Synthesis of the C10-C24-Bis-spiroacetal Core of 13-Desmethyl Spirolide C, Based on a Sila-Stetter-acetalization Process

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Jessica Labarre-Lainé,[a] Ignacio Periñan,[a] Valérie Desvergnes,*[a] and Yannick Landais*[a]

Dedicated to Prof. Max Malacria for his 65th birthday and his contribution to radical and organometallic chemistry

Abstract: The synthesis of the bis-spiroacetal core of 13-desmethyl spirolide C has been completed based on a sila-Stetter-acetalization process. The acylsilane and enone partners in the Stetter reaction were prepared respectively in 7 and 11 steps from (*S*) and (*R*)-aspartic acid. The quaternary center at C19 in the enone moiety was controlled relying on the Seebach's chiral self reproduction method using an enantiopure (*S*)-lactic acid based dioxolanone. The final acid-catalyzed spiroacetalization provided the desired spiroacetal as a mixture of diastereoisomers in 13 linear steps. Whatever the conditions used, the non-natural transoid- isomer was formed preferentially. Both cisoid and transoid-isomers were however isolated pure and their structure assigned unambiguously through NMR studies.

Introduction

Spirolides **1a-f** and their congeners (gymnodimine **2**, pinnatoxins **3**, pteriatoxines (not shown)) are macrocylic imine phycotoxins isolated from the digestive glands of mussels and scallops. The spirolides are metabolites of the dinoflagellate *Alexandrium ostenfeldii* and *Alexandrium peruvianum* (Figure 1).[1] These toxins are transferred and concentrated in shellfish edible tissues and can finally reach marine animals and humans by vectorial transport.[2] Shellfish poisoning thus constitutes a potent threat to human health but also to shellfish industry. Oysters and mussels are thus regularly banned from harvesting and consumption due to this potent toxicity.[3a] Toxicological studies have mainly been carried out on macrocycles **2** and **3**, which have recently succumbed to total synthesis.[4,5] Spirolides were shown to induce fast lethal toxicity when administrated through intraperitoneal injection to mice and rats but were also found to be less toxic when ingested by oral administration.[3b] Recent reports have shown that 13-desmethyl spirolide C is a potent antagonist of nicotinic acetylcholine receptors in the subnanomolar range.[3c,d] It was also shown to be neuroprotective and to reduce simultaneously intracellular Aβ and hyperphosphorylated Tau *in vitro*.[6] Consequences of these effects on the treatment of Alzheimer's disease were recently demonstrated in transgenic mouse models.[7] Nevertheless, no toxicological studies have been carried out to evaluate the long term impact of spirolides on human health. Unfortunately, spirolides are only available in small amount, thus preventing thorough biological studies. This has led several research groups around the world to study the synthesis of spirolide fragments but to date,[2a,8] no total synthesis of a member of the spirolide family has ever been completed.

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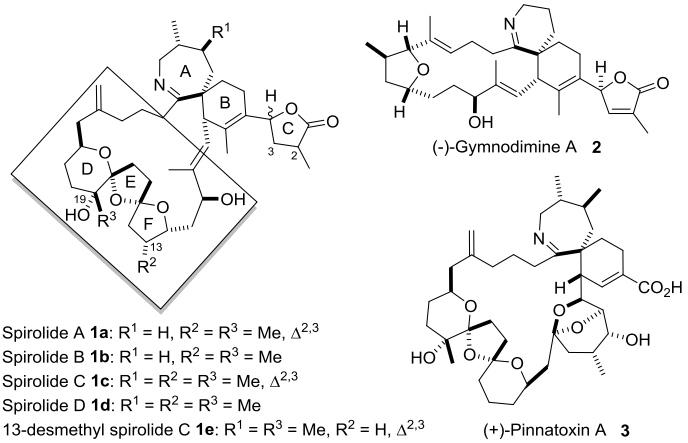


Spirolide A **1a**: R^1 = H, R^2 = R^3 = Me, $\Delta^{2,3}$
Spirolide B **1b**: R^1 = H, R^2 = R^3 = Me
Spirolide C **1c**: R^1 = R^2 = R^3 = Me, $\Delta^{2,3}$
Spirolide D **1d**: R^1 = R^2 = R^3 = Me
13-desmethyl spirolide C **1e**: R^1 = R^3 = Me, R^2 = H, $\Delta^{2,3}$
13,19-didesmethyl spirolide C **1f**: R^1 = Me, R^2 = R^3 = H, $\Delta^{2,3}$

Figure 1. Spirolides **1a-f**, gymnodimine **2** and pinnatoxin **3**, macrocylic imine phycotoxins.

We recently embarked on the study of the total synthesis of 13-desmethyl spirolide C **1e**, the most potent member of this family, following the strategy depicted in Figure 2, involving the disconnection of **1e** into three main fragments, *i.e.* a 5,5,6-bis-spiroacetal **4**, a spiroimine **5** and a furan **6**. While several approaches to the 6,5,6-bis-spiroacetal skeleton have been devised, notably in the context of the pinnatoxin synthesis,[5] less effort has been devoted to the preparation of 5,5,6-analogues.[9] Amongst the previous strategies to access the bis-spiroacetal core of spirolides, Ishihara *et al.* used as a key step the acetalization of a triketone fragment,[10] the formation of the quaternary center at C19 being controlled in a late stage through addition of a methyl Grignard reagent onto the remaining ketone. Brimble and co-workers also proposed an elegant access to the

5,5,6-bis-spiroacetal using an iterative hypervalent iodine-mediated radical oxidative cyclization.[11] This approach although straightforward, also led to the non-natural diastereoisomer.[11a] We describe here our own efforts to access the bis-spiroacetal fragment **4** of spirolide **1e**, using a novel sila-Stetter-acetalization process (Figure 2).

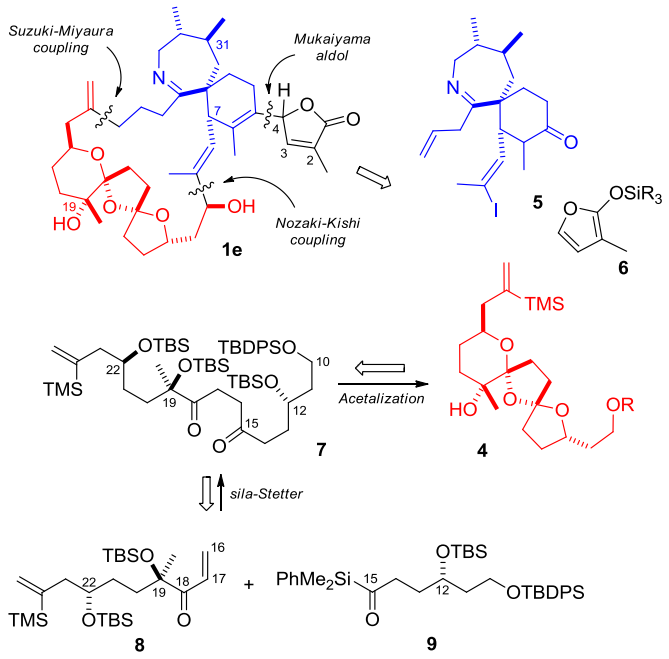


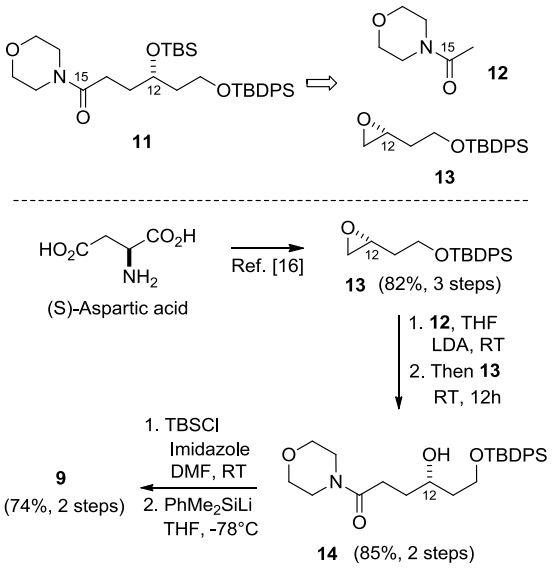
Figure 2. Retrosynthetic analysis of spirolide **1e** and bis-spiroacetal fragment **4**.

Such spiroacetalizations starting from readily available 1,4-diketones have been used on purpose in the synthesis of pinnatoxin **3**.[5] In the search for a convergent and rapid assembly of 1,4-diketones, the Stetter[12] and sila-Stetter[13] reactions appeared as convenient processes, which conditions would be compatible with many functional groups. The elaboration of the bis-spiroacetal **4**, would thus start with the coupling between enone **8** and acylsilane **9**, and the formation of C15-C16 bond of diketone **7**, which protecting groups would be removed under acidic conditions, thus triggering the acetalization. Protection of the alcohol functional groups at C12, C19 and C22 would be carried out using *tert*-butyldimethylsilyl (TBS) groups as these should be easily removable under acidic catalysis, while a more stable *tert*-butyldiphenylsilyl (TBDPS) group would be introduced at C10. Preliminary studies in this direction effectively demonstrated that spiro- and bis-spiroacetals could be efficiently assembled in a limited number of steps, giving rise to 5,5,6- as well as 6,5,6-bis-spiroacetal skeletons.[14] We also showed that the two steps could be carried out in a single pot operation. Application of this strategy to the elaboration of the C10-C24 bis-spiroacetal skeleton of spirolide **1e** has been carried out and is discussed in full details below.

Results and Discussion

Synthesis of acylsilane 9

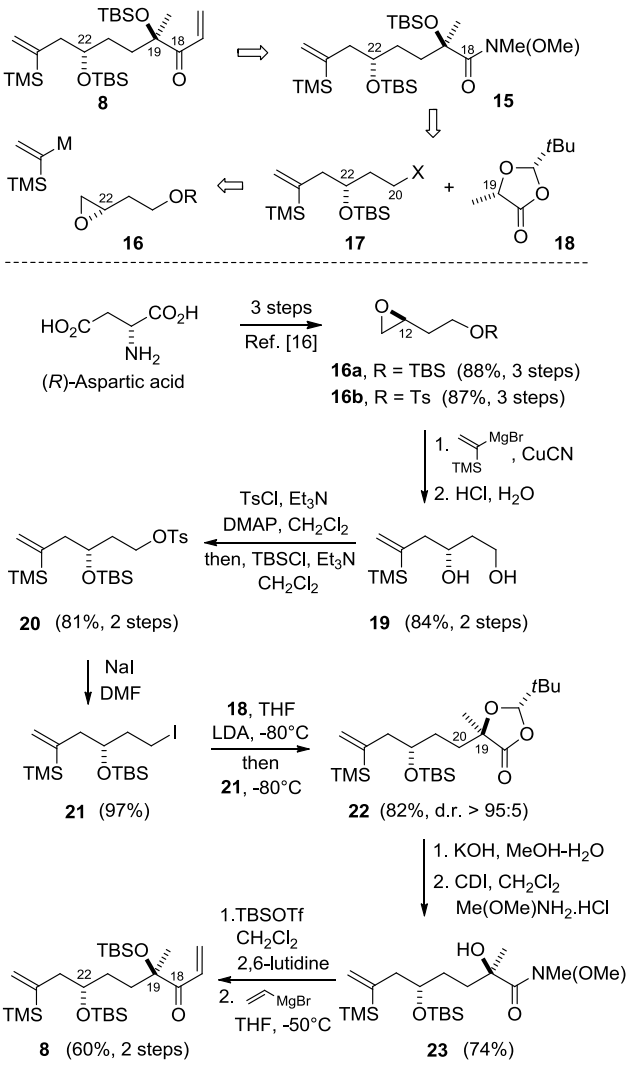
Preliminary studies showed unambiguously that the acylsilanes were superior to aldehydes in the Stetter coupling with enones.[13,14] The required acylsilane **9** was thus prepared starting from morpholine amide **11** following Scheidt procedure (Scheme 1).[15] **11** was itself available through the coupling of the amide enolate of **12** and epoxide **13** issued from the chiral pool. All our attempts to prepare **13** with high enantioselectivity having failed, the latter was obtained through a 3-steps synthesis starting from (*S*)-aspartic acid, using a literature protocol[16] (see supporting information). Addition of $PhMe_2SiLi$ onto **11**, finally led to gram quantities of acylsilane **9** in 51% overall yield and 7 steps from (*S*)-aspartic acid.



Scheme 1. Synthesis of acylsilane **9**.

Synthesis of enone 8

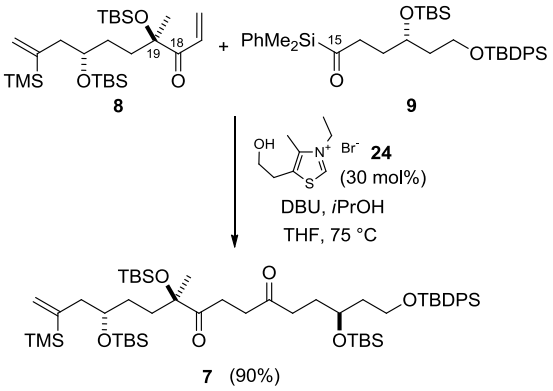
With **9** in hand, we then turned our attention to fragment **8** and toward the introduction of tertiary alcohol at C19. In contrast with Ishihara's and Brimble strategies,[2a,10,11] it was decided to set up the stereochemistry of the C19 center prior to the acetalization. The stereoselective introduction of the quaternary center was carried out relying on Seebach's chiral self reproduction method using enantiopure 2-*tert*-butyl-5-substituted-1,3-dioxolanone **18**, easily prepared by condensation of (*S*)-lactic acid with pivalaldehyde.[17] The alkylation of **18** using **17** (X = I or OTs) should allow the formation of the C19-C20 bond, while controlling the stereochemistry at C19. Precedent from the literature showed that functionalized electrophiles could effectively be introduced in this way with high yield and diastereocontrol.[18] Hydrolysis of the dioxolanone and amidification would then afford the Weinreb amide **15**, precursor of the enone **8** (Scheme 2). Tosylate **20** was initially prepared from epoxide **16a**, which, as above, was obtained from (*R*)-aspartic acid through a high-yielding 3-steps sequence.[16] Silyl-protected epoxide **16a** was reacted with a TMS-vinyl Grignard reagent[19] and the protecting group was removed under acidic conditions to afford diol **19**. Tosylation of the primary alcohol group, followed by protection of the secondary one led to **20** in 81% yield. **20** was also obtained through a shorter route (2 steps from **16b**, 69% yield), involving an epoxide ring opening of tosylate **16b** with the TMS-vinyl Grignard reagent,[20] followed by silylation with TBSCl, thus avoiding the previous protection-deprotection sequence.



Scheme 2. Synthesis of enone **8**.

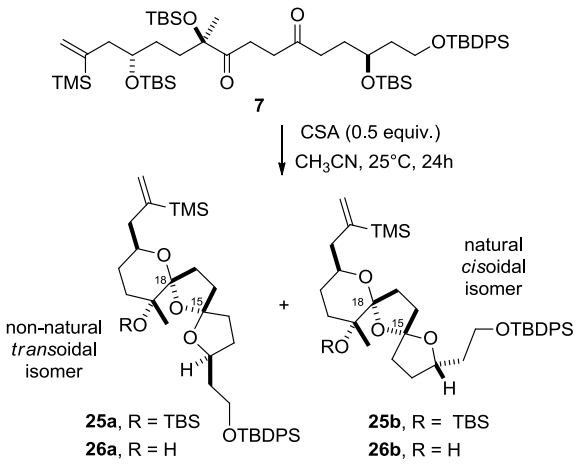
Direct alkylation of dioxolanone **18** with tosylate **20** met with failure, but better results were obtained starting from the corresponding iodide **21**.[18] The alkylation occurred with high diastereocontrol, leading to **22** in 82% yield as a single stereoisomer with the relative configuration as shown.[17] Dioxolanone ring-opening under basic conditions,[21] followed by coupling of the resulting carboxylic acid with the *N*-methyl-*N*-methoxy amine led to the Weinreb amide **23**.[22] Protection of the tertiary hydroxy group in **23** followed by addition of a vinyl Grignard reagent finally led to the desired enone **8** in 11 steps (longest linear sequence) and 21% overall yield from (*R*)-aspartic acid.

The sila-Stetter reaction was then carried out using equimolar amount of enone **8** and acylsilane **9** in THF at 75°C, with thiazolium salt **24** (30 mol%) as precatalyst,[13,14] DBU as a base, and *i*PrOH as the desilylating agent (Scheme 3). These conditions afforded the 1,4-diketone **7** along with the unreacted acylsilane **9**, which could not be separated by chromatography, the mixture being used as such in the acetalization step. Yields estimated through ^{1}H NMR indicated that **7** was obtained in a satisfying 70% yield when 1 equiv. of **9** was used. Increasing the amount of **9** to 1.3 then 1.5 equivalents led to **7** in 73% and 85% NMR yield respectively. The coupling was finally found to be highly reproducible as shown by the reaction carried out with **8** on a 2.4 mmol scale, in which diketone **7** was obtained in 90% yield (^{1}H NMR).



Scheme 3. Sila-Stetter reaction between enone **8** and acylsilane **9**.

Spiroacetalization was first carried out using camphorsulfonic acid (CSA) in CH_3CN (Scheme 4, Table 1, entry 1). Disilylated bis-spiroacetals were obtained in a 73% isolated yield as a 2.5:1.5:1 inseparable mixture of 3 diastereoisomers **25a-c** (**25c** not shown). Another compound **26a**, which had lost its silyl group at C19 was also isolated pure in 25% yield. The stereochemistry of **26a** was assigned unambiguously, revealing a non-natural transoid- stereochemistry by two-dimensional NMR NOESY experiments.[23] For **26a**, correlations between OH and H12 and complementary selective NOESY experiment established the stereochemistry to be transoid as depicted in Figure 3 (see supporting information). As previously reported in literature for spirolides B and D,[10,11] the transoid stereochemistry adopted by **26a** represents the thermodynamically favored isomer. Stabilization of **26a** can be explained through hydrogen bonding between the free hydroxyl group and the spiroacetal oxygen atoms. Based on the respective NMR shifts of various isomers, **25b** was deduced to exhibit the natural cisoid-configuration. Under the conditions used, the cisoid-isomer **26b** was never detected.

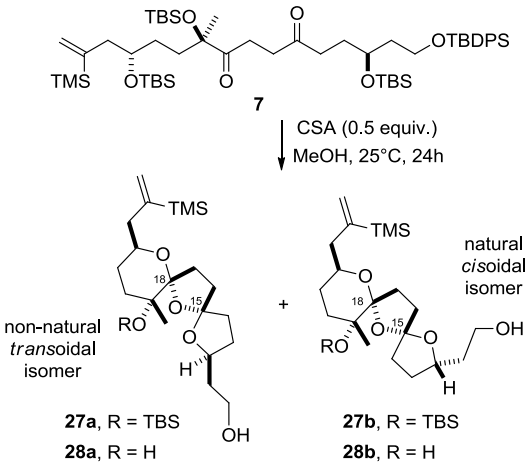


Scheme 4. Spiroacetalization of 1,4-diketone **7** in CH_3CN.

DFT Calculations at the MO62x-31+G(d,p) level using have also been performed with TMS protecting groups instead of the

TBDPS used experimentally. For both isomers, the more stable conformation exhibits distances between H12 and OH which are in good agreement with connectivies observed in NOESY experiments (See supporting information).[24]

A different result was obtained when treating diketone **7** with CSA in MeOH (Scheme 5, Table 1, entry 2). Under these conditions, the *tert*-butyldiphenylsilyl group at C10 was removed leading to two sets of compounds. The major compound was obtained in 70% yield as a separable 1.25:1 mixture of isomers **27a-b** along with a smaller amount (18%) of the totally desilylated and separable bis-spiroacetals **28a-b** in a 8:1 ratio. A third isomer **27c** (not shown), which stereochemistry could not be determined, was also present (7%). When the reaction was carried out using HCl as an acid (generated through treatment of AcCl with MeOH), similar results were obtained with diol **28a** as the major compound (Entry 3). As mentioned above, hydrogen bonding between OH at C19 and the acetal oxygens likely favors the undesired transoid isomer. Hexafluoro-2-propanol (HFIP), known to exhibit strong hydrogen-bonding properties,[25] was thus added to MeOH. Under these conditions, diastereoisomers **28a** and **28b** were obtained in a 3:1 ratio, albeit in modest yield (Entry 4). For the same purpose, treatment of the acetal mixture **26a-b** with acetic anhydride or acetyl chloride led to the desired tertiary acetate at C19, but in low yield and no stereoselectivity improvement. Treatment of **7** with a large excess of HF-Pyridine (entry 5) led to the diastereomerically pure transoid isomer **26a**, along with a mixture of fully deprotected **28a-b** and degradation products. Finally, alternative conditions such as PPTS in CH_3CN were also studied, but no conversion was observed, while degradation of **7** occurred with TFA or $ZnCl_2$ in CH_2Cl_2.



Scheme 5. Spiroacetalization of 1,4-diketone **7** in MeOH.

Table 1. Spiroacetalization of 1,4-diketone **7**.

Entry	Conditions	**25a/25b**[e]	**26a/26b**[e]	**27a/27b**[e]	**28a/28b**[e]	Yield[f]
1	CH_3CN/CSA[a,b]	36/22	25/0	-	-	98
2	MeOH/CSA[a,c]	-	-	39/31	16/2	95
3	MeOH/AcCl[c]	-	-	27/21	28/3	84
4	MeOH[d]/CSA	-	-	-	26/8	34
5[g]	CH_3CN/HF-Pyr	-	39/0	-	4/6	49

[a] 0.5 equiv. of CSA were added. [b] a third isomer **25c** was detected but not identified. [c] a third isomer **27c** was detected but not identified. [d] with HFIP (MeOH/HFIP 10:1). [e] Isolated yields in %. [f] Overall isolated yields in % including non identified isomers. [g] 25°C, 72 h.

As previously noticed by Ishihara[10] and Brimble,[8a,11] on related compounds, the non-natural transoid- isomer is formed preferentially in all cases. All our efforts to reverse the stereocontrol upon acetalization failed whatever the conditions used. Both cisoid and transoid isomers were however isolated pure and their structure assigned through ^{1}H NMR. All transoid isomers exhibiting the same range of chemical shifts, some NMR shifts tables were listed and compared to the supposed cisoid isomers. These data are discussed in supporting information.

As a final experiment, we performed a one-pot sila-Stetter-acetalization cascade starting from enone **8** and acylsilane **9** (Scheme 3). CSA was added at room temperature after completion of the sila-Stetter process in THF. Under these conditions (24 h, RT), we were pleased to observe that the fully protected bis-spiroacetal stereoisomeric mixture **25a-c** was formed in high yield (95%) in a 2.5:1.5:1 ratio. Deprotection of **25a-c** using nBu$_4$NF (TBAF) in THF led to deprotected bis-spiroacetals **26a-c** with the same diastereoisomeric ratio.

Conclusion

We reported here the synthesis of the C10-C24-bis-spiroacetal fragment of 13-desmethyl spirolide C **1e** using, as a key-step, a sila-Stetter-acetalization cascade. The spiroacetal motif was obtained as a mixture of diastereomers in 13 steps (longest linear sequence) and 18% overall yield from (*R*)-aspartic acid. As observed by Ishihara, Brimble and co-workers,[10,11] the spiroacetalization led to a mixture of the non-natural transoid and natural cisoid isomers, in the favor of the former. Our attempts to reverse the selectivity using various conditions unfortunately failed. The natural isomers (**27b** and **28b**) were however obtained pure through chromatography. As pointed out by Brimble,[2a,11a] 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 spiroacetal 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 **1e**.

Experimental Section

One-pot sila-Stetter reaction-Acetalization

DBU was freshly distilled in a Kugelrohr apparatus and *i*PrOH was dried over molecular sieves. In a Schlenk tube, 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide **24** (10.4 mg, 0.04 mmol, 35 mol%) was dried overnight under vacuum at 45 °C. The tube was placed under an argon atmosphere and a solution of acylsilane **9** (96.5 mg, 0.16 mmol, 1.5 eq.) in THF (0.3 mL) was added, followed by DBU (5 µL, 0.03 mmol, 30 mol%). The reaction mixture turned orange and a solution of enone **8** (55.8 mg, 0.11 mmol, 1 eq.) in THF (0.3 mL) was added, followed by *i*PrOH (26 µL, 0.30 mmol, 2.7 eq.). The mixture was stirred for 2 h at 75°C then cooled to room temperature. CSA was then introduced by portions (of 12 mg, 0.06 mmol, 0.5 eq.) until completion of the reaction (24 h at RT). The solvent was then removed under reduced pressure and the residue purified by flash chromatography over silica gel (pentane/EtOAc) to afford a mixture of 3 diastereoisomers **25a-c** (79.3 mg, 98 %). Further treatment with TBAF (1 M in THF, 0.12 mL, 0.12 mmol, 1.1 eq.) in THF (1 mL) provided products **27a-c** in a 2.5:1.5:1 ratio. Spectroscopic data (see supporting information) were in good agreement with those obtained from spiroacetals prepared through the 2 steps sequence.

Acknowledgements

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Keywords: Phycotoxin • spirolide • sila-Stetter reaction • acylsilane • acetalization • bis-spiroacetal

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