

Ti(III)-Mediated Radical-Induced Approach to a Bicyclic δ -Lactone with a Bridgehead β -Hydroxy Group

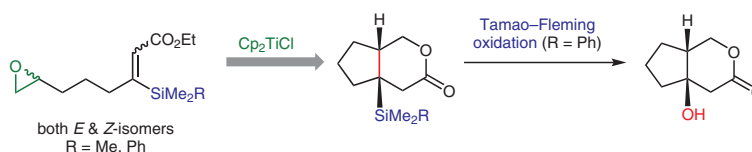
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Abstract Herein, we portray a synthetic route to a bicyclic lactone containing a bridgehead hydroxy group, a structure that is present in many natural products of biological and medicinal relevance. Ethyl (E)-3-(dimethylphenylsilyl)-7,8-epoxyoct-2-enoate underwent radical-mediated reductive epoxide opening with concomitant intramolecular cyclization using $\text{Cp}_2\text{Ti(III)Cl}_3$ to give *cis*-6-(dimethylphenylsilyl)-3-oxabicyclo[4.3.0]nonan-4-one, a bicyclic lactone with a bridgehead silyl group serving as a masked hydroxy group. Furthermore, the bridgehead C-Si bond underwent stereoretentive oxidative cleavage to give *cis*-6-hydroxy-3-oxabicyclo[4.3.0]nonan-4-one in high yield under Tamao-Fleming oxidation conditions; this demonstrates the potential utility of this strategy in the synthesis of many natural products bearing similar hydroxylated bridgehead chiral center embedded in a bicyclic lactone framework.

Key words quaternary center, bridgehead hydroxy, Cp_2TiCl_3 , bicyclic lactone, radical cyclization, Tamao-Fleming oxidation

The development of methodologies that employ reactive species that enable the synthesis of valuable molecules and advanced synthons owing to their unique reactivity is of significant importance in synthetic organic chemistry. A plethora of useful and elegant chemistry has been developed over the years using radical intermediates, despite the accepted notion that these species are chaotic, uncontrollable, and non-stereoselective.^{1,2}

In these endeavors, methods based on $\text{Cp}_2\text{Ti(III)Cl}_3$ mediated radical epoxide-opening reactions, first reported by Nugent and RajanBabu,⁴ have been used by several research groups, including ours, as the key step in the synthesis of many natural products⁵⁻⁷ and medicinally relevant compounds.^{8,9} We began our journey with $\text{Cp}_2\text{Ti(III)Cl}_3$ with the development of an iterative synthetic strategy that allowed the synthesis of chiral 2-methyl-1,3-diols by selective opening of a trisubstituted chiral 2,3-epoxy alcohol at the

more substituted carbon.¹⁰ The designed tactic was extended later in the stereoselective construction of chiral quaternary stereocenters by trapping the radical intermediate with suitable acceptors, particularly in an intramolecular mode, to provide carbocycles,¹¹ oxacycles,¹² azacycles,¹³ and dioxafenestranes.¹⁴

After successful implementation of the titanocene(III) chemistry for the construction of quaternary centers, we next intended to extend our iterative methodology to build hydroxylated bridgehead chiral centers in bicyclic ring systems, structural features of various natural products and natural product inspired synthons.¹⁵

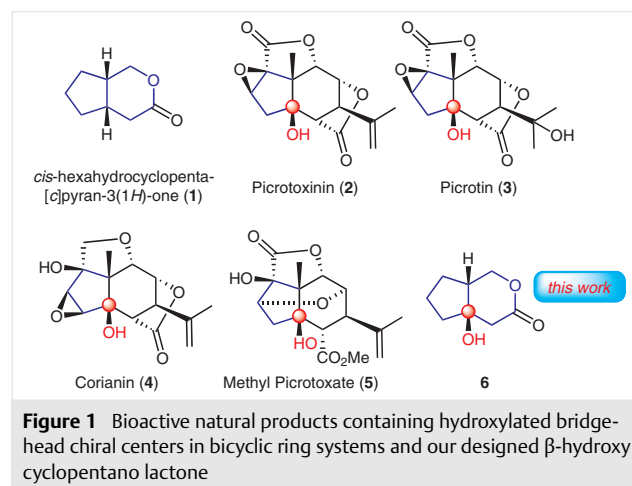
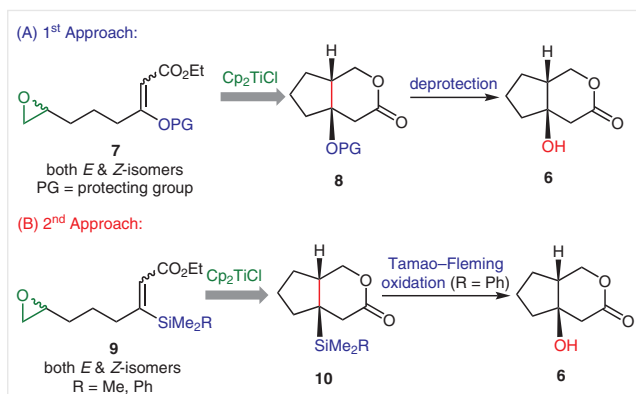


Figure 1 Bioactive natural products containing hydroxylated bridgehead chiral centers in bicyclic ring systems and our designed β -hydroxy cyclopentano lactone

As the process of isolation, structure elucidation, and biological evaluation of new natural products is rather laborious and time consuming, the concept of the development of natural product hybrids and analogues, containing two or more different pharmacophoric subunits, is being actively pursued.¹⁶ Cyclopentano-monoterpene lactone **1** rep-

resents one of the parent frameworks common to a large number of plant families and in various species of *Iridomyrmex*¹⁷ known to exhibit highly excitative activity towards cats and other *Felidae* animals and used by ants as agents of defense against preying insects.¹⁸ Insertion of a bridgehead hydroxy group into the core scaffold of **1** leads to the structure **6**, which can be regarded as a biologically pre-validated scaffold owing to the fact that many natural products based on this hydroxylated bicyclic ring system possess a wide array of densely functionalized structures **2–5**^{15,19} with diverse biological activities (Figure 1).

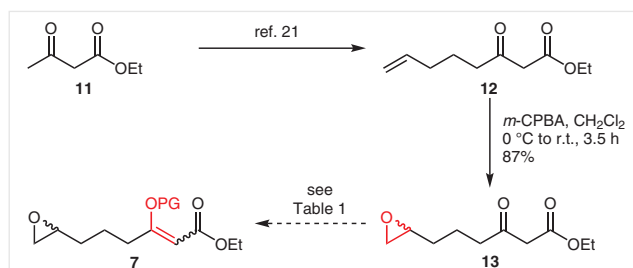
Herein, we disclose the viability of the Ti(III)-mediated reductive epoxide opening–cyclization sequence to build hydroxylated bridgehead stereogenic centers following two approaches summarized in Scheme 1. The direct approach (A) employing an epoxy- β -alkoxy- α,β -unsaturated ester was backed up by an alternate strategy (B) starting with an epoxy- β -(triorganosilyl)- α,β -unsaturated ester in which the silyl group could serve as a surrogate for the eventual oxygen functionality. The stereoretentive oxidative cleavage of the C–Si bond using the Tamao–Fleming method²⁰ was expected to provide a synthetic strategy to access the desired bridgehead-oxygenated bicyclic ring systems (Scheme 1). We report here the full detail of our systematic study toward the target scaffold.



Scheme 1 Generalized scheme of our approach

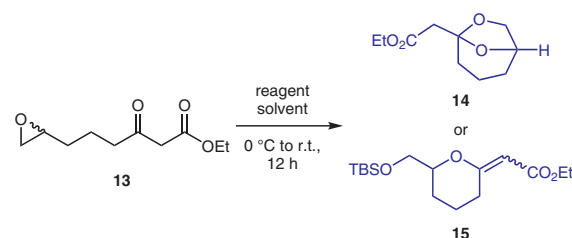
To evolve an approach efficaciously, at the outset, we devised a simple strategy to access epoxide **7** with a tethered enol ether serving as a precursor for the key Ti(III)-mediated reductive epoxide opening–cyclization to access the bridgehead-oxygenated bicyclic ring in one go (Scheme 1, A).

The reaction of the dianion of ethyl acetoacetate (**11**) with 4-bromobut-1-ene afforded ethyl 3-oxooct-7-enoate (**12**) by following the procedure documented in literature (Scheme 2).²¹



Scheme 2 Preparation of the epoxide **13**

Table 1 Attempted Preparation of the Silyl Enol Ether^a



Entry	Reagents	Solvent	Product	Yield (%) ^b
1	DIPEA/TBSOTf	CH ₂ Cl ₂	14	88
2	K ₂ CO ₃ /18-crown-6/TBSOTf	THF	14	72
3	Et ₃ N/TBSOTf	CH ₂ Cl ₂	14	81
4	imidazole/TBSCl	toluene	–	– ^c
5	DBU/TBSCl	CH ₂ Cl ₂	–	– ^c
6	2,6-lutidine/TBSOTf	CH ₂ Cl ₂	15	63
7	Et ₃ N/TBSOTf	hexane	15	57

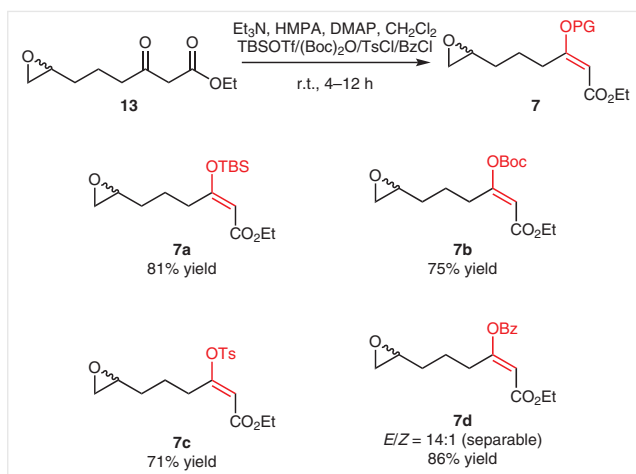
^a Reaction conditions: **13** (1.0 equiv), base (2.0 equiv), silylating agent (1.5 equiv), solvent (3 mL/mmol).

^b Isolated yield after silica gel column chromatography.

^c No reaction; starting material was recovered.

Next, epoxide **13** was synthesized from **12** in 87% yield using *m*-CPBA (Scheme 2) and was subsequently subjected to various reaction conditions to deliver the desired silyl enol ether **7a**. A summary of these efforts using different bases and additives is documented in Table 1.

To begin with, when epoxide **13** was treated with DIPEA/TBSOTf in CH₂Cl₂ for 12 h, it furnished an unusual bicyclic ketal moiety **14**²² (Table 1, entry 1), failing to provide the desired silyl enol ether **7a**. The use of K₂CO₃/18-crown-6/TBSOTf in THF and Et₃N/TBSOTf in CH₂Cl₂ led to the same result (Table 1, entries 2 and 3). Treatment of **13** with TBSCl/imidazole or TBSCl/DBU did not initiate any reaction and led to the recovery of starting material (Table 1, entries 4 and 5). Whereas formation of the THP derivative **15** (*E/Z* 1:5) resulted from the use of 2,6-lutidine and Et₃N with TBSOTf in CH₂Cl₂ and hexane, respectively (Table 1, entries 6 and 7).



Scheme 3 Preparation of the protected enol ethers **7a–d**

Gratifyingly, the reaction occurred to produce the desired silyl enol ether **7a** in 81% yield when epoxide **13** in CH_2Cl_2 was stirred with Et_3N /HMPA/TBSOTf/DMAP at room temperature for 12 h (Scheme 3). The synthesis of the epoxide with a tethered enol ether **7a** set the stage for the implementation of our crucial epoxide opening–cyclization step.

Table 2 Ti(III)-Mediated Reductive Cyclization of Epoxy Esters^a

Entry	Compound (PG)	Product	Yield (%) ^b
1	7a (TBS)	16	72
2	7b (Boc)	17	43
3	7c (Ts)	17	47
4	7d (Bz)	complex mixture	– ^c

^a Reaction conditions: epoxide (1.0 equiv), Cp_2TiCl_2 (3.0 equiv), Zn (9.0 equiv), THF (45 mL/mmol).

^b Isolated yield after silica gel column chromatography.

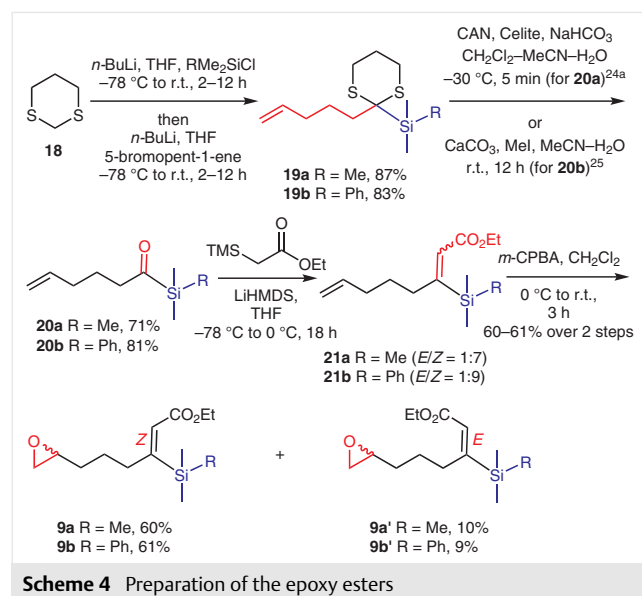
^c Not determined.

Compound **7a** failed to undergo reductive epoxide cleavage mediated by $[\text{Cp}_2\text{Ti(III)Cl}]$ with cyclization onto the pendant enol ether and instead provided the deoxygenated product **16** (Table 2, entry 1). The outcome sheds light onto

the fact that the occupancy of the *O*-silyl group probably made the β -carbon less prone to the radical attack. With the aim to optimize the electron density at the β -carbon, it was decided to switch to the acetyl enol carbonate **7b**, enol sulfonate ester **7c**, and enol ester **7d** following the optimum conditions developed for **7a** using $(\text{Boc})_2\text{O}$, TsCl, and BzCl, respectively (Scheme 3).

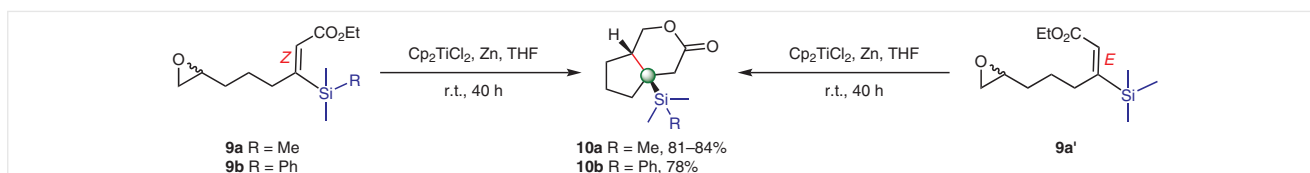
Compounds **7b–d** were subjected to the key $\text{Cp}_2\text{Ti(III)Cl}$ -mediated reductive epoxide cleavage and radical cyclization (Table 2, entries 2–4). Optimization of the electron density at the β -carbon with the aim to achieve the cyclize product worked out for **7b** and **7c**, but with the loss of the oxygen functionality present at the β -carbon leading to the formation of cyclopentylidene derivative **17**.²³ While subjecting of **7d** to the Cp_2TiCl -reaction resulted in a complex mixture of products.

The failure to furnish the expected bicyclic lactone **6** with a bridgehead hydroxy group directly from **7** led us to try the alternative route starting with the epoxy- β -(triorganosilyl)- α,β -unsaturated ester **9** in which the silyl group was expected to serve as a surrogate for the bridgehead oxygen functionality (Scheme 1, B).

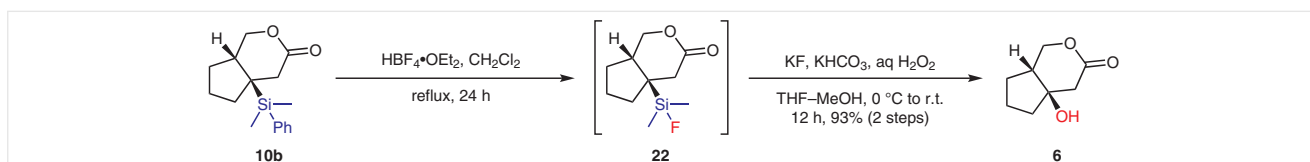


Scheme 4 Preparation of the epoxy esters

Synthesis of **9** started with 1,3-dithiane (**18**) which, following a modified literature procedure,^{24a,b} was silylated with triorganosilyl chloride followed by alkylation using 5-bromopent-1-ene to deliver the dithianes **19a** and **19b** in one pot. The desired acylsilane **20a** was synthesized by a reported procedure^{24a} using the oxidizing agent CAN, while **20b**^{24c,d} resulted with a poor yield. After investigating a number of alternative methods, removal of the thioketal was performed using CaCO_3/MeI (Scheme 4).²⁵ The Peterson olefination reaction²⁶ of acylsilanes **20a** and **20b** with the lithium enolate of ethyl (trimethylsilyl)acetate produced the (*Z*)- α,β -unsaturated ester predominantly togeth-



Scheme 5 Ti(III)-mediated reductive epoxide opening and radical cyclization



Scheme 6 Construction of the hydroxy-substituted quaternary center

er with an inseparable mixture of the *E*-isomer and residual reagents (**21a** *E/Z* = 1:7; **21b** *E/Z* = 1:9). Exploration of the Horner–Wadsworth–Emmons reaction²⁷ on **20a** using triethyl phosphonoacetate also gave the required product, but with reverse stereoselectivity (**21a** *E/Z* = 4:1) and in lower yield (53%). Among the alternate possible routes available for the synthesis of **21b**, hydrosilylation reaction of ethyl oct-7-en-2-ynoate²⁸ with PhMe_2SiH catalyzed by cyclopentadienyl-ruthenium complex $[\text{Cp}^*\text{Ru}(\text{MeCN})_3]\text{PF}_6$ was also explored.²⁹ But for scaling up purposes, we continued with the route depicted in Scheme 4. With better stereoselectivity and yield, the crude products of Peterson olefination reaction **21a** and **21b** were subjected to epoxidation with *m*-CPBA which resulted in a separable mixture of the pure (*Z*)-epoxy- α,β -unsaturated esters **9a** and **9b** (*Z*-isomer **9a** = 60%, *E*-isomer **9a'** = 10%; *Z*-isomer **9b** = 61%, *E*-isomer **9b'** = 9%) (Scheme 4).

Next, the *Z*-isomers **9a** and **9b** were subjected to reductive epoxide cleavage mediated by $\text{Cp}_2\text{Ti(III)Cl}$ (generated in situ from Cp_2TiCl_2 and activated Zn dust) with concomitant 5-*exo-trig* cyclization onto the pendant β -silyl- α,β -unsaturated ester to successfully give the bicyclic lactones with the *cis* ring junction embedded with bridgehead C–Si bond **10a** and **10b** (Scheme 5) in good yields. Further, inspection of the stereochemical outcome led us to set up the $\text{Cp}_2\text{Ti(III)Cl}$ reaction also with the *E*-isomer **9a'**. ¹H NMR and ¹³C NMR of the product from the reaction of the *E*-isomer **9a'** showed that it was identical to that from the *Z*-isomers **9a** and **9b**. NOE experiments were carried out to establish the stereochemical outcome of the ring junction (see the Supporting Information).

The next crucial step was the Tamao–Fleming oxidation,²⁰ which permits silyl group to be used as ‘masked hydroxy group’. Although the TMS group shows extremely high tolerability to a range of reaction conditions, its use in Tamao–Fleming oxidation is limited. The single step reaction protocol documented in the literature for this transformation using TBHP and KH^{30} failed to install the bridgehead

hydroxy group in **10a**, although it was effective for other molecular frameworks. The same conversion of the TMS group into the hydroxy group could possibly be achieved in a multistep sequence through a recently reported procedure which involves an initial iridium-catalyzed $\text{C}(\text{sp}^3)\text{--H}$ borylation of the methyl group on silicon.³¹

An alternate two-step protocol, shown in Scheme 6, required the use of the dimethylphenylsilyl group in place of trimethylsilyl. To render this transformation, the non-hydrolysable dimethylphenylsilane in **10b** was first activated to a fluorosilane **22** followed by the oxidation of the resulting functionalized silicon atom using H_2O_2 to install the desired bridgehead hydroxyl group to furnish hydroxylated-cyclopentano lactone **6** in 93% overall yield. The stereostructure of **6** was confirmed by 2D NMR and NOE studies (see the Supporting Information).

Subsequently, an extension of the aforementioned strategy to access 6,6-fused ring systems was also attempted. In this regard, the requisite epoxy- β -(triorganosilyl)- α,β -unsaturated ester was synthesized by dimethylphenylsilylation of 1,3-dithiane, alkylation using 6-bromohex-1-ene and then following the same strategy used for synthesizing compound **9** as shown in Scheme 4. However, implementation of the key $\text{Cp}_2\text{Ti(III)Cl}$ -mediated reaction resulted in a mixture of deoxygenated and reduced products with no trace of the required 6,6-fused bicyclic product.

In conclusion, as part of our ongoing research endeavor, we successfully widen the viability of Ti(III)-mediated epoxide opening cyclization protocol to forge a hydroxylated bridgehead chiral center, the structural feature observed in a countless number of natural products and natural product inspired synthons. The β -silyl functionality turned out to be very effective to fix the bridgehead stereocenters in the 6,5-fused bicyclic β -hydroxy lactone and serve as a valuable synthon for later stage functionalization to give the hydroxy group and build the desired hydroxylated bridgehead stereocenter with excellent diastereoselectivity and in reasonable overall yield, amenable to scale up. Further application

of the strategy will be demonstrated in due course by the successful synthesis of natural products containing similar 6,5-fused ring systems.

All the reactions were carried out under an inert atmosphere in oven-dried glassware using dry solvents, unless otherwise stated. All chemicals purchased from commercial suppliers were used as received unless otherwise stated. Reactions and chromatography fractions were monitored by Merck silica gel 60 F-254 glass TLC plates and visualized using UV light, 7% ethanolic phosphomolybdic acid/heat or 2.5% ethanolic anisaldehyde (with 1% AcOH and 3.3% concd H₂SO₄)/heat as developing agents. Flash column chromatography was performed with 100–200 mesh silica gel and yields refer to chromatographically and spectroscopically pure compounds.

All NMR spectra were recorded in CDCl₃ or in DMSO-*d*₆ on a 400 MHz instrument at 300 K and are calibrated to residual solvent peaks [CHCl₃ δ = 7.26 (¹H) and 77.0 (¹³C), DMSO δ = 2.50 (¹H) and 40.0 (¹³C)]. FT-IR spectra were recorded as neat liquid or KBr pellets using Perkin-Elmer Spectrum BX spectrophotometer. HRMS was performed on Micromass Q-TOF Micro instrument.

Ethyl 7,8-Epoxy-3-oxooctanoate (13)

To a solution of **12** (1.0 g, 5.43 mmol, 1.0 equiv) in CH₂Cl₂ (15 mL) at 0 °C was added portionwise *m*-CPBA (77%, 2.43 g, 10.86 mmol, 2.0 equiv); the mixture was warmed to r.t. and stirred for 3.5 h. The reaction was then quenched with sat. aq Na₂SO₃ and extracted with EtOAc. The combined extracts were washed with sat. aq NaHCO₃ solution, water, and brine, dried (anhyd Na₂SO₄), and concentrated. Purification by column chromatography [silica gel, 20% EtOAc/hexane; *R*_f = 0.52 (silica gel, 40% EtOAc/hexane)] afforded epoxide **13** (945 mg, 87%) as a colorless oil.

IR (neat): 3403, 2983, 2934, 1742, 1715, 1638, 1318, 1022 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ = 4.18 (q, *J* = 7.1 Hz, 2 H), 3.43 (s, 2 H), 2.91–2.86 (m, 1 H), 2.75–2.71 (m, 1 H), 2.65–2.59 (m, 2 H), 2.45 (dd, *J* = 4.9, 2.7 Hz, 1 H), 1.81–1.73 (m, 2 H), 1.67–1.59 (m, 1 H), 1.49–1.39 (m, 1 H), 1.26 (t, *J* = 7.1 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ = 202.34, 167.15, 61.35, 51.88, 49.28, 46.71, 42.27, 31.48, 19.85, 14.05.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₀H₁₆O₄Na: 223.0946; found: 223.0944.

Ethyl 6,8-Dioxabicyclo[3.2.1]octan-5-ylacetate (14); General Procedure

To a solution of **13** (1.0 equiv) in CH₂Cl₂ or in THF (3 mL/mmol) at 0 °C were added Et₃N (2 equiv), DIPEA (2 equiv), or K₂CO₃ (2.0 equiv)/18-crown-6 (2.0 equiv) and TBSOTf (1.5 equiv). Then the mixture was stirred at r.t. for 12 h and quenched with sat. aq NH₄Cl. The mixture was extracted with EtOAc and the combined extracts were washed with water and brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. Purification by column chromatography [silica gel, 15% EtOAc/hexane; *R*_f = 0.43 (silica gel, 32% EtOAc/hexane)] afforded **14** (72–88%) as a colorless oil.

IR (neat): 3432, 2943, 2859, 2361, 1731, 1643, 1451, 1367, 1253, 1171, 1109, 1028 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ = 4.58–4.54 (m, 1 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 3.95–3.91 (m, 1 H), 3.88–3.83 (m, 1 H), 2.73 (s, 2 H), 1.96–1.74 (m, 4 H), 1.69–1.60 (m, 1 H), 1.51–1.44 (m, 1 H), 1.26 (t, *J* = 7.1 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ = 169.07, 106.37, 75.10, 69.10, 60.55, 43.44, 33.76, 27.93, 16.65, 14.15.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₀H₁₆O₄Na: 223.0946; found: 223.0948.

Ethyl 6-[(*tert*-Butyldimethylsiloxy)methyl]tetrahydro-2H-pyran-2-ylideneacetate (15); General Procedure

To a solution of **13** (1.0 equiv) in CH₂Cl₂ or hexane (3 mL/mmol) at 0 °C were added 2,6-lutidine (2.0 equiv) or Et₃N (2.0 equiv) and TBSOTf (1.5 equiv). Then the mixture was stirred at r.t. for 12 h and quenched with sat. aq NH₄Cl. The mixture was extracted with EtOAc and the combined extracts were washed with water and brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. Purification by flash column chromatography [silica gel, 15% EtOAc/hexane; *R*_f = 0.60 (silica gel, 10% EtOAc/hexane)] gave **15** (57–63%) as a colorless oil.

IR (neat): 3439, 2924, 2852, 2361, 1729, 1644, 1460, 1369, 1279, 1252, 1166, 1028 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ = 4.67–4.60 (m, 1 H), 4.14 (q, *J* = 7.1 Hz, 2 H), 3.91–3.84 (m, 1 H), 3.73 (dd, *J* = 10.5, 5.2 Hz, 1 H), 3.62 (dd, *J* = 10.5, 6.0 Hz, 1 H), 2.99 (br s, 2 H), 2.16–1.96 (m, 2 H), 1.90–1.76 (m, 1 H), 1.64–1.52 (m, 1 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 0.88 (s, 9 H), 0.05 (s, 6 H).

¹³C NMR (CDCl₃, 100 MHz): δ = 170.54, 147.49, 98.89, 76.09, 65.26, 60.67, 40.34, 25.86, 23.55, 19.78, 18.33, 14.15, –5.30, –5.35.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₆H₃₀O₄SiNa: 337.1811; found: 337.1815.

Ethyl (E)-3-(*tert*-Butyldimethylsiloxy)-7,8-epoxyoct-2-enoate (7a)

To a stirred solution of **13** (100 mg, 0.5 mmol, 1.0 equiv) in CH₂Cl₂ (2.5 mL) at r.t., Et₃N (0.42 mL, 3.0 mmol, 6.0 equiv) and HMPA (0.4 mL) were added. After 15 min, TBSOTf (0.23 mL, 1.0 mmol, 2.0 equiv) and DMAP (12 mg, 0.1 mmol, 0.2 equiv) were added sequentially. After stirring for 12 h at r.t., the mixture was quenched with sat. aq NH₄Cl and extracted with Et₂O. The combined organic layers were washed with 1 M aq HCl, water, and brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. The resulting residue [*R*_f = 0.43 (silica gel, 20% EtOAc/hexane)] was subjected to the Cp₂TiCl-mediated cyclization reaction without any further purification.

Ethyl (E)-3-(*tert*-Butoxycarbonyloxy)-7,8-epoxyoct-2-enoate (7b)

To a stirred solution of **13** (100 mg, 0.5 mmol, 1.0 equiv) in CH₂Cl₂ (2.5 mL) at r.t., Et₃N (0.21 mL, 1.5 mmol, 3.0 equiv) and HMPA (0.2 mL) were added. After 15 min, Boc₂O (0.23 mL, 1.0 mmol, 2.0 equiv) and DMAP (12 mg, 0.1 mmol, 0.2 equiv) were added sequentially. After stirring for 5 h at r.t., the mixture was quenched with sat. aq NH₄Cl and extracted with Et₂O. The combined organic layers were washed with water and brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. The resulting residue was purified by flash column chromatography [silica gel, 10% EtOAc/hexane; *R*_f = 0.70 (silica gel, 20% EtOAc/hexane)] to afford **7b** (113 mg, 75%) as a colorless liquid.

IR (neat): 3419, 2361, 1763, 1644, 1456, 1399, 1372, 1253, 1221, 1114, 1017 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ = 5.79 (s, 1 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 2.96–2.85 (m, 3 H), 2.76–2.72 (m, 1 H), 2.47 (dd, *J* = 4.9, 2.6 Hz, 1 H), 1.79–1.55 (m, 4 H), 1.51 (s, 9 H), 1.27 (t, *J* = 7.1 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ = 166.04, 165.92, 150.10, 109.46, 84.08, 60.23, 51.86, 47.02, 31.78, 30.36, 27.57, 23.12, 14.18.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₅H₂₄O₆Na: 323.1471; found: 323.1476.

Ethyl (*E*)-7,8-Epoxy-3-(tosyloxy)oct-2-enoate (7c)

To a stirred solution of **13** (100 mg, 0.5 mmol, 1.0 equiv) in CH_2Cl_2 (2.5 mL) at r.t., Et_3N (0.21 mL, 1.5 mmol, 3.0 equiv) and HMPA (0.2 mL) were added. After 15 min, TsCl (143 mg, 0.75 mmol, 1.5 equiv) and DMAP (12 mg, 0.1 mmol, 0.2 equiv) were added sequentially. After stirring for 12 h at r.t., the mixture was quenched with sat. aq NH_4Cl and extracted with Et_2O . The combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting residue was purified by flash column chromatography [silica gel, 8% EtOAc/hexane; $R_f = 0.50$ (silica gel, 40% EtOAc/hexane)] to afford **7c** (126 mg, 71%) as a light-yellow oil.

IR (neat): 3435, 2929, 2361, 1719, 1650, 1596, 1455, 1373, 1218, 1185, 1122, 1032, 980, 879 cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): $\delta = 7.85\text{--}7.80$ (m, 2 H), 7.40–7.36 (m, 2 H), 5.82 (s, 1 H), 4.14 (q, $J = 7.1$ Hz, 2 H), 2.89–2.82 (m, 1 H), 2.79–2.73 (m, 2 H), 2.73–2.70 (m, 1 H), 2.47 (s, 3 H), 2.42 (dd, $J = 5.0, 2.6$ Hz, 1 H), 1.70–1.41 (m, 4 H), 1.26 (t, $J = 7.1$ Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 165.22, 165.10, 145.83, 132.82, 130.00, 128.19, 110.13, 60.55, 51.70, 46.91, 31.52, 30.92, 22.79, 21.72, 14.10$.

HRMS (ESI): m/z [$M + \text{Na}$] $^+$ calcd for $\text{C}_{17}\text{H}_{22}\text{O}_6\text{SiNa}$: 377.1035; found: 377.1036.

Ethyl (*E*)-3-(Benzoyloxy)-7,8-epoxyoct-2-enoate (7d)

To a stirred solution of **13** (100 mg, 0.5 mmol, 1.0 equiv) in CH_2Cl_2 (2.5 mL) at r.t., Et_3N (0.21 mL, 1.5 mmol, 3.0 equiv) and HMPA (0.2 mL) were added. After 15 min, BzCl (0.12 mL, 1.0 mmol, 2.0 equiv) and DMAP (12 mg, 0.1 mmol, 0.2 equiv) were added sequentially. After stirring for 4 h at r.t., the mixture was quenched with sat. aq NH_4Cl and extracted with Et_2O . The combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting crude (mixture of *E/Z* isomer 14:1) was purified by flash column chromatography [silica gel, 5% EtOAc/hexane; $R_f = 0.43$ (silica gel, 20% EtOAc/hexane)] to afford **7d** (*E*-isomer) (131 mg, 86%) as a light-yellow oil.

IR (neat): 3424, 2361, 1739, 1717, 1647, 1453, 1372, 1254, 1224, 1179, 1122, 1088, 1020 cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): $\delta = 8.09\text{--}8.05$ (m, 2 H), 7.66–7.60 (m, 1 H), 7.52–7.46 (m, 2 H), 5.85 (s, 1 H), 4.19 (q, $J = 7.1$ Hz, 2 H), 3.06–2.97 (m, 2 H), 2.96–2.90 (m, 1 H), 2.74 (t, $J = 4.5$ Hz, 1 H), 2.46 (dd, $J = 4.9, 2.7$ Hz, 1 H), 1.86–1.54 (m, 4 H), 1.29 (t, $J = 7.1$ Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 166.47, 165.74, 163.89, 133.88, 130.08, 128.89, 128.66, 110.77, 60.28, 51.85, 47.03, 31.87, 30.66, 23.17, 14.19$.

HRMS (ESI): m/z [$M + \text{Na}$] $^+$ calcd for $\text{C}_{17}\text{H}_{20}\text{O}_5\text{Na}$: 327.1208; found: 327.1208.

 Cp_2TiCl_2 -Mediated Radical Cyclization of **7a–d, **9a,b** and **9a'**; General Procedure**

In a flame-dried round-bottom flask containing THF (30 mL/mmol) were added Zn (9.0 equiv) and Cp_2TiCl_2 (3.0 equiv) under an inert atmosphere and the mixture was stirred for 1 h at r.t. (the color changed from deep red to green). The epoxide (1.0 equiv) in THF (15 mL/mmol) was cannulated into this solution at r.t. under N_2 atmosphere. The mixture was brought to r.t. and continuously stirred for 40 h. The mixture was quenched with sat. aq NH_4Cl and stirred for an additional 15 min. The solvent was evaporated in vacuo and the residue was extracted with Et_2O ; the combined extracts were washed

with water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography (silica gel) afforded the product.

Ethyl (*E*)-3-(*tert*-Butyldimethylsiloxy)octa-2,7-dienoate (16)

Following the general procedure using **7a** (90 mg, 0.29 mmol) with purification by column chromatography [100–200 mesh silica gel, 5% EtOAc/hexane; $R_f = 0.80$ (silica gel, 20% EtOAc/hexane)] gave **16** as a colorless oil; yield: 62 mg (72%).

IR (neat): 3443, 2930, 2361, 1709, 1626, 1464, 1368, 1259, 1134, 1044, 913, 837 cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): $\delta = 5.87\text{--}5.76$ (m, 1 H), 5.07 (s, 1 H), 5.04–4.92 (m, 2 H), 4.11 (q, $J = 7.1$ Hz, 2 H), 2.76–2.70 (m, 2 H), 2.09 (dd, $J = 14.6, 7.1$ Hz, 2 H), 1.68–1.59 (m, 2 H), 1.26 (t, $J = 7.1$ Hz, 3 H), 0.94 (s, 9 H), 0.23 (s, 6 H).

^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 173.18, 167.67, 138.46, 114.66, 99.05, 59.27, 33.35, 32.81, 26.27, 25.45, 18.04, 14.39, -4.67$.

HRMS (ESI): m/z [$M + \text{Na}$] $^+$ calcd for $\text{C}_{16}\text{H}_{30}\text{O}_3\text{SiNa}$: 321.1862; found: 321.1863.

Ethyl 2-(Hydroxymethyl)cyclopentylideneacetate (17)

Following the general procedure using **7b** (80 mg, 0.27 mmol) or **7c** (80 mg, 0.22 mmol) with purification by column chromatography [100–200 mesh silica gel, 15% EtOAc/hexane; $R_f = 0.40$ (silica gel, 20% EtOAc/hexane)] gave **17** as a colorless oil; yield: 22 mg (43% from **7b**); 23 mg (47% from **7c**).

IR (neat): 3436, 2959, 2361, 1709, 1647, 1463, 1371, 1201, 1129, 1032, 957, 863 cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): $\delta = 5.83$ (dd, $J = 4.5, 2.2$ Hz, 1 H), 4.15 (q, $J = 7.1$ Hz, 2 H), 3.71–3.62 (m, 2 H), 3.00–2.89 (m, 1 H), 2.81–2.68 (m, 2 H), 1.95–1.78 (m, 2 H), 1.72–1.56 (m, 2 H), 1.28 (t, $J = 7.1$ Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 168.27, 166.77, 112.69, 64.46, 59.66, 48.91, 33.14, 28.67, 24.26, 14.29$.

HRMS (ESI): m/z [$M + \text{Na}$] $^+$ calcd for $\text{C}_{10}\text{H}_{16}\text{O}_3\text{Na}$: 207.0997; found: 207.0995.

2-(Pent-4-enyl)-2-(silyl)-1,3-dithianes (19a and 19b)

Dithianes **19a** and **19b** were synthesized by modifying the literature procedure.^{24a,b} A solution of 1,3-dithiane (3.0 g, 24.95 mmol, 1.0 equiv) in dry THF (75 mL) was cooled to -78 °C and treated with 1.3 M *n*-BuLi in hexane (20.2 mL, 26.2 mmol, 1.05 equiv). After stirring for 30 min at 0 °C, the solution was cooled to -78 °C and treated with TMSCl (3.5 mL, 27.44 mmol, 1.1 equiv) or Me_2PhSiCl (4.6 mL, 27.44 mmol, 1.1 equiv). The resulting solution was stirred for 2 h at r.t. and then cooled to -78 °C, and additional of *n*-BuLi (20.2 mL) was added. After stirring for 30 min at 0 °C, the solution was cooled to -78 °C and treated with 5-bromopent-1-ene (3.6 mL, 29.94 mmol, 1.2 equiv). Then the mixture was warmed to r.t. and stirred for 12 h. The reaction was quenched with sat. aq NH_4Cl and extracted with Et_2O . The combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting residue was purified by chromatography (neutral alumina, 5% EtOAc/hexane) to afford **19a** (5.6 g, 87%) or **19b** [6.9 g, 83%; $R_f = 0.63$, (silica gel, 8% EtOAc/hexane)] as light-yellow oils.

Data for 19a

The spectroscopic data were in full accord with those reported in the literature.^{24a,b}

Data for 19b

IR (neat): 3739, 2314, 1645, 1543, 1516, 1421, 1253, 1111, 912, 821 cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): δ = 7.69–7.64 (m, 2 H), 7.43–7.34 (m, 3 H), 5.78–5.67 (m, 1 H), 4.99–4.91 (m, 2 H), 3.01–2.92 (m, 2 H), 2.47–2.39 (m, 2 H), 2.12–2.06 (m, 2 H), 2.05–1.95 (m, 3 H), 1.94–1.82 (m, 1 H), 1.55–1.45 (m, 2 H), 0.53 (s, 6 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ = 138.41, 135.58, 134.79, 129.55, 127.55, 114.77, 39.00, 36.59, 33.94, 26.59, 24.85, 23.68, –3.94.

HRMS (ESI): m/z [$M + \text{Na}$] $^+$ calcd for $\text{C}_{17}\text{H}_{26}\text{S}_2\text{SiNa}$: 345.1143; found: 345.1145.

Hex-5-enoyltrimethylsilane (20a)

Acylsilane **20a** was synthesized by using CAN following the literature procedure^{24a} and the spectroscopic data were in full accord with those reported.

Hex-5-enoyldimethylphenylsilane (20b)

To a solution of **19b** (3.0 g, 9.3 mmol, 1.0 equiv) in $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (4:1, 50 mL) were added CaCO_3 (2.79 g, 27.9 mmol, 3.0 equiv) and MeI (11.5 mL, 186 mmol, 20.0 equiv). After stirring at r.t. for 12 h, the resulting mixture was diluted with Et_2O and H_2O . The layers were separated, and the aqueous layer was extracted with Et_2O . The combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting crude was purified by flash column chromatography [silica gel, 5% EtOAc/hexane; R_f = 0.50 (silica gel, 5% EtOAc/hexane)] to afford the acylsilane **20b** (1.75 g, 81%) as a light-yellow oil (synthesis adapted from ref. 25).

IR (neat): 3072, 2933, 1726, 1641, 1429, 1251, 1111, 997, 912, 831 cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): δ = 7.57–7.52 (m, 2 H), 7.43–7.32 (m, 3 H), 5.74–5.61 (m, 1 H), 4.95–4.88 (m, 2 H), 2.61–2.54 (m, 2 H), 1.98–1.89 (m, 2 H), 1.61–1.51 (m, 2 H), 0.48 (m, 6 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ = 246.21, 138.09, 134.46, 133.94, 129.84, 128.12, 114.94, 47.85, 33.04, 21.13, –4.78.

HRMS (ESI): m/z [$M + \text{Na}$] $^+$ calcd for $\text{C}_{14}\text{H}_{20}\text{OSiNa}$: 255.1181; found: 255.1184.

Ethyl (E/Z)-3-(Trimethylsilyl)octa-2,7-dienoate (21a) by HWE Olefination

A mixture of triethyl phosphonoacetate (278 mg, 1.24 mmol, 2.1 equiv) and NaH (60%, 47 mg, 1.18 mmol, 2.0 equiv) in THF (3 mL) was stirred at 0 °C for 1 h. Then the solution of **20a** (100 mg, 0.59 mmol, 1.0 equiv) in THF (2 mL) was cannulated into the mixture at the same temperature. After stirring for 15 min, the mixture was brought to r.t. and stirred for 12 h. The mixture was then quenched with sat. aq NH_4Cl and extracted with Et_2O . The combined organic extracts were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to give the crude product of **21a** (75 mg, 53%; E/Z 4:1) as light-yellow oil.

Ethyl 3-(Silyl)octa-2,7-dienoates 21a,b; General Procedure for the Peterson Olefination Reaction

To a solution of ethyl (trimethylsilyl)acetate (1.3 equiv) in THF (3 mL/mmol) was added 1.0 M LiHMDS in THF (1.2 equiv) at –78 °C under argon. After stirring for 20 min at –78 °C, a solution of acylsilane **20a** or **20b** (1.0 equiv) in THF (2 mL/mmol) was cannulated at –78 °C. The mixture was warmed to 0 °C and stirred for 18 h. The reaction was quenched by the addition of sat. aq NaHCO_3 solution and extract-

ed with Et_2O . The combined organic extracts were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to give the crude products as light-yellow oils, which were used in the next step without further purification.

Compound 21a

Following the general procedure using **20a** (500 mg, 2.94 mmol) gave **21a**; R_f = 0.63 (silica gel, 5% EtOAc/hexane); E/Z 1:7 (^1H NMR of the crude product).

Compound 21b

Following the general procedure using **20b** (500 mg, 2.15 mmol) gave **21b**; R_f = 0.53 (silica gel, 5% EtOAc/hexane); E/Z 1:9 (^1H NMR of the crude product).

Ethyl (Z)- and (E)-7,8-Epoxy-3-(trimethylsilyl)oct-2-enoates (9a and 9a')

To a solution of **21a** (500 mg, 2.08 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at 0 °C was added portionwise *m*-CPBA (77%, 1.16 g, 5.2 mmol, 2.5 equiv). The mixture was warmed to r.t. and stirred for 3 h. The reaction was then quenched with sat. aq Na_2SO_3 and extracted with Et_2O . The combined extracts were washed with sat. aq NaHCO_3 solution, water, and brine, dried (anhyd Na_2SO_4), and concentrated. Purification by flash column chromatography (silica gel, 3% EtOAc/hexane) afforded the epoxide **9a** [*Z*-isomer, 320 mg, 60%; R_f = 0.46 (silica gel, 8% EtOAc/hexane)] and **9a'** [*E*-isomer, 52 mg, 10%; R_f = 0.38 (silica gel, 8% EtOAc/hexane)] as colorless oils.

Ethyl (Z)-7,8-Epoxy-3-(trimethylsilyl)oct-2-enoate (9a)

IR (neat): 2937, 2358, 1717, 1597, 1336, 1250, 1197, 1033, 846 cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): δ = 6.05–6.02 (m, 1 H), 4.15 (q, J = 7.1 Hz, 2 H), 2.96–2.91 (m, 1 H), 2.76–2.68 (m, 3 H), 2.46 (dd, J = 5.0, 2.7 Hz, 1 H), 1.66–1.52 (m, 4 H), 1.28 (t, J = 7.1 Hz, 3 H), 0.14 (s, 9 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ = 165.86, 165.28, 126.80, 59.71, 52.07, 47.04, 32.79, 30.94, 26.08, 14.28, –1.83.

HRMS (ESI): m/z [$M + \text{Na}$] $^+$ calcd for $\text{C}_{13}\text{H}_{24}\text{O}_3\text{SiNa}$: 279.1392; found: 279.1391.

Ethyl (E)-7,8-Epoxy-3-(trimethylsilyl)oct-2-enoate (9a')

IR (neat): 2919, 2850, 2362, 2336, 1735, 1644, 1337, 1251, 1199, 1036, 820 cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): δ = 6.28–6.22 (m, 1 H), 4.15 (q, J = 7.1 Hz, 2 H), 2.98–2.82 (m, 1 H), 2.78–2.72 (m, 1 H), 2.46 (dd, J = 4.9, 2.6 Hz, 1 H), 2.36–2.27 (m, 2 H), 1.65–1.47 (m, 4 H), 1.28 (t, J = 7.1 Hz, 3 H), 0.19 (s, 9 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ = 166.74, 165.45, 130.34, 60.03, 51.99, 46.99, 38.60, 32.09, 25.89, 14.25, –0.53.

HRMS (ESI): m/z [$M + \text{Na}$] $^+$ calcd for $\text{C}_{13}\text{H}_{24}\text{O}_3\text{SiNa}$: 279.1392; found: 279.1391.

Ethyl (Z)- and (E)-3-(Dimethylphenylsilyl)-7,8-epoxyoct-2-enoates (9b and 9b')

To a solution of **21b** (500 mg, 1.65 mmol, 1.0 equiv) in CH_2Cl_2 (8 mL) at 0 °C was added portionwise *m*-CPBA (77%, 924 mg, 4.12 mmol, 2.5 equiv). The mixture was warmed to r.t. and stirred for 3 h. The reaction was then quenched with sat. aq Na_2SO_3 and extracted with Et_2O . The combined extracts were washed with sat. aq NaHCO_3 solution, water, and brine, dried (anhyd Na_2SO_4), and concentrated. Purifica-

tion by flash column chromatography (silica gel, 3% EtOAc/hexane) afforded the epoxide **9b** [Z-isomer, 320 mg, 61%; R_f = 0.45 (silica gel, 5% EtOAc/hexane)] and **9b'** [E-isomer, 46 mg, 9%; R_f = 0.33, silica gel (5% EtOAc/hexane)] as colorless oils.

Ethyl (Z)-3-(Dimethylphenylsilyl)-7,8-epoxyoct-2-enoate (**9b**)

IR (neat): 2981, 2935, 1716, 1597, 1456, 1369, 1336, 1251, 1197, 1109, 1037, 918, 823 cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): δ = 7.54–7.49 (m, 2 H), 7.34–7.30 (m, 3 H), 6.40–6.36 (m, 1 H), 4.00 (q, J = 7.1 Hz, 2 H), 2.79–2.74 (m, 1 H), 2.70–2.67 (m, 1 H), 2.37 (dd, J = 5.0, 2.6 Hz, 1 H), 2.29–2.24 (m, 2 H), 1.58–1.39 (m, 4 H), 1.15 (t, J = 7.1 Hz, 3 H), 0.51–0.48 (m, 6 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ = 166.52, 162.59, 138.83, 133.75, 131.75, 128.65, 127.52, 60.08, 51.88, 46.99, 38.90, 32.03, 25.72, 14.07, –1.73.

HRMS (ESI): m/z [$M + \text{Na}$] $^+$ calcd for $\text{C}_{18}\text{H}_{26}\text{O}_3\text{SiNa}$: 341.1549; found: 341.1549.

Ethyl (E)-3-(Dimethylphenylsilyl)-7,8-epoxyoct-2-enoate (**9b'**)

IR (neat): 2953, 2929, 1714, 1641, 1600, 1456, 1369, 1340, 1255, 1172, 1111, 1039, 918, 823 cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): δ = 7.52–7.48 (m, 2 H), 7.41–7.33 (m, 3 H), 6.09 (s, 1 H), 4.15 (q, J = 7.1 Hz, 2 H), 2.83–2.77 (m, 1 H), 2.72–2.64 (m, 3 H), 2.36 (dd, J = 5.0, 2.7 Hz, 1 H), 1.53–1.37 (m, 4 H), 1.28 (t, J = 7.1 Hz, 3 H), 0.45–0.42 (m, 6 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ = 165.18, 163.89, 136.41, 133.99, 129.47, 128.31, 127.94, 59.82, 51.99, 46.97, 32.65, 31.13, 25.96, 14.26, –3.34, –3.37.

HRMS (ESI): m/z [$M + \text{Na}$] $^+$ calcd for $\text{C}_{18}\text{H}_{26}\text{O}_3\text{SiNa}$: 341.1549; found: 341.1549.

cis-6-(Silyl)-3-oxabicyclo[4.3.0]nonan-4-ones (**10a** and **10b**)

Following the general procedure for Cp_2TiCl -mediated radical cyclization using **9a/9a'** (100 mg, 0.39 mmol) or **9b** (300 mg, 0.94 mmol) gave **10a** and **10b**, respectively.

cis-6-(Trimethylsilyl)-3-oxabicyclo[4.3.0]nonan-4-one (**10a**)

Purification by flash column chromatography [100–200 mesh silica gel, 8% EtOAc/hexane; R_f = 0.47 (silica gel, 16% EtOAc/hexane)] gave **10a** as a colorless liquid; yield: 72 mg (84% from **9a**); 69 mg, (81% from **9a'**).

IR (neat): 2949, 2358, 1745, 1254, 1186, 1023, 843 cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): δ = 4.11 (d, J = 4.3 Hz, 2 H), 2.42 (d, J = 15.0 Hz, 1 H), 2.33–2.26 (m, 1 H), 2.24 (d, J = 15.0 Hz, 1 H), 1.87–1.62 (m, 4 H), 1.53–1.40 (m, 2 H), 0.03 (s, 9 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ = 174.24, 70.62, 39.09, 36.71, 36.47, 31.09, 29.26, 25.35, –4.41.

HRMS (ESI): m/z [$M + \text{Na}$] $^+$ calcd for $\text{C}_{11}\text{H}_{20}\text{O}_2\text{SiNa}$: 235.1130; found: 235.1132.

cis-6-(Dimethylphenylsilyl)-3-oxabicyclo[4.3.0]nonan-4-one (**10b**)

Purification by flash column chromatography [100–200 mesh silica gel, 8% EtOAc/hexane; R_f = 0.46 (silica gel, 20% EtOAc/hexane)] gave **10b** as a colorless liquid; yield: 201 mg (78%).

IR (neat): 2953, 1743, 1427, 1382, 1257, 1186, 1112, 1082, 1035, 947, 835 cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): δ = 7.54–7.50 (m, 2 H), 7.41–7.34 (m, 3 H), 4.04 (dd, J = 11.4, 3.7 Hz, 1 H), 3.83 (dd, J = 11.4, 3.7 Hz, 1 H), 2.47–2.39 (m, 2 H), 2.22 (d, J = 14.9 Hz, 1 H), 1.98–1.89 (m, 1 H), 1.72–1.54 (m, 3 H), 1.50–1.41 (m, 1 H), 1.36–1.24 (m, 1 H), 0.37–0.34 (m, 6 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ = 174.11, 135.49, 134.24, 129.63, 127.96, 70.49, 39.20, 36.89, 36.79, 30.95, 29.54, 25.32, –6.14, –6.16.

HRMS (ESI): m/z [$M + \text{Na}$] $^+$ calcd for $\text{C}_{16}\text{H}_{22}\text{O}_2\text{SiNa}$: 297.1287; found: 297.1285.

cis-6-Hydroxy-3-oxabicyclo[4.3.0]nonan-4-one (**6**) by Tamao–Fleming Oxidation of the Cycloadduct **10b**

To a solution of **10b** (200 mg, 0.73 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added $\text{HBF}_4 \cdot \text{OEt}_2$ (1.49 mL, 10.95 mmol, 15.0 equiv) at 0 °C. When the addition was complete, the ice bath was removed, and the mixture was refluxed for 48 h. Then the reaction was quenched by dropwise addition of sat. aq NaHCO_3 (at 0 °C). The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried (anhyd Na_2SO_4), filtered, and concentrated under vacuo to give the crude fluorosilane **22**, which was dissolved in THF/MeOH (1:1, 14 mL). The solution was cooled to 0 °C and KF (212 mg, 3.65 mmol, 5.0 equiv) and KHCO_3 (365 mg, 3.65 mmol, 5.0 equiv) were added followed by 30% aq H_2O_2 (1.7 mL, 14.6 mmol, 20.0 equiv). The resulting mixture was allowed to warm to r.t. and stirred for 12 h. Then the reaction was quenched with 1 M aq HCl and extracted with EtOAc. The combined organic extracts were dried (anhyd Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash column chromatography [silica gel, 60% EtOAc/hexane; R_f = 0.33 (silica gel, 80% EtOAc/hexane)] gave the alcohol **6** (106 mg, 93%) as a colorless oil.

IR (neat): 3413, 2955, 2925, 2866, 2362, 2336, 1736, 1388, 1257, 1180, 1060, 1033 cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): δ = 4.38 (dd, J = 11.6, 5.4 Hz, 1 H), 3.92 (dd, J = 11.6, 7.6 Hz, 1 H), 2.75 (d, J = 14.9 Hz, 1 H), 2.67 (d, J = 14.9 Hz, 1 H), 2.54 (br s, 1 H), 2.34–2.26 (m, 1 H), 2.11–2.00 (m, 1 H), 1.95–1.86 (m, 1 H), 1.85–1.74 (m, 1 H), 1.73–1.61 (m, 2 H), 1.40–1.29 (m, 1 H).

^{13}C NMR (CDCl_3 , 100 MHz): δ = 172.27, 80.18, 69.52, 46.75, 43.16, 42.75, 29.16, 24.59.

^1H NMR ($\text{DMSO}-d_6$, 400 MHz): δ = 5.01 (s, 1 H), 4.26 (dd, J = 11.4, 5.8 Hz, 1 H), 3.89 (dd, J = 11.4, 9.2 Hz, 1 H), 2.68 (d, J = 14.6 Hz, 1 H), 2.52 (d, J = 14.6 Hz, 1 H), 2.15–2.06 (m, 1 H), 1.93–1.83 (m, 1 H), 1.76–1.68 (m, 1 H), 1.68–1.44 (m, 3 H), 1.22–1.13 (m, 1 H).

^{13}C NMR ($\text{DMSO}-d_6$, 100 MHz): δ = 172.65, 79.58, 69.41, 46.63, 43.34, 42.57, 28.88, 24.81.

HRMS (ESI): m/z [$M + \text{Na}$] $^+$ calcd for $\text{C}_8\text{H}_{12}\text{O}_3\text{Na}$: 179.0684; found: 179.0681.

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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0037-1609586>.

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