde **4** to epoxyaldehyde **3** and 10 mol % of proline in the absence of MS afforded aldol reaction products with only a small amount of condensation product **24**. However, inclusion of 4 Å MS under otherwise identical conditions significantly increased the formation of **24**, rendering it the predominant product. Ultimately, with 100 mol % of proline and 4 Å MS, the condensation product **24** was produced as the sole product in 66% isolated yield (E/Z = 12.5:1). Notably, self-condensation of **4** was not observed under these conditions.

After separation of E/Z-isomers, the C13 hydroxyl group of **24** was liberated by the selective removal of diphenylsilyl group with silver fluoride and Et$_3$N·3HF to generate **25**. The trimethylsilyl group, an array of double bonds, and the epoxyaldehyde moiety remained unchanged under these conditions. At this point saponification of the methyl ester in the presence of these sensitive functionalities was achieved by heating **25** with 10 equiv of Me$_3$SnOH[26] in dichloroethane at 100 °C for 2.5 h. The

quantitatively obtained seco-acid **2** was then subjected to the Yamaguchi macrolactonization[27] conditions affording 61% combined yield of macrocyclic epimers along with 6% of a dimeric product. The undesired C13 epimer was separated at this stage affording macrocycle **26** as a single isomer in 50% yield. After reduction of **26** with NaBH$_4$ in MeOH, asymmetric epoxydation of allylic alcohol **27** delivered diepoxide **28** as a single diastereomer. Exposure of **28** to I$_2$/PPh$_3$ provided iodide **29**, the reductive opening of which was examined under various conditions.[28] Gratifyingly, we found that addition of t-BuLi to a dilute solution (0.002 M) of **29** in Et$_2$O at −120 °C afforded epoxyalcohol **30** in 80% yield.[29] However, addition of t-BuLi to a more concentrated solution of iodide **29** delivered the desired product **30** in much reduced yield due to the reaction of t-BuLi with the lactone moiety. The final removal of the trimethylsilyl group was accomplished with AgF in a solvent mixture of THF-MeOH-H$_2$O,[30] furnishing (−)-amphidinolide V (**1**). The spectroscopic data of the synthetic material are identical to those reported.[3]

In conclusion, an asymmetric total synthesis of (−)-amphidinolide V has been accomplished in a longest linear sequence of 22 steps from commercially available starting materials with 3.3% overall yield. This approach illustrates the prowess of the silicon-tethered ring-closing enyne and diene metathesis as well as the allylic transposition of silyl ethers to enable stereoselective construction of 1,3- and 1,5-diene motifs. Moreover, the silicon tethers were utilized as efficient protecting groups along the synthesis whereby the number of unnecessary protecting group manipulations was reduced. Another salient future of this synthesis is the direct proline-mediated cross-aldol condensation of two nonequivalent advanced aldehydes, which allowed for rapid construction of a complex synthetic intermediate. Investigations directed toward the development of catalytic cross-aldol condensation and its application to the synthesis of chiral building blocks and other natural products will be reported in due course.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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