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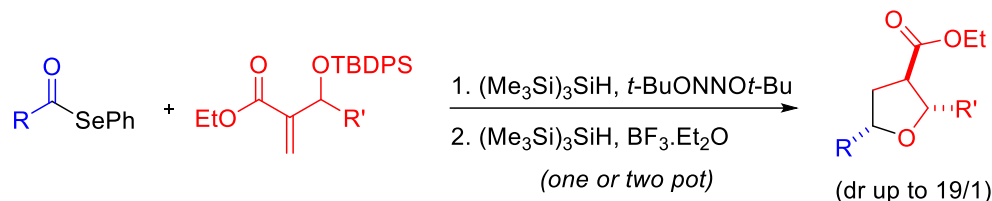
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Stereocontrolled $(\text{Me}_3\text{Si})_3\text{SiH}$ -Mediated Radical and Ionic Hydride Transfer in Synthesis of 2,3,5-Trisubstituted THF

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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 acrylate, 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 using $(\text{Me}_3\text{Si})_3\text{SiH}$ as a radical then 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 complex marine macrocycles gymnodimine **1**¹ and chagosensine **2**² (Figure 1). The broad array of biological activities associated with the widespread occurrence of these compounds have 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.

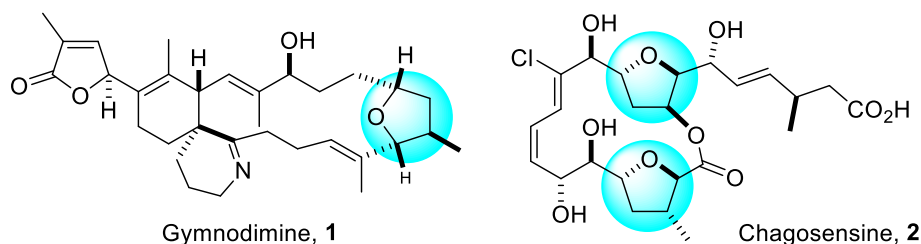


Figure 1. Tetrahydrofuran fragments in marine natural products.

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 acrylate **IV** (Figure 2). The assembly of the THF skeleton would involve the successive formation of C4-C5 then C5-O bonds, respectively through: (1) a diastereocontrolled addition of a nucleophilic acyl radical **III** onto the acrylate **IV**, followed by (2), a reductive cyclization after *in situ* deprotection of the silyl ether. Both reactions would be mediated by an 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 the same hydride in both steps would potentially allow the whole sequence to be carried out in one-pot.

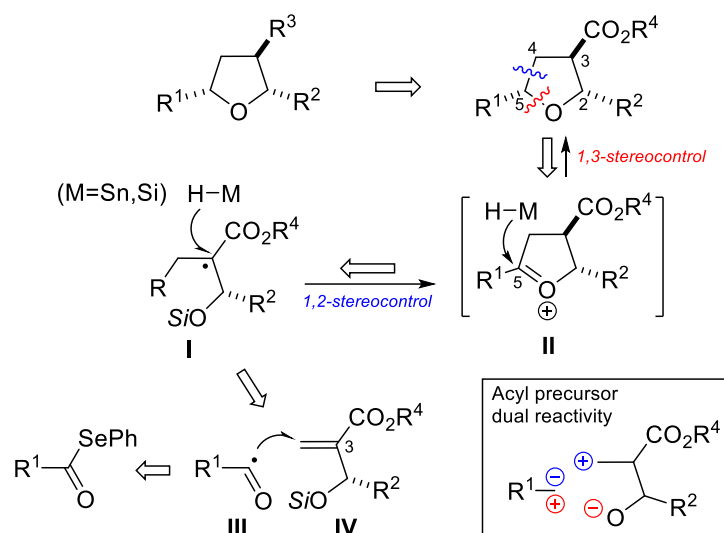
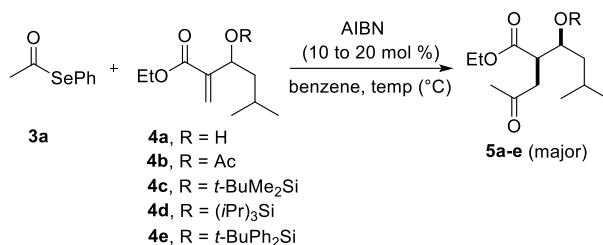


Figure 2. Strategic disconnections to 2,3,5-trisubstituted tetrahydrofurans.

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*-C₃H₁₇).^{4b} Moreover, in spite of the wealth of data in the field,^{4,5,6} 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 then Woerpel et al.⁸ to rationalize stereocontrol in nucleophilic additions onto 5-membered ring oxocarbeniums. However, in our case, R² and CO₂R⁴ 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 (Me₃Si)₃SiH (TTMSH) acting as a radical then 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 high level of 1,2- and 1,3-diastereocontrol.

Table 1. Optimization of the acyl radical addition to β -silyloxy acrylates **4a-e**.

entry	ester	M-H	temp (°C)	5 , yield ^a (%)	dr ^b
1	4a	Bu ₃ SnH	90	70	n.d. ^c
2	4b	Bu ₃ SnH	90	90	2.4:1
3	4c	Bu ₃ SnH	90	90	3.5:1
4 ^d	4c	Bu ₃ SnH	0	81	4.4:1
5 ^d	4d	Bu ₃ SnH	0	62	1:1
6 ^d	4e	Bu ₃ SnH	0	75	6.5:1
7 ^{d,e}	4e	Bu ₃ SnH	-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 ¹H 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.

The acyl radical was generated from phenyl selenoesters,¹⁰ using Bu₃SnH 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 provided **5b** in excellent yield albeit with low stereocontrol (Table 1, entry 2). Increasing stereocontrol was observed with **4c** having a *t*-BuMe₂Si substituent (Table 1, entry 3), by lowering the temperature (Table 1, entry 4), and in **4e** with sterically more hindered *t*-BuPh₂Si substituent^{5d} (Table 1, entries 6-7). Surprisingly, the TIPS substituent in **4d** led to disappointing result (Table 1, entry 5).^{5h} Finally, the best results were observed using (Me₃Si)₃SiH instead of Bu₃SnH (Table 1, entries 8-9), 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 based on X-ray diffraction studies on a crystalline analogue, *i.e.* **6h**, *vide infra*) may be rationalized invoking a staggered transition state model, in which the bulky silane approaches *anti* relative to the large silyloxy group, the small hydrogen nearly eclipsing the ester group (Figure 3). This early transition state resembles 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

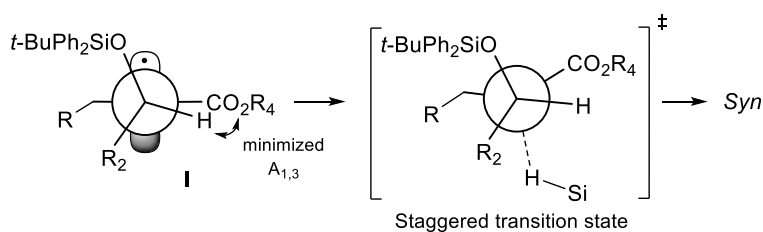
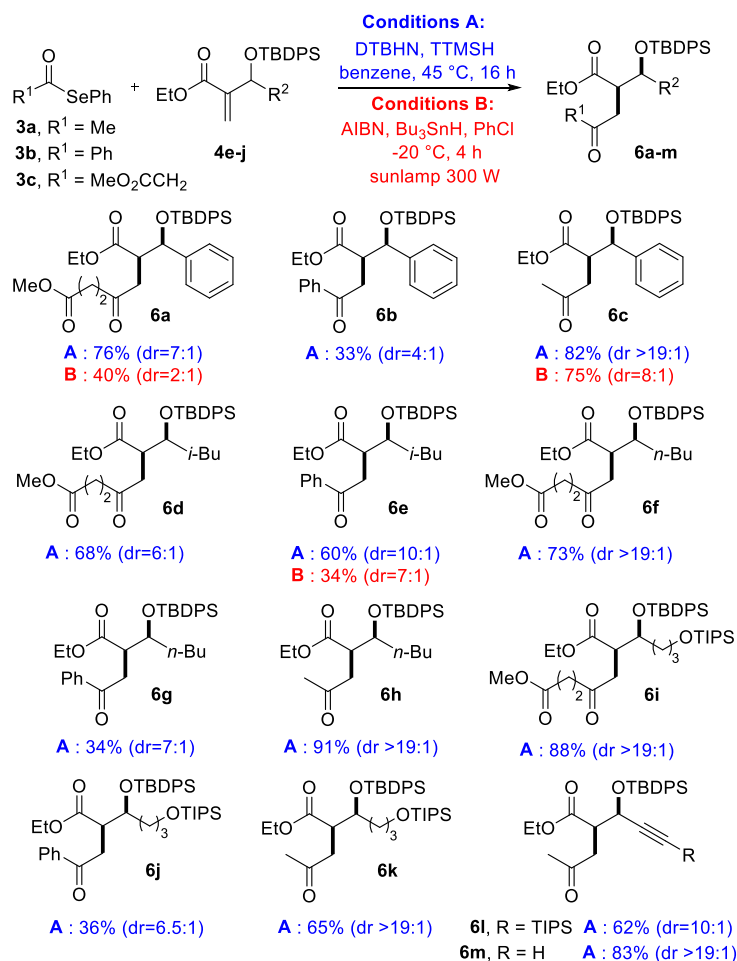


Figure 3. Transition state model for acyl addition to acrylates.

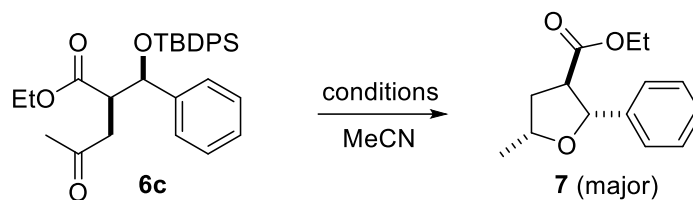
Scheme 1. TTMSH-mediated addition of acyl radicals to β -silyloxyacrylic esters.



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 studied in order to establish the comparative efficiency of Bu₃SnH 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 of note that the reaction could also be performed on a larger scale. For instance, esters **6c** and **6m** were prepared in up to 4.5 mmol in 79 and 83% yield respectively. Finally, 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 agent was anticipated to trigger the desilylation, then 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 $i\text{Pr}_3\text{SiH}$ was found to be detrimental to the reaction (Table 2, entry 2). Stoichiometric amount of TMSOTf with Et_3SiH showed little efficiency (Table 2, entry 3). A good yield, albeit low stereocontrol was observed when using 2 equivalents of $\text{BF}_3 \cdot \text{OEt}_2$ associated to Et_3SiH .^{7,15b}

Table 2. Optimization of the tandem cyclization-reduction of β -silyloxy ester **6c**.

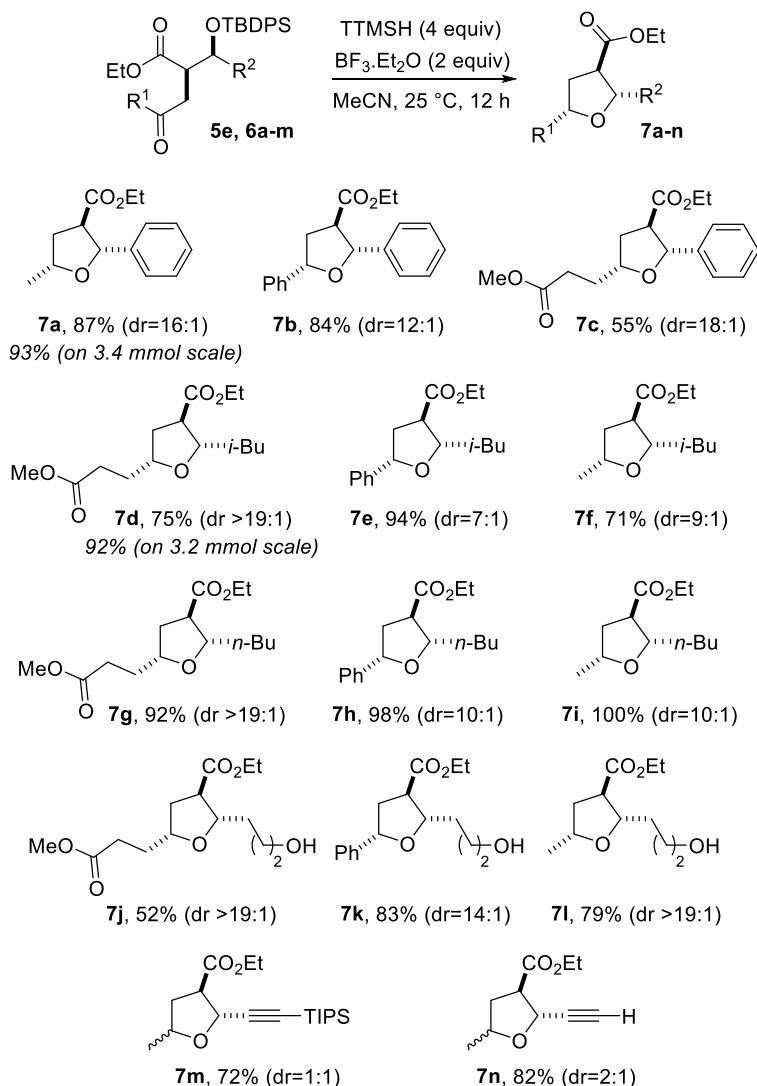


entry	Lewis acid (equiv.)	MH (4 equiv)	temp (°C)	7 , yield ^a (%)	dr ^b
1	BiBr_3 (0.1)	Et_3SiH	25	87	1.8:1
2	BiBr_3 (0.1)	$i\text{Pr}_3\text{SiH}$	25	0	-
3 ^c	TMSOTf (1)	Et_3SiH	- 78	29	1.4:1
4	$\text{BF}_3 \cdot \text{Et}_2\text{O}$ (2)	Et_3SiH	- 40	78	2.4:1
5	$\text{BF}_3 \cdot \text{Et}_2\text{O}$ (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.

More satisfyingly, a high level of diastereocontrol was attained again using TTMSH as an hydride transfer agent, affording the desired THF **7** with up to 16:1 d.r. 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 in large scale, as experiments performed with **6c** (3.4 mmol) and **6d** (3.2 mmol), afforded the corresponding THF **7a** and **7d** respectively in 93% and 92% yield. The 2,3,5-*trans,trans* relative configuration of tetrahydrofurans **7a-n** was assigned, based on the X-ray diffraction studies of a crystalline derivative (*i.e.* **10**, *vide infra*).

Scheme 2. TTMSH-mediated reductive cyclization of ketoesters **6**.



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 oxocarbenium ions, where cheaper Et_3SiH generally affords satisfying results. The high level of stereocontrol observed with TTMSH may be rationalized invoking a transition state model such as **A** (Figure 4), in which the 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.

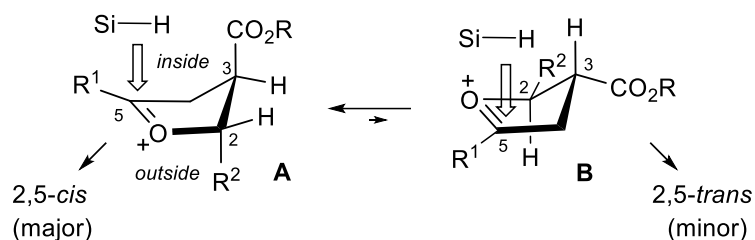
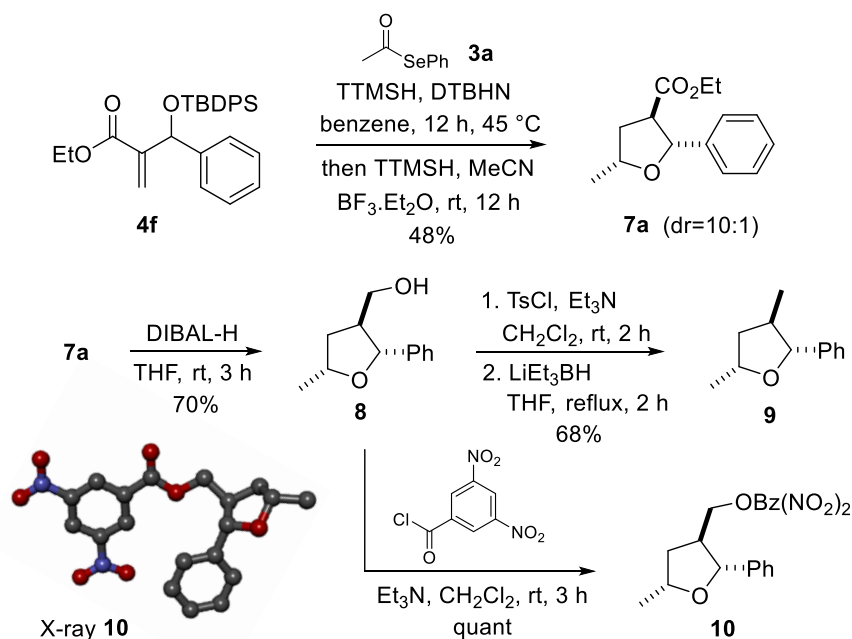


Figure 4. Transition state models for the TTMSH-reduction of oxocarbeniums.

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 simple Baylis-Hillman adduct in a single step and selective manner (Scheme 3). Further manipulations of these THFs are also allowed. The ester function of **7a** was also transformed into a methyl, in 34% overall yield and 5 steps from **4f**, to produce the corresponding THF **9** having 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**.

Scheme 3. One-pot synthesis and further elaboration of **7a**.



In summary, we reported straightforward access to 2,3,5-substituted tetrahydrofurans using radical then ionic $(\text{Me}_3\text{Si})_3\text{SiH}$ 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.

REFERENCES

- (1) (a) Seki, T.; Satake, M.; Mackenzie, L.; Kasper, H. F.; Ysumoto, T. *Tetrahedron Lett.* **1995**, *36*, 7093. For a total synthesis of **1**, see: Kong, K.; Romo, D.; Lee, C. *Angew. Chem. Int. Ed.* **2009**, *48*, 7402.
- (2) Rezanka, T.; Hanus, L.; Dembitsky, V. M. *Eur. J. Org. Chem.* **2003**, 4073.
- (3) (a) Lorente, A.; Lamariano-Merketegi, J.; Albericio, F.; Alvarez, M. *Chem. Rev.* **2013**, *113*, 4567. (b) Lee, E. *Pure & Appl. Chem.* **2005**, *77*, 2073. (c) Martins da Silva, F.; Jones, J., Jr.; de Mattos, M. C. S. *Curr. Org. Synth.* **2005**, *2*, 393. (d) Donohoe, T. J.; Pullin, R. D. C. *Chem. Commun.* **2012**, *48*, 11924. (e) Jalce, G.; Franck, X.; Figadère, B. *Tetrahedron: Asymmetry* **2009**, *20*, 2537. (f) Cheikh, N. S. *Org. Biomol. Chem.* **2014**, *12*, 9492. (g) Rjabovs, V.; Turks, M. *Tetrahedron* **2013**, *69*, 10693. (h) Wolfe, J. P. *Synlett* **2008**, 2913. (i) Padwa, A. *J. Organomet. Chem.* **2005**, *690*, 5533.
- (4) (a) Bulliard, M.; Zeitz, H.-G.; Giese, B. *Synlett* **1991**, 423. (b) Giese, B.; Bulliard, M.; Dickhaut, J.; Halbach, R.; Hassler, C.; Hoffmann, U.; Hinzen, B.; Senn, M. *Synlett* **1995**, 116.
- (5) For reviews, see: (a) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1995. (b) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296-304. (c) Hart, D. J.; Krishnamurthy, R. *Synlett* **1991**, 412. (d) Curran, D. P.; Ramamoorthy, P. S. *Tetrahedron* **1993**, *49*, 4841. (e) Durkin, K.; Liotta, D.; Rancourt, J.; Lavallée, J.-F.; Boisvert, L.; Guindon, Y. *J. Am. Chem. Soc.* **1992**, *114*, 4912. (f) Hart, D. J.; Krishnamurthy, R. *J. Org. Chem.* **1992**, *57*, 4457. (g) Schubert, S.; Renaud, P.; Carrupt, P. A.; Schenk, K. *Helv. Chim. Acta* **1993**, *76*, 2473. (h) Renaud, P.; Stojanovic, A. *Tetrahedron Lett.* **1996**, *37*, 2569.
- (6) Guérin, B.; Ogilvie, W. W.; Guindon, Y. in *Radicals in Organic Synthesis*; VCH: Weinheim, 2001; Vol. 1, pp 441-460. (b) Guindon, Y.; Rancourt, J. *J. Org. Chem.* **1998**, *63*, 6554. (c) Denissova, I.; Maretti, L.; Wilkes, B. C.; Scaiano, J. C.; Guindon, Y. *J. Org. Chem.* **2009**, *74*, 2438.
- (7) (a) Schmitt, A.; Reissig, H.-U. *Synlett* **1990**, 40. (b) Brückner, C.; Holzinger, H.; Reissig, H.-U. *J. Org. Chem.* **1988**, *53*, 2450. (c) Reissig, H.-U.; Holzinger, H.; Glomsda, G. *Tetrahedron.* **1989**, *45*, 3139.
- (8) (a) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 10879. (b) van Rijssel, E. R.; van Delft, P.; Lodder, G.; Overkleeft, H. S.; van der Marel, G. A.; Filippov, D. V.; Codée, J. D. C. *Angew. Chem. Int. Ed.* **2014**, *53*, 10381.
- (9) Chatgililoglu, C. *Chem. Eur. J.* **2008**, *14*, 2310.
- (10) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1992**, *57*, 1429.
- (11) The absence of selectivity with very bulky TIPS group cannot be rationalized by TS in Figure 3, and remains unexplained.
- (12) (a) Maulide, N.; Markó, I. E. *Chem. Commun.* **2006**, 1200. (b) Yamaguchi, K.; Kazuta, Y.; Abe, H.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2003**, *68*, 9255.
- (13) Kopping, B.; Chatgililoglu, C.; Zehnder, M.; Giese, B. *J. Org. Chem.* **1992**, *57*, 3994.
- (14) Competing reduction of benzoyl radical with TTMSH might explain such low yields, see: Chatgililoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991.
- (15) (a) Evans, P. A.; Cui, J.; Gharpure, S. J.; Hinkle, R. J. *J. Am. Chem. Soc.* **2003**, *125*, 11456. (b) Backes, J. R.; Koert, U. *Eur. J. Org. Chem.* **2006**, 2777.
- (16) Codée, J. D. C.; van den Bos, J. J.; de Jong, A.-R.; Dinkelaar, J.; Lodder, G.; Overkleeft, H. S.; van der Marel, G. A. *J. Org. Chem.* **2009**, *74*, 38. Referees are gratefully acknowledged for their useful comments.