

# Synthesis of the C1–C52 Fragment of Amphidinol 3, Featuring a $\beta$ -Alkoxy Alkylolithium Addition Reaction

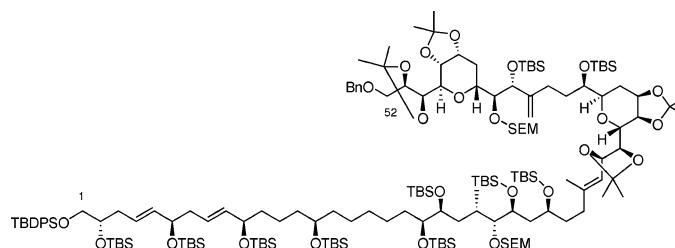
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## ABSTRACT



An advanced intermediate for the synthesis of amphidinol 3 has been prepared. A cross-metathesis reaction was used to couple the C1–C12 and C13–C26 segments. An unusual  $\beta$ -alkoxy alkylolithium reagent was generated from this segment and added to a Weinreb amide to assemble the C1–C52 section of amphidinol 3. These compounds represent some of the most advanced intermediates reported to date for the synthesis of amphidinol 3.

The amphidinols are a fascinating group of metabolites isolated from the marine dinoflagellates *Amphidinium klebsii* and *Amphidinium carterae*.<sup>1</sup> Amphidinol 3 (**1**) exhibits potent hemolytic activity against human erythrocytes as well as antifungal activity against *Aspergillus niger*.<sup>1</sup> A variety of amphidinols have been reported, along with the structurally similar compounds luteophanol A and lingshuiol A and B.<sup>2</sup> Common structural features of these natural products are two highly substituted tetrahydropyran (THP) rings, a long, irregular polyol domain, and a skipped polyene chain. Among this family of natural products, only the configuration of amphidinol 3 has been assigned. The absolute stereochemistry of amphidinol 3 was elucidated by Murata and co-workers

using a new and powerful *J*-based NMR spectroscopic technique.<sup>3</sup> Amphidinol 3 has emerged as an important synthetic target, and a number of groups, including our own,<sup>4</sup> have reported progress toward its synthesis.<sup>5</sup> Herein, we describe the synthesis of the fully protected C1–C52 fragment.

Our retrosynthetic analysis for amphidinol 3 is illustrated in Figure 1. The three components are a bis-tetrahydropyran **2**, a polyene sulfone **3**, and the protected polyol **4**. The bis-THP **2** is similar to and derived from an intermediate we have previously reported.<sup>4</sup> Synthesis and coupling reactions with the polyene sulfone have also been described.<sup>4a</sup> The synthesis of protected polyol phenylthio ether **4** and strategies for its coupling will be the focus of this discussion.

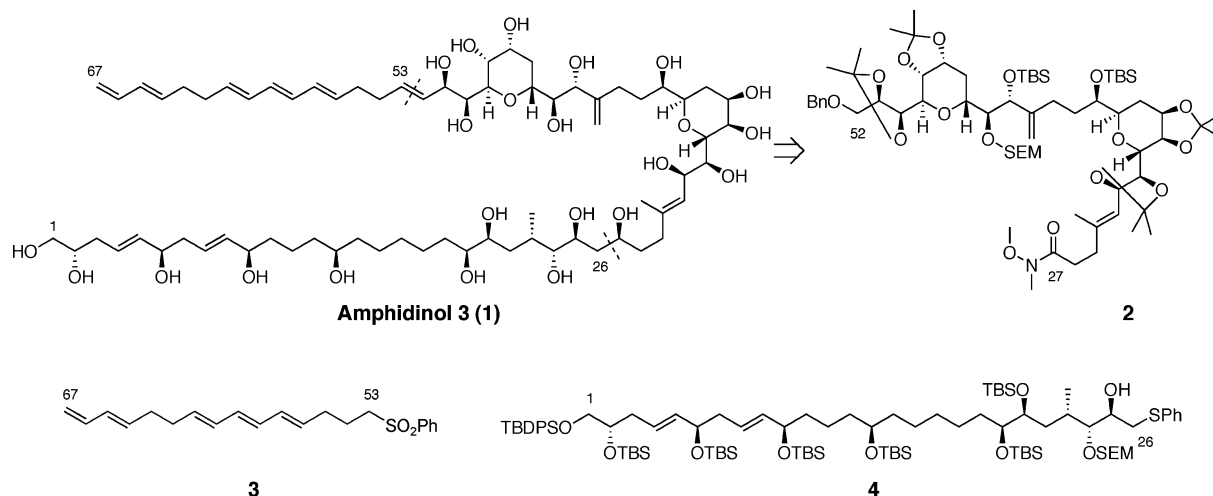
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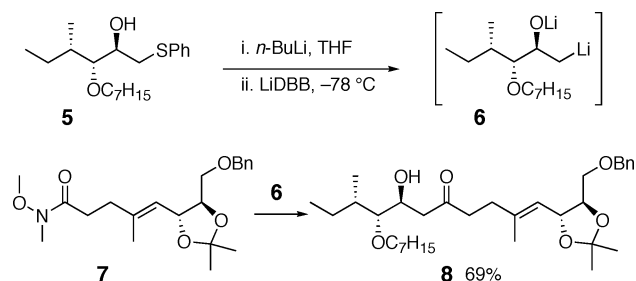


**Figure 1.** Retrosynthetic analysis of amphidinol 3

The key coupling reaction between phenylthio ether **4** and Weinreb amide **2** was envisioned as an addition of the alkyl-lithium reagent derived from **4** to the amide **2**. The resulting  $\beta$ -hydroxy ketone would be suitable for stereoselective reduction. Elimination of the C25 oxygen would be avoided by masking it as a lithium alkoxide. Such  $\beta$ -alkoxy alkyl lithium reagents are known. They have been prepared by mercury–lithium exchange,<sup>6</sup> reductive lithiation of chlorohydrins,<sup>7</sup> reductive lithiation of oxiranes,<sup>8</sup> and from  $\beta$ -hydroxy phenylthio ethers.<sup>9</sup> Several reasonably complex  $\beta$ -alkoxy alkyl-lithium reagents have been prepared by reduction of oxiranes,<sup>10</sup> but these reagents have not been used to couple complex fragments.

A model coupling reaction was investigated as outlined in Scheme 1. The  $\beta$ -hydroxy phenyl sulfide **5** was prepared

**Scheme 1.** Model Coupling of  $\beta$ -Alkoxy Alkyl lithium **6** with Weinreb Amide **7**



and deprotonated with *n*-BuLi. Addition of lithium di-*tert*-butylbiphenylide (LiDBB)<sup>11</sup> at low temperature generated the  $\beta$ -alkoxy alkyl lithium **6**. Subsequent addition of the Weinreb amide **7** produced the desired  $\beta$ -hydroxy ketone **8** in 69% yield. The encouraging outcome of this model study emboldened us to move forward with the amphidinol 3 synthesis.

The synthesis of Weinreb amide **2** from the bis-THP intermediate<sup>4a</sup> **9** is presented in Scheme 2. Low-temperature

TBAF treatment selectively removed the primary TBS group, and oxidation gave the expected C31 aldehyde. Additions to this aldehyde were very problematic, perhaps because of the steric crowding. A 2-propenyllithium addition failed, and the corresponding Grignard addition gave only trace quantities of the expected allylic alcohol products. Finally, a Nozaki–Hiyama–Kishi reaction<sup>12</sup> with 2-bromopropene led to the desired alcohol diastereomers in good yield, and acylation gave ester **10**. Ireland–ester Claisen rearrangement<sup>13</sup> using Nakai's in situ method for generating the silyl ketene acetal<sup>14</sup> produced the expected unsaturated silyl ester in good yield. Hydrolysis of the silyl ester and coupling with *N*-methoxy-*N*-methylamine produced the Weinreb amide **2** as a single alkene isomer.

The C14–C26 segment of amphidinol **3** was prepared from (*S*)-glyceraldehyde acetonide (**11**) as illustrated in Scheme 3. The *syn*-crotyl adduct **12** was prepared by Roush's procedure.<sup>15</sup> A set of standard transformations led to the phenyltetrazole sulfone **13**, which was coupled with aldehyde

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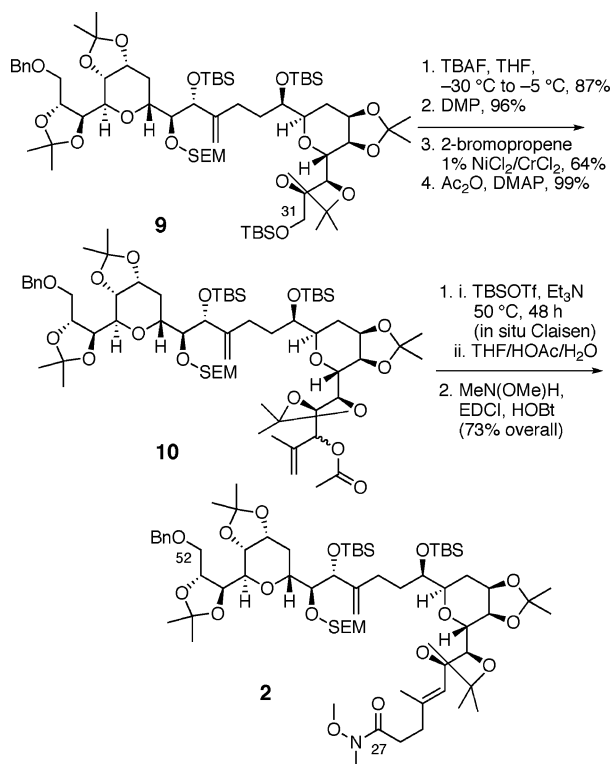
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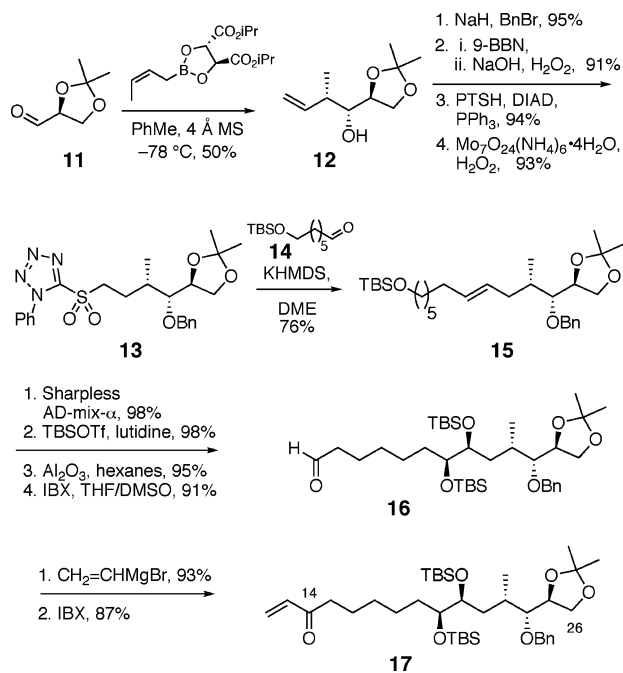
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**Scheme 2.** Synthesis of the C27–C52 Weinreb Amide **2**



**14** using the Julia–Kocienski method<sup>16</sup> to produce the (*E*)-alkene **15** as a single isomer. The reaction was optimized (KHMDs, DME, Barbier conditions) to produce high *E/Z* selectivity to avoid subsequent problematic separations of

**Scheme 3.** Synthesis of the C14–C26 Aldehyde **16** and Enone **17**



alkene or diol diastereomers. Sharpless asymmetric dihydroxylation led to a single diastereomer by <sup>1</sup>H NMR analysis.<sup>17</sup> Protection of the diol, selective deprotection of the primary TBS ether,<sup>18</sup> and oxidation delivered the aldehyde **16** in excellent overall yield. The enone **17** was prepared by addition of vinylmagnesium bromide to the aldehyde and oxidation. Both **16** and **17** were plausible intermediates for the C14–C26 segment of amphidinol **3**.

Initially, we planned to add a C1–C13 organozinc reagent to aldehyde **16** to assemble the C1–C26 fragment.<sup>19</sup> We prepared the protected polyol **18** using a modification of Cossy's elegant metathesis route (Scheme 4).<sup>5a,20</sup> Unfortunately, numerous attempts to prepare a dialkylzinc reagent from **18** failed; the hydroboration was successful, but the transmetalation was not. Ultimately, the successful coupling strategy used a cross-metathesis reaction (Scheme 4).<sup>21</sup> Enone **17** was combined with triene **18** in a 1:1 molar ratio and exposed to the Grubbs–Hoveyda catalyst (10 mol %).<sup>22</sup> The reaction produced enone **19** in 69% yield. Stereoselective reduction of the C14 ketone was accomplished using the CBS reagent<sup>23</sup> to deliver the required C14-*R* diastereomer with 17:1 selectivity in 92% yield. Following Roush's precedent,<sup>5b</sup> hydroxyl-directed reduction using Noyori's catalyst<sup>24</sup> saturated the C12–C13 alkene and produced the C1–C26 segment **20** after protection. The proposed dialkylzinc strategy would have required fewer steps, but the metathesis route was very effective.

To set up the coupling between the bis-THP fragment and the C1–C26 polyol segment, the phenyl sulfide needed to be introduced and the protecting groups adjusted. Selective hydrolysis of the acetonide was accomplished by enol ether formation and hydrolysis.<sup>25</sup> Removal of the benzyl ether, epoxide formation, SEM protection, and treatment with thiophenol and base delivered the desired C1–C26 synthon **4** in good overall yield.

The final segment coupling between protected polyol **4** and bis-THP **2** is illustrated in Scheme 4. Deprotonation of

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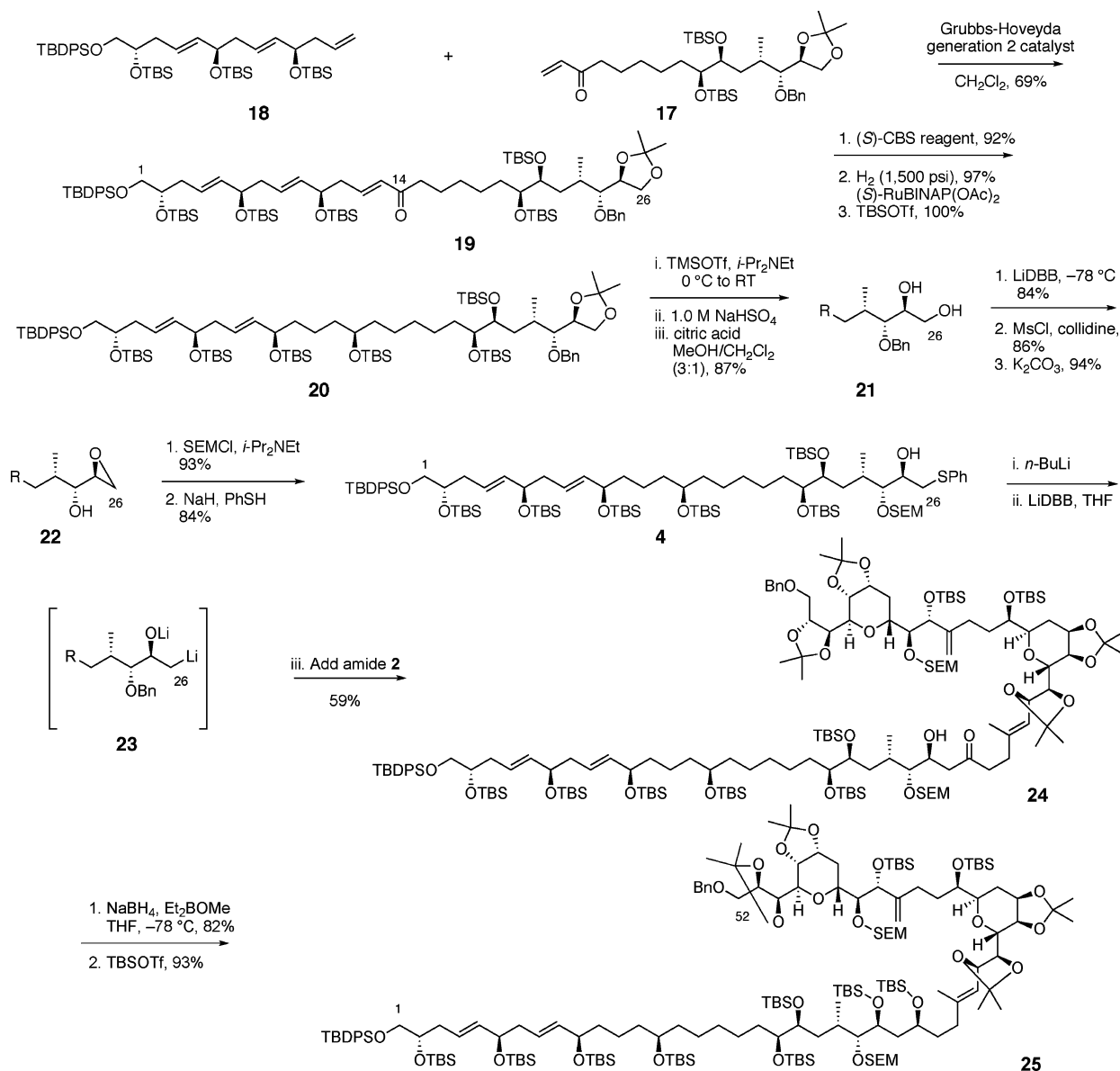
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**Scheme 4.** Coupling Fragments to Assemble the C1–C52 Segment of Amphidinol 3



the C25 alcohol with  $n\text{-BuLi}$ , followed by reductive lithiation with LiDBB, generated the  $\beta$ -alkoxy alkyl lithium **23**. The bis-THP Weinreb amide **2** was added to the alkyl lithium solution in THF at  $-78^\circ\text{C}$ , and the reaction was allowed to proceed for 21 h at that temperature. The  $\beta$ -hydroxy ketone **24** was isolated in 59% yield. A 4-fold excess of the C1–C26 segment was used in the coupling, but this ratio was largely dictated by the relative abundance of the two coupling partners. Model studies to prepare ketone **8** used a 3-fold excess, but neither of these ratios were optimized. Synthesis of the C1–C52 segment of amphidinol 3 was completed by hydroxyl-directed reduction of the C27 ketone using Prasad's conditions,<sup>26</sup> followed by alcohol protection to produce the amphidinol 3 intermediate **25**.

We have developed an efficient construction of an advanced intermediate for the synthesis of amphidinol 3. The route features segment coupling reactions using a cross-metathesis and a  $\beta$ -alkoxy alkyl lithium addition to a Weinreb amide. These validated coupling strategies will undoubtedly be useful in the synthesis of other complex natural products.

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**Supporting Information Available:** Preparation and characterization of compounds **2–4** and **10–25** are described. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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