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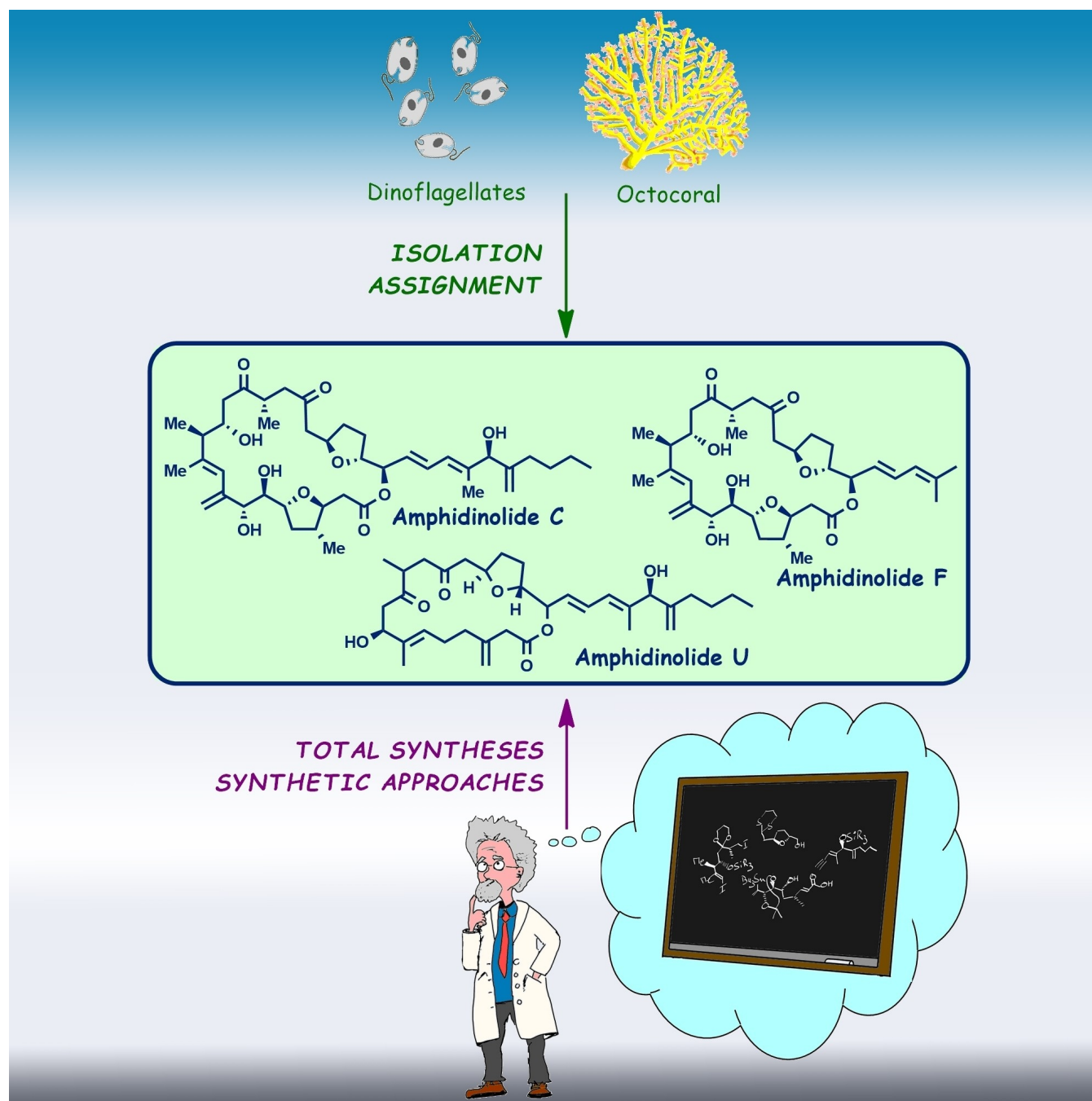
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Advances Toward Amphidinolides C, F and U: Isolations, Synthetic Studies and Total Syntheses

Ismaila Ciss,^[a, b] Matar Seck,^[b] Bruno Figadère,^[a] and Laurent Ferrière^{*[a]}



Amphidinolides C, F, and U, including C2-C4 analogs, are highly cytotoxic marine macrolides, mainly isolated from dinoflagellates of the genus *Amphidinium*. All these polyketides share a 75% or more similar structure, highlighted by a macrolactone ring, at least one *trans*-2,5-substituted-THF motif and a characteristic polyenic side chain. From their isolation and absolute configurational assignment, the total synthesis of these marine macrolides represented an intense challenge to the organic synthesis community over the last 15 years, with around 14 research groups engaged in this inspiring task. In the first part

of this review, we present the different approaches to the isolation and characterization of these natural products, including the most recent analogs, which may cast doubt on the biogenetic origin of these compounds. The various synthetic approaches to the total synthesis of C, F, and U amphidinolides are presented in a second part, focusing on key reactions and/or innovative strategies. The review concludes in a third section summarizing the successful approaches leading to the total synthesis of one of the members of this amphidinolide subfamily.

1. Introduction

Amphidinolides (AMPs) are marine macrolides generally isolated from dinoflagellates of *Amphidinium* species.^[1,2] They were mainly reported by Jun'ichi Kobayashi's group from *Amphidinium* sp. strains collected around Okinawa islands. Besides, caribenolide was also isolated from Caribbean *Amphidinium* species by Shimizu,^[3] but was confirmed later to correspond to Amphidinolide N (AMP-N), also isolated by Kobayashi from Okinawan *Amphidinium* species.^[4] A more recent report also hints that AMPs could result from a mutualism with microorganisms since those structures were also isolated from octocoral species on Brazilian coasts.^[5] These marine products generally exhibit very high cytotoxicity, as low as 0.08 nM (KB or L1210 cell lines, for AMP-N), which attracted considerably the synthetic community to access this family of compounds by total synthesis as promising anti-tumoral agents. From a structural point of view, all AMPs feature macrolactones with different functions characteristic of this family of compounds. Although most polyketides bear only hydroxy groups, AMPs also show their oxidized state as a ketone function. Similarly, some alkenes are present as epoxides. Besides these structural characteristics, all AMPs generally display very diverse structures.

The total synthesis of amphidinolides early took the attention of the organic synthesis community, culminating in dozens of synthetic studies or total synthesis. Several reviews on amphidinolides were reported, which can be general and synthetic,^[6] specific for one AMP sub-class,^[7,8] focused on a synthetic strategy or a specific reaction to reach them,^[9-11] testifying the appeal for these natural products.

Among all amphidinolides, AMP-F (5)^[12] and -C(1)^[13] particularly attracted the attention of the synthetic community by bearing two THF rings with a *trans* configuration (Figure 1). Indeed, these natural substances are a good target for total synthesis, illustrating synthetic methods for obtaining these motifs. AMPs-C (1) and -F (5) bear the same macrolactone core, but the lateral chain of AMP-C (1) is longer by five carbons with an additional stereogenic center at C₂₉. Natural analogs of AMP-C (1) were also isolated; AMP-C2 (2)^[14] carries an acetate function at C₂₉; AMP-C3 (3) has the hydroxy function oxidized as a ketone at the same position; AMP-C4 (4) is deoxygenated at C₈, and bears a *n*-propyl lateral chain rather a *n*-butyl group.^[5] AMP-U (6) is a 20-membered macrolide with a single THF ring and two carbonyl groups.^[15] The C₉-C₂₉ sequence of AMP-U (6) is identical to the C₁₄-C₃₄ sequence of AMP-C (1), representing 75% of structural similitude.

The complexity and structural diversity of these AMPs makes exploring their structure-activity relationships a significant challenge for synthetic chemists. AMP-C (1) remains the most active one of this sub-family, with cytotoxicity reported at the nanomolar range, hence the importance of the nature of the function present at position C₂₉. Nevertheless, the structure of the macrolactone also seems crucial since the AMP-C4 (4) analog does not show significant cytotoxicity, lacking the hydroxyl group at C₈. (Table 1)

Table 1. Biological activities, isolation year and yield of amphidinolides C, C2, C3, F et U.

Amphidinolide	Year of Isolation	Isolation yield	IC ₅₀ (μg/mL)	
			L1210	KB
C (1)	1988[13]	0.0015%	0.0058	0.0046
C2 (2)	2004[14]	0.00015%	0.8	3.0
C3 (3)	2010[16]	0.00006%	7.6	10
C4 (6)	2016[5]	-	7.1 (HCT-116)	
F (4)	1991[12]	0.0006%	1.5	3.2
U (5)	1999[15]	0.0002%	12	20

[a] Dr. I. Ciss, Dr. B. Figadère, Dr. L. Ferrie
BioCIS, Faculté de Pharmacie
Université Paris-Saclay, CNRS,
91400, Orsay, France
E-mail: laurent.ferrie@universite-paris-saclay.fr

[b] Dr. I. Ciss, Prof. M. Seck
Laboratoire de Chimie Organique et Chimie Thérapeutique,
Faculté de Médecine, de Pharmacie et d'Odontologie
Université Cheikh Anta Diop de Dakar – BP 5005, Dakar-Fann, Sénégal

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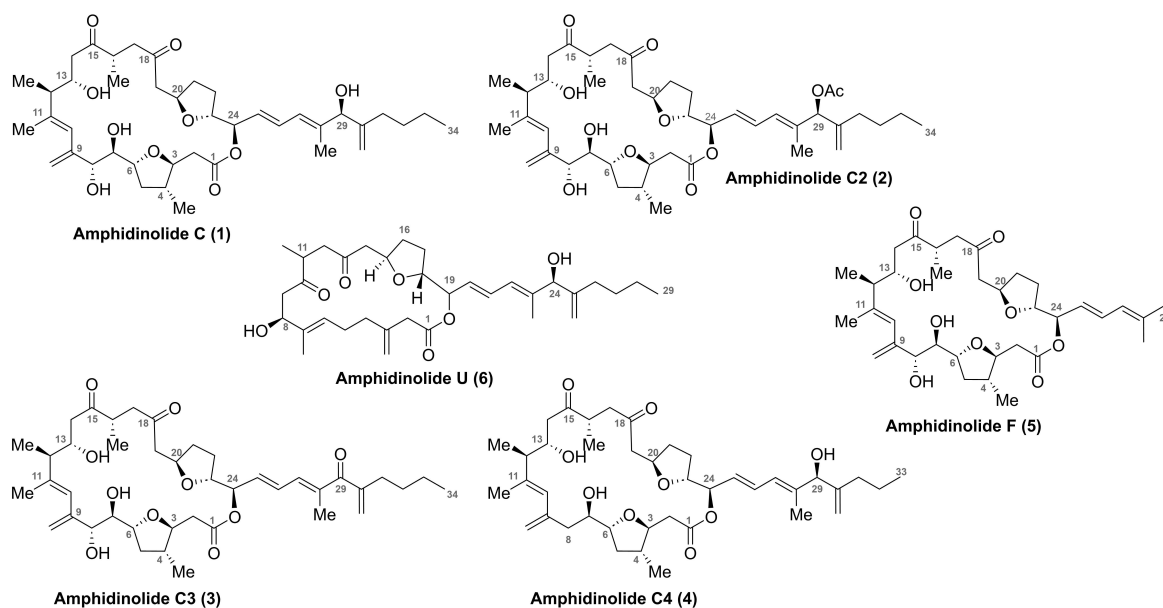


Figure 1. Structures of amphidinolides C, C2, C3, C4, F and U.

2. Isolation, Structure and Biosynthesis

2.1. Amphidinolides C, C2, C3, C4, F and U Isolation

A protocol was applied to AMP-C (1) and used for the other sub-family members. Thus, Kobayashi *et al.* collected okinawan flatworms *Amphiscolops* sp., which live in mutualism with the dinoflagellates *Amphidinium* sp. The dinoflagellates (strain Y-5) were thus separated from their symbiotic host and cultured for

two weeks in sterilized seawater enriched with Provasoli's supplement.^[17] Their isolation by suction yields from 0.3 to 0.5 g/L of wet cells; 375 g of wet cells were thus obtained. They were extracted with a methanol/toluene mixture, and the extract was subjected to repeated chromatographies on silica gel with methanol/chloroform and hexane/acetone mixtures. Ultimately, a reversed-phase HPLC on ODS with 88% methanol gave AMP-C (1) as a colorless amorphous solid (6 mg, 0.0015%



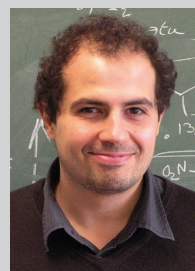
Ismaila Ciss graduated from Cheikh Anta Diop University, Dakar, Senegal, and pursued his studies under joint supervision of thesis at BioCIS, in Université Paris-Saclay, France, under the direction of Dr. Laurent Ferrié, Pr. Matar Seck and Dr. Bruno Figadère, where he participated in total synthesis studies towards amphidinolides C2 and U. He obtained his PhD in 2022 and continued to work at BioCIS for one year for a post-doctoral fellowship. He is currently working at Ecole Polytechnique in Palaiseau, France, in the Bastien Nay group.



After graduating in chemistry in 1986, Matar Seck obtained his PhD in 1991 at the University of Paris XI under the supervision of Robert Bloch. He was recruited at the Faculty of Medicine, Pharmacy and Odontology-Cheikh Anta Diop University of Dakar in November 1992. He completed several postdoctoral stays from 1999 to 2005 at the University Paris-Sud/Paris-Saclay-Faculty of Pharmacy in Bruno Figadère's group. Full professor since October 2016, his research interests focus on bioactive molecules: organic synthesis, isolation and pharmacomodulation.



Bruno Figadère graduated in chemistry in 1984 and obtained his PhD in 1987 from Université Pierre et Marie Curie in Paris. He was a post-doctoral fellow at the University of California at Riverside with Professor William Okamura, working on the total synthesis of natural products. In 1990, he became Chargé de Recherche in the CNRS at the University of Paris-Sud/Paris-Saclay-Faculty of Pharmacy and was promoted in 1997 to Directeur de Recherche. His research interests are in the field of natural product chemistry: total synthesis, isolation, structure determination and pharmacomodulation.



Laurent Ferrié graduated from Université de Lyon and then moved from 2004 to Paris at ESPCI to complete his PhD under the supervision of Pr. Janine Cossy. He joined then, Pr. Peter Wipf in 2008 at the university of Pittsburgh for a postdoctoral internship and was finally hired in 2009 at CNRS in BioCIS at Université Paris-Sud/Paris-Saclay. His research interests focus on natural product total synthesis, synthesis of endoperoxides and discovery of new drug candidates for treatment of Parkinson's disease.

yield).^[13] Strains Y56, Y-59, and Y-71 also yielded AMP-C (1) in relatively large amounts.^[14]

Using a similar protocol, AMP-C2 (2) was isolated from strains Y-71 (1.8 mg, 0.00015%),^[14] AMP-C3 (3) analog from strains Y-26 and Y-71 (0.6 mg, 0.0001%),^[16] AMP-F (5) from strain Y-26 (0.00001%)^[12] and later from the Y-56 in a more significant amount (0.0006%).^[15] AMP-U (6) was obtained from strain Y-56 (0.8 mg, 0.0002%).^[15]

AMP-C4 (4) was more recently isolated from octocoral *Stragulum bicolor* (0.2 mg, from 700 mg of MeOH extract). *S. bicolor* was collected in the intertidal zone of the beach rocks on the coast of Caponga Beach (Cascavel, Ceará, Brazil).

2.2. Structural Determination

The structural determination of this subfamily of amphidinolides was accomplished first on AMP-C (1). FABMS and HREIMS gave the following empirical formula: C₄₁H₆₂O₁₀. The structural determination was carried out on the 7,8,13,28-tetraacetate derivative of AMP-C (1), for which 2D NMR analyses (COSY, COSY-double relay) allowed the structure of the C₂-C₁₄, C₁₆-C₁₇, and C₁₉-C₃₄ segments to be determined. Those segments were joined together by HMBC analysis using long-range correlations of the individual carbonyls to construct the backbone of AMP-C (1). The configuration of the double bonds was determined with NOESY experiments. The gross structure of AMP-U (6) and -F (5) was elucidated with a similar methodology.^[12,15]

2.3. Determination of the Relative and Absolute Configurations

The determination of the relative and absolute configurations of AMP-C (1) was driven over a decade and solved with the combination of several techniques. First, the relative stereochemistry around the two THF rings was proposed to be *trans* from NOESY experiments.^[18] The relative configuration of the methyl group at the C₄ position was also determined using the same technique.

To further assign relative and absolute configuration, the chemical degradation of AMP-C (1) was needed to make small fragments that could be compared to synthetic samples. It thus also required a larger amount of natural AMP-C (1) to perform these experiments. Therefore, several campaigns of isolation through the study of different *Amphidinium* strains were needed to realize this objective. Kobayashi reported a first tentative approach to preparing the C₁-C₉ segment of AMP-C (1) from (S)-Roche ester 6.^[19] This chiral building block could install the stereochemistry of the methyl group at position C₄. The procedure reported by Yonemitsu^[20] allowed the preparation of compound 7 in 6 steps. The applied strategy required a large number of steps (27 steps) to obtain compound 11 and is based mainly on the Wittig olefination/reduction/Sharpless epoxidation sequence to control the configuration at C₃, C₆, and C₇. On the other hand, the hydroxy group at C₈ was installed by

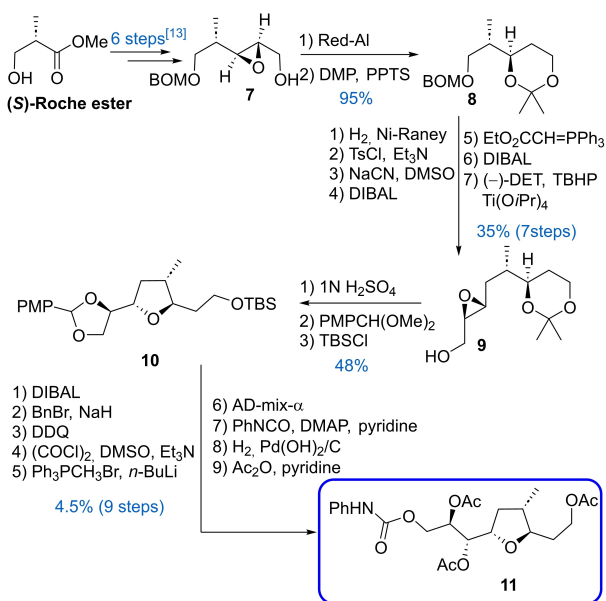
using Sharpless asymmetric dihydroxylation.^[19] Acetate-protecting groups could be used to compare this segment to the peracetylated AMP-C (1) derivative.^[13] (Scheme 1)

Five years later, Kobayashi finally took advantage of a supplement of AMP-C (1) isolated from other strains of dinoflagellates (Y-56, Y-59 and Y-71) to make degradation experiment and Mosher ester derivatization to determine, firstly, the relative configuration of the stereogenic centers, in a first step, and, secondly, their absolute configuration.

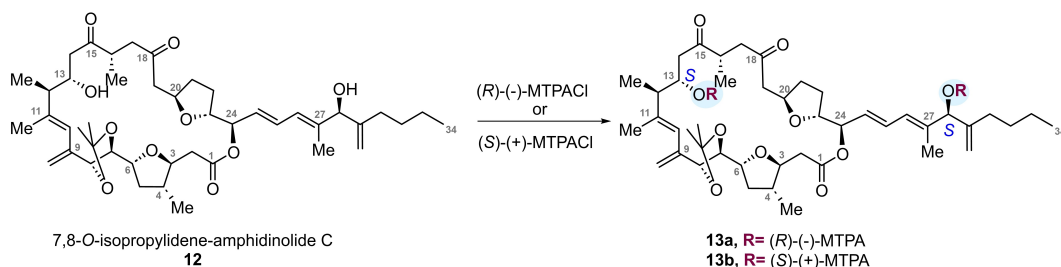
Although the *anti*-relationship between the protons H₃-H₆ and H₂₀-H₂₃ of the two THF rings could be deduced from the NOESY experiments performed previously on 1, the analysis of the coupling constants of the 7,8-O-isopropylidene derivative (12) of AMP-C (1) obtained by Hetero Half-filtered TOCSY (HETLOC) allowed to confirm the confirmation of the *anti*-relationship between the protons H₁₂ and H₁₃ as well as between the protons H₂₃ and H₂₄. Acetonide 12 was then double esterified with (*R*)- and (*S*)-2-methoxy-2-trifluoromethyl-2-phenylacetyl chloride (MTPA), leading to derivatives 13a and 13b, respectively, allowing to deduce the absolute (*S*) configuration of the C₁₃ and C₂₉ centers (Scheme 2).^[21]

The configuration of the C₃, C₄, and C₆ centers was extrapolated using a modified Mosher method. The latter was applied to compound 15a, obtained in four steps from the degradation of natural 1, and compounds 15a and 15b, attained synthetically from D-glutamic acid. Comparison of the ¹H spectra of synthetic 15a and 15a obtained from the natural product allowed the deduction of the (*S*), (*R*) and (*S*) configurations at the C₃, C₄ and C₆ centers, respectively.^[21] (Scheme 3)

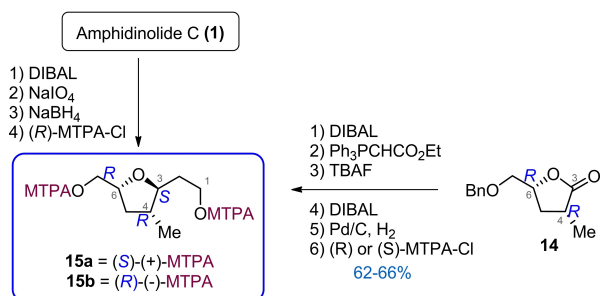
Finally, the modified Mosher method was applied to the backbone of AMP-C (1) derivatives. After methanolysis of the macrolactone, the free hydroxy-group was per-esterified as (*R*) or (*S*)-Mosher ester 16a and 16b. This experiment allowed the elucidation of the absolute configuration of the C₇, C₈, and C₂₄



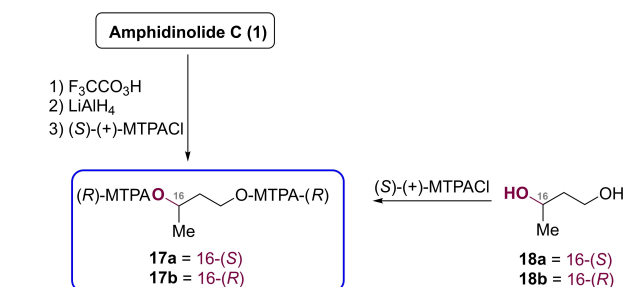
Scheme 1. First Kobayashi's attempts to prepare the C₁-C₉ segment of amphidinolide C (1).



Scheme 2. Preparation of (R)/(S)-MTPA derivatives 13a and 13b.



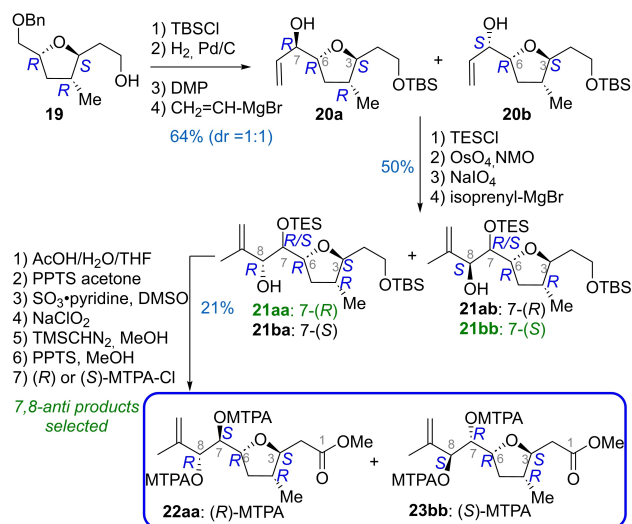
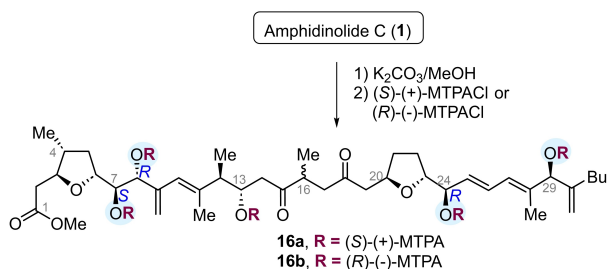
Scheme 3. Synthesis of (S) and (R)-MTPA esters 15a and 15b from the chiral pool or by degradation of natural amphidinolide C (1).

Scheme 5. Determination of the absolute configuration at C₁₆ by degradation of 1 and Mosher ester methods.

centers as (S), (R), and (R) configurations, respectively, and confirmed the (S) configurations found previously at C₁₃ and C₂₉,^[21] (Scheme 4)

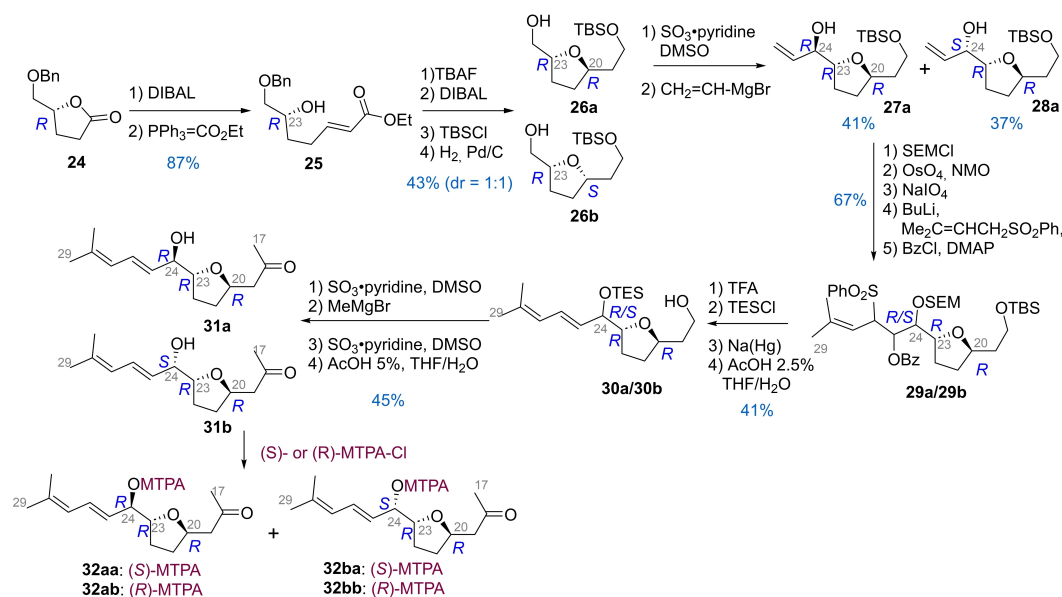
Nevertheless, methanolysis has led to an epimerization at the C₁₆ center. A last experiment was thus necessary to remove the uncertainty on this position. Using a three-step degradation sequence from 1 (Baeyer-Villiger oxidation, reduction, and esterification), the authors managed to isolate the C₁₆-C₁₈ degradation product 17. By comparing the ¹H NMR data of the synthetic (R)-MTPA derivatives 17a and 17b, derived from commercial chiral 1,3-butanediols, the authors were able to assign the absolute (S) configuration of the C₁₆ stereogenic center by matching the natural derivative with 17a (Scheme 5).

The determination of the absolute and relative configurations of AMP-C (1) was later confirmed using a stereodivergent synthesis of the different diastereomers of the C₁-C₁₀ and C₁₇-C₂₉ fragments of AMP-C (1) and comparison with AMP-C (1) backbone (Scheme 6)

Scheme 6. Kobayashi's synthesis of the C₁-C₁₀ fragment of amphidinolide C (1) using a stereodivergent strategy. Preparation of MTPA esters 22aa and 23bb for further ¹H NMR comparison.

Scheme 4. Preparation of (R)- and (S)-MTPA derivatives 16a and 16b from natural amphidinolide C (1) backbone.

The synthesis of the different possible diastereomers of the C₁-C₁₀ residue started from THF 19, obtained previously during the synthesis of 14.^[21] A vinyl addition to an aldehyde afforded both isomers 20a and 20b at C₇. A homologation strategy was used to obtain the stereogenic center at C₈, affording 4 possible diastereoisomers. The 7,8-anti products were selected, and functional group modification followed by esterification with (R) or (S)-Mosher ester afforded isomers 22aa and 23bb, respectively. Comparison of ¹H NMR chemical shifts of 22aa and 23bb to (S)-MTPA derivative 16a confirmed the original assignment to be 3S, 4R, 6R, 7S, 8R (22aa). (Scheme 6)



Scheme 7. Synthesis of the C₁₇-C₂₉ fragment of amphidinolide C (1) using a stereodivergent strategy. Preparation of MTPA esters **32aa**, **32ab**, **32ba** and **32bb** for further ¹H NMR comparison.

Similarly, the synthesis of the C₁₇-C₂₉ fragment was driven from chiral lactone **24** (available from D-glutamic acid). Wittig reaction to intermediate lactol afforded enoate **25** and intramolecular Michael-addition, followed by functional group modifications, gave a 1:1 mixture of diastereomers at C₂₀. The *trans*-THF **26a** was selected to continue the study, and the alcohol at C₂₄ was oxidized, and a vinyl Grignard reagent was added to give isomers **27a** and **28a**. The rest of the synthesis was driven with both isomers in parallel. It consisted of homologation with an isobutyl on one side and the formation of a methyl ketone on the other side. The remaining alcohol was finally esterified as (*R*) or (*S*)-Mosher ester to give compounds **32aa**, **32ab**, **32ba**, and **32bb**. Comparison of the ¹H NMR spectra of those derivatives to (*S*)-MTPA derivative **16a** confirmed the original assignment to be 20*R*, 23*R*, 24*R* (**32aa**). (Scheme 7)

The structural determination of AMP-C2 (**2**), -C3 (**3**), -C4 (**4**) was deduced from the work on AMP-C (**1**).^[5,14,16] The absolute configuration of AMP-F (**5**) could be deduced from AMP-C (**1**), and was also confirmed by total synthesis (see Section 4).^[12] The structure of AMP-U (**6**) was elucidated by NMR spectroscopy, the relative *trans*- configuration of the THF ring was assigned by NOESY, and the absolute configurations of the asymmetric carbons at C₈ and C₂₄ were solved by the modified Mosher method. The relationship between C₁₈ and C₁₉ was described as *anti*,^[15] whereas it was proved to be *syn* between C₂₃ and C₂₄ for AMP-C (**1**).^[21,22]

However, that last assignment should be treated with caution. H₁₉ makes a triplet with *J* ≈ 7 Hz for AMP-U (**6**), such as H₂₄ for AMP-C (**1**) or -F (**5**). In the stereodivergent synthesis of the C₁₇-C₂₉ fragment of AMP-C (**1**) (Scheme 7), H₂₄ in *syn*-isomers **32aa** and **32ab** makes a triplet with *J* ≈ 8 Hz, whereas H₂₄ in *anti*-isomers **32ba** and **32bb** is presented as a doublet of

the doublet with *J* ≈ 8 and 4 Hz.^[22] These data would contradict this original assignment.

2.4. Biosynthesis

The biosynthesis of AMP-C (**1**) was studied based on ¹³C NMR data of ¹³C enriched samples of the natural product obtained by feeding dinoflagellates *Amphidinium* sp. with [1-¹³C], [2-¹³C], or [1,2-¹³C₂] sodium acetate (Figure 2).^[23] This work suggests that AMP-C (**1**) biosynthesis is not only successive incorporations of acetates that form the backbone of AMP-C (**1**). Some parts, such as C₁₀-C₁₂ and C₂₇-C₃₀ segments, are constituted exclusively of C₂ of acetate, likely AMP₅-G and -H.^[24] Both THFs were also built identically with only one C₁ acetate incorporation. Noteworthy, the taxonomy differences of the organism sources of AMPs (dinoflagellates and octocoral for the C4 analog^[5]), along with the variable productivity of laboratory cultures of the dinoflagellate,^[1] suggest that AMPs might be produced by a

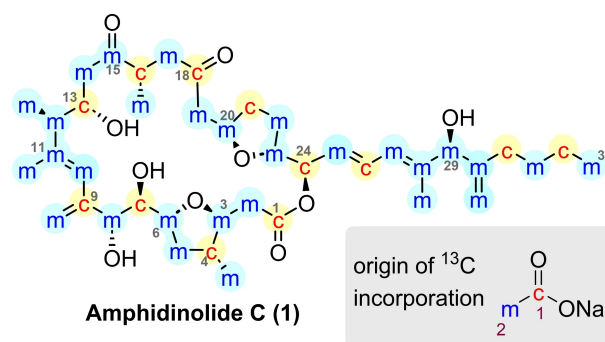


Figure 2. Labeling patterns of amphidinolide C, resulting from feeding experiments with ¹³C-labeled acetates.

mutualism with a microorganism, which remains still to be identified.^[5]

3. Synthetic Studies Toward the Fragments of Amphidinolides F, C, and U

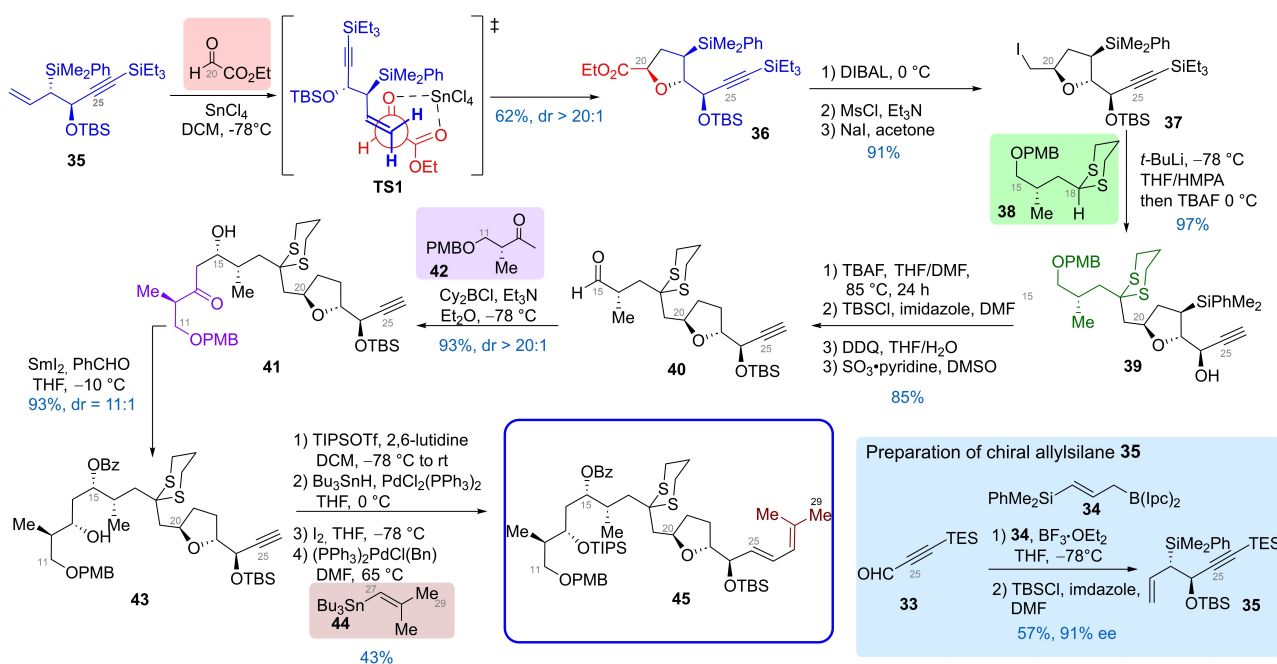
Given the complexity of their structures and the promising biological activities of AMPs—C (1), -F (5), and -U (6), many synthetic groups have been involved in their total synthesis. Interest in these molecules has given rise to an important literature production whose main challenges have been the efficient creation of the two THF units for the AMPs—C (1) and -F (5), and one for the AMP—U (6), as well as the selective formation of the diene units. The efforts of the different groups have led, among other things, to develop new tools for forming these structures. The following sections will detail the different synthetic approaches published on the synthesis of the skeletons in question, emphasizing the key reactions. A grouping by research team will be privileged, and the order of presentation of these teams will consider the chronology of the reported communications on the subject. To keep coherence, the synthetic approaches that led to total syntheses will not be presented in this section, although these studies may predate and have inspired many of the synthetic works presented below.

3.1. Roush's Studies

3.1.1. Roush's Synthesis of the C₁₁-C₂₉ Fragment of Amphidinolide F (5)

In 2004, W. Roush's team published the synthesis of the C₁₁-C₂₉ fragment of AMP—F (5).^[25] Their approach is based on the formation of the THF ring by a stereoselective [3 + 2] annulation methodology developed in their laboratory.^[26,27]

The starting chiral allylsilane **35** was prepared by silyl allylboration of aldehyde with chiral reagent **34** (Scheme 8).^[28] This sequence's key step consisted of the [3 + 2] annulation of allylsilane **35** with ethyl glyoxylate to provide 2,5-*trans* THF **36** with excellent diastereoselectivity *via* a syn-synclinal transition state (**TS1**). Ester in **37** was then transformed into iodide, and **37** was alkylated with dithiane **38** to give compound **39**. The C—Si bond at C₂₂ was cleaved with TBAF in THF/DMF at 85 °C, and functional group modifications led to **40**. The C₁₅ center was incorporated by the Paterson aldol reaction^[29] with the boron enolate of methyl ketone **42** to give **41** with excellent diastereoselectivity (*dr* > 20:1). Subsequently, the stereochemical information at C₁₅ was transferred to C₁₃ *via* an Evans-Tishchenko reduction^[30] to provide the 1,3-*anti*-hydroxybenzoate **43** with good diastereoselectivity (*dr* = 11:1). Finally, functionalization of the triple bond at C₂₅ followed by Stille coupling with vinylstannane **44** afforded the C₁₁-C₂₉ fragment (**45**) of AMP—F (5). The synthesis of the C₁₁-C₂₉ fragment was achieved in 17 steps from aldehyde **33**, with an overall yield of about 11%.



Scheme 8. Roush's synthesis of C₁₁-C₂₉ fragment of amphidinolide F (5).

3.1.2. Roush's Synthesis of the C₁-C₉ Fragment of AMPs-C (1) and -F (5)

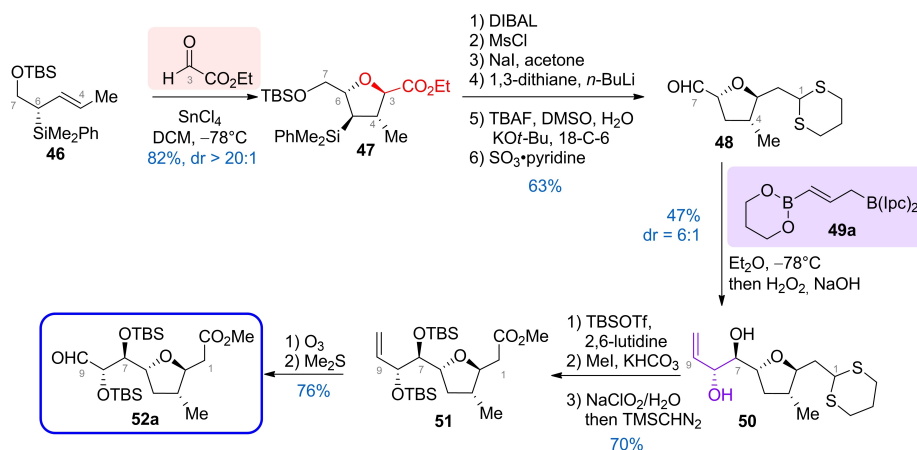
After this preliminary work, Roush *et al.* later published their approach toward the C₁-C₉ fragment of AMPs-C (1) and -F (5).^[31] The authors again considered the formation of the THF ring by their [3 + 2] aldehyde annulation methodology. Despite failures to form 2,5-*trans*-THF by reaction between allylsilane **46** and protected glycolaldehydes under numerous conditions, using the more electrophilic ethyl glycolate allowed the authors to yield 2,5-*trans*-THF **47** efficiently (Scheme 9).^[31] The following six steps to build **48** consisted of functional group modifications and the introduction of the dithiane by alkylation. The ensuing critical step involved the chiral allyl diboron reagent **49a**, which formed *anti*-diol **50** with modest diastereoselectivity and yield. The transformation of the dithiane in methyl ester **51** was then followed by the oxidative cleavage of the terminal olefin by ozonolysis to give aldehyde **52a**. This C₁-C₉ fragment could be obtained in 7% overall yield after seventeen steps, including the preparation of **46**.

3.1.3. Roush's Alternative Synthesis of the C₁-C₉ Fragment

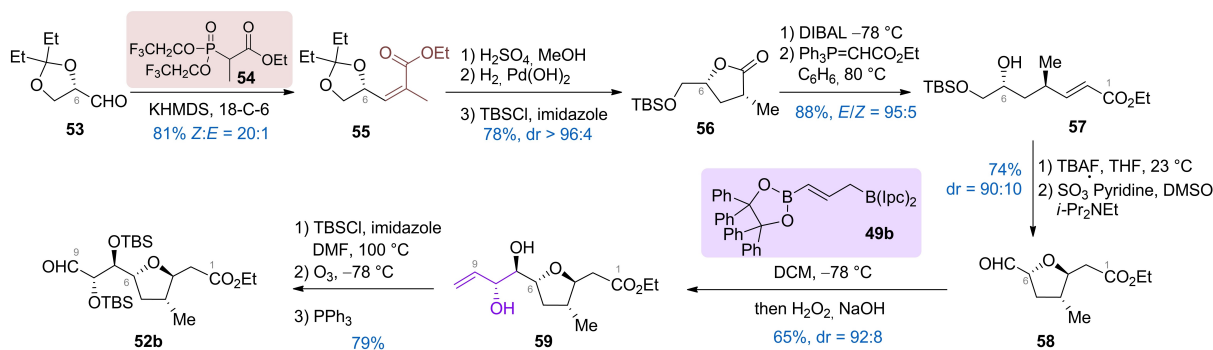
Faced with the length of the synthetic approach obtaining **52a** for a synthon of this size, notably attributable to the

homologation of the ester present in **47**, the authors focused their study on a more efficient and compatible alternative to their total synthesis project. This second-generation strategy is based on a THF ring closure by an oxo-Michael reaction (Scheme 10).^[31]

In this objective, glycerinaldehyde derivative **53** was functionalized to γ -butyrolactone **56** in four steps, including a Still-Gennari olefination and selective hydrogenation to the less hindered face of the butenolide to control the orientation of the methyl group at position C₄.^[32] A Wittig reaction on the lactol from **56** afforded the cyclization precursor **57**. A kinetic cyclization reaction in the presence of TBAF led to the corresponding 2,5-*trans*-THF with good diastereoselectivity (*dr* = 90:10). However, equilibration experiments performed on the 2,5-*cis* isomer could not afford 2,5-*trans*-THF, citing kinetic control of this cyclization. This THF was then oxidized by Parikh-Doering oxidation forming **58**. The aldehyde **58** was engaged in an asymmetric Brown-type allylation,^[33] using this time, allyl borylborane **49b**, furnishing diol **59**. This reagent allowed a better yield and enantioselectivity than borylborane **49a** on the formation of diol **50** (Scheme 9). A sequence similar to the one depicted in scheme 9 led to the C₁-C₉ fragment (**52b**) of the AMP-C (1) and -F (5) with an overall yield of 21% over 11 steps. It constitutes a significant improvement compared to the first approach (previously 17 steps and 11% total yield).



Scheme 9. Roush's first approach to the C₁-C₉ fragment of amphidinolides C (1) and F (5).



Scheme 10. Roush's second approach to the C₁-C₉ fragment of amphidinolides C (1) and F (5).

3.2. Mohapatra's Studies

3.2.1. Mohapatra's C₁₉-C₃₄ Fragment of Amphidinolide C (1)

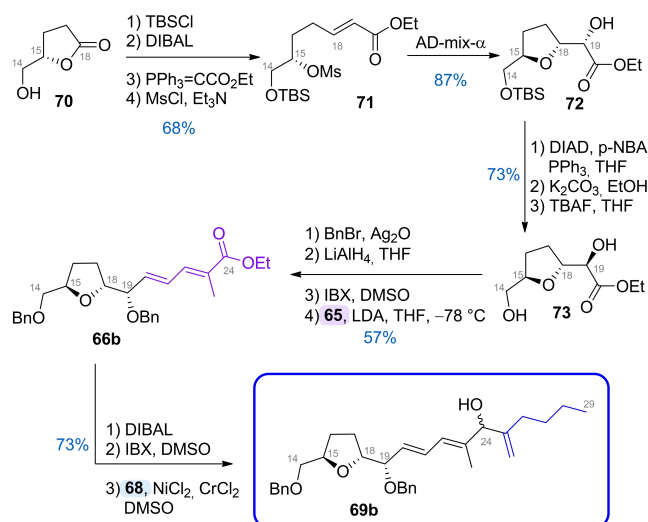
In 2007, Mohapatra's team published the synthesis of the C₁₉-C₃₄ fragment of AMP-C (1) (Scheme 11).^[34] Their approach is based on building the THF ring by ring-closing metathesis reaction of olefins and a Nozaki-Hiyama-Kishi (NHK) reaction to bring the C₃₀-C₃₄ segment.^[35]

Their synthesis began with epoxide **60** (prepared from desymmetrization of Z-butenediol),^[36] which reacted with allyl alcohol **61** to lead to precursor **62**, thereby fixing the *syn* relationship between C₂₃ and C₂₄. The reaction took place in the most reactive allylic position. After protection and exposure to the second-generation Grubbs catalyst (Grubbs II),^[37] dihydrofuran **63** was obtained. The diene unit on **66** was installed by HWE olefination between aldehyde **64** and phosphonate **65**. The NHK reaction performed on aldehyde **67a** allowed the introduction of the C₃₀-C₃₄ segment.^[35] The authors thus completed the synthesis of **69a** as a mixture of epimers at C₂₉ with an overall yield of 12% in 14 steps.

3.2.2. Mohapatra's C₁₄-C₂₉ Fragment of Amphidinolide U (6) [Second Approach to the C₁₉-C₃₄ Fragment of AMP-C (1)]

After studying the C₁₉-C₃₄ fragment of AMP-C (1), Mohapatra *et al.* worked on the C₁₄-C₂₉ fragment of AMP-U (6).^[38] According to Kobayashi's structural assignment, both segments are identical except for the stereochemistry of the carbon closing the macrolactone at C₁₈/C₂₄, which was initially reported to have an *anti*-configuration in contrast to AMPs-C (1) and -F (5). (see Section 2.3) However, due to structural similarities, this work could be considered like Mohapatra's second approach toward the C₁₉-C₃₄ fragment of AMP-C (1).

This synthetic approach started from chiral lactone **70**, and it was then transformed into intermediate **71** through a reduction in lactol, Wittig olefination, and mesylation (Scheme 12).^[38] Sharpless asymmetric dihydroxylation^[39] led directly to THF **72** through a spontaneous intramolecular S_N2 process. No diastereoselectivity was given for the reaction with

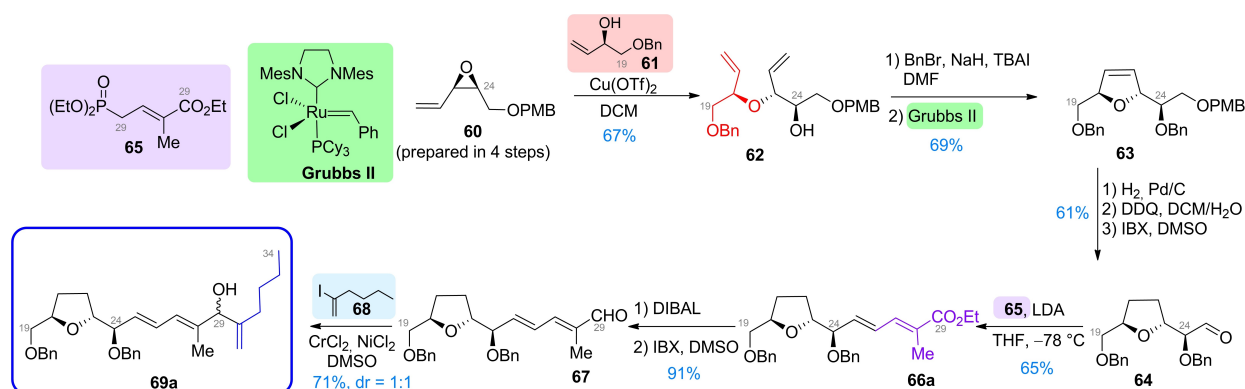


Scheme 12. Mohapatra's synthesis of the C₁₄-C₂₉ fragment of amphidinolide U (6) (second approach of the C₁₉-C₃₄ fragment of amphidinolide C).

71, but it is most likely high for this type of olefin. Inversion of the stereochemistry of the alcohol was achieved using the Mitsunobu reaction, and ethyl ester in **73** was then homologated to dienic ester **66b** through olefination with phosphonate **65**. The end of the synthesis was then the same as that reported previously by the authors (Section 3.2.1, Scheme 11), to afford compound **69b**, the diastereomer of **69a** at C₁₉. Thus, this new approach was accomplished in 16 steps with a 17% overall yield.

3.2.3. Mohapatra's Synthesis of the C₁-C₉ Fragment of Amphidinolides C (1) and F (5)

Lastly, Mohapatra's group studied the C₁-C₉ fragment of AMPs-C (1) and -F (5).^[40] Their approach for the construction of the 2,5-*trans*-THF ring is identical to their reported work toward AMP-U (6) total synthesis (Scheme 12),^[38] *i.e.*, a tandem Sharpless asymmetric dihydroxylation reaction followed by a spontaneous cyclization *via* an S_N2 process.



Scheme 11. Mohapatra's synthesis of the C₁₉-C₃₄ fragment of amphidinolide C (1).

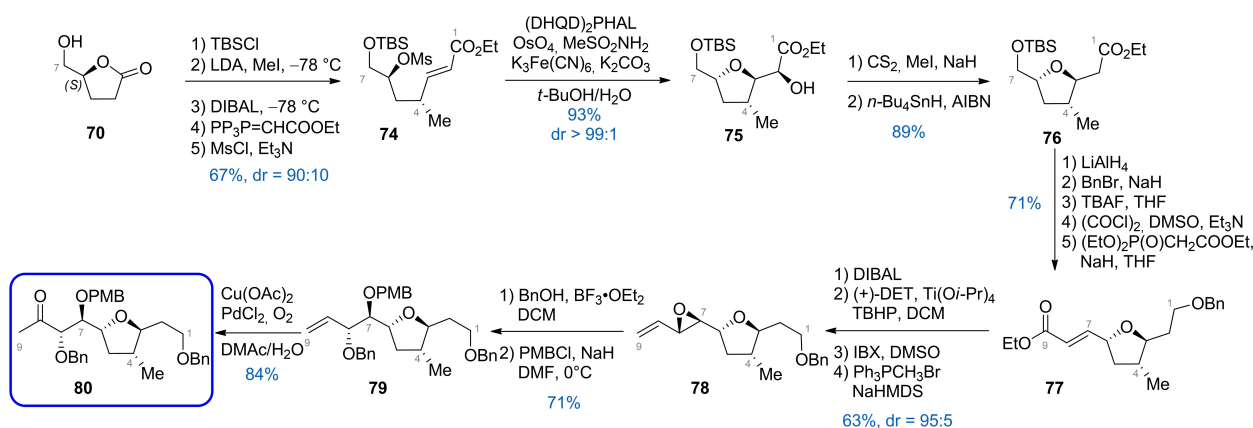
Thus, following their past studies, Mohapatra started from chiral building block **70**, which was converted to THF **75** in five steps (Scheme 13).^[38] The only difference with the approach depicted in Scheme 10 lies in the selective methylation of lactone **70** at position C₄. The diastereoselectivity was not given but was reported to be 90:10 on the same substrate.^[41] Deoxygenation *via* a Barton McCombie deoxygenation gave **76**. Functional group modification and HWE olefination led to **77**. Reduction of ester and Sharpless epoxidation installed the stereochemistry at C₇ and C₈. Oxidation of the alcohol and Wittig olefination furnished epoxide **78**. Finally, Lewis acid mediated ring-opening of the epoxide was regioselective on allylic position, and Wacker oxidation^[42] gave rise to methyl ketone **80**, common C₁-C₉ fragment to AMPs-C (1) and -F (5). This fragment was obtained a 14% overall yield over 20 steps.

3.3. Armstrong's Studies

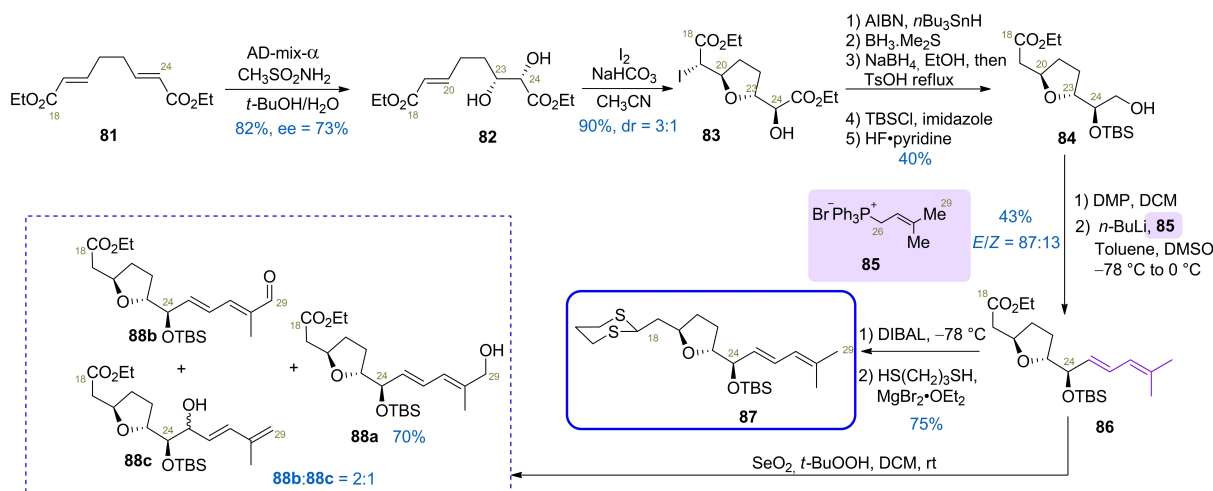
In 2009, Armstrong's group published their studies on the C₁₈-C₂₉ segment of AMP-F (5) and -C (1).^[43] Their approach is based on forming the 2,5-*trans* THF ring by iodocyclization reaction

and a Wittig olefination to introduce the double bond at C₂₅-C₂₆. They also studied the selective oxidation of position C₂₉ on an advanced intermediate to further obtain the whole AMP-C (1) side chain.

The synthesis started with desymmetrizing diester **81** by AD-mix- α ,^[39] affording diol **82** with a modest enantiomeric excess of 73% (Scheme 14).^[43] The direct oxo-Michael addition was ineffective by producing a 3:2 mixture of *trans*:*cis* isomers. In contrast, the same reaction driven on the THF segment between C₃ and C₆ led to excellent *trans* diastereoselectivity due to the methyl group at C₄, such as in Roush's studies (Section 3.1.3, Scheme 10). An iodocyclization reaction was performed to overcome this situation, leading to **83** with improved diastereoselectivity toward *trans*-THF (3:1), although it stays moderate. After a sequence including diastereomers separation, free radical dehalogenation, and selective reduction of the α -hydroxy ester, alcohol **84** could be obtained. A Wittig reaction was performed on the corresponding aldehyde with phosphonium **85**, giving the diene **86** with predominant (*E*) isomer (*E/Z* = 87:13). The ester was finally converted to 1,3-dithiane to form the C₁₈-C₂₉ fragment (**87**) of AMP-F (5). Fragment **87** was prepared in 12 steps from butanediol with



Scheme 13. Mohapatra's synthesis of the C₁-C₉ fragment by Mohapatra of amphidinolides C (1) and F (5).



Scheme 14. Armstrong's synthesis of the C₁₈-C₂₉ segment of amphidinolides C (1) and F (5).

about 6.8% overall yield. Alternatively, the SeO_2 -mediated allylic oxidation of the side chain was studied. The experience led predominantly to synthesizing **88a**, whose C_{29} methyl group was oxidized to an alcohol. Overoxidation product **88b** and transpositive oxidation product **88c** were also observed (Scheme 14).

3.4. Spilling's Studies

3.4.1. Spilling's C_1 - C_9 Fragment of Amphidinolides C (1) and F (5)

In 2010, Spilling's group first published the synthesis of the C_1 - C_9 fragment of AMPs—C (1) and -F (5).^[44] The authors used a Tamaru homoallylation^[45] to fix the relative configuration of the C_4 and C_6 centers and construct the 2,5-*trans* THF ring *via* an oxo-Michael reaction.

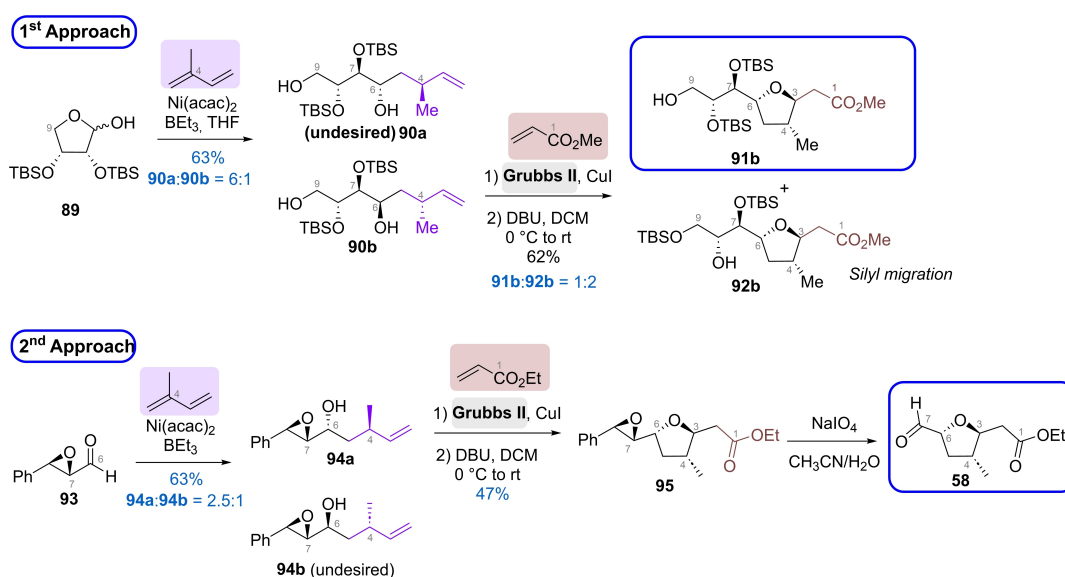
In the first approach, D-erythronolactol derivative **89** was exposed to isoprene in the presence of nickel (II) acetoacetate and triethylborane to perform a homoallylation reaction (Scheme 15).^[45] The reaction provided a 1:6 mixture of diastereomers, but unfortunately, the desired isomer **90b** was only produced in a 1:6 ratio relative to **90a**. The synthesis continued with this minor isomer, and an olefin cross-metathesis reaction with methyl acrylate, followed by an intramolecular oxo-Michael reaction using DBU gave the C_1 - C_9 fragment **91b** along with its isomer **92b**. This reaction outcome results from a migration of the silyl group (from C_8 to C_9) in a 1:2 ratio. An alternative was also studied from diol **89**, protected as an acetonide rather than as silyl ethers. The results were also contrasted; the authors obtained a 1:3 ratio for the desired isomer during nickel-catalyzed homoallylation, but they could never get the desired stereotriade as the predominant compound (Scheme 15, 1st approach).

A second approach was investigated to overcome these difficulties using a starting material whose chirality will only serve to induct the stereochemistry at C_4 and C_6 and later C_3 during the oxo-Michael cyclization. The stereochemistry at C_7 and C_8 will be installed further using another method. Thus, Spilling and coworkers started from epoxy aldehyde **93** and performed the Tamaru nickel-catalyzed homoallylation again. They obtained, this time, a 2.5:1 mixture of diastereomers **94a** and **94b** in favor of the desired product. Olefin cross-metathesis reaction and conjugated addition provided *trans*-THF **95** as a single detectable isomer. Oxidative cleavage of the epoxide afforded aldehyde **58**, and this compound corresponds to the same intermediate synthesized by Roush *et al.* in their synthetic studies of the C_1 - C_9 fragment of AMP—C (1) and -F (5). (see Scheme 10) This second approach can thus be considered a formal synthesis of Roush's C_1 - C_9 fragment **52b**.^[31] Aldehyde **58** was thus obtained in 10 steps from commercial materials in 21% overall yield (Scheme 15, 2nd approach).

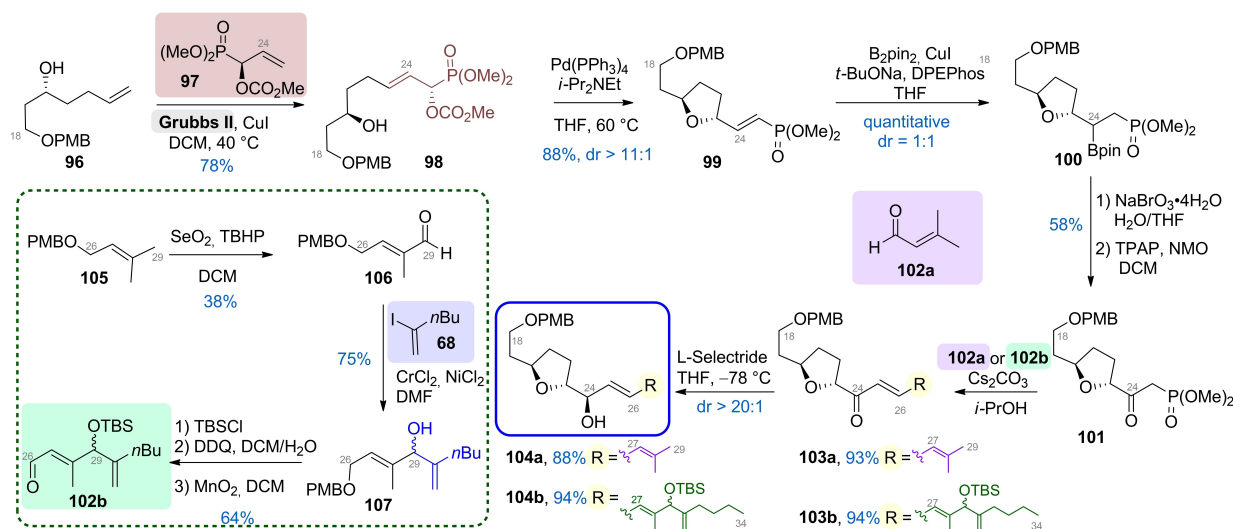
3.4.2. Spilling's Synthesis of the C_{18} - C_{34} / C_{29} Fragments of Amphidinolide C (1) and F (5)

After publishing its studies towards the C_1 - C_9 fragment of AMPs—C (1) and -F (5),^[44] Spilling's group reported the same year the synthesis of the C_{18} - C_{34} and C_{18} - C_{29} fragments of AMPs—C (1) and -F (5).^[46] Their approach is based on forming the 2,5-*trans*-THF ring by Tsuji-Trost-like palladium-catalyzed cyclization with chiral phosphonoallyl carbonate.^[47]

The synthesis began with a cross-metathesis reaction^[48] between olefin **96** (obtained *via* allylation of a chiral epoxide) and chiral phosphonic-carbonate **97**^[49] to provide the cyclization precursor **98** as a stereoisomeric mixture (*E/Z* > 9:1), (Scheme 16).^[46] Exposure of **98** with palladium (0) afforded THF **99** with good diastereoselectivity (*dr* > 11:1) through an $\text{S}_{\text{N}}2'$ alkylation pathway.^[47] The oxidation of the vinyl phosphonate



Scheme 15. Spilling's synthetic studies toward the C_1 - C_9 fragment of amphidinolides C (1) and F (5).



Scheme 16. Spilling's synthesis of the C₁₈-C_{34/29} fragment of amphidinolides C (1) and F (5).

unit to β -ketophosphonate **101** was achieved in three steps, as the direct oxidation under Wacker conditions failed.^[42] Thus, the conjugate addition of copper(I) borylate gave boronate **100** in quantitative yield. Oxidative boron hydrolysis and subsequent alcohol oxidation into ketone finally provided **101**. The ketophosphonate was wisely used to bring the dienic chain *via* the HWE reaction. Depending on the use of aldehyde **102a** or **102b**, this transformation gave access to either the C₁₈-C₂₉ fragment of AMP-F (5) (**103a**) or the C₁₈-C₃₄ of AMP-C (1) (**103b**). Selective reduction of the ketone in **103a** and **103b** afforded **104a** and **104b** as single diastereomer at C₂₄ (dr > 20:1).

The side chain synthesis of AMP-C (1) was accomplished by selective oxidation of the allylic position of **105** with selenium oxide, such as in Armstrong's studies, furnishing **106** (see Section 3.3.1, Scheme 14). It was followed by an NHK reaction^[35] on aldehyde **106** to afford **107**, such as in Mohapatra studies (Sections 3.2.1 and 3.2.2, Schemes 11 and 12), and after some functionalizations, aldehyde **102b** was obtained. However, this synthetic sequence does not control the stereogenic center at C₂₉. Fragments **104a** and **104b** were prepared in 10 steps along the longest linear sequence in 14% overall yield.

3.5. Pagenkopf's Studies

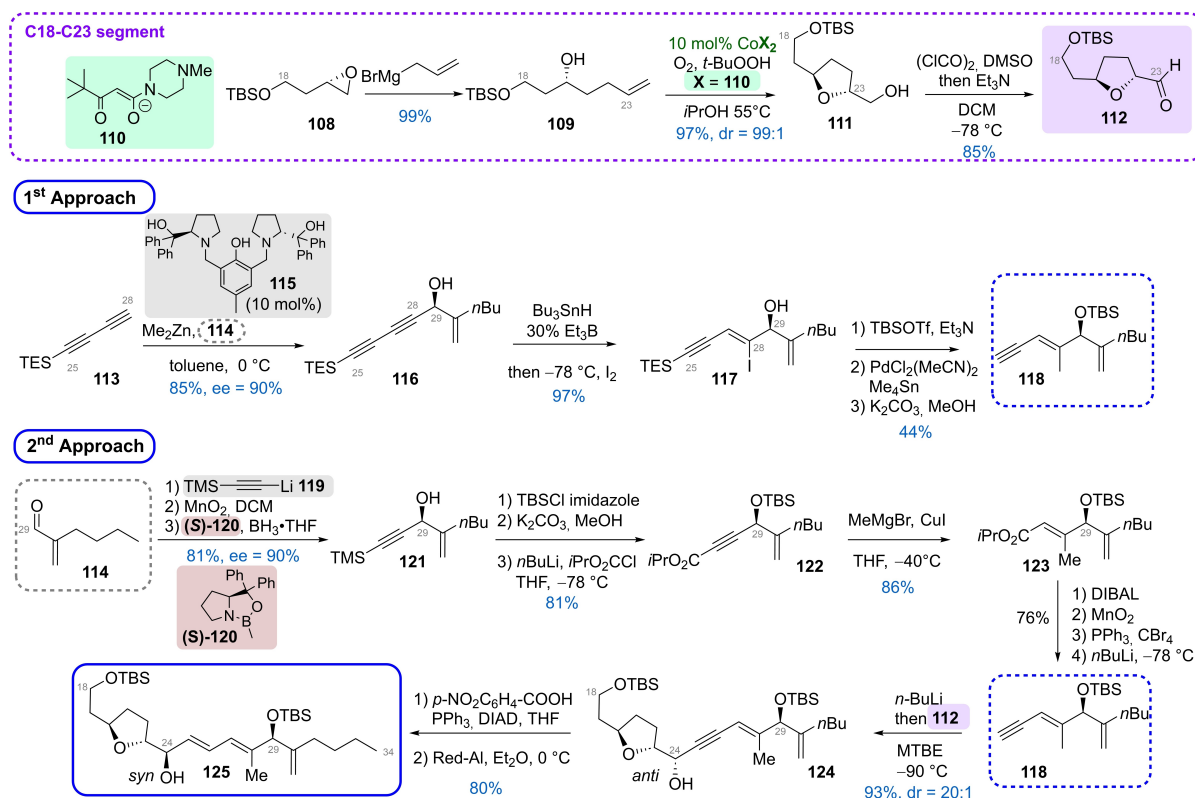
3.5.1. Pagenkopf's Synthesis of the C₁₈-C₃₄ fragment of Amphidinolide C (1)

In 2011, Pagenkopf et al. published their study on synthesizing the C₁₈-C₃₄ fragment of AMP-C (1).^[50] The authors relied on a Mukaiyama oxidative cyclization to form the 2,5-*trans* THF motif.^[51] The side chain synthesis of AMP-C (1) was studied through two approaches: an asymmetric alkylnylzinc addition to an aldehyde or an asymmetric ketone reduction to control the stereogenic center at C₂₉.

Their synthesis of the THF moiety started from chiral epoxide **108**, easily obtainable by Jacobsen hydrolytic resolution^[52] of racemic epoxide (Scheme 17).^[50] Ring-opening by allylation furnished alcohol **109**, and an oxidative cyclization was performed with catalytic cobalt (II) bearing **110** as ligands. Pagenkopf's group developed this catalyst, which allows increasing yields and the facility of purification due to its water solubility property.^[53] The reaction worked with a very high yield and diastereoselectivity toward *trans*-THF **111**. Observed diastereoselectivity is much higher than conjugate addition or iodocyclization (see Section 3.3.1). The primary alcohol was then oxidized in aldehyde **112** by Swern oxidation. (Scheme 17, top)

The AMP-C (1) side chain synthesis was also investigated in parallel. Thus, diyne **113** was engaged in an asymmetric alkylation with 2-methylenehexenal (**114**). The use of Trost ligand **115** proved to be the most effective, giving **116** with 90% ee.^[54] Radical-mediated hydrostannylation was regioselective toward the non-silylated alkyne and chemoselective, giving the *Z*-isomer **117** exclusively after iodolysis. Further palladium-catalyzed methylation and protection/deprotection steps have resulted in segment **118**. Although this strategy was effective by providing **118** in only 6 steps with a 34% yield from aldehyde **114**, the authors experienced issues scaling up the asymmetric alkylation. Furthermore, the high cost of Me₂Zn was also an issue in continuing the total synthesis using this strategy. (Scheme 17, first approach)

Therefore, they elaborated a second approach, which was still starting from aldehyde **114** but was exposed to an addition/oxidation sequence followed by an asymmetric reduction in the presence of Corey-Bakshi-Shibata (CBS) reagent **120** to control the C₂₉ stereogenic center.^[55] A carboxylate group was incorporated into the alkyne, providing **122**, allowing methylcopper(I) species to be added to the electron-deficient position. Functional group modifications, which include a Corey-Fuchs reaction to prepare the terminal alkyne, delivered



Scheme 17. Pagenkopf's synthesis studies of the C₁₈-C₃₄ fragment of amphidinolide C (1).

this time synthon 118 in 46% yield over eleven steps. The final coupling consisted of the lithiation of alkyne 118 to the previous aldehyde 112 in MTBE at -90°C . Those conditions were very selective towards the Felkin-Anh type product, providing 124 with the *anti*-configuration. A Mitsunobu reaction with the nitrobenzoic acid followed the cleavage of the ester, inverting the stereochemistry to obtain *syn* product 125. This synthon was thus prepared in 11 or 6 steps with an overall yield of 22 or 26%, according to the first or second approach and the most extended linear sequence (Scheme 17, second approach).^[50]

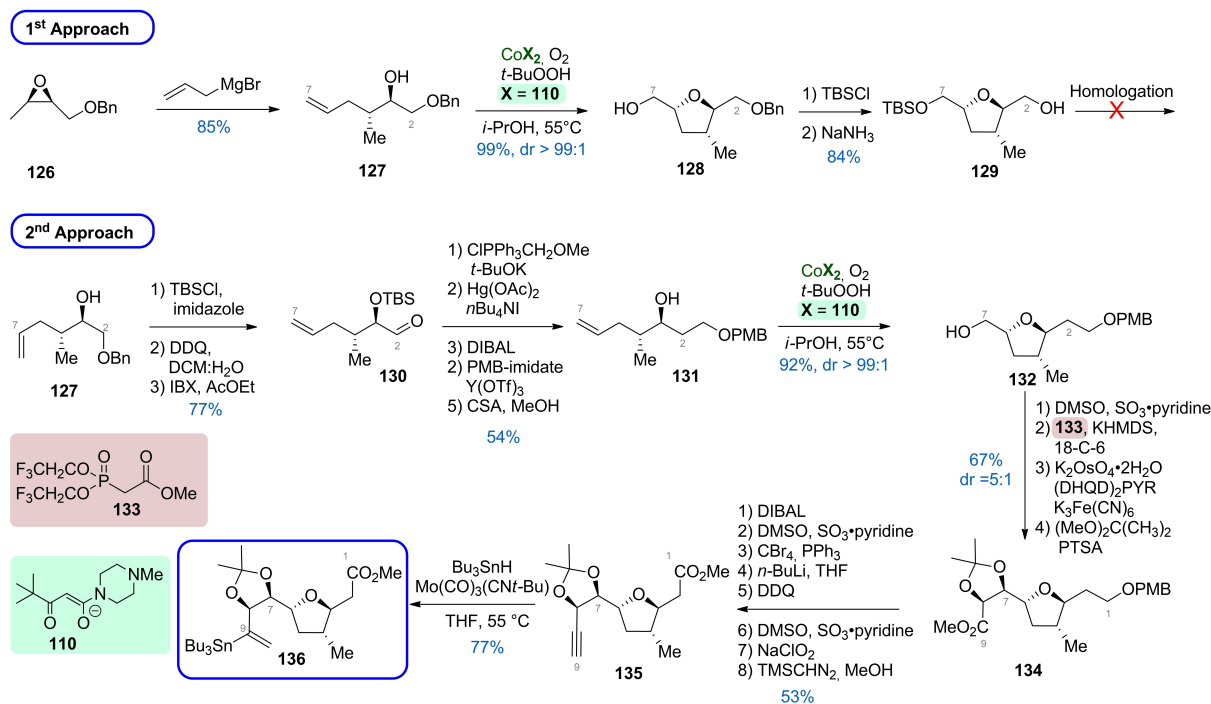
3.5.2. Pagenkopf's Synthesis of the C₁-C₉ Segment of Amphidinolides C (1) and F (5)

In 2013, Pagenkopf's group published the continuation of their work with their study toward preparing the C₁-C₉ fragment of AMPs-C (1) and -F (5).^[56] Again, the authors sought to take advantage of their improvement of oxidative cyclization to prepare the 2,5-*trans* THF present in this fragment.^[53]

In the first approach, authors could quickly access intermediate 129 using cobalt(II) salt-bearing ligands 110 through an oxidative cyclization process to build the THF (Scheme 18).^[56] The diastereoselectivity was also very high in this case. However, it was not possible to homologate position C₂, leading to no reaction or ring-opening of the THF (Scheme 18, 1st Approach).

Therefore, a slightly different strategy was investigated, with the cost of additional steps to build this fragment. Indeed, from compound 127, they obtained homolog 131 in eight steps *via* 130. In counterpart, oxidative cyclization was again very effective in building *trans*-THF 132. The C₇-functionalization sequence first led to the formation of the diol derivative 134 with moderate enantioselectivity using the Sharpless asymmetric epoxidation. Indeed, *Z*-isomers require the use of (DHQD)₂PYR ligand for the best enantioselectivities, and those substrates are less appropriate for this asymmetric reaction than *E* isomers.^[39,57] After installation of the stereogenic centers at C₇ and C₈, methyl ester 134 was converted to 135 in six steps using the Corey-Fuchs reaction as the key step. Finally, a regioselective hydrostannylation reaction yielded the C₁-C₉ fragment 136,^[58,59] after 25 steps from *cis*-butenol with an overall yield of 7% (Scheme 18, 2nd approach).

Pagenkopf's group has also reported earlier studies about preparing intermediate 131 by a regioselective and stereospecific epoxide reduction with NaBH₃CN and BF₂OBN-Et₂O.^[60] However, this strategy was finally not retained.

Scheme 18. Pagenkopf's synthesis of the C₁-C₉ fragment of amphidinolides C (1) and F (5).

3.6. Forsyth's Studies

3.6.1. Forsyth's First Study toward Amphidinolides C (1) and F (5)

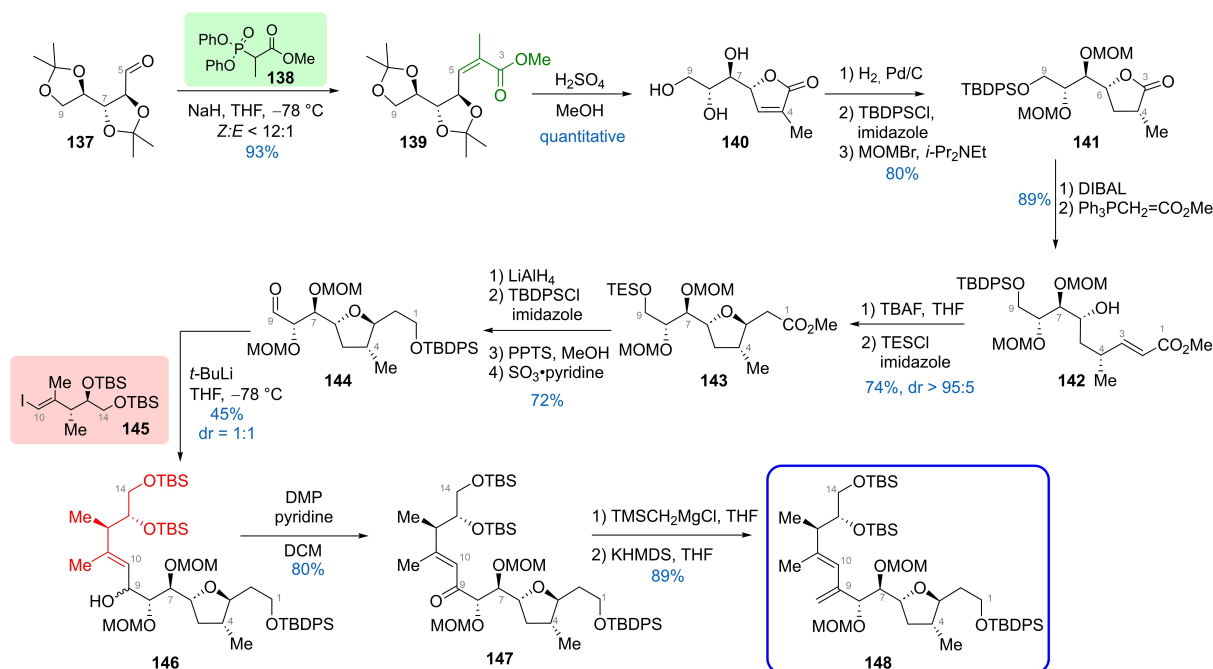
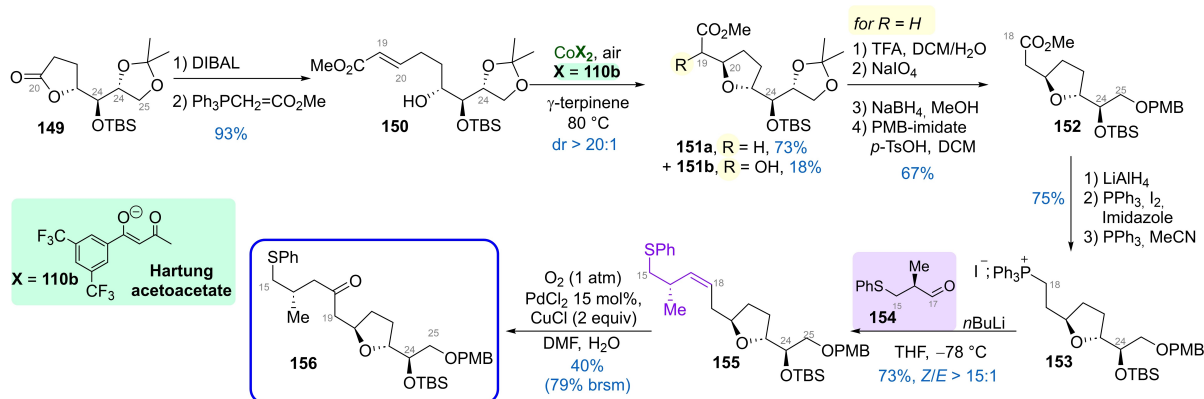
In 2013, C. Forsyth's group published their first study on synthesizing the C₁-C₁₄ and C₁₅-C₂₅ fragments of AMPs-C (1) and -F (5), which thus constitutes all the backbone of the macrolactone.^[61]

The synthetic approach of the C₁-C₁₄ fragment of AMP-C (1) by Forsyth et al. was based on an oxo-Michael reaction and the installation of the diene unit *via* a methylenation of the corresponding α,β -unsaturated ketone. This approach is inspired mainly by earlier studies by Roush,^[31] Ferri&Figadère,^[59] and Carter.^[62] (see Sections 3.1, 4.3.1, 4.1.1 and Schemes 11, 46, 37, respectively)

The synthetic sequence starts with the bis-acetonide **137**,^[63] obtained from D-gluconolactone in three steps (Scheme 19).^[61] Z-selective HWE olefination^[64] on **137** with phenoxy phosphate **138** afforded **139**. Then, acid-catalyzed lactonization led quantitatively to known lactone **140**.^[59] Selective hydrogenation on the less hindered face of the ring allows perfect control of the diastereoselectivity at C₄. Such as in Roush's studies (Section 3.1.3, Scheme 10), lactone **141** was transformed into conjugated ester **142**, and a TBAF-mediated oxo-Michael addition led exclusively to 2,5-*trans* THF **143**, thanks to the methyl group at C₄. After functional group modifications, aldehyde **144** was obtained. The formation of the diene unit to continue the construction of the C₁-C₁₄ segment was strongly inspired by Carter's study (Section 4.1.1, Scheme 35) toward AMP-C (1). Carter's vinyl iodide **145**^[62] was added to aldehyde

144 to give adduct **146**. Dess-Martin periodinane oxidation finally provided enone **147**, and Peterson olefination sequence finally provided the C₁-C₁₄ segment of AMPs-C (1) and F **148**.

Considering the C₁₅-C₂₅ of AMPs-C (1) and -F (5), the strategy to build the THF-ring was also based on an oxo-Michael addition.^[61] Since the direct conjugated addition is unselective on this THF due to the absence of the methyl group in the ring, a different approach that used radical conditions, such as Pagenkopf studies, which used the Mukaiyama cyclization,^[51,53] (see Section 3.5) offered excellent alternative conditions. Regioselective Wacker oxidation was also a key step of this sequence, which allowed the positioning of the ketone function at C₁₈. Therefore, the synthesis begins with the homologation of acetonide **149** (prepared from vinylogous Mukaiyama aldol reaction between siloxyfuran and acetonide-protected glyceraldehyde)^[65,66] to acrylate **150** *via* a Wittig reaction (Scheme 20).^[61] Because any condition for direct oxo-Michael addition was poorly selective (maximum dr=2:1), a Mukaiyama cyclization under Hartung conditions^[67] yielded the same product **151a** with a different mechanistic pathway but with high diastereoselectivity toward *trans*-THF, inherent to that transformation.^[51] The role of γ -terpinene is to scavenge the intermediate radical to avoid the hydroxylation/hydroperoxidation process in the α -position of the ester function. Nevertheless, **151a** was accompanied by a non-negligible percentage of α -oxidation product **151b** (18%). THF **151a** was then converted to **152** in four steps, and phosphonium salt **153** was prepared from the ester function in three steps. The reaction of the ylide from **153** and aldehyde **154** (prepared from (*S*)-Roche ester in two steps),^[68] led to Z-olefin **155** with a good stereoselectivity (Z:E > 15:1). Finally, a Wacker reaction was used to

Scheme 19. Forsyth's first synthesis of the C₁-C₁₄ fragment of amphidinolides C (1) and F (5).Scheme 20. Forsyth's first synthesis of the C₁₅-C₂₅ fragment.

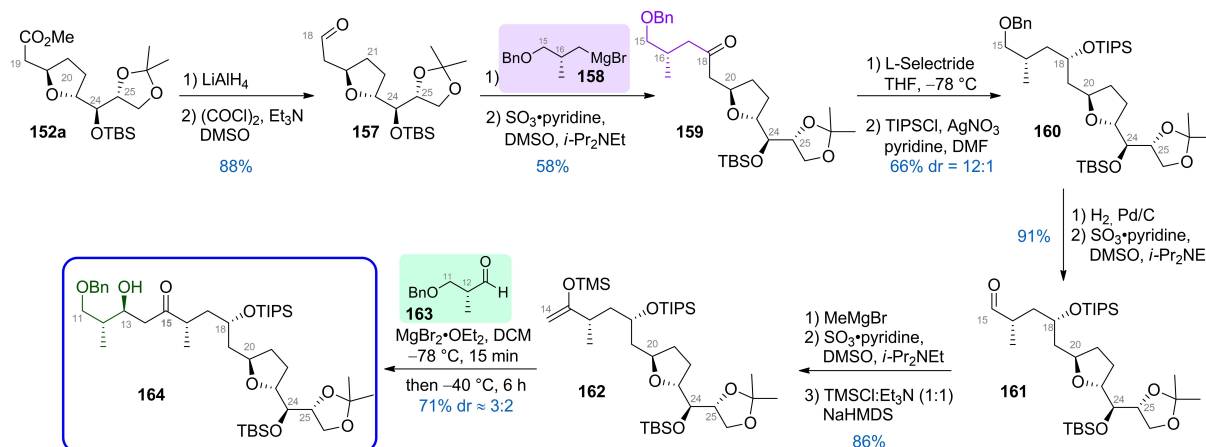
regioselectively install the ketone at C₁₈, according to a method described by Raghavan.^[42] The regioselectivity of this reaction can be explained by the chelation of the palladium with a sulfide, allowing only a 5-*exo-trig* addition of water at C₁₈. The synthesis of the C₁₅-C₂₉ segment was thus achieved in a 2.9% yield over 20 steps from D-glucuronolactone.

3.6.2. Forsyth's Second-Generation Strategy: Synthesis of the C₁₁-C₂₅ Fragment of Amphidinolides C (1) and F (5)

In 2017, Forsyth's team reported a new approach to the C₁₁-C₂₅ fragments of AMPs-C (1) and -F (5). This report relies on a different disconnection compared to the first approach, which was used to synthesize the C₁-C₁₄ and C₁₅-C₂₅ fragments.^[69] The synthesis of the C₁-C₉ segment was also described herein;

however, it discloses precisely the same synthetic sequence as previously^[61] but with minor optimizations (see Scheme 19). This report's significant contribution was using two consecutive (*R*)-Roche ester synthons to build the C₁₁-C₁₇ segment instead of Carter's vinyl iodide 145 during the previous construction of the C₁-C₁₄ backbone (see Scheme 19).

Therefore, the new approach started from the known THF moiety 152a, whose ester function was converted into an aldehyde. Subsequently, Grignard reagent 158 [derived from (*R*)-Roche ester] was added to aldehyde 157 to give ketone 159 after oxidation (Scheme 21).^[69] Reduction of the carbonyl group with L-Selectride was very selective, affording the required diastereomer in a 12:1 ratio. After the protection of alcohol with a TIPS group, compound 160 was manipulated at the C₁₄ position selectively and was thus converted into aldehyde 161. The transformation of 161 in silyl enol ether 162 involved the



Scheme 21. Forsyth's second approach toward the total synthesis of amphidinolide C (1) and F (5): Synthesis of the C₁₁–C₂₅ common fragment.

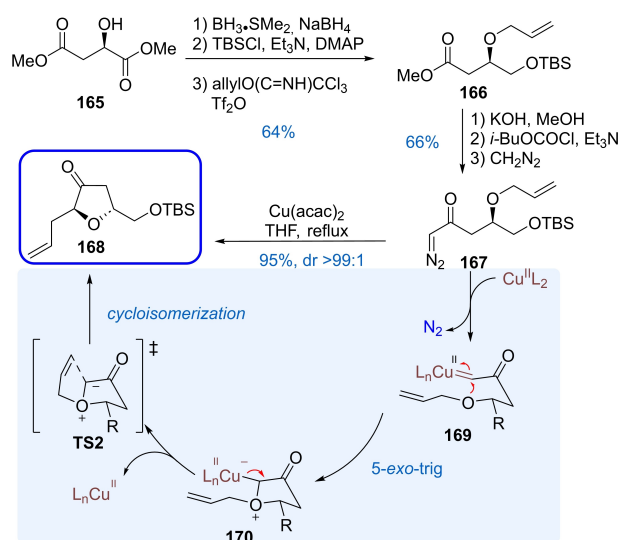
addition of MeMgBr, reoxidation and enolization reactions. Finally, the reuse of (*S*)-Roche ester *via* aldehyde **163** in a Mukaiyama aldol reaction, under conditions allowing Cram-Chelate diastereoselectivity, afforded product **164** but with poor control (*dr* ≈ 3:2). Thus, the C₁₁–C₂₅ fragment was prepared in 23 steps and 3.6% overall yield from D-glucuronolactone.

3.7. Clark's Studies

3.7.1. Clark's First Approach

In 2013, Clark's group published their first study on synthesizing AMPs–C (1) and –F (5). This study is separated into two parts: the C₁–C₁₇^[70] and C₁₈–C₃₄/C₁₈–C₂₉^[71] fragments for AMPs–C (1) and –F (5), respectively. The main highlight in their reports is using a common intermediate, the dihydrofuranone **160**, to build both THF-rings of AMPs–C (1) or –F (5). It could be prepared efficiently and diastereoselectively using the authors' carbenoid-promoted oxonium rearrangement reaction.^[73] The unifying strategy to make both THF was also applied efficiently by Carter in the total synthesis of AMPs–C (1) and –F (5).^[72] (see Section 4.1)

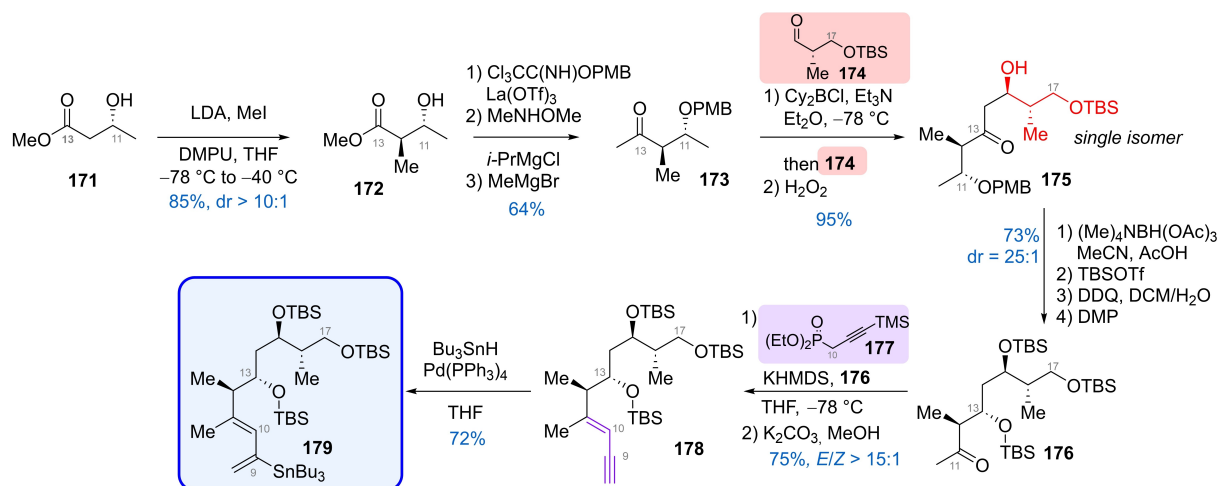
The synthesis of **168** started from the chiral building block methyl malate **165** (Scheme 22).^[71] A directed regioselective reduction of the ester function adjacent to hydroxygroup and further selective TBS protection and allylation gave intermediate **166**. Activation of the remaining carboxyl group and the insertion of diazomethane furnished diazoketone **167**. The key step was to heat **167** with Cu(acac)₂ to promote the rearrangement reaction. The mechanism of this featured transformation presumably involves the formation of the cuprocarbene species **169**. The process is followed by adding the surrounding oxygen atom to the carbene, which leads to the oxonium species **170**. Finally, a cycloisomerization process with the orientation of the allyl group on the less hindered face of the THF ring occurs *via* **TS2** to give **168** with high diastereoselectivity. This common building block was synthesized in 7 steps with a 40% overall yield.



Scheme 22. Clark's synthesis of the key dihydrofuranone **168** *via* carbenoid-promoted oxonium rearrangement reaction.

Following, the synthesis of the C₁–C₁₇ fragment was reported to be a coupling between the C₁–C₈ and the C₉–C₁₇ segments *via* adding an organolithium reagent to an aldehyde. The *trans*-THF was prepared *via* the common intermediate **168**.

The C₉–C₁₇ sub-fragment was prepared from chiral building block **171** (Scheme 23),^[70] which involved a Fráter-Seebach alkylation to give the *anti*-product **172** with a good diastereoselectivity (*dr* > 10:1).^[74] It was then converted to methyl ketone **173** by adding methylmagnesium bromide to a Weinreb amide. The latter was engaged in a Patterson aldol reaction with the (*S*)-Roche ester-derived aldehyde **174**, allowing C₁₂, C₁₅, and C₁₆ stereogenic centers to be installed.^[29] A directed reduction of the ketone fixed the C₁₃ stereogenic center in **176** with a high *anti*-stereoselectivity (*dr* = 25:1) by the support of the hydroxygroup at C₁₆.^[75] A HWE olefination reaction between methyl ketone **176** and phosphonate **177** gave enyne **178** with excellent stereoselectivity (*E:Z* > 15:1). Finally, the palladium-catalyzed hydrostannylation reaction gave stannane **179** as a



Scheme 23. Clark's first Synthesis of the C₉-C₁₇ sub-fragment **179** of amphidinolides C (**1**) and F (**5**).

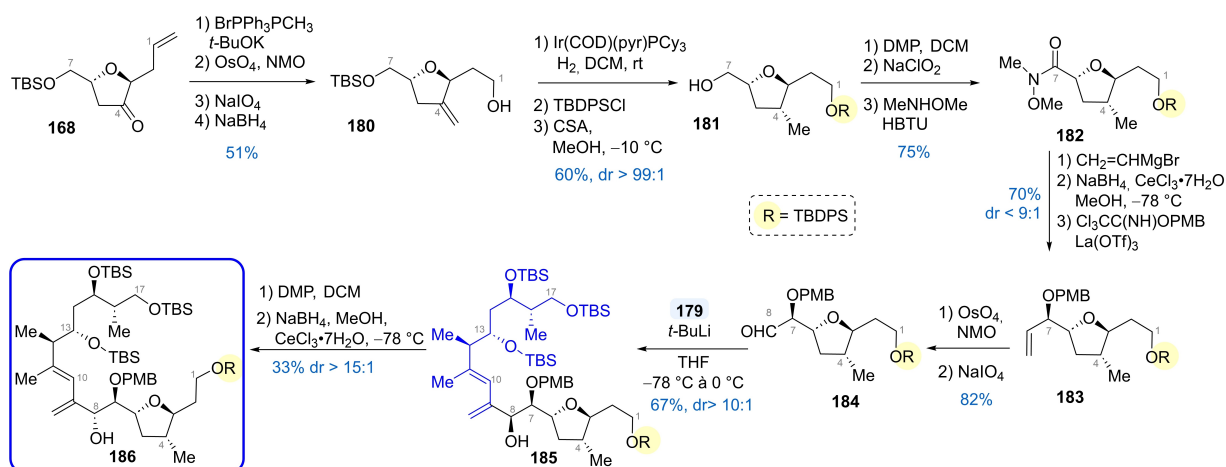
single isomer. The synthesis of the C₉-C₁₇ sub-fragment was accomplished in 11 steps from **171** with an overall yield of 20%.

In parallel, the C₁-C₈ fragment (**184**) synthesis was accomplished and further coupled to the C₉-C₁₇ fragment (Scheme 24).^[70] Thus, furanone **168** was functionalized in four steps to give THF **180**. The exo-methylene at position C₄ was then reduced *via* stereo-directed hydrogenation with Crabtree catalyst to give **181**.^[76] Following, it was converted to Weinreb amide **182** in three steps. After vinyl Grignard addition and Luche reduction with Felkin-Anh diastereoselectivity, **183** was obtained and transformed into aldehyde **184**, corresponding to the C₁-C₈ sub-fragment. The final steps consisted of coupling reaction with **179**. Thus, stannane **179** was lithiated by transmetallation with *t*-BuLi, and the vinyl lithium reagent was added to **184**. High 7,8-*syn* diastereoselectivity was observed for adduct **185**, in opposition to the general observations with lithium reagents regarding the Felkin-Anh model. However, the authors could reverse the stereochemistry by oxidation of the alcohol at C₈ followed by its diastereoselective reduction under

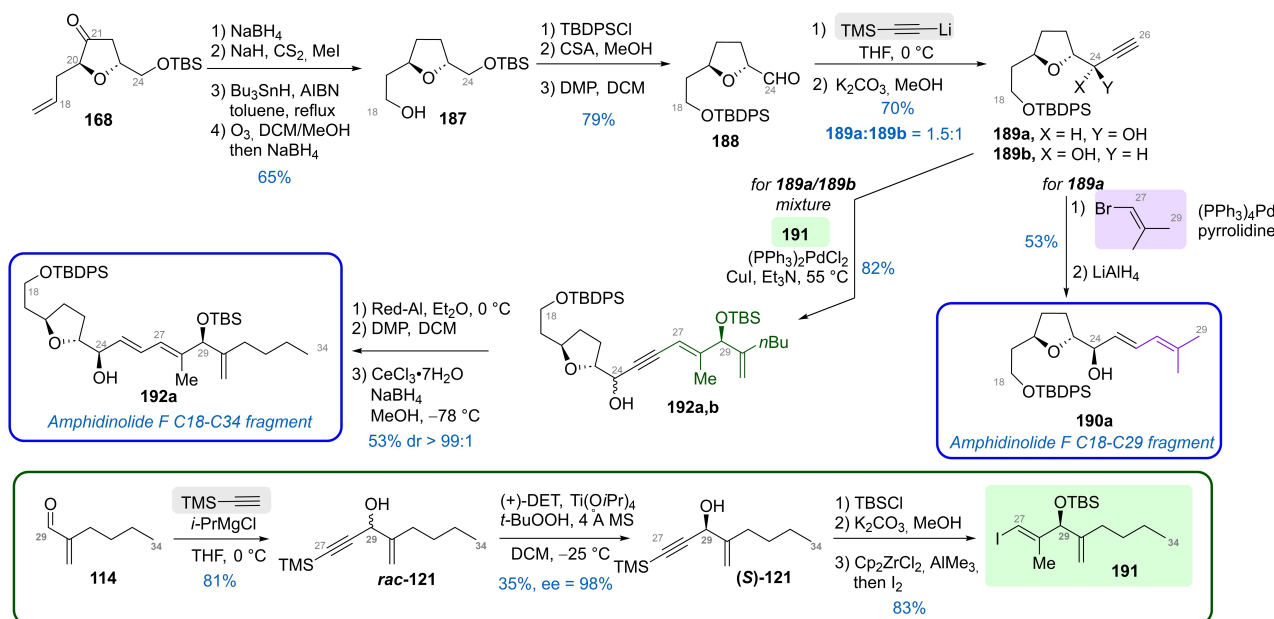
Luche conditions, which led predominantly to the 7,8-*anti* product. Therefore, synthesizing the C₁-C₈ segment **175** was achieved in 15 steps from **168** with a 13% overall yield. Considering the synthesis of **168**, seven steps should be added to reach 22 steps in total with an overall yield of 5.3%.

The next target was the synthesis of the C₁₈-C₃₄ and C₁₈-C₂₉ fragments of AMPs-C (**1**) and F (**5**), which also rely on the common intermediate **168**.^[71] The stereogenic centers at C₂₄ and C₂₉ were controlled, respectively, *via* a diastereoselective reduction and a kinetic resolution.

Therefore, the synthesis started from **168**, which underwent a Barton-McCombie deoxygenation and ozonolysis to give **187** (Scheme 25).^[71] Protecting group manipulation and oxidation afforded aldehyde **188**. This compound was converted to propargyl alcohol **189 a-b** by adding lithium trimethylsilylacetylide, followed by methanolysis. It should be noted that various acetylide addition protocols were explored without successfully controlling the diastereoselectivity; thus, **189 a** and **189 b** were obtained only as a 1.5:1 mixture. Moreover, several reduction tests were performed on the corresponding ketone without



Scheme 24. Clark's synthesis of the whole C₁-C₁₇ **186** fragment of amphidinolides C (**1**) and F (**5**).



Scheme 25. Clark's first synthesis of the C₁₈-C₃₄ and C₁₈-C₂₉ fragments **192** and **190a** of amphinolides **C** (**1**) and **F** (**5**).

improving diastereoselectivity. On the one hand, the correct isomer **189a** was submitted to a Sonogashira cross-coupling with 1-bromo-2-methylpropene. This reaction was followed by a selective, directed reduction of acetylene with LiAlH₄ to give the C₁₈-C₂₉ fragment of AMP-F (**5**) (**190a**).

On the other hand, the mixture of **189a** and **189b** was coupled with vinyl iodide **191** to furnish a mixture of isomers at C₂₄, **192a**, and **192b**. **192a** was exclusively obtained *via* an oxidation/Luche reduction sequence. It should be noted that vinyl iodide **191** was prepared from aldehyde **114** analogously to Pagenkopf's work.^[50] (see Section 3.5.1, Scheme 18) The significant difference relies on using a Sharpless kinetic resolution^[77] to impose the stereochemistry at C₂₉ from racemate **121**. (*S*)-Isomer was thus obtained in high enantioselectivity *via* this method. Transformation of the terminal alkyne in vinyl iodide **191** was accomplished *via* a Negishi carboalumination.^[78,79] Therefore, the synthesis of the C₁₈-C₂₉ fragment of AMP-F (**5**) (**190a**) was prepared in ten steps in 38% from advanced intermediate **168**, whereas the C₁₈-C₃₄ fragment of AMP-C (**1**) (**192a**) was built in 13 in an overall yield of 22%. Seven steps would be added if the synthesis of the furanone **168** is considered.

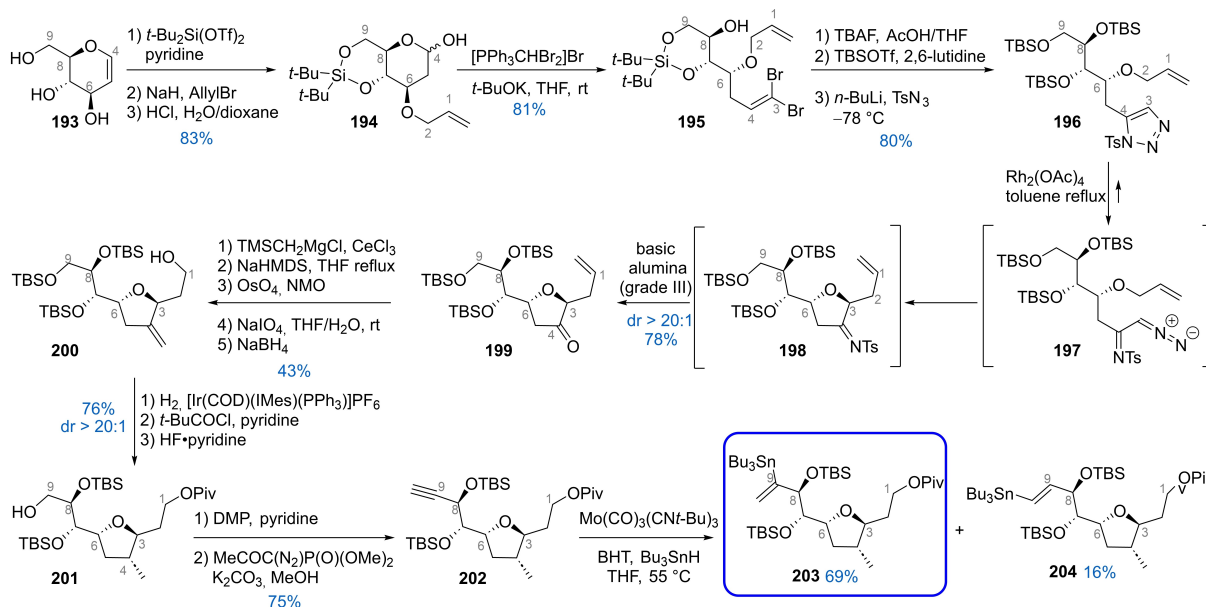
3.7.2. Clark's Second Approach toward Amphinolide F (**5**)

Although the authors considered the first strategy "both convergent and logical," they also mentioned the lack of efficiency due to the high number of steps needed to prepare each fragment. Moreover, the described disconnections limit the versatility of building the entire framework. As AMP-F (**5**) is one step easier to construct than AMP-C (**1**), authors focused on that natural substance in the second-generation synthesis reported in 2021.^[80] Although they were finally never able to

reach this objective, the Clark group is undoubtedly the team that was the closest to obtaining the natural product among chemists reporting only synthetic studies of AMPs-C (**1**) or -F (**5**). Indeed, Clark reached the entire skeleton of AMP-F (**5**). Overall, the group took the most effective methodologies they applied in the first-generation synthesis with some improvements and took the most step-saving approaches from other reported synthetic studies.^[80]

The second-generation synthesis of the C₁-C₉ fragment of AMPs-C (**1**) or -F (**5**) still relies on an oxonium ylide rearrangement to build the THF.^[80] However, a modification was brought by the authors with the use of a rhodium-catalyzed denitrogenative rearrangement of tosyl-triazoles.^[81,82] This method prevents hazardous diazomethane use compared to the first reported strategy to build furanone **168**.

The new approach of the C₁-C₉ segment started from D-glucal **193**, selectively protected with a silylene, allylated at C₆, and hydrated to form the lactol product **194** (Scheme 26).^[80] Olefination gave rise to vinyl dibromide **195**, and this function was converted into tosyl triazole. **196** underwent a rhodium-catalyzed denitrogenative rearrangement of tosyl-triazole,^[81,82] which allowed the formation of intermediate **197**. The latter rearranged spontaneously into tosylimine-dihydrofuran **198**, according to Clark's pioneering work^[73] (see also Scheme 20). Tosylimine **198** was then hydrolyzed into ketone **199** with basic alumina at the end of the reaction. Functionalization of **199**, including a Peterson olefination and regioselective oxidative cleavage of the terminal olefin, afforded **200**. Directed hydrogenation with Iridium Kerr's catalyst provided the right diastereoisomer,^[83] whereas Crabtree catalyst^[76] was unsuccessful for this substrate. Some protecting group manipulations led to the obtaining of **201**. Seyferth-Gilbert homologation drove to alkyne **202**,^[84] and a final regioselective hydrostannylation afforded more predominantly stannane **203** (69%) over *E*-

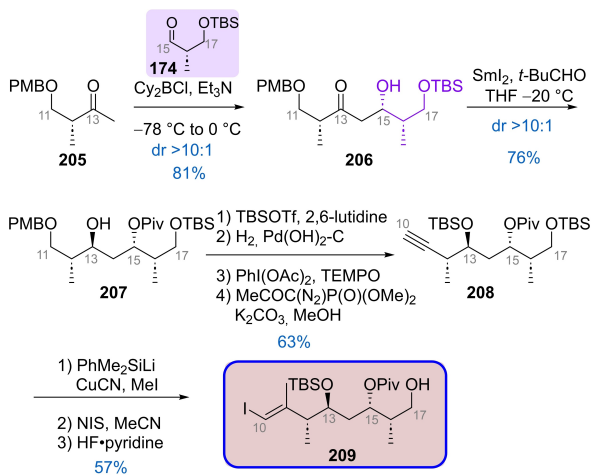


Scheme 26. Clark's 2nd Generation synthesis of C₁–C₉ fragment of amphidinolide F (5), via a rhodium-catalyzed denitrogenative rearrangement of tosyl-triazole.

alkene **204** (16%).^[58] The new synthesis of this fragment was achieved in 20 steps with an overall yield of 7.1%.

According to the new disconnections, the second synthesis of the C₁₁–C₁₇ fragment of AMP–F (5) or C (1) still used the methods described in Clark's first strategy but with some fittings.^[70]

Therefore, Clark et al. used methyl ketone **205** (prepared in three steps and 85% yield from (*R*)-Roche ester)^[85] as the starting material, which underwent a Paterson boron aldol reaction^[29] with aldehyde **174** to furnish adduct **206** as the key step of the sequence (Scheme 27).^[80] Evans-Tishchenko's reaction allowed the directed reduction of the carbonyl group with concomitant protection of the hydroxygroup at C₁₅ as pivalic ester giving **207**.^[30] Gilbert-Seyfert homologation^[84] at C₁₁ provided alkyne **208**, and it was then transformed into vinyl



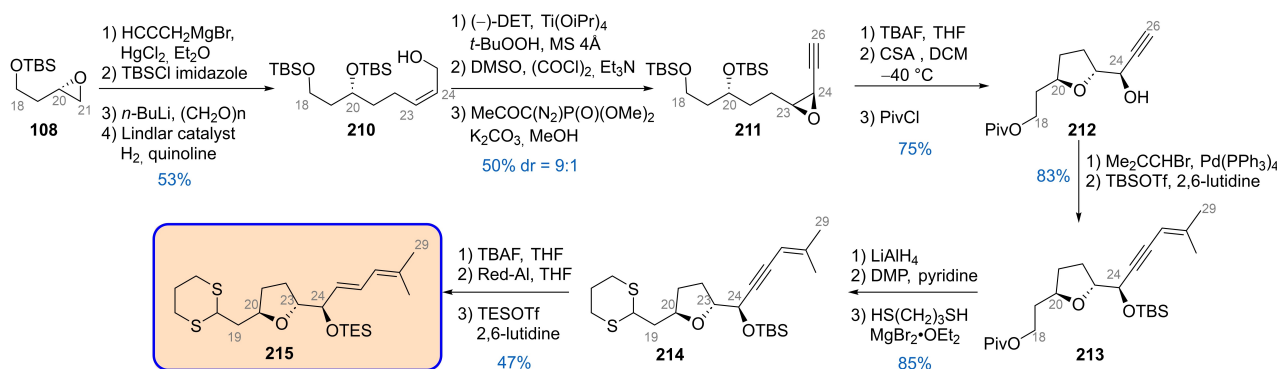
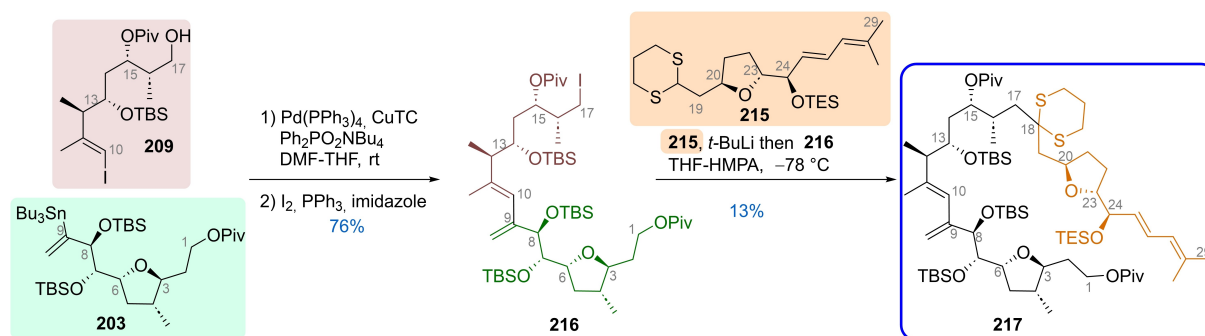
Scheme 27. Clark's second-generation synthesis of the C₁₀–C₁₇ fragment of amphidinolide F (5), via a Paterson aldol reaction as the key step.

iodide **209** by a silylcupration reaction followed by an iodolysis of the silyl group. Thus, this fragment was prepared from (*R*)-Roche ester in 12 steps with a 22% overall yield.^[80]

Whereas the first generation involved an oxonium ylide rearrangement to build the THF core at the C₁₉–C₂₄ segment, the second-generation synthesis relies on a more classical epoxide ring opening strategy to construct the five-member ring.^[80] The construction of the side chain is similar to what was described previously during their first strategy.

Thus, the synthesis of C₁₈–C₂₉ fragment **215** was achieved from epoxide **108**, which was opened with propargylmagnesium bromide, and the alkyne was then alkylated with formaldehyde and reduced selectively in *Z*-alkene with Lindlar catalyst to give **210** (Scheme 28).^[80] Sharpless epoxidation^[77] and Seyfert-Gilbert homologation^[84] afforded epoxide **211** and good stereoselectivity. Acid-catalyzed cyclization afforded *trans*-THF **212**. A synthetic sequence including a selective acylation on the primary position, protection of the alcohol at position C₂₄ as a TBS ether, and Sonogashira cross-coupling provided enyne **213**. Functionalizing the final position as dithiane **214** followed by directed reduction of alkyne in *E*-alkene with Red-Al afforded the last fragment **215**. Its synthesis was performed in 18 steps with a 6.6% overall yield from epoxide **108**. It can also be noted that three more steps are needed to prepare **108** through hydrolytic kinetic resolution.

The synthesis of the different segments culminated in the synthesis of the complete backbone of AMP–F (5).^[80] Thus, vinyl iodide **209** could be coupled with stannane **203** with the conditions set up by Fürstner^[86] consisting of the use of both Copper(I) thiophene carboxylate (CuTC) and tetrabutylammonium diphenylphosphinate as additives (Scheme 29).^[80] Substituting the hydroxy group in C₁₇ by an iodide afforded C₁–C₁₇ segment **216**. Alkylation of **216** by lithiated dithiane **203** gave rise to C₁–C₂₉ backbone **217** but in poor yield. Inverse polar-

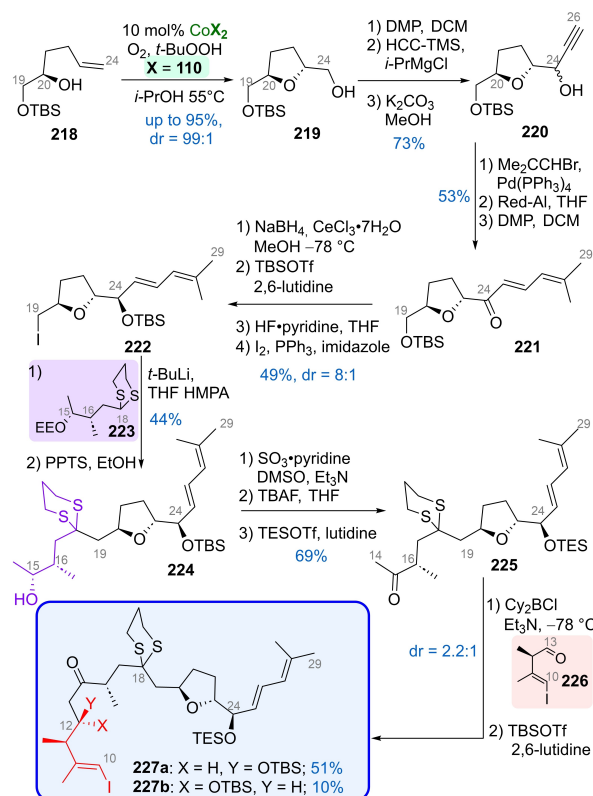
Scheme 28. Clark's second-generation synthesis of the $\text{C}_{18}\text{-C}_{29}$ of amphidinolide F (5) fragment.Scheme 29. Clark's synthesis of the $\text{C}_1\text{-C}_{29}$ backbone of amphidinolide F (5).

ization demand, through halogen-metal exchange on iodide **216** and addition on an aldehyde derived from **215**, could not allow any coupling either. Due to the inefficiency of the last step combined probably with the choice of the protecting groups, *i.e.*, one pivaloyl ester to be selectively removed, cyclization studies could not likely lead to the macrolactone. Thus, more modifications in the strategy would be needed to give rise to AMP-F (5).

3.7.3. Third Approach toward Amphidinolide F

Although Clark et al. could obtain the backbone of AMP-F (5), they could not reach the macrolactone and, by extension, the natural product. According to Clark, the choice of the coupling partners did not provide them with the versatility to overcome possible difficulties during the cross-coupling conditions. Therefore, they used a third approach to reach AMP-F (5).^[87] One of the most significant modifications was using the Mukaiyama oxidative cyclization,^[51] with Pagenkopf's improvement,^[53] to build the 2,5-*trans*-THF motif between C_{19} and C_{24} .

Thus, homoallyl alcohol **218** underwent a cyclization with oxygen under Pagenkopf's cobalt catalysis^[53] (see Section 3.5.1) (Scheme 30).^[87] The introduction of an acetylene function was performed in three steps and according to Clark's previous studies (see Scheme 28), Sonogashira cross-coupling, directed reduction of the alkyne in *E*-olefin, and diastereoselective reduction of the ketone at C_{24} position with Luche conditions

Scheme 30. Clark's third approach: $\text{C}_{10}\text{-C}_{29}$ segment of amphidinolide F (5).

afforded compound **222**. Alkylation of the dithiane **223** with iodide **222** gave rise to **224** in acceptable yield after ethoxyethyl (OEE) protecting group removal. Oxidation of the alcohol at C₁₅ followed by replacement of the TBS group by the TES group led to **225**. Paterson boron aldol reaction^[29] provided the C₁₀–C₂₉ segments **227a** and **227b** in fewer steps. However, the reaction gave predominantly **227a** with the 11,12-*syn* configuration, which is usually observed in this aldol reaction, while the required stereochemistry is *anti*, e.g., minor compound **227b**. (Scheme 30)

Although the synthesis is straightforward (21 steps from glycidol, in about 3.3% overall yield considering both **227a–b**), it also requires the preparation of dithiane **223** in 5 steps from malic acid and the obtaining of vinyl iodide **226** in 6 steps from (S)-Roche ester.

After planning different connection strategies, the C₁₀–C₂₉ segment was ultimately coupled with the C₁–C₉ fragment. Firstly, stannane **203** was transformed either in alcohol **228** by removal of the pivaloyl group or in carboxylic acid **229** by oxidation of **228** (Scheme 31).^[87] Therefore, different cross-coupling attempts under Fürstner conditions^[86] could be tried between **227b** and **228** or **229**. However, all attempts drove to no coupling reaction. Given that this transformation was performed successfully by Ferrié&Figadère on similar cross-coupling partners, it is reasonable to think that the dithiane may poison both copper and palladium.^[88] Alternatively, from **227a**, dithiane was deprotected simultaneously with the TES group, giving **232**, and the carboxyl **229** was esterified at C₂₄ with an excellent yield. The goal was then to achieve a Stille cross-coupling reaction for macrolactonization on **234**; however, the reaction did not lead to macrolactone **234**. Considering this palladium-catalyzed cyclization^[89] is way more challenging than macrolactonization,^[11] the failure is not unexpected.

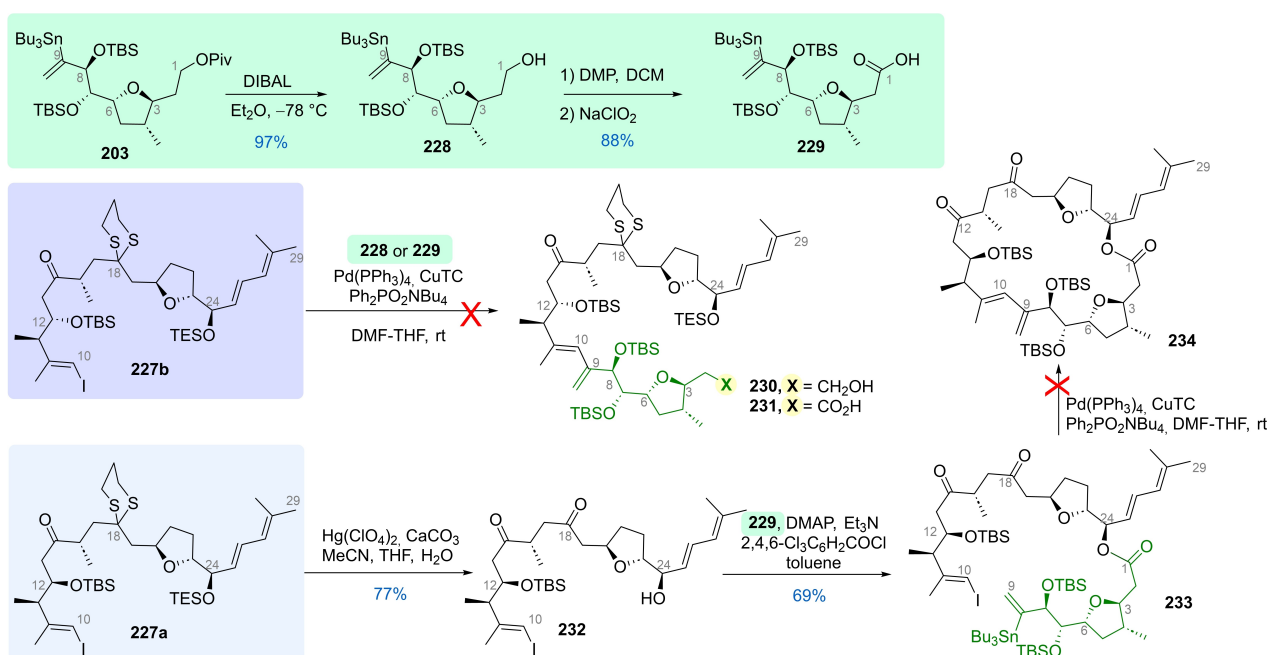
More optimization and/or different protecting groups would be necessary to complete the total synthesis. However, Stille cross-coupling involving **228** or **229** with **232** would have overcome the hypothetical dithiane poisoning and successfully led to AMP–F (**5**) backbone and macrolactone core.

3.8. White's Study

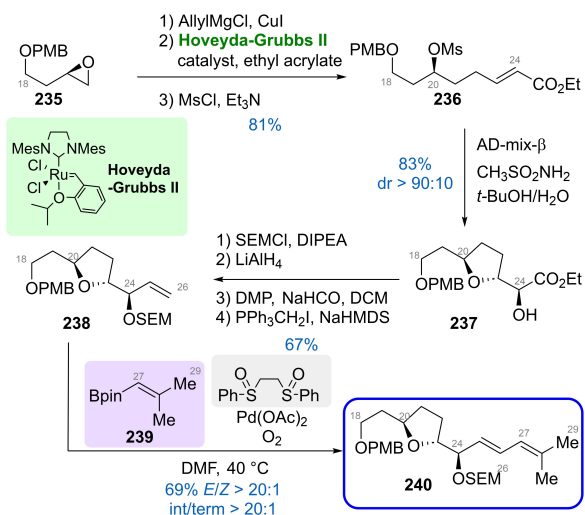
In 2013, White's group set out to illustrate their C–H activation/oxidative Heck coupling method by applying this methodology to the synthesis of the diene unit of AMP–F (**5**).^[90] Therefore, their goal was more to point out their technology's effectiveness in synthesizing functionalized molecules rather than reaching the total synthesis. Nevertheless, it shows how the technique can be a good tool for introducing a vinyl group in a late-stage synthesis.

The authors started their sequence with the opening and homologation of epoxide **235** to mesylate **236** in three steps *via* an olefin cross-metathesis reaction with Hoveyda-Grubbs II catalyst^[91] (Scheme 32).^[90] An asymmetric Sharpless dihydroxylation^[39] formed the 2,5-*trans*-THF **237** like Mohapatra's group^[38] (see Section 3.2.2, Scheme 12). This latter was functionalized in four steps to give terminal olefin **238**. Its treatment with boronate **239** in the presence of palladium (II) acetate and 1,2-bis(phenylsulfinyl)ethane ligand led to the coupling product **240** in a highly regioselective and stereoselective manner.^[90]

The C₁₈–C₂₉ fragment **240** was prepared in 12 steps from homoallyl alcohol with an overall yield of 13%, illustrating the potential of C–H activation in total synthesis.



Scheme 31. Clark's third approach: Synthesis of the C₁₀–C₂₉ segment of amphidinolide F (**5**).



Scheme 32. Synthesis of the C₁₈-C₂₉ fragment of amphidinolide F by White via a final oxidative Heck coupling as the key step.

3.9. Dai's Study

In 2018, the Dai group reported the synthesis of the C₁₈-C₂₆ fragment common to all congeners of AMPs-C (1) and -F (5) and, by extension, the C₁₃-C₂₁ fragment of AMP-U (6).^[92] The process leading to the formation of *trans*-THF is based on an asymmetric dihydroxylation reaction^[39] followed by a spontaneous S_N2-type cyclization, such as Mohapatra and White's previous reports (see Section 3.2.2 and 3.8).

To prepare this C₁₈-C₂₆ fragment, the Dai group tried several approaches. However, it was imperative to be selective for the configuration of the double bond at C₂₃-C₂₄ to control the stereochemistry after asymmetric dihydroxylation; thus, the most efficient study is presented below among the several approaches reported. The synthesis started from methyl acetoacetate **241**, which underwent an alkylation with *E*-1-chloroallylchloride (Scheme 33).^[92] This reaction was followed by a modified Noyori hydrogenation,^[93] which led to **242** with a high enantiomeric excess. Functional group modifications and Sonogashira cross-coupling reaction furnished enyne **243**. A Sharpless asymmetric dihydroxylation led directly to the

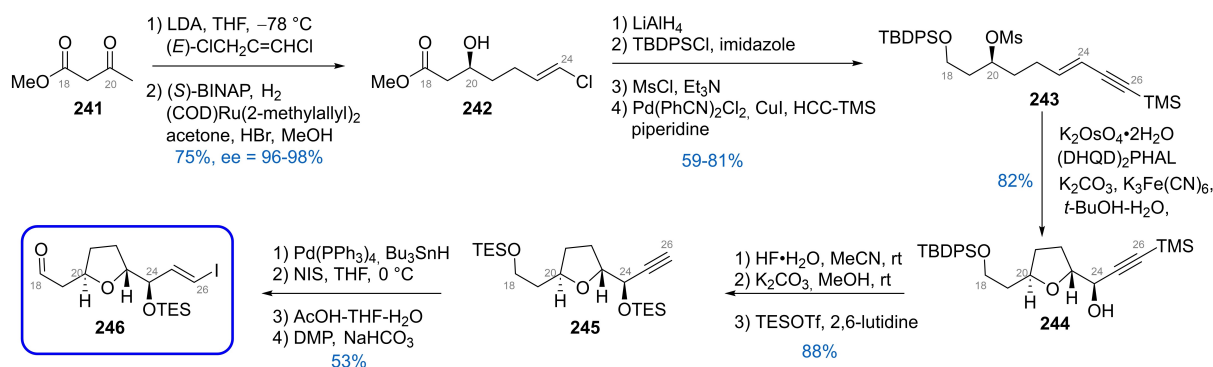
formation of **244**, and several other deprotection/protection steps gave **245**. Ultimately, **246** was obtained after the hydrostannylation/iodolysis sequence and oxidation of the C₁₈ hydroxy group in aldehyde. Therefore, this C₁₉-C₂₆ fragment was obtained from methyl acetoacetate in 14 steps with an overall yield of about 20% (Scheme 33).^[92]

3.10. Williams' Studies

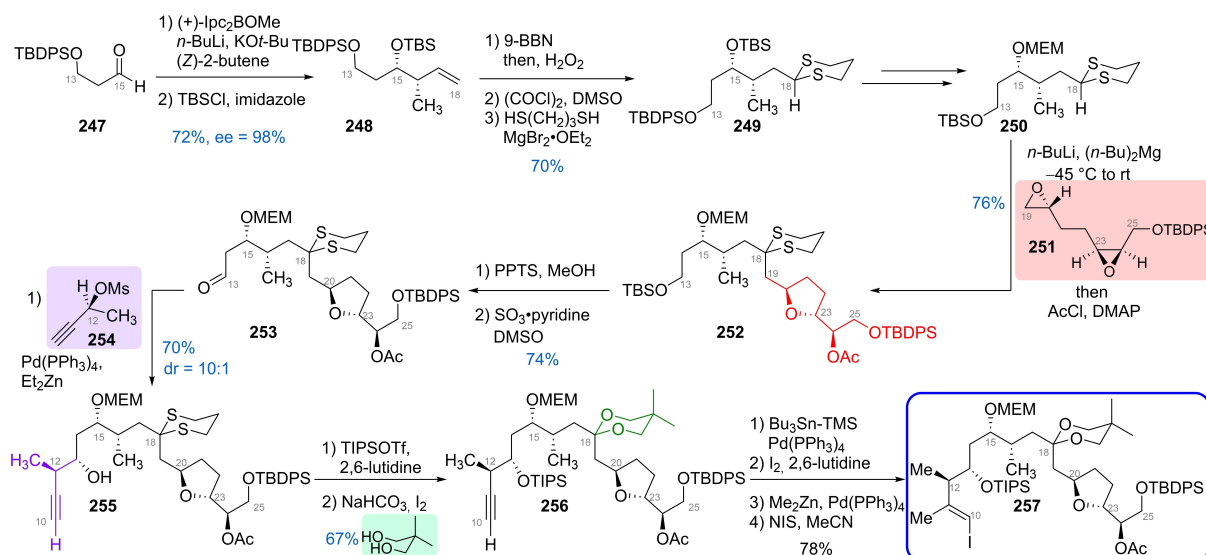
3.10.1. Williams' Synthesis of the C₁₀-C₂₅ Fragment Amphidinolides C (1) and F (5)

In 2020, the Williams group reported the synthesis of the C₁₀-C₂₅ segment of AMPs-C (1) and -F (5).^[94] The featured key step of the strategy involves a cascade ring opening of epoxides from a lithiated dithiane to yield the *trans*-THF moiety.

Therefore, the synthetic sequence started by the Brown crotylation^[95] of aldehyde **247** (prepared in two steps) with *Z*-crotylborane to yield after TBS protection **248** with *syn*-configuration (Scheme 34).^[94] Hydroboration, oxidation, and dithioacetal formation led to **249**, which was further converted into **250** after protecting group manipulations. Deprotonation of **250** required *n*-BuLi/*n*-Bu₂Mg premix, followed by the addition of diepoxide **251** and ultimately AcCl and DMAP. The so-obtained product **252** could furnish the *trans*-THF directly through a ring-opening cascade reaction. It is also noteworthy that diepoxide **251** was prepared via Sharpless asymmetric epoxidation^[77] followed by Salen-mediated Katsuki-Jacobsen epoxidation^[96,97] on the terminal olefin to yield about 80% enantiomeric purity. After two more steps, aldehyde **253** was obtained, and Marshall asymmetric allenylation^[98] with chiral building block **254** provided **255** in a 10:1 diastereomeric ratio; transketalization then afforded **256**. Final acetylene manipulation yielded vinyl iodide **257** over four steps, according to a modified approach introduced by Pattenden,^[99] since the direct Negishi carboalumination was ineffective.^[78,79] Therefore, Williams and coworkers obtained the C₁₀-C₂₅ fragment of AMP-C (1) in approximately eighteen steps and with less than 10% yield, considering some missing information about the synthesis of **250**.^[94] (Scheme 34)



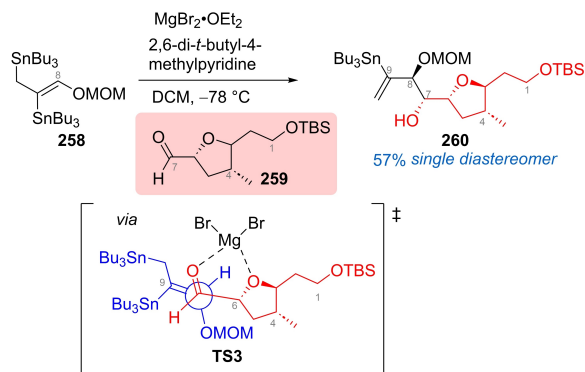
Scheme 33. Dai's synthesis of the C₁₈-C₂₆ fragment of amphidinolides F (5) and C (1).



Scheme 34. Williams' synthesis of the C₁₀-C₂₅ fragment of amphidinolides C and F, via an epoxide ring-opening cascade reaction as the key step.

3.10.2. Williams' Methodological Study Involving the C₁-C₉ Backbone of Amphidinolides-C (1) and F (5)

Although the synthesis of the C₁-C₉ fragment by the Williams group has never been mentioned in the literature, it seems that a methodological work involving the structure of the C₁-C₉ fragment of AMPs-C (1) and -F (5) was reported in 2005.^[100] For this reason, Williams' studies on AMP-C (1) or -F (5) have not been ranked favorably, chronologically speaking, in this review. This work highlights a method of stereo-controlled allylation of aldehydes using allyl-bis-stannane reagents. Therefore, **258** was added to aldehyde **259** through a chelation control addition with MgBr₂·OEt₂, as depicted in transition state **TS3** (Scheme 35).^[100] The highly selective reaction provided **260** in 57% yield as a single diastereomer. It should be noted that the description of the synthetic sequence used to obtain **259** is also missing, making it impossible to use elements of comparison with other syntheses of the same segment.



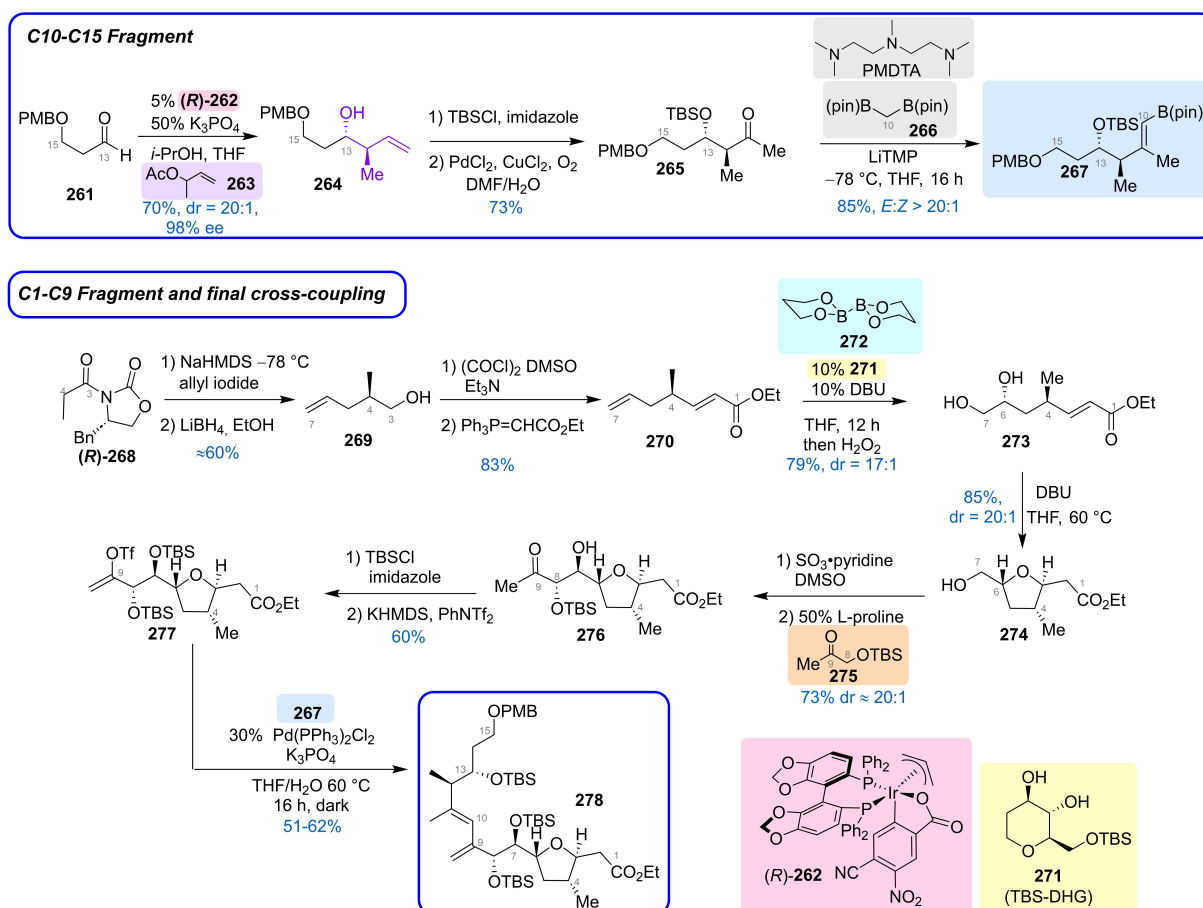
Scheme 35. Williams' synthetic study involving the C₁-C₉ structure of amphidinolides C and F backbone via a chelation control allylstannylation.

3.11. Morken's Study

In 2020, the Morken group reported a new approach toward synthesizing the C₁-C₁₅ fragment of AMP-C (1) or -F (5).^[101] The strategy is highlighted by employing modern versions of asymmetric crotylation or dihydroxylation. A focus is also undertaken on using boron in the synthesis, a specialty of the research group. Thus, this work is a good illustration of the power of methodologies developed in their team.

Thus, Morken's synthesis started by preparing the C₁₀-C₁₅ fragment, which consisted of the *anti*-crotylation of aldehyde **261** (Scheme 36).^[101] The Krische iridium-catalyzed asymmetric method furnished **264** with very high enantioselectivity and diastereoselectivity from crotyl acetate **263** and chiral iridium catalyst (*R*)-**262**.^[102,103] After protection and Wacker-Tsuji oxidation,^[104] methyl ketone **265** was obtained. The final use of a modified boron-Wittig reaction provided the vinyl boronate **267** with high *E* stereoselectivity.^[105,106] The C₁₀-C₁₅ fragment **267** was prepared in 7 steps from 1,3-propanediol with an overall yield of about 36%. (Scheme 36, top)

In parallel, the synthesis of the C₁-C₉ fragment started with the alcohol **269**, prepared from Evans-auxiliary (*R*)-**268**, according to Parrain & Commeiras' reported procedure.^[107] Wittig homologation yielded enoate **270**, and asymmetric dihydroxylation of the terminal olefin afforded diol **273** with high stereoselection (dr = 17:1). The reaction passes by the diboration of the alkene through the reaction with a chiral diboron ester, formed *in-situ* through the transesterification of **272** with glycol derivative TBS-DHG **271**.^[108] Then, according to Roush's procedure,^[31] **273** underwent an intramolecular cyclization in the presence of DBU at 60 °C (see Section 3.1.3). After oxidation of the primary alcohol at the C₇ position, the continuation of the work was strongly inspired by Fürstner total syntheses^[109,110] (see Section 4.2.1). Consequently, the L-proline organocatalyzed aldol reaction with methyl ketone **275** led to **276** with high stereocontrol.^[111,112] After TBS protection, the vinyl triflate was

Scheme 36. Morcken's synthesis of the C₁-C₁₅ fragment of amphidinolides C (1) and F (5).

prepared from Comins reagent to give the C₁-C₉ fragment **277** of AMPs-C (1) and -F (5). The C₁-C₉ fragment was prepared in ten steps from chiral auxiliary (*R*)-**268** in about 15% overall yield (Scheme 34, bottom).

The Suzuki-Miyaura cross-coupling reaction between the C₁-C₉ and C₁₀-C₁₅ segments **277** and **267** was then undertaken. Several investigations were driven to obtain coupling product **278**. The authors found that the nature of the base and absence of light was crucial to avoiding isomerization of the unsaturation at C₉ to shift to the C₈-C₉ bond. Moreover, the low base amount could negatively influence the cross-coupling by inducing a protodeboration of **267**. Thus, five equivalents of K₃PO₄ were needed to limit this side reaction (Scheme 36, bottom).

4. Total Synthesis of Amphidinolide C and F

4.1. Carter's Studies and Total Syntheses

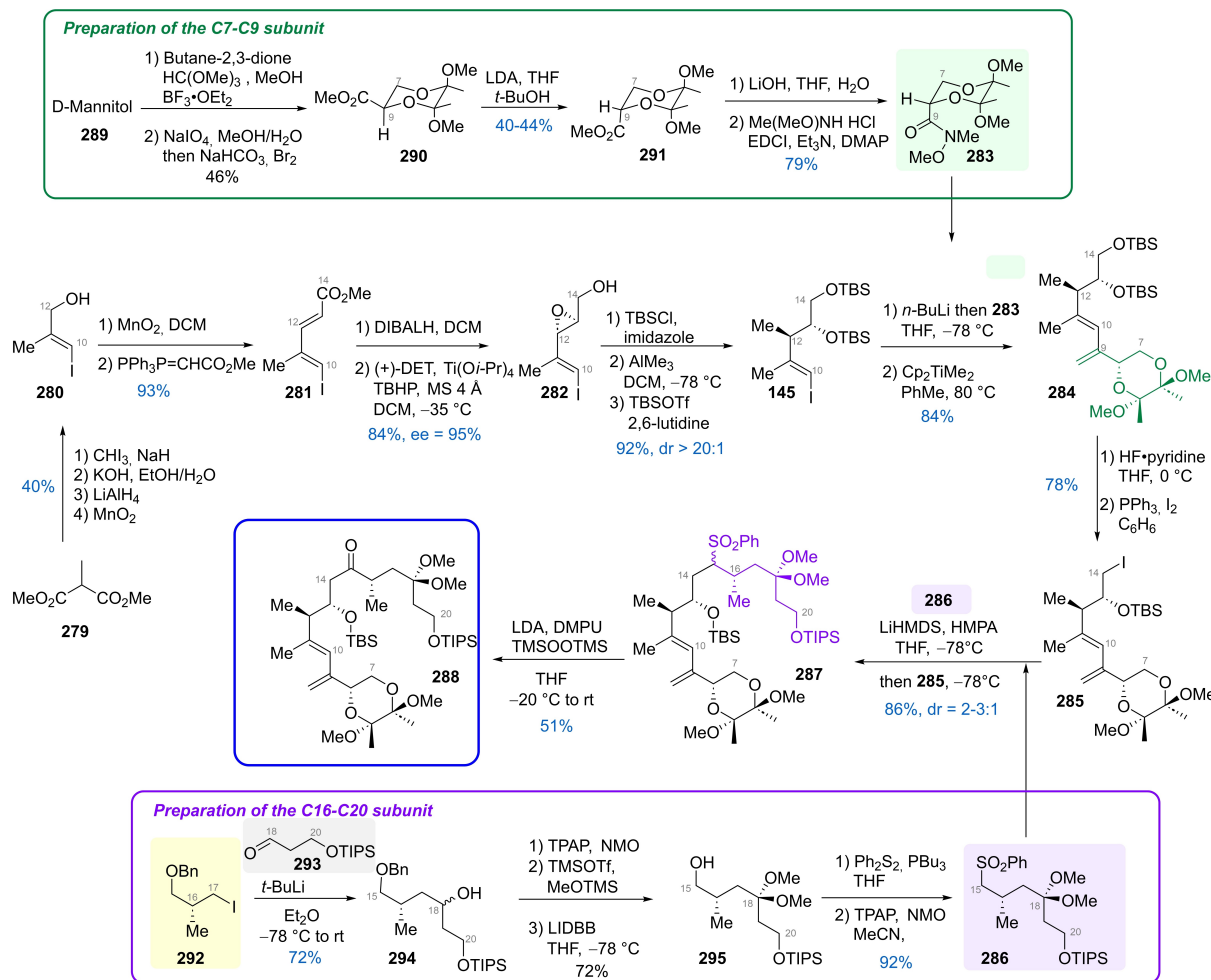
4.1.1. Carter's Preliminary Study toward the C₇-C₂₀ Fragment

Before achieving the total synthesis of AMPs-C (1) and -F (5), Carter's group published a preliminary study in 2009 focusing on forming the C₇-C₂₀ subunit of those natural products. The

fashion reactions involved a Me₃Al-mediated ring opening of an epoxide to install the C₁₂-C₁₃ *anti*-relationship and a sulfone alkylation/oxidative desulfonation sequence to link the C₇-C₁₄ to the C₁₅-C₂₀ fragment.^[62]

Thus, their synthesis started with preparing iodo-diene **281** in six steps from malonate **279** via a reported procedure^[113] (Scheme 37).^[62] Although the synthesis of building-block **280** required many steps, it allowed large-scale synthesis compared with the Negishi carboalumination pathway.^[78,79] Reduction of dienoate **281** and Sharpless asymmetric epoxidation gave rise to epoxide **282**. After TBS protection, the epoxide was selectively ring-opened with AlMe₃, furnishing selectively **145**. Halogen-metal exchange and addition to Weinreb amide **283**, followed by Petasis olefination,^[114] gave diene **284**. Selective cleavage of TBS ether and iodination of primary alcohol at C₁₄ led to **285**. Cross-coupling by alkylation with lithium anion of sulfone **286** yielded C₇-C₂₀ backbone **287**, and α -oxidation of the sulfone function by lithiation and peroxide trap finally drove to the final product **288**.

For this synthetic sequence, Weinreb amide **283** was prepared in 5 steps from D-mannitol according to a procedure set up by Ley's group.^[115] Diketals **290** and **291** are excellent and stable alternatives to glyceraldehyde acetonide, allowing access to both enantiomers from the natural configuration. For sulfone **286**, it was prepared in nine steps from (*R*)-Roche ester,



Scheme 37. Carter's preliminary study toward the C₇-C₂₀ backbone of amphidinolides C (1) and F (5).

which was converted in three steps into iodide **292**. Lithiation and addition to aldehyde **293** provided **294**, and this intermediate underwent different functional group modifications to yield **287**.

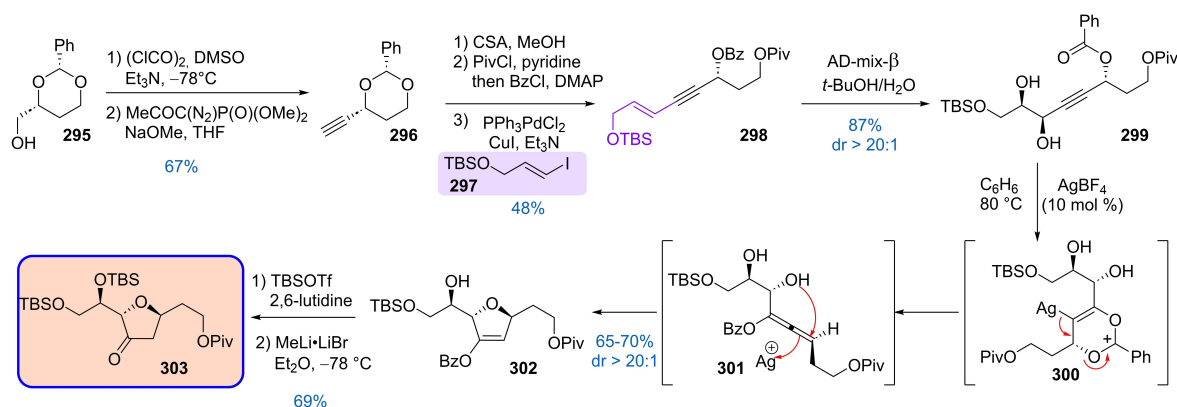
This model study demonstrated the feasibility of sulfone alkylation/oxidative desulfurization coupling for this highly functional backbone type. Finally, this study enabled access to the *exo*-diene unit relatively quickly. The C₇-C₂₀ segment of AMPs-C (1) or -F (5) was synthesized in 17 steps along the longest linear sequence and in about 8.2% yield (33 total steps). Thus, the following objectives were to achieve the total synthesis of AMP-F (5), followed by the C analog.

4.1.2. Uncovering of a Hidden symmetry: Carter's Synthesis of the Tetrahydrofuranly Common Intermediate

The continuation of their study toward the total synthesis of AMPs-C (1) and -F (5) was based on the observation of hidden symmetry in those natural products concerning the two THF rings. Indeed, the C₁-C₈ and C₁₈-C₂₃ segments are identical in structure and absolute configuration. The only difference

remains the methyl substituent at the C₄ position. As previously described (see Section 3.7.1), Clark's team reused the same strategy of a common intermediate in their first synthetic studies toward AMPs-C (1) and -F (5).^[70,71] The common THF ring intermediate is built on a metal-catalyzed propargyl ester rearrangement into dihydrofuranone.^[72,116]

Applying the key oxonium rearrangement required the preparation of benzoate **299** (Scheme 38).^[116] Thus, chiral building block **295** was prepared in two steps from malic acid with 84% yield,^[117] and then underwent a Seyferth-Gilbert homologation^[84] into alkyne **296**. The synthesis involved protecting group manipulations and a Sonogashira cross-coupling with vinyl iodide **297** to yield enyne **298**. Sharpless asymmetric dihydroxylation selectively reacted on the olefin and installed the desired stereochemistry. At this stage, the rearrangement of propargyl benzoate **299** took place under silver catalysis to yield furanone **302** with a good yield and a high diastereoselectivity.^[118] The rearrangement passed presumably through a first 6-endo-dig cyclization to give intermediate **300**, and β -elimination gave rise to allene **301**. A 5-endo-trig cyclization followed by a protodemetalation yielded dihydrofuran **302**. Protection of secondary alcohol as TBS ether and

Scheme 38. Synthesis of Carter's common tetrahydrofuran intermediate **303**.

cleavage of enol benzoate furnished the common intermediate **303**, which was thus prepared in 9 steps with about 11% overall yield from malic acid. (Scheme 38)

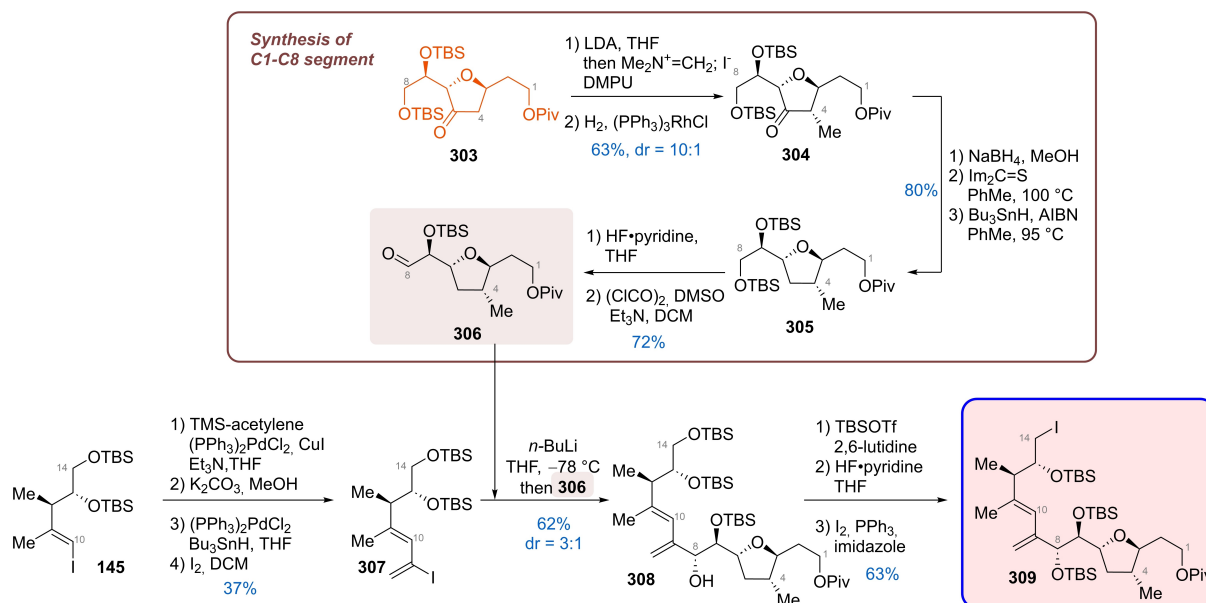
4.1.3. Carter's Synthesis of the C₁-C₁₄ Fragment of Amphidinolides C (1) and F (5)

The synthesis C₁-C₁₄ fragment of AMPs—C (1) and -F (5) was performed mainly by using the synthetic route designed in Carter's preliminary studies,^[62] (i.e., re-use of intermediate **145**, see scheme 35) with an update allowing the introduction of the THF ring *via* the common intermediate **303**.^[72,116]

The synthetic route began with introducing a methylene group in the α-position of ketone **303**, using the Eschenmoser salt. This reaction was followed by a hydrogenation with the Wilkinson catalyst, installing the C₄ center with good diastereoselectivity (dr = 10:1) (Scheme 39).^[116] Direct alkylation with

methyl iodide provided the undesired diastereoisomer. A Barton-McCombie deoxygenation^[119] provided THF **305**, and selective deprotection of the primary TBS ether followed by a Swern oxidation led to aldehyde **306**.

In parallel, vinyl iodide **145** was homologated to **307** by a Sonogashira cross-coupling, followed by a selective hydrostannylation/iodolysis sequence. Lithiation of **307** followed by its addition onto **306** yielded **308** with a modest Felkin-Anh type diastereoselectivity toward *anti*-product **308**. Thus, the synthesis of the C₁-C₁₄ fragment ended by functionalizing the primary ether function into iodide **309**. The C₁-C₁₄ fragment was synthesized in 18 steps with a 4.2% overall yield from malonate **279**.

Scheme 39. Carter's synthesis of the C₁-C₁₄ fragment of amphidinolides C (1) and F (5).

4.1.4. Carter's Synthesis of the C₁₅-C₂₉ Fragment of Amphidinolide F (5)

The strategy for the C₁₅-C₂₉ fragment of AMP-F (5) relied on preparing the sulfone function at C₁₅ and introducing the THF moiety from the common precursor **303**. The side chain synthesis was also studied, involving a modified Wittig olefination to build the diene.^[72,116]

Thus, the ketone function in common intermediate **303** was directly deoxygenated, leading to THF **310**, in contrast to the previous sequence in Scheme 39 (Scheme 40).^[116] The pivalic ester at the C₁₈ position was cleaved, and the remaining hydroxy group was oxidized in aldehyde to react with an organolithium derived from iodide **292**. Alcohol **311** was isolated as an inseparable mixture of two diastereomers. Nevertheless, an oxidation/reduction sequence involving L-selectride as a bulky reducing reagent could finally provide **311** with a high level of stereocontrol (from dr = 1.5:1, dr = 15:1 was obtained). After several investigations, the protection of the C₁₈ alcohol as an ethoxyethyl acetal proved to be the most suited for a selective deprotection, although it creates a mixture of diastereomers inherent to this class of protecting group. Therefore, it considerably complexified the characterizations of the following compounds holding it. It was followed by introducing a sulfone function at C₁₈ to yield **312**. Selective functionalization of the hydroxy group at C₂₅ allowed the formation of aldehyde **313** via a deprotection/oxidation sequence. Modified Wittig olefination^[120,121] with the ylide of phosphonium salt **314** allowed the introduction of the dienic chain with a high (*E*)-selectivity. Finally, a protecting group exchange from TBS to TES at C₂₄ completed the sequence, giving **316**. Thus, the C₁₅-C₂₉ fragment was obtained in 17 steps with a 23% overall yield from common intermediate **303**, which increases the number of steps to 28 and decreases the yield to 2.1%, considering the synthesis of the common intermediate **303**.

4.1.5. Carter's Total Synthesis of Amphidinolide F (5)

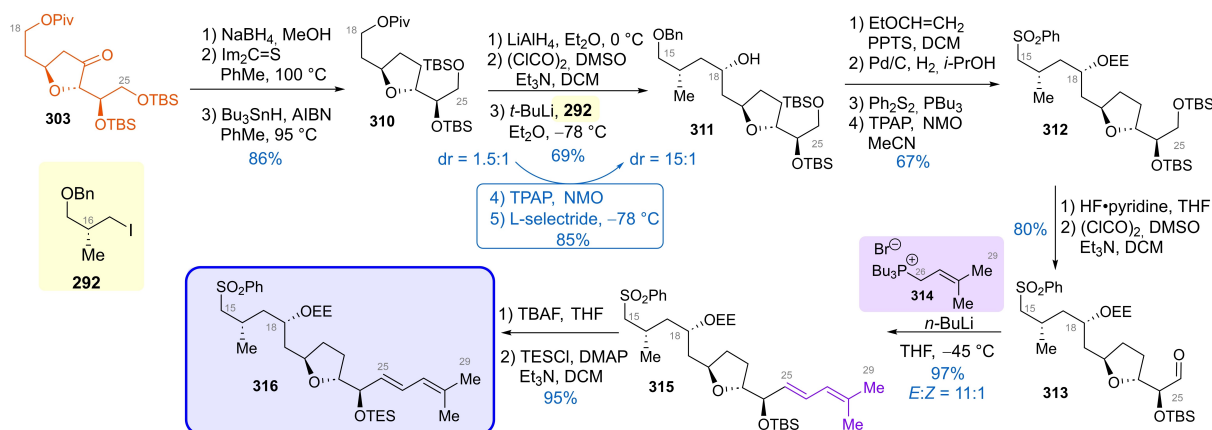
The total synthesis of AMP-F (5) consisted of the union of the two fragments C₁-C₁₄ and C₁₅-C₂₉ via an alkylation followed by an oxidative desulfonation, as studied in their preliminary report,^[62] followed by a macrolactonization to obtain the 23-membered ring. Final stage functional group manipulations and selective deprotections were crucial for the total synthesis.^[72,116]

Therefore, sulfone **316** was alkylated with iodide **309**, leading to the adduct **317** as a mixture of diastereomers (Scheme 41).^[116] Oxidative desulfurization was then performed by alkylation type reaction with Davis oxaziridine **318** as the oxygen source,^[122] TMS peroxide being unreactive on this substrate, unlike in the preliminary study (see Section 4.1.1).^[62] During the oxidation into **319**, a partial cleavage of the pivalate ester was noticed, but the product was easily recycled by skipping the deprotection step. Pivalate ester was then completely removed by reduction with LiAlH₄, and the hydroxy function was converted into carboxylic acid **320** via Swern oxidation and Lindgren-Pinnick oxidation.^[123,124] Selective acid-catalyzed hydrolysis of TES ether and Yamaguchi macrolactonization^[125] yielded macrolide **322**. The final steps consisted of the selective hydrolysis of the OEE ketal function at the C₁₈ position, its oxidation, and the smooth cleavage of the TBS-protecting groups with Et₃N·HF. Therefore, this work described the first total synthesis of AMP-F (5).

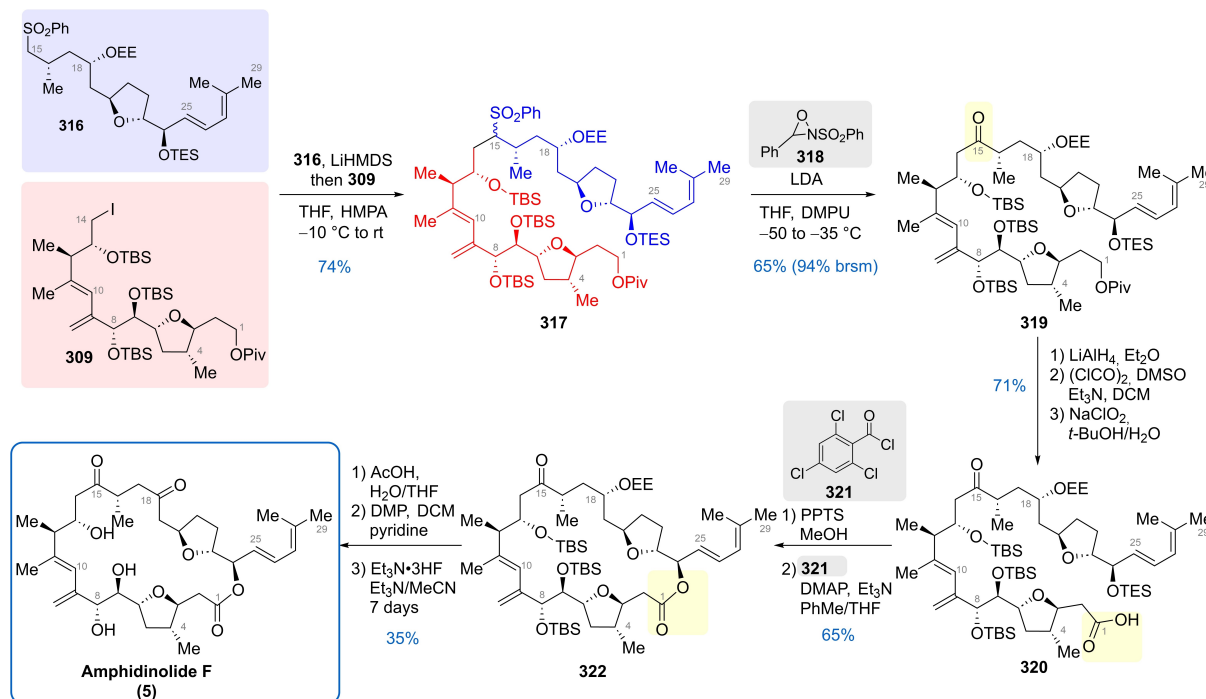
Rigorous inspection of ¹H, ¹³C NMR data validated the structure and the relative and absolute configuration proposed by Kobayashi. It also confirmed that the initial proposed AMP-C's absolute configuration was identical to that of AMP-F (5). The total synthesis was achieved in 36 steps along the longest linear sequence with about 2% overall yield (67 total steps).

4.1.6. Carter's Total Synthesis of Amphidinolide C

After achieving the total synthesis of AMP-F (5), Carter's group tackled the total synthesis of AMP-C (1). The planned strategy was identical to that described for AMP-F (5). However, some



Scheme 40. Carter's synthesis of the C₁₅-C₂₉ fragment of amphidinolide C (5).



Scheme 41. Final cross-coupling and Carter's total synthesis of amphidinolide F (5).

modification would be needed to attach the right-side chain corresponding to AMP-C (1).^[72]

Therefore, intermediate **312** was re-used to synthesize AMP-C (1) and was transformed into aldehyde **323** after switching the TBS at C₂₄ by a TES-protecting group and oxidizing the terminal position (Scheme 42).^[72] In parallel, the synthesis of the side chain was investigated. It relied on an asymmetric addition of the alkynyl zinc derived from methyl propiolate in the presence of Trost ligand **115**.^[54] This method was also applied previously and with success by Pagenkopf during the construction of the side chain (see Section 3.5.1).^[50] The conjugate addition of methyl magnesium bromide in the presence of copper(I) iodide to the protected propiolate generated the trisubstituted (*E*)-double bond and a reduction of the ester led to the allylic alcohol **325**. Finally, bromination under Appel conditions and a displacement of the allylic bromide by tributylphosphine gave the phosphonium salt **326**. The Vedejs-Tamura olefination^[120,121] between the phosphonium ylide from **326** and aldehyde **323** afforded triene **327** with good (*E*)-selectivity. Noteworthy is that the deprotonation of phosphonium salt could induce a conjugated elimination; processing the reaction at a lower temperature than $-60\text{ }^{\circ}\text{C}$ with phosphonium **314** was crucial to avoid degradation reactions. The C₁₅-C₃₄ segment was thus reached in 27 steps and 2.9% overall yield.

The following reaction sequence was identical to the one used for the total synthesis of AMP-F (5) (see Scheme 42). It consisted of the coupling with iodide **309** and oxidative desulfonation, which afforded **328**; functional group modification and macrolatonization to obtain **329**; selective manipu-

lation at C₁₈ to install the ketone function; and final silyl deprotection to yield a synthetic sample of AMP-C (1).

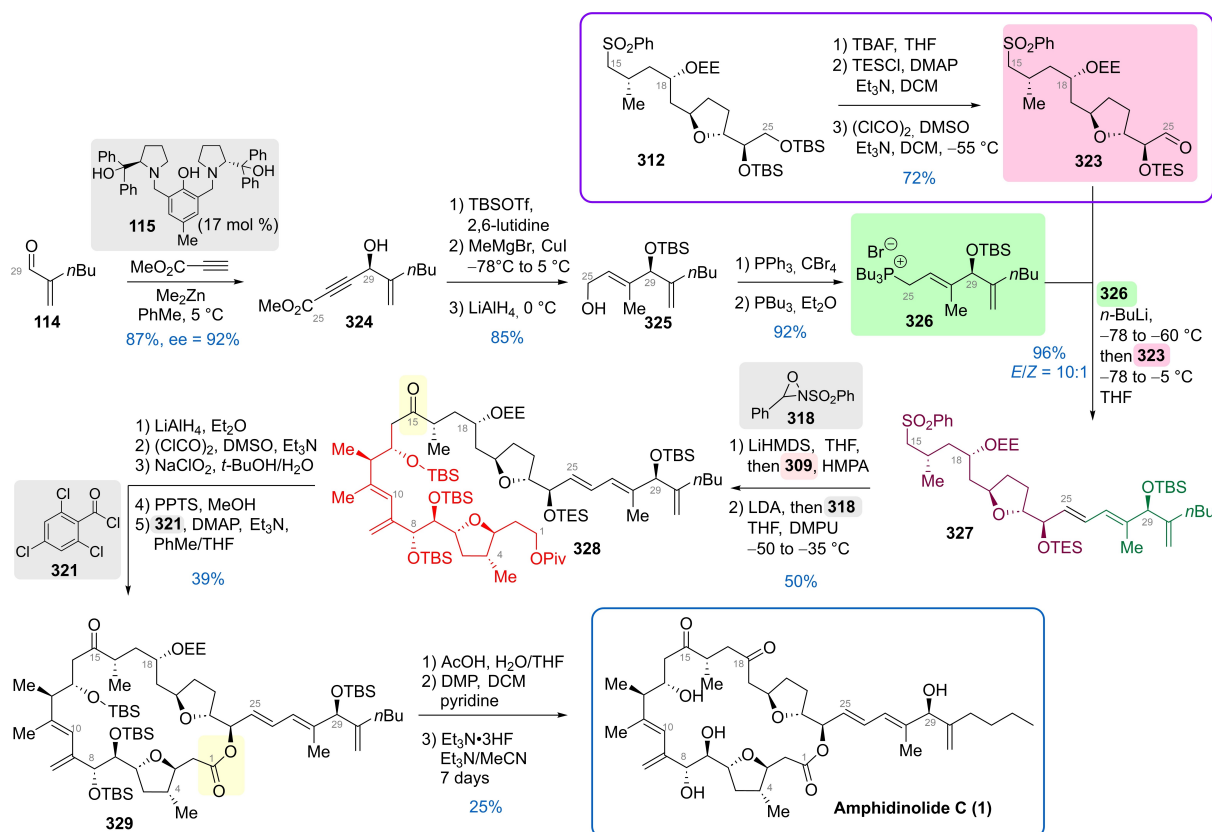
Thus, Carter's group achieved the first total synthesis of amphidinolide C, in 35 steps along the longest linear sequence with about 1.4% overall yield (72 total steps) following the same approach used to obtain AMP-F (5).^[72]

4.2. Fürstner's Total Syntheses

4.2.1. Fürstner's Total Synthesis of Amphidinolide F (5)

In 2013, Fürstner's group published the second total synthesis of AMP-F (5).^[109] The key sequence of their strategy was using a ring-closing alkyne metathesis (RCAM),^[126] followed by directed hydration of the alkyne function to build the 1,4-diketone unit at C₁₅ and C₁₈ positions. Their strategy is also highlighted by cross-coupling three main fragments, making their synthesis very efficient. Among the reported total syntheses of AMPs-C (1) or-F (5), their work is undoubtedly the most remarkable and efficient in terms of design.

The first target was the C₁-C₉ fragment, which was synthesized using a strategy similar to Roush's^[31] (see Section 3.1.3, Scheme 10), notably by building the 2,5-*trans* THF by an Oxo-Michael reaction. However, some improvements shortened the number of steps. Thus, butanolide **330** (available in 3 steps from D-glutamic acid) was methylated but furnished the wrong diastereoisomer, forcing a kinetic epimerization to **331**, with a 6:1 ratio according to the literature.^[127] Wittig homologation afforded **332** and TBAF-mediated oxo-Michael cyclization, followed by oxidation of position C₇, led to known



Scheme 42. Carter's first total synthesis of amphidinolide C (1).

aldehyde **58**. Subsequently, L-proline organocatalyzed aldol reaction with ketone **275** followed by protection as -TBS delivered the methyl ketone **276**. Although no comment was also given concerning the diastereoselectivity of **276**, subsequent Morcken's work on the same substrate^[101] (see Section 3.11), reported a 20:1 ratio. Activation of the methyl ketone as a vinyl triflate, palladium catalyzed stannylation, and saponification yielded **333**. The C₁-C₉ fragment **333** was synthesized in 15 steps from D-glutamic acid, with a 12.4% overall yield. (Scheme 43, top route)

On the other hand, the synthesis of the C₁₈-C₂₉ fragment was studied, consisting of applying Pagenkopf's oxidative cyclization (see Section 3.5.1).^[50,53] Thus, chiral epoxide **334**, accessible by HKR reaction,^[52] was ring opened with propynyl lithium to give **335**. This compound underwent oxidative cyclization, and the primary position at C₂₄ was oxidized to furnish aldehyde **337**. In parallel, the synthesis of the side chain was accomplished. It consisted of preparing bromide **338** using a homologation through sulfone chemistry and was developed originally by Julia.^[128] The asymmetric addition of divinyl zinc derivative of **338**, using (-)-N-methyl ephedrine as a chiral ligand, allowed an excellent stereocontrol of the addition to fragment **340**. The synthesis of the C₁₈-C₂₉ fragment was accomplished in 5 steps from *rac*-**334** with about 20% overall yield. (Scheme 43, bottom route).

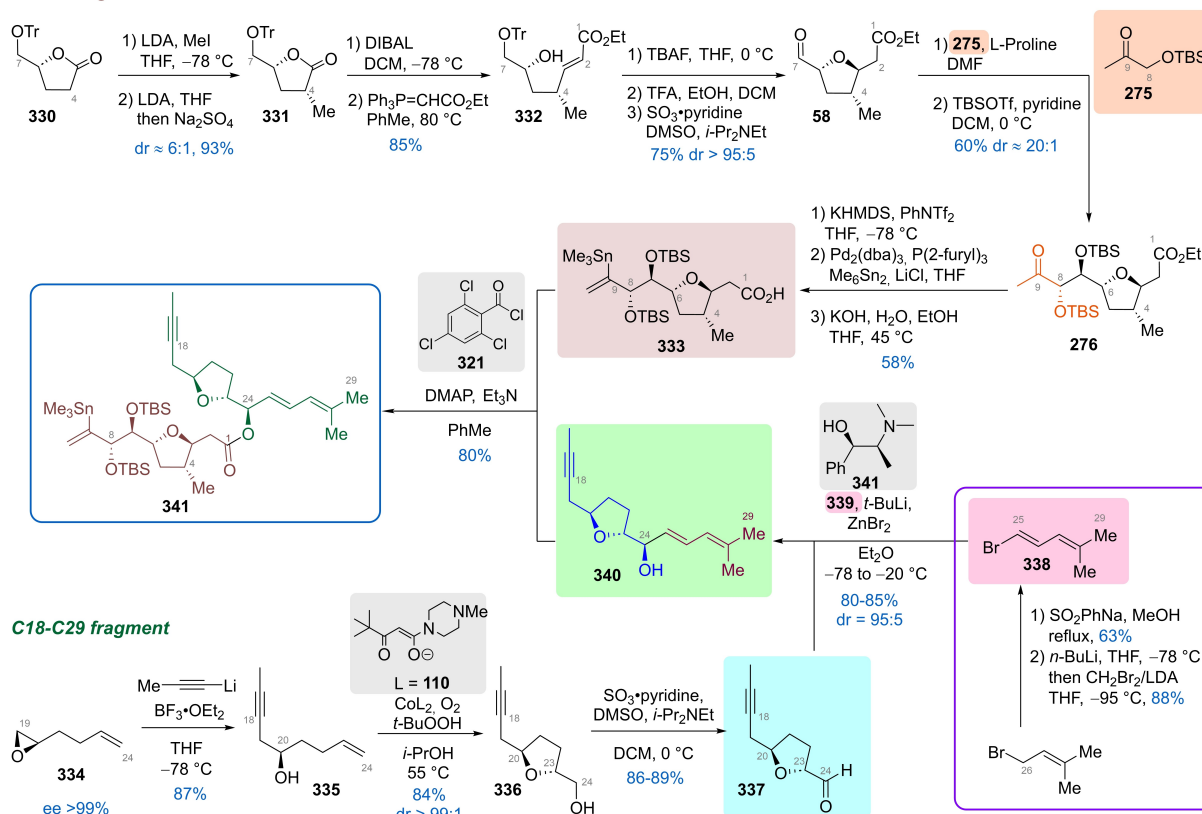
The C₁-C₉ fragment **333** was coupled to the C₁₈-C₂₉ segment **340** by esterification. The conditions used Yamaguchi reagent **321** and afforded **341** with an 80% yield. (Scheme 43)

The last fragment to synthesize corresponds to the C₁₀-C₁₇ backbone of AMPs-F (**5**) and C (**1**). This section presents a hidden symmetry, which allows the repetition of the same synthetic sequence from each side and introduces subtle variations to differentiate functions. Installing stereogenic centers at C₁₅-C₁₆ and C₁₁-C₁₂ relied on two iterative Marshall asymmetric propargylations.^[98]

Thus, its synthesis started from aldehyde **342** (available in two steps from propanediol), which underwent a first Et₂Zn-mediated propargylation reaction with chiral mesylate **343** under palladium catalysis^[98,129] (Scheme 44).^[109] Subsequently, functional group manipulation allowed the oxidation of the hydroxy group at the C₁₃ position and protection of the one at C₁₅ as the TES group, leading to **345**. A second asymmetric propargylation was then achieved with mesylate **254**, which used this time indium mediation,^[130] leading to **346**. Silylcupration followed by trapping with MeI modified the free alkyne selectively, as required. Finally, **347** was transformed into vinyl iodide **348** via iodolysis of the vinylsilane at C₁₀. The C₁₀-C₁₇ fragment **348** was thus synthesized in 13 steps from 1,3-propanediol with about 19.5% overall yield.

Iodide **348** was then coupled with adduct **341** under palladium catalysis. The modified Stille conditions allowed a first transmetalation between copper and tin to facilitate the

C1-C9 fragment

Scheme 43. Fürstner's syntheses of the C₁-C₉ and C₁₈-C₂₉ fragments of amphidinolide F (5).

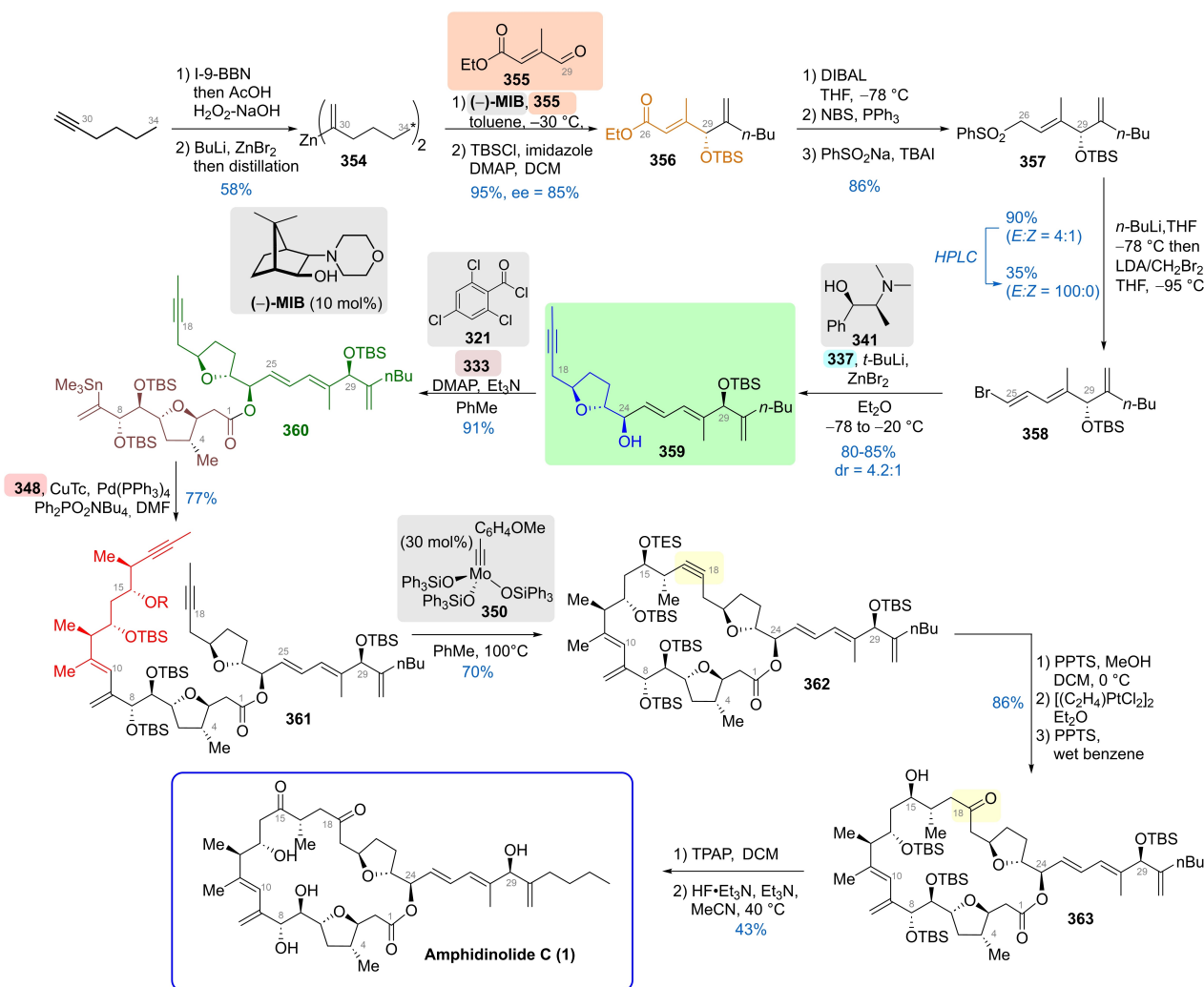
second with palladium.^[86] This transformation was followed by the scavenging of tributyltin from the reaction process by the diphenylphosphinate additive.^[131] Thus, **349** was obtained in decent yield after selective TES ether cleavage. The macrocyclization critical step was achieved in the presence of molybdenum complex **350**,^[132] which catalyzed the alkyne metathesis,^[126,133] furnishing macrocycle **351**. Steric hindrance was crucial with catalyst **350** and required the prior deprotection of the hydroxy group at C₁₅. Subsequently, The platinum-catalyzed 5-endo-dig cyclization took place smoothly with [(C₂H₄)PtCl₂]₂, yielding dihydrofuran **352**. The hydration of the furan ring was performed with PPTS catalysis and furnished **356** as a complex mixture of isomers and conformers, which were hard to characterize by NMR. Indeed, TBS protecting groups induce slow conformational rotations on the macro-lactones, and the hydration of the dihydrofuran led to a mixture of cyclic and acyclic products, which are all in equilibrium. Oxidation of the position at C₁₅ with TPAP and final deprotection produced synthetic AMP-F (5). (Scheme 44)

As in Carter's work, the characterization data of Fürstner's synthetic sample matched with the natural substance. Amphidinolide F (5) was obtained in 23 steps along the longest linear sequence from D-glutamic acid, with about 1.5% overall yield (47 total steps). Moreover, because of the efficiency of his synthesis, Fürstner was able to yield a high amount of synthetic amphidinolide -F (5), *i. e.*, 50 mg.

4.2.2. Fürstner's Total Synthesis of Amphidinolide C

In 2015, Fürstner et al. published the second total synthesis of AMP-C (1).^[110] The strategy is similar to that used for AMP-F (5), but involves the prior preparation of the side chain and control of the stereogenic center at the C₂₉ position *via* an organozinc asymmetric addition to an aldehyde.

Therefore, the synthesis of the C₂₄-C₃₄ segment started from 1-hexyne and consisted first in preparing the divinyl zinc reagent **354**, *via* iodoboration/protodeboration sequence (Scheme 45).^[110] The resulting vinyl iodide underwent a halogen-metal exchange with *n*-BuLi, and distillation afforded pure **354**. Indeed, the absence of lithium-ion was crucial to the next step involving an asymmetric addition to aldehyde **355**.^[134,135] Using (–)-MIB as a ligand in the reaction between **354** and **355**, followed by the alcohol protection as TBS ether provided the adduct **356** with moderate 85% ee. DIBAL reduced the ester function, and the resulting alcohol was converted to sulfone **357**. Julia homologation^[128] in the conditions set up previously by the authors (see Section 4.2.1) led to vinyl bromide **358**. The isomeric purity was unsatisfactory with this method (*E*:*Z* = 4:1), and preparative HPLC improved the *E* purity to 100%, albeit with a material loss. A new organozinc addition was used *via* zinc-transmetalation of **358**, and its addition on aldehyde **337** under the same conditions used previously for the side chain of AMP-F (5) led to a 4.2:1 ratio towards the desired product **359**.



Scheme 45. Synthesis of the side chain and Fürstner total synthesis of amphidinolide C (1).

methyl-2(5H)-furanone in one step^[143] was diastereoselectively coupled to chiral aldehyde **364** through a vinylogous Mukaiyama aldol reaction^[144,145] (Scheme 46).^[59] Only Felkin-Anh adducts were obtained, but the orientation of the furan was harder to control at position C₆, resulting in the obtention of a 3:1 mixture of separable isomers **366 a** and **366 b**. Selective catalytic hydrogenation, such as in Roush's studies^[31] (see Section 3.1.2), followed by protection of all hydroxy groups with TBS ethers, gave **367**. Activation of the lactone as a lactol acetate was performed, and the diastereoselective alkylation toward *trans* THFs was achieved using the titanium enolate of *N*-acetyloxazolidone **368**.^[140] Methyl ester **369** was thus obtained as a single isomer after methanolysis. Subsequently, the primary alcohol function at C₉ was selectively deprotected with HF-pyridine and, after oxidation, underwent a Seyferth-Gilbert homologation with Bestman-Ohira reagent,^[84] furnishing **370**. Finally, regioselective hydrostannylation of the alkyne in the presence of Mo(CO)₃(N₂Ct-Bu)₃,^[58] provided **371** and **371'** as a mixture of separable regioisomers (**371**:**371'** = 82:18).^[59] The saponification to **229** was finally accomplished later with TMSOK.^[137] Therefore, the C₁-C₉ segment **229** was built in 11

steps from commercial 3-methyl-2(5H)-furanone with an 8.2% overall yield.

4.3.2. Ferrié & Figadère's Synthetic Studies toward the Side Chain of Amphidinolides C (1) and F (5) (C₂₀-C_{34/29} Segment)

After their first work on AMPs—C (1) and -F (5), the Ferrié & Figadère group reported in 2015 a synthetic study toward the C₂₀-C_{29/34} of those natural products, focusing on the synthesis of the side chain and its incorporation into the THF moiety.^[136] Their work emphasized the use of the Liebeskind-Srogl cross-coupling reaction to attach the side chain to a thioester residue and a Lewis base-mediated Hiyama reduction, which established the stereochemistry at C₂₄.^[146] The C₂₉ stereogenic center was installed by reductive elimination of a chiral epoxide.

The study started from thioesters **372 a–b** as hinge compounds (Scheme 47).^[136] On the one hand, a Liebeskind-Srogl cross-coupling reaction was accomplished with boronate **373** and copper(I) thiophenecarboxylate^[147] (CuTC) to yield **374** with an acceptable yield. A screening of reduction conditions

4.3.3. Ferrié & Figadère's Total Synthesis of Amphidinolide F

After two synthetic studies, the Ferrié & Figadère group reported the third total synthesis of AMP-F (5).^[137] The goal was to use the successful synthetic sequences developed in the two previous synthetic studies,^[59,136] but with some modifications to reach their objectives. Indeed, early disconnection at the C₁₉-C₂₀ bond proved unsuccessful; consequently, the cross-coupling was shifted to the C₁₇-C₁₈ bond. Thus, it enabled reusing the selective C-glycosylation reaction involving titanium enolate of *N*-acetyl-oxazolidinethiones,^[139,140] building the northern *trans*-THF. The C₁₀-C₁₇ segment was constructed *via* iterative ring opening of epoxides.

Like in Fürstner's studies, the hidden symmetry of the C₁₀-C₁₇ segment was capitalized by using successive ring openings of epoxides (Scheme 48).^[137] Thus, butynol **385** underwent a selective reduction to *Z*-olefin, a Sharpless asymmetric epoxidation, and a tosylation. A regioselective ring-opening of the less hindered side of epoxide **386** was achieved with AlMe₃-Li trimethylsilylacetylide ate complex, and BF₃-OEt₂^[151] furnished the desired addition product. Subsequent displacement of the tosylate yielded epoxide **387**. A second ring opening was achieved with *Z*-propenylmagnesium bromide, followed by a diastereoselective vanadium-catalyzed directed epoxidation.^[152] The protection of the alcohol as a TBS ether led to compound **388**. The acetylene was deprotected, and the third epoxide was opened with lithiated PhSO₂Me to give **389** and **389'** with about a 2:1 ratio. The process was high-yielding, albeit with moderate regioselectivity, but both isomers were easily separable. The alcohol in C₁₅ for **389** was protected orthogonally with TES protecting group, and highly regioselective trimethylsilylstannylation of the alkyne^[153] was accomplished to afford **390**. Iodolysis of the stannane was followed by substituting iodine with dimethyl cuprate, and iodolysis of the TMS group finally furnished the C₁₀-C₁₇ fragment **391**.^[99] The synthesis of **391** was achieved in 15 steps from **385** with a 10.9% overall yield (Scheme 48, top).

The synthetic approach used for the C₁₈-C₂₉ segment was inspired mainly by the previous synthetic studies^[136] (See Section 4.3.2). Thus, the synthesis started from lactone **392**, available in three steps from D-glutamic acid. Lactone **392** was transformed into lactol acetate by a one-pot reduction-acetylation sequence, and a diastereoselective C-glycosylation reaction involving titanium enolate of **393**^[139] was performed, which led to the formation of *trans*-THF **394** with a high diastereoselectivity after methanolysis of the auxiliary. A four-step sequence was achieved to transform the silyloxy group into thioester **395**. (Scheme 48, middle)

At this step, a Liebeskind-Srogl cross-coupling between **395** and stannane **396** was accomplished, leading to **398** with a 70% yield. The coupling with boronic acid **373** in the presence of CuTC gave non-reproducible results (15–61% yield) due to its instability; thus, those conditions were not selected. Stannane **396** was prepared in three steps from propargyl alcohol *via* hydrostannylation and Julia-Kocienski olefination with sulfone **397**. Selective reduction of the ketone under Luche conditions, such as in Clark studies (see Section 3.7.1), led to the syn-

product. After protecting the hydroxy group at C₂₄ with TMS, a controlled reduction of the ester function into aldehyde with DIBAL furnished the C₁₈-C₂₉ segment **399**. It was thus prepared in 14 steps from D-glutamic acid with about 19.8% overall yield. (Scheme 48, middle)

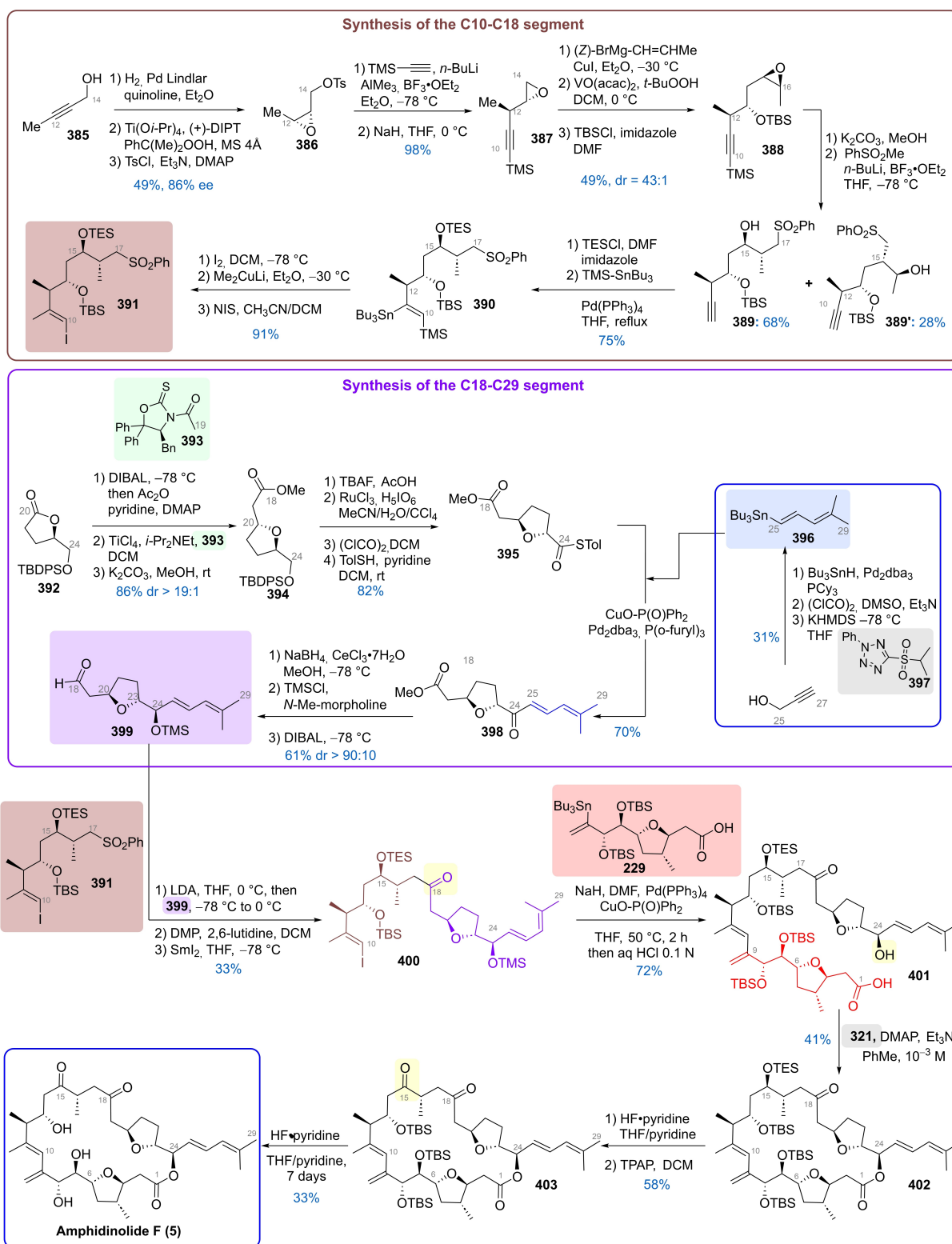
The main fragments being in hands, the end of the game consisted of their couplings, the macrolactonization and the functionalization into AMP-F (5). Therefore, sulfone **391** was lithiated with LDA and added to aldehyde **399**. The newly formed alcohol was oxidized into the corresponding ketone, and the sulfone was removed by reduction with Sml₂, giving rise to compound **400**. The C₁-C₉ segment was incorporated into vinyl iodide residue by modified Stille cross-coupling, inspired by the conditions set up by Fürstner.^[86] Treatment with dilute HCl at the end of the coupling allowed the selective removal of the TMS-protecting group, giving **401**. Macrolactonization using Yamaguchi reagent **321**^[125] led to the macrolide **402**. Selective deprotection of the TES group with HF-pyridine and oxidation with the conditions set up by Fürstner^[109,110] (see Section 4.2) at the C₁₅ position gave rise to **403**. Ultimately, exposure to HF-pyridine over one week furnished a synthetic sample of AMP-F (5). Spectral data agreed to those reported for other total syntheses and the natural product. AMP-F (5) was synthesized in 23 steps along the longest linear sequence with about 2.0% overall yield (53 total steps).^[137] (Scheme 48, bottom)

4.3.4. Ferrié & Figadère's Total Synthesis of Amphidinolide C2 (2)

After completion of the total synthesis of AMP-F (5), Ferrié & Figadère's group was interested in exploring the total synthesis of AMP-C (1), -C2 (2), and -C3 (3) since the analogs were not attained in total synthesis.^[138] The goal was thus to set up a divergent strategy allowing access to all members at the end of the synthesis. Unfortunately, due to the chemical transformations suffering low yield at the end of the total synthesis, only access to AMP-C2 (2) could be attained. The work reuses the synthetic study of the side chain (see Section 4.3.2).^[136]

The synthesis of AMPs-C (1), -C2 (2), and -C3 (3) needed a modification of the side chain compared to the report on the total synthesis of AMP-F (5).^[137] Accordingly, stannane **375** was coupled with thioester **395** (Scheme 49).^[138] Dienone **404** was then converted into aldehyde **405** using the same condition described in the previous study.^[137] The most notable difference relied on the protection of position C₂₉ with a TES group, which would allow an orthogonal cleavage at this position, compared with Fürstner's^[110] and Carter's works.^[72] The C₁₈-C₃₄ fragment **405** was synthesized from D-glutamic acid in 15 steps with a 13.6% overall yield. (Scheme 49, top)

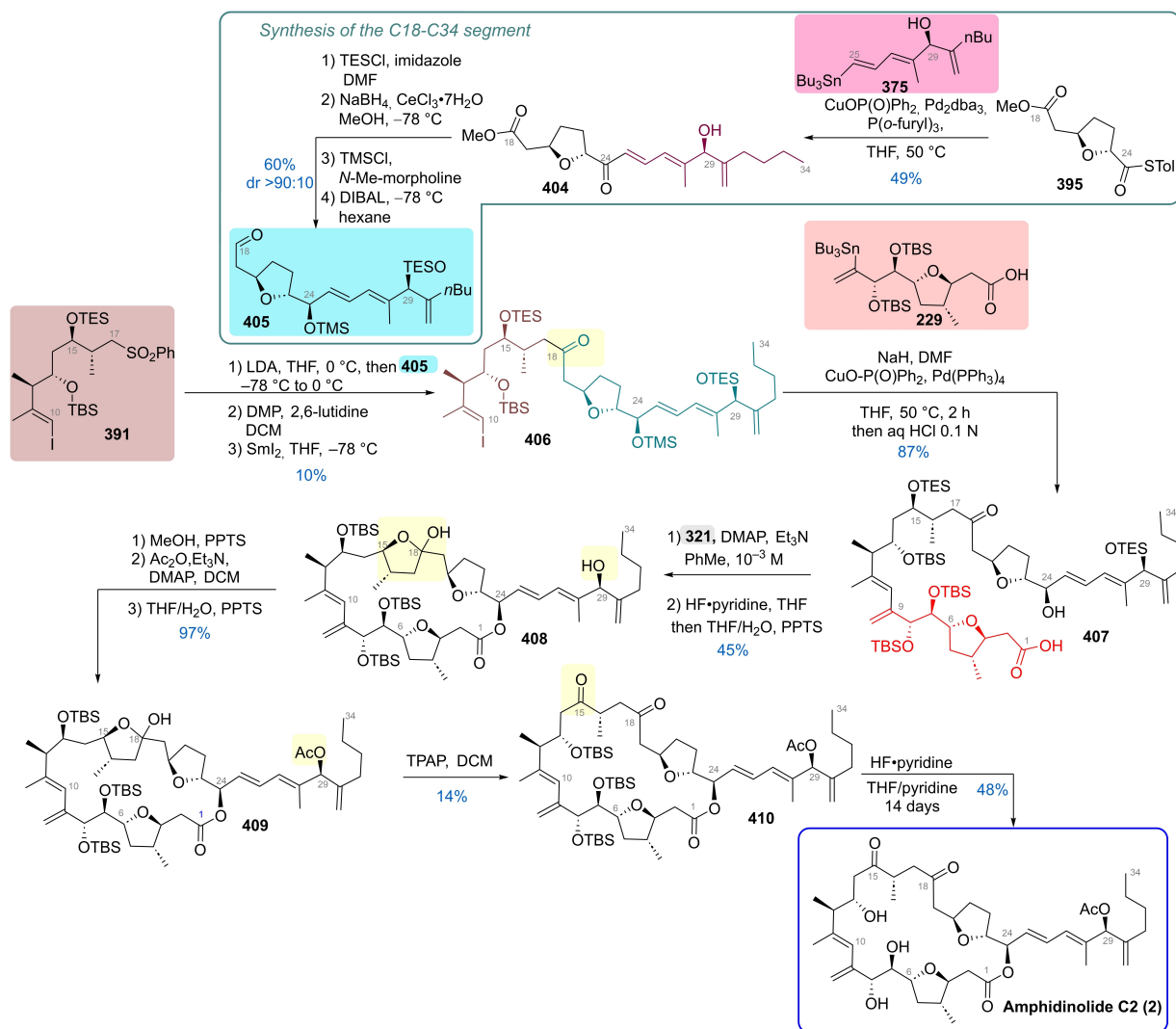
The coupling sequence used the same conditions as those described previously for the F analog. However, modifying the side chain brought significant difficulties in reproducing experiments, such as the desulfonylation with Sml₂, which brought many unidentified side products, resulting in the obtaining of **406** with a poor yield. Stille cross-coupling with **229** was, in



Scheme 48. Ferrié & Figadère's total synthesis of amphidinolide F (5).

contrast, high yielding to the formation of **407**. Macrolactonization and concomitant TES deprotections afforded **408**. Direct acetylation was performed to synthesize the C2 analog; however, the acetylation of position C₁₅ was also occurring,

although the predominant ketal form. Consequently, selective protection of hydroxy at the C₁₅ position, through blocking this position as a methyl acetal, allowed the selective acetylation at C₂₉. Acid hydrolysis of the ketal yielded **409**. Another tedious



Scheme 49. Ferrié & Figadère's final steps to the total synthesis of amphidinolide C2 (2).

step transformation was the oxidation of position C₁₅. It seemed that the quality of TPAP was crucial, as the reagent reduces over time, forcing the authors to use several reagent additions. However, this action significantly decreased the amount of diketone **410** isolated. Consequently, a few amounts of **410** could be exposed to deprotection, isolating synthetic AMP-C2 (**2**). Although the initial objective was to access all analogs, only the C2 was attainable, but it still constituted a significant success. The total synthesis of AMP-C2 (**2**) was achieved in 26 steps along the longest linear sequence and about 0.028% overall yield (66 total steps). (Scheme 49, bottom)

4.3.5. Ferrié & Figadère's Study toward Amphidinolide U (6)

Very recently, in 2023, the Ferrié & Figadère group reported a synthetic study of the C₁-C₁₂ segment of AMP-U (**6**).^[154] Considering that they reached the C₁₃-C₂₉ segment of AMP-U (**6**) because this part is identical to the C₁₈-C₃₄ backbone of AMP-C (**1**),^[138] half of the natural product was already in hand.

As for the C₁₀-C₁₈ segment of AMPs-C (**1**) and -F (**5**),^[138] they proposed using consecutive epoxide ring-opening to reach their objective.^[138]

The synthesis started from (*R*)-glycidol, protected and ring-opened with (*Z*)-propenylmagnesium bromide. Directed epoxidation^[152] of **411** afforded only the detectable diastereoisomer **412** after silyl protection. Selective functionalization of the primary hydroxy group at C₇ allowed the homologation as an acetylene function with the help of the Colvin protocol,^[155] giving rise to **413**. Ring-opening of the epoxide with the lithiated methyl phenyl sulfone gave predominantly regioisomer **414a** in 65% yield, accompanied by **414b** with 20% yield. Acetylene functionalization to vinyl iodide **415** was driven in four steps, with the same sequence depicted previously (see Scheme 46). With the C₆-C₁₂ segment in hand, the authors tried to make the sp²-sp³ coupling with iodide **417**, prepared in 3 steps from alcohol **416**. Whereas the Suzuki cross-coupling was effective between the borane derived from **417** and model substrate **391** (see Scheme 46), the same reaction with **415** proved nearly ineffective, with only traces of the expected

product. The reactivity difference was attributed to the adjacent protected hydroxy group's higher steric hindrance than the methyl group in **391**. Surely, conditions and substrates must be optimized to synthesize segment **418**. (Scheme 50)

5. Summary and Outlook

In conclusion, this review summarized all the past works concerning the subclass family of amphidinolides, AMPs–C (1), –C2 (2), –C3 (3), –C4 (4), –F (5) and –U (6), which share from 75% structure similitudes. The first section emphasizes Kobayashi's efforts to isolate these complex and highly cytotoxic natural substances from *Amphidinium* dinoflagellates. Another difficult task was to prove the relative and absolute configuration of the twelve stereogenic centers of AMP–C (1) *via* derivatization, degradation, and divergent synthesis of small fragments. Nevertheless, the recent isolation of AMP–C4 (4) from octocoral indicates a symbiotic microorganism might produce these natural products.

Sections 2 and 3 presented the synthetic effort towards those amphidinolides, focusing on the key steps. To confirm Kobayashi's attribution and validate synthetic access to these natural products, a considerable number of groups of chemists have embarked on the project of achieving their total synthesis. AMPs–C (1) and –F (2) were excellent platforms to design and illustrate original methods to build *trans*-THF, shown through the contributions of all research groups presented in this review.

Table 2 below summarizes all the reports concerning the total synthesis of AMPs–C (1) and –F (5), which were predominantly studied. Despite the fourteen groups involved in the total synthesis of AMPs–C (1) and –F (5), only three achieved the total synthesis of some members. The possible reasons for this low success rate are unsuspected difficulties of these natural products. The presence of ketone derivatives at positions C₁₅

and C₁₈ forces using an orthogonal strategy for protecting groups, increasing the number of total steps and leading to late-stage deprotection regioselectivity issues. The efficiency of the applied strategies seemed to have played a significant role in the success of all reported total syntheses. Fürstner and Ferrié & Figadère prepared the main fragments in a relatively limited number of steps (10 to 15), which helped greatly in reaching the total synthesis. With the smart use of a common segment, Carter achieved the first total syntheses of AMPs–C (1) and –F (5). In a similar manner, Clark was close to obtaining such success. Even in the case of the most ideal strategy by Fürstner, 47 total steps, including the preparation of small synthons, were needed to obtain AMP–F (5) in 50 mg from a gram quantity of the three main fragments. Thus, underperforming strategies make the total synthesis of such complex natural products highly challenging.

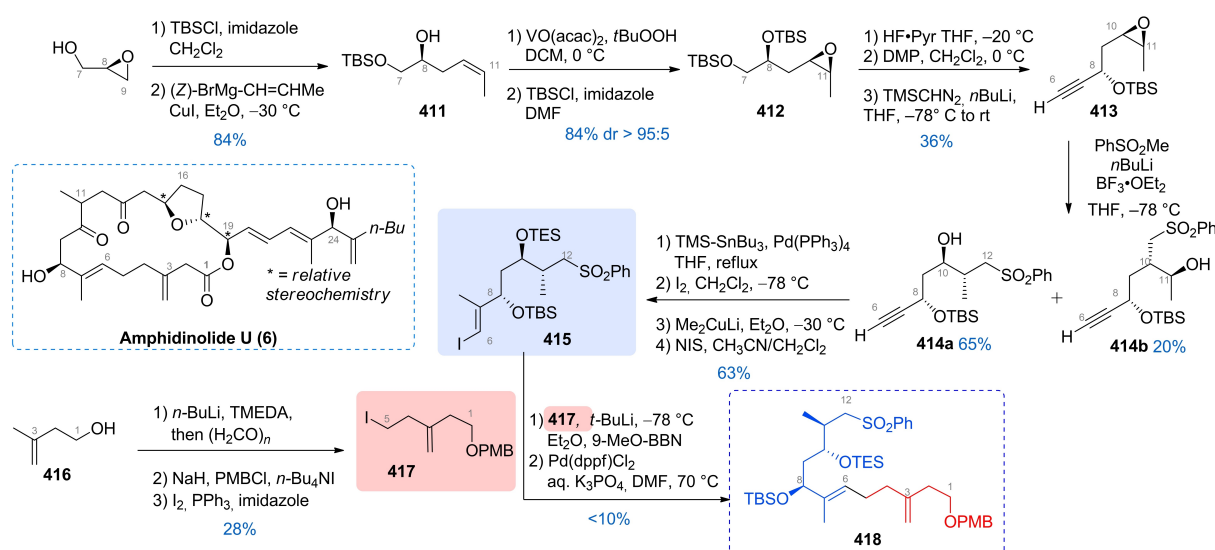
Despite the difficulties and successes met by all the groups involved in the total synthesis of AMPs–C (1) and –F (5), reported works share excellent information for current and future chemists to design the next generation total synthesis of polyketides.

Acknowledgements

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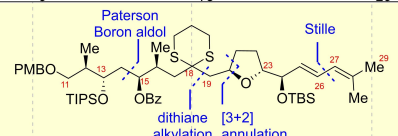

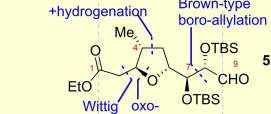
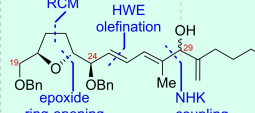
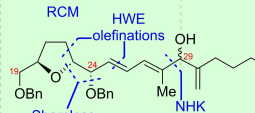

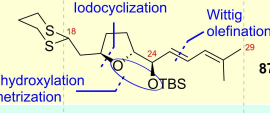

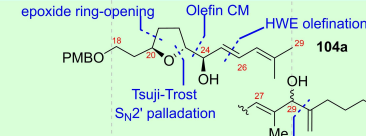
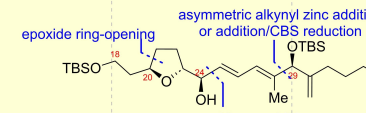
Conflict of Interests

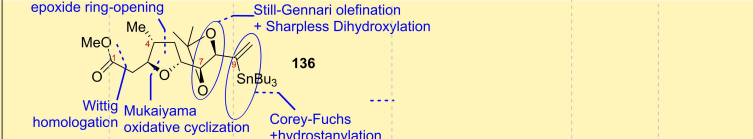
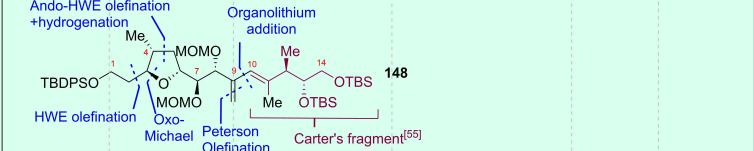
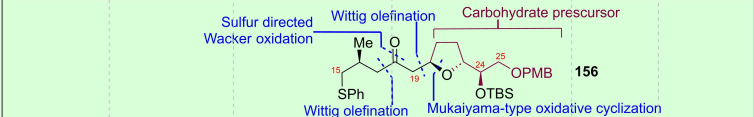
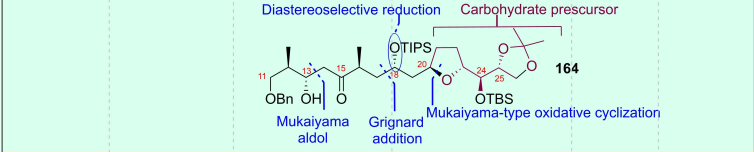
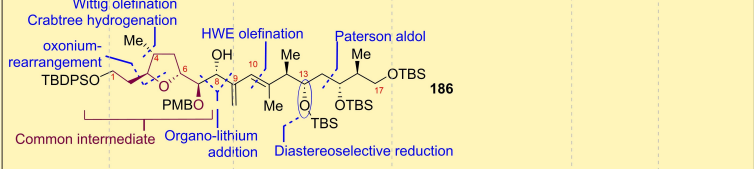
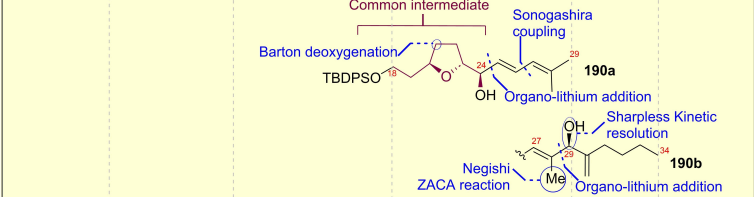
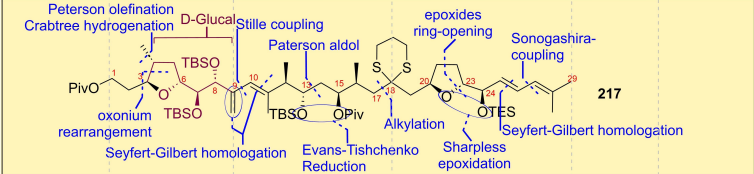
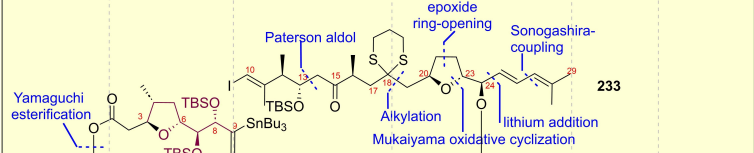
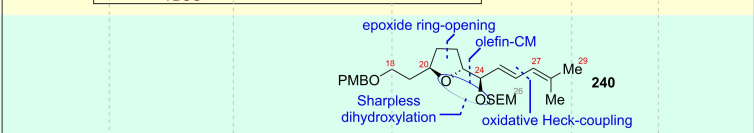
The authors declare no conflict of interest.



Scheme 50. Ferrié & Figadère's Synthetic studies towards the synthesis of the C₁-C₁₂ segment of amphidinolide U (6).

Table 2. Summary of all the synthetic studies towards AMPs–C (1), -C2 (2) and F (5): key disconnections, featured reactions, authors, overall yields and the number of steps of main segments and natural products.

Carbon positioning, features reactions, and key disconnections of the most advanced intermediates					Group of research, year of report, number of steps and overall yields
C ₁	C ₉	C ₁₈	C ₂₉	C ₃₄	
		 <p>Paterson Boron aldol Stille dithiane alkylation [3+2] annulation</p>			Roush 2004 ^[19] C ₁₁ -C ₂₉ segment 11% yield over 17 steps
	 <p>Brown-type boro-allylation dithiane alkylation [3+2] annulation</p>				Roush 2008 ^[24] C ₁ -C ₉ segment - 1st approach 7% yield over 17 steps
	 <p>Still-Gennari +hydrogenation Brown-type boro-allylation Wittig oxo-Michael Wacker oxidation</p>				Roush 2008 ^[24] C ₁ -C ₉ segment - 2 nd approach 21% yield over 11 steps
		 <p>RCM epoxide ring-opening HWE olefination NHK coupling</p>			Mohapatra 2007 ^[24] C ₁₉ -C ₃₄ segment - 1 st approach 12% yield over 14 steps
		 <p>RCM olefinations Sharpless dihydroxylation HWE olefination NHK coupling</p>			Mohapatra 2008 ^[31] C ₁₉ -C ₃₄ segment - 2 nd approach (C ₁₄ -C ₂₉ segment of amphinolide U) 16.7% yield over 16 steps
	 <p>HWE olefination Sharpless epoxidation Wacker oxidation Oxo-Michael</p>				Mohapatra 2009 ^[33] C ₁ -C ₉ segment 14% yield over 20 steps
		 <p>Iodocyclization Wittig olefination Sharpless dihydroxylation-desymmetrization</p>			Armstrong 2009 ^[36] C ₁₈ -C ₂₉ segment 6.8% yield over 12 steps
	 <p>Tamaru homoallylation Olefina CM Oxo-Michael</p>				Spilling 2010 ^[37] C ₁ -C ₇ segment (2 nd strategy) 21% yield over 10 steps
		 <p>epoxide ring-opening Olefin CM HWE olefination Tsuji-Trost S_N2' palladation NHK coupling</p>			Spilling 2010 ^[39] C ₁₈ -C ₂₉ and C ₁₈ -C ₃₄ segments ≈14% yield over 10 steps
		 <p>epoxide ring-opening asymmetric alkynyl zinc addition or addition/CBS reduction Alkyne addition OTBS</p>			Pagenkopf 2011 ^[43] C ₁₈ -C ₃₄ segment (two approaches) 22 or 26% yield over 11 or 16 steps according the approach

	<p>Pagenkopf 2013^[49]</p> <p>C₁-C₉ segment</p> <p>7% yield over 25 steps</p>
	<p>Forsyth 2013^[54]</p> <p>C₁-C₉ segment</p> <p>32.8% yield over 13 steps</p> <p>C₁-C₁₄ segment</p> <p>10.5% yield over 17 steps</p>
	<p>Forsyth 2013^[54]</p> <p>C₁₅-C₂₅ segment</p> <p>3.6% yield over 23 steps</p>
	<p>Forsyth 2017^[62]</p> <p>C₁₁-C₂₅ segment</p> <p>3.6% yield over 23 steps</p>
	<p>Clark 2013^[63]</p> <p>C₁-C₈ segment: 5.3% over 23 steps</p> <p>C₉-C₁₇ segment: 20% over 11 steps</p> <p>C₁-C₁₇ segment: 1.2% over 26 steps</p>
	<p>Clark 2013^[64]</p> <p>C₁₈-C₂₉ segment: 15.1% over 17 steps</p> <p>C₁₈-C₃₄ segment: 8.8% over 20 steps</p>
	<p>Clark 2022: second approach^[73]</p> <p>C₁-C₉ segment: 7.1% over 20 steps</p> <p>C₁₀-C₁₇ segment: 22.1% over 12 steps</p> <p>C₁₈-C₂₉ segment: <6.6% over 21 steps</p> <p>C₁-C₂₉ segment: 0.8% over 24 steps</p>
	<p>Clark 2022: third approach^[80]</p> <p>C₁₀-C₂₉ segment: 3.3% over 21 steps</p> <p>C₁-C₉ segment: 6.1% over 23 steps (second approach strategy)</p> <p>C₁₀-C₉ segment: 3.6% over 25 steps</p>
	<p>White 2013^[84]</p> <p>C₁₈-C₂₉ segment:</p> <p>13% yield over 12 steps</p>

<p>246</p>	<p>Dai 2018^[86]</p> <p>C₁₈-C₂₆ segment: 20% yield over 14 steps</p>
<p>257</p>	<p>Williams 2020^[88]</p> <p>C₁₀-C₂₅ segment: <10% yield over 18 steps</p>
<p>278</p>	<p>Morken 2020^[95]</p> <p>C₁-C₉ segment: 15% over 10 steps C₁₀-C₁₅ segment: 36% over 7 steps C₁-C₁₅ segment: 9.3% over 11 steps</p>
<p>5</p>	<p>Carter 2012^[110]</p> <p>C₁-C₁₄ segment: 4.2% over 18 steps C₁₅-C₂₉ segment: 2.1% over 28 steps Total synthesis : 67 total steps ≈2% yield over 36 steps (LLS) (67 total steps)</p>
<p>1</p>	<p>Carter 2013^[65]</p> <p>C₁₅-C₃₄ segment: 2.9% over 27 steps Total synthesis : 72 total steps ≈1.4% yield over 35 steps (LLS)</p>
<p>5</p>	<p>Fürstner 2013^[103]</p> <p>C₁-C₉ segment: 12.4% over 15 steps C₁₀-C₁₇ segment: 19.5% over 13 steps C₁₈-C₂₉ segment: 20% over 5 steps Total synthesis : 47 total steps ≈1.5% yield over 23 steps (LLS)</p>
<p>1</p>	<p>Fürstner 2015^[104]</p> <p>C₁₈-C₃₄ segment: 14.1% over 9 steps Total synthesis : 55 total steps ≈2.2% yield over 23 steps (LLS)</p>
<p>5</p>	<p>Ferrié 2018^[131]</p> <p>C₁-C₉ segment^[92]: 8.2% over 11 steps C₁₀-C₁₇ segment: 10.9% over 15 steps C₁₈-C₂₉ segment: 19.8% over 14 steps Total synthesis : 53 total steps ≈2.0% yield over 23 steps (LLS)</p>
<p>2</p>	<p>Ferrié 2022^[132]</p> <p>C₁₉-C₃₄ segment: 13.6% over 15 steps Total synthesis : 66 total steps ≈0.028% yield over 26 steps (LLS)</p>

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: polyketide · structure determination · total synthesis · tetrahydrofuran · natural product isolation

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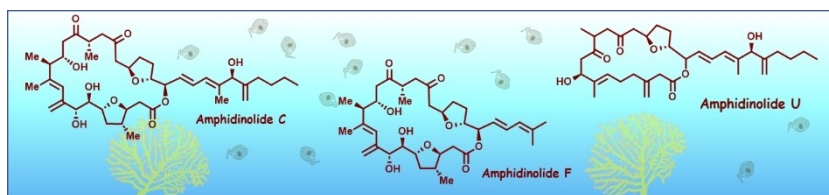
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REVIEW



Amphidinolides C, F and U are a subclass of polyketides sharing a similar structure, isolated from dinoflagellates or octocoral sponges and exhibiting high cytotoxic activity. This review

discloses the progress made in their isolations and structural determinations and the various synthetic approaches and successful attempts leading to their total syntheses.

*Dr. I. Ciss, Prof. M. Seck, Dr. B. Figadère,
Dr. L. Ferrié**

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**Advances Toward Amphidinolides C,
F and U: Isolations, Synthetic Studies
and Total Syntheses**