Convergent Synthesis of the C18–C30 Fragment of Amphidinol 3

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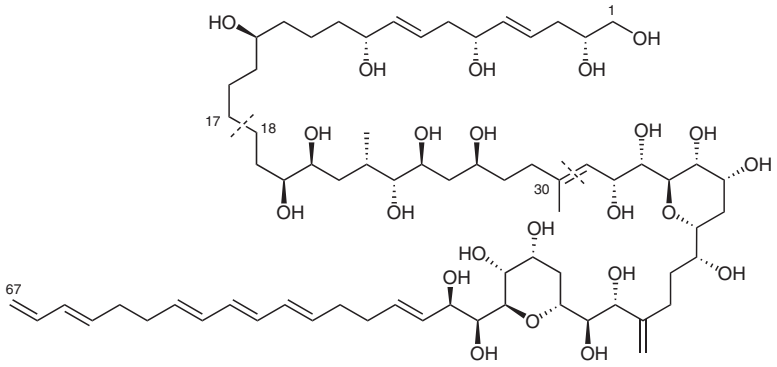
Abstract: The C18–C30 fragment of amphidinol 3 has been synthesized in a convergent fashion by employing two asymmetric Sharpless dihydroxylations, a Julia–Kocienski olefination and a Wittig reaction as the key steps.

Key words: amphidinol, Julia–Kocienski olefination, Wittig olefination, Sharpless dihydroxylation

Marine dinoflagellates, a type of primitive unicellular algae, are a rich source of natural products such as long-chain polyketides, amphidinolides, or cyclic polyethers.[1,2] Among dinoflagellates, the genus *Amphidinum klebsii* has been recognized as a source of novel bioactive secondary metabolites such as amphidinol 3 (AM3), an antifungal and haemolytic compound, which was isolated for the first time by Yasumoto et al. in 1991.[3] Amphidinol 3 is a polyhydroxylated and polyenic compound whose structure was first elucidated by Murata et al. in 1999.[4] Recently, the configuration of the C2 stereocenter has been revised (Scheme 1).[5,6] The structural complexity of AM3, coupled with its interesting biological properties, has stimulated a wide range of synthetic activity from organic chemists and an array of fragments have been prepared,[7–10] but the total synthesis of AM3 has not been completed yet.

Previously, we have reported the synthesis of the C1–C13 fragment[7a] and two syntheses of the C50–C67 fragment of AM3.[7b,c] As we plan to construct the C17–C18 and C30–C31 bonds by using Julia–Kocienski olefinations, we report here the synthesis of the C18–C30 fragment which possesses six of the 25 stereogenic centers present in AM3. According to our retrosynthetic analysis, fragment C18–C30 **A** could be disconnected into two simplified subunits, phosphonium salt **B** and aldehyde **C** (Scheme 2). These two fragments would be coupled by



Scheme 1 Amphidinol 3 revised structure and fragment C18–C30

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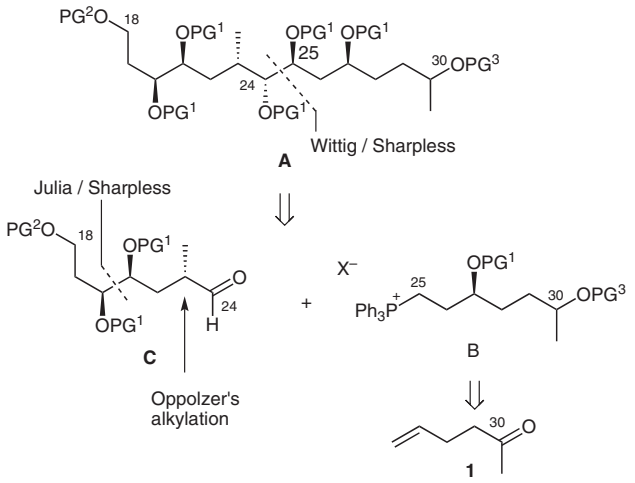
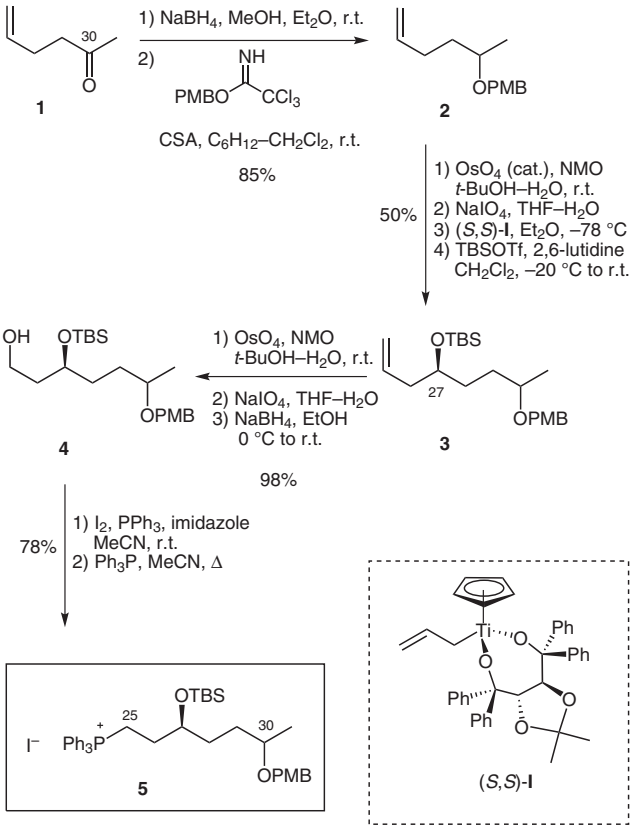
employing a Wittig olefination, in order to install a double bond at C24–C25 possessing a *Z*-configuration. Indeed, this geometry is required for the Sharpless asymmetric dihydroxylation to provide us with the correct oxygenated stereogenic centers at C24 and C25. Fragment **B** would be easily prepared from hex-5-en-2-one (**1**) (Scheme 2). Concerning fragment **C**, the C20 and C21 oxygenated stereocenters would be installed by applying a Sharpless asymmetric dihydroxylation to the corresponding *E*-olefin, whereas the C23 stereogenic center would be generated by alkylation of Oppolzer's chiral sultam.



Scheme 2 Retrosynthetic analysis of fragment C18–C30

The synthesis of the C18–C30 fragment of AM3 started with the transformation of unsaturated ketone **1** into a phosphonium salt of type **B** (Scheme 3). After reduction of the ketone function in **1** ($NaBH_4$, MeOH–Et_2O, r.t.) and protection of the obtained alcohol as a *p*-methoxybenzyl (PMB) ether [PMBOC(=NH)CCl_3, CSA (cat.)], the unsaturated ether **2** was isolated (85% overall yield for the two steps). Oxidative cleavage of the terminal double bond in **2** [OsO_4 (cat.), NMO, then $NaIO_4$] was followed by the treatment of the crude aldehyde with the highly face-selective Duthaler allyltitanium complex (*S,S*)-**I**[11] in order to install the C27 stereogenic center. The obtained alcohol was then protected as a *tert*-butyldimethylsilyl (TBS) ether (TBSOTf, 2,6-lutidine, CH_2Cl_2), and **3** was isolated in 50% overall yield (4 steps, starting from **2**). In order to synthesize the phosphonium salt **5** (compound of type **B**), **3** was transformed into alcohol **4** by oxidative cleavage of the terminal double bond (OsO_4 cat., NMO, then $NaIO_4$) and reduction of the intermediate aldehyde with sodium borohydride (98% over three steps). Alcohol **4** was then iodinated (I_2, Ph_3P, imidazole) and further reacted with triphenylphosphine to yield the desired phosphonium salt **5** in 78% overall yield (Scheme 3).

Having prepared **5** (C25–C30 fragment), the synthesis of the C18–C24 fragment (compound of type **C**) was performed (Scheme 4). The optically active protected alcohol **7** was prepared by alkylation of Oppolzer's chiral sultam.[12] Compound **6** was first treated with LiHMDS, in



Scheme 3 Synthesis of phosphonium salt **5**

the presence of HMPA, and then reacted with allyl bromide. After removal of the chiral auxiliary (lithium pyrrolidinoborohydride, THF, 0 °C) and protection of the hydroxy group (TBSCl, imidazole, DMAP, DMF–THF, r.t.), **7** was isolated in 74% overall yield (over three steps). The terminal olefin of the chiral silyl ether **7** was subjected to ozonolysis (O_3, CH_2Cl_2, –78 °C then Et_3N)[13] to form the corresponding aldehyde which was condensed with phenyltetrazolyl sulfone **8**[14] under Julia–Kocienski conditions (KHMDS, THF, –78 °C then r.t.) to generate the *E*-alkene **9** in 55% yield over two steps (*E*/*Z* > 95:5). In order to control the absolute and relative configurations of the stereogenic centers at C20 and C21, *E*-alkene **9** was subjected to a Sharpless asymmetric dihydroxylation using AD-mix-α to furnish two diols **10** and **10′** as a 80:20 mixture. After separation by flash chromatography on silica gel, the major diol was protected with TBSOTf (2,6-lutidine, CH_2Cl_2, –78 °C then r.t.) to yield **10** in 69% yield from **9**. A selective deprotection of the primary hydroxy group at C24 present in **10** was achieved by treatment with ammonium fluoride in methanol at 60 °C (79% yield), as the reaction was ineffective at room temperature. The resulting primary alcohol was then oxidized using Dess–Martin periodinane to form aldehyde **11** in quantitative yield. The key intermediate **11** (fragment C18–C24), bearing three stereogenic centers, was efficiently prepared in nine steps and with an overall yield of 22%. With compounds **11** (fragment C18–C24) and **5** (fragment C25–C30) in hand, we turned our attention towards the crucial

final coupling reaction. The Wittig olefination of **11** by a phosphonium ylide was essential as an asymmetric dihydroxylation of a *Z*-double bond will generate a diol with the *anti* relative stereochemistry. When the Wittig reaction of aldehyde **11** with the phosphonium ylide, generated from **5** with KHMDS, was performed in toluene, the *Z*-olefin was isolated in moderate yield (48%) but a good stereocontrol of the configuration of the double bond was observed (*Z*/*E* > 95:5).[15] Although asymmetric dihydroxylation of *Z*-olefins utilizing AD-mix are generally less stereoselective than those of *E*-olefins, the asymmetric dihydroxylation of the *cis*-olefin **12** provided two diastereomers **13** (62% isolated yield) and **14** in a ratio of 4:1. These two diastereomers were separated by flash chromatography on silica gel. We have to point out that the reaction was sluggish with the commercially available AD-mix-β (1.4 mg/mmol) at 0 °C, and additional OsO_4 and chiral ligand $(DHQD)_2PHAL$ (4 mol% each) were necessary for the reaction to go to completion.[16] The configuration of the two newly created stereogenic centers at C24 and C25 were determined after transformation of both diols **13** and **14** into their corresponding acetonides **15** (89%) and **15′**[18] [2,2-dimethoxypropane, CSA (cat.)]. NOE experiments on both acetonides, as well as literature comparison with chemical shifts and coupling constants of similar compounds,[17] strongly indicated that the major isolated diastereomer had the correct relative and absolute configuration at the C23 and C24 stereogenic centers.[18]

In order to complete the synthesis of alcohol **16** (C18–C30 fragment of AM3), selective cleavage of the benzyl ether at C18 over the *p*-methoxybenzyl ether at C30 was achieved upon treatment of **15** with Raney nickel W-4.[19] Alcohol **16** was obtained in 70% yield[20] (Scheme 5).

In summary, a convergent approach to the C18–C30 fragment of amphidinol 3 was achieved in 15 steps and in 6.3% overall yield for the longest linear sequence (the total number of steps is 24). The use of a diastereoselective alkylation of Oppolzer's chiral sultam, two Sharpless asymmetric dihydroxylations and an enantioselective allyltitanation enabled us to control the six stereogenic centers present in this fragment.

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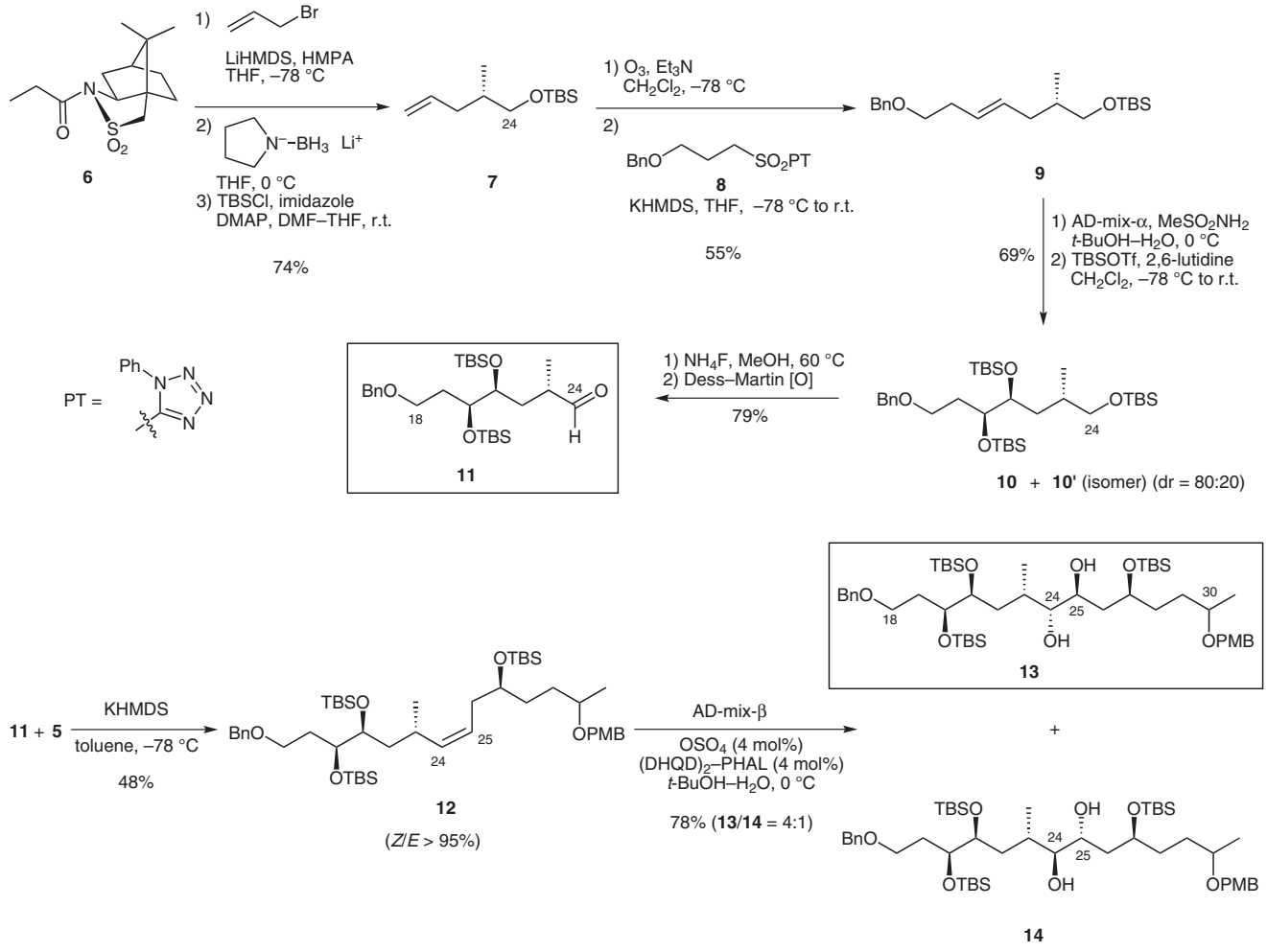
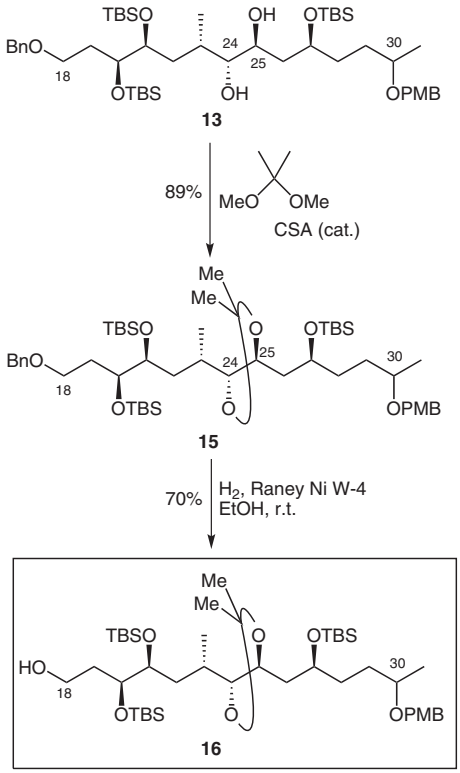


Scheme 4 Synthesis of aldehyde **11** and synthesis of diol **13**



Scheme 5 Synthesis of alcohol **16**

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(14) Compound **8** was prepared from 3-bromopropan-1-ol in 3 steps (40% yield).

(15) The starting aldehyde **11** (20%) was recovered as the corresponding alcohol after the reductive workup and no improvement in conversion was observed when the phosphonium bromide was utilized.

(16) On large scale, longer reaction times of up to one week and vigorous stirring were required.

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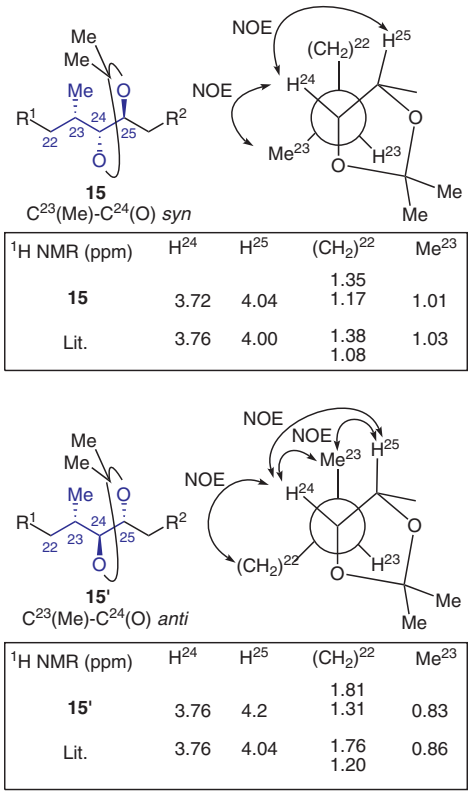
(18) NMR study (see ref. 17 for literature data): A *syn* relationship between the substituents at C23 and C24 was observed for compound **15** (Figure 1).



^{1}H NMR (ppm)	H^{24}	H^{25}	$(CH_2)^{22}$	Me^{23}
15	3.72	4.04	1.35 1.17	1.01
Lit.	3.76	4.00	1.38 1.08	1.03

^{1}H NMR (ppm)	H^{24}	H^{25}	$(CH_2)^{22}$	Me^{23}
15'	3.76	4.2	1.81 1.31	0.83
Lit.	3.76	4.04	1.76 1.20	0.86

Figure 1

(19) Other Raney nickel were less selective and both the benzyl and *p*-methoxybenzyl groups were cleaved.

(20) **Compound 16 (Mixture of Epimers at C30)**
Colourless oil; $[\alpha]_D^{20}$ –49.3 (*c* 0.5, $CHCl_3$). IR (film): 2927, 2855, 1712, 1608, 1513, 1462, 1378, 1248, 1217, 1169, 1094, 1062, 1039, 1006 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6): δ = 7.19–7.13 (m, 2 H), 6.79–6.74 (m, 2 H), 4.40–4.27 (m, 2 H), 3.96–3.86 (m, 2 H), 3.70 (s, 3 H), 3.69–3.60 (m, 3 H), 3.57–3.46 (m, 2 H), 3.40–3.31 (m, 1 H), 1.89–1.79 (m, 1 H), 1.78–1.68 (m, 2 H), 1.66–1.55 (m, 1 H), 1.54–1.31 (m, 4 H), 1.38 (s, 3 H), 1.30–1.01 (m, 7 H), 1.24 (s, 3 H), 0.96–0.89

(m, 3 H), 0.86–0.71 (m, 27 H), 0.02 to –0.07 (m, 18 H). ^{13}C NMR (100 MHz, C_6D_6): δ = 159.1 (s), 130.9 (s), 129.5 and 129.1 (d), 113.7 (d), 107.7 and 107.5 (s), 82.9 (d), 75.1 (d), 75.1 and 74.9 (d), 72.5 and 72.3 (d), 71.6 (d), 69.8 and 69.7 (t), 68.8 and 68.7 (d), 60.6 and 60.4 (t), 55.2 (q), 36.5 and 36.1 (t), 34.2 (t), 33.5 and 33.5 and 33.5 (t), 31.0 (t), 30.7 and 30.6 (t), 29.7 (t), 28.7 and 28.7 (q), 28.5 and 28.4 (d), 26.1 (2C, q), 26.1–25.8 (q), 22.6 and 22.6 (t), 19.8 and 19.8 (q), 18.0–17.9 (s), 16.5 (q), –4.1 to –4.7 (q). ESI-HRMS: *m/z* calcd for $C_{44}H_{86}O_8Si_3 + Na^+$: 849.5523; found: 849.5506.