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Synthesis of the Bis-tetrahydropyran Core of Amphidinol 3

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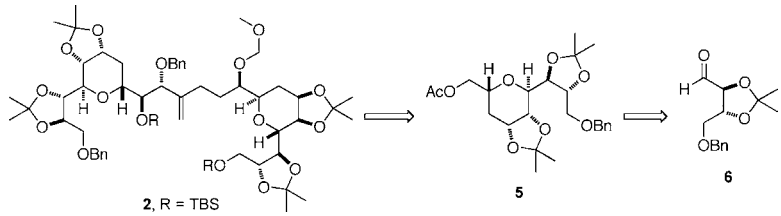
ABSTRACT



A convergent synthesis of the C31−C52 bis-tetrahydropyran core of the natural product amphidinol 3 is reported. A common intermediate was synthesized from D-tartaric acid utilizing an asymmetric glycolate alkylation/ring-closing metathesis sequence to construct the THP rings. Differential elaboration of the common intermediate allowed the synthesis of two distinct coupling partners which were joined through a modified Horner−Wadsworth−Emmons olefination to provide the bis-tetrahydropyran core.

Amphidinol, isolated from *Amphidinium klebsii*, was discovered in 1991 by Yasumoto and co-workers and determined to be the first member of a new class of polyketide metabolites.[1] The amphidinols, unlike polycyclic ethers isolated from other dinoflagellates, are mainly characterized by long carbon chains with multiple hydroxyl groups and polyolefins. Amphidinol 3 (**1**, Scheme 1) was discovered in 1996 from the same organism and is reported to have the greatest antifungal and hemolytic activity of any of the amphidinols reported to date.[2] The 67-carbon backbone contains 25 stereocenters, a highly oxygenated bis-tetrahydropyran core (C31−C51), a heavily unsaturated region featuring a unique (*E*,*E*,*E*)-triene (C52−C67), and a polyol domain consisting of repeating 1,5-diol moieties (C1−C30).[3] In 2008, Murata published a revised structure, in which the absolute configuration at C2 had been changed to *R*.[4]

Because of its biological activity and challenging structure, amphidinol 3 has garnered much attention from the synthetic community. Although no total syntheses have been reported to date, fragment syntheses have been reported by several laboratories[4−10] including contributions from Markó,[6] Oishi,[7] Paquette,[8] Roush,[9] and Rychnovsky[10] toward the synthesis of the tetrahydropyran core.

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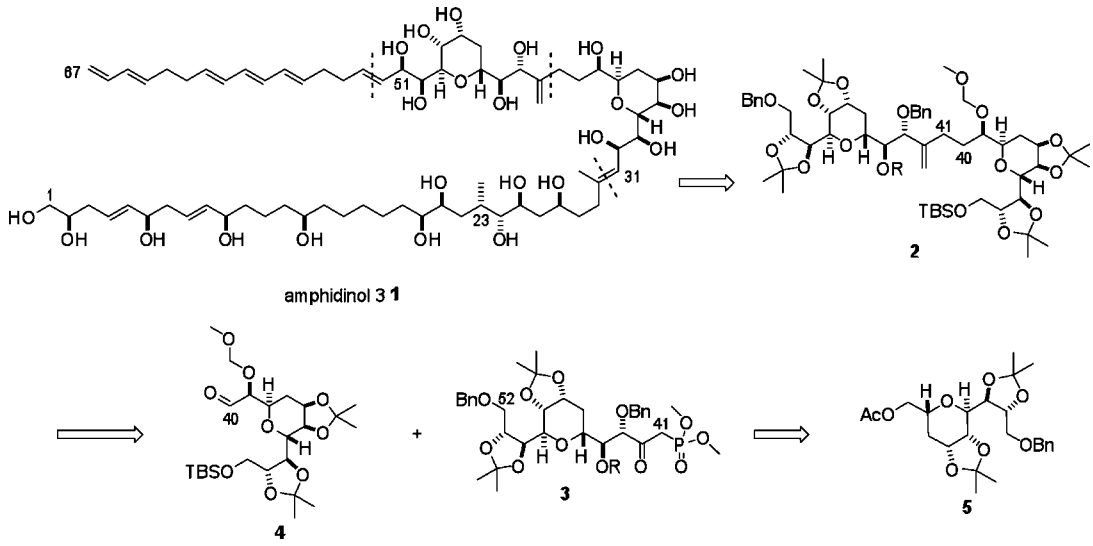
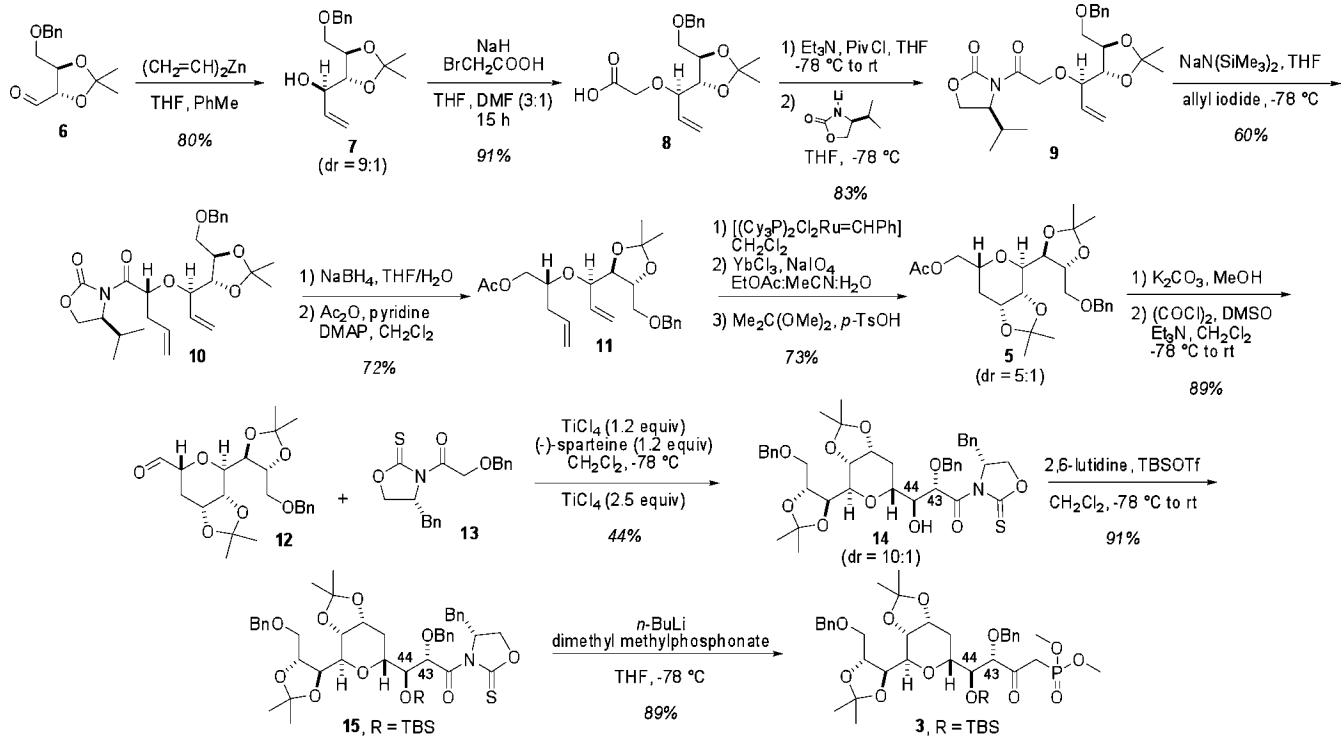
Scheme 1. Retrosynthetic Analysis



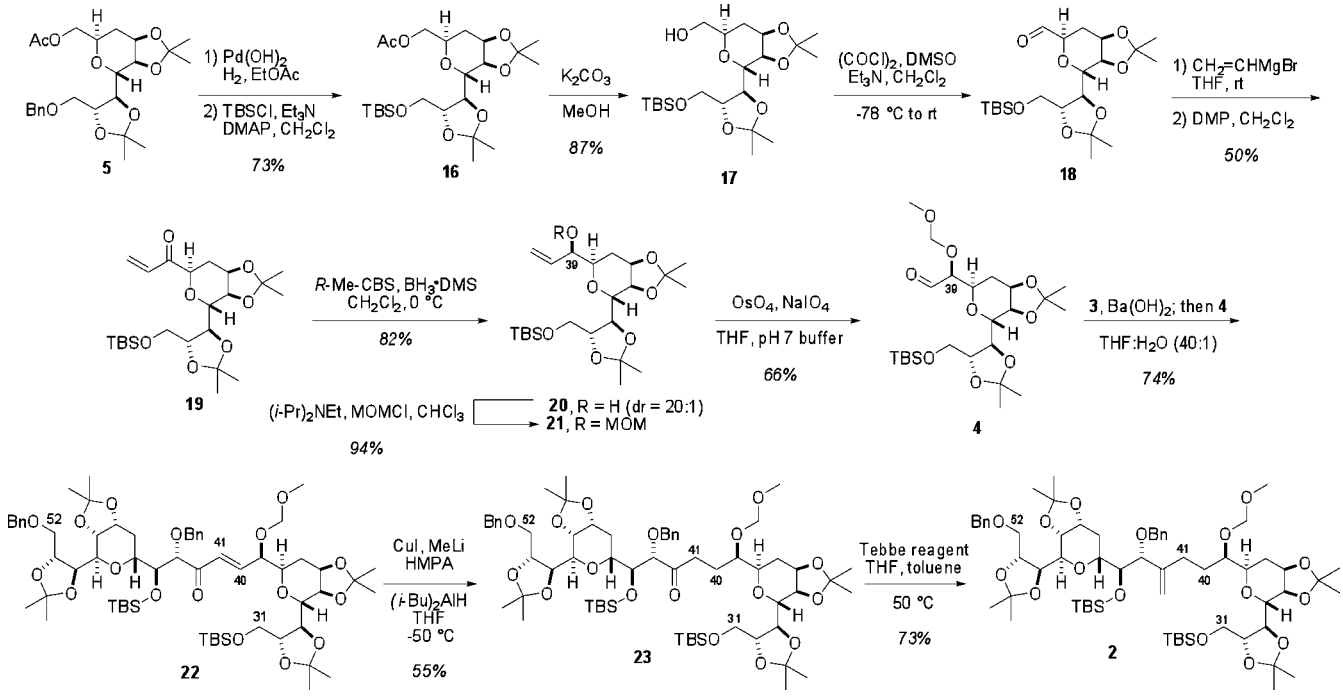
Scheme 2. Synthesis of Tetrahydropyran **5** and Elaboration to β-Ketophosphonate **3**



On the basis of the retrosynthetic plan illustrated in Scheme 1, bis-tetrahydropyran core **2** was established as the initial target. Our strategy focused on exploitation of the symmetry of the C31−C39 and C44−C52 tetrahydropyran moieties to access the core bis-tetrahydropyran unit. A Horner−Wadsworth−Emmons olefination would introduce the desired C40−41 bond as an enone that could be further elaborated. Tetrahydropyran **5** would be obtained utilizing the asymmetric glycolate alkylation/ring-closing metathesis strategy developed in our laboratories.[11]

Synthesis of tetrahydropyran **5** is illustrated in Scheme 2. Known aldehyde **6** was accessed via D-tartaric acid, following a four-step protocol (Scheme 2).[12] Several conditions for the vinyl addition to aldehyde **6** were tested, and ultimately Felkin−Ahn controlled divinyl zinc addition was deteremined to deliver allylic alcohol **7** as a 9:1 ratio of inseparable

Scheme 3. Synthesis of Aldehyde **4** and Fragment Coupling



diastereomers in 80% yield. Alkylation of alcohol **7** with bromoacetic acid afforded acid **8**, which could be coupled with a valine-derived oxazolidinone to afford *N*-glycolyl oxazolidinone **9**. At this point the two diastereomers could be readily separated by chromatography.

Alkylation of the sodium enolate of **9** with allyl iodide introduced a key stereocenter with excellent diastereoselectivity (>95:5).[11] Reductive removal of the auxiliary followed by protection of the resultant alcohol afforded diene **11**. The alkylation could be performed on 20 g scale and carried forward without purification to diene **11**. From diene **11**, a ring-closing metathesis followed by a dihydroxylation would provide the requisite functionality of common intermediate **5**.

Thus, direct exposure of the unpurified RCM product to sodium periodate followed by protection of the diol as an acetonide provided tetrahydropyran **5**. As shown previously in the literature,[13] addition of a Lewis acid decreased the amount of undesired overoxidation during dihydroxylation. Following this procedure, tetrahydropyran **5** could be obtained in up to 73% yield over three steps as a 5:1 mixture of diastereomers in multigram quantities. The selectivity of this sequence is comparable to other conditions explored for dihydroxylation and requires no chromatography between reactions. Although the sequence could be performed with the primary alcohol unprotected, it was found that conversion of the primary alcohol to an acetate was required to facilitate separation of the diastereomers.

Having accessed tetrahydropyran **5**, NOESY analysis revealed the desired trans ring fusion of the major product. This is in agreement with the expected Felkin addition of the divinyl zinc reagent, as well as the chiral auxiliary directed glycolate alkylation. 2D NMR analysis of the intermediate dihydropyran also supports the assignment of trans ring fusion. NOESY analysis was further employed to determine the structure of the major diastereomer obtained as a result of the dihydroxylation of the dihydropyran.

With common intermediate **5** in hand, our attention turned to the synthesis of the two coupling partners, β-ketophosphonate **3** and aldehyde **4**. Synthesis of the C41−C52 tetrahydropyran coupling partner **3** was initiated by methanolysis of the acetate followed by Swern oxidation[14] to access aldehyde **12** (Scheme 2). A glycolate *anti* aldol reaction[15] between aldehyde **12** and *N*-glycolyl oxazolidinethione **13** introduced the C43 and C44 stereocenters as a 10:1 ratio of separable diastereomers in 44% yield. Varying the amount of Lewis acid used in the reaction in an attempt to increase the yield resulted in decomposition or decreased selectivities. Simple conversion of aldol adduct **14** to the desired coupling partner, β-ketophosphonate **3**, was effected by protection of the alcohol as the TBS ether and direct displacement of the auxiliary with lithiated dimethyl methylphosphonate[16] in 89% yield.

As a consequence of utilizing a common intermediate for the synthesis of both coupling partners, the two primary alcohols at C32 and C52 were both protected as benzyl ethers. However, differential protection of the two primary

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alcohols is required for the selective introduction of the polyene and polyol domains of amphidinol 3. To this end, before completing aldehyde **4** from common intermediate **5**, the benzyl ether was cleaved, and the resulting primary alcohol was protected with TBSCl to afford silyl ether **16** (Scheme 3).

Removal of the acetate protecting group afforded alcohol **17**, which was oxidized under Swern conditions. Various conditions were tested to introduce the C39 stereocenter; however, a stereoselective vinyl addition remained elusive. The allylic alcohol was obtained at best in 86% yield as a 3.5:1 mixture of diastereomers. Addition of nucleophiles to similar aldehydes has been previously reported with comparable results.[8,10]

In light of these difficulties, an alternative oxidation/stereoselective reduction sequence was pursued. Oxidation of the mixture of allylic alcohols derived from **18** with Dess−Martin periodinane[17] provided enone **19**, which upon CBS reduction[18] afforded a single diastereomer of allylic alcohol **20**. Advanced Mosher ester analysis[19] was used to determine that the stereocenter at C39 was indeed the desired *R* configuration. With the stereochemistry confirmed, the allylic alcohol was then protected as a methoxymethyl ether to afford alkene **21**. Several oxidation conditions to access aldehyde **4** were tested, including ozonolysis and oxidative cleavage with ruthenium chloride and sodium periodate. However, it was found that the Johnson−Lemieux oxidation utilized by Paquette[8b] provided the best yields of aldehyde **4**.

With both coupling partners in hand, a modified Horner−Wadsworth−Emmons reaction[20] was pursued (Scheme 3). Initial attempts at union of the two fragments were carried out with the C39 hydroxyl group protected as a TBS ether instead of the MOM ether. It was found that the desired enone could be accessed in 52% yield, as an inconsequential mixture of *E*:Z isomers. Switching to the MOM ether saw an increase in yield and a decrease in reaction times. Treatment of β-ketophosphonate **3** with barium hydroxide followed by addition of aldehyde **4** afforded the desired enone **22** in 74% yield and granted access to the carbon backbone of the C31−C52 domain of amphidinol 3.

To complete the synthesis of the fragment, reduction of the C40−C41 alkene and formation of the 1,1-disubstituted alkene at C42 remained. A conjugate reduction was performed on enone **18** utilizing methyl copper and diisobutylaluminum hydride[21] to provide ketone **23**. Subsequent transformation of ketone **23** to the bis-tetrahydropyran core **2** via a methylene Wittig reaction[22] proved inconsistent and low yielding on a variety of similar systems. Treatment of ketone **23** with the Tebbe reagent[23] at lower temperatures resulted in recovered starting material, even after prolonged reaction, however it was found that heating the reaction mixture for six hours resulted in formation of the 1,1-disubstituted alkene in 73% yield, providing the fully assembled bis-tetrahydropyran core **2** of amphidinol 3 (**1**).

In conclusion, we report the convergent synthesis of the C31−C52 bis- tetrahydropyran core **2** of amphidinol 3 utilizing our asymmetric glycolate alkylation/ring-closing metathesis strategy. This approach allows for the synthesis of the C31−C40 and C41−C52 tetrahydropyrans from a common intermediate (**5**) that is accessible on multigram scale. Future work will focus on the synthesis of the polyol and polyene domains and their union with the bis-tetrahydropyran core.

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Supporting Information Available: Experimental details and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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