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The Polyol Domain of Amphidinol 3. A Stereoselective Synthesis of the Entire C(1)–C(30) Sector

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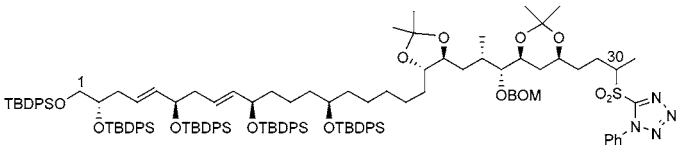
ABSTRACT



The richly oxygenated C(1)–C(30) polyol segment of amphidinol 3 has been synthesized in protected form. Incorporated in this long chain are 10 of the 25 stereogenic centers housed in the target. The asymmetric pathway that has been developed is based on the efficient union of three independently prepared subunits.

The amphidinols (AMs) comprise a small group of architecturally unique marine metabolites that exhibit potent hemolytic and antifungal properties. AM1 was discovered in the primitive alga *Amphidinium klebsii* during the routine screening of dinoflagellates and was immediately recognized to be the first member of an exciting new class of long-chain polyhydroxypolyene natural products.[1] The isolation of AM2 was reported in 1995,[2] to be followed by the complete structural characterization of AM3 (**1**) at the hands of Murata and co-workers in 1999.[3] Among the particularly notable features of this actinomycetous polyketide are the 25 stereogenic centers distributed over much of the flexible backbone and two extensively oxygenated tetrahydropyrans.[4] The skipped acyclic polyolefin segment, C(52)−C(67), that forms the northern sector is also a distinctive facet of the global ensemble.

As fascinating as the biosynthetic lineage of **1** is, its structure and promising biological activity are the elements that engaged our interest in its total synthesis. The successful generation of three fragments of AM3 have previously been reported by others. BouzBouz and Cossy devised a route to C(1)−C(14) based on iterative enantioselective allyltitanations and chemoselective cross-metathesis reactions.[5] A double-allylboration sequence was applied by Flamme and Roush to arrive at a protected C(1)−C(25) subunit.[6] Very recently, the Rychnovsky group has successfully implemented a C-glycosidation approach to the C(39)−C(52) sector of this polyketide.[7] To us, adaptation of the Julia−Kocienski olefination[8] was considered to offer a serviceable means for assembling subunits **2** and **3** in Scheme 1. These targeted intermediates have in turn proven to be amenable to merging with **4** so as to arrive at the largest fragment of **1**, C(1)−C(30), yet yielding to synthesis.

The synthesis of building block **2** was initiated by the homologation of crotonaldehyde to carbinol **5a**. The ensuing

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(2) Paul, G. K.; Matsumori, N.; Murata, M.; Tachibana, K. *Tetrahedron Lett.* **1995**, *36*, 6279.
(3) Murata, M.; Matsuoka, S.; Matsumori, N.; Paul, G. K.; Tachibana, K. *J. Am. Chem. Soc.* **1999**, *121*, 870.
(4) For biosynthetic and other studies, consult: (a) Houdai, T.; Matsuoka, S.; Murata, M.; Satake, M.; Ota, S.; Oshima, Y.; Rhodes, L. L. *Tetrahedron* **2001**, *57*, 5551. (b) Paul, G. K.; Matsumori, N.; Konoki, K.; Murata, M.; Tachibana, K. *J. Mar. Biotech.* **1997**, *5*, 124.
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(7) deVicente, J.; Betzemeier, B.; Rychnovsky, S. D. *Org. Lett.* **2005**, *7*, 1853.
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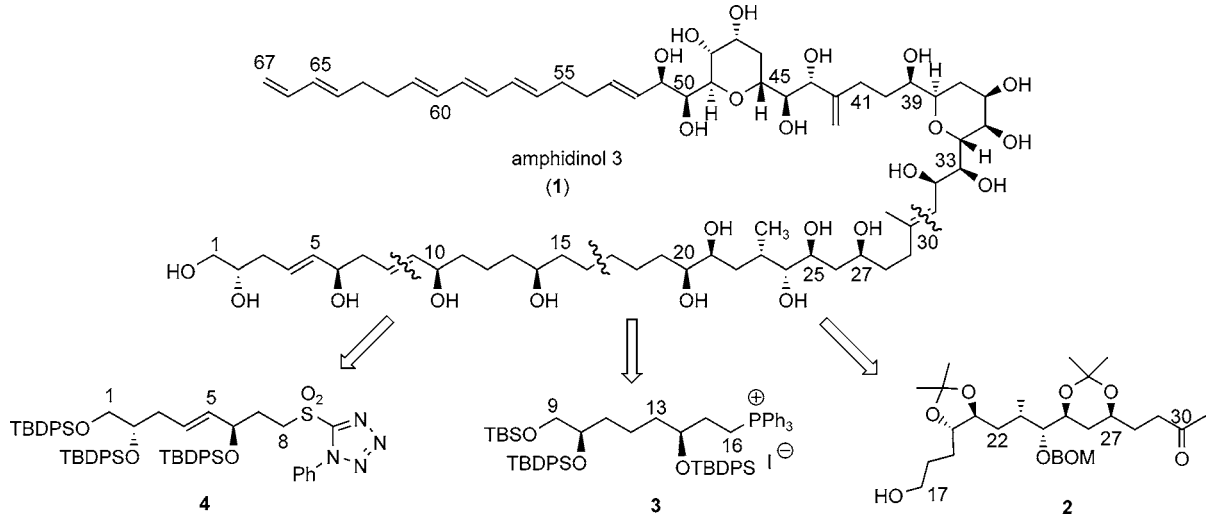
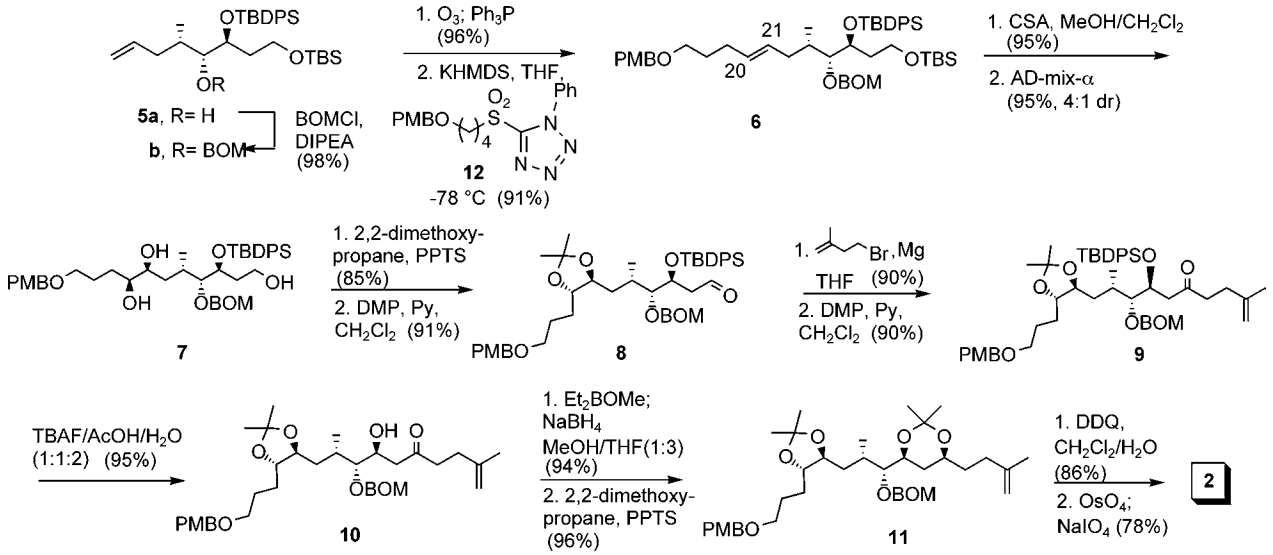
Scheme 1. Retrosynthetic Analysis of the C(1)−C(30) Subsector of Amphidinol **3**



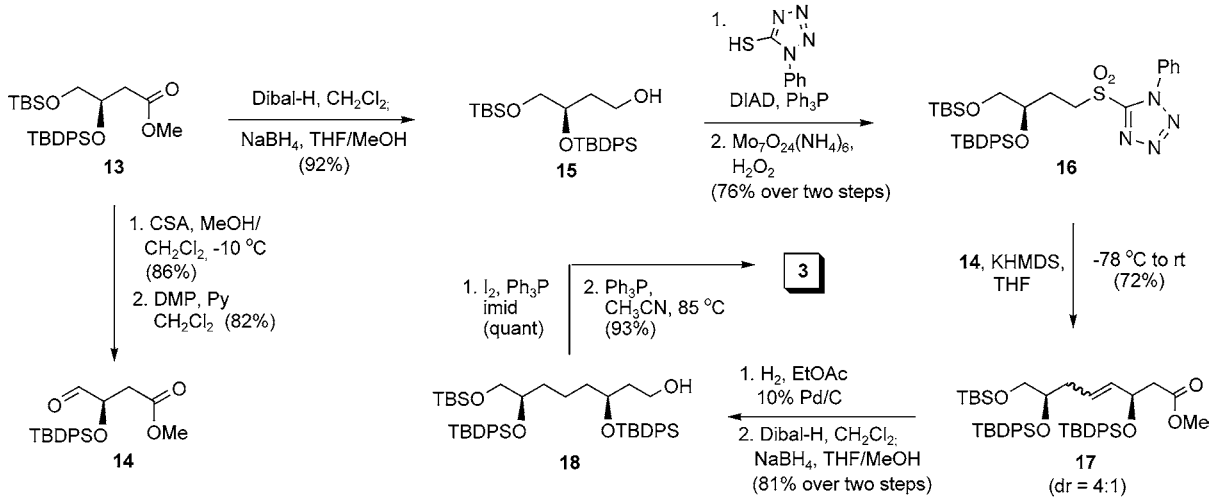
conversion to **5b** resulted in critical differential blocking of the three oxygenated sites (Scheme 2). The acyclic backbone was extended by ozonolytic cleavage of the terminal double bond in **5b** prior to union of the aldehyde so formed with the potassium salt of sulfone **12** under conventional Julia−Kocienski conditions. The latter fragment was generated via a Mitsunobu protocol.[9] The first important observation relates to the exclusive *E* configuration of **6**. Another key finding was our awareness that chemoselective desilylation of the OTBS group in **6** in advance of asymmetric dihydroxylation allowed for the chromatographic purification of triol **7**, which arose as the major diastereomer (4:1 dr). Aldehyde **8** was secured by sequential acetalization with 2,2-dimethoxypropane and reaction with the Dess−Martin periodinane. This intermediate proved to be sensitive to β-elimination, thus setting aside the possibility of its coupling to lithium-based reagents. On the other hand, the Grignard derived from 4-bromo-2-methyl-1-butene added smoothly, leading ultimately to **9** after oxidation. The need to avoid alkaline requirements persisted in **9**, thereby requiring that removal of the TBDPS functionality be brought about with TBAF in the presence of acetic acid.[10] These nonbasic conditions gave rise to **10** in 95% yield, thereby making possible the diastereoselective 1,3-syn reduction of this β-hydroxy ketone with diethylmethoxyborane.[11] The preparation of **2** was completed after acetalization, PMB deprotection, and Johnson−Lemieux cleavage of the double bond.

The conversion of D-malic acid into **13** was designed to allow differential protection of the hydroxyl groups with TBS at the primary position and TBDPS at the secondary (Scheme 3). Arrival at **13** allowed for the bifurcative construction of the aldehyde ester **14** and the primary alcohol **15**. Both pathways gave cause to be concerned with competing lactonization. For this reason, the controlled desilylation of

Scheme 2. Synthesis of Hydroxy Ketone **2**



Scheme 3. Synthesis of Phosphonium Salt **3**



13 was induced with CSA in CH_3OH/CH_2Cl_2 at −10 °C. Temperature control proved to be critical to the realization of an 86% yield of the hydroxy ester. The latent potential for ring closure during Dibal-H reduction was similarly minimized by maintaining a temperature no greater than −10 °C and not exceeding this upper limit during ensuing treatment with $NaBH_4$.

With these two subunits in hand, conditions for their union were investigated. To evaluate the applicability of the Julia−Kocienski olefination in this setting, **15** was transformed into sulfone **16**. Reliable conditions were soon uncovered for efficient reaction with **14** to provide **17** in an *E*/*Z* ratio of 4:1. This isomer distribution is not of consequence since arrival at alcohol **18** is founded on subsequent catalytic hydrogenation, followed by hydride reduction of the ester functionality. The resulting alcohol **18** was transformed via the iodide into the phosphonium salt **3**.

The next series of transformations involved the union of **2** to **3**. The oxidation of **2** with the Dess−Martin reagent proceeded straightforwardly to generate keto aldehyde **19**, whose Wittig reaction with **3** proceeded with involvement of the carboxaldehyde functionality and resulted in formation of the (*Z*)-olefin (^{1}H NMR analysis), the catalytic hydrogenation of which provided **20** in 77% overall yield (Scheme 4). The preparation of subunit **21** was completed by sequential sodium borohydride reduction and Mitsunobu reaction with 1-phenyl-1*H*-tetrazole-5-thiol.[8] This application of the S_N2 reaction expectedly required longer times (up to 2 days) to proceed to completion in view of the secondary nature of the seat of reaction. The two diastereomers of **21** (dr = 5:1) could be secured in pure form by chromatography on silica gel. Our inability to assign configuration to C(30) in **21** is of little consequence since a double bond is ultimately positioned at this site and both isomers hold comparable synthetic importance. They were therefore processed independently through the later steps. Excellent functional group tolerance was operational when **21** was treated with NBS in aqueous DMSO. Under these conditions, conversion to the alcohol proceeded smoothly with exclusive loss of the TBS group. Subsequent periodinane oxidation was also efficient, leading uniquely to the targeted aldehyde **22**.

We next undertook to explore the development of a possible route to **4**. Gratifyingly, recourse to **23** as the starting point proved to be well suited to the task at hand. Reduction of dimethyl (*S*)-malate as reported by Saito et al. with subsequent acetonide formation provided **23**.[12] Once again, the Mitsunobu reaction was employed to activate the terminal primary carbon. Ensuing molybdate-promoted oxidation[9] furnished **24**, the availability of which made possible efficient coupling to aldehyde **14**, which had previously been generated. This olefination afforded **25** as a 3:1 mixture of (*E*)- and (*Z*)-isomers (^{1}H NMR analysis). This isomeric ratio was increased to 6:1 by radical-induced isomerization involving thiophenol and AIBN in refluxing benzene over a period of 1 day.[13] Extension of the reaction time to 3 days led to a still more favorable distribution of 12:1, a value that remained unchanged at more prolonged time intervals. Although access to alcohol **26** and sulfone **27** was realized with high efficiency, neither product lent itself to chromatographic separation of the major constituent. This objective was, however, conveniently met by replacement of the acetonide group by two *tert*-butyldiphenylsilyl residues as in **4**.

With **4** and **22** in hand, their merger in the Julia−Kocienski olefination was accomplished in the usual one-pot operation. A significant bias toward trans stereoselection (dr = 8.6:1) was evident from the large coupling constant between H(8) and H(9) (J = 15.6 Hz) observed in the dominant product.

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(11) Wanderwal, C. D.; Weller, S.; Sorensen, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5393.
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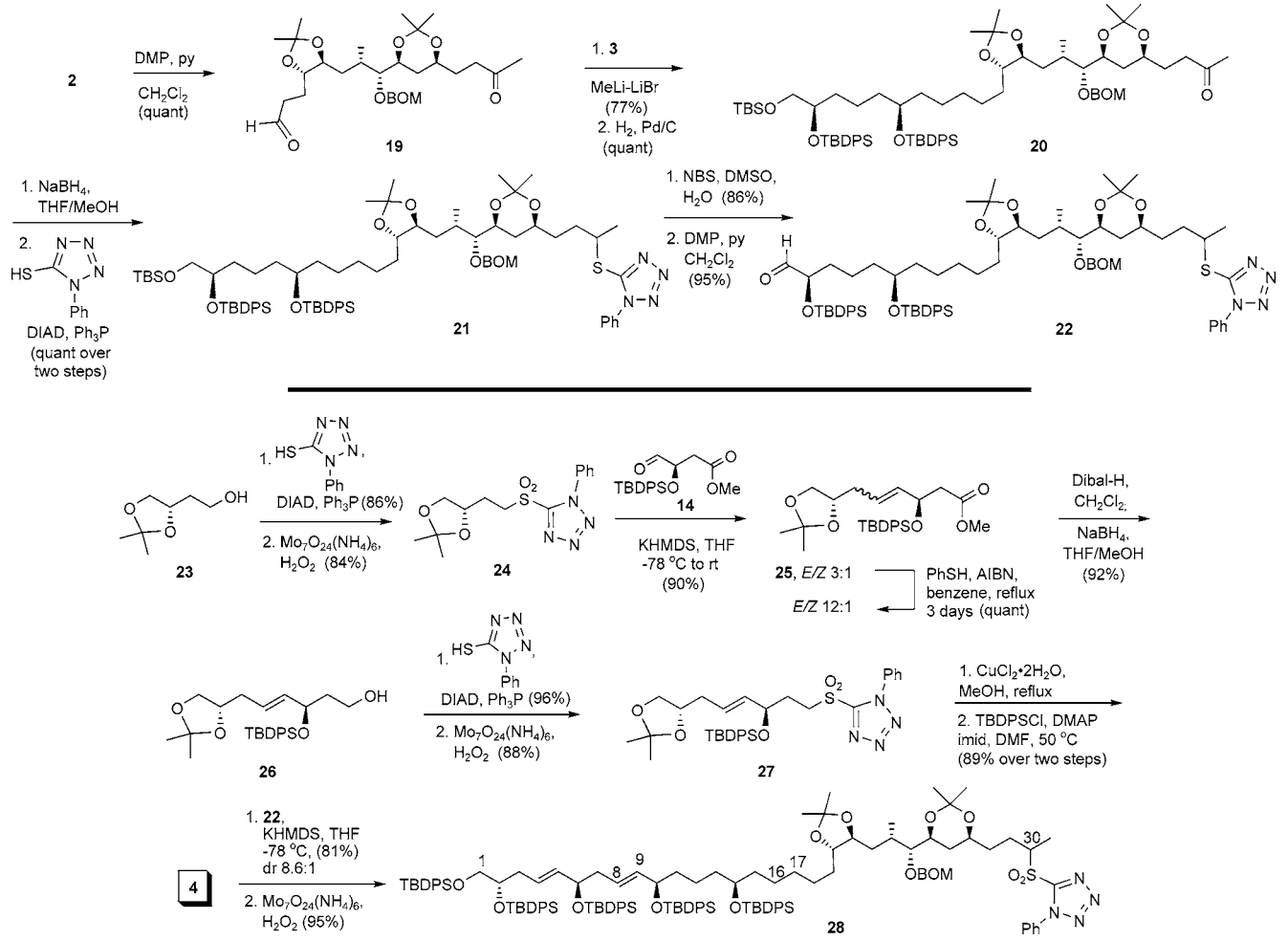
(13) Schwarz, M.; Graminski, G. F.; Waters, R. M. *J. Org. Chem.* **1986**, *51*, 260.

Scheme 4. Assembly of the Protected C(1)−C(30) Polyhydroxylated Chain



Further oxidation was accomplished with a complex of ammonium molybdate and hydrogen peroxide to deliver **28**.

In conclusion, the convergent route to **28** documented here offers considerable insight into an approach toward construction of a polyoxygenated chain by repeated application of the Kocienski modification of the Julia reaction. Another key to our success includes the economic manner in which the antipodal malic acids can be transformed into enantiopure building blocks directly suited to the present objectives. Effort is now being directed toward the completion of an efficient total synthesis of natural amphidinol 3.

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

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