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Synthesis of amphidinolide Y precursors

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ABSTRACT

The Negishi coupling between a chiral C3 synthon and an iodoalkene arising from 3-butyn-1-ol, which gave the C3–C9 fragment of amphidinolide Y, was the starting point of a formal total synthesis of this marine natural product. By means of Sharpless ADH and TADDOL-mediated crotylation, the full western fragment (C1–C11) was obtained, which was coupled with the eastern fragment (3-hydroxyoxolane derivative). The penultimate step (ring-closing metathesis, with G-II, H–G-II, or Nitro-Grela reagents, under several conditions) posed great difficulties. The cyclization was achieved with **15c** (7,9-bis-*O*-TES) and **15d** (7-*O*-TES, 9-*O*-TBS); more than stoichiometric amounts of the H–G-II Ru complex were required for complete conversion.

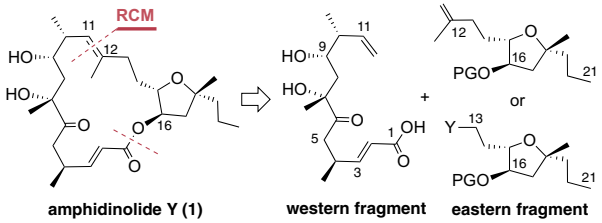
Amphidinolide Y (**1**) is a cytotoxic macrolide that was isolated from a marine *Amphidinium* dinoflagellate by Kobayashi et al.[1] Two total syntheses have been reported:[2] the first based on the formation of the C12–C13 bond by a variant of Suzuki coupling and Yamaguchi macrolactonization,[2a] while the second relies upon a ring-closing metathesis (RCM) approach to create the C11–C12 double bond.[2b] We describe here a third synthesis, also with a RCM reaction as the penultimate step. When we designed total syntheses of **1** and its biogenetic derivative[1] amphidinolide X[3] we faced such a disconnection (Scheme 1). The stereo selective formation of trisubstituted double bonds by RCM was (and is) challenging, but the shortcomings of the methods are a stimulus to improve them. Compound **1** might behave as a G-actin assembly inhibitor, as amphidinolides X and J.[4]

The eastern fragment (C12–C21, Scheme 1) was not expected to be a problem, since we had prepared several closely related synthons and precursors of the terminal olefin (Y = CHO, CN, COMe, C≡CH, CH=CH_2) and stereoisomers, when working on the synthesis of amphidinolide X.[3a,b] Problems were expected to appear in the coupling of the two fragments. The failure to achieve the desired (*E*)-double bond in the RCM leading to the 16-membered ring of amphidinolide X had forced us to opt for a Si-tethered CM reaction that, unfortunately, involved several further steps,[3a,5] followed by a final macrolactonization. As **1** has a slightly larger size (17-membered ring), the chances of success might be slightly higher either by a direct RCM,[6] through cascade or relay RCM (RRCM),[6c,d] or via other types of RCM.[7]

In fact, the publication of Dai et al.[2b] (40% of the desired RCM product) when our project was starting reinforced our initial strategy of adopting the shortest approach (direct RCM). We report here one successful synthesis of the western fragment (Scheme 1), its union with the eastern fragment by esterification, and the efforts to carry out the final RCM. Most attempts were unfruitful, but in our opinion they deserve to be reported as an evaluation of the scope of the current RCM methods when applied to densely functionalized substrates.

First of all, we synthesized the C3–C9 enantiopure fragment (**4**) shown in Scheme 2, starting from commercially available 3-butyn-1-ol and methyl (*R*)-3-hydroxy-2-methylpropanoate (Roche's ester, 99% ee). The key step, the formation of bond C5–C6 between **2** and **3** by a Negishi reaction, according to careful conditions for the preparation of the organozinc,[8] took place in high yield.

The asymmetric dihydroxylation (Sharpless' ADH, see Scheme 3) of **4** with AD-mix-β[9] was complete, but diol **5** was contaminated with 20% of its diastereomer (dihydroxylation by the opposite face). Separation was performed by flash chromatography. We observed later that it was easier after conversion of the mixture into the isopropylidene acetals (**6** and its stereomer).



Scheme 1. Main fragments of amphidinolide Y.

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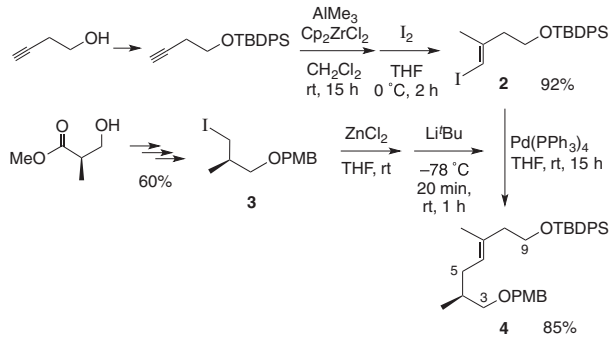
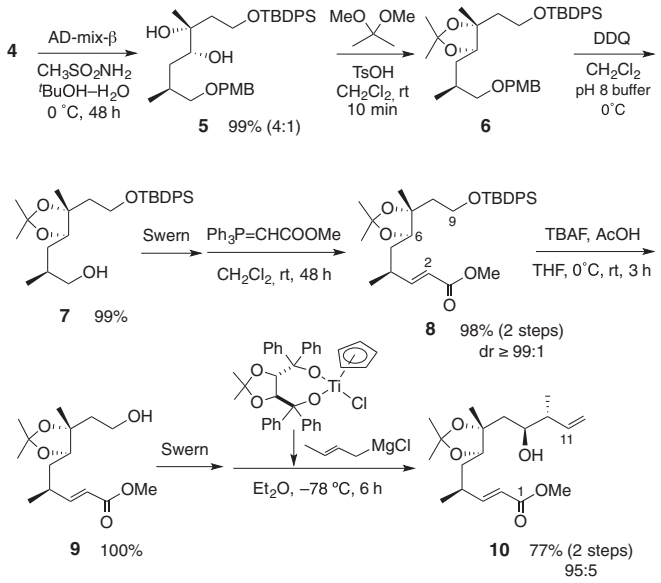


Scheme 2. Synthesis of fragment C3–C9.



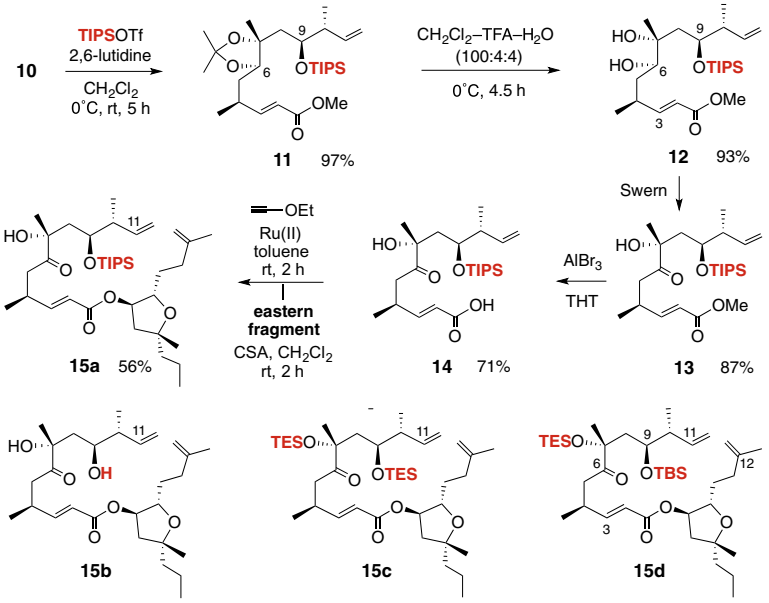
Scheme 3. From fragment C3–C9 to C1–C11.

Removal of PMB[10] from **6** with DDQ, followed by Swern oxidation[11] of alcohol **7** and a standard Wittig reaction, gave fragment C1–C9 (**8**).[12] Removal of the TBDPS group to give **9**[12] was followed by another Swern oxidation. To secure the *anti*-relationship of the hydroxy group at C9 and methyl at C10 (see **10**) we applied the crotylation procedure of Hafner–Duthaler et al.[13] Other known asymmetric allylation and crotylation procedures, which we have used in other syntheses, could have been checked and compared, but the method with Ti-TADDOL-ate[13] was sufficiently efficient in the first trials, with *anti*/*syn* ratios between 90:10 and 95:5. Stereoisomer **10** was purified by column chromatography.

We protected the free hydroxy group of **10** as its TBS ether, but later attempts to hydrolyze the 1,3-dioxolane (isopropylidene acetal) without removing the TBS group were unsuccessful. The oxidation of the secondary OH group at C6 should not be postponed until the end of the synthesis, as we had noted a tendency of the free C6-OH to add to the double bond (conjugate addition under base catalysis) to afford a stable oxolane derivative. It therefore seemed wise to oxidize C6-OH to ketone as soon as possible, while C9-OH was protected. Thus, as shown in Scheme 4, the hydroxy group at C9 was protected with TIPS (**11**), which allowed the selective cleavage of the isopropylidene acetal[14] to yield **12**. The Swern oxidation, conversion of the ester group of **13** into carboxylic acid **14** (under special conditions,[15] to prevent the conjugate addition of the C7-OH to the double bond with formation of a THP/oxane ring), activation of the COOH group with ethoxyethyne and [$RuCl_2$(*p*-cymene)]$_2$,[16] and reaction with the appropriate eastern fragment[3] (with the hydroxy group free) in the presence of 10-camphorsulfonic acid gave **15a**. A portion of **15a** was deprotected with TBAF/AcOH in THF to afford **15b**. Protection of a sample of **15b** with an excess of TESOTf and 2,6-lutidine gave **15c**.

We were ready to examine the RCM reactions of **15a–c** with three available initiators (Fig. 1).[6] A long series of trials, each with 5 mg of substrate, were performed by addition of up to 60 mol % of these initiators in three batches, either in CH_2Cl_2 at 40 °C for 3 days or in toluene at 90 °C for 2 days, with or without *p*-benzoquinone[17] as an additive. The screening was better followed by electrospray ionization MS (ESIMS).[18]

With the TIPS derivative (**15a**) no reaction was noted. With unprotected **15b** no reaction occurred either.[19] The most encouraging result was with **15c** and H–G-II (up to 60 mol %) in toluene at



Scheme 4. Esters **15a–d**.

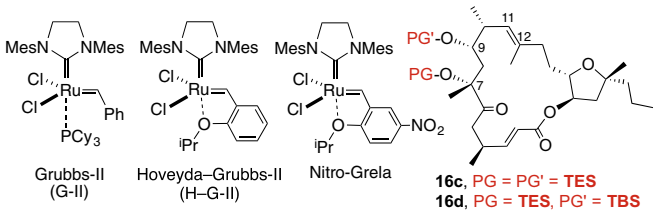


Figure 1. Initiators/catalysts examined. Expected products **16c** and **16d**.

90 °C for 2 days, but the signal that may be attributable to **16c** (ESIMS, *m*/*z* 696.51, M+NH_4^+, contaminated or not with its *Z* isomer) was less intense than that of remaining **15c** (*m*/*z* 724.54, M+NH_4^+). We had to subject this mixture to a second round for a complete conversion (overall ⩾1.2 equiv of the H–G-II reagent), which made the isolation and purification of the product very difficult.

For comparison purposes, we prepared a few mg of the known precursor **15d** (by reaction of **15b** with TBSOTf/2,6-lutidine and then with TESOTf/2,6-lutidine). As mentioned in the introduction, Dai et al.[2b] subjected **15d** to a RCM reaction, using 50 mol % of G-II in refluxing CH_2Cl_2 for 3 days, and isolated **16d** (C11–C12 double bond of *E* configuration) in 40% yield (but 0% with the Schrock catalyst). By deprotection of the silyl ethers, these authors obtained **1**. Thus, having **15d** in our hands we had accomplished a formal total synthesis of **1**. Nevertheless, we repeated the experiment with 5 mg of **15d** and 60 mol % of G-II (added in three portions) in refluxing CH_2Cl_2 for 3 days. The ESIMS peaks of the desired compound (**16d**, *m*/*z* 696.51, M+NH_4^+) and of **15d** (*m*/*z* 724.53, M+NH_4^+) were of similar intensity. Thus, under our conditions, part of **15d** remained unreacted.

We performed a final experiment with the remaining amount of **15d** but with up to ca. 150 mol % of H–G-II (as always added in 3 portions, in CH_2Cl_2 at 40 °C for 3 days). To our delight, the ESIMS peak at *m*/*z* 724.54 disappeared completely while that at *m*/*z* 696.51 was clearly observed (HRESIMS, calcd for $C_{38}H_{74}NO_6Si_2^+$, M+NH_4^+, *m*/*z* 696.5049, found 696.5040). As in the case of **15c**, an excess of H–G-II allowed us the complete consumption of **15d**. Unfortunately, our efforts to isolate **16d**[2b] in a pure condition were unsuccessful, due to the decomposition products of the reagent.

In summary, we have accomplished a new synthesis of open precursors (**15a–d**) of **1**, which is a formal total synthesis of **1** via **15d** and relies upon the elaboration of western fragment **10**. Our approach to **15b–d** consists of fourteen independent steps from **4**. The reluctant RCM reaction was only feasible with fully protected precursors (**15c** and **15d**). However, more than stoichiometric amounts of the H–G-II reagent were required for a complete conversion, which is very inconvenient. It is urgent to develop novel RCM reagents capable of forming trisubstituted double bonds embedded in natural macrolides and other complex macrocycles under high-dilution conditions, with ⩽10 mol % of catalyst, as well as, although it was not the problem in this particular case, capable of producing a stereoselective cyclization.

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra of the new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12.047.

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19. There seems that this cyclization is too sensitive to the conformational preferences of the open precursors, owing to steric effects and H-bonding (and perhaps, in the case of **15b**, to the partial formation of the internal hemiketal).