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Total Synthesis of Spirolides

"SpiroSynth"

Final Report

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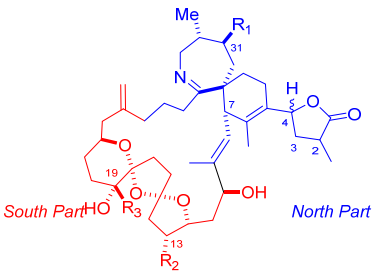
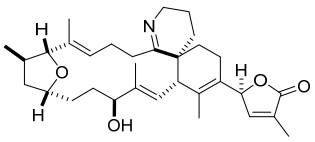
I. Introduction

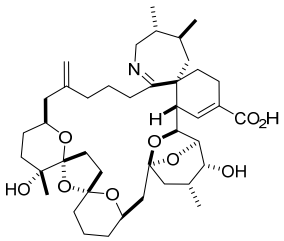
Spirolides **1-6** (Figure 1) and their congeners (gymnodimines, pinnatoxins and pteriatoxins) are novel macrocyclic imine phycotoxins produced by the dinoflagellate *Alexandrium ostenfeldii*, first isolated from the digestive glands of mussels, scallops and phytoplankton harvested from aquaculture sites on the Atlantic coast of Nova Scotia, Canada, in the early 1990s.[1] They were later found around New Zealand coastline but have since been isolated from shellfish from 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 in the months of 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, fishs, birds, marine mammals and ultimately to humans, thus menacing wild life and human health. Thus, shellfish poisoning constitutes a threat to public health and also to the shellfish industry. As an example, spirolides 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 comsumption.[3] Similar problems occurred in other part of the world.



Spirolide A (**1**) : R_1 = H, R_2 = R_3 = Me, $\Delta^{2,3}$
Spirolide B (**2**) : R_1 = H, R_2 = R_3 = Me
Spirolide C (**3**) : R_1 = R_2 = R_3 = Me, $\Delta^{2,3}$
Spirolide D (**4**) : R_1 = R_2 = R_3 = Me
13-desmethyl spirolide C (**5**) : R_1 = R_3 = Me, R_2 = H, $\Delta^{2,3}$
13,19-didesmethyl spirolide C (**6**) : R_1 = Me, R_2 = R_3 = H, $\Delta^{2,3}$



(–)-Gymnodimine A (**7**)



(+)-Pinnatoxin A (**8**)

Figure 1

Among these phycotoxins, the spirolides **1-6**, gymnodimine A **7**[4] and pinnatoxin A **8**[5] members of the spiroimine family, have been the most intensively studied phycotoxins

due to their occurrence and intriguing biological activities. Spirolides **1-6** 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 LD_{50} values are in the 7-9 mg/kg range[6] and death was observed within 3-20 minutes after i.p. injection. Later studies proved that the molecular targets of 13-desmethyl spirolide C **5** are nicotinic acetylcholine receptors (nAChR)[7] and revealed that the toxin is a potent antagonist of nAChR in the subnanomolar range with moderate specificities for the various subtypes.[8] To date, no toxicological studies have been carried out to evaluate the long term impact of spirolides on human health.

Recently, 13-desmethyl spirolide C **5** and gymnodimine A **7**, two representative members of the family, 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.8 These data provide crucial information relative to the functional determinants and binding regions of both the toxins and receptors.

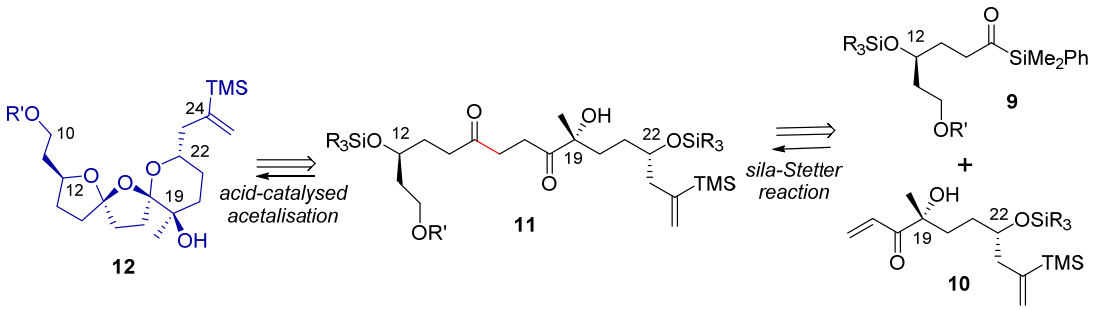
The synthesis of spirolides fragments but also total synthesis of phycotoxins is currently at the heart of an intense research activity, involving very competitive teams over the world, both in biology and organic chemistry. To date, fourteen different spirolides have been identified.[9] While the total synthesis of gymnodimine **7** has recently been completed by the Romo's group[10] and that several groups have reported their efforts toward the synthesis of spirolides,[11,12] no total synthesis of spirolides has ever been described.

In this context, it is our objective to provide a straightforward access to 13-desmethyl spirolide C **5**. This will be achieved by developing new and convergent methods to access the spiroimine and bis-spiroketal fragments of spirolide **5**. The results obtained during this program will contribute to the development of new methodological methods in organic synthesis to access original architectures. It should ultimately provide an access to larger amount of rare complex marine macrocycles and afford, to biologists, sufficient amount to carry out toxicological studies.

II. Present work

Natural products of interest are usually isolated in low concentrations from natural sources. Developing new synthetic strategies and methods towards such compounds is therefore an attractive option to obtain larger quantities of the natural product without putting strain on the natural resource and to provide fragments and/or analogues.

A straightforward disconnection leading to the south bis-spiroketal fragment implies at some stage the generation of a 1,4-diketone, which upon ketalization under acidic conditions should provide the desired tricycle. The retrosynthetic pathways depicted below indicates that access to such a 1,4-diketone could involve a sila-Stetter reaction as a key-coupling process.

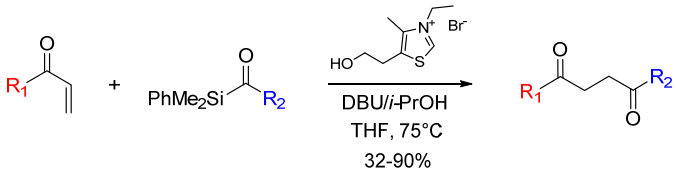


Scheme 1

Sub-task 2.1 Developpement of the methodology

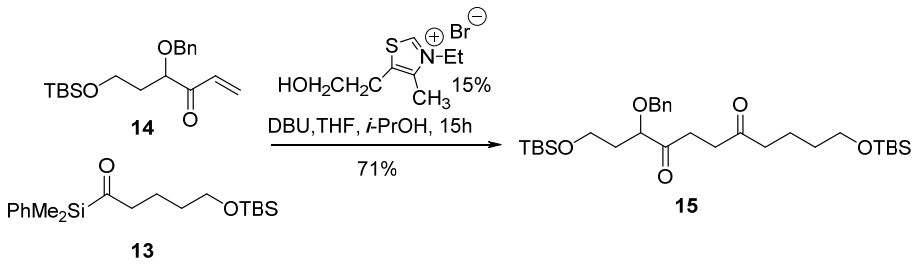
Sila-Stetter reaction onto aliphatic alkyl partners

Before starting the synthesis of both designed fragments for the synthetic approach to the southern fragment, a methodological study of sila-Stetter reaction involving aliphatic enones and acylsilanes partners has been developed in the lab.[13]



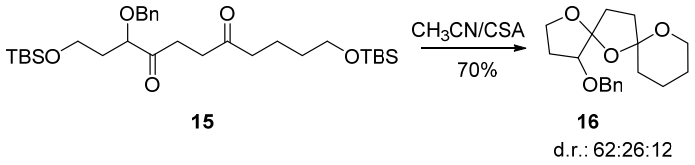
Scheme 2

In particular, enone **14** and acylsilane **13** provided efficiently the 1,4-diketone **15**. (Scheme 3)



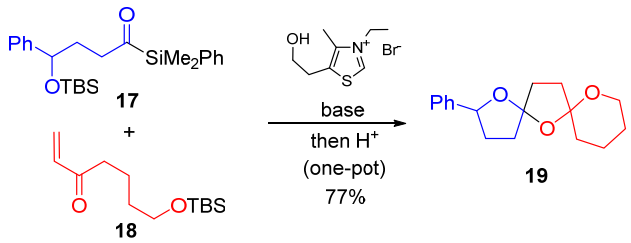
Scheme 3

A model reaction of deprotection/ketalisation was efficiently performed following classical acidic conditions, providing the bis-spiroketal skeleton **16** in good yield. (Scheme 4)



Scheme 4

A sequential one-pot sila-Stetter/ketalisation-cyclisation reaction was also successfully performed using other partners.



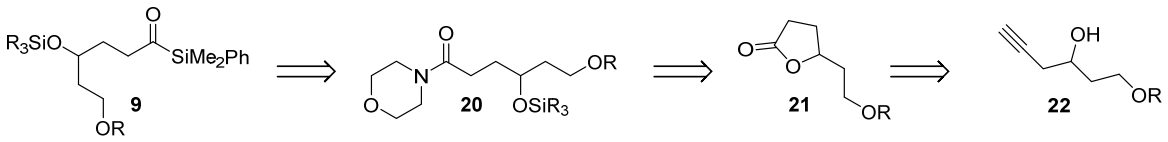
Scheme 5

Having in hands a convergent methodology to provide efficiently functionalized bis-spiroketal skeleton, the synthesis of acylsilane and enone partners for the natural product fragment was planned.

<u>Sub-task 2.2 Application to the total synthesis of the south fragment</u>

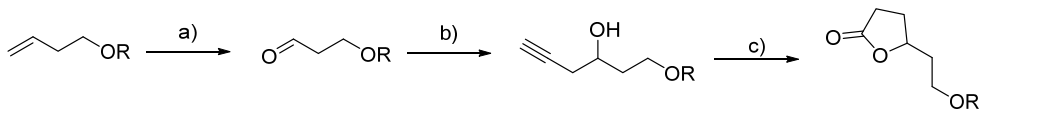
Synthesis of the acylsilane partner

The retrosynthetic pathway for the acylsilane **9** synthesis was firstly envisioned as follow:



Scheme 6

The first synthesic approach of the acylsilane fragment was firstly envisioned using a gold-catalyzed tandem cycloisomerization/oxidation of homopropargyl alcohol **22** to provide the intermediate γ-lactone **21**.[14] The morpholine amide **20** would be obtained after the classical ring opening of the lactone and easily converted into acylsilane **9**.[15] Two synthetic routes have been explored for the synthesis of the precursor homopropargylic alcohol. The first one was based on the addition of a propargyl Grignard reagent onto a suitable aldehyde **23**. The second one consisted in epoxyde **26** opening with the lithium anion of trimethylsilylacetylene. The lactonization reaction was studied varying the protective groups (TIPS, TBS, Bn, TBDPS). TBDPS was found to provide the lactone with the best yield (Scheme 7).



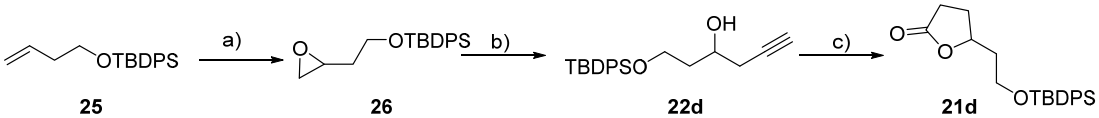
24a, R = TIPS
24b, R = TBS
24c R = Bn
24d, R = TBDPS

23a, R = TIPS (68%)
23b, R = TBS (70%)
23c, R = Bn (75%)
23d, R = TBDPS (70%)

22a, R = TIPS (73%)
22b, R = TBS (75%)
22c, R = Bn (65%)
22d, R = TBDPS (80%)

21a, R = TIPS (degradation)
21b, R = TBS (degradation)
21c, R = Bn (55%)
21d, R = TBDPS (67%)

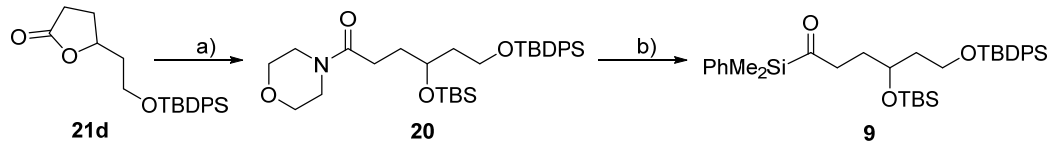
a) 1) OsO_4/NMO, 2) $NaIO_4$; b) THF, Propargyl bromide, Mg reflux; c)(4-$CF_3C_6H_4)_3PAuNTf_2$ (5 mol%), MCPBA (1.5 eq), MsOH (1 eq), DCE, rt.



a) CH_2Cl_2, MCPBA, 80%; b) 1)THF, -78ºC TMSCCH, BuLi, Et_2O-BF_3. 2) MeOH, K_2CO_3, 80%; c) (4-$CF_3C_6H_4)_3PAuNTf_2$ (5 mol%), MCPBA (1.5 eq), MsOH (1 eq), DCE, rt. 67%.

Scheme 7

Opening of the lactone **21d** with morpholine provided the suitable morpholine amide **20**, precursor of the acylsilane **9** partner following Scheidt's method (Scheme 8).[15]

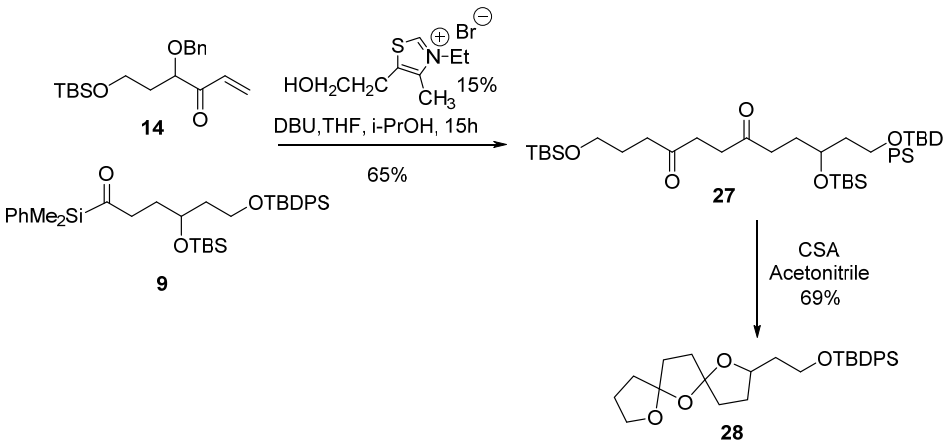


21d **20** **9**

a) 1)THF, Morpholine, BuLi. 2) DMF, Imidazole, TBSCl. 80%. b) $PhMe_2SiLi$ -78ºC. 70%

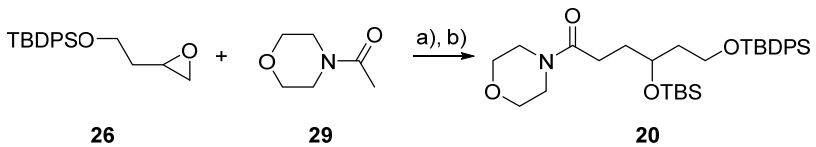
Scheme 8

The acylsilane **9** was reacted with the vinylketone **14** previously synthetised to provide the 1,4-diketone **27** and the bis-spiroketal **28** after subsequent deprotection/ketalization-cyclization sequence. (Scheme 9)



Scheme 9

A shorter synthetic pathway towards **9** was designed, based on the known high nucleophilicity of amide enolates and their reactivity towards electrophiles including epoxides.[16] The reaction of *N*-Acetyl morpholine enolate onto the suitable epoxide **26** and subsequent hydroxyl protection provided the desired morpholine amide **20** precursor in only two steps and an excellent yield (Scheme 10).

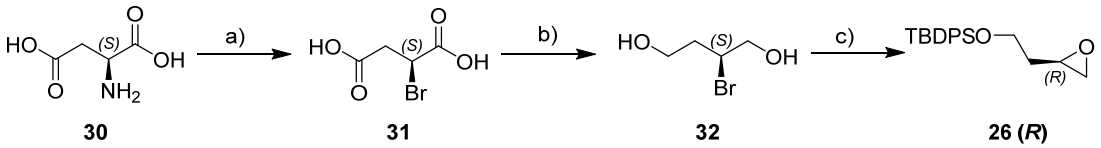


26 **29** **20**

a) THF, LDA; b) DMF, imidazole, TBSCl, 75%

Scheme 10

Approaches based on Shi's epoxidation[17] of a suitable terminal olefin or kinetic resolution of terminal epoxides using a Co(II)-Salen complex (Jacobsen reaction[18]) were envisioned for the extension of the above strategy to an enantioselective approach. The results were disappointing in terms of yields and enantioselectivities and we turned our attention to the use of (*S*)-aspartic acid as starting material. The preparation of the optically pure epoxide is depicted below in Scheme 11.



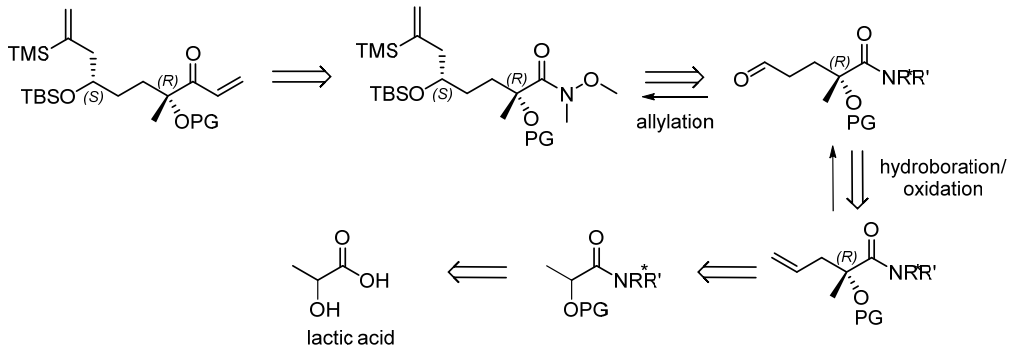
a) H_2SO_4/H_2O, KBr, $NaNO_2$, 98%; b) THF, BMS, 99%; c) 1) THF, NaH, 2) TBDPSCl, 80%, 98% ee

Scheme 11

Synthesis of the vinylketone partner

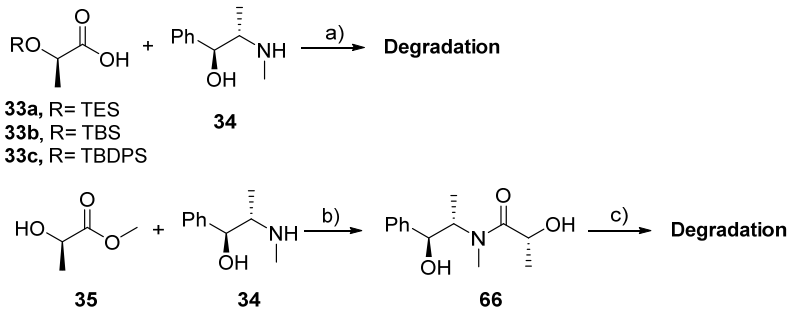
Several approaches were explored in parallel, on the one hand by Jessica Labarre-Lainé during her Ph.D and on the other hand during this post-doctoral work.

The general retrosynthetic pathway for the vinylketone partner could be envisioned as follows:



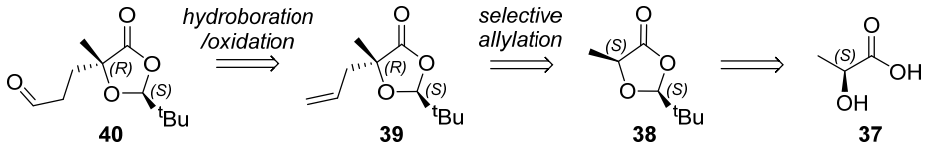
Scheme 12

The synthesis of this fragment implied the challenging introduction of a quaternary center in a stereocontrolled manner. Two synthetic routes, based on the use of diastereoselective allylation key steps were envisioned. The first one relying on the use of the Myers's chiral auxiliary[19] **34** unfortunately met with failure (Scheme 13).



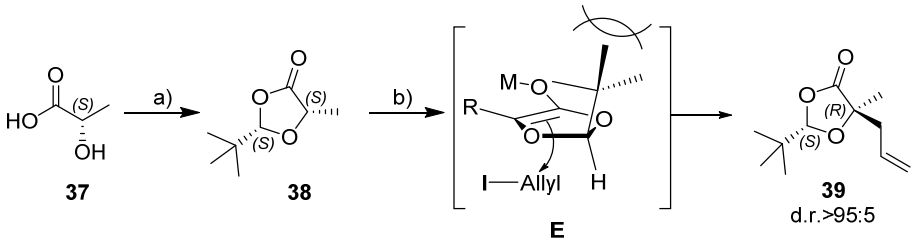
Scheme 13

In the second approach, we turned our attention to the Seebach's alkylation of an enantiomerically pure dioxolanone **38**[20] (Scheme 14).



Scheme 14

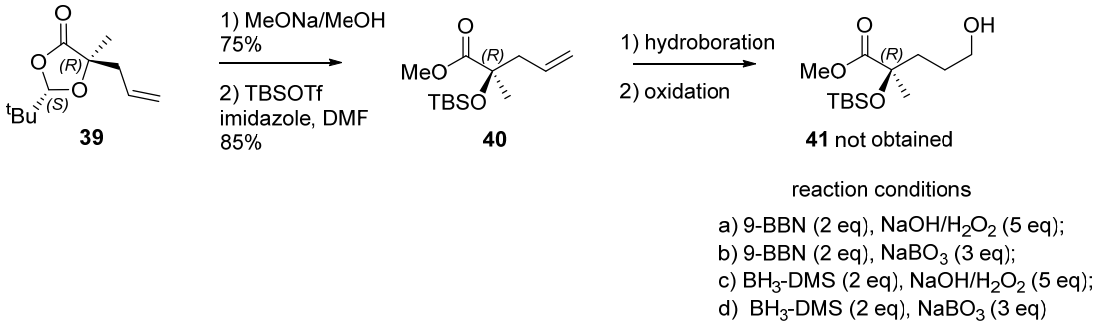
Addition of allyl iodide onto the enolate **E** issued from **38**, led to the desired compound **39** in good yield and high diastereoselectivity (NMR data showed only one stereoisomer).



a) 1) $CH_3(OCH_3)_3$/Cyclohexene, 2) Pivalaldehyde, p-TsOH/Hexane, 65%; b) THF, -78ºC, LDA, Allyl Iodide, 70 %.

Scheme 15

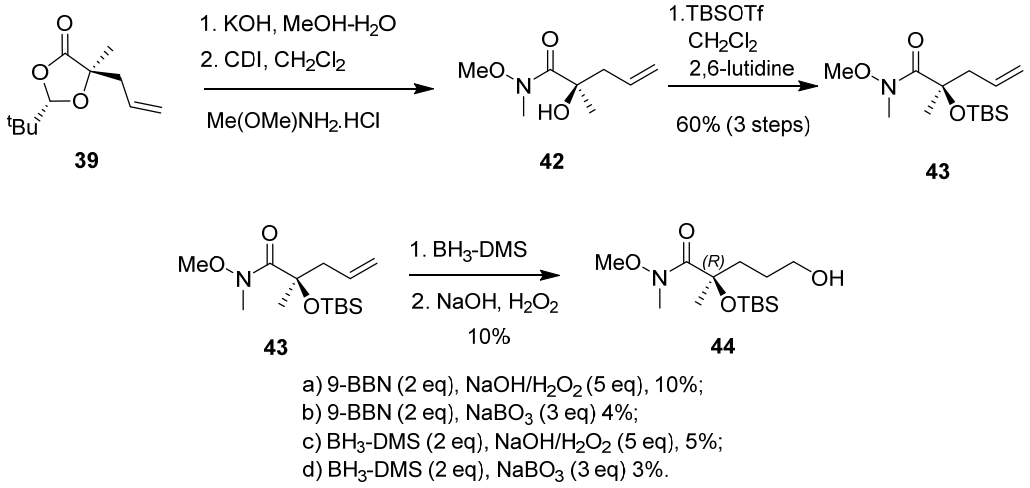
Preliminary experiments onto **39** have shown that hydroboration under various conditions led to complex mixtures of products, due to the relative instability of the dioxolanone. Current investigations are trying to functionalize the alkene at a later stage, using the ester intermediate **40** easily obtained from the dioxolanone. (Scheme 16)



Scheme 16

Hydroboration/oxidation tests performed with this ester resulted in a complex mixture of products. These attempts, when conducted with 9-BBN and BH_3-DMS reagents and under various oxidation conditions, always led to the same disappointing results.

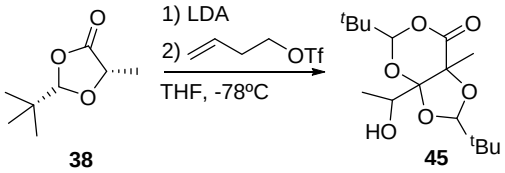
Regarding to these problems, the dioxolanone **39** was converted into the Weinreb amide **42** which was in turn submitted to the hydroboration-oxidation sequence leading to the corresponding amide alcohol **44** in only 10% yield for the best results. Following the same conditions as previously described, the desired product **44** was detected but the yields happened to be very low despite a good conversion. This could be explained by to the polarity of the product and difficulty to purify it.



Scheme 17

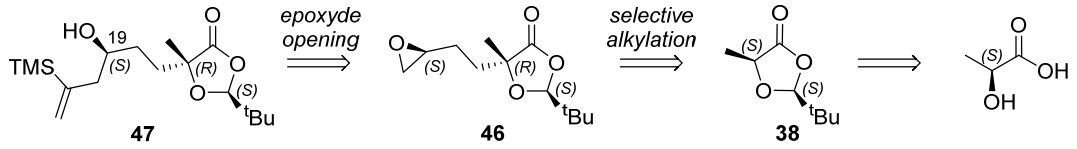
To avoid the obviously sensitive hydroboration-oxidation step, the dioxolanone **38** was alkylated using an alkene triflate bearing one more carbon than the allyliodide. In this case, an oxidative cleavage of the double bound would provide the suitable aldehyde

function. Unfortunately, only the product **45** resulting from the dioxolanone autocondensation was observed.



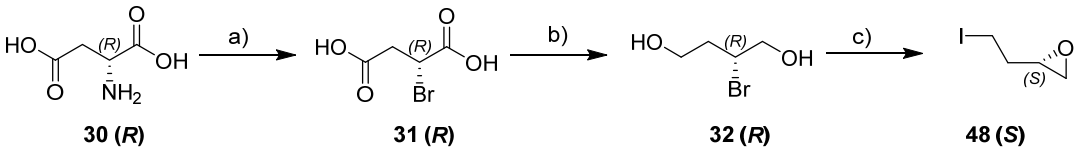
Scheme 18

Another synthetic pathway was then planned, also based (Scheme 19) on alkylation reaction onto dioxolanone to introduce the quaternary center. In this case, alkylation of the enolate would be performed with a fully functionalized electrophile, avoiding problems of a later stage functionalization. The chiral homoallylic alcohol **47** should be obtained *via* the nucleophilic opening of a chiral epoxide **46** using suitable vinylmetal reagents.



Scheme 19

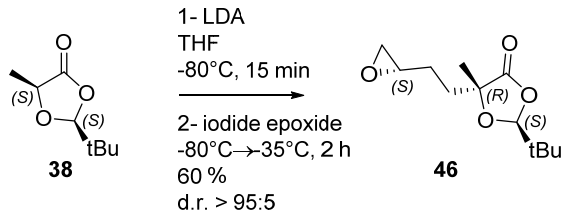
The optically pure epoxide **48 (*S*)** was synthesized using the same sequence as epoxide **26 (*R*)**, starting from (*R*) aspartic acid.



a) H_2SO_4/H_2O, KBr, $NaNO_2$, 98%; b) THF, BMS, 99%; c) 1) THF, NaH, 2) TosCl, 85%, 98% ee, 3) NaI, acetone reflux 95%.

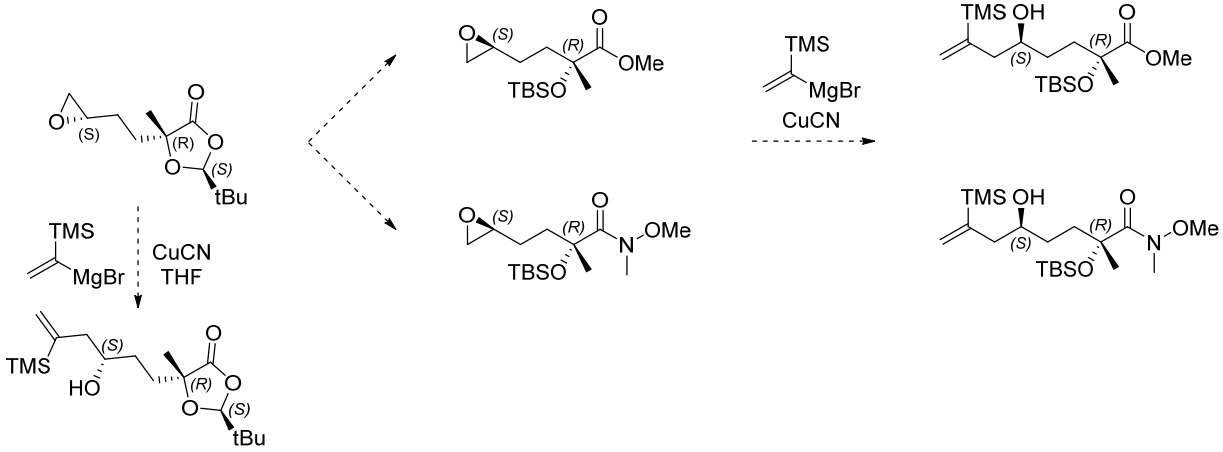
Scheme 20

The alkylation of the dioxolanone **38** was performed successfully leading to the desired epoxide **46** as a single isomer in 60% yield.



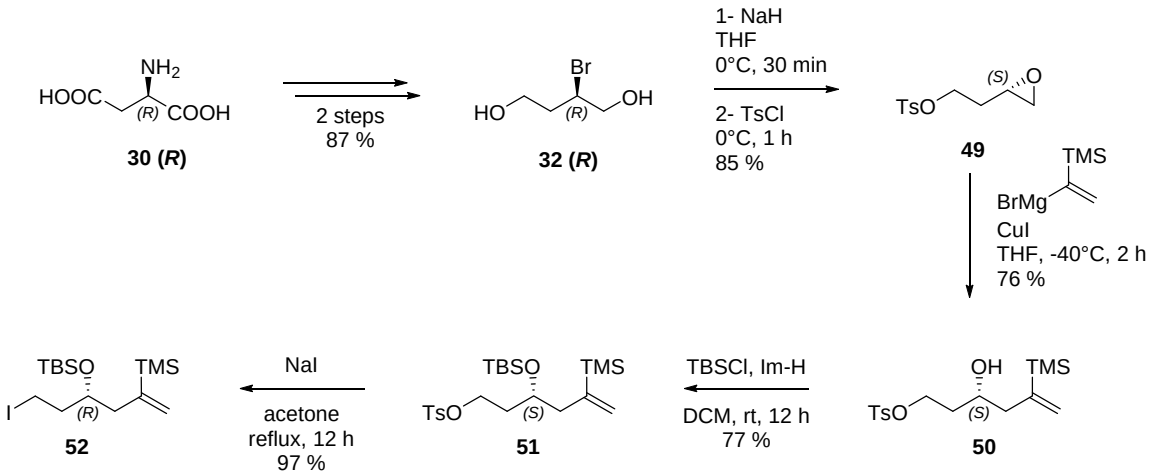
Scheme 21

Despites our efforts, it was not possible in our hands to provide ring epoxide opening neither on the dioxolanone specie, nor on the derived ester or Weinreb amide.



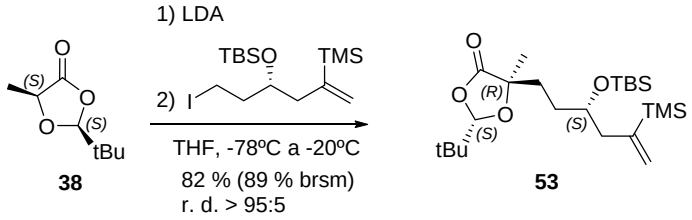
Scheme 22

The electrophile **52** bearing the vinylTMS moiety resulting from the epoxyde opening was then designed and synthetized. Epoxide **49** previously described was initially reacted with a TMS-vinyl Grignard reagent[21], the resulting alcohol was protected as TBS and tosylate was then converted into the suitable iodide electrophile.



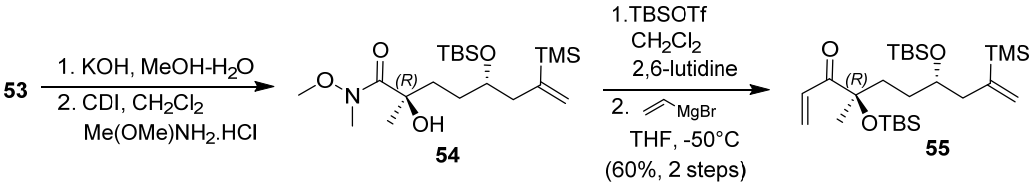
Scheme 23

Direct alkylation of dioxolanone **38** with corresponding iodide **52**[22] occurred with high diastereocontrol, leading to **53** in 82% yield as a single stereoisomer



Scheme 24

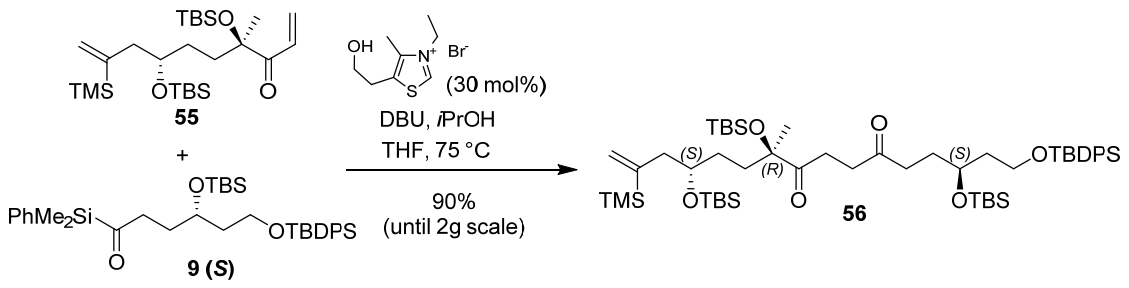
Dioxolanone ring-opening under basic conditions,[23] followed by coupling of the resulting carboxylic acid with the *N*-methyl-*N*-methoxy amine led to the Weinreb amide **54**.[24] Protection of the tertiary hydroxy group in **54** followed by addition of a vinyl Grignard reagent finally led to the desired enone **55** in 10 steps and 15% overall yield from (*R*)-aspartic acid



Scheme 25

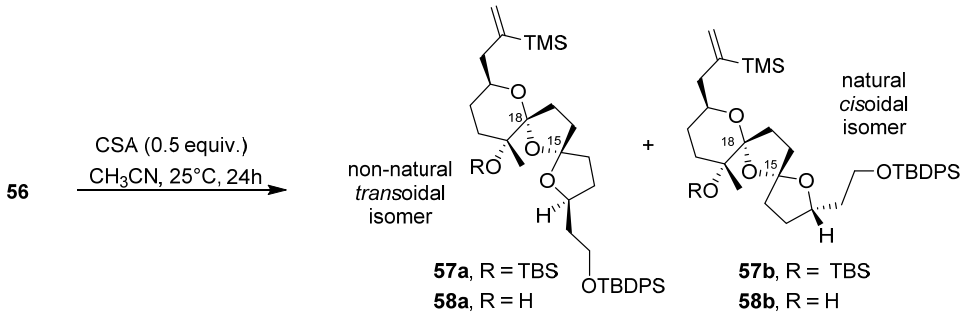
<u>Sila-Stetter reaction: towards the key intermediate 1,4-diketone</u>

The sila-Stetter reaction was then carried out using equimolar amount of enone **55** and acylsilane **9 (*S*)** in THF at 75°C following the reaction conditions previously set up in our metholology study.[13] The 1,4-diketone **56** was obtained as a mixture with the excess of acylsilane **9 (*S*)**, which could not be separated by chromatography. The mixture was subsequently submitted the spiroketalisation step.



Scheme 26

Spiroketalization was first performed using camphorsulfonic acid (CSA) in CH_3CN (Scheme 27). Desilylated bis-spiroketals were then obtained in a 73% isolated yield as a 2.5:1.5:1 inseparable mixture of 3 diastereoisomers **57a-c** (**57c** not shown). Another compound **58a**, which had lost its silyl group at C19 was also isolated in 25% yield. The stereochemistry of **58a** was assigned unambiguously, revealing a non-natural transoid-stereochemistry by two-dimensional NMR NOESY experiments.[25] For **58a**, correlations between OH and H12 and complementary selective NOESY experiment established the stereochemistry to be *transoid*. As previously reported in literature for spirolides B and D, the transoid stereochemistry adopted by tertiary alcohol **58a** represents the thermodynamically favored isomer. Stabilization of **58a** can be explained through hydrogen bonding between the free hydroxyl group and the spiroketal oxygen atoms. Based on the ratios observed and the respective NMR shifts of various isomers, **57b** was deduced to exhibit the natural cisoid-configuration. Under the conditions used, the cisoid-isomer **58b** was never detected. This synthetic approach towards the C10-C24 bis-spiroketal fragment of 13 desmethyl spirolide C was recently published.[26]



Scheme 27

Many attempts to isomerize transoidal compound into the natural cisoidal isomer unfortunately failed.

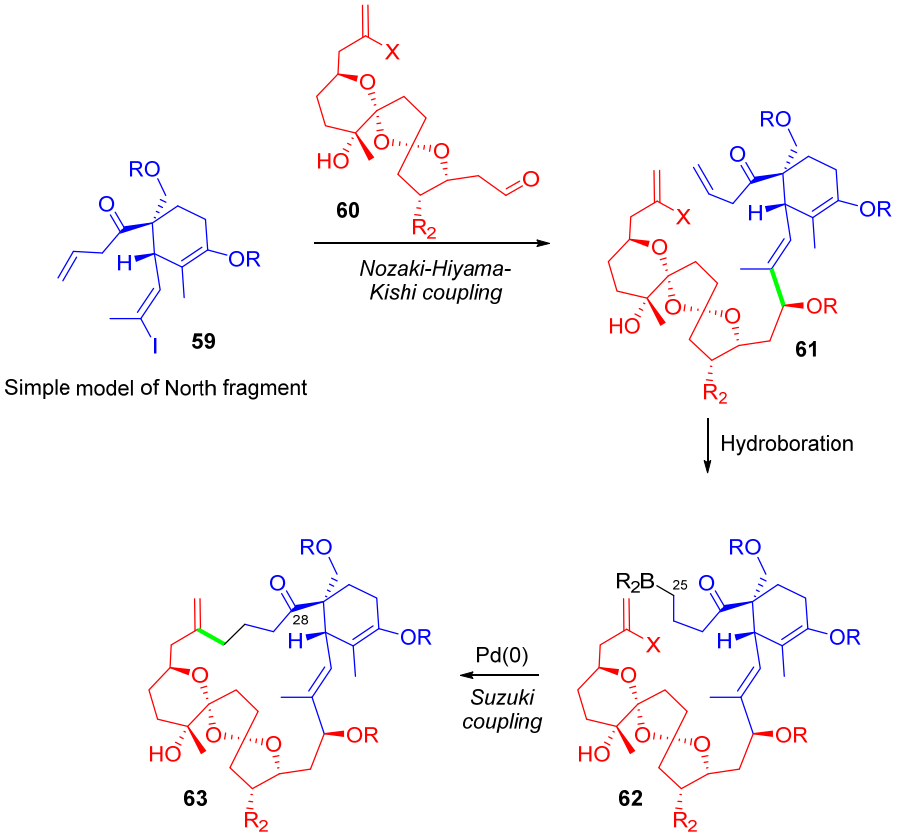
Sub-task 3.3 Total synthesis of the spirolide macrocycle

As pointed out in litterature, the incorporation of the thermodynamically more stable transoid isomer into the macrocyclic core of the spirolide should however allow the re-equilibration and the control of the spirocetal stereochemistry. Efforts are now underway

to access the spiroimine moiety and to connect the different fragments en route to the total synthesis of 13-desmethyl spirolide C.

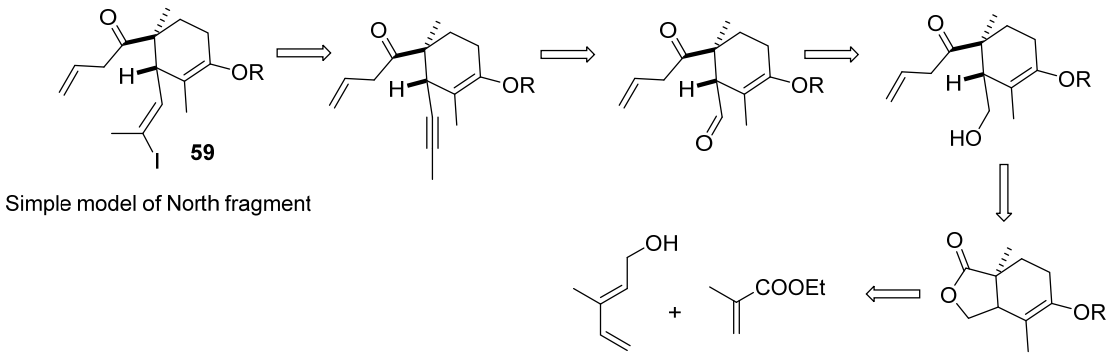
Simple North Fragment approach

The last months of this postdoctoral work were dedicated to the development of a methodology for the synthesis of a cyclohexene skeleton **59** designed as a simple spiroimine model fragment. Studies to modify bis-spiroketal skeketon and incorporate on one side a vinylbromide and on the other side an aldehyde, both necessary functions for the coupling, were performed on the transoidal isomer **58a**.



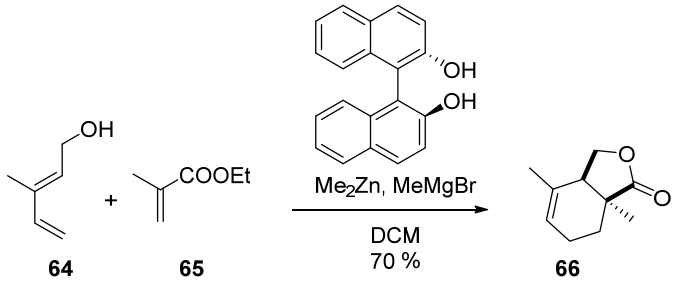
Scheme 28

The retrosynthesis envisioned for this cyclohexene approach, based on a Diels-Alder reaction, is detailed above.



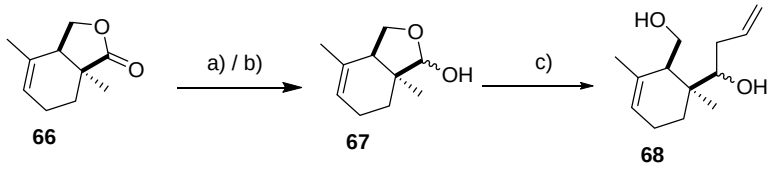
Scheme 29

Several lactone type cycloadducts as **66** were prepared enantioselectively according to a specific Lewis-acid catalyzed Diels-Alder reaction. (Scheme 30)[27]



Scheme 30

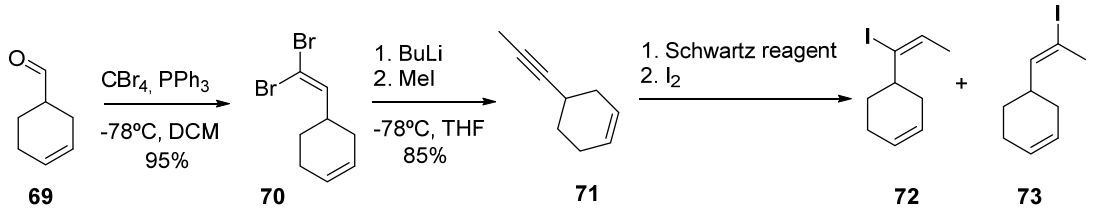
The lactone **66** was submitted to the hydroboration/oxidation reaction with 9-BBN and BH_3-DMS reagents, in both cases the lactol **67** was formed in 60% and 72% yield, which was treated with allylmagnesium bromide to give the product **68** in 58% yield as a mixture of diastereoisomers 1: 1 (Scheme 31).



a) 9-BBN (2 eq), $NaOH/H_2O_2$ (5 eq), 60%; b) BH_3-DMS (2 eq), $NaOH/H_2O_2$ (5 eq),72%; allylmagnesium bromide (2 eq), THF, 0ºC, 58%.

Scheme 31

At the same time, a simplest substrate bearing the suitable iodide for the Nozaki-Hiyama-Kishi cross-coupling, was synthesized. (Scheme 32)



Scheme 32

A classical Corey-Fuchs reaction provided easily the alkyne **71**. In the next step compound **71** was treated with bis(cyclopentadienyl)zirconium chloride hydride (Schwartz reagent)[28] in THF/benzene (1:1) to provide the undesired terminal iodide in 59% yield with 45% of its regioisomer. Initially we had expected higher regioselectivity since similar systems were reported to provide essentially one regioisomer in good yields.[29] Nevertheless, a detailed analysis of product distributions under various conditions such as elevated temperatures and different solvents to favor equilibrating conditions did not improve the selectivity. Even more surprisingly these conditions reported in the literature (benzene, 45ºC, 4 h) gave only a 1:1 mixture of regioisomers.

III. Conclusion

Our objective was to provide a straightforward access to 13-desmethyl spirolide C **5**. The results obtained during this program have contributed to the development of new methodological methods in organic synthesis. In particular, a straightforward access to functionalized 1,4 diketones based on an efficient organocatalyzed sila-Stetter reaction was developed. A convergent sila-Stetter-acidic spiroketalisation one-pot sequence was also worked out providing various bis-spiroketal skeletons. This methodology was applied successfully to the synthesis of C10-C24 bis-spiroketal fragment of 13 desmethyl spirolide C **5**.

Macrocyclization with simple spiroimine fragments model, as same as spiroimine fragment synthesis are still under investigation in the laboratory.

IV. References

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