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Total Synthesis of Amphidinolide Q

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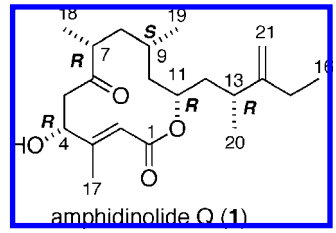
ABSTRACT



Asymmetric synthesis of amphidinolide Q, a cytotoxic macrolide from the cultured dinoflagellate *Amphidinium* sp., has been accomplished with Julia coupling, Myers alkylation, and Yamaguchi lactonization. The absolute configuration of amphidinolide Q was confirmed to be 1 from comparison of the NMR data and $[\alpha]_D$ values of synthetic and natural amphidinolide Q.

Amphidinolide Q (**1**) is a cytotoxic 12-membered macrolide having C1 branches at vicinal carbons (C-13 and C-14) and an α,β-unsaturated ester moiety, isolated from the cultured dinoflagellate *Amphidinium* sp. (Y-5 strain).[1] Recently, we have proposed the stereoconfiguration of amphidinolide Q as **1** on the basis of extensive NMR experiments, molecular modeling, and chemical derivatization.[2] In this paper, we describe the first total synthesis of amphidinolide Q (**1**) and establish our proposed absolute stereochemistry.

As outlined retrosynthetically in Scheme 1, amphidinolide Q (**1**) could be obtained by Yamaguchi lactonization[3] of *seco*-acid **2**, which could be provided by aldol reaction of the C-1-C-5 segment (**3**) and the C-6-C-16 segment (**4**). Key aldehyde **4**, containing four stereogenic centers, could be derived from iodide **5** via Myers alkylation,[4] which is conceived to be obtained through Julia coupling[5] between sulfone **6** and aldehyde **7**.

The synthesis of iodide **5** is described in Scheme 2. Alcohol **8**[6] was transformed with $(PhS)_2$-Bu_3P[7] into sulfide, which was oxidized with *m*-chloroperoxybenzoic acid to sulfone **6**. Alcohol **9**[8] was oxidized with Dess−Martin periodinane[9] to the corresponding aldehyde **7**, which was then subjected to Julia coupling[5] with **6** to afford hydroxy sulfone. Ketone **10** was obtained following oxidation and reductive removal of the sulfone group.[10] Reduction of ketone **10** with $NaBH_4$ gave diols **11** and **12** (37% and 32%, respectively). Selective protection of the primary hydroxy group in **11** provided pivaloate ester **13**, the secondary hydroxy group of which was treated with MOMCl and *i*-Pr_2NEt to afford MOM ether **14**. After removal of the pivaloyl group in **14**, the corresponding alcohol was oxidized to an aldehyde, then treated with EtMgBr and oxidized to yield ketone **15**. Wittig olefination was followed by deprotection and iodination to afford iodide **5**.

The absolute configuration at C-11 in **13** was elucidated by a modified Mosher's method.[11] Treatment of **13** with (*R*)-(−)- and (*S*)-(+)-2-methoxy-2-trifluoro-2-phenylacetyl chloride (MTPACl) provided the (*S*)- and (*R*)-MTPA esters (**13a**

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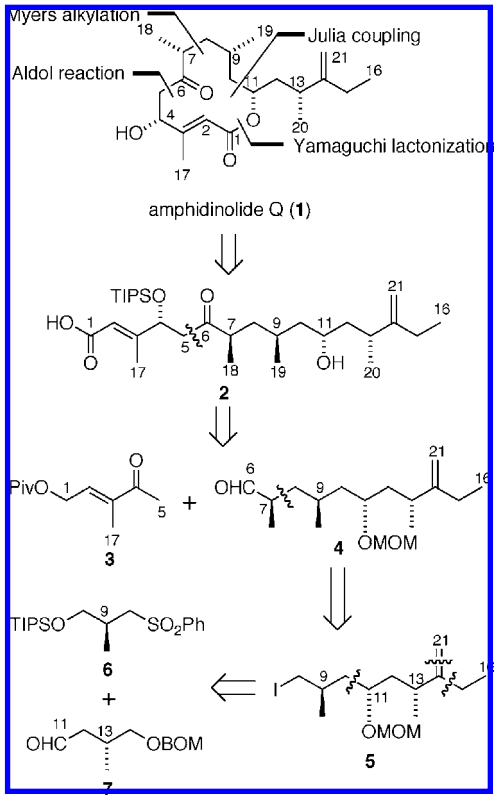
Scheme 1. Retrosynthetic Analysis of Amphidinolide Q (**1**)



and **13b**, respectively) of **13**. $\Delta\delta$ values ($\Delta\delta = \delta_S - \delta_R$) obtained from ^{1}H NMR data of **13a** and **13b** are shown in

Figure 1. The $\Delta\delta$ values for H_2-8, H-9, H_2-10, and H_3-19

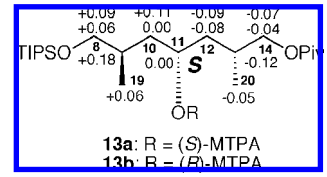


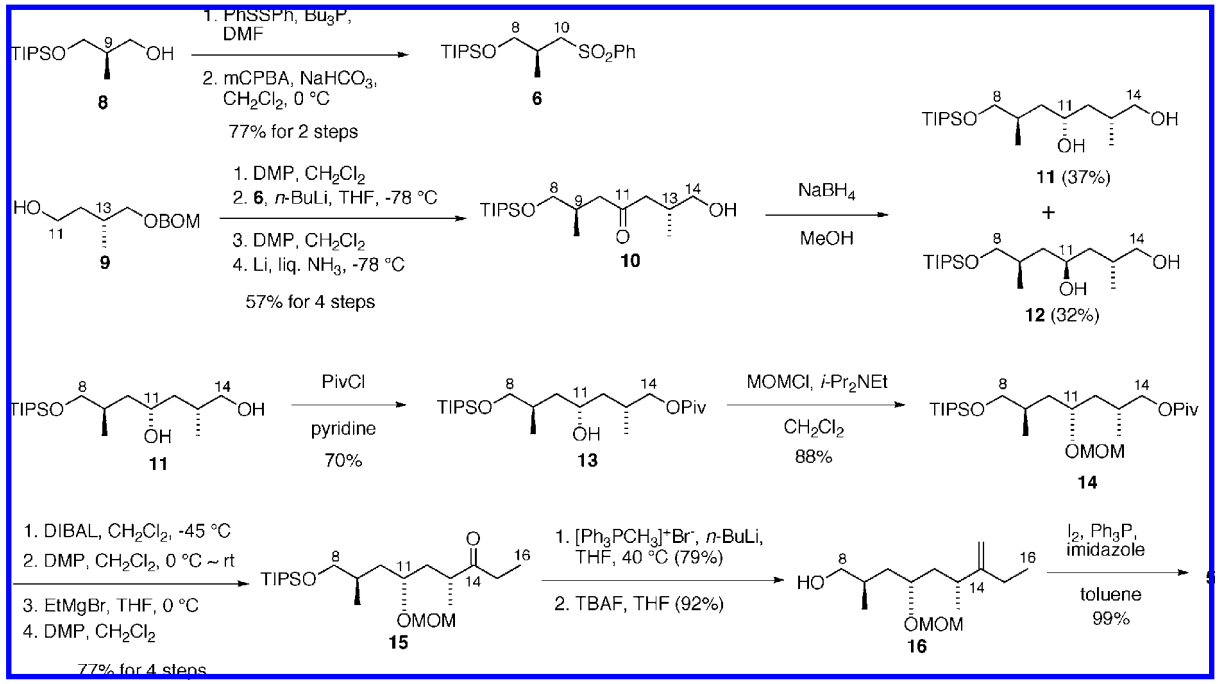
Figure 1. $\Delta\delta$ values [$\Delta\delta$ (in ppm) $= \delta_S - \delta_R$] obtained for (*S*)- and (*R*)-MTPA esters at C-11 (**13a** and **13b**, respectively) of alcohol **13**.

were positive, while negative $\Delta\delta$ values are observed for H_2-12, H-13, H_2-14, and H_3-20. These results indicated that the absolute configuration at C-11 was *S*.

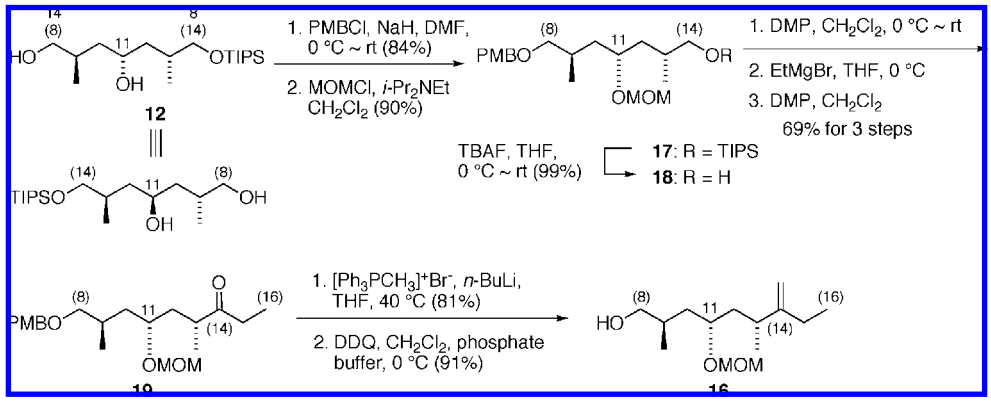
As shown in Scheme 3, alcohol **12** was also converted into **16**. Selective hydroxy group protections furnished **17**. After removal of TIPS ether in **17**, alcohol **18** was oxidized to the corresponding aldehyde and then treatment with EtMgBr afforded alcohol, which was oxidized with Dess−Martin periodinane to ketone **19**. Wittig reaction to install an exomethylene followed by treatment of DDQ yielded alcohol **16**, which was transformed into iodide **5** as described in Scheme 2.

Alcohol **20**[12] was protected as pivaloate ester to afford the C-1-C-5 segment (**3**) (Scheme 4). Myers alkylation[4] was used to install the C-7 stereocenter essentially as a single diastereomer. Reductive cleavage of the auxiliary by using LDA-BH_3·NH_3 complex provided alcohol **22**. Oxidation of **22** with Dess−Matin periodinane and then aldol reaction of

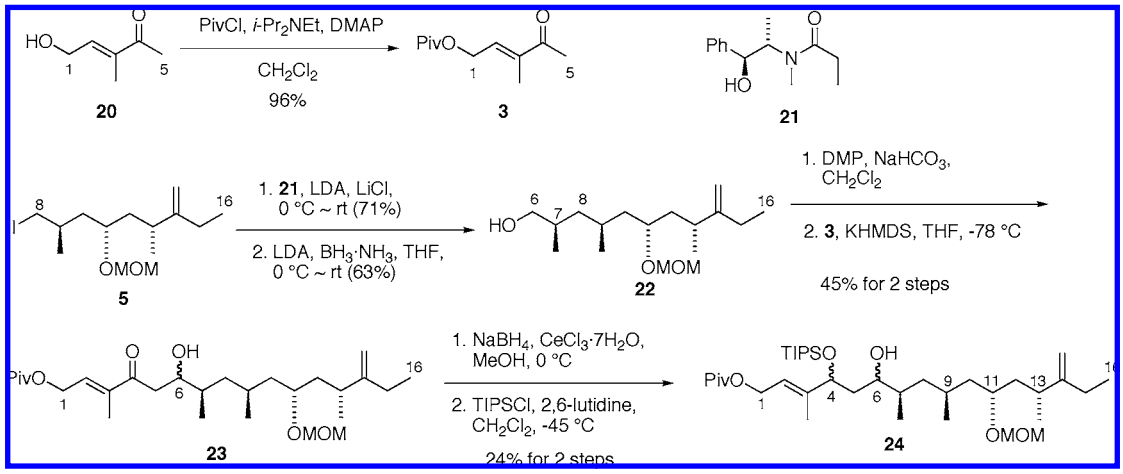
Scheme 2. Synthesis of the C-8-C-16 Segment (**5**) from **8**



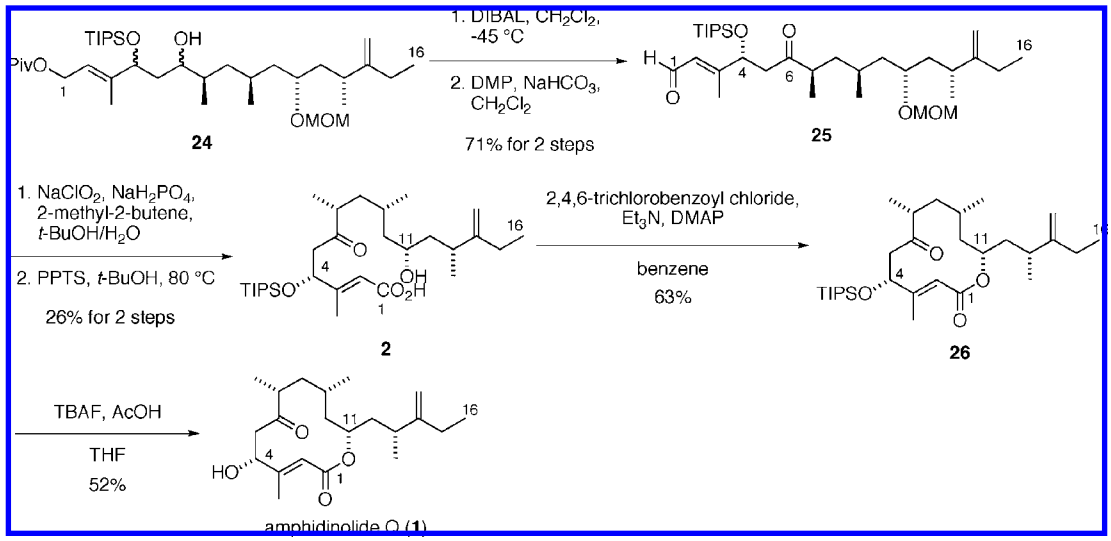
Scheme 3. Synthesis of the C-8-C-16 Segment (**16**) from **12**



Scheme 4. Synthesis of the C-1-C-16 Segment (**24**) from **5**



Scheme 5. Synthesis of Amphidinolide Q (**1**) from **24**



the corresponding aldehyde and **3** with KHMDS afforded β-hydroxy ketone **23**. Reduction of **23** with $NaBH_4$ and $CeCl_3 \cdot 7H_2O$ followed by selective protection of the allylic hydroxy group yielded TIPS ether **24** as a diasteromeric mixture.

Removal of the pivaloyl group in **24** with DIBAL followed by oxidation with Dess−Martin periodinane provided aldehyde **25** as a single diastereomer after silica gel column separation (Scheme 5). After aldehyde **25** was oxidized under Pinnick oxidation conditions[13] to carboxylic acid, the MOM group was removed with PPTS to afford *seco*-acid **2**. The *seco*-acid (**2**) was then subjected to macrolactonization by using the Yamaguchi procedure[3] to provide macrolactone **26**. Finally, removal of the TIPS group in **26** with TBAF and AcOH furnished amphidinolide Q (**1**). The absolute configuration at C-4 in **1** was confirmed by a modified Mosher's method as in the previous report.[2] Synthetic amphidinolide Q (**1**) was identical with natural amphidinolide Q (^{1}H and ^{13}C NMR, IR, UV, MS, and optical rotation),[1,2] thus allowing confident assignment of the absolute configurations and validating our earlier proposal.[2]

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

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