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Synthesis of Functionalized γ-Lactone via Sakurai *exo*-Cyclization/Rearrangement of 3,3-Bis(silyl) Enol Ester with a Tethered Acetal

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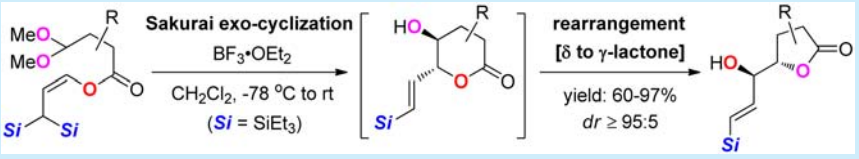
Supporting Information



ABSTRACT: An efficient synthesis of functionalized γ-lactones has been developed involving Sakurai *exo*-cyclization/rearrangement of 3,3-bis(silyl) enol esters with a tethered acetal. While the steric and electronic effects of geminal bis(silane) favor the desired Sakurai pathway, the methoxy species formed in the deprotection step also facilitates both cyclization and rearrangement. The synthetic value of this approach has been demonstrated by efficiently transforming the *E*-vinylsilane into enyne and the γ-lactone moiety into multisubstituted THF.

Multisubstituted γ-lactones and their analogous tetrahydrofurans (THF) are ring structures that occur often in a broad range of natural products (Figure 1).[1] Considerable efforts have been devoted to developing stereoselective methods for constructing these motifs.[2] One approach involves intramolecular C−C bond formation via addition of nucleophilic alkenes such as enol ether or allylsilane to oxacarbenium, which is embedded in the resulting THF, thus leading to an *endo*-cyclization of **1** (Scheme 1, eq 1).[3] The corresponding *exo*-cyclization of **2**, in which the oxygen in the resulting THF tethers both nucleophilic alkene and oxacarbenium, is far more challenging. The process requires efficient umpolung,[4] since the nucleophilic alkene is also shared by the enol ether moiety, which might undergo a competitive Mukaiyama aldol[5]-type addition at the β-position. Even more attractive is the *exo*-cyclization pathway, which would lead to vicinal tetrahydrofuranol diastereoselectively, while this skeleton would be difficult to achieve by *endo*-cyclization. In studies on the synthesis of brevetoxin B, Yamamoto and co-workers developed an elegant intramolecular *exo*-cyclization involving umpolung, generating

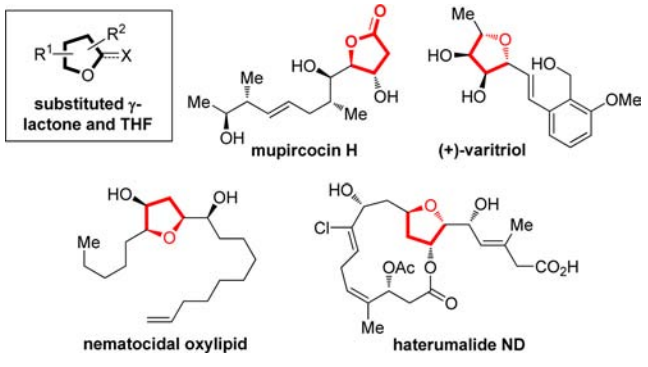
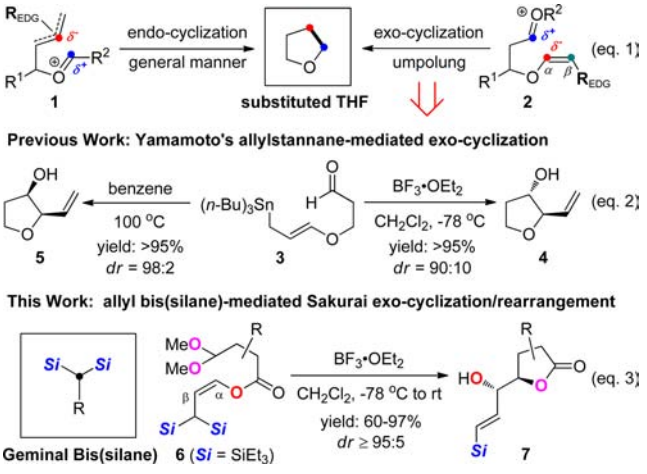


Figure 1. Representative natural products containing substituted γ-lactones and THFs.

Scheme 1. *Endo*- and *Exo*-Cyclization To Form Substituted THF (eq 1); Yamamoto's Allylstannane-Mediated *Exo*-Cyclization To Form THF (eq 2); Allyl Bis(silane)-Mediated Sakurai *Exo*-Cyclization/Rearrangement To Form γ-Lactone (eq 3)



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Scheme 2. Synthesis of Model Substrate 6a

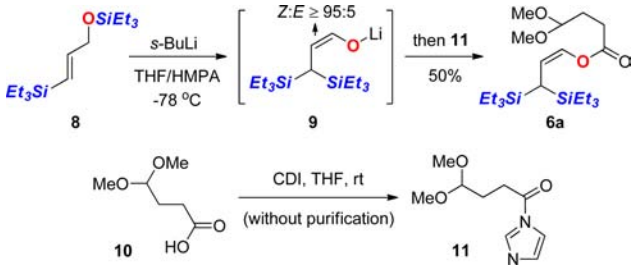
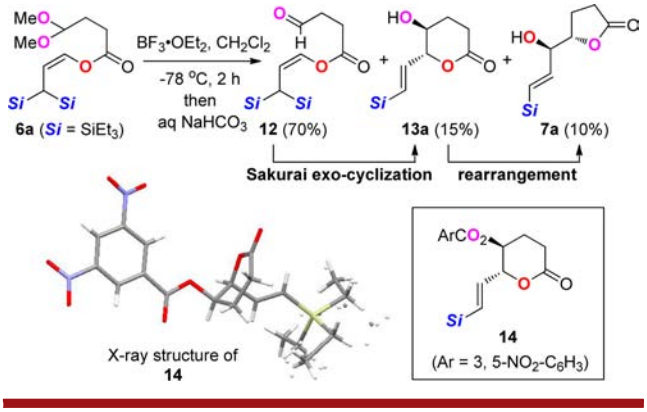


Table 1. Screening of Reaction Conditions[a]

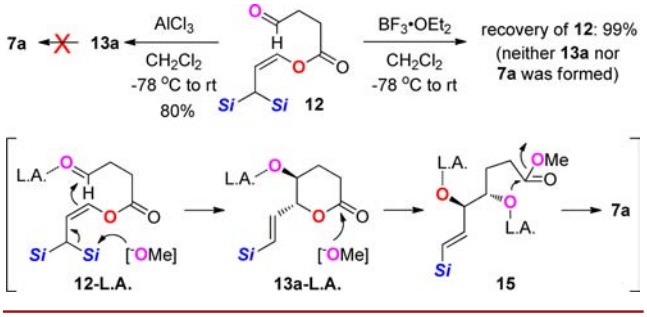
entry	L.A.	7a[b] (%)	12[c] (%)	dr[d] (7a)
1	TMSOTf		90	
2	$TiCl_4$		92	
3	$AlCl_3$		91	
4	$SnCl_4$	complex		
5	$BF_3{\cdot}OEt_2$	80		≥95:5

[a]Reaction conditions: 0.1 mmol of **6a** and 0.3 mmol of Lewis acid in 6.0 mL of CH_2Cl_2, −78 °C to rt. [b]The *anti*-stereochemistry of **7a** was determined based on X-ray analysis of **14** (Scheme 3). [c]Isolated yields after purification by silica gel column chromatography. [d]The ratio was determined by ^{1}H NMR spectroscopy.

Scheme 3. Formation of 12, 13a, and 7a

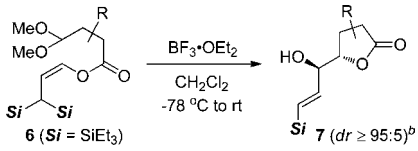


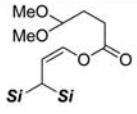
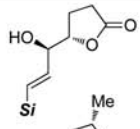
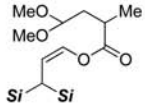
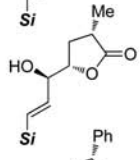
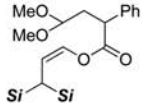
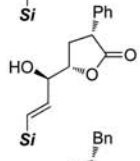
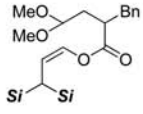
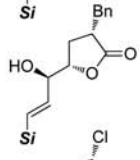
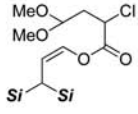
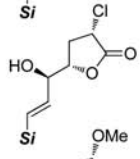
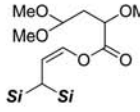
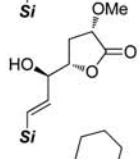
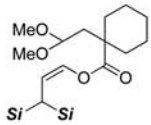
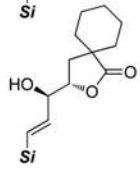
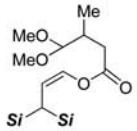
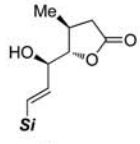
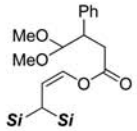
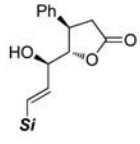
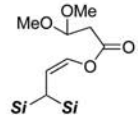
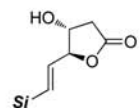
Scheme 4. Methoxy Equivalent Promotes Both Cyclization and Rearrangement



THF stereoselectively (eq 2).[6] While $BF_3{\cdot}OEt_2$-promoted addition of allylstannane to *O*-tethered aldehyde in **3** predominantly gave the 2,3-*trans* THF **4**, performing the cyclization at 100 °C without Lewis acid led to *cis*-isomer **5** as the major product.

Table 2. Scope of 3,3-Bis(silyl) Enol Ester[a]



entry	substrate		product		yield[d]
1		6a		7a	80%
2		6b		7b[c]	85%
3		6c		7c	60%
4		6d		7d	96%
5		6e		7e	70%
6		6f		7f	80%
7		6g		7g	84%
8		6h		7h[c]	97%
9		6i		7i	91%
10		6j		7j[c]	85%

[a]Reaction conditions: 0.1 mmol of **6** and 0.3 mmol of $BF_3{\cdot}OEt_2$ in 6.0 mL of CH_2Cl_2, −78 °C to rt, 20 h. [b]The ratio was determined using ^{1}H NMR spectroscopy. [c]The stereochemistry of *anti*/*cis*-**7b** and *anti*/*trans*-**7h** was assigned on the basis of NOE experiments. The stereochemistry of *trans*-**7j** was assigned by comparing its ^{1}H NMR spectrum to that of a similar known structure.[14] [d]Isolated yields after purification by silica gel column chromatography.

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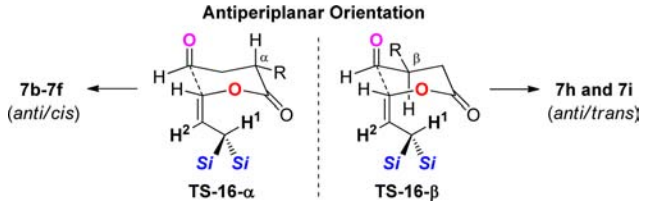
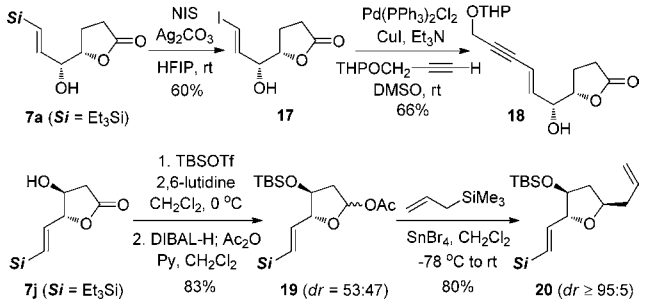
Scheme 5. Model Analysis To Explain Observed Stereochemical Outcomes



Scheme 6. Functionalization of *E*-Vinylsilane and γ-Lactone



We recently launched a series of investigations on structurally novel geminal bis(silanes), in which two silyl groups are attached to one carbon center.[7] This species duplicates the steric and electronic effects of silicon, thereby facilitating certain transformations or creating certain regio- or diastereoselectivities that would be impossible or difficult to achieve by other methods. For example, in 3,3-bis(triethylsilyl) enol ester **6**, the bis(silyl) moiety not only shields both sides of the β-position of enol but also provides a double hyperconjugation effect[8] between the two C−Si bonds and the enol double bond (eq 3). Combining these two effects makes the shared alkene behave as an allyl bis(silane) rather than as an enol, leading to a Sakurai allylation[9] with the γ-tethered acetal that generates δ-lactone diastereoselectively. This intermediate subsequently undergoes in situ rearrangement to afford the thermodynamically more stable γ-lactone **7**.[10] The ester linker was chosen because we reasoned that its electron-withdrawing effect should favor the desired umpolung to Sakurai pathway more so than the ether linker used by Yamamoto. In addition, using an ester linker would generate a γ-lactone, which is a versatile precursor for synthesizing diverse THFs.

The model substrate **6a** was synthesized from 3-silyl allyloxysilane **8**, which underwent *s*-BuLi/HMPA-promoted retro-[1,4] Brook rearrangement at −78 °C to generate *Z*-lithium enolate **9** (Scheme 2).[11] This intermediate was trapped with γ-acetal-substituted acyl imidazole **11**, which was prepared from **10** by condensation with carbonyldiimidazole,[12] to give **6a** in 50% yield.

Initial attempts using 3.0 equiv of TMSOTf, $TiCl_4$, or $AlCl_3$ in CH_2Cl_2 resulted only in deprotection of the acetal to give aldehyde **12** as the sole product (Table 1, entries 1−3). No further cyclization to form δ-lactone **13a** was observed, even at room temperature. Using $SnCl_4$ led to a complex mixture, but using 3.0 equiv of $BF_3{\cdot}OEt_2$ at −78 °C followed by warming to room temperature for 20 h cleanly afforded a cyclized product in 80% yield (entry 5). Surprisingly, this compound proved to be neither δ-lactone **13b**, reflecting direct cyclization of **6a**, nor **13a**, reflecting cyclization of **12**. Instead, the product was γ-lactone **7a** with *anti*-stereochemistry.

Further studies revealed that quenching the $BF_3{\cdot}OEt_2$-promoted reaction at −78 °C after 5 min afforded a mixture of aldehyde **12** (70%), δ-lactone **13a** (15%), and γ-lactone **7a** (10%) (Scheme 3). This result, and additional studies in which reaction was monitored by thin-layer chromatography, indicated that the process was initiated by deprotection of acetal to give the corresponding aldehyde **12**. Substrate **6a** disappeared immediately upon addition of $BF_3{\cdot}OEt_2$, prior to formation of **13a** and **7a**. Subsequent $BF_3{\cdot}OEt_2$-promoted Sakurai *exo*-cyclization of **12** at room temperature gradually generated δ-lactone **13a**, which simultaneously rearranged into γ-lactone **7a** under the acidic conditions. The stereochemistry of *trans*-**13a** and its rearrangement product *anti*-**7a** was confirmed by X-ray analysis of **14**,[13] which was generated by esterification of **13a** with 3,5-dinitrobenzoyl chloride.

Unexpectedly, cyclization of the aldehyde **12** with 3.0 equiv of $BF_3{\cdot}OEt_2$ provided neither **13a** nor **7a**, leading to recovery of **12** in 99% yield (Scheme 4). Switching the Lewis acid from $BF_3{\cdot}OEt_2$ to $AlCl_3$ gave δ-lactone **13a**, which did not rearrange into γ-lactone **7a**. These interesting results imply that the methoxy species formed in the deprotection step might promote both cyclization and rearrangement. We proposed the following rationales to explain these results. First, the methoxy equivalent attacks $SiEt_3$ in **12-L.A.**, accelerating silyl group elimination and thereby facilitating cyclization into **13a-L.A.** Second, the methoxy equivalent mediates ring opening to give the methyl ester intermediate **15**, since rearrangement of **13a-L.A.** by a boatlike transition state via intramolecular attack of the hydroxyl group on the carbonyl carbon would be energetically unfavorable.

Next, the scope of this approach was tested. The reaction showed wide applicability to 3,3-bis(silyl) enol esters **6b−f** containing various α-substituents such as methyl, benzyl, phenyl, chloride, and methoxy groups (Table 2, entries 2−6). The γ-lactones **7b−f** were obtained in good yield with complete *anti*/*cis*-stereochemical control. Cyclization was compatible with the construction of the spirocyclic γ-lactone **7g** in 84% yield (entry 7). The β-substituted 3,3-bis(silyl) enol esters **6h** and **6i** were suitable substrates for generating, respectively, **7h** and **7i** with *anti*/*trans*-stereochemistry (entries 8 and 9). *Exo*-cyclization of **6j** with a β-tethered acetal proved similarly efficient as the corresponding reaction with γ-acetal-substituted enol esters. The γ-lactone **7j**, which did not rearrange to β-lactone, was obtained in 85% yield with $a \geq 95{:}5$ *trans*/*cis* ratio.[14] No competitive *endo*-cyclization via a Mukaiyama aldol type pathway was observed in any of the examples.

To rationalize the stereochemical outcomes of cyclization, we proposed the existence of 6-membered chairlike transition states **TS-16-*α*** and **TS-16-*β*** in reactions of α- and β-substituted enol esters, respectively (Scheme 5). In both transition states, allyl bis(silane) and aldehyde adopt an antiperiplanar orientation,[15] and the R group adopts a favorable equatorial position. In this way, *anti*/*cis*-**7b−f** form from **TS-16-*α*** and *anti*/*trans*-**7h−i** from **TS-16-*β*** via cyclization/rearrangement. At the same time, H^1 and H^2 should lie *trans* to each other to avoid $A^{1,2}$ strain,[16] such that elimination of one of the silyl groups generates the observed *E*-vinylsilane.

The *E*-vinylsilane and γ-lactone moieties generated in the approach are useful building blocks for further transformations (Scheme 6). Iodination of **7a** with NIS in HFIP[17] gave the vinyl iodide **17** in 60% yield with retention of the *E*-configuration. Subsequent Sonogashira cross-coupling[18] with terminal alkynes afforded *E*-enyne **18** in 66% yield. On the other hand, TBS protection of **7j** and subsequent reduction/acylation gave **19** in 83% yield as a 53:47 mixture. Subjecting **19** to $SnBr_4$-promoted

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cis-allylation[19] with allyltrimethylsilane afforded functionalized THF **20** in 80% yield with dr ≥ 95:5.

In summary, we have described an efficient synthesis of functionalized γ-lactones via Sakurai *exo*-cyclization/rearrangement of 3,3-bis(silyl) enol esters with a tethered acetal. While the steric and electronic effects of geminal bis(silane) favor the desired Sakurai pathway, the methoxy species formed in the deprotection step facilitates both cyclization and rearrangement. We have demonstrated the synthetic value of this approach by efficiently transforming the *E*-vinylsilane into enyne and the γ-lactone moiety into multisubstituted THF. Studies of further applications of this method are underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral data for products, and X-ray data of **14**. These materials are available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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