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Alexandre Guthertz, Jonathan Lusseau, Valérie Desvergnès, Stéphane Massip, Yannick Landais.
An Approach towards the Synthesis of the Spiroimine Fragment of 13-Desmethylspiroside C
and Gymnodimine A. *Chemistry - A European Journal*, 2019, 25 (6), pp.1553-1560.
10.1002/chem.201804972 . hal-02374607

HAL Id: hal-02374607

<https://hal.science/hal-02374607v1>

Submitted on 15 Jan 2021

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An Approach toward the Synthesis of the Spiroimine Fragment of 13-Desmethylspiroside C and Gymnodimine A.

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Abstract: A general access to the spiroimine skeleton of gymnodimine and spiroside is described relying on the construction of the cyclohexene fragment using an enantiocontrolled Diels-Alder reaction, the installation of the all-carbon quaternary stereocenter through a stereocontrolled alkylation or aldolisation and the elaboration of the lateral chains at C7 and C22 using Wittig-Horner olefinations. The spiroimine core of gymnodimine is thus made available through a 16 steps linear sequence in a 21% overall yield.

Keywords: Phycotoxin • Enantioselective Diels-Alder • Wittig-Horner reaction • Spiroimine • nitrile

13-Desmethylspiroside **1** and its congeners, gymnodimine A **2**, pinnatoxins and pteriatoxins (not shown) are macrocyclic imine phycotoxins produced by the dinoflagellate *Alexandrium ostenfeldii* and *peruvianium*, first isolated from the digestive glands of mussels, scallops and phytoplankton harvested from aquaculture sites on the Atlantic coast of Nova Scotia, Canada.^[1] They were also found around New Zealand coastline and isolated from shellfish in Tunisia, Italy, Spain, USA, Scotland and Norway.^[2] *A. ostenfeldii* which was first thought to be an organism from cold-water is also found in temperate waters throughout the entire world. Mediterranean and Adriatic seas were thus recently contaminated. Usually, micro-organism concentration rapidly increases during June and July, causing dinoflagellate blooms. Bivalve mollusks (clams, mussels, oysters or scallops) feed from these harmful dinoflagellates and get contaminated. Shellfish can then concentrate these phycotoxins in their tissues and act as vectors for transferring these toxic chemical compounds to crabs, fish, birds, marine mammals and ultimately to humans, thus menacing wildlife and human health. Shellfish poisoning thus constitutes a threat to public health and also to the shellfish industry. As an example, spiroside were found in 2005 and 2007 in the temperate water of Arcachon bay in France, an event which prompted the local administrators to declare a prolonged ban of the shellfish harvest and consumption.^[3] Similar problems occurred in other part of the world.

Among these phycotoxins, the spiroside, gymnodimine A **2**^[4] and pinnatoxin A^[5] members of the spiroimine family, have been the most intensively studied phycotoxins due to their occurrence and intriguing biological activities. Spiroside induce fast lethal toxicity when administrated by intraperitoneal (i.p.) injection to either mouse or rat but they are less toxic by oral administration. The LD₅₀ values are in the 5-8 µg/kg range and death was observed within 3-20 minutes after i.p. injection. Later studies proved that the molecular targets of 13-desmethyl spiroside C **1** are nicotinic acetylcholine receptors (nAChR)^[6] and revealed that the toxin is a potent antagonist of nAChR in the subnanomolar range with moderate specificities for the various subtypes.^[7] To date, no toxicological studies have been carried out to evaluate the long-term impact of spiroside on human health. Recently, **1** and **2**, have been co-crystallized with the “acetylcholine binding protein” (AChBP), a soluble structural and functional surrogate for the ligand binding domain of the nAChR, and structures of the complexes have been solved.^[7] These data provide crucial information relative to the functional determinants and binding

regions of both the toxins and receptors. These studies suggest that the spiroimine moiety is the main pharmacophore and plays an important role in the biological activities of these phycotoxins.^{2e}

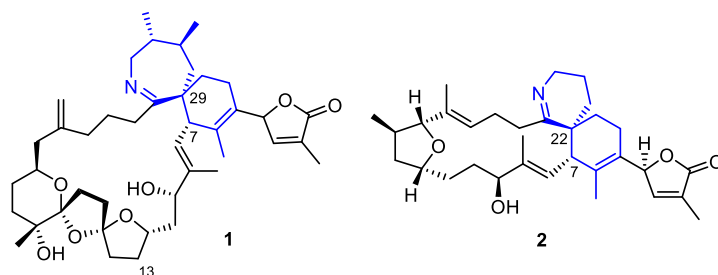


Figure 1. 13-Desmethylspirolide C **1** and Gymnodimine A **2**.

The synthesis of spirolide fragments, but also total synthesis of phycotoxins is still at the heart of an intense research activity, both in biology and organic synthesis. While the total synthesis of gymnodimine **2** has been completed by the Romo's group^[8] and that several groups have reported their efforts toward the synthesis of spirolides,^[9,10] no total synthesis of spirolide has ever been described. In this context, we recently embarked on the synthesis of the various fragments of **1** and **2**, following general strategies depicted in Figure 2. We achieved the synthesis of the bis-spiroketal^[11] and tetrahydrofuran^[12] cores of phycotoxins **1** and **2** respectively (Figure 2) and report here our efforts to access the spiroimine moiety of **2**. Our general approach should in theory allow an access to spiroimines of both phycotoxin's families and relies on the use of the Ward enantioselective Diels-Alder reaction^[13] between an acrylate and a suitably functionalized dienol, carried out in the presence of a BINOL-type ligand. Using this strategy, the preparation of a spiroimine skeleton precursor of natural product **2** (closely related to **B**, Figure 2) was thus achieved through a 16 steps linear sequence and a remarkable 21% overall yield.

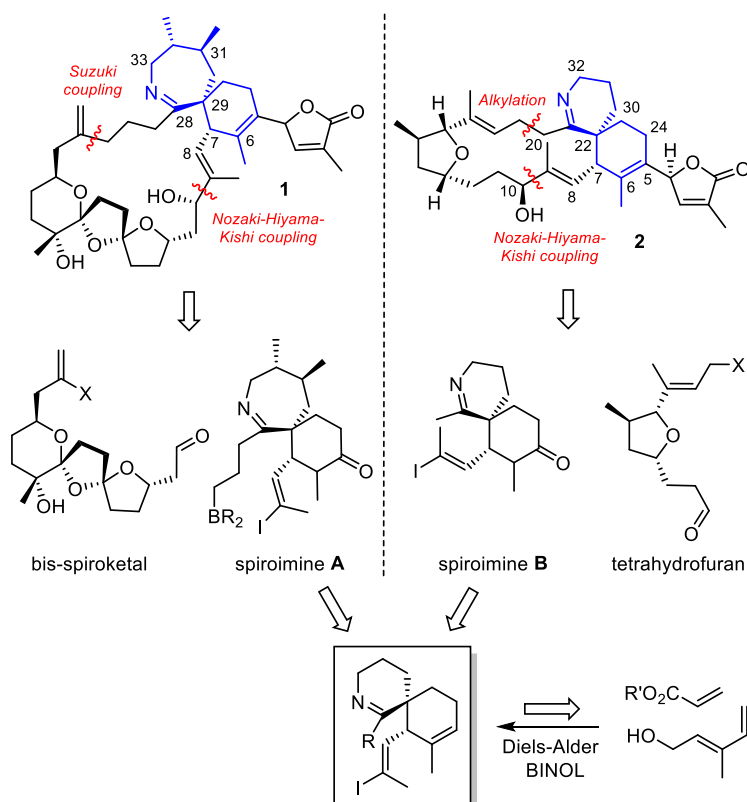


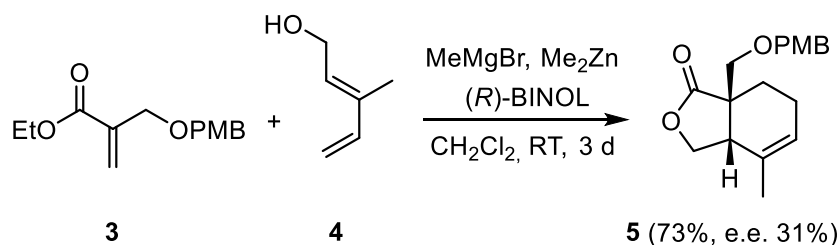
Figure 2. General disconnection strategies to access 13-desmethylspirolide C **1** and gymnodimine **2**.

Results and Discussion

Enantioselective Diels-Alder based construction of the cyclohexene fragment

The major difficulty in the synthesis of the spiroimine fragment is the introduction of the all-carbon quaternary stereocenter (C29 in **1**, C22 in **2**). Diels-Alder's reaction has been widely used to meet this synthetic challenge. Kishi's^[14] pioneering biomimetic approach to gymnodimine employed a late stage intramolecular Diels-Alder process to assemble **2**, albeit with low selectivities. Early studies by White *et al.*^[15] used an intermolecular Diels-Alder reaction between a suitably substituted Meldrum acid as a dienophile partner to construct the cyclohexene fragment of **2**, which also led to low diastereocontrol. More recently, however, a copper catalyzed Diels-Alder reaction enabled Romo and co-workers^[8] to set up the quaternary center with the correct configuration of the natural product with very good enantioselectivities. In the spiroamide series, Brimble *et al.* also used a Diels-Alder approach to elaborate a functionalized cyclohexene with the quaternary stereocenter with a satisfying diastereocontrol, using a Danishefsky diene and a chiral dienophile.^[10] Other approaches based on nucleophilic processes (Ireland-Claisen rearrangement Birch reductive alkylation, alkylation) respectively by Zakarian,^[16] Guillou^[17] and Hiram^[18] and co-workers were used to elegantly elaborate the 6-membered ring having the all-carbon quaternary stereocenter.

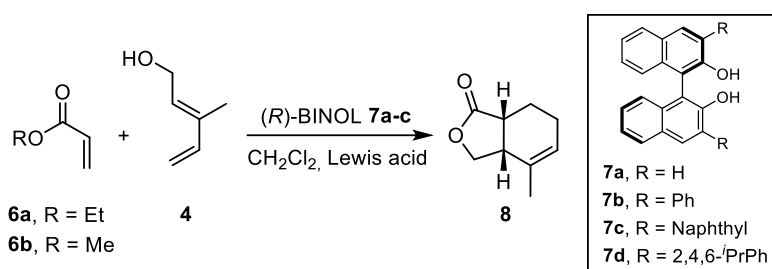
Our preliminary experiments were designed to incorporate the quaternary stereocenter during the Diels-Alder process using dienophile **3**^[19] and diene **4**^[20] as precursors in the presence of MeMgBr and Me₂Zn and (*R*)-BINOL as described in Ward's standard conditions.^[13] The expected cyclohexene **5** was obtained in good yield, albeit with low enantiocontrol, after 3 days at room temperature (Scheme 1). Absolute configuration was assumed to be that observed by Ward *et al.* during their seminal studies using the same (*R*)-BINOL.^[13]



Scheme 1. BINOL-mediated Diels-Alder reaction with diene **4**.

Anticipating a deleterious effect of the CH₂OPMB substituent in **3**, which likely hinders the required assembly of the partners around the Mg-Zn-BINOL complex, a second approach was conceived using simple acrylate **6a-b** as dienophiles. Formation of **8** would then be followed by alkylation α - to the lactone to set-up the quaternary stereocenter.

Table 1. Diels-Alder reaction between dienol **4** and acrylates **6a-b**.

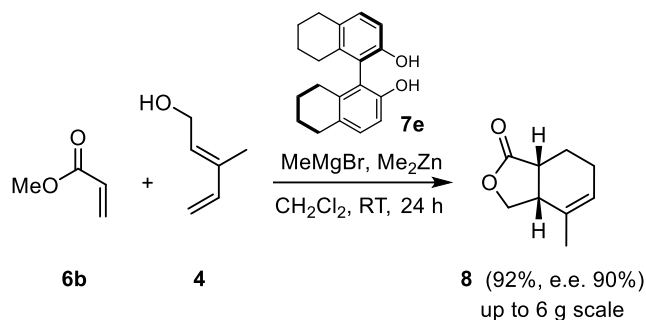


Entry	6	BINOL 7	Lewis Acid, T (°C) ^[a]	Yield [%] ^[b]	e.e. [%] ^[c]
1	6a	7a	Me ₂ Zn, MeMgBr, 20°C	58	70
2	6a	7a	Me ₂ Zn, MeMgBr, 20°C ^[d]	80	46
3	6a	7a	Me ₂ Zn, MeMgBr, -20°C	0	-
4	6a	7a	AlMe ₃ , 20°C	63	70
5	6a	7a	AlMe ₃ , 0°C	37	67
6	6b	7a	Me ₂ Zn, MeMgBr, 20°C	81	80
7	6b	7a	Me ₂ Zn, MeMgBr, 0°C	28	30
8	6b	7a	AlMe ₃ , 20°C	36	55
9	6b	7a	Me ₂ Zn, MeMgBr, 20°C ^[e]	95	50
10	6b	7b	Me ₂ Zn, MeMgBr, 20°C	62	-41
11	6b	7b	AlMe ₃ , 20°C	70	74
12	6b	7c	Me ₂ Zn, MeMgBr, 20°C	71	-41
13	6b	7c	AlMe ₃ , 20°C	42	66
14	6b	7d	Me ₂ Zn, MeMgBr, 20°C	90	5
15	6b	7d	AlMe ₃ , 20°C	-	-

[a] Typical conditions: diene **4** (1 equiv.), **6** (15 equiv.), BINOL **7a-d** (1 equiv.), MeMgBr (1 equiv.) or AlMe₃ (1 equiv.), Me₂Zn (1 equiv.) in a 0.02 M CH₂Cl₂ at the given temperature for 2 days. [b] Yield of isolated product. [c] Enantioselectivity measured through HPLC on a Chiralcel OD-A. [d] 1.3 equiv. of Me₂Zn was used. [e] C = 0.04 M instead of 0.02 M.

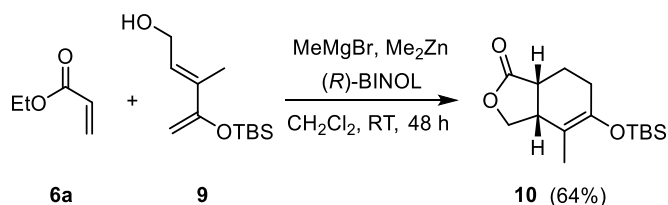
These preliminary studies showed that, under standard Ward's conditions, a satisfying yield and a moderate enantioselectivity was observed (Table 1, entry 1). Increasing the amount of zinc reagent led to an improved yield (entry 2), albeit with a drop in enantioselectivity, which may be ascribed to a competitive Zn-catalysis in the absence of the BINOL ligand. Lowering the temperature decreased dramatically the kinetic of the process (entry 3). When the MeMgBr-ZnMe₂ couple was replaced with AlMe₃, results were slightly improved (compare entry 4 vs 1), but again as in entry 3, lowering the temperature led to rapid decrease of the reactivity (entry 5). Both the yield and enantioselectivity were slightly improved using acrylate **6b** (entry 6), emphasizing on the subtle influence of steric effect on the reaction outcome. As above, lowering the temperature had a deleterious effect (entry 7) and the use of AlMe₃ did not improve further the process (entry 8). Finally, an increase of the concentration led to quantitative yield, albeit with a modest selectivity (entry 9). Although a reasonable yield and enantioselectivity were attained using **6b** as a dienophile in conditions summarized in entry 6, the level of enantioselectivity did not meet the requirement for a total synthesis. We therefore continued further the optimization, looking at the effect of the BINOL structure^[21] on the enantioselectivity of the process. Interestingly, the use of BINOL **7b** instead of **7a** produced the other enantiomer of **8**, albeit with a lower selectivity (entry 10). Although we have no clear explanation for this reversal of enantioselectivity, it is anticipated that the increasing steric hindrance in **7b** modifies the coordination around zinc, and consequently the topology of the process. Using AlMe₃ as an additive and BINOL-**7b** restored the enantioselectivity, leading to the same enantiomer as that using **7a** (entry 11). Similar trends were

followed with BINOL-**7c** (entries-12-13), and finally sterically hindered BINOL-**7d** led to nearly racemic compound (entry 14). During the course of this work, Ishihara, Hatakeyama and co-workers^[22] reported the same reaction using partially hydrogenated H₈-BINOL-**7e**.^[23] In our hand, this ligand, which can now be used in catalytic amount, led to high and reproducible yields and enantioselectivities on scales ranging from 100 mg to 6 g. This improvement in the enantioselectivity may be rationalized invoking an increase of the dihedral angle for H₈-BINOL as compared to BINOL.^[24]



Scheme 2. H₈-BINOL **7e**-catalyzed Diels-Alder reaction between diene **4** and acrylate **6b**.

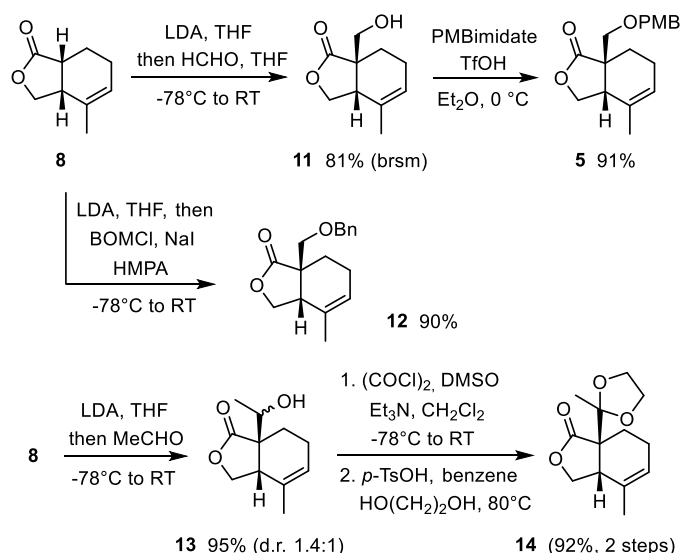
We studied in parallel another diene **9** bearing a silyl enol ether,^[25] anticipating a higher reactivity of this diene as well as the formation of a more functionalized cyclohexene as final product, which would be beneficial later in the synthesis (for instance for the coupling with the butenolide fragment at C5). As depicted in Scheme 3, Diels-Alder reaction between diene **9** and acrylate **6a** under Ward's conditions effectively led to silyl enol ether **10** in satisfying yield. Unfortunately, we were unable to estimate the enantioselectivity of this reaction, even after hydrolysis of the enol ethers, which led to a mixture of epimeric ketones. Therefore, considering the high yield and good level of enantiocontrol obtained using H₈-BINOL **7e** in cycloaddition between **4** and **6b**, this approach was selected for the remaining part of our study (*vide infra*).



Scheme 3. Diels-Alder reaction between diene **9** and acrylate **6a**.

Functionalization of the cyclohexene core

The installation of the *all*-carbon quaternary stereocenter was performed through aldolisation or alkylation of the cyclohexene **8**, using LDA as a base and formaldehyde^[26] or BOMC^[27] respectively as electrophiles, affording compounds **11** and **12** in excellent yields as single *cis*-diastereomers (Scheme 4). Protection of the alcohol function of **11** as a PMB ether under acidic conditions led to **5** in high overall yield. Alternatively, aldol reaction from **8**, under similar conditions, using acetaldehyde, led to alcohol **13** as a mixture of diastereomers, albeit with low diastereocontrol. Oxidation of **13** under Swern conditions followed by the protection of the keto functional group with ethane-1,2-diol eventually led to cyclic ketal **14** in excellent yield.



Scheme 4. Installation of the all-carbon quaternary stereocenter.

The rapid assembly of fused lactones **5**, **12** and **14** opens an access either to the spiroimine moiety of spiroolides for the former or that of gymnodimines for the latter. We thus concentrated our efforts on the elaboration of **14** in order to access the spiroimine skeleton of **2**. The formation of the spirane system in spiroimine **I** (Figure 3) would require the incorporation early in the sequence of the C30-C32 aminoalkyl chain. This could be realized either through a nucleophilic addition at C30 of lactone **14** of a fragment containing a nitrile functional group or *via* the coupling of a vinyl-metal at C30 of the lactone as in **III** (Figure 3).

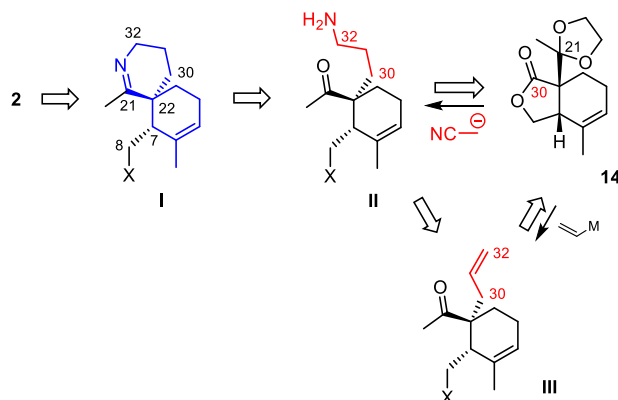
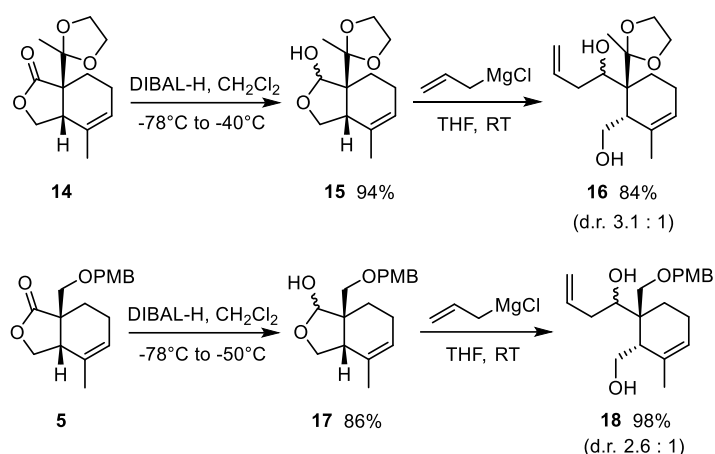


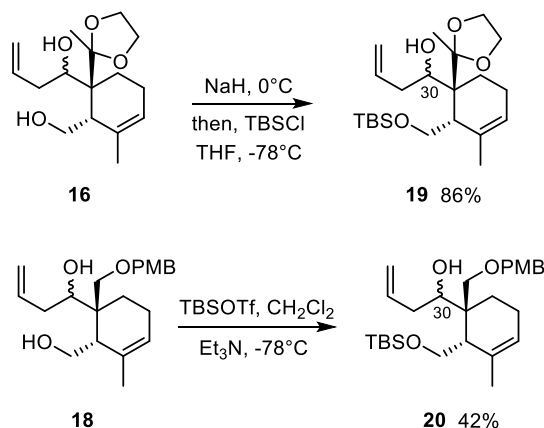
Figure 3. Introduction of the C30-C32 aminoalkyl chain.

Addition of a vinyl Grignard reagent was thus attempted after prior reduction of **14** into the corresponding lactol **15** using DIBAL-H (Scheme 5). No conversion of **15** was observed whatever the conditions. The use of vinyl-lithium led to the same observation, emphasizing on the difficult functionalization of this sterically hindered lactone. More satisfying results were obtained using the allyl Grignard analogue,^[28] which led to the corresponding diol **16** as a mixture of two diastereomers, albeit with a modest d.r. A high yield and a similar diastereocontrol was observed with lactol **17** issued from **5**, which led to the formation of diol **18**. Our plan then relying on the oxidative cleavage of the double bond, to access the corresponding aldehyde, deoxygenation at C30 was first required.



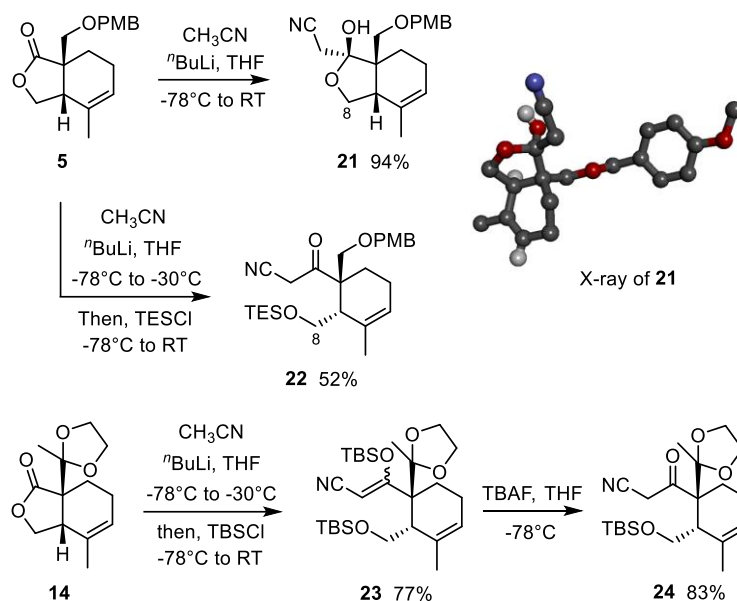
Scheme 5. Alkylation of lactones **5** and **14**.

Selective protection of the primary alcohol was carried out on both compounds **16** and **18** (Scheme 6). Silylation of **16** using standard conditions (TBSOTf, NEt_3) affording essentially the bis-silylation product, the selective protection was carried out through the treatment of the diol with 2 equiv. of NaH ,^[29] followed by the addition of 1 equiv of TBSCl at low temperature, leading to **19** in excellent yield. These conditions were inefficient with diol **18**, which was finally monosilylated into **20**, using the corresponding triflate in the presence of Et_3N . Deoxygenation at C30 was then tested. However, all our attempts to remove this hydroxy group, either through radical deoxygenation of a xanthate, or deoxygenation of the corresponding ketone through a Wolff-Kishner process, unfortunately failed.



Scheme 6. Selective silylation of diols **16** and **18**.

An alternative strategy was thus devised, which would afford the correct chain length, based on the addition of a carbanion α - to a nitrile as depicted in Figure 3. It was anticipated that the small size of the CN group would allow the approach of the anion at C30.^[30] Following this plan, the addition of the C31-C32 aminoalkyl chain was realized by simply adding the anion of acetonitrile onto the model lactone **5** (Scheme 7). This led to the formation of lactol **21**, which structure was assigned through ^1H and ^{13}C NMR as well as X-ray diffraction studies. Our efforts to open the lactol in **21** and protect the alcohol at C8 met with failure. Better results were obtained by directly quenching the reaction mixture after the first step (addition of acetonitrile anion) with a chlorosilane. Following this procedure, nitrile **22** was obtained in modest yield. The same approach was extended to lactone **14**, which led first to silylenol ether **23**, the treatment of which afforded nitrile **24** using TBAF at low temperature.

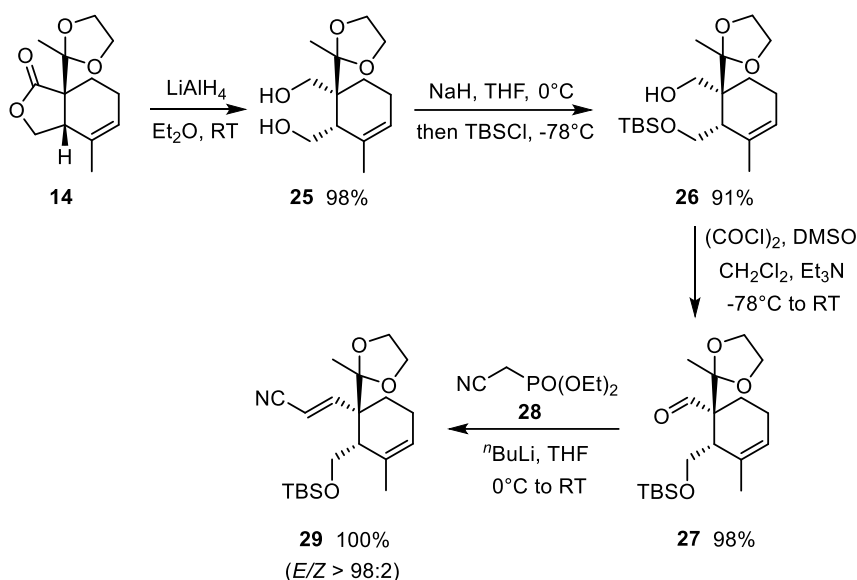


Scheme 7. Addition of the acetonitrile carbanion to install the C30-32 chain.

With the C30-C32 chain installed, the ensuing removal of the free ketone proved to be tedious, as experienced above with the hydroxy group in **16** and **18**. Formation of a tosyl-hydrazone or reduction of the ketone with NaBH_4 or LiBH_4 all failed likely as a result of the steric hindrance. Addition of a 1,2-dithiol or the Lawesson reagent also failed, emphasizing on the difficulties to functionalize the carbon center next to the quaternary stereocenter.

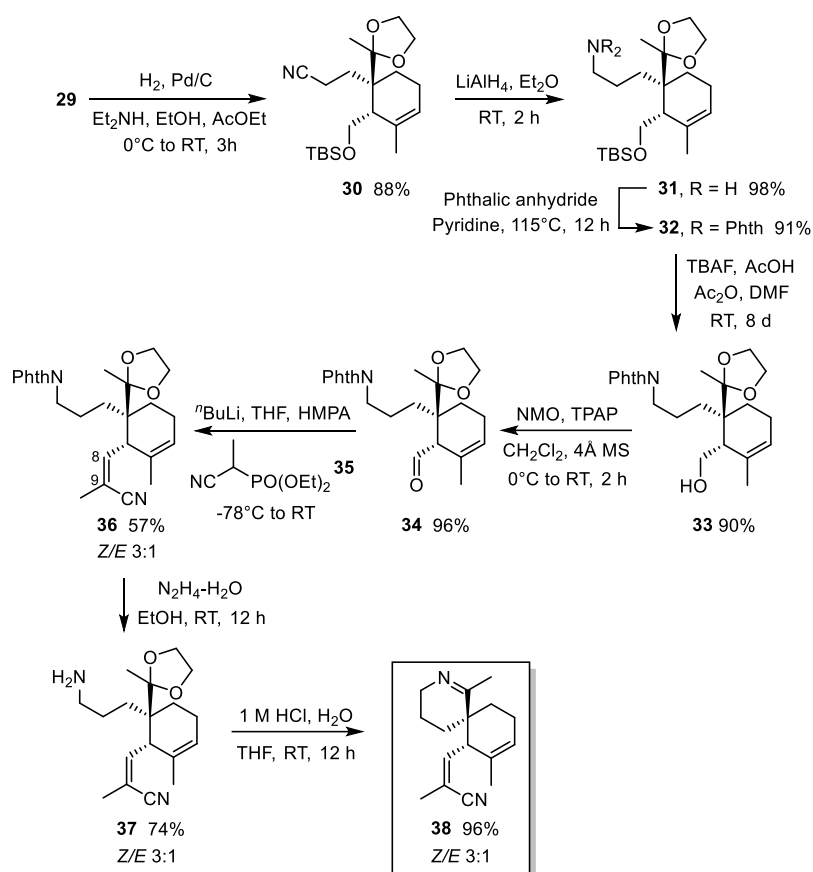
The “nitrile” routes. An access to the gymnodimine spiroimine fragment

Considering our difficulty to modify the resident functionalities in the vicinity of the quaternary center at C22, but also the option to add nucleophiles at C30 (Schemes 5 and 7), we envisioned elaborating the C30-C32 aminoalkyl chain through an olefination process at the C30 center. This approach would allow the incorporation of the remaining 2-carbons and avoid a late and tedious manipulation of a functional group at C30. The selective silylation of lactol **15** (Scheme 5) was first attempted to generate the corresponding aldehyde at C30, ready for the olefination process, but this failed whatever the conditions. The lactone precursor **14** was thus reduced instead into the corresponding diol **25** using LiAlH_4 (Scheme 8). The selective silylation at C8 was then performed as described above for diol **16**,^[29] to give the alcohol **26** in high yield. The oxidation of the latter using Dess-Martin periodinane led to the desired aldehyde **27** in 84% yield. The more economical Swern oxidation was however preferred to produce **27** on larger scale, but also in higher yield. **27** was finally submitted to a Wittig-Horner olefination using cyanophosphonate **28**,^[15] affording the unsaturated nitrile **29** in quantitative yield as a single *E*-isomer. It is worth noticing that the olefination using the ester analogue of **28** under similar conditions led to full recovery of **27**, highlighting the influence of the size of the CN substituent in these nucleophilic additions onto a sterically congested aldehyde.^[30]



Scheme 8. Elaboration of the C30-C32 chain using a Wittig-Horner approach.

The next step involved the chemoselective hydrogenation of the unsaturated nitrile in the presence of the cyclohexene double bond. Various conditions were tested, including single electron transfer process using Mg in MeOH,^[31] but the best results were obtained with hydrogenation using H₂ under Pd-C catalysis. Treatment of **29** with H₂, Pd-C in ethyl acetate led to a mixture of the desired saturated nitrile **30** in equimolar amount with the fully hydrogenated compound. Finally, using Et₂NH as a co-solvent led to the selective hydrogenation of the electron-poor olefin affording **30** in a satisfying 88% yield (Scheme 9). The nitrile was then reduced into the corresponding amine **31** using LiAlH₄ and the free amine protected as a phthalimide to afford **32** in high yield.^[32] The deprotection of the primary alcohol in **32** in the presence of an acid-sensitive ketal proved to be more troublesome than expected and after extensive studies, this was finally accomplished using an excess of TBAF (6 equiv.) in acetic acid, with acetic anhydride added to trap residual water present in the ammonium fluoride.^[33] 2 g of alcohol **33** could thus be prepared in 90% yield (96% brsm), albeit at a slow rate. **33** was then oxidized using Ley's TPAP reagent^[34] to afford aldehyde **34**. At this stage, we envisioned the conversion of **34** into the corresponding alkyne (C8-C9), a potent precursor of the vinyl iodide (i.e. spiroimine **B**, Figure 2) required for the Nozaki-Hiyama-Kishi coupling. All our efforts to transform the C8 aldehyde following Ohira-Bestmann^[35] or Corey-Fuchs^[36] procedures to install the triple bond however failed, leading to no reaction or complete degradation of **34**. The latter was eventually engaged in a Wittig-Horner reaction with phosphonate **35** to give the unsaturated nitrile **36** as a 3:1 mixture of *Z/E* stereoisomers,^[37] thus installing the C8-C9 fragment. It is worth mentioning at this point that the reaction with the ester analogue of **35** led to degradation of **34**. Phosphonium reagents did not react with **34**, while Peterson elimination using the enolate of MeCH(SiMe₃)CO₂Et (LDA, THF, -78°C) led to a 6:4 *E/Z* mixture of the ester analogue of **36** in only 39% yield.^[38] Nitrile **36** was finally converted into spiroimine **38** in high yield, after removal of the phthalimide group using hydrazine,^[39] followed by the ketal deprotection and ring closure of the corresponding amine **37** under acidic conditions. The synthesis of **38** has thus been realized through a linear 16 steps sequence in a remarkable 21% overall yield from dienol **4**. **38** constitutes a valuable synthon for further incorporation into the preparation of the macrocyclic core of gymnodimine **2**.



Scheme 9. Final steps in the synthesis of the spiroimine core of gymnodimine **2**.

Conclusions

In summary, we reported a general access to the fully functionalized cyclohexene skeleton of spiroides and gymnodimine, macrocyclic phycotoxins produced by the dinoflagellate *Alexandrium ostenfeldii* and *peruvianum*. The key-cyclohexene fragment is elaborated relying on an enantiocontrolled Diels-Alder process between readily available dienol and acrylates in the presence of H₈-BINOL as a chiral inducer. This step was performed on multi-gram scale, furnishing the desired cyclohexene in high yield and enantioselectivity. The all-carbon quaternary stereocenter was then installed through an alkylation or an aldolisation with complete diastereocontrol. The C30-C32 aminoalkyl chain was elaborated based on a Wittig-Horner process between a cyanophosphonate and the aldehyde function at C30. A related olefination process was used to install the C8-C9 vinylic moiety. Further manipulation finally allowed the ring closure and access to the spiroimine core of gymnodimine **2**. This study thus opens an access to one of the three key-synthons of **2** in high overall yield, also highlighting the difficulties to manipulate functional groups at the neighborhood of an all-carbon quaternary stereocenter. This hurdle was finally circumvented using two different cyanophosphonates to install C8-C9 and C31-C32 fragments relying on the small size of the cyano group. The access to synthon **38** has somewhat modified the original plan based on a Nozaki-Hiyama-Kishi coupling (Figure 2). Although intermediate **38** is not appropriate for a further conversion into the spiroide spiroimine fragment, the present Diels-Alder strategy has the potential for application to the elaboration of other spiroimine systems. Intermediate **8** may for instance be alkylated with the suitable C31-C33 aminoalkyl chain present in **1**. Efforts are now underway to isomerize synthon **38** under photochemical conditions^[40] and test a direct coupling^[41] between the tetrahydrofuran fragment and the C10 nitrile to create the C10-C11 bond and link THF and spiroimine fragments.

Experimental Section

Preparation of lactone **5b** from acrylate **3b** and dienol **4**

To a solution of dienol **4** (57.8 mg, 0.589 mmol) in CH₂Cl₂ (3 mL) was added a 0.85 M solution of Me₂Zn in toluene (0.69 mL, 0.589 mmol) at 0 °C. In a separated flask, a 2.5 M solution of MeMgBr in Et₂O (0.23 mL, 0.589 mmol) was added at 0 °C to a solution of (*R*)-BINOL (168.9 mg, 0.589 mmol) in CH₂Cl₂ (3 mL). After 5 min., the solution of the first vessel was added at 0 °C to the solution of MeMgBr/BINOL. After 5 min., the resulting reaction mixture was diluted with CH₂Cl₂ (10 mL) and the acrylate **3b** (737 mg, 2.94 mmol) in CH₂Cl₂ (10 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred for 2 days. The reaction was then quenched by addition of saturated NaHCO₃ (ca. 2 mL). The resulting mixture was filtrated over Na₂SO₄/Celite (1/1), washed with CH₂Cl₂ and concentrated under vacuum. The crude residue was purified by flash chromatography (SiO₂, PE-AcOEt 90:10 to 85:15) to give the lactone **5b** (129 mg, 73%) as a colorless oil. R_f= 0.4 (PE-AcOEt 85:15); IR (ATR) ν_{\max} (cm⁻¹) 2914, 1765, 1611, 1512, 1246, 1031, 816, 734; ¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.25-7.18 (m, 2H), 6.93-6.82 (m, 2H), 5.62-5.52 (m, 1H), 4.58-4.36 (m, 3H), 3.95 (dd, *J* = 8.4, 5.7 Hz, 1H), 3.80 (s, 3H), 3.63 (d, *J* = 8.9 Hz, 1H), 3.46 (d, *J* = 8.9 Hz, 1H), 2.99 (t, *J* = 7.0 Hz, 1H), 2.01-1.92 (m, 2H), 1.81-1.71 (m, 1H), 1.70-1.68 (m, 3H), 1.53-1.41 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 180.4, 159.3, 131.8, 130.0, 129.3, 123.4, 113.1, 73.3, 73.3, 71.1, 55.4, 47.3, 41.9, 24.3, 21.9, 21.6; HRMS (ESI) calculated for C₁₀H₁₄O₃Na [M+Na]⁺ 325.1410, found : 325.1418.

Lactone **13**

To a solution of diisopropylamine (2.37 mL, 16.76 mmol) in THF (50 mL) was added a 1.8 M solution of ^tBuLi in hexane (9.3 mL, 16.76 mmol) at -30 °C. The reaction mixture was stirred at -30 °C for 15 min. then cooled to -78 °C and a solution of lactone **8** (1.7 g, 11.17 mmol) in THF (35 mL) was added. The light yellow solution was warmed up to -30 °C in 30 min. and cooled to -78 °C again. Acetaldehyde (1.88 mL, 33.51 mmol) was added. The reaction mixture was then warmed up to 0 °C overnight. The reaction mixture was quenched with an aqueous solution of NaHCO₃ (100 mL), extracted with Et₂O (3 x 50 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under vacuum. The crude residue was purified by flash chromatography, (SiO₂, PE-AcOEt 80:20 to 70:30) to give **13** as a light yellow oil and a 1.4:1 mixture of 2 diastereoisomers (2.08 g, 95%). [α]_D²⁵ = -160.75 (c=1.0, CHCl₃). R_f= 0.2 (PE-AcOEt 85:15); IR (ATR) ν_{\max} (cm⁻¹) 3455, 2918, 1759, 1667, 1375, 1150, 1012, 785; ¹H NMR (300 MHz, CDCl₃) δ (ppm) 5.58 (s, 1H), 4.51 (td, *J* = 8.3, 3.8 Hz, 1H), 3.98-3.74 (m, 2H), 3.01-2.76 (m, 2H), 2.68-2.46 (m, 1H), 2.11-1.85 (m, 2H), 1.75-1.54 (m, 5H), 1.32 (d, *J* = 6.5 Hz, 1H), 1.22 (d, *J* = 6.4 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 181.6, 180.3, 132.0, 131.9, 124.0, 123.5, 123.3, 77.2, 71.8, 71.6, 71.5, 69.7, 51.4, 50.6, 42.7, 40.5, 24.0, 23.8, 21.9, 21.8, 18.8, 18.3; HRMS (ESI) calculated for C₁₁H₁₆O₃Na [M+Na]⁺ 219.0991, found : 219.0984.

Unsaturated nitrile **29**

To a solution of diethyl cyanomethylphosphonate **28** (0.215 mL, 1.35 mmol) in THF (6 mL) was added a 2.1 M solution of ^tBuLi in hexane (0.5 mL, 1 mmol) at 0 °C. The resulting mixture was stirred at this temperature for 1 h, then the aldehyde **27** (124 mg, 0.35 mmol) was added at 0 °C in THF (3 mL). The reaction mixture was slowly allowed to warm to RT overnight. The reaction mixture was quenched with a sat. aqueous solution of NH₄Cl (20 mL), and the aqueous layer extracted with Et₂O (3 x 10 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under vacuum. The crude residue was purified by flash chromatography (SiO₂, PE-AcOEt 95:5) to give the **29** (133 mg, 100%) as a colorless oil. [α]_D²⁵ = +121.07 (c=1.27, CHCl₃). R_f= 0.41 (PE-AcOEt 95:5); IR (ATR) ν_{\max} (cm⁻¹) 3956, 2221, 1258, 1092, 1020, 835, 797; ¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.23 (d, *J* = 17.1 Hz, 1H), 5.48 (s, 1H), 5.36 (d, *J* = 17.1 Hz, 1H), 4.00 – 3.73 (m, 4H), 3.68-3.57 (m, 2H), 2.28 (s, 1H), 2.13 -1.81 (m, 3H), 1.74 (d, *J* = 1.8 Hz, 3H), 1.71 – 1.65 (m, 1H), 1.17 (s, 3H), 0.88 (s, 9H), 0.02 (d, *J* = 3.7 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 161.2, 132.5, 123.6, 118.5, 113.2, 98.5, 65.6, 64.2, 62.1, 51.1, 45.1, 26.0, 24.6, 22.9, 22.7, 20.9, -5.4, -5.5; HRMS (ESI) calculated for C₂₁H₃₅NO₃SiNa [M+Na]⁺ 400.2278, found : 400.2280.

Spiromine **38**

To solution of protected ketone **37** (36.9 mg, 1.12 mmol) in THF (2.5 mL) was added 1 M HCl in water (0.36 mL, 0.36 mmol) and the mixture was stirred overnight at RT. The reaction mixture was then quenched with a sat. aqueous solution of NaHCO₃ (2 mL) to reach pH≈7, and the aqueous layer was extracted with AcOEt (3 x 5 mL) then CH₂Cl₂ (3 x 5 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under vacuum. The crude residue was purified by flash chromatography (SiO₂, DCM-MeOH-NH₄OH 95:4:1) to afford the desired spiromine **38** as a as a yellow oil and a 3:1 mixture of *E/Z* isomers (28mg,

96%). $[\alpha]_D^{25} = +55.08$ ($c = 1.3$, CHCl_3). $R_f = 0.5$ (DCM-MeOH-NH₄OH 95:4:1); IR (ATR) ν_{max} (cm^{-1}) 2930, 2853, 2215, 1643, 1436, 917, 729; ¹H NMR (300 MHz, CDCl_3) δ (ppm) 6.25-6.13 (m, 0.22H), 6.04-5.88 (m, 0.78H), 5.54-5.45 (m, 1H), 3.58-3.28 (m, 3H), 2.07-1.96 (m, 5H), 1.91 (s, 2.3H), 1.89 (s, 1.4H), 1.86-1.61 (m, 2.4H), 1.56-1.37 (m, 7.6H); ¹³C NMR (75 MHz, CDCl_3) δ (ppm) 172.5, 148.0, 147.7, 131.3, 131.1, 123.4, 122.9, 118.2, 111.5, 49.3, 49.2, 48.5, 44.9, 41.5, 31.2, 31.0, 26.7, 26.5, 23.4, 23.4, 22.7, 22.5, 22.0, 22.0, 20.6, 20.0, 19.7, 15.5; HRMS (ESI) calculated for $\text{C}_{16}\text{H}_{22}\text{N}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 265.1675, found : 265.1678.

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