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Development of an Access Route to the C31–C52 Central Core of Amphidinol 3

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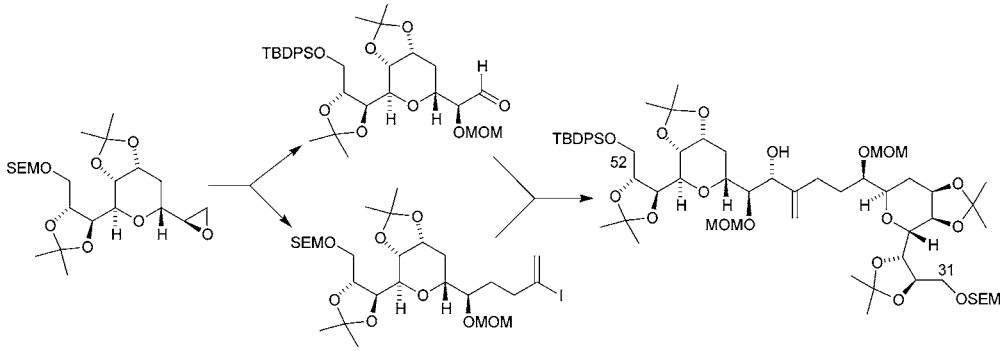
ABSTRACT



An asymmetric synthesis of the heavily oxygenated inner sector of amphidinol 3 constituted of C31–C52 is described. The successful pathway highlights construction of the pair of identical tetrahydropyran subunits from a common intermediate.

Amphidinol 3 (**1**) is the key member of a family of novel, biologically active polyketide metabolites isolated in 1991[1] from the marine dinoflagellates of the *Amphidinium* species.[2] It has been found to exhibit potent antifungal activity in addition to hemolytic properties against human erythrocytes.[3] The intriguing complexity of the structure of **1** arises in part from the incorporation therein of an irregular polyol sector, a skipped polyene chain, a pair of oxygenated tetrahydropyran (THP) rings, and a flexible backbone consisting of 67 carbon atoms that house 25 stereogenic centers. These unprecedented features have prompted considerable interest on the part of the synthetic community.[4,5] Our retrosynthetic analysis of **1** led to three subunits, the syntheses of two (the C1−C30 and C43−C67 sectors) of which have been recently detailed.[5] Herein, we describe an effective route to the C31−C52 fragment. As seen in Scheme 1, the identity of the two THP rings in **2** and **3** formed the basis of our decision to devise a route that stems from the common intermediate **4**. This choice has allowed us to capitalize on the ready availability of this epoxide.[5b]

The selective removal of the TBDPS group from **5** with TBAF in THF, which had previously served well as a selective route to diol **6a** (85% isolated yield),[5b] proved not to be conveniently scalable. Accordingly, a pathway to **8** from both isomers required development. This subgoal was realized readily by monotosylation of the mixture in the presence of catalytic amounts of dibutyltin oxide,[6] with

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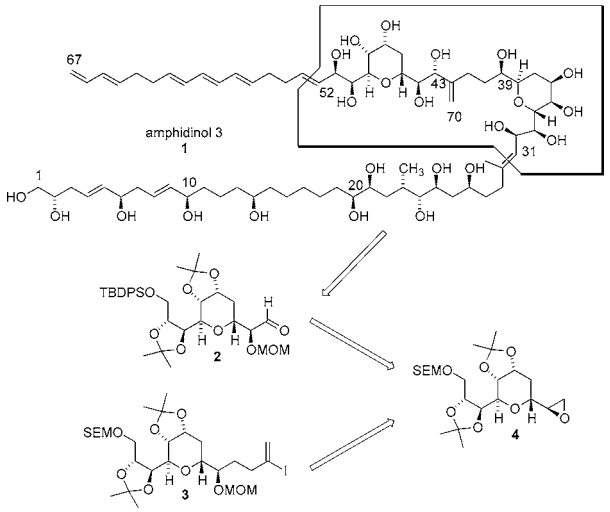
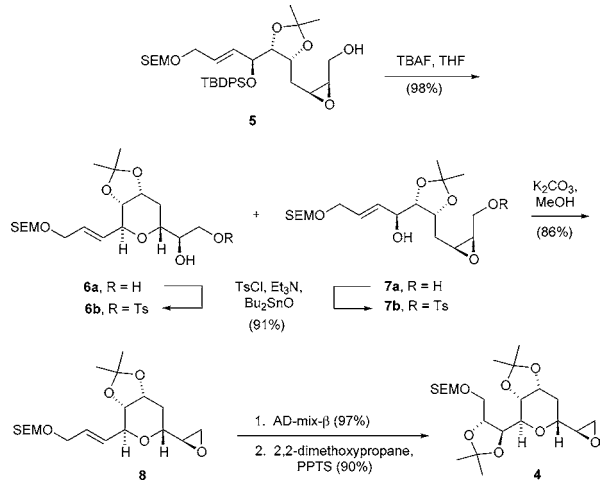
Scheme 1. Retrosynthetic Analysis of the C31−C52 Subsection of Amphidinol 3



subsequent exposure to potassium carbonate in methanol[7] (Scheme 2). Added progress was achieved by the asymmetric

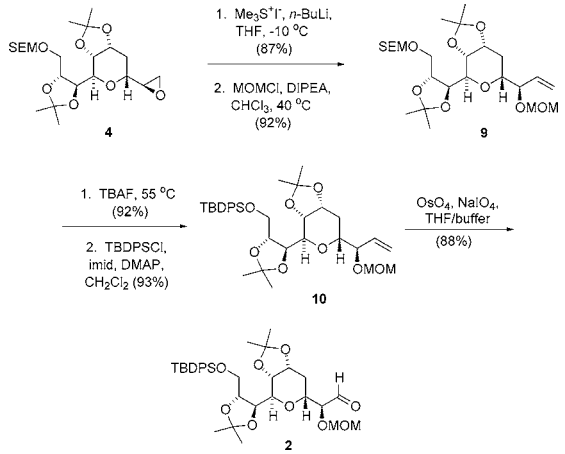
Scheme 2. Synthesis of Epoxide **4**



dihydroxylation of **8** with AD-mix-β[8] followed by acetonide formation in the presence of 2,2-dimethoxypropane.

The oxirane ring in **4** was cleaved efficiently using trimethylsulfonium iodide (TMSI) and *n*-butyllithium at −10 °C,[9] giving rise smoothly to the terminal allylic alcohol (Scheme 3). Treatment of this functionalized intermediate with MOMCl and Hünig's base furnished **9**. The requisite attachment of the polyol and polyene chains to the opposite ends of the bis-THP unit made the use of two different

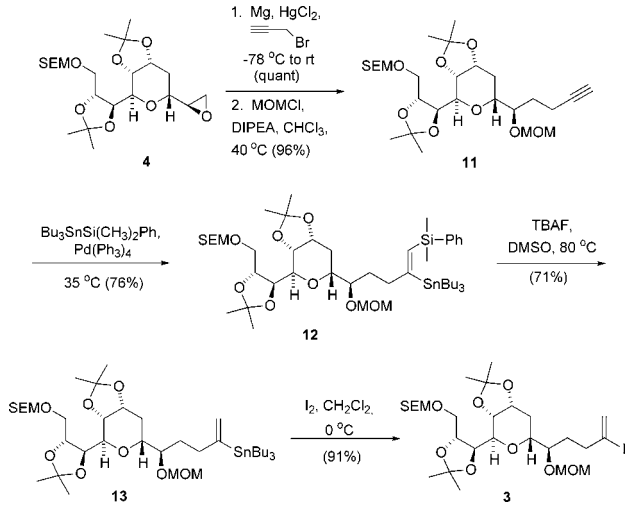
Scheme 3. Assembly of Aldehyde **2**



protecting groups obligatory. In line with these considerations, replacement of the primary SEM group by TBDPS[10] was carried out in the belief that the substitution residing in **10** would be particularly well suited to our purpose. The latent carboxaldehyde functionality in **2** was subsequently liberated by application of the Johnson−Lemieux oxidation.[11]

The pathway from **4** to vinyl iodide **3** initially proved not to be as direct (Scheme 4). Reaction of **4** with the Grignard

Scheme 4. Acquisition of Vinyl Iodide **3**



reagent derived from propargyl bromide[12] and ensuing MOM protection of the resulting secondary carbinol afforded **11**

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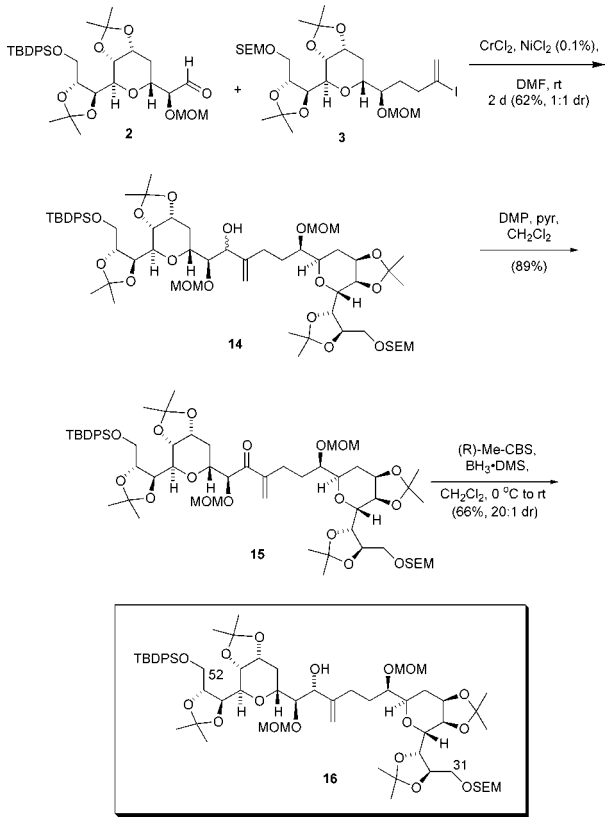
in 96% overall yield. It will be recognized that this process constitutes the early installation stage of the three-carbon spacer constituted of C41/C42/C70. The Pd-catalyzed silylstannation of alkynes is a well-documented process involving trimethylsilyltributyl stannane to provide regioselectively the product carrying the C−Sn bond at the most substituted position.[13] In the present context, this transformation resulted in isolation of the corresponding adduct in good yield.[14] However, selective removal of the trimethylsilyl group proved more demanding than expected. The use of a large excess of TBAF at elevated temperatures for long periods of time resulted in loss of the SEM protecting group and general degradation. To facilitate this process, alternative recourse was made to the dimethylphenylsilyl derivative[15] (Scheme 4) as a direct consequence of the documented milder conditions required for vinyl−$Si(CH_3)_2Ph$ bond cleavage.[16] In the final analysis, the formation of **12** and its conversion to **13** proved to be notably workable when proper conditions were applied. These included the heating to 35 °C of **11** with neat dimethylphenylsilyl tributylstannane in the presence of 3 mol % of $Pd(Ph_3)_4$ for 3 h and the exposure of **12** to TBAF in DMSO at 80 °C for 30 min.

The bonding arrangement in **13** can be appreciated by regarding this stannane to be an immediate precursor of the functionalized vinyllithium via transmetalation. The union of **13** with aldehyde **2** in this fashion was projected until extensive experimental investigation was met with only one successful trial (2.5 equiv of *t*-butyllithium, −78 °C) in poor (7%) yield.[14] These findings contrast markedly with the recent findings of Rychnovsky who has successfully exploited this strategy in a related context.[4e] This disclosure has added to our belief that differences in the nature and relative location of oxygenated functionality are likely responsible for these divergent outcomes.

The alternate strategy explored for uniting the two THP segments began with tin−iodide exchange to deliver **3** followed by application of the Nozaki−Hiyama−Kishi reaction[17] to conjoin **3** with aldehyde **4** (Scheme 5). The reaction, when performed in DMF, furnished the pair of diastereomeric alcohols **14** in a ratio approximating 1:1. The absence of a modest controlling effect involving the α-alkoxy group via a Felkin−Ahn cyclic transition state was not initially expected[18] but did not thwart our objective. The oxidation of **14** to the conjugated ketone **15** was well accommodated by the Dess−Martin periodinane (DMP) reagent.[19] When this step was followed by enantioselective *R*-Me−CBS reduction,[20] as driven by borane-dimethyl sulfide,[21] a much improved dr of 20:1 was realized. The assignment of configuration to C43 in **16** derives from extensive precedent established for this reaction in complex structural networks,[22] extensive NOESY and COSY measurements at 500 MHz in both $CDCl_3$ and C_6D_6 solution, and the close similarity of the signals for (OH)43, H43, and H70 to those exhibited by the natural product.[3b] Relevantly, the C43(OH) proton was identified as giving rise to the doublet at 3.10 ppm (C_6D_6) by virtue of the lack of any $^1H-^{13}C$ correlations in the HMQC spectrum. The COSY data for **16** revealed that C43(OH) exhibited one $^1H-^1H$ coupling ($J = 5.0$ Hz) with the carbinol C43(H) located at 4.48 ppm. The ultimate configurational status of the C43 stereocenter was then confirmed by the existence of a 2.6% NOE enhancement between the C70(H) furthest downfield (5.37 ppm) and C43(H). A small NOE signal was also noted involving C43(OH) and the purported C45(H) on the THP ring (3.95 ppm) as observed in the original structure elucidation.[1]

In summary, efficient assembly of the central C31−C52 core of amphidinol 3 has been developed and executed in the context of a convergent strategy. This accomplishment

Scheme 5. Union of the Two Tetrahydropyran Building Blocks



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was made possible because of the identity of the C32−C39 and C44−C51 THP subunits, which allowed their construction from the common epoxide precursor **4**. The incorporation of additional functionality into building blocks **2** and **3** was achieved effectively in such a way as to permit rapid access to **16**. The present work is expected to set the stage for advancement to **1**, which we hope to disclose in due course.

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Supporting Information Available: Experimental procedures and ^{1}H NMR data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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