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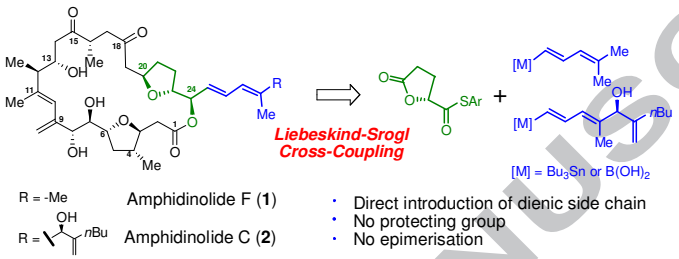

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Liebeskind–Srogl Cross-Coupling on γ-Carboxyl-γ-Butyrolactone Derivatives: Application to the Side Chain of Amphidinolides C and F.

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ABSTRACT

The synthetic approach for the C20-C29 and C20-C34 fragment of amphidinolide F and C was based on an original Liebeskind–Srogl cross-coupling reaction with a glutamic acid-derived building-block. Further highly diastereoselective reduction of the ketone was achieved by using an uncommon Ph_3SiH/TBAF/HMPA system. The Amphidinolide C side chain was built through a reductive elimination of chiral epoxide to install the stereogenic center at C29.

Amphidinolides belong to a wide and original family of more than 30 members of marine macrolactones isolated by Kobayashi from dinoflagellates *Amphidinium* sp., which live in symbiosis with okinawan flatworm *Amphiscolops* sp. These molecules had shown important cytotoxicity against solid tumors. In particular, amphidinolide C is one of the most potent cytotoxic agents of this family (IC_{50} = 5.8 and 4.6 ng/mL against murine lymphoma and human epidermoid carcinoma cells, respectively).[2] Curiously amphidinolide F (**1**), which is structurally closely related to amphidinolide C (**2**) is however about 1000 fold less active (Figure 1). This intriguing observation suggests an important role of the side chain, and opens a door for chemical modulations and the synthesis of analogues. Due to their important cytotoxicity and their original structures these natural substances has attracted the attention of the scientific community,[3] and recent total syntheses of these two molecules were reported confirming their original structural assignments.[4]

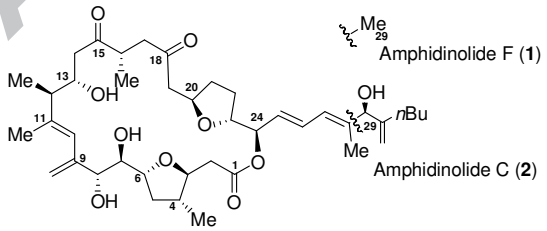

Figure 1. General structure of amphidinolides F and C.

Our group is currently involved in the total synthesis of some THF-containing amphidinolides such as amphidinolide N/caribenolide[5] and amphidinolides C and F.[3h] Our general retrosynthesis for these two last molecules rely on a *C*-glycosylation to elaborate the C19-C20 bond, followed by a macrocyclisation of the resulting seco-acid. Here we describe our synthesis of the C20-C29 and C20-C34 fragment of amphidinolides F (**1**) and C (**2**) through a direct introduction of the dienic side chain of both congeners. For this purpose, we suggested to use D-glutamic acid derivative **D** as a common precursor for the butyrolactone core, which could react with metallated-diene **E** to build those fragments (Scheme 1).

We first studied the synthesis of C20-C29 fragment of amphidinolide F as it remains a simple and better model to apply specific methodologies. The addition of sp^3 organo-magnesium, -manganese, -copper, -cadmium reagents to acyl chloride **3** is well documented;[6] however the addition of sp^2 organometallic to **3** seems more difficult to proceed as no work is reported. Indeed, we were unable ourselves to perform such a reaction with metallodienes of type **E** whatever the metal was: magnesium, lithium, copper, manganese, zinc or tin under various conditions. (Scheme 2).

A first solution was the installation of dienone by isomerization of a propargylic ketone.[7] Ketone **6** was prepared by

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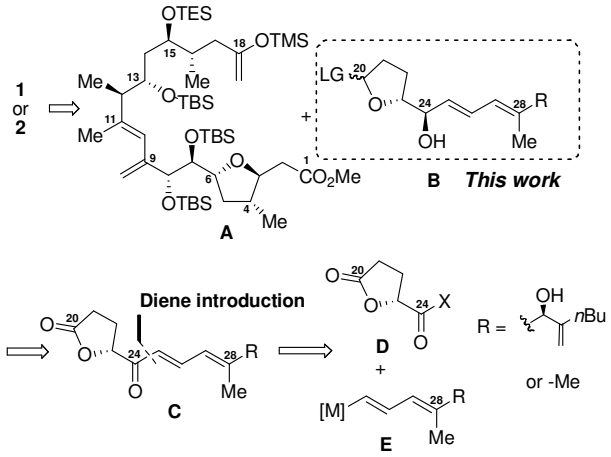
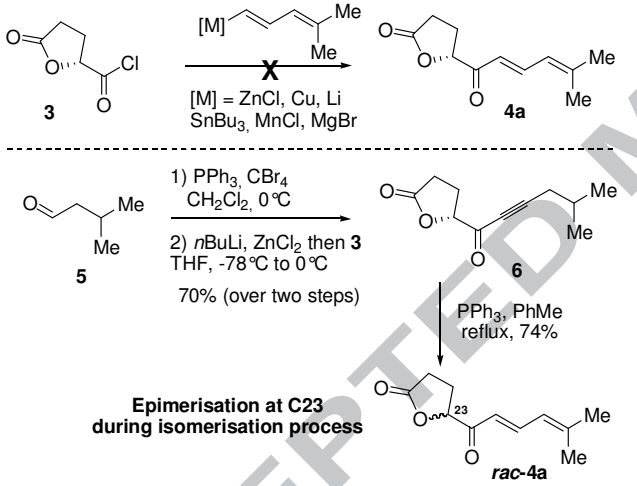
addition of zinc acetylide derived from isovaleraldehyde (**5**) onto acyl chloride **3** (70% yield). Isomerization of the triple bond to conjugated diene under different conditions ($Pd(OAc)_2/PPh_3$, THF, 60 °C or PPh_3, PhMe, reflux) gave us expected dienic ketone **4a** in modest yield (55-66%). Unfortunately, under these reaction conditions, an epimerization of the stereogenic center at C23 was observed (Scheme 2).



Scheme 1. General retrosynthesis for amphidinolides F and C.



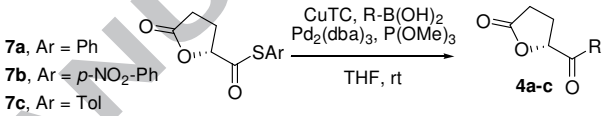
Scheme 2. Efforts toward the introduction of the dienic side chain on acyl chloride **3**.

At this point, this approach was abandoned and a new synthesis of **4** has been designed to keep the chiral information. Acyl chloride **3** was maybe not the most appropriated electrophile and instead, we turned our attention to thioester derivatives, which could be ideal substrates through a Liebeskind–Srogl cross-coupling. This reaction relies on an original copper mediated and palladium catalyzed cross-coupling between thioesters and boronic acids to afford ketones.[8] This transformation was described as being very chemoselective and as avoiding any epimerization.[9] Moreover, this transformation has the advantage to be very simple to be carried out: room temperature, strong base free, not strictly dry conditions and easy available reagents.

We decided to evaluate the potential of this transformation for the direct introduction of dienic moiety of amphidinolide F and C. Required thioesters **7a-c** were synthesized by reaction of acyl chloride **3** with the corresponding thiol in the presence of pyridine. Preliminary experiments between thioester **7a** and phenylboronic acid **8a** using conditions described in the literature (CuTC, $P(OMe)_3$, $Pd_2(dba)_3$, THF, rt) gave ketone **4b** in 52% isolated yield (Table 1, entry 1). Vinylic boronic acid **8b** also gave ketone **4c** in a similar yield (Table 1, entry 2).

Motivated by these results, catechol boronate **9** was synthesized by hydroboration of 4-methyl-pent-3-enyne[10] with catechol borane (CatB-H).[11] Hydrolysis of **9** (H_2O, 50°C) to the corresponding boronic acid needed extended reaction time and substantial decomposition was observed. Instability of vinyl boronic acids is well documented,[12] we thus planned an *in situ* hydrolysis of **9**. When crude catechol boronate **9** was treated with thioester **7a** in a THF/H_2O (9/1) mixture (Table 1, entry 3), coupled product **4a** was obtained in 55% yield without epimerization of the C23 center (98% ee). Slight improvement of the reaction was obtained by using more activated thioester **7b** (Table 1, entry 4), which gave ketone **4a** in 66% yield. The yields are modest, but this reaction seems to be up to now the only general method to obtain these chiral conjugated ketones **4a-c** in decent yield.

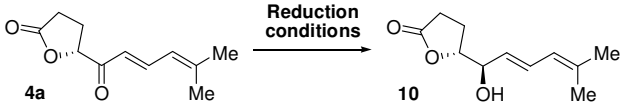
Table 1
Liebeskind–Srogl cross-coupling with γ-arylthiocarbonyl-γ-butyrolactones.



Entry	Thioester	Boronic acid derivatives		Product	Yield[a]
1	**7a**	**8a,**	$(HO)_2B$–Ph	**4b**	52%
2	**7a**	**8b,**	$(HO)_2B$–*n*Bu	**4c**	52%
3	**7a**	**9,**[b]	(Cat)B–CH=CH–CHMe–Me	**4a**	55%
4	**7b**	**9,**[b]	(Cat)B–CH=CH–CHMe–Me	**4a**	66%

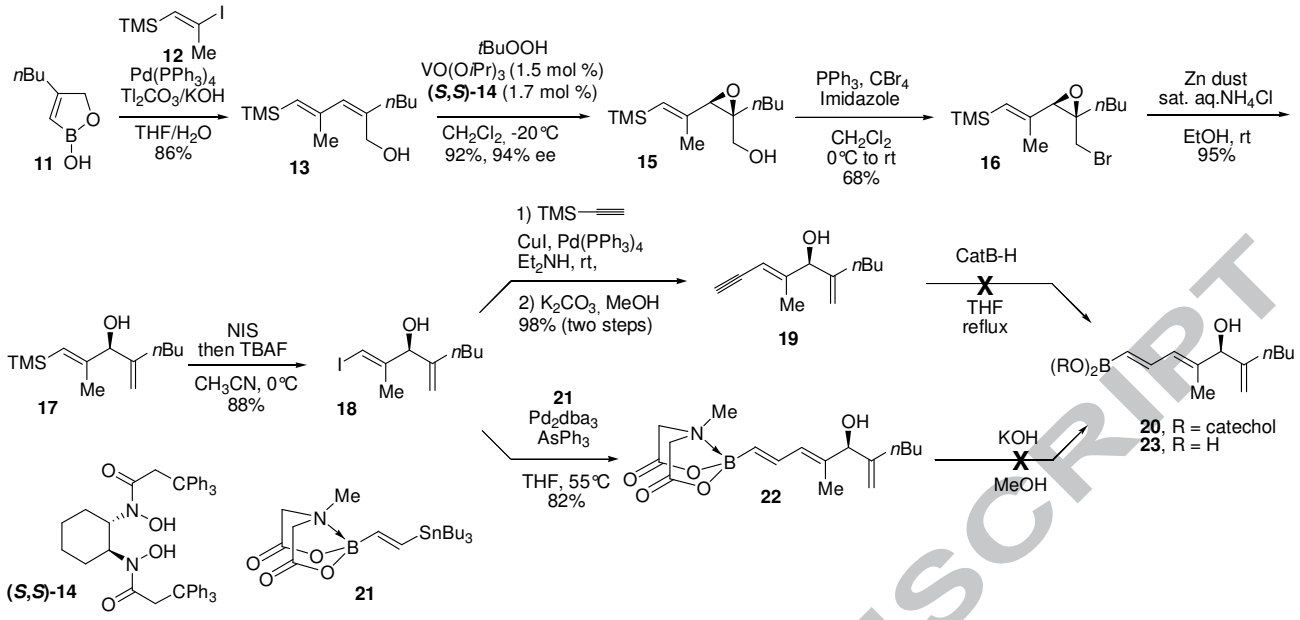
[a]Isolated yield. [b]Reaction was performed in THF/H_2O (9/1) to generate *in situ* the boronic acid by hydrolysis of **9**. CuTC = copper (I) thiophene-2-carboxylate. Tol = Tolyl. Cat = catechol.

Table 2
Diastereoselective reduction of ketone **4a**



Entry	Conditions	dr (*syn*/*anti*)[a]	Overall yield[b]	Product yield (**10**)[c]
1	$NaBH_4/CeCl_3$, MeOH, 0 °C	61/39	85%	52%
2	$NaBH_4/MnCl_2$, MeOH, 0 °C	48/52	93%	45%
3	$LiAlH(OtBu)_3$, THF, -78 °C	50/50	66%	33%
4	L-Selectride, THF, -78 °C	85/15	67%	42%
5	Et_3SiH/TBAF, HMPA, rt	90/10	40%	34%
6	Ph_3SiH/TBAF, HMPA, rt	95/5	nd	67%

[a]Determined by HPLC of the crude mixture. [b]Sum of the two isolated *syn* and *anti* diastereoisomers. [c]Isolated yield of the syn product. nd = not-determined.



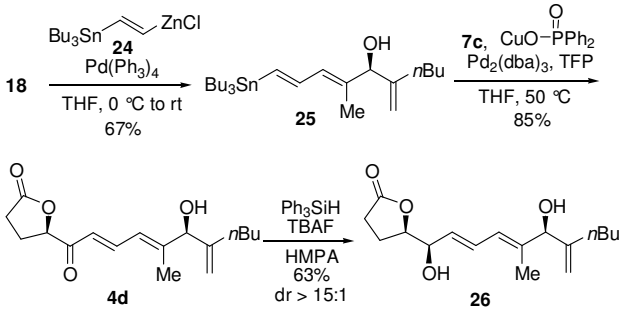
Scheme 3. Synthesis of the side chain of amphidinolide C.

Next, we focused our efforts to perform a challenging chemo- and stereo-selective reduction of ketone **4a** in order to obtain *syn*-alcohol **10**. Several reducing agents were screened (Table 2). Use of Luche's conditions (Table 2, entry 1)[13] and its manganese alternative[14] (Table 2, entry 2) could not furnish any selectivity despite a decent isolated yield of *syn*-product **10**. Hindered reducing agent such as $LiAlH(OtBu)_3$ showed no selectivity and low yield (Table 2, entry 3) whereas L-Selectride afforded better selectivity (dr = 85/15) but formation of numerous undetermined by-products was observed decreasing the yield. Next we turned our attention to silane reagents as proposed by Hiyama.[15] Et_3SiH/TBAF (15 mol%) in HMPA (Table 2, entry 5) gratifyingly afforded Felkin–Anh product with a good diastereoselectivity (dr = 90/10) albeit in a low yield. Finally, the use of Ph_3SiH (Table 2, entry 6) gave the best results in terms of stereoselectivity (dr = 95/5) and yield (67%).

Having the C20-C29 fragment of amphidinolide F **10** in our hands, we turned our attention to the synthesis of C20-C34 fragment of amphidinolide C through a similar approach. In order to reach this objective, we designed a stereoselective synthesis of boronic acid **23**. Installation of the stereogenic center at C29 was planned by performing a reductive elimination of a chiral epoxi-alcohol (Scheme 3). Suzuki cross-coupling between boronate **11**[16] and vinyl iodide **12**[17] in the presence of Tl_2CO_3/KOH furnished *E,Z* diene **13** in 86% yield. Application of Sharpless epoxidation[18] to **13** afforded epoxide **15** with surprisingly low enantioselectivity (52% ee). Fortunately, the utilization of vanadium-catalyzed Yamamoto asymmetric epoxidation of allylic alcohol with bis-hydroxamic ligand (*S,S*)-**14**[19] afforded finally target product **15** with an excellent enantioselectivity (94% ee, 92% yield). Reductive elimination of the corresponding α-bromo-epoxide (**16**) in the presence of zinc dust afforded desired alcohol **17**, with retention of the chiral information at C29. Iodolysis of TMS with NIS in acetonitrile gave us *E*-vinyl iodide **18** in 88% yield.[20] Efforts into the preparation of boronate **20** was conducted through two strategies. First, vinyl iodide **18** was coupled with TMS-acetylene through a Sonogashira cross-coupling followed by TMS cleavage (K_2CO_3/MeOH) to yield enyne **19** (98% over two steps). Introduction of boron atom at C25 was first planned with CatB-H, but, to our dismay, extended reaction times were required leading only to a complex mixture of by-products whatever the conditions used (heating, catalysis with or without TBS protection at C29). (Scheme 3)

In front of this failure, we envisioned to introduce the boron atom at the specified position by the mean of *N*-methyl-iminodiacetic (MIDA) boronate as a stable boronic acid surrogate.[21] Use of bis-metalled compound **21**[22] through a selective Stille cross-coupling finally gave us MIDA boronate **22** in 82% yield. However, cleavage of the MIDA moiety under different reported conditions (1 M NaOH/THF or $NaHCO_3$/MeOH 40 °C)[23] did not furnish desired boronic acid **23**, degradations being only observed (Scheme 3). As the generation of free boronic acid **23** seems to be delicate in our hands, we decided to modify slightly our original strategy in the synthesis of the C20-C34 fragment of amphidinolide C as depicted in Scheme 4.

Indeed, the utilization of the tin version of Liebeskind–Srogl cross coupling[24] could finally allow us to obtain the target compound as organotin compounds are known to be pretty stable compared to boronic acids. Selective Negishi cross-coupling applied on vinyl iodide **18** with excess of organozinc **24**[25] gave us desired stannane **25** in 67% yield. To our delight, Liebeskind cross-coupling of **25** with tolyl-thioester **7c** in the presence of $Pd_2(dba)_3$, tri-*ortho*-furyl phosphine (TFP) and copper diphenylphosphinate (CuDPP)[26] allowed us to obtain ketone **4d** in 85% yield. Subsequent reduction of the ketone with Ph_3SiH/TBAF in HMPA furnished the C20-C34 fragment of amphidinolide C (**26**) in 63% isolated yield and with high diastereoselectivity (dr > 15:1, Scheme 4).



Scheme 4. Synthesis of the C20-C34 fragment of amphidinolide C.

In conclusion, we synthesized both C20-C29 and C20-C34 fragments of amphidinolides F and C by using an original Liebeskind–Srogl cross-coupling as a key step for direct introduction of their side chain. We showed for the first time not only the boronic acids but some boronates such as catechol boronate can be used in this reaction by an *in situ* hydrolysis. In case of unstable boronic acid derivatives, the tin version of Liebeskind–Srogl cross-coupling can be a helpful alternative. We also found the reduction of unsaturated γ-butyrolactone-γ-ketones such as **4a** and **4d** is highly diastereoselective by using Ph_3SiH/TBAF in HMPA. Installation of the stereogenic center at C29 for the synthesis of the side chain of amphidinolide C was created from a successful reductive elimination of an epoxy alcohol. Vanadium-catalyzed Yamamoto epoxidation showed to be far superior to the classical Sharpless epoxidation on 2,3-trisubstituted allylic alcohols. This represents the first application of this asymmetric reaction toward the synthesis of natural products.

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The Agence Nationale de la Recherche (ANR) through AMPHICTOT project supported the work. We thank Karine Leblanc of our internal analysis service for acquisition of HRMS and HPLC analysis. We gratefully acknowledge Mr. Ron New of UC Riverside's Analytical Chemistry Instrumentation Facility for recording LIFDI mass spectra.

Supplementary data

Supplementary data (experimental details, copies of ^{1}H and ^{13}C NMR spectra for products, chromatograms for diastereoisomeric and enantiomeric measurements. This material is available free of charge via the Internet at the doi.) associated with this article can be found, in the online version, at.

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