ORGANIC LETTERS

2001
Vol. 3, No. 10
1451−1454

Chemoselective Cross-Metathesis Reaction. Application to the Synthesis of the C1–C14 Fragment of Amphidinol 3

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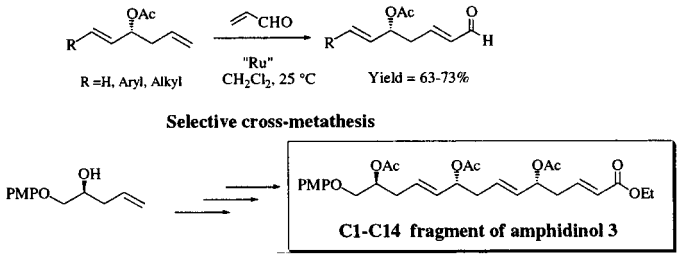
Received February 14, 2001

ABSTRACT



An efficient synthesis of the C1–C14 fragment of amphidinol 3 is described. The synthesis is based on chemoselective cross-metathesis reactions and enantioselective allyltitanations.

Marine dinoflagellates are a rich source of natural products with diverse structures and highly specific bioactivity, e.g., brevetoxins as a voltage-sensitive Na^+ channel activator,[1] maitotoxin as a Ca^{2+} influx stimulator,[2] and okadaic acid as a protein phosphatase inhibitor.[3] Among other dinoflagellates, the genus *Amphidinium* has been recognized as a source of novel bioactive secondary metabolites with unique chemical structures.[4−8] Among these metabolites, amphidinol 3 (Figure 1), a polyoxygenated diether with antifungal activities,[9] has been isolated from *Amphidinium klebsii* and its complete structural elucidation was recently described.[9]

The difference between amphidinol 3 and most other dinoflagellates is that amphidinol 3 possesses an extended chain of unsaturated alcohols, in particular, a sequence of allylic and homoallylic 1,5-diols also present in tetrafibricin.[10]

The cross-metathesis reaction is an important reaction which allows the synthesis of a substituted olefin.[11] Here,

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10.1021/ol0157095 CCC: $20.00
Published on Web 04/24/2001

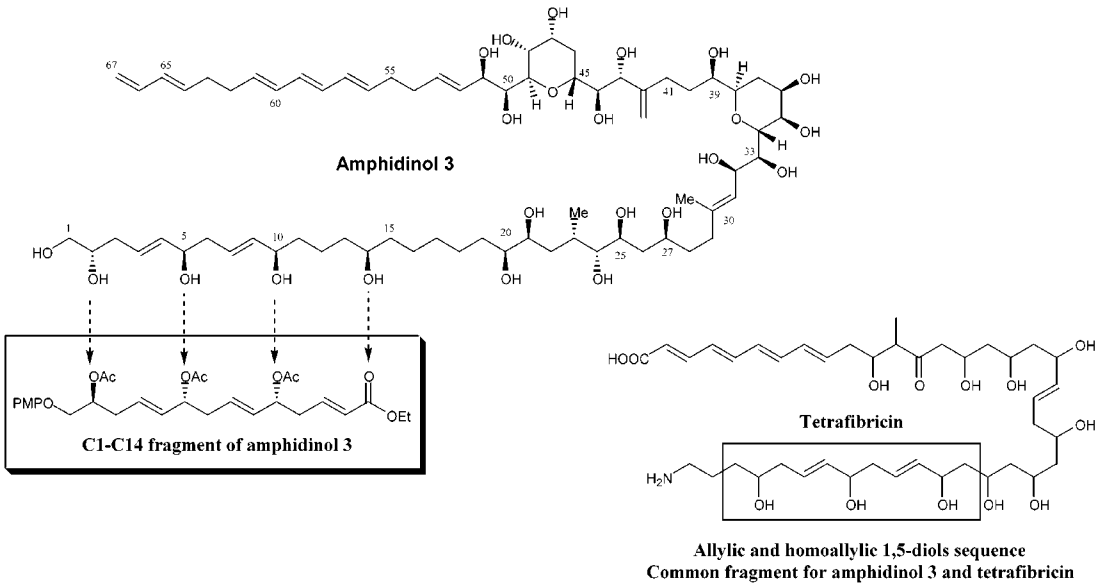
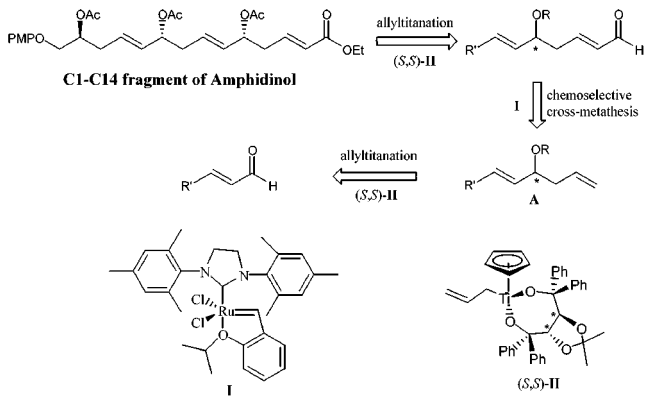


Figure 1.

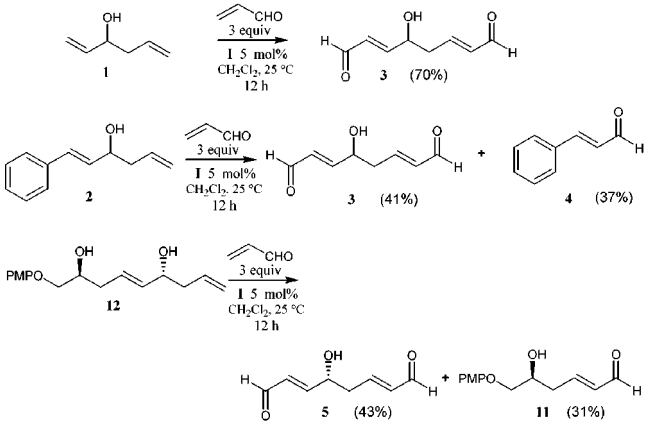
we report a diastereoselective synthesis of 1,5-diols and, consequently, the synthesis of the C1−C14 fragment of amphidinol 3 by using an iterative sequence of enantioselective allytitanations and chemoselective cross-metathesis reactions[12] by using Hoveyda's recyclable catalyst **I**[13] (Scheme 1).

Scheme 1

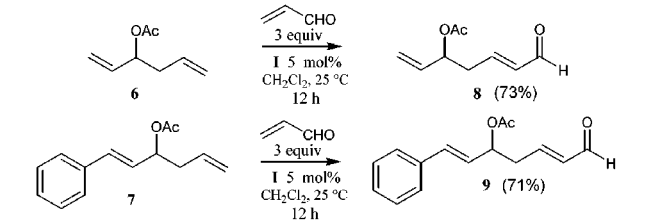


As we wished to employ nonprotected alcohols of type **A** (R = H) (Scheme 1) in this synthesis, preliminary studies were conducted on dienols **1** and **2** (Scheme 2). When dienol **1** was treated with catalyst **I** (5 mol %), in CH_2Cl_2 at room temperature for 4 h in the presence of acrolein (3 equiv), the unsaturated dialdehyde **3** was isolated in 70% yield. This

Scheme 2



Scheme 3



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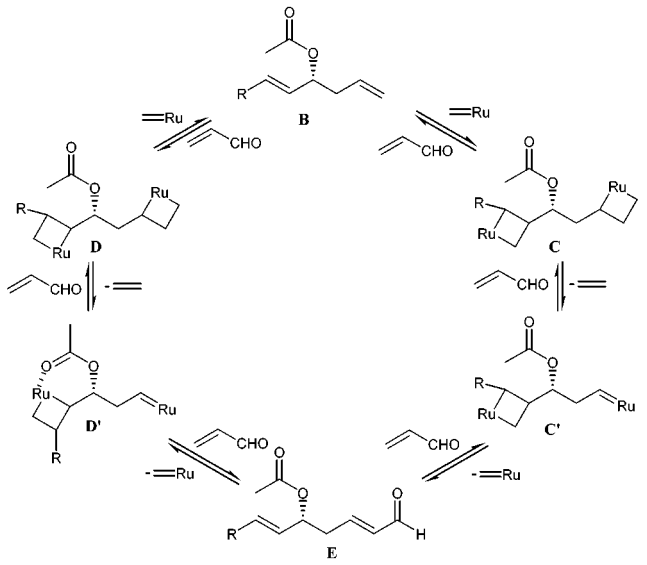
Scheme 4. Proposed Mechanism for the Selective Cross-Metathesis Reaction



result demonstrates that the allylic and homoallylic olefins have a similar reactivity under the cross-metathesis conditions used. When the allylic olefin was disubstitued, as in dienol **2**, the cross-metathesis reaction was not selective as compounds **3** and **4** were isolated in 41% and 37% yields (Scheme 2). In the case of dienol **12** (for its synthesis, see Scheme 5), the unsaturated dialdehyde **5** (43%) and aldehyde **11** (31%) were isolated from the cross-metathesis reaction.

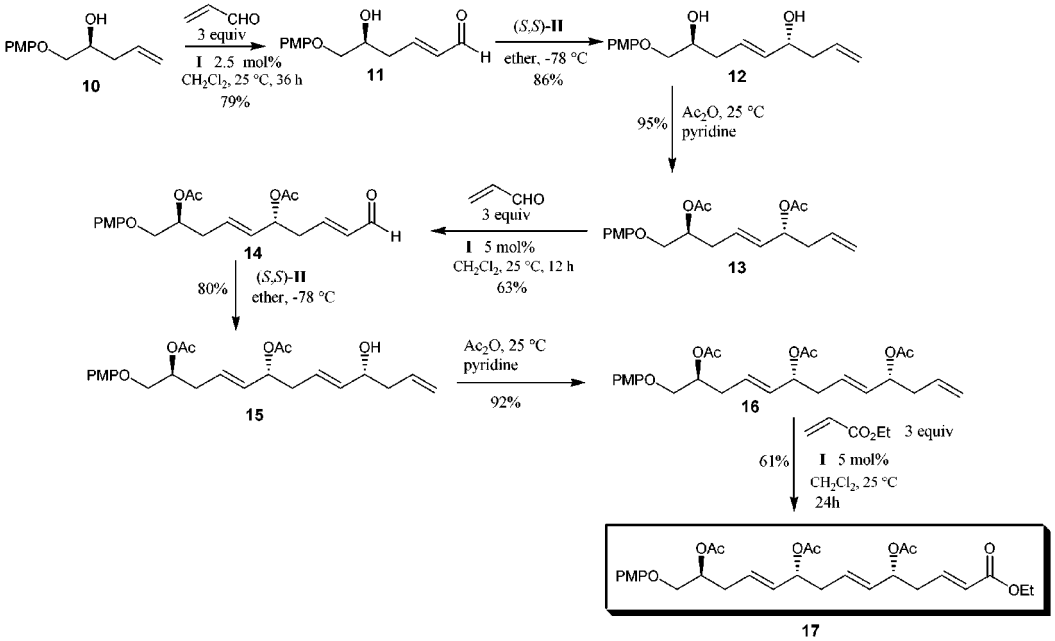
It is worth noting that under these conditions the cross-metathesis reaction is not chemoselective but highly stereoselective as the unsaturated dialdehyde **3** and the unsaturated aldehydes **4** and **5** were obtained with *E*:*Z* ratios up to 30/1.

As the cross-metathesis reaction was not selective on alcohols of type **A** (R = H), they were transformed to their corresponding acetates. When acetates **6** and **7** were treated with acrolein (3 equiv) in the presence of catalyst **I** (5 mol %) in CH_2Cl_2 at room temperature, the unsaturated aldehydes **8** (73%) and **9** (71%) were isolated, indicating that the acetate group deactivates the allylic double bond. Furthermore, the stereoselectivity was again high as the *E*:*Z* ratio of isomers of unsaturated aldehydes **8** and **9** was 30/1. The results are summarized in Scheme 3.

The chemoselectivity of the cross-metathesis reaction of unsaturated acetates of type **B** (Scheme 4) can result from the deactivation of the allylic acetate double bond due to the electron-withdrawing effect of the acetate group (complexes **C** → **C′**) or, it could be due to a nonreactive complex such as **D′**, which comes from **D**, where one metalla complex is deactivated through complexation of the ruthenium atom with the acetate group. Because of this complexation, only one metallacyclobutane can react with acrolein to produce the observed cross-metathesis product (Scheme 4).

On the basis of these results, the synthesis of the C1−C14 fragment of amphidinol 3 was initiated from the enantiomerically pure homoallylic alcohol **10**.[14] When compound **10** was treated with acrolein in the presence of catalyst **I** (5 mol %) at room temperature for 12 h, unsaturated aldehyde **11** was formed (79% yield) stereoselectively (*E*:*Z* > 50/1). The addition of the allyltitanium complex (*S*,*S*)-**II** to **11** led to dienediol **12**[15] diastereoselectively in 86% yield (Scheme 5). A second chemoselective cross-metathesis reaction was envisaged to elaborate the C8−C10 fragment

Scheme 5



C1-C14 fragment of amphidinol 3

of amphidinol 3 from diacetate **13**. The acetylation of **12** by using acetic anhydride in pyridine at 25 °C afforded the diacetate **13** (dr = 95/5)[16] in 95% yield. This latter compound was then subjected to the cross-metathesis with acrolein, under the conditions used previously [acrolein (3 equiv); **I** (5 mol %); rt; 12 h] which led to aldehyde **14** (yield = 63%, *E*:*Z* > 50/1).

When aldehyde **14** was treated with the allyltitanium complex (*S*,*S*)-**II**, the corresponding alcohol **15** was isolated in 80% yield with excellent diastereoselectivity (dr > 95/5).[15] A third cross-metathesis reaction was then conducted on triacetate **16**[16] with ethyl acrylate [ethyl acrylate (3 equiv); 25 °C; 12 h; **I** (5 mol %)] to furnish the unsaturated ester C1−C14 fragment **17** of amphidinol 3 in 61% yield.

The present route to the C1−C14 fragment of amphidinol 3 was achieved in seven steps from the homoallylic alcohol **10** with an overall yield of 17.5%. It offers certain advantages over a more traditional Wittig−Horner route by virtue of minimizing protection and deprotection steps and allowing the use of highly base-sensitive intermediates. Because of high chemoselectivity observed in the cross-metathesis reaction, mechanistic and synthetic studies are under investigation.

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(15) The diastereoselectivity has been determined from the corresponding acetate.

(16) The diastereoselectivity has been determined by GC/MS (electron impact ionization using a 5971 Hewlett-Packard instrument at 70 eV).

Acknowledgment. The authors are indebted to Dr. R. O. Duthaler for a generous gift of chiral cyclopentadienyldialkoxytitanium chloride complexes, Dr. A. H. Hoveyda for a generous gift of ruthenium catalyst, and Eli Lilly (Indianapolis, IN) for financial support.

Supporting Information Available: Experimental procedure and analytical and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0157095