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Efficient Synthesis of the C(1)−C(9) Fragment of Amphidinolides C, C2, and F

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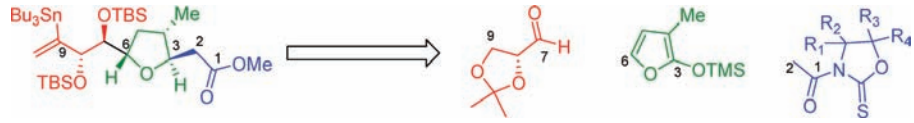
ABSTRACT



The synthesis of the C(1)−C(9) fragment of amphidinolides C, C2, and F was achieved by using a vinyloguous Mukaiyama aldol reaction on a chiral aldehyde with a silyloxyfuran and by using a C-glycosylation of a lactol derivative with an acetyl oxazolidinethione. From the available chiral acetonide−glyceraldehyde, all the stereogenic centers were perfectly induced along the synthesis. The C(1)−C(9) fragment was synthesized as a vinyl stannane at C(9) in 10 steps, with 16% yield.

Amphidinolides are a group of marine natural products isolated from the dinophlagellate *Amphidinum* sp. Interestingly, these dinophlagellates live in symbiosis with the marine worm *Amphiscolops* sp., and more than 30 different structures have been discovered since 1986.[1] The production of natural amphidinolides was achieved by culture of *Amphidinum* sp. in an about 1000 L reactor. Most of these marine products exhibited strong cytotoxicities against human cancer cell lines. However, only a few milligrams of active marine products could be isolated despite the high scale of the cultures.

Amphidinolide C is one of the most active members of this family,[2] exhibiting excellent cytotoxicities in vitro against murin lymphoma L1210 and epidermoid carcinoma KB cells (5.8 and 4.6 ng/mL, respectively).[2a] It is noteworthy that amphidinolide C2[3] and F[4] are about 1000 times less cytotoxic on these cells, although their structure is closely analogous to amphidinolide C suggesting that the side chain is important in the biological activity. Due to their unique structure and potent biological activity, amphidinolides C, C2, and F have become desirable targets for total synthesis. The syntheses of several fragments of these molecules have already been reported,[5] but no total synthesis has been accomplished, yet.

Our retrosynthetic analysis was based on the structural particularity of amphidinolide C, C2, and F to contain two quasi-identical *trans*-THF moieties (circled with a dotted line, Scheme 1). For several years, our laboratory developed efficient methodologies to obtain this sort of structure. Amphidinolide C would be divided into three fragments as

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(1) For recent reviews, see: (a) Kobayashi, J.; Ishibashi, M. *Chem. Rev.* **1993**, *93*, 1753. (b) Chakraborty, T.; Das, S. *Curr. Med. Chem.: Anti-Cancer Agents* **2001**, *1*, 131. (c) Kobayashi, J.; Shimbo, K.; Kubota, T.; Tsuda, M. *Pure Appl. Chem.* **2003**, *75*, 337. (d) Kobayashi, J.; Tsuda, M. *Nat. Prod Rep.* **2004**, *21*, 77.

(2) (a) Kobayashi, J.; Ishibashi, M.; Wälchli, M.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Ohizumi, Y. *J. Am. Chem. Soc.* **1988**, *110*, 490. (b) Ishiyama, H.; Ishibashi, M.; Kobayashi, J. *Chem. Pharm. Bull.* **1996**, *44*, 1819. (c) Kubota, T.; Tsuda, M.; Kobayashi, J. *Org. Lett.* **2001**, *3*, 1363. (d) Kubota, T.; Tsuda, M.; Kobayashi, J. *Tetrahedron* **2003**, *59*, 1613.

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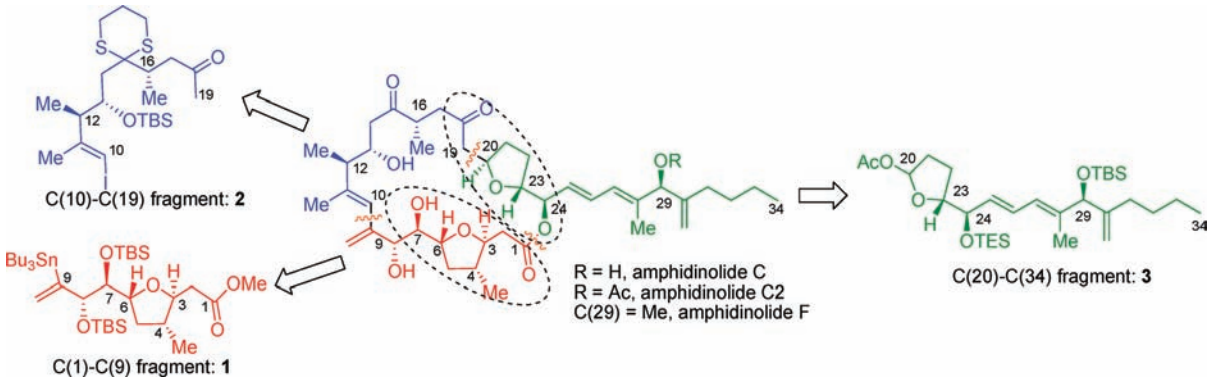
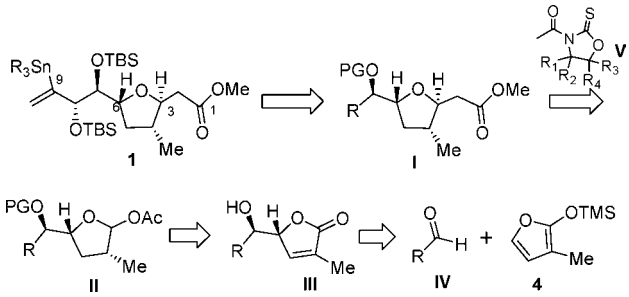
Scheme 1. General Retrosynthetic Analysis of Amphidinolides C, C2, and F



outlined in Scheme 1. We describe here the synthesis of the C(1)−C(9) fragment **1**.

To obtain the C(1)−C(9) fragment **1**, the stannyl function would be installed from generic compound **I**. The methyl ester functionality would be incorporated with the *trans*-configuration from lactol derivative **II** by C-glycosylation with acetyloxazolidinethione **V**.[6] The configuration of the methyl group at C(4) could be induced by a diastereoselective reduction of the double bond of lactone **III**. Lactone **III** should be synthesized by using a stereoselective vinylogous Mukaiyama aldol reaction with silyloxyfuran **4**[7] (Scheme 2).

Scheme 2. Retrosynthetic Analysis



The beginning of the synthesis involved the utilization of the 2-methyl-silyloxyfuran **4** and the chiral aldehyde **5**. The first starting material can be easily obtained in four steps from the inexpensive citraconic acid[8] or in one step from the commercially available 3-methyl-2(5*H*)-furanone.[9] The second one is also commercially available or can be prepared easily from inexpensive D-mannitol.[10] Although we developed an enantioselective vinylogous aldolization with silyloxyfuran,[7] we preferred to use the diastereoselective version,[11] as we could take advantage of the hydroxy group of aldehyde **5** in our synthesis. The vinylogous addition of furan **4** on aldehyde **5** in the presence of $BF_3{\cdot}OEt_2$ at −78 °C furnished the corresponding adducts **6**/**6′** exclusively with the *anti* relationship between C(7)−C(8),[12] whereas the relative relationship between C(6)−C(7) was less controlled but gave nevertheless a separable mixture of *syn* (**6**):*anti* (**6′**) (3:1) in 71% yield.[13] It can be noted that the TBS version of silyloxyfuran **4** gave a slightly better ratio for this reaction (**6**/**6′** = 4:1) because it is more bulky; however, it gave a poorer yield (50%) because it is less reactive (reaction at −20 °C).[14] For reasons of TBS cost and yields, we preferred to keep working with the TMS ether **4**.

The hydrogenation of the double bond of lactone **6** under atmospheric pressure proceeded quantitatively only on the less hindered face of the lactone to give exclusively compound **7**.[15] The hindered alcohol was then protected as a TBS ether with TBSOTf and lutidine in refluxing CH_2Cl_2 in 95% yield to afford compound **8**. The reduction and the acetylation of lactone **8** to produce lactol derivative

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(11) (a) Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Synlett* **1999**, 1333. (b) Casiraghi, G.; Colombo, L.; Rassu, G.; Spanu, P. *J. Org. Chem.* **1991**, *53*, 2135. (c) Casiraghi, G.; Colombo, L.; Rassu, G.; Spanu, P.; Gaspari Fava, G.; Ferrari Belicchi, M. *Tetrahedron* **1990**, *46*, 5807.

(12) The C(7)−C(8) *anti* configuration is a consequence of the nonchelating conditions of the Lewis acid promoter favoring strongly a Felkin−Anh-type approach. See: Mengel, A.; Raiser, O. *Chem. Rev.* **1999**, *99*, 1191.

(13) This addition gives always the *syn* adduct as the major product, see: Jefford, C. W.; Jaggi, D.; Boukouvalas, J. *Tetrahedron Lett.* **1987**, *35*, 4037. Nethertheless, the stereochemistry between C(6)−C(7) can be unambiguously assigned by using NMR spectroscopy or specific optical rotation as described in ref 11b. For *syn* products $J_{6-7} \approx 3$ Hz (for **6**, $J_{6-7} = 3.6$ Hz), whereas $J_{6-7} \approx 5$ Hz for *anti* products (for **6′**, $J_{6-7} = 4.6$ Hz). Unsaturated lactones having *R* absolute configuration at C(6) are dextrorotatory, whereas those with *S* absolute configuration are levorotatory (*syn* **6** (6*R*), $[\alpha]_D^{20} = +56.3$; *anti* **6′**(6*S*), $[\alpha]_D^{20} = -79.7$).

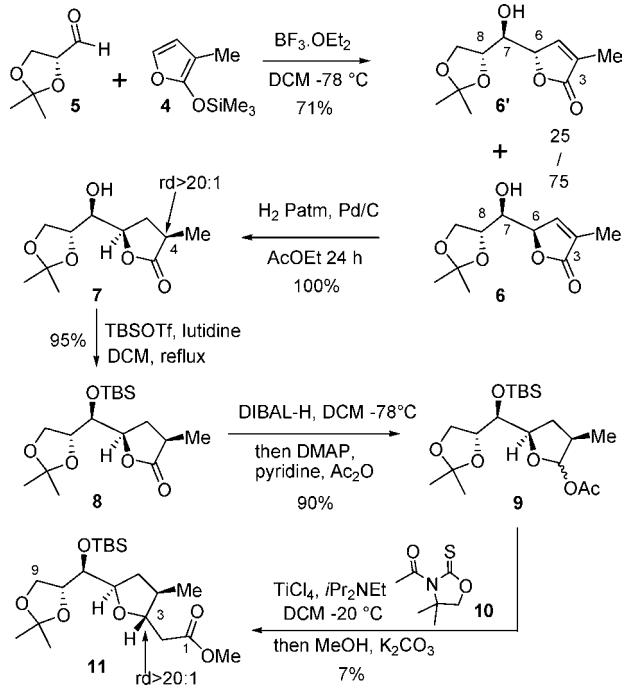
(14) Szlozek, M.; Jullian, J.-C.; Hocquemiller, R.; Figadere, B. *Heterocycles* **2000**, *52*, 1005.

(15) Kong, K.; Romo, D. *Org. Lett.* **2006**, *8*, 2909.

9 was performed using DIBAL-H at −78 °C, followed by a treatment in Ac_2O, pyridine, and DMAP with 90% yield.[16]

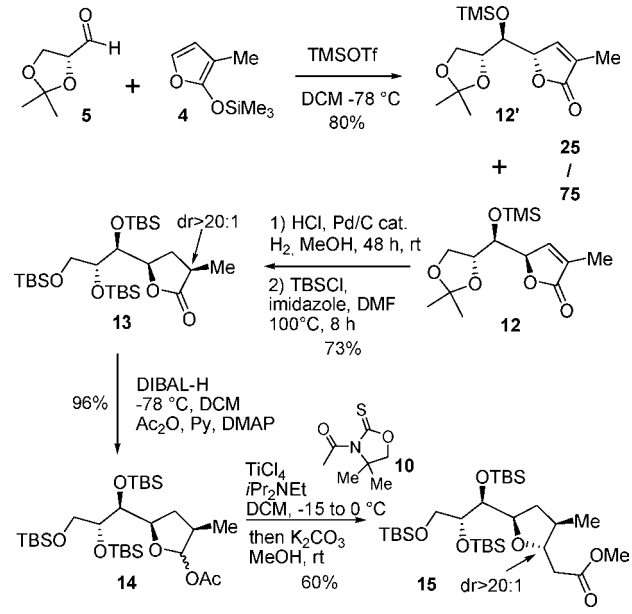
The next key reaction was the C-glycosylation of compound **9** with an acetyloxazolidinethione. Although oxazolidinethione **10** was not the best reagent we developed in terms of selectivity,[6b] it is nevertheless the more practical, as the amino-alcohol used in its synthesis is commercially available and inexpensive. Here, only one diastereoisomer was detectable by NMR when oxazolidinethione **10** was used on **9** as a titanium enolate. Unfortunately, the yield of **11** after methanolysis was very poor (7%) because the titanium is obviously still a quite good Lewis acid in its enolate form. Indeed the ^1H NMR spectrum of crude material showed almost no acetonide signal after reaction. As the acetonide protection gave some troubles at this step, we envisioned to modify the synthetic strategy (Scheme 3).

Scheme 3. First Synthetic Approach



For the second approach, we started from the same materials, but we changed some conditions of the reaction. The vinylogous aldol reaction with silyloxyfuran **4** in the presence of $BF_3{\cdot}OEt_2$ gave **6** and **6′** acceptable results in terms of yield (Scheme 3), but some TMS adducts **12**/**12′** resulting from a silylium transfer were always observed with 10−30% yield (depending on the batch). For these reasons we decided to change the Lewis acid $BF_3{\cdot}OEt_2$ to TMSOTf (10 mol %). These conditions allowed us to exclusively convert the adducts in TMS ether **12** and **12′** (**12**:**12′** = 3:1) in a better yield (80%) and simplified the purification by chromatography as only two compounds are formed instead of four. A catalytic hydrogenation of major diastereoisomer **12** under acidic conditions in MeOH was performed and allowed us to obtain directly in one-pot the intermediate triol as all protecting groups were hydrolyzed under these conditions. Because of its extreme viscosity, the triol was converted directly without purification in tri-TBS ether **13** in 73% yield for the two steps. At this stage, we used the previous methodologies depicted in Scheme 3. Lactone **13** was transformed into compound **14** by reduction and acetylation in 96% yield,[15] then **14** was C-glycosylated with oxazolidinone **10**[6b] as a titanium enolate. This time, after methanolysis, the yield of **15** was more consistent (60%), and the control of the diastereoselectivity was still excellent as only one product was observed by NMR (Scheme 4).

Scheme 4. Second Synthetic Approach



Once all the stereogenic centers in fragment **1** were installed, the vinyl stannane functionality could be inserted from compound **15**. A selective cleaveage of the primary TBS ether of **15** with HF·pyridine in the THF/pyridine mixture was performed to furnish alcohol **16** in 90% yield. The oxidation of alcohol **16** in aldehyde **17** was accomplished with catalytic TEMPO and trichloroisocyanuric acid as the co-oxidant.[17] The crude aldehyde was then directly converted to alkyne **18** (64% in two steps) with Bestmann−Ohira reagent **19** and K_2CO_3 in MeOH at 0 °C.[18] To complete the synthesis, vinyl stannane **1** was prepared by using a regioselective hydrostannation by using molybdenum complex $Mo(CO)_3(CN\mathit{t}Bu)_3$[19] in THF at 55 °C. Due to the extreme

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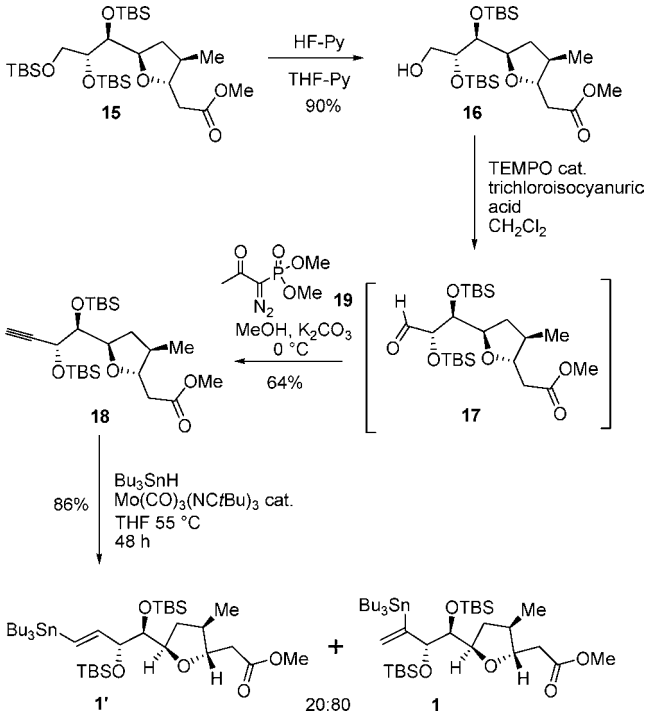
(19) For the synthesis of this molybdenum complex from $Mo(CO)_6$ and *t*-butyl isocyanide, see: Albers, M. O.; Coville, N. J.; Ashworth, T. V.; Singleton, E.; Swanepoel, H. E. *J. Organomet. Chem.* **1980**, *199*, 55.

Scheme 5. Synthesis of C(1)−C(9) Fragment **1**



steric hindrance of all TBS groups in compound **18**, the regioselective hydrostannation proceeded slowly in 48 h.[20] We obtain 1,1-disubstituted olefin **1** as the major product (70% yield) and (*E*)-disubstituted olefin **1′** as the minor product (16% yield) (**1**/**1′** = 80:20). We were pleased to see that these two isomers were separable by chromatography on silica gel to afford pure fragment **1** (Scheme 5).

In conclusion, after a compromised first approach, we were able to efficiently synthesize fragment **1** of amphidinolides C, C2, and F in 9 steps (16% overall yield) from well-known or commercially available materials. We utilized as key steps a diastereoselective vinylogous Mukaiyama aldolization with a silyloxyfuran derivative and a diastereoselective C-glycosylation to construct the whole carbon skeleton. Our work seems to present the shortest and the more functionalized synthesis of the C(1)−C(9) fragment known thus far. Furthermore, our synthetic strategy should allow us to easily prepare multigram-scale of fragment **1** as most of the reagents utilized are relatively inexpensive or were used in a catalytic amount. This detail is important to bring up material and ongoing efforts to complete total syntheses of amphidinolides C, C2, and F. Further studies on the total synthesis of these amphidinolides are underway.

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

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