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Convergent Access to Bis-spiroacetals through a Sila-Stetter–Ketalization Cascade

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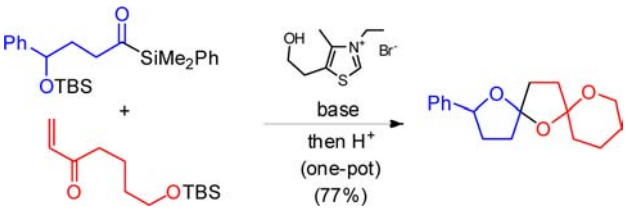
ABSTRACT



An NHC-catalyzed sila-Stetter reaction between aliphatic acylsilanes and vinylketones bearing silyl ether substituents affords functionalized 1,4-diketones, which upon treatment under acidic conditions leads to the corresponding bis-spiroacetals. The two-step sequence may also be carried out in a one-pot operation leading to high yields of the desired bis-spiroacetals.

The bis-spiroacetal skeleton is found in various bioactive marine phycotoxins including pinnatoxin A (**1**), spirolide C (**2**) (Figure 1), or pteriatoxins (not shown).[1] These toxins have led recently to intensive research due to their potent acute neurotoxicity.[2] The nature of the tricyclic system, embedded in a complex macrocycle, varies with the size of the oxygenated rings (5- and 6-membered rings) forming the bis-spiroacetal. Several strategies directed toward the elaboration of these bis-spiroacetals have been devised en route to the total synthesis of **1** and **2**.[3,4] A straightforward disconnection leading to this skeleton implies the generation of a 1,4-diketone, which upon ketalization under acidic conditions provides the desired tricyclic framework.[4]

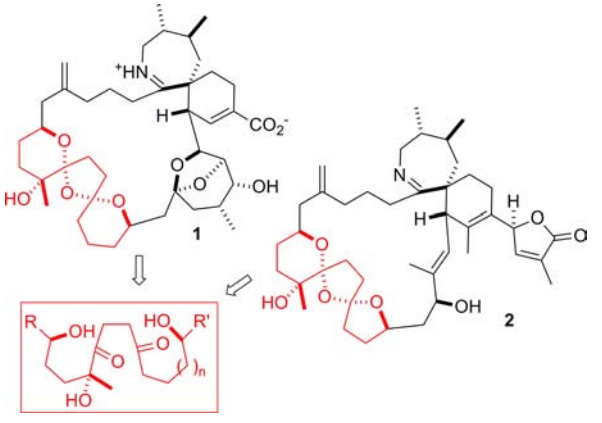


Figure 1. Bis-spiroacetal skeleton in marine phycotoxins.

This spiroacetalization has been elegantly pioneered by Kishi[5] and then by Inoue–Hirama,[6] Nakamura–Hashimoto,[7] and Zakarian[8] in their respective total syntheses of pinnatoxin (**1**), as well as by Ishihara et al. in their

† These authors contributed equally to this work.

(1) For a review on the isolation, structure, and biogenesis of these marine toxins, see: Kita, M.; Uemura, D. *Chem. Lett.* **2005**, *34*, 454–459.

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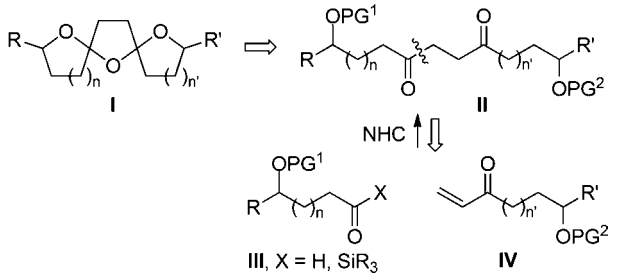
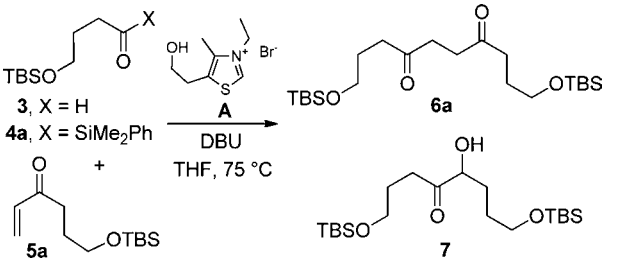
preparation of the bis-spiroacetal core of spirolide B.[9] The 1,4-diketone motif may be constructed by a number of ways, often requiring several steps.[10] In the search for a convergent strategy, allowing the presence of functionality and protecting groups on the carbon backbone, the Stetter reaction appeared as an attractive method to elaborate efficiently the bis-spiroacetal **I** present in toxins **1** and **2** (Scheme 1). It was thus envisioned that the coupling of an aldehyde (or an acylsilane) **III** and a vinyl ketone such as **IV** in the presence of a suitable organocatalyst (usually a N-heterocyclic carbene (NHC)) would deliver the 1,4-diketone framework **II**. A careful choice of the protecting groups on the alcohol functions within the chain would then allow the construction of the desired bis-spiroacetal **I** after acid-catalyzed deprotection and ketalization. We report here that NHC-mediated Stetter and sila-Stetter processes followed by the acid-catalyzed ketalization effectively offer a straightforward access to the bis-spiroacetal skeleton. A cascade process also allows both events to be carried out in a one-pot operation.

Scheme 1. Retrosynthetic Analysis



Although the pioneering work by Stetter[11] and others has shown that this coupling may be carried out starting from a large variety of aldehydes, few examples have been reported to date on aliphatic partners. Moreover, acyloins resulting from the homocoupling of the aldehyde are often present as byproducts. Recent work by Scheidt et al[12] however showed that this could be circumvented, using acylsilanes instead of aldehydes, although mostly aromatic acylsilanes were tested during this work. We thus studied first the influence of the nature of the partner **III** in the Stetter reaction, using as precursors, aldehyde **3** or acylsilane **4a** and vinylketone **5a** in the presence of NHC-catalyst precursor **A**.[13] As summarized in Table 1, using aldehyde **3** and various amounts of catalyst invariably led to a mixture of both the desired product **6a** and the corresponding acyloin **7** (entries 1–3, Table 1). In contrast, we were pleased to observe that acylsilane **4a** led to **6a** in good yield, without a trace of **7** (entries 4–5), thus notably extending the scope of the sila-Stetter reaction.[12] Increasing the quantity of acylsilane however produced small amount of **7** (entry 6).

Table 1. Stetter versus Sila-Stetter Reaction



entry	**3** or **4a** (equiv)	**A** (mol %)	time (h)	**6a**/**7**[a]	yield[b] (%)
1	**3** (1.0)	30	2	81:19	61
2	**3** (1.5)	15	2.5	72:28	68
3	**3** (2.0)	30	2	65:35	77
4	**4a** (1.0)[c]	30	1.5	100:0	67
5	**4a** (1.5)[c]	15	3	100:0	89
6	**4a** (2.0)[c]	30	3	80:20	90

[a] Measured by ^{1}H NMR of the crude reaction mixture. [b] Isolated yield of **6a** after column chromatography. [c] 4 equiv of *i*-PrOH were used.

Optimization of the sila-Stetter reaction showed that decreasing the quantity of acylsilane was detrimental to the conversion, with 1.5–2 equiv leading to optimal results. Dry isopropyl alcohol (4 equiv) and DBU as a base were also shown to provide the highest yields. With these optimized conditions in hand, the methodology was extended to a large variety of aliphatic acylsilane[14] and enone[15] precursors (Supporting Information), as illustrated in Scheme 2.

tert-Butyldimethylsilyl and benzyl substituents were selected as orthogonal protecting groups for alcohol functions, so that they can be deprotected selectively if needed (vide infra). 1,4-Diketones were obtained in good to excellent yields.[16] Reaction time ranged between 3 and

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(13) A screening of other thiazolium salts led to similar results (Supporting Information). Catalyst **A** was finally selected, being the easiest to handle.
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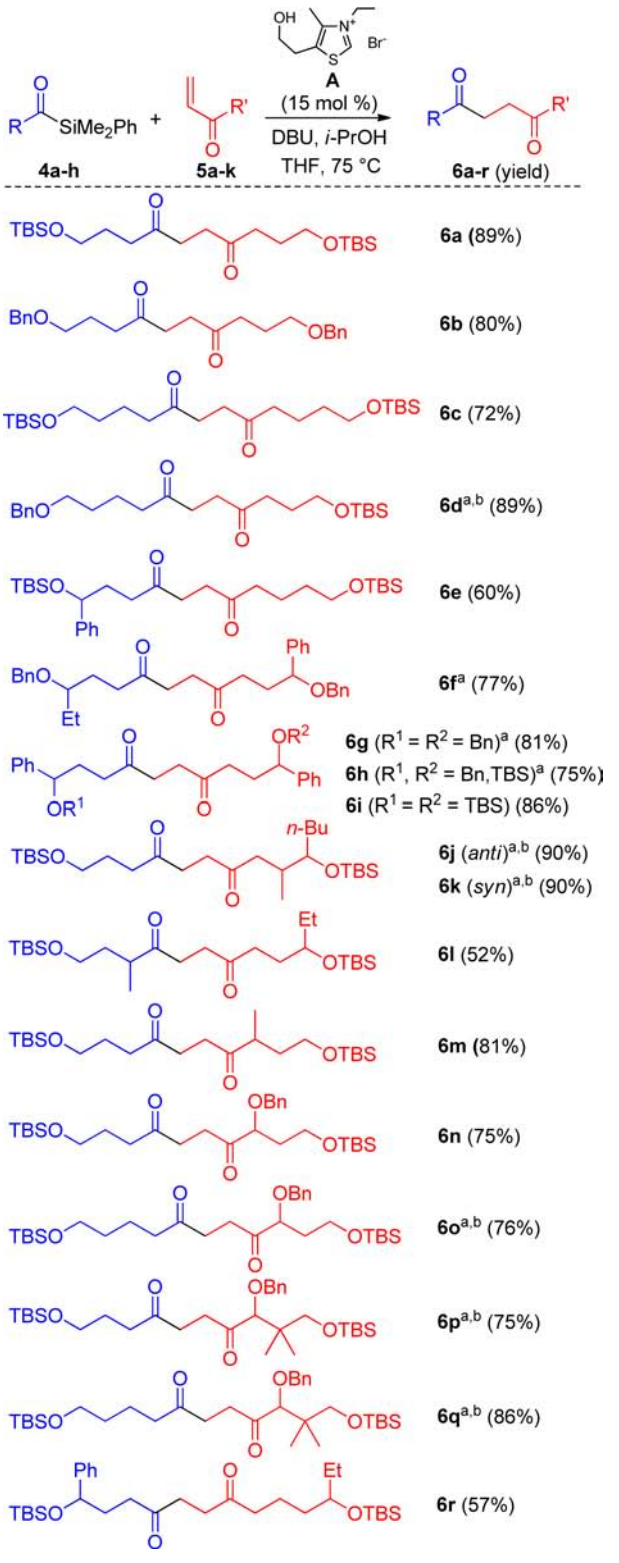
(16) It was also possible to perform the reaction between acylsilanes **4** and other Michael acceptors such as acrylonitrile (51%), methylacrylate (36%), and vinylsulfone (26%) (unoptimized yields) (Supporting Information).

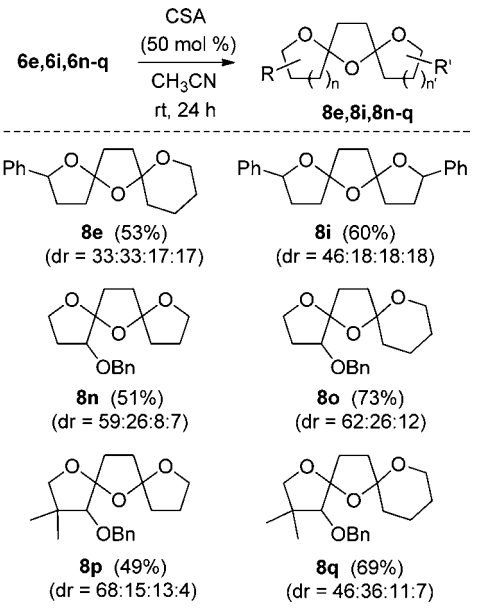
Scheme 2. Sila-Stetter Reaction between Aliphatic Acylsilanes **4** and Vinylketones **5**



[a] 2 equiv of **4** was used. [b] 30 mol % of **A** was used.

24 h depending on the nature of the substrate. 1.5 Equivalent of acylsilane was generally used except when indicated. As mentioned above, the reaction was carried out using 15 mol % of salt **A**, except for the preparation of **6d**,**j**–**k**, **o**–**q**, where 30 mol % was employed. It is noteworthy that substitution on the carbon chain is allowed on both partners, but α-substitution in acylsilane was shown to slow down the process, leading to lower yields.[17] Removal of the *tert*-butyldimethylsilyl protecting group was then carried out under standard acidic conditions, leading to a spontaneous cyclization,[5–8] producing the desired bis-spiroacetals in moderate to good yields as a mixture of diastereomers (dr estimated using both ^{1}H NMR and GC–MS) (Scheme 3).[18] Various acidic conditions were tested (TfOH, HCl, $MgBr_2$, $BF_3 \cdot OEt_2$, TMSOTf, $Sc(OTf)_3$), but camphorsulfonic acid (CSA) in CH_3CN at room temperature was found to be optimal in terms of yields. In some cases, major diastereomers were obtained pure after chromatography, but their structures could not be determined based solely on 1D and 2D NMR data. Attempts at obtaining crystals for X-ray diffraction studies unfortunately failed.

Scheme 3. Spiroacetalization of 1,4-Diketones **6e**,**i**,**n**–**q**



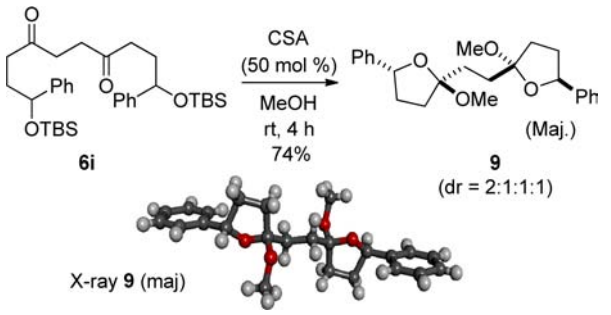
When the deprotection was carried out using CSA in MeOH as reported by Ishihara et al,[9] bis-acetal **9** was obtained as a mixture of diastereomers instead of the corresponding bis-spiroacetal (Scheme 4). Interestingly, the structure of the major isomer could be determined through X-ray diffraction studies.

Having demonstrated the efficiency of the sila-Stetter reaction and the acid-mediated spiroacetalization of the resulting 1,4-diketones, we then developed a one-pot process in order to avoid the purification of the sensitive diketone intermediate. The sila-Stetter reaction was performed using as above precatalyst **A**, DBU, and *i*-PrOH.

(17) Increasing the amount of acylsilane **4h** to 2.5 equiv resulted in the isolation of **6l** but in only 42% yield.

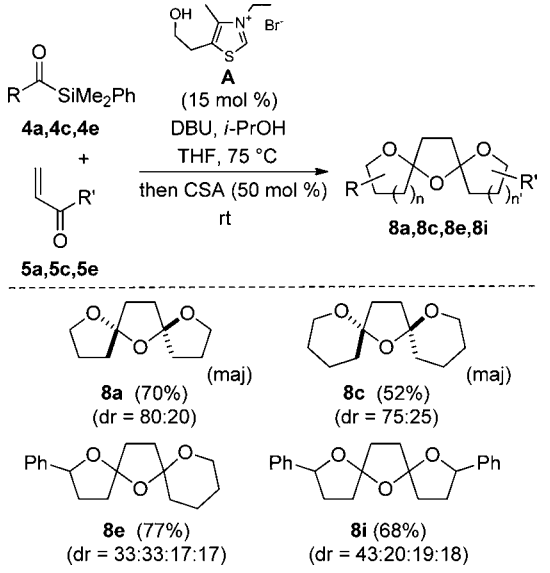
(18) Estimated thermodynamic ratio under the given conditions.

Scheme 4. Spiroacetalization of **6i** in MeOH



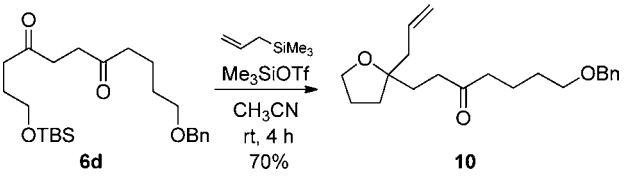
After the mixture was heated at 75 °C until complete disappearance of enone **5**, CSA (50 mol %) was added and the reaction mixture stirred at room temperature. This afforded the required bis-spiroacetals **8a**,**c**,**e**,**i** in good yields (Scheme 5). It is worthy of note that **8e** and **8i** were obtained with slightly better yields than those observed using the two-pot protocol (77% vs 53% and 68% vs 60% respectively). The major diastereomer for **8a** and **8c** was obtained pure in each case, and the relative configuration was attributed based on literature reports.[3e,19]

Scheme 5. One-Pot Sila-Stetter/Spiroacetalization Cascade



Finally, orthogonal protecting groups on 1,4-diketones allow for the monodeprotection and the selective formation of tetrahydrofurans. For instance, treatment of 1,4-diketone **6d** under Lewis acidic conditions, triggered the selective deprotection of the TBS group, followed by the cyclization and the formation of an oxonium intermediate, which was eventually trapped in situ by a nucleophilic allylsilane, leading to THF **10** in good yield (Scheme 6).

Scheme 6. One-Pot Mono-deprotection/Cyclization/Allylation of 1,4-Diketone **6d**



In summary, we report here the sila-Stetter coupling between a series of aliphatic acylsilanes and vinylketones, which afforded in generally good yields, 1,4-diketones bearing ether substituents on the chain. Subsequent acid-mediated deprotection of silyl ether protecting groups triggered an efficient spiroacetalization, leading to bis-spiroacetal motifs, which are present in marine natural products such as pinnatoxin (**1**). Both successive transformations may be carried out in a one-pot operation with high efficiency. Application of this strategy to the synthesis of bis-spiroacetal fragments of spirolides and analogues is now underway and will be reported in due course.

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Supporting Information Available. Experimental procedures and spectroscopic data for compounds **4**–**10** and morpholine and Weinreb amide precursors. ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.