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Stereocontrolled $(Me_3Si)_3SiH$-Mediated Radical and Ionic Hydride Transfer in Synthesis of 2,3,5-Trisubstituted THF

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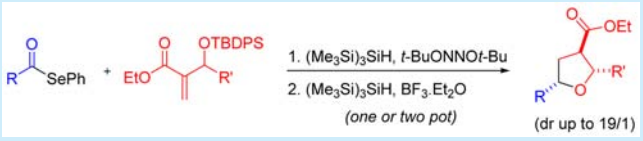
Supporting Information

ABSTRACT: 2,3,5-Trisubstituted tetrahydrofurans were prepared stereoselectively through a two-step process involving the addition of an acyl radical to a β-silyloxy acrylic ester followed by an acid-catalyzed desilylation−ketalization sequence and a final oxocarbenium reduction step. High levels of 1,2- and 1,3-stereocontrol were attained when $(Me_3Si)_3SiH$ was used as a radical followed by a ionic hydrogen transfer agent.



The tetrahydrofuran (THF) skeleton is ubiquitous in nature and is found in many classes of natural products, as illustrated below with the complex marine macrocycles gymnodimine (**1**)[1] and chagosensine (**2**)[2] (Figure 1). The

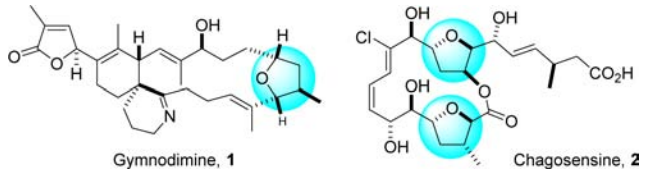


Figure 1. Tetrahydrofuran fragments in marine natural products.

broad array of biological activities associated with the widespread occurrence of these compounds has generated considerable interest. However, despite the development of a large number of methods to access these heterocycles,[3] some limitations have appeared, such as the unsatisfactory control of the stereochemistry in certain cases or the narrow scope of some synthetic routes. Therefore, the development of new strategies to assemble such small rings in a straightforward and stereocontrolled fashion still remains an active field of research.

In the course of a program on the total synthesis of gymnodimine (**1**), a straightforward access to a 2,3,5-trisubstituted tetrahydrofuran was required. It was envisioned that such THF could be formed starting from a phenyl selenoester and a β-alkoxy-substituted acrylic ester **IV** (Figure 2). The assembly of the THF skeleton would involve the successive formation of C4−C5 and then C5−O bonds, respectively, through (1) a diastereocontrolled addition of a nucleophilic acyl radical **III** onto the acrylic ester **IV** followed by (2) a reductive cyclization after in situ deprotection of the silyl ether. Both reactions would be mediated by a hydride-transfer agent (R_3SnH or R_3SiH), setting up the stereochemistry at the C3 and C5 positions. Such a strategic disconnection of THF, relying on a dual reactivity of the acyl precursor, has to our knowledge, not been described to date. Noteworthy, the use of

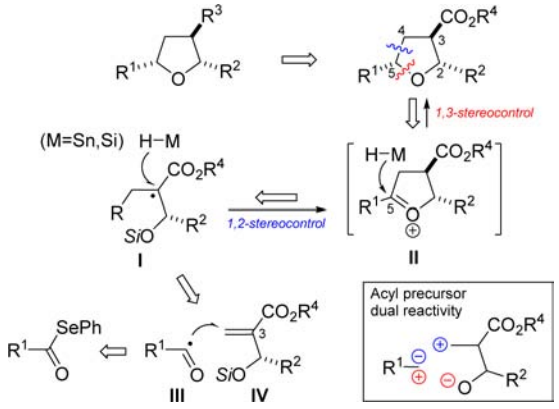


Figure 2. Strategic disconnections to 2,3,5-trisubstituted tetrahydrofurans.

the same hydride in both steps would potentially allow the whole sequence to be carried out in one pot.

This approach, however, raised several issues concerning the level of diastereocontrol during the reduction of the β-silyloxy ester radical **I** and that of the oxocarbenium intermediate **II**. Diastereocontrolled additions of alkyl radicals to Baylis−Hillman adducts, first reported by Giese and co-workers,[4] were shown to provide the corresponding esters with high diastereocontrol when using sterically hindered alkyl groups (**I**, R = *t*-Bu) and much lower selectivity with primary alkyl groups (**I**, R = *n*-C_8H_{17}).[4b] Moreover, in spite of the wealth of data in the field,[4−6] there was no report on the diastereocontrol arising from the conjugate addition of a rather small acyl radical **III** onto an α-substituted acrylate ester. An even more critical issue was raised by the stereochemical outcome of the ionic hydride transfer to oxonium **II**. Models relying on stereoelectronic and steric effects have been proposed by Reissig et al.[7] and then Woerpel et al.[8] to rationalize stereocontrol in nucleophilic additions onto 5-

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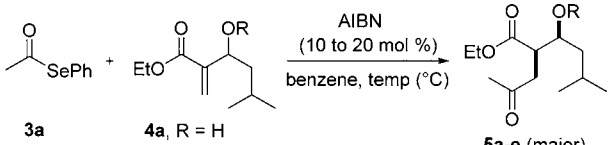
membered ring oxocarbeniums. However, in our case, R^2 and CO_2R^4 substituents, *trans* to each other, might induce opposite stereochemistry at C5 during hydride transfer to **II**, the stereochemical outcome of the process thus remaining uncertain. We report here that the acyl radical addition to β-silyloxy acrylic esters, followed by the reduction of the oxocarbenium ion, may be mediated, in both steps, by $(Me_3Si)_3SiH$ (TTMSH) acting as a radical and then an ionic hydride transfer agent.[9] This offers an entry to a series of 2,3,5-trisubstituted tetrahydrofurans in one- or two-pot processes in good yield and with high levels of 1,2- and 1,3-diastereocontrol.

The acyl radical was generated from phenyl selenoesters[10] using Bu_3SnH as a reducing agent and AIBN as an initiator. Under these conditions, addition of **3a** onto the unprotected acrylic ester **4a** led to the desired product **5a** in good yield but no stereocontrol as a mixture of free hydroxyketone and lactol (Table 1, entry 1). Protection of the alcohol as an acetate

Table 1. Optimization of the Acyl Radical Addition to β-Silyloxy Acrylates 4a−e



3a

4a, R = H
4b, R = Ac
4c, R = *t*-BuMe$_2$Si
4d, R = (*i*Pr)$_3$Si
4e, R = *t*-BuPh$_2$Si

5a-e (major)

entry	ester	M − H	temp (°C)	**5**, yield[a] (%)	dr[b]
1	**4a**	Bu_3SnH	90	70	nd[c]
2	**4b**	Bu_3SnH	90	90	2.4:1
3	**4c**	Bu_3SnH	90	90	3.5:1
4[d]	**4c**	Bu_3SnH	0	81	4.4:1
5[d]	**4d**	Bu_3SnH	0	62	1:1
6[d]	**4e**	Bu_3SnH	0	75	6.5:1
7[d,e]	**4e**	Bu_3SnH	−20	65	8:1
8	**4e**	TTMSH	90	91	5:1
9[f]	**4e**	TTMSH	45	87	>19:1

[a]Isolated yields. [b]Estimated through ^{1}H NMR of the crude reaction mixture. [c]The product was obtained as a mixture of diastereoisomeric hydroxyketone and hemiacetal. [d]UV initiation using a sunlight lamp (300 W). [e]Chlorobenzene was used instead of benzene. [f]*t*-BuON=NO*t*-Bu (DTBHN) was used instead of AIBN.

provided **5b** in excellent yield albeit with low sterecocontrol (Table 1, entry 2). Increasing stereocontrol was observed with **4c** having a *t*-BuMe$_2$Si substituent (Table 1, entry 3), by lowering the temperature (Table 1, entry 4), and in **4e** with sterically more hindered *t*-BuPh$_2$Si substituent[5d] (Table 1, entries 6 and 7). Surprisingly, the TIPS substituent in **4d** led to disappointing results (Table 1, entry 5).[5h] Finally, the best results were observed using $(Me_3Si)_3SiH$ instead of Bu_3SnH (Table 1, entries 8 and 9), which led to **5e** in 87% yield and up to >19:1 diastereoselectivity, showing that an increase of the steric hindrance of the hydride donor was able to secure the level of stereocontrol, whatever the size of the R group in radical **I** (Figure 2). The *syn* stereochemistry of **5a−e** (assigned on the basis of X-ray diffraction studies on a crystalline analogue, i.e., **6h**, vide infra) may be rationalized by invoking a staggered transition state (TS) model in which the bulky silane approaches *anti* relative to the large silyloxy group, with the small hydrogen nearly eclipsing the ester group (Figure 3). This early transition

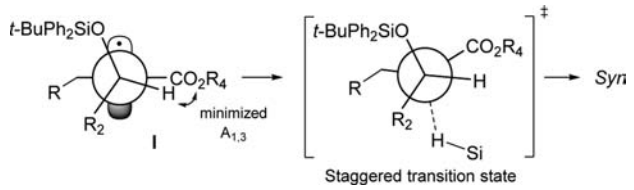
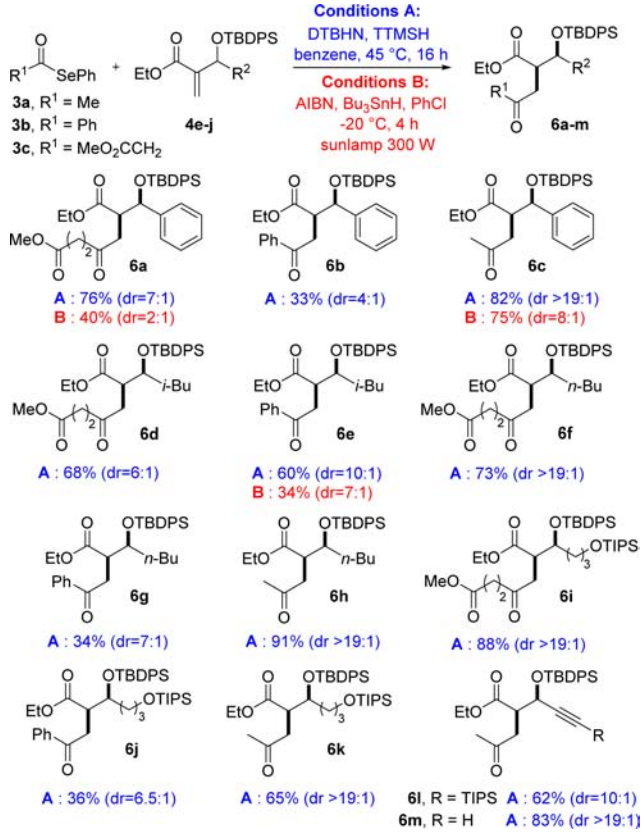


Figure 3. Transition-state model for radical hydrogen transfer.

state resembles the ground-state conformation of the radical intermediate **I** where $A_{1,3}$-strain is minimized.[4,5c,d] As reported by Giese, stereocontrol increases with the size of the silyl protecting group.[11] The crucial role of TTMSH is noteworthy as this reagent is well-known to increase stereoselectivity in radical hydride transfers in cyclic systems,[12] but more rarely in acyclic ones.[13]

These reaction conditions were then extended to a series of phenyl selenoesters **3a−c** and β-silyloxyacrylic esters **4e−j** (Scheme 1). Two sets of reaction conditions (A and B) were

Scheme 1. TTMSH-Mediated Addition of Acyl Radicals to β-Silyloxyacrylic Esters



studied in order to establish the comparative efficiency of Bu_3SnH and TTMSH (Scheme 1). Reactions with the silane were carried out at a higher temperature but led consistently to higher yields and stereocontrol. The benzoyl radical led to slightly lower yields and stereocontrol as compared to other acyl precursors (see, for instance, **6b**, **6g**, and **6j**).[14] The nature of the β-alkyl or aryl chain did not influence the selectivity to a large extent. Adding a bulky TIPS group on the alkynyl chain as in **6l**, however, slightly lowered the diastereocontrol as compared to the unprotected alkyne **6m**. It is worth noting that the reaction could also be performed on a larger scale. For instance, esters **6c**

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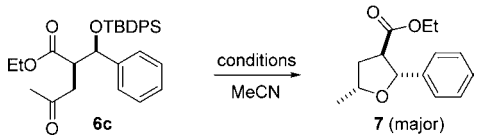
and **6m** were prepared in up to 4.5 mmol in 79 and 83% yield, respectively. Finally, X-ray diffraction studies performed on crystalline **6h** allowed us to assign the *syn*-relative configuration for compounds **5a−e** and **6a−m**.

With ketoesters **6** in hand, the one-pot silyl group deprotection, hemiacetal formation, and oxocarbenium ion reduction was then studied using **6c** as a model substrate (Table 2). The combination between a Lewis acid and a reducing

Table 2. Optimization of the Tandem Cyclization−Reduction of *β*-Silyloxy Ester 6c



entry	Lewis acid (equiv)	MH (4 equiv)	temp (°C)	7, yield[a] (%)	dr[b]
1	$BiBr_3$ (0.1)	Et_3SiH	25	87	1.8:1
2	$BiBr_3$ (0.1)	iPr_3SiH	25	0	
3[c]	TMSOTf (1)	Et_3SiH	−78	29	1.4:1
4	$BF_3.Et_2O$ (2)	Et_3SiH	−40	78	2.4:1
5	$BF_3.Et_2O$ (2)	TTMSH	25	87	16:1

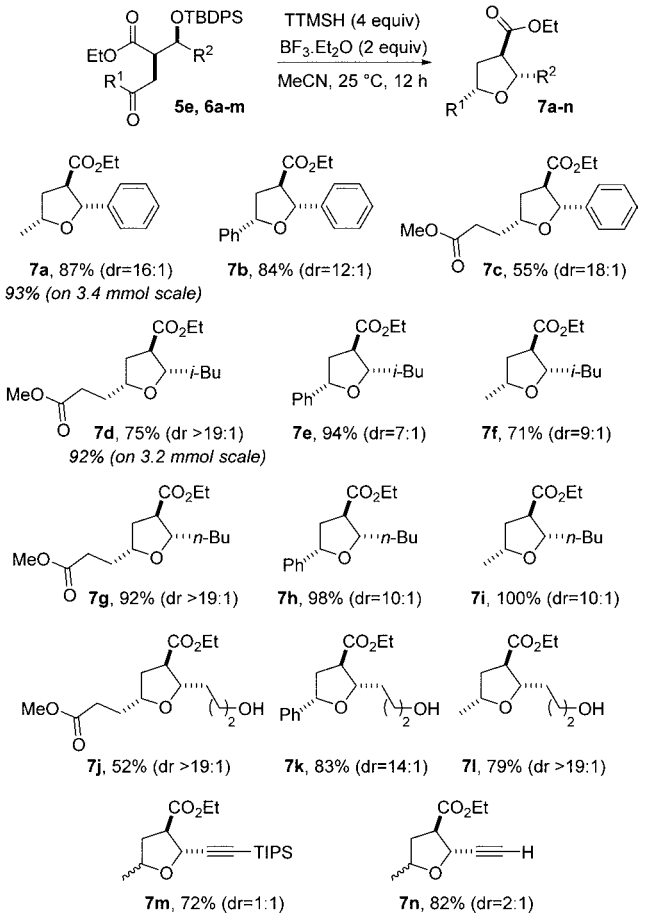
[a]Isolated yields. [b]Estimated through ^1H NMR of the crude reaction mixture. [c]CH_2Cl_2 instead of MeCN.

agent was anticipated to trigger the desilylation, the cyclization into an hemiacetal, and the subsequent formation of the oxocarbenium intermediate. Several Lewis acids were thus tested as well as silanes. A catalytic amount of $BiBr_3$[15a] was first shown to efficiently mediate both processes, but reduction with Et_3SiH led to poor diastereofacial differentiation (Table 2, entry 1). Increasing the steric hindrance around silicon using *i*-Pr_3SiH was found to be detrimental to the reaction (Table 2, entry 2). Use of a stoichiometric amount of TMSOTf with Et_3SiH showed little efficiency (Table 2, entry 3). A good yield but low stereocontrol was observed when using 2 equiv of $BF_3{\cdot}OEt_2$ associated with Et_3SiH.[7,15b]

More satisfyingly, a high level of diastereocontrol was attained again using TTMSH as a hydride transfer agent, affording the desired THF **7** with up to 16:1 dr at room temperature (Table 2, entry 5). These conditions were then extended to ketoesters **5e** and **6a−m** described above (Scheme 2). The cascade reaction proceeded in generally high yields and level of diastereocontrol ranging between 7:1 to >19:1. An exception was however observed with THF **7m** and **7n**, which led to poor diastereocontrol, likely as a result of the lesser steric hindrance of the linear alkynyl substituent at C2. In **7j−l**, deprotection of the TIPS group on the C2 chain was also observed. The reductive cyclization was shown to be even more efficient on a large scale, as experiments performed with **6c** (3.4 mmol) and **6d** (3.2 mmol) afforded the corresponding THFs **7a** and **7d**, respectively, in 93% and 92% yield. The 2,3,5-*trans,trans* relative configuration of tetrahydrofurans **7a−n** was assigned on the basis of the X-ray diffraction studies of a crystalline derivative (i.e., **10**, vide infra).

TTMSH is a choice reagent for radical reductive processes,[9,13] but to our knowledge its use has not been reported for the reduction of oxocarbeniums ions, where cheaper Et_3SiH generally affords satisfying results. The high level of stereocontrol observed with TTMSH may be rationalized by invoking a transition-state model such as **A** (Figure 4), in which the

Scheme 2. TTMSH-Mediated Reductive Cyclization of Ketoesters 6



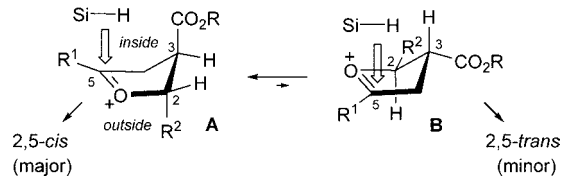


Figure 4. Transition-state models for the TTMSH reduction of oxocarbeniums.

oxocarbenium ion adopts an envelope conformation with the polar substituent at C3 in a pseudoaxial position, as recently reported by Woerpel for closely related 5-membered-ring oxocarbenium ions bearing an alkoxy group at C3.[8a] The nucleophile would thus approach from *inside* the envelope to provide the 2,5-*cis* THF. The importance of the proximity of a partially negatively charged substituent in a pseudoaxial position at C3, close to the cationic C5 center (electrostatic effects), has been clearly established in these systems with alkoxy groups, but not with esters.[8a] However, recent studies on glycosylation of mannuronate esters suggest that an ester group may also be an efficient stereodirecting group.[16] TS model **A** may finally provide an explanation for the low diastereocontrol observed with compounds **7m−n**, as linear alkynyl groups (R^2) at C2 should also allow the approach of the silane from *outside* the envelope.

The whole sequence was also performed in one pot, as shown with the conversion of **4f** into **7a** occurring with a high stereocontrol and satisfying overall yield, demonstrating that such trisubstituted tetrahydrofurans may be generated from a

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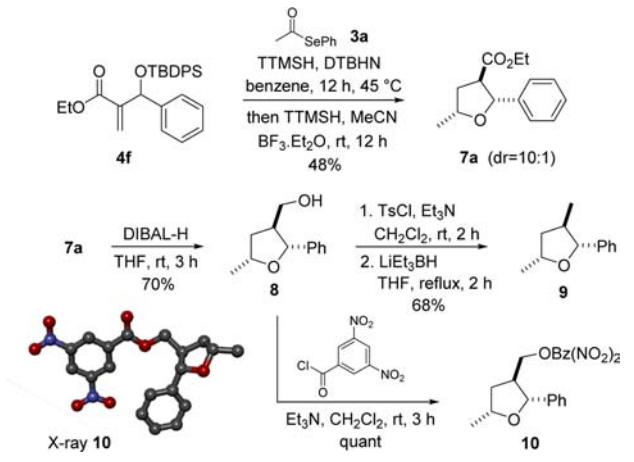
simple Baylis–Hillman adduct in a single step and selective manner (Scheme 3). Further manipulations of these THFs are

Scheme 3. One-Pot Synthesis and Further Elaboration of 7a



also allowed. The ester function of **7a** was also transformed into a methyl, in 34% overall yield and five steps from **4f**, to produce the corresponding THF **9** having the substituent and stereochemistry present in gymnodimine (**1**). Finally, X-ray diffraction studies on benzoate **10** secured the relative configuration of the tetrahydrofuran series **7a–n**.

In summary, we report straightforward access to 2,3,5-substituted tetrahydrofurans using radical, followed by ionic $(Me_3Si)_3SiH$-mediated hydrogen transfers. High levels of 1,2- and 1,3-stereocontrol were achieved, relying in both cases on the steric hindrance of the above silane. Application of this methodology to the construction of the gymnodimine THF framework is currently underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00303.

Crystallographic data for **6h** (CIF)
Crystallographic data for **10** (CIF)
Experimental details and characterization data for the starting material and products (PDF)

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Notes

The authors declare no competing financial interest.

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