Transition Metal-Assisted Transformations of Diversely Functionalized Dienynes

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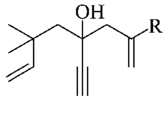
We report the triphenyltin-mediated free-radical cyclization of 4-ethynyl-2,6,6-trimethylocta-1,7-dien-4-ol (**1**) and 4-ethynyl-6,6-dimethylocta-1,7-dien-4-ol (**2**), along with some chemical manipulations of the resulting stannylidene derivatives **3** and **7**. The reaction of intermediates **3** and **7** with BuLi afforded the protodestannylated compounds **5** and **8**, respectively, in good yield, while the reaction of the mixture of adducts **3** and **4** with iodine gave the chloro(diphenyl)stannylidene derivatives **6** and **6′**. The palladium dichloride catalyzed reaction of dienyne **1** with tributyl(trimethylsilyl)stannane has also been described. All these cycloisomerization reactions were highly stereoselective, affording unique isomers at the newly formed stereocenters.

Introduction

Transition metal-assisted transformations of 1,*n*-diversely functionalized enynes currently are often-used tools for the synthesis of carbocycles.[1] In two recent communications from our laboratories, we have described the Pauson−Khand reaction[2a] and the platinum dichloride-mediated cycloisomerization reaction[2b] of some diversely substituted dienynes, transformations that have resulted in the synthesis of complex polycyclic arrays that are difficult to prepare by other methodologies. Continuing our studies on these substrates, and exploiting the rich functionality embodied in these compounds, we report here (a) the triethylborane/triphenyltin-mediated free-radical cyclization of 4-ethynyl-2,6,6-trimethylocta-1,7-dien-4-ol[2a] (**1**) and 4-ethynyl-6,6-dimethylocta-1,7-dien-4-ol[2a] (**2**) (Figure 1) along with some chemical manipulations of the resulting stannylidene derivatives, and (b) the palladium dichloride-catalyzed reaction of dienyne **1** with tributyl(trimethylsilyl)stannane ($Me_3SiSnBu_3$).

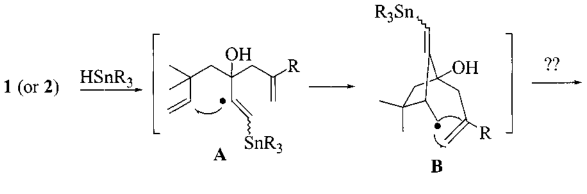


1 R= CH_3

Figure 1. Free-radical precursors

Results and Discussion

The stannane-mediated free-radical cyclization of enynes has been reported often in the literature[3] and constitutes a convenient method for the preparation of stannylidene-containing carbocyclic derivatives that can be transformed under standard protocols (i.e., protodestannylation, halogenation, Heck or Stille reactions) into useful synthetic intermediates.[4] In this context, we wanted to investigate this reactivity on the readily available dienyne derivatives **1** and **2**,[2a] whose functionality led us to anticipate possible free radical cascade processes.[5] It was expected that the selective and reversible attack of organostannyl radical species onto the triple bond[6] would result in a vinyl radical (**A**) that after 5-*exo*-trig cyclization would give species **B** from which the two modes of cyclization (6-*exo* or 7-*endo*) could be envisaged leading to carbocycles by free radical cascade cyclizations (Scheme 1).



Scheme 1. Presumed free radical cascade cyclization reaction of precursors **1** and **2**

With this scenario in mind, we started the project by submitting compound **1** to reaction with triphenyltin hydride in the presence of triethylborane,[7] a combination that has proven to be efficient in some of our previously reported free radical cascade cyclizations.[8] Under these conditions (see Exp. Sect.) we observed a fast reaction at room tem-

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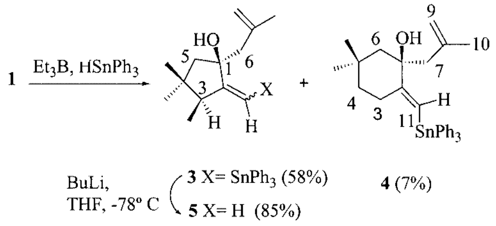
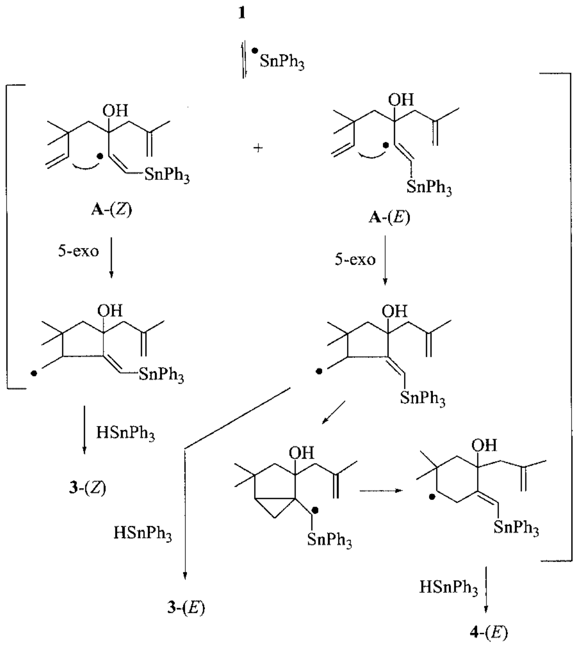
perature that afforded carbocycles **3** (58%) and **4** (7%) (Scheme 2). Compounds **3** and **4** were the cyclization products corresponding to the 5-*exo-trig* and 6-*endo-trig* modes of cyclization, respectively. Their spectroscopic and analytical data clearly supported these structures. Compound **3** was isolated as a mixture of isomers (in a 2.5:1 ratio), which we could determine in the ^{1}H NMR spectra by integrating the signals for the vinylic protons [H_2C=C(Me)−; major isomer: δ = 4.59 (m) and 3.97 ppm (m); minor isomer: δ = 4.30 (m) and 4.00 ppm (m)]. These products were assigned as the (*Z*)-**3** (major) and (*E*)-**3** (minor) isomers at the *exo* double bond, because only one diastereoisomerically pure compound (**5**, Scheme 2) was isolated after a protodestannylation reaction (see below). After careful chromatography of the mixture we isolated the pure major isomer (*Z*)-**3**, whose ^{1}H and ^{13}C spectra clearly showed the significant data for the key structural features {$H-C(SnPh_3)=C$ (δ = 5.97 ppm, d, *J* = 2.3 Hz; 112.4 ppm), $H-C(3)(CH_3)C$ (δ = 2.32 ppm, qd, *J* = 6.6, 2.3 Hz), $H-C(3)(CH_3)C$ (δ = 1.04 ppm, d, *J* = 6.6 Hz)}. Finally, the stereochemistry at the *exo* double bond in the major isomer (*Z*)-**3** was assigned as (*Z*) by observing an NOE enhancement between the corresponding vinylic proton at δ = 5.97 ppm and the methyl group at δ = 1.04 ppm [HC(CH_3)C], while the relative *cis*/*trans* stereochemistry at carbon atoms C-1 and C-3 could be assigned only after a protodestannylation reaction (i.e., in compound **5**; see below) (Scheme 2).



Scheme 2. Free-radical cyclization of precursor **1**, and reaction of intermediate (*Z*)-**3** with BuLi

The structure of the minor, more-polar compound **4** was established by inspection of the ^{1}H NMR spectrum where, in addition to the vinylic signals at δ = 6.11 (11-H), 4.97 and 4.79 ppm (2 × 9-H), two AB systems for protons at carbons C-6 and C-7, and the singlets corresponding to three methyl groups, we observe two multiplets at δ = 2.43−2.30 and 1.40−1.22 ppm that integrate for two protons each, which correspond to 3-H and 4-H, respectively; accordingly, in the HMQC experiment these protons correlate with the signals of two carbon atoms at δ = 32.5 and 40.7 ppm. Product **4** was isolated as a diastereoisomerically pure compound whose stereochemistry at the *exo* double bond was tentatively assigned as (*E*), based on the clear NOE enhancements between the vinylic proton at δ = 6.11 ppm and the methylene protons (δ = 2.33 ppm and 2.75 ppm) at C-7 and a clear NOE between 11-H and the OH group at δ = 2.18 ppm.

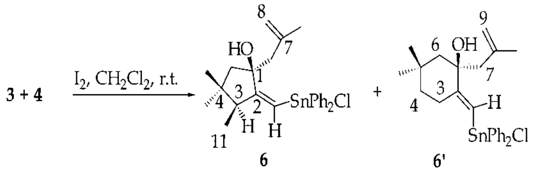
In summary, it appears that the **A**-(*Z*) radical species derived from compound **1** cyclizes in the 5-*exo-trig* mode giving product (*Z*)-**3**, while the **A**-(*E*) radical species cyclizes also in the 5-*exo* mode to afford compounds (*E*)-**3** and (*E*)-**4** via rearrangement of the homoallyl radical[9] (Scheme 3). No products derived from a cascade cyclization process were detected (Scheme 1).



Scheme 3. Mechanism for the formation of compounds **3** and **4** from dienyne **1**

To ascertain the relative stereochemistry at C-1/C-3 and desiring also to transform compound **3** into more simple derivatives, we submitted it to reaction with BuLi for the protodestannylation protocol[10] (the reaction with *p*-toluenesulfonic acid proved unsuccessful). Under the usual conditions, compound **5** was obtained in good yield and was diastereoisomerically pure (Scheme 2). The analytical and spectroscopic data (HMQC, HMBC) of this product supported this structure and allowed us to assign the chemical shifts for all the protons and carbon atoms in the NMR spectra (see Exp. Sect.). The ^{1}H NMR spectrum is particularly informative because no aromatic signals are detected, two sets of methylene protons appear as multiplets at δ = 5.13/4.88 (2 d, *J* = 2.8 Hz) and 4.92−4.90/4.80 ppm, and there are along with two AB systems corresponding to protons 5-H and 6-H. NOE experiments were carried out by irradiating the multiplet at δ = 2.08 ppm (3-H), which clearly indicated its proximity to 5a-H, C(4)(α-CH_3)(β-CH$_3$) and C(3)-CH$_3$; analogously, irradiation of the signal at δ = 0.82 ppm [C(4)(α-CH$_3$)(β-CH_3)] affected the signals at δ = 0.96 [CH(3)−CH_3], 1.01 [C(4)(α-CH_3)(β-CH$_3$] and 1.66 (5-H$_β$) ppm. As no NOE effects were observed in the last experiment between the signal at δ = 0.82 ppm and the doublets corresponding to 6-H, and assuming the correct stereochemical assignment was made on intermediate (*Z*)-**3** (see above), we tentatively favor the relative *trans* configuration between the alkyl chains at carbon atoms C-1 and C-3, as shown in compound **5** (Scheme 2).

A crude mixture of compounds **3** and **4** (see Exp. Sect.) was submitted to reaction with iodine in dichloromethane at room temp., a reaction that is known to give vinyl iodides from the stannylidene precursors.[11] In our hands, this reaction was complete in 1 h, affording two more-polar products. After workup and chromatography we isolated two fractions (**a** and **b**), which were inseparable mixtures of compounds **6** and **6′** in 4:1 and 1:8.4 ratio, respectively (Scheme 4). The overall yield was 68%. The analytical and spectroscopic data of these products did not agree with the expected (*E*)- and/or (*Z*)-vinyl iodides.[12] Conversely, major product **6** in fraction **a** (or major product **6′** in fraction **b**) displayed spectroscopic data quite similar to those observed for compound (*Z*)-**3** [analogously, product **6′** showed spectroscopic data similar to those observed for (*E*)-**4**], the only difference being the number of aromatic protons (now 10) in the ^{1}H NMR spectrum (see Exp. Sect.). These results (including a full set of NMR spectroscopic experiments, namely ^{13}C NMR, DEPT, HMQC, COSY) lead us to conclude that products **6** and **6′** are diphenylstannylidene derivatives from adducts (*Z*)-**3** and (*E*)-**4**, respectively, with an additional fourth substituent at the tin atom, whose nature — a chlorine atom — could be determined only after X-ray diffraction analysis of a crystal of compound **6** (Figure 2).[13] In agreement with this result, the elemental analysis and the mass spectrum of product **6′** were in good agreement with the structure of this molecule ($C_{25}H_{31}ClOSn$).



Scheme 4. Iodination reaction of compounds **3** and **4**

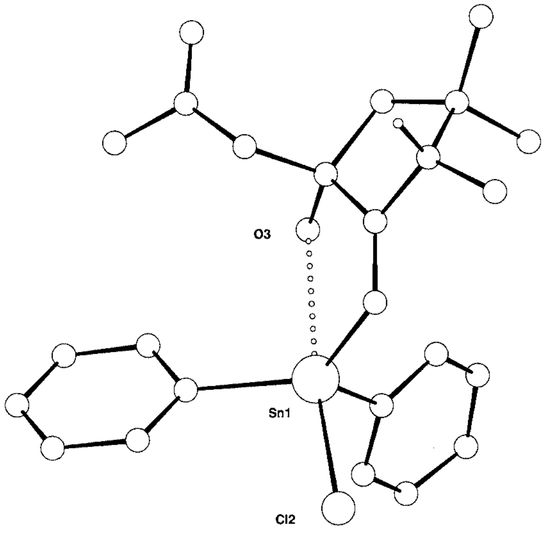


Figure 2. X-ray diffraction analysis of compound **6**

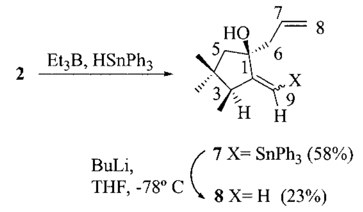
The X-ray analysis[13] confirmed also the stereochemical assignment that we have previously made regarding the geometry of the *exo* double bond and the *trans* relationship between the alkyl side chains at carbon atoms C-1 and C-3 in compound (*Z*)-**3**, which were based on NMR spectroscopic experiments.

The formation of these chlorodiphenylstannylidene derivatives (**6**, **6′**) was not completely unexpected in view of the presumed high steric hindrance around the *exo* vinyl group resulting from the branched allylic carbon atoms present in the carbocycle moiety. In fact, it is known that methyldiphenyltin(IV) chloride can be prepared from the cleavage of methyltriphenyltin by elemental iodine in chloroform (Scheme 5), but no mechanism has been advanced to explain this observation.[14] Obviously, it is possible that the use of other non-chlorinated solvents, as diethyl ether, could overcome the formation of this product and yield the vinyl derivatives. Studies are now being conducted in our laboratory to gain more insight into these transformations.

$$\mathrm{MePh_3Sn} \xrightarrow[44\%]{\mathrm{I_2,\ CHCl_3}} \mathrm{MePh_2ClSn} \quad \text{(Ref. 14)}$$

Scheme 5. Synthesis of methyldiphenyltin(IV) chloride from methyltriphenyltin and iodine in chloroform

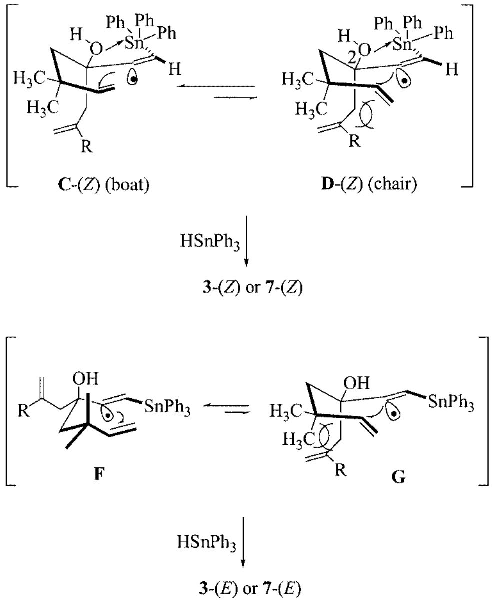
The interesting results observed on dienyne **1** prompted us to analyze whether substrate **2** had similar reactivity (Figure 1). Under the same experimental conditions, this precursor gave compound **7** in 53% yield (Scheme 6). Product **7** was isolated as an inseparable mixture of (*Z*) and (*E*) isomers (3:1 ratio, determined by integration of the signals for 9-H at δ = 6.01 and 5.79 ppm, respectively, in the ^{1}H NMR spectrum). Although no specific NMR spectroscopic experiments were performed to determine the stereochemistry at the *exo* double bond, the (*Z*) assignment for the major isomer was tentatively made by comparison of the spectroscopic data observed for major compound **7** with those of product (*Z*)-**3**.



Scheme 6. Free-radical cyclization of precursor **2**, and reaction of intermediate **7** with BuLi

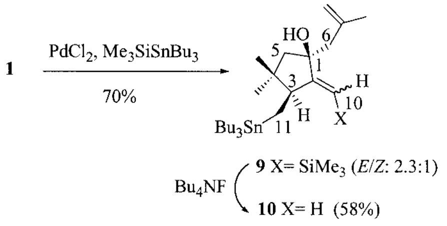
The reaction of cyclopentanol **7** with BuLi gave alcohol **8** in low yield (23%, not optimized) (Scheme 6). The analytical and spectroscopic data of this compound supported this structure. Furthermore, the close similarity of these data with those of compound **5** prompted us to assign it with the same stereochemical features.

The high stereoselection observed in the 5-*exo* free-radical cyclization of dienynes **1** and **2** giving exclusive *trans* products at carbon atoms C-1 and C-3 can be explained possibly as depicted in Scheme 7. According to Beckwith's model,[15] conformers **C** (boat) and **D** (chair) are considered, assuming in both cases that the formation of major (*Z*) isomers should be due to the well-known propensity of propargylic alcohols to form cyclic vinyl ethers upon reaction with tin species.[11] Note that in this picture (Scheme 7) the transition state of the vinyl radical species in the chair-like conformer possesses a strong and unfavorable 1,3-diaxial interaction between the radical trap — the double bond — and the alkyl chain at C-2 (radical numbering), which displaces the equilibrium between the conformers toward the boat-like conformation[16] in which this unfavorable interaction does not exist. As shown in Scheme 7, the more-populated conformer for the (*E*)-vinyl radical species should be **F**, rather than conformer **G** for steric reasons, which again explains the formation of *trans* products (*E*)-**3** or (*E*)-**7**.



Scheme 7. Stereoselective 5-*exo* cyclization of radical intermediates formed from dienynes **1** and **2**

While we were obtaining the results described above, we became aware of the reactivity of diynes and enynes toward mixed bismetallic species such as tin−silicon reagents.[17] Prompted by the reported high selectivity of these reactions and the presumed synthetic utility of the resulting intermediates, we submitted dienyne **1** to the palladium dichloride-catalyzed reaction with tributyl(trimethylsilyl)stannane ($Me_3SiSnBu_3$). As shown in Scheme 8, in this reaction we obtained compound **9** as a mixture of (*E*) and (*Z*) isomers in 70% yield, in a 2.3:1 ratio. After chromatography, we could isolate pure only isomer (*E*)-**9**, whose spectroscopic and analytical data were in good agreement with the structure depicted. The regiochemical location of the tributylstannylidene group at C-11 and the trimethylsilyl moiety at C-10 was predicted based on previously known reports for this type of chemistry.[17d] In fact, 10-H in the (*E*)-**9** and (*Z*)-**9** isomers resonates at δ = 5.53 and 5.47 ppm, respectively [ca. 0.5 ppm more shielded than in compound (*Z*)-**3**], and the typical H−Sn long-range coupling constants were not observed. The assigned *E* stereochemistry for the major isomer **9** is in sharp contrast with the results that we have obtained in the free-radical cyclization of product **1**, but they are in good agreement with the results reported for related substrates.[17a,17d] In fact, in some of the NOE experiments that we have performed with compound (*E*)-**9** we see clear and strong enhancements for 6-H (δ = 2.57 ppm) when irradiating the vinyl proton at δ = 5.53 ppm, and vice versa, and simultaneous irradiation of both 6-H and 3-H (δ = 2.53 ppm), not only affected 6′-H (δ = 2.05 ppm) as expected, but also 5-H (δ = 1.93 ppm), which establishes that 3-H and 5-H_α are in the same plane of the molecule, suggesting that, as in the case of compound (*Z*)-**3** (see above), in product **9** the dialkyl substituents are orientated *trans* to each other (Scheme 8).



Scheme 8. Reaction of compound **1** with tributyl(trimethylsilyl)stannane in the presence of palladium dichloride

Finally, after treatment with tetrabutylammonium fluoride, the mixture of isomers (*E*)-**9** and (*Z*)-**9** gave compound **10** in 58% yield, whose analytical and spectroscopic data were in good agreement with the structure depicted.

In summary, in this work we have analyzed the reactivity of dienynes **1** and **2**[18] with triphenyltin hydride in the presence of triethylborane and with tributyl(trimethylsily)stannane. In both cases highly regio- and stereoselective processes have been observed leading to interesting carbocyclic systems in good yield.

Experimental Section

General Methods: Reactions were monitored by TLC by using aluminium plates precoated with silica gel containing a fluorescent indicator (Merck, 5539). Detection was made by UV (254 nm) followed by charring with sulfuric−acetic acid spray, 1% aqueous potassium permanganate solution or 0.5% phosphomolybdic acid in 95% EtOH. Anhydrous Na_2SO_4 was used to dry organic solutions during workups and the removal of solvents was carried out under vacuum with a rotary evaporator. Flash column chromatography was performed using silica gel 60 (230−400 mesh, Merck). ^{1}H and ^{13}C spectra were recorded with a Varian VXR-300S spectrometer, using tetramethylsilane as the internal standard. Values denoted by (*) can be interchanged. Compounds **1** and **2** have been prepared according to our previously described protocol.[2a]

General Method for the Free-Radical Cyclization Reaction: A solution of triphenyltin hydride (1.1 equiv.) in toluene was added over 5 min to a solution, previously deoxygenated by bubbling argon through it, of the radical precursor and triethylborane (0.5 equiv.) in toluene (0.016 M). The mixture was stirred at room temp. for 2 h. The solvent was evaporated and the residue was dissolved in diethyl ether and treated with 15% aqueous solution of potassium fluoride, and then stirred overnight. The organic phase was separated, dried, filtered, evaporated, and the crude product submitted to chromatography.

General Method for the Protodestannylation Reaction: BuLi (2.2 equiv., 1.6 M in hexane) was slowly added under argon to a solution of the stannane in dry THF at −78 °C, and the mixture was then stirred at this temperature for 1 h. The mixture was quenched with aqueous saturated ammonium chloride solution, diluted with ethyl acetate and washed with brine. The organic phase was separated, dried, filtered, evaporated, and the crude product submitted to chromatography.

Free-Radical Cyclization of Compound 1: Following the general method for the free-radical cyclization above, compound **1** (184 mg, 0.95 mmol) was treated with triethylborane (0.47 mL, 0.47 mmol, 0.5 equiv., 1.0 M in hexane) and triphenyltin hydride (351 mg, 1.0 mmol, 1.1 equiv.) to give, after chromatograhpy (hexane/EtOAc, 2%), compound **3** [305 mg, 58%; isolated as a mixture of (*Z*) and (*E*) isomers in a 2.5:1 ratio; after another careful chromatography, we isolated pure (*Z*)-**3**] and diastereoisomerically pure (*E*)-**4** (41 mg, 7%). Total: 346 mg (65%).

(*Z*)-3: M.p. 86−88 °C. IR (KBr): ṽ = 3523, 3060, 3011, 2958, 1625, 1480, 1428, 1374, 1259, 1218, 1074 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.60−7.52 (m, 5 H) and 7.40−7.30 (m, 10 H) [$Sn(C_6H_5)_3$], 5.97 (d, *J* = 2.3 Hz, 1 H, 10-H), 4.59 (s, 1 H, 8-H), 3.97 (s, 1 H, 8′-H), 2.32 (qd, *J* = 6.6, 2.3 Hz, 1 H, 3-H), 2.11 (d, *J* = 14.0 Hz, 1 H, 6-H), 2.09−2.00 (m, 2 H, OH, 6′-H), 1.58−1.50 (m, 2 H, 2 × 5-H), 1.48 (s, 3 H, 9-H), 1.05 (s, 3 H), 1.04 (d, *J* = 6.6 Hz), 0.83 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 173.6 (C-2), 142.0 (C-7), 136.1, 135.3, 129.3−128.5 [$Sn(C_6H_5)_3$], 114.9 (C-8), 112.4 (C-10), 79.4 (C-1), 53.2 (C-5), 51.1 (C-6), 49.2 (C-3), 38.6 (C-4), 28.0 (C-12)*, 24.2 (C-9), 22.8 (C-13)*, 10.4 (C-11) ppm. MS (70 eV): *m*/*z* = 543 [M^{+} + 1] (1), 527 [M^{+} − 15] (1), 489 (7), 467 (2), 449 (2), 411 (74), 351 (64), 275 (17), 215 (100), 196 (53), 175 (25), 141 (12), 120 (16). $C_{31}H_{36}OSn$ (543.3): calcd. C 68.53, H 6.68; found C 68.60, H 6.91.

(*E*)-4: Oil. IR (KBr): ṽ = 3544, 3064, 2953, 1640, 1604, 1480, 1429, 1365, 1259, 1074 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.60−7.52 (m, 5 H) and 7.40−7.30 (m, 10 H) [$Sn(C_6H_5)_3$], 6.11 (s, 1 H, 11-H), 4.97 (m, 1 H, 9-H), 4.79 (s, 1 H, 9′-H), 2.75 (d, *J* = 13.3 Hz, 1 H, 7-H), 2.43−2.30 (m, 3 H, 2 × 3-H, 7′-H), 2.18 (s, 1 H, OH), 1.78 (s, 3 H, 10-H), 1.68 (dd, *J* = 13.8, 1.7 Hz, 1 H, 6-H), 1.54 (d, *J* = 13.8 Hz, 1 H, 6′-H), 1.40−1.22 (m, 2 H, 2 × 4-H), 1.02 (s, 3 H), 0.95 (s, 3 H) ppm. $C_{31}H_{36}OSn$ (543.3): calcd. C 68.53, H 6.68; found C 68.41, H 6.94.

3,4,4-Trimethyl-2-methylene-1-(2-methylprop-2-en-1-yl)cyclopentanol (5): Following the general method for the protodestannylation, product **3** (261 mg, 0.48 mmol) and BuLi (0.62 mL, 1.0 mmol) reacted to give alcohol **5** (80 mg, 85%) after chromatography (hexane, EtOAc, 5%): oil. IR (KBr): ṽ = 3478, 3074, 2956, 2870, 1641, 1453, 1366, 1053 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.13 (d, *J* = 2.8 Hz, 1 H, 10-H), 4.92−4.90 (m, 1 H, 8-H), 4.88 (d, *J* = 2.8 Hz, 1 H, 10′-H), 4.80 (m, 1 H, 8′-H), 2.40 (d, *J* = 13.5 Hz, 1 H, 6-H), 2.23 (d, *J* = 13.5 Hz, 1 H, 6′-H), 2.18 (s, 1 H, OH), 2.08 (qdd, *J* = 7.0, 2.8, 2.8 Hz, 1 H, 3-H), 1.82 (s, 3 H, 9-H), 1.80 (d, *J* = 13.9 Hz, 1 H, 5-H), 1.66 (d, *J* = 13.9 Hz, 1 H, 5′-H), 1.01 (s, 3 H, 12-H), 0.96 (d, *J* = 7.0 Hz, 3 H, 13-H), 0.96 (s, 3 H, 11-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 164.4 (C-2), 142.8 (C-7), 114.8 (C-8), 105.5 (C-10), 78.6 (C-1), 53.4 (C-5), 51.6 (C-6), 48.3 (C-3), 39.2 (C-4), 27.6 (C-12), 24.4 (C-9), 22.0 (C-13), 10.5 (C-11) ppm. MS (electrospray): *m*/*z* = 177.3 [M^{+} − 17 (OH)], 217.3 (100) [M^{+} + 23 (Na)], 233.3 (35) [M^{+} + 39 (K)]. $C_{13}H_{22}O$ (194.3): calcd. C 80.35, H 11.41; found C, 80.12, H 11.62.

Iodination of Compounds 3 and 4: A solution of the mixture of products **3** and **4** (obtained as reported above) (296 mg, 0.54 mmol) in dry dichloromethane (5 mL) was treated with iodine (152 mg, 0.6 mmol, 1.1 equiv.) at room temp. for 1 h. The mixture was diluted with dichloromethane, and then washed with aqueous 10% sodium thiosulfate and brine. The organic phase was separated, dried, filtered, evaporated, and the crude product submitted to chromatography (hexane/EtOAc, 50%) to give fraction **a** [a mixture of compounds **6** and **6′** in a 4:1 ratio (140 mg)] and fraction **b** [a mixture of compounds **6** and **6′** in a 1:8.4 ratio (41 mg)]. Total: 181 mg (68%).

Fraction a: M.p. 98−101 °C. IR (KBr): ṽ = 3436, 3050, 2959, 1631, 1430, 1375, 1272, 1075 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (major **6** isomer) = 7.90−7.75, 7.71−7.58, 7.51−7.32 [m, 10 H, $Sn(C_6H_5)_2$], 6.03 (d, *J* = 2.1 Hz, 1 H, 10-H), 4.63 (s, 1 H, 8-H), 3.87 (s, 1 H, 8′-H), 3.32 (s, 1 H, OH), 2.40 (qd, *J* = 6.6, 2.1 Hz, 1 H, 3-H), 2.23 (d, *J* = 14.4 Hz, 1 H, 6-H)*, 2.12 (d, *J* = 14.6 Hz, 1 H, 5-H)*, 2.07 (d, *J* = 14.4 Hz, 1 H, 6′-H)*, 1.63 (d, *J* = 14.6 Hz, 1 H, 5′-H)*, 1.51 (s, 3 H, 9-H), 1.09 (s, 3 H), 1.06 (d, *J* = 6.6 Hz, 3 H, 11-H), 0.81 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ (major **6** isomer) = 171.1 (C-2), 141.2 (C-7), 136.3−135.7, 129.6−128.7 [$Sn(C_6H_5)_2$], 116.1 (2 C, C-8, C-10), 80.6 (C-1), 52.3 (C-5)*, 51.0 (C-6)*, 47.7 (C-3), 38.8 (C-4), 28.5 (C-12)*, 24.5 (C-9), 23.8 (C-13)*, 10.2 (C-11) ppm. MS (API-ES+): *m*/*z* = 520 (5) [M + NH_4^{+}], 467 (100) [MH^{+} − HCl]. $C_{25}H_{31}ClOSn$ (501.7): calcd. C 59.75, H 6.22, Cl 6.96; found C 60.02, H 6.31, Cl 7.20.

Fraction b: Oil. IR (film): ṽ = 3403, 3050, 2954, 1613, 1430, 1374, 1273, 1076 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (major **6′** isomer) = 7.90−7.75, 7.71−7.58, 7.51−7.32 [m, 10 H), $Sn(C_6H_5)_2$], 6.02 (s, 1 H, 11-H), 4.43 (m, 1 H, 9-H), 3.91 (s, 1 H, 9′-H), 3.43 (s, 1 H, OH), 2.56−2.40 (m, 4 H, 2 3-H, 2 7-H), 1.84 (dd, *J* = 2.0, 13.6 Hz, 1 H, 6-H), 1.66−1.50 (m, 2 H, 2 4-H), 1.64 (s, 3 H, 9-H), 1.53 (d, *J* = 13.6 Hz, 1 H, 6′-H), 1.14 (s, 3 H), 0.97 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ (major **6′** isomer) = 163.1 (C-2), 141.2 (C-8), 136.1, 135.3, 129.3−128.5 [$Sn(C_6H_5)_2$], 121.2 (C-11), 118.1 (C-9), 77.5 (C-1), 53.3 (C-6), 47.2 (C-3)*, 41.9 (C-4), 33.9 (C-12)**, 32.8 (C-7)*, 32.5 (C-5), 26.9 (C-13)**, 24.4 (C-10) ppm. MS (70 eV): *m*/*z* = 467 (4), 449 (5), 411 (76), 389 (10), 369 (51), 351 (26), 309 (78), 257 (12), 213 (55), 197 (34), 177 (36), 154 (100), 129 (20), 115 (25).

Free-Radical Cyclization of Compound 2: Following the general method for the free-radical cyclization, compound **2** (112 mg, 0.62 mmol) was treated with triethylborane (0.31 mL, 0.31 mmol, 0.5 equiv., 1.0 M in hexane) and triphenyltin hydride (242 mg, 0.69 mmol, 1.1 equiv.) to give, after chromatography (hexane/EtOAc, 2%), compound **7** (177 mg, 53%): oil. IR (KBr): ṽ = 3546, 3062, 3011, 2957, 1624, 1480, 1428, 1365, 1264, 1073 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ [major (*Z*) isomer] = 7.60−7.52 (m, 5 H) and 7.40−7.30 [m, 10 H, $Sn(C_6H_5)_3$], 6.01 (d, *J* = 2.4 Hz, 1 H, 9-H), 5.69−5.51 (m, 1 H, 7-H), 4.85 (d, *J* = 9.9 Hz, 1 H, 8-H_{cis}), 4.08 (d, *J* = 16.8 Hz, 1 H, 8-H_{trans}), 2.34 (qd, *J* = 6.4, 2.4 Hz, 1 H, 3-H), 2.11 (br d, *J* = 13.0 Hz, 1 H, 6-H), 2.00 (br d, *J* = 13.0 Hz, 1 H, 6-H′), 1.90 (d, *J* = 13.7 Hz, 1 H, 5-H), 1.56 (s, 1 H, OH), 1.52 (d, *J* = 13.7 Hz, 1 H, 5-H′), 1.08−1.05 [6 H, C(10)H_3, C(11)H_3], 0.85 (s, 3 H) ppm. MS (70 eV): *m*/*z* = 453 (32), 435 (11), 411 (10), 351 (18), 291 (8), 197 (26), 161 (100), 119 (10), 105 (11). $C_{30}H_{34}OSn\cdot H_2O$: calcd. C 65.84, H 6.63; found C, 65.71, H 6.81.

3,4,4-Trimethyl-2-methylene-1-(prop-2-en-1-yl)cyclopentanol (8): Following the general method for the protodestannylation, product **7** (140 mg, 0.26 mmol) and BuLi (0.35 mL, 0.57 mmol) gave alcohol **8** (11 mg, 23%) after chromatography (hexane/ EtOAc, 5%): oil. IR (KBr): ṽ = 3466, 3077, 2956, 2871, 1640, 1466, 1366, 1259, 1158, 1042 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.90−5.76 (m, 1

H, 7-H), 5.14 (d, J = 11.7 Hz, 1 H, 8-H), 5.12 (d, J = 16.0 Hz, 1 H, 8′-H), 5.10 (d, J = 2.9 Hz, 1 H, 9-H), 4.89 (d, J = 2.9 Hz, 1 H, 9′-H), 2.35 (dd, J = 7.6, 13.6 Hz, 1 H, 6-H), 2.27 (dd, J = 7.0, 13.6 Hz, 1 H, 6′-H), 2.15−2.01 (m, 1 H, 3-H), 1.70 (d, J = 13.9 Hz, 1 H, 5-H), 1.61 (d, J = 13.9 Hz, 1 H, 5′-H), 1.57 (s, 1 H, OH), 0.98 (s, 3 H, 11-H), 0.93 (d, J = 6.7 Hz, 3 H, 10-H), 0.79 (s, 3 H, 12-H) ppm.

4,4-Dimethyl-1-(2-methylprop-2-en-1-yl)-3-(tributytin)methyl-2-[(*E*)-(trimethysilyl)methylene]cyclopentanol (9): Compound **1** (103 mg, 0.53 mmol) dissolved in dry THF (33 mL, 0.016 M) was treated with palladium dichloride (6 mg, 0.031 mmol 6%) and tributyl(trimethylsilyl)stannane (0.3 mL, 0.79 mmol, 1.5 equiv.) and stirred at room temp. for 48 h. The solvent was evaporated and the crude product submitted to chromatography (hexane/EtOAc, 1%) to give adduct (*E*)-**9** (22 mg) and a mixture of (*E*)-**9** and (*Z*)-**9** (192 mg, 2:1 ratio). Total: 214 mg, 70%. (*E*)-**9**: oil. IR (KBr): $\tilde{\nu}$ = 3469, 3071, 2955, 1641, 1617, 1464, 1376, 1247, 1072 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.53 (d, J = 0.9 Hz, 1 H, 10-H), 4.89 (m, 1 H, 8-H), 4.76 (br s, 1 H, 8′-H), 2.57 (d, J = 14.2 Hz, 1 H, 6-H), 2.45 (dm, J = 12.7 Hz, 1 H, 3-H), 2.05 (d, J = 14.2 Hz, 1 H, 6′-H), 1.93 (d, J = 13.9 Hz 1 H, 5-H), 1.83 (s, 3 H, 9-H), 1.82 (d, J = 13.9 Hz 1 H, 5-H′), 1.54 (s, 1 H, OH), 1.52−1.42 (m, 6 H), 1.35−1.16 (m, 8 H), 0.97 (s, 3 H, 12-H)*, 0.90 (s, 3 H, 13-H)*, 0.88 (t, J = 7.1 Hz, 9 H), 0.89−0.80 (m, 6 H) [$CH_2Sn(CH_2CH_2CH_2CH_3)_3$], 0.12 [s, 9 H, $Si(CH_3)_3$] ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 176.8 (C-2), 143.9 (C-7), 118.8 (C-10), 114.8 (C-8), 79.8 (C-1), 52.7 (C-3), 50.4 (C-6), 50.2 (C-5), 39.1 (C-4), 30.3 (C-12)*, 25.4 (C-13)*, 24.8 (C-9), 29.4, 27.7 (2 C), 13.9, 10.3 [$CH_2Sn(CH_2CH_2CH_2CH_3)_3$], 0.5 [$Si(CH_3)_3$] ppm. MS (70 eV): *m*/*z* = 481 (61), 443 (23), 291 (31), 247 (34), 233 (28), 209 (25), 193 (36), 177 (41), 73 (100). $C_{28}H_{56}OSiSn$ (555.5): calcd. C 60.54, H 10.16; found C 60.94, H 9.77.

4,4-Dimethyl-2-methylene-1-(2-methylprop-2-en-1-yl)-3-(tributyltin)methylencyclopentanol (10): A solution of a mixture of (*E*)-**9** and (*Z*)-**9** (192 mg, 0.34 mmol) in dry THF (4 mL) was treated with tetrabutylammonium fluoride (0.6 mL, 0.64 mmol, 2 equiv.) at room temp. overnight. The solvent was evaporated and the crude product submitted to chromatography (hexane/EtOAc 2%) to give product **10** (101 mg, 58%): oil. IR (KBr): $\tilde{\nu}$ = 3486, 3073, 2955, 1641, 1463, 1376, 1247, 1047 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.00 (d, J = 2.6 Hz, 1 H, 10-H), 4.80 (m, 1 H, 8-H), 4.79−4.65 (m, 2 H, 8′-H, 10′-H), 2.23 (d, J = 13.8 Hz, 1 H, 6-H), 2.11 (d, J = 13.8 Hz, 1 H, 6′-H), 2.04 (dm, J = 11.2 Hz, 1 H, 3-H), 1.70 (s, 3 H, 9-H), 1.61 (d, J = 13.9 Hz 1 H, 5-H), 1.53 (d, J = 13.9 Hz 1 H, 5′-H), 1.46 (s, 1 H, OH), 0.86 (s, 3 H, 12-H)*, 0.66 (s, 3 H, 13-H)*, 1.44−1.31 (m, 6 H), 1.29−1.12 (m, 6 H), 0.77 (t, J = 7.0 Hz, 9 H), 0.86−0.70 (m, 7 H), 0.48 [dd, J = 13.2, 11.2 Hz, 1 H, $CH_2Sn(C\mathit{H}_2CH_2C\mathit{H}_2CH_3)_3$] ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 165.1 (C-2), 143.1 (C-7), 115.2 (C-8), 106.0 (C-10), 78.5 (C-1), 53.7 (C-5), 52.8 (C-3), 52.1 (C-6), 41.1 (C-4), 28.0 (C-12)*, 24.9 (C-9), 21.8 (C-13)*, 29.6, 28.0, 14.0, 9.8, 4.9 [$\mathit{C}H_2Sn(CH_2CH_2CH_2CH_3)_3$] ppm. $C_{25}H_{48}OSn$ (483.3): calcd. C 62.12, H 10.01; found C 61.92, H 9.71.

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[13] CCDC-199232 (**6**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk]. Formula: $C_{25}H_{31}ClOSn$. Unit cell parameters: a = 11.181(3), b = 10.238(5), c = 20.835(7), β = 92.99(2). Space group $P21/c$.

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[18] We have analyzed the cycloisomerization reaction of compound **1** — with or without allyltrimethylsilane — in the presence of Grubbs' catalyst, but without success (a complex reaction mixture was observed, and we recovered most of the starting material unaltered).

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