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A silicon-position dependent 6-*endo-trig* cyclization during Tsuji–Trost alkylation

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ABSTRACT

Two silylated cyclohexenes products have been prepared by using a Tsuji–Trost palladium-catalyzed cyclization. It involves the generation of a cationic π-allylic palladium complex bearing a triethylsilyl group on C-3, which cyclizes via a 6-*endo-trig* process to afford the cyclohexene derivatives. It is also demonstrated that the position of the silyl group on the starting allylic substrate strongly influenced the reaction. It could favor either the production of the expected cyclohexenyl ring or a diene by an elimination that occurs on the silyl-substituted C-2 π-allylic palladium complex.

1. Introduction

Palladium-catalyzed allylic alkylation represents one of the most versatile protocols in organic chemistry.[1] After the pioneering work of Tsuji and Trost,[2] it has been applied successfully to the synthesis of many biological active molecules, natural products, and other important organic skeletons.[3] This alkylation occurred via a π-allylic palladium complex intermediate generated from the oxidative addition of Pd(0) into allylic substrates. Steric effects usually govern the regioselectivity of this reaction, but electronic properties of the substituents also greatly control the nucleophilic attack.[4] Along with various applications of this protocol, many reports on palladium-catalyzed cyclization have been published.[5] As well exposed by J.E. Baldwin, cyclization processes are mostly governed by the created ring size, the hybridization of the attacked carbon as well as the inside or outside position of the break bond in comparison to the formed cycle.[6] Thus, the angle of approach of the nucleophile on the π-allylic complex is indicative of the feasibility of the reaction. It has been reported that malonyl vinylepoxides, in the presence of palladium catalyst, led to cyclobutanols in place of cyclohexenols via a 4-exo-trig process.[7] Ionic 6-*endo-trig* cyclizations in carbon skeleton remain a challenging area and methods to synthesize cyclohexenes are still required even after the development of ring closing metathesis reactions.[8]

Since the pioneering work of Hirao, it is admitted that the presence of a silyl groups usually direct the attack of the nucleophiles to the distal position (relative to the silicon atom) of the palladium π-allylic cationic complex leading to the corresponding vinyl silanes.[9] Such a regioselectivity may be accounted for in terms of steric factors, charge distribution of the allyl complex, as well as stability of the newly formed olefin–Pd(0) complex. We reported a very strong silicon effect that afforded highly chemo- and stereoselective palladium-catalyzed alkylations[10] that we later applied in synthesis.[11] This directing group has been used to force the 5-*endo-trig* processes versus the classical 3-exo-trig but was unsuccessful for the 7-*endo-trig* versus the 5-*exo-trig* ones.[12] All above facts drew our attention to study the effect of the position of a silyl group to direct a 6-*endo-trig* cyclization through the palladium-catalyzed allylation process. Considering this, we envisaged the synthesis of silylated cyclohexene products **C** through the formation of the π-allylic intermediates **B**, which in turn, could be generated from the reaction of allylic acetate or carbonate precursors **A** with Pd(0) catalyst (Scheme 1).

2. Results and discussion

We first considered the precursor **C** bearing one hydroxyl function on allylic position (Scheme 1; R′=OH). The expected resulting cyclohexene presents the correct functionalization for the synthesis of carbocycles of biological interest, such as Shikimic acid, for example.

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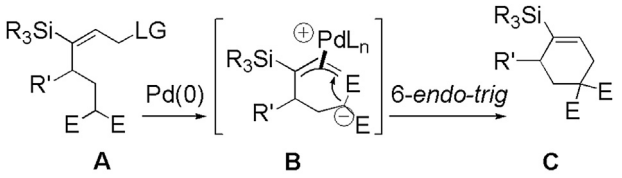
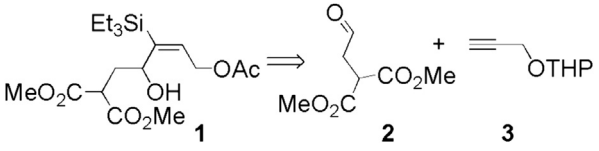


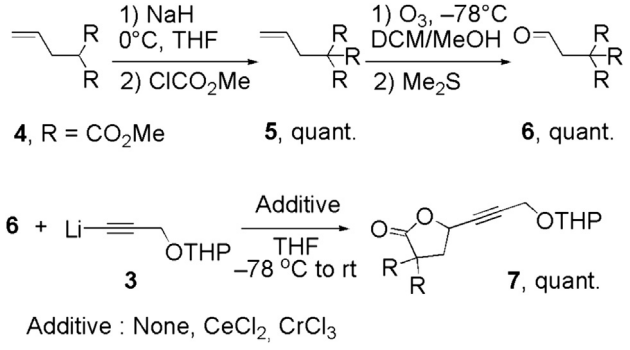
Scheme 1. Silylated precursor **A** for 6-*endo-trig* cyclization.

We reasoned that the precursor **1** required for the cyclization could be prepared in few steps (hydrosilylation, acylation) via the alkyne resulting from the addition of the propargylic alcohol **3** to the malonyl aldehyde **2** (Scheme 2).



Scheme 2. Approach towards the cyclization precursor **1**.

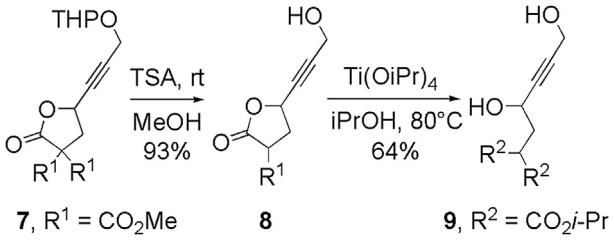
We observed degradation products during the condensation step between the malonyl aldehyde **2** and the propargylic alcohol derivative **3**. It is noteworthy to mention here that the hydrogen atom present at α-position related to the ester groups is acidic enough to give side reactions under the operating conditions. We thus masked this acidic proton by replacing it with a third ester function (Scheme 3).



Scheme 3. Preparation of triester aldehyde **6** and synthesis of lactone **7**.

Thus, the allyl malonate **4** was converted into the triester **5** by alkylation with methyl chloroformate.[13] The ozonolysis of the double bond delivered the expected aldehyde **6** in good yield over the two steps. Our next target was the preparation of the allylic acetate **1**. For that purpose, we performed the alkylation of the aldehyde **6** with the lithiated anion of *O*-protected propargylic alcohol **3**. The reaction was fast but the expected allylic alcohol was not observed. In its place, we isolated in nearly quantitative yield, the lactone **7** resulting from the intramolecular attack of the generated alkoxide ion to one of the ester functions. The more hindered triethyl ester also delivered the corresponding lactone. To avoid the formation of the lactone **7**, we considered performing the alkylation in the presence of Cerium (III) or Chromium (III) chlorides or with the preformed ceric anion of **3**. These conditions also led to the formation of the heterocyclic compound **7** with comparable yields.

Even if this lactone could be considered as a protection of the hydroxyl group, this ring should be open before the final cyclization step due to strong steric constraints. Moreover, both the THP protective group and the third ester should also be replaced. Starting from **7**, we performed the simultaneous deprotection of the primary alcohol and the decarboxylation of one of the ester. Using a catalytic amount of *p*-TSA in MeOH at room temperature, we isolated the lactone **8** in 93% yield. Transesterification of **8** was then performed using Ti(O*i*-Pr)$_4$ in refluxing isopropanol. Delightfully, this protocol resulted in the formation of the corresponding diol **9** with 64% yield (Scheme 4).



Scheme 4. Preparation of alkynyl diol **9**.

We then performed the hydrosilylation of the triple bond of the alkynyl diol **9** by using Et$_3$SiH in presence of catalytic amount of H_2PtCl_6 (Fig. 1).[14] Surprisingly, when the reaction was performed in *i*-PrOH as solvent, no hydrosilylation was noticed after one night at 50 °C (Table 1, entry 1). In acetonitrile, only 20% of hydrosilylation product was obtained with the recovery of 70% of starting material (Table 1, entry 2). In neat conditions, the conversion was also not completed, affording mostly degradation products (Table 1, entry 3). In all cases, no selectivity was apparent. Finally, the best result was obtained in THF, giving the corresponding regioisomers **10** and **11** in 90% yield in a 1:1 ratio. We also tested the direct hydrosilylation of the lactone **7** with *tert*-butyldimethylsilane, but this also led to a mixture of two isomers in a 59% yield.

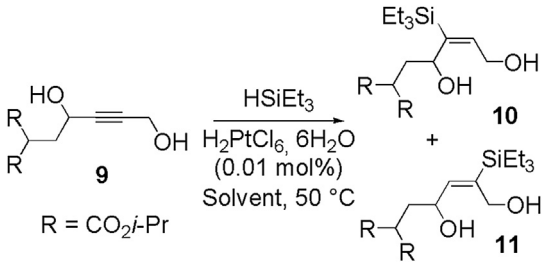


Fig. 1. Hydrosilylation of **9**.

Table 1
Solvent screening for the hydrosilylation of **9**

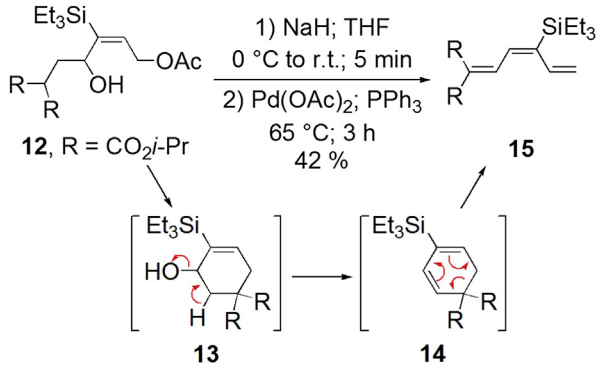
Entry	Solvent	Conversion (%)	Ratio **10**:**11**	Yield (%)[a]
1	*i*-PrOH	—	—	—
2	CH_3CN	30	1:1	20
3	Neat	70	1:1	20
4	THF	100	1:1	90

[a] Combined isolated yield of both regioisomers.

The two regioisomers **10** and **11** were separated by flash chromatography, and **10** was quantitatively converted into the corresponding allylic acetate **12** by using acetic anhydride and NEt_3 in CH_2Cl_2. It should be noted that **10**, **11**, and **12** slowly cyclized into the

corresponding more stable lactones (see Experimental part for characterization). Therefore, it is essential to engage them relatively quickly after their preparation.

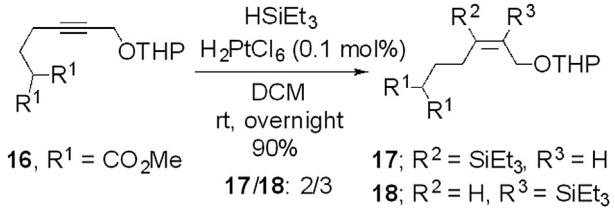
After the synthesis of the allylic acetate precursor **12**, we performed the palladium-catalyzed 6-*endo*-*trig* cyclization.[15] This reaction was carried out in presence of sodium hydride followed by the addition of 5 mol % of $Pd(PPh_3)_4$ catalyst. The reaction worked well in THF at 65 °C and we observed the consumption of the starting material in less than 3 h. After purification, we did not observe the formation of the expected silylated cyclohexenol **13** but we isolated the conjugated trienic ester **15** in 42% yield. The ^1H and ^{13}C NMR indicated the presence of five vinylic protons and six vinylic carbons. HRMS definitively confirmed the proposed structure (Scheme 5).



Scheme 5. Palladium-catalyzed cyclization of **12**.

We examined the formation of this compound, and hypothesized that the 6-*endo*-*trig* cyclization has taken place as expected. Indeed, we propose the formation of the desired cyclohexenol **13** followed by a dehydration reaction. The palladium complex could eventually mediate this undesired elimination.[16] The resulting cyclohexadiene **14** then underwent a 6-π retro-electrocyclization giving the more stable conjugated triene **15**.[17] To validate the hypothesis that the formation of compound **15** occurred through a 6-*endo*-*trig* cyclization, and not merely a direct degradation of the precursor **12**, we decided to synthesize a simplified precursor, which did not possesses a secondary hydroxyl function (Scheme 1, **C**; R′=H). This model, required to validate our strategy, could be prepared by hydrosilylation of an alkyne precursor **16** previously reported by Deslongchamps (Table 3).[18]

The introduction of the triethylsilyl group onto **16** was conducted under standard H_2PtCl_6-catalyzed hydrosilylation. It delivered a mixture of two regioisomers **17** and **18** in a 2:3 ratio with an overall yield of 90% (Scheme 6). Few organometallic complexes were tested without real improvement. For example, when the rhodium dimer $[RhCl(cod)]_2$ was used the yield decreased to 74%, whereas the platine(II) precursor $PtCl_2(PhCN)_2$ gave a slightly better 95% yield. The use of cationic ruthenium complexes mainly degradated the starting alkyne.



Scheme 6. Hydrosilylation of **16**.

The two tetrahydropyranyl derivatives **17** and **18** could be separated by careful flash chromatography. However, it is preferable, with these substrates, to first remove the THP group in acidic conditions (*p*-TSA/MeOH)[18] and then to separate the corresponding allylic alcohols **19** and **20**. Acylation of **19** delivered the expected allylic acetate **21** in 89% yield over these two steps.[19] We treated **21** with NaH followed by the palladium catalyst [prepared from $Pd(OAc)_2$ and phosphines, such as mono- and diphosphine (PPh_3 or dppe), phosphite or ferrocenyl ligands]. Various solvents, such as THF, toluene, and DMF were tested for the present protocol. No product was detected and, in all cases, the starting material **21** was fully recovered. Under the same conditions, precursors bearing either a trifluoroacetate or a carbonate as leaving group also did not lead to the expected cyclohexene but degradation mostly occurred.

Given the non-reactivity of the starting material, we concluded that under the operating conditions, degradation of the catalytic system should be faster than the cyclization. To test this hypothesis, we quickly heat the reaction mixture containing, the sodium anion of **21** and the catalyst to 90 °C. Gratifyingly, under these new reaction conditions, we obtained the desired cyclization product **22**. A marked difference in reactivity was observed depending on the ligands of the palladium (Fig. 2, Table 2).

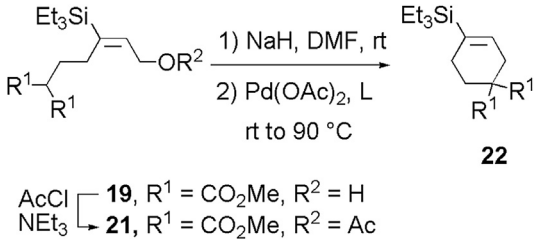


Fig. 2. Palladium-catalyzed cyclization of **21**.

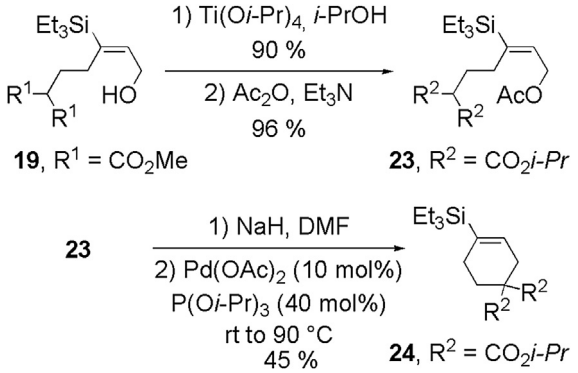
Table 2
Ligand optimization for 6-*endo*-*trig* cyclization

Entry	Ligand (L)	Time (h)	Conversion (%)	Yield (%)[a]
1	dppf	24	38	n.d.
2	$P(OPh)_3$	24	42	n.d.
3	dppe	24	65	n.d.
4	PPh_3	24	72	30
5	$P(OEt)_3$	24	74	34
6	$P(Oi\text{-}Pr)_3$	2	100	66

[a] Isolated yield; not determined when conversion was too low.

Regardless of the ligand used, the 6-*endo*-*trig* cyclization process has consistently held. However, the reactivities remained generally modest and the conversions did not exceed 74% after 24 h (Table 2, entries 1–5). The use of tri-isopropylphosphite allowed the full conversion of the substrate **21** a significant acceleration in the reaction rate as the starting material disappeared within 2 h. It afforded the expected cyclohexene **22** in 66% isolated yield as well as some unidentified degradation products (Table 2, entry 6).

We also prepared a precursor having bulkier isopropyl ester functions. At this end, we performed the *trans*-esterification of compound **19** mediated by $Ti(Oi\text{-}Pr)_4$ in isopropanol. The expected diisopropylic malonate was isolated in 90% yield then acylated by using the standard conditions (Ac_2O, NEt_3) to provide the allylic acetate **23** in 96% yield (Scheme 6). Using the optimized reaction conditions (vide supra), total conversion of the starting material was observed and the corresponding cyclohexene **24** was isolated in a moderated 45% yield in addition to unidentified degradation products (Scheme 7).



Scheme 7. Preparation of precursor **23** and cyclization into **24**.

To demonstrate the strong influence of the position of the silyl group during the cyclization, we also tested the allylic acetate **25**. This compound is supposed to produce a highly reactive π-allyl palladium complex unsuitable for cyclization (Fig. 3).[11a,12b]

Thus, engaged in the palladium-catalyzed reaction at room temperature, the starting acetate **25** was recovered (Table 3, entry 1). As expected, upon heating, the diene **26** was isolated quantitatively regardless of the solvent or the ligand used (Table 3, entries 2–6). We explain these results by the competition between the unfavorable cyclization with the fast elimination on the intermediate cationic π-allylic palladium complex.

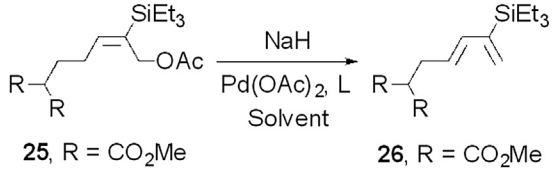


Fig. 3. Palladium-catalyzed elimination into diene **26**.

Table 3
Effect of ligand in palladium-catalyzed elimination

Entry	Ligand (L)	Solvent	Temp (°C)	Yield (%)[a]
1	PPh_3	THF	rt	n.r.
2	PPh_3	THF	65	quant.
3	dppe	THF	50	quant.
4	dppe	Toluene	80	quant.
5	dppe	DMF	90	quant.
6	$P(Oi\text{-}Pr)_3$	DMF	90	quant.

[a] Isolated yield.

3. Conclusion

We have developed conditions allowing the preparation of functionalized silylated cyclohexenes. The position of the vinylic silyl group on the starting allylic substrate strongly influenced the palladium-catalyzed cyclizations. It could favor either the production of an open chain diene by a direct elimination on the palladium intermediate or a cyclohexenyl ring via a 6-*endo*-*trig* process. In addition, the presence of a hydroxyl group at the allylic position of the starting material, allowed the cyclization to proceed smoothly. It is followed by dehydration and a 6-π electrocyclic rearrangement giving a conjugated trienic product.

4. Experimental section

4.1. General

The characterization data for compounds **2**, **3**, **4**, **5**, and **16** was previously reported. All reactions requiring anhydrous conditions were carried out under an atmosphere of nitrogen or argon in flame-dried glassware using standard syringe techniques. ^1H NMR spectra were recorded on 200 and 400 MHz NMR spectrometers using $CDCl_3$ (δ=7.26 ppm) as the internal reference. ^{13}C NMR spectra were recorded at 50 or 100 MHz using $CDCl_3$ (δ=77.16 ppm) as the internal reference. Infrared spectra were recorded on an FT-IR spectrophotometer and signals are reported in cm^{-1}. Mass spectra were recorded either through electrospray ionization (ESI) or electron impact (EI) on an instrument operating at 70 eV.

*4.1.1. 2-Allyl-2-methoxycarbonyl-malonic acid dimethyl ester (**5**).*[13] At 0 °C, to a suspension of NaH (60% in mineral oil) (5.85 g, 146.2 mmol, 1.5 equiv) in THF (150 mL), was added **4** (16.78 g, 97.4 mmol) and the mixture was warmed to rt and stirred during 1 h. Then, freshly distilled $ClCO_2Me$ (20 mL, 258.0 mmol, 2.6 equiv) was slowly added at 0 °C and the solution was warmed to rt and stirred during 2 h. The reaction mixture was diluted in diethyl ether and washed with saturated aqueous solution of ammonium chloride and brine, dried over $MgSO_4$, filtered, and concentrated. Pure compound **5** (20.41 g, 88.6 mmol, 91%) was obtained as a colorless oil. ^1H NMR ($CDCl_3$, 200 MHz) δ 5.95–5.77 (ddt, J=17.2; 10.3 and 7.4 Hz, 1H, $H_2C{=}CHCH_2$); 5.09 (dd, J=17.2 and 1 Hz, 1H, $HC{=}CH_{trans}$); 4.99 (dd; J=10.3 and 1 Hz, 1H, $HC{=}CH_{cis}$); 3.70 (s, 9H, CO_2CH_3); 2.78 (d, J=7.4 Hz, 2H, $H_2C{=}CHCH_2$). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.9 (CO_2CH_3); 132.4 ($H_2C{=}CHCH_2$); 119.4 ($H_2C{=}CHCH_2$); 65.7 ($C(CO_2CH_3)_3$); 53.1 (CO_2CH_3); 37.6 ($H_2C{=}CHCH_2$). IR (neat), cm^{-1}: 2900; 1740; 1460; 1370; 1230. Anal. for $C_{10}H_{14}O_6$ (M=230.22 g mol^{-1}): calcd (%) : C=52.17; H=6.13. found (%) : C=52.06; H=6.32.

*4.1.2. 2-Methoxycarbonyl-2-(2-oxo-ethyl)-malonic acid dimethyl ester (**6**).* In a flask without septum, ozone was added to a cold (−78 °C) solution of allyl malonate **5** (1.38 g, 6.0 mmol) in a mixture CH_2Cl_2/MeOH: 3:1 (20 mL) until a persistent blue color was perceived or until total disparition of S.M. was observed by TLC. Then, O_3 in excess was removed by bubbling a N_2 flow. Methyl sulfide (2.15 mL, 30 mmol, 5 equiv) was added and the solution is stirred 10 min at −78 °C, then slowly warmed to rt in 3 h. Me_2S was removed under reduced pressure using a NaClO trap. After removal of the solvent, diethyl ether was added and the crude product, which precipitate was filtered. Pure compound **6** (1.33 g, 5.7 mmol, 96%) was obtained as a white powder. TLC (PE/EA=7:3): R_f=0.40. Mp: 75 °C. ^1H NMR ($CDCl_3$, 200 MHz) δ 9.68 (s, 1H, O=*CH*); 3.78 (s, 9H, CO_2CH_3); 3.17 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 196.5 (O=CH); 166.5 (CO_2CH_3); 62.4 ($C(CO_2CH_3)_3$); 53.9 (CO_2CH_3); 45.5 (CH_2). IR (neat), cm^{-1}: 2975; 1720; 1435; 1240. Anal. for $C_9H_{12}O_7$ (M=232.19 g mol^{-1}): calcd (%): C=46.56; H=5.21. Found (%): C=46.68; H=5.24.

*4.1.3. 2-Oxo-5-[3-(tetrahydro-pyran-2-yloxy)-prop-1-ynyl]-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (**7**).* To a solution of **3** (23.45 mL, 166.8 mmol, 1.1 equiv) in THF (250 mL), at −78 °C, was added dropwise a 2 M solution of *n*-BuLi (83.4 mL, 166.8 mmol, 1.1 equiv) and the mixture was stirred 30 min at this temperature. Then, the anion was canulated onto a solution of aldehyde **6** (35.2 g, 151.6 mmol) in THF (50 mL) and the mixture warmed to rt and stirred 2 h. Then, Et_2O and NH_4Cl were added. The aqueous phase was extracted with Et_2O. Combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude compound **7** was obtained as an

orange oil and was directly engaged in the next step. TLC (PE/EA=7:3): R_f=0.35. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.31 (t, J=6.9 Hz, 1H, OC*H*CC); 4.73 (s, 1H, OC*H*O); 4.23 (s, 2H, CCCH_2O); 3.63 (s, 6H, CO_2CH_3); 3.60–3.42 (m, 2H, CH_2CH_2O); 2.41 (t, J=6.9, 2H, CH_2CCO_2Me); 1.73–1.50 (m, 6H, $(CH_2)_3CHO$). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.9 (*C*O_2Me); 154.5 (*C*(O)CCO$_2$Me); 96.8 (OC*H*O); 83.7 (CCCH$_2$OCHO); 81.2 (*C*CCH$_2$OCHO); 65.8 (O*C*HCC); 62.0 (CH_2CH_2O); 54.0 (CCCH_2OCHO); 52.8 (CO_2CH_3); 47.8 (*C*CO$_2$Me); 33.6 (CH_2CCO_2Me); 30.2 (CH_2CH_2CHO); 25.3 (CH_2CH_2CHO); 19.0 (CH_2CH_2O). IR (ATR), cm^{-1}: 2953; 1736; 1439; 1339; 1258; 1119; 1024; 941; 902.

*4.1.4. 5-(3-Hydroxy-prop-1-ynyl)-2-oxo-tetrahydro-furan-3-carboxylic acid methyl ester (**8**).* To a solution of crude **7** (16.35 g, 48.03 mmol) in MeOH (50 mL) was added at rt *p*-TSA (3.66 g, 19.2 mmol, 40%) and the mixture was stirred overnight. Then, the solution was diluted in Et_2O and a saturated aqueous solution of $NaHCO_3$ was added. The aqueous phase was extracted with Et_2O. Combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude compound was purified by flash chromatography and **8** (8.92 g, 45 mmol; 93% over 2 steps from **6**) was obtained as a pale yellow oil. TLC (PE/EA=7:3): R_f=0.10. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.32 (t, J=6.4 Hz, 1H, OC*H*CC); 4.26 (s, 2H, CH_2OH); 3.77 (s, 3H, CO_2CH_3); 3.63 (t, J=7.4 Hz, 1H, C*H*CO$_2$CH$_3$); 2.44 (dd, J=7.4 and 6.4 Hz, 2H, CH_2CHCO$_2$); 2.23 (s, 1H, O*H*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.0 (*C*O_2Me); 154.6 (*C*(O)CHCO$_2$Me); 86.1 (CCCH$_2$OH); 80.4 (*C*CCH$_2$OH); 65.8 (O*C*HCC); 52.8 (CO_2CH_3); 50.5 (*C*H$_2$OH); 47.8 (*C*HCO$_2$Me); 33.5 (*C*H$_2$CHCO$_2$Me). IR (neat), cm^{-1}: 3499; 2958; 1755; 1441; 1268; 1027; 939.

*4.1.5. 2-(2,5-Dihydroxy-pent-3-ynyl)-malonic acid diisopropyl ester (**9**).* To a solution of **8** (2.47 g, 12.46 mmol) in *i*-PrOH (20 mL) was added, at rt, Ti(O*i*-Pr)$_4$ (3.7 mL, 12.46 mmol, 1 equiv). The mixture was warmed to 80 °C and stirred overnight. After completion of the reaction, Et_2O and a saturated aqueous solution of Na_2SO_4 were added. Ti salts were filtered and the compound **9** (2.29 g, 8.0 mmol, 64%) was obtained as translucent oil. TLC (PE/EA=5:5): R_f=0.40. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.26 (t, J=5.1 Hz, 1H, *C*H*O*H); 5.05 (sept, J=6.1 Hz, 2H, $CO_2CH(CH_3)_2$); 4.26 (d, J=5.6 Hz, 2H, CH_2OH); 3.68 (t, J=8.1 Hz, 1H, C*H*(CO$_2$*i*-Pr)$_2$); 2.88–2.46 (m, 2H, CH_2CHOH); 2.24 (s br, 2H, 2× CHO*H*); 1.23 (d, J=6.1 Hz, 12H, $CO_2CH(CH_3)_2$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.9 ($CO_2CH(CH_3)_2$); 86.8 (*C*CCHOH); 80.9 (*C*CCH$_2$OH); 70.4 (O*C*H(CH$_3$)$_2$); 68.3 (*C*CHOH); 50.6 (*C*H$_2$OH); 46.7 (*C*H(CO$_2$*i*-Pr)$_2$); 33.5 (CHCH$_2$); 21.6 ($CO_2CH(CH_3)_2$). IR (ATR), cm^{-1}: 3482; 2983; 1778; 1721; 1454; 1258; 1147; 1101; 1007.

4.2. General procedure A for hydrosilylation

Under Ar, to a solution of alkyne (1 equiv) in THF (3 M), silane (1.2 equiv), and a 0.1 M solution of H_2PtCl_6, $6H_2O$ (0.01 mol %) in THF were added. The mixture was warmed to 50 °C overnight. The solution was filtered at room temperature over a short pad of Celite, concentrated in vacuo, and purified by flash chromatography.

*4.2.1. 2-(2,5-Dihydroxy-3-triethylsilanyl-pent-3-enyl)-malonic acid diisopropyl ester (10) and 5-(3-hydroxy-1-triethylsilanyl-propenyl)-2-oxo-tetrahydro-furan-3-carboxylic acid isopropyl ester (**10′**).* These compounds were prepared according to the general procedure A from **9** (1.88 g, 6.5 mmol) to give a mixture of two regioisomers **10**/**11** in a 1/1 *ratio* (pale yellow oil, 2.4 g, 5.9 mmol). **10** was isolated by flash chromatography, and cyclized slowly into **10′** when stored at rt. **10**: TLC (PE/EA=7:3): R_f=0.40. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.89 (t, J=6.1 Hz, 1H, =C*H*); 5.05 (sept, J=6.6 Hz, 2H, $CO_2CH(CH_3)_2$); 4.53 (dd, J=10.6 and 3.0 Hz, 1H, SiCC*H*OH); 4.28 (dd, J=6.1 and 2.0 Hz, 2H, CH_2OH); 3.54 (dd, J=8.6 and 5.6 Hz, 1H, C*H*CO$_2$*i*-Pr); 2.45 (s br, 1H, O*H*); 2.13 (ddd, J=14.7, 10.6 and 5.6 Hz, 1H, part of CH_2CHOH); 1.96 (ddd, J=14.7, 8.6 and 3.0 Hz, 1H, part of CH_2CHOH); 1.66 (s br, 1H, O*H*); 1.25 (d, J=6.6 Hz, 12H, $CO_2CH(CH_3)_2$); 0.92 (t, J=7.6 Hz, 9H, SiCH$_2$CH_3); 0.65 (q, J=7.6 Hz, 6H, SiCH_2CH$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.3 (CO_2*i*-Pr); 140.6 (=*C*Si); 138.1 (=CH); 69.2 ($CO_2CH(CH_3)_2$); 61.7 (*C*HOH); 54.8 (*C*H$_2$OH); 49.1 (*C*H(CO$_2$*i*-Pr)$_2$); 33.3 (CH$_2$CH(CO$_2$*i*-Pr)$_2$); 21.6 ($CO_2CH(CH_3)_2$); 7.2 (SiCH$_2$CH$_3$); 3.4 (SiCH$_2$CH$_3$). IR (ATR), cm^{-1}: 3450; 2954; 2876; 1728; 1456; 1375; 1262; 1166; 1102; 1004; 721.

10′: TLC (PE/EA=7:3): R_f=0.50. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.94 (t, J=5.1 Hz, 1H, =C*H*); 5.53 (t, J=8.6 Hz, 1H, C*H*OCO); 5.05 (sept, J=6.1 Hz, 1H, C*H*(CH$_3$)$_2$); 4.31–4.16 (m, 2H, CH_2OH); 3.54 (m, 1H, C*H*CO$_2$*i*-Pr); 2.68–2.07 (m, 2H, CH_2CHO); 1.25 (d, J=6.1 Hz, 6H, $CO_2CH(CH_3)_2$); 0.92 (t, J=7.6 Hz, 9H, SiCH$_2$CH_3); 0.65 (q, J=7.6 Hz, 6H, SiCH_2CH$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.8 (CO_2*i*-Pr); 167.4 (O*C*=O); 142.1 (=CH); 138.9 (=*C*Si); 81.3 (*C*HO); 70.4 ($CO_2CH(CH_3)_2$); 59.9 (CH$_2$OH); 47.7 (*C*H(CO$_2$*i*-Pr)); 33.9 (*C*H$_2$CHO); 21.7 ($CO_2CH(CH_3)_2$); 7.4 (SiCH$_2$CH$_3$); 3.6 (SiCH$_2$CH$_3$). IR (ATR), cm^{-1}: 2954; 2876; 1780; 1729; 1456; 1375; 1256; 1164; 1103; 1004; 971; 722. Anal. for $C_{17}H_{30}O_5Si$ (M=342.50 g mol^{-1}): calcd (%) : C=59.62; H=8.83. found (%): C=59.71; H=8.74.

4.3. General procedure B

*4.3.1. 2-(5-Acetoxy-2-hydroxy-3-triethylsilanyl-pent-3-enyl)-malonic acid diisopropyl ester (**12**).* To a solution of **10** (430 mg, 1.15 mmol), in dry CH_2Cl_2 (2 mL), distilled Et_3N (0.4 mL, 2.8 mmol, 2.5 equiv) was added and the resulting suspension was allowed to stir at room temperature until dissolution was completed. Freshly distilled acetyl chloride (80 μL, 1.15 mmol, 1 equiv) was then added dropwise at 0 °C to the reaction mixture. The reaction was then allowed to warm to room temperature and stirred overnight. The mixture was treated with a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with CH_2Cl_2. The collected organic layers were washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The crude product was purified by flash chromatography to give **12** (511 mg, 1.15 mmol, quant.) as a colorless oil. TLC (Pent/EA=95:5): R_f=0.60. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.81 (t, J=6.8 Hz, 1H, =C*H*); 5.54 (m, 1H, SiCC*H*OH); 5.05 (sept, J=6.3 Hz, 2H, $CO_2CH(CH_3)_2$); 4.62 (m, 2H, CH_2OAc); 3.51 (m, 1H, C*H*CO$_2$*i*-Pr); 2.69–2.37 (m, 2H, CH_2CHOH); 2.05 (s, 3H, OCOCH_3); 1.27 (d, J=6.3 Hz, 12H, $CO_2CH(CH_3)_2$); 0.90 (t, J=7.8 Hz, 9H, SiCH$_2$CH_3); 0.66 (q, J=7.8 Hz, 6H, SiCH_2CH$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.6 (O*C*OCH$_3$); 167.3 (CO_2*i*-Pr); 141.7 (=*C*Si); 136.3 (=CH); 81.2 (*C*HO); 70.5 ($CO_2CH(CH_3)_2$); 61.3 (CH$_2$O); 47.7 (*C*H(CO$_2$*i*-Pr)); 33.7 (*C*H$_2$CHO); 21.8 ($CO_2CH(CH_3)_2$); 21.1 (OCOCH$_3$); 7.5 (SiCH$_2$CH$_3$); 3.6 (SiCH$_2$CH$_3$). IR (ATR), cm^{-1}: 3440; 2954; 2873; 1727; 1455; 1375; 1260; 1168; 1101; 1004; 720. Anal. for $C_{22}H_{40}O_7Si$ (M=444.63 g mol^{-1}): calcd (%): C=59.43; H=9.07. found (%): C=59.69; H=8.68.

*4.3.2. 5-(3-Acetoxy-1-triethylsilanyl-propenyl)-2-oxo-tetrahydro-furan-3-carboxylic acid isopropyl ester (**12′**).* The formation of this compound (pale yellow oil) sometime occurs during acylation of **10** or when **12** was stored at rt. TLC (PE/EA=7:3): R_f=0.30. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.83 (t, J=5.4 Hz, 1H, =C*H*); 5.54 (t, J=6.6 Hz, 1H, C*H*OCO); 5.05 (sept, J=6.1 Hz, 1H, C*H*(CH$_3$)$_2$); 4.65–4.58 (m, 2H, CH_2O); 3.57 (m, 1H, C*H*CO$_2$*i*-Pr); 2.70–2.37 (m, 2H, CH_2CHO); 2.07 (s, 3H, OCOCH$_3$); 1.24 (d, J=6.1 Hz, 6H, $CO_2CH(CH_3)_2$); 0.90 (t, J=7.6 Hz, 9H, SiCH$_2$CH_3); 0.62 (q, J=7.6 Hz, 6H, SiCH_2CH$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.5 (O*C*OCH); 171.6 (O*C*OCH$_3$); 167.8 (CO_2*i*-Pr); 142.4 (=*C*Si); 137.1 (=CH); 81.9 (*C*HO); 71.2 ($CO_2CH(CH_3)_2$); 62.0 (CH$_2$O); 48.4 (*C*H(CO$_2$*i*-Pr)); 34.5 (*C*H$_2$CHO); 22.6 ($CO_2CH(CH_3)_2$); 21.8 (OCOCH$_3$); 8.2 (SiCH$_2$CH$_3$); 4.4 (SiCH$_2$CH$_3$). IR (ATR), cm^{-1}: 2954; 2876; 1782; 1733; 1455; 1375; 1227; 1163;

1105; 1019; 970; 722. Anal. for $C_{19}H_{32}O_6Si$ (M=384.54 g mol^{-1}): calcd (%): C=59.34; H=8.39. Found (%): C=59.27; H=8.40.

4.4. General procedure C

*4.4.1. 2-(3-Triethylsilanyl-penta-2,4-dienylidene)-malonic acid diisopropyl ester (**15**).* To a suspension of sodium hydride (19 mg, 0.475 mmol, 0.95 equiv) in THF (2 mL), was added, at 0 °C, a solution of **12** (215 mg, 0.5 mmol) in THF (0.5 mL). The mixture was warmed to rt and stirred during 10 min. Then, a beforehand made solution of $Pd(OAc)_2$ (6 mg, 5 mol %), PPh_3 (26 mg, 20 mol %) in THF (2 mL) was added and the mixture was warmed to reflux. After 1 h, Et_2O and NH_4Cl were added and after a standard work-up, the crude product was purified by flash chromatography and **15** (77 mg, 0.21 mmol, 42%) was obtained as a colorless oil. TLC (Pent/AE=95:5): R_f=0.95. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74 (d, J=12.2 Hz, 1H, C*H*CO$_2$*i*-Pr); 6.68 (dd, J=17.3 and 11.2 Hz, 1H, C*H*CH$_2$); 6.63 (d, J=12.2 Hz, 1H, SiC=C*H*); 5.34 (d, J=11.2 Hz, 1H, CH=CH$_{cis}$); 5.22 (d, J=17.3 Hz, 1H, CH=CH$_{trans}$); 5.20 and 5.09 (2sept, J=6.1 Hz, 2× 1H, 2× CO$_2$C*H*(CH$_3$)$_2$); 1.31 and 1.25 (2d, J=6.1 Hz, 2× 6H, 2× CO$_2$CH(C*H*$_3$)$_2$); 0.90 (t, J=8.1 Hz, 9H, CH$_2$C*H*$_3$); 0.69 (q, J=8.1 Hz, 6H, C*H*$_2$CH$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.4 and 164.5 (2× *C*O$_2$CH(CH$_3$)$_2$); 154.4 (*C*CO$_2$*i*-Pr); 137.6 (*C*HCCO$_2$*i*-Pr); 135.7 (*C*HCH$_2$); 132.9 (SiC=*C*H); 127.2 (CH=*C*H$_2$); 119.8 (Si*C*=CH); 69.1 and 68.9 (2× *C*O$_2$CH(CH$_3$)$_2$); 21.9 (2× CO$_2$CH(*C*H$_3$)$_2$); 7.4 (CH$_2$*C*H$_3$); 3.3 (*C*H$_2$CH$_3$). IR (neat), cm^{-1}: 2950; 1720; 1605; 1375; 1255; 1110; 740. HRMS (IC, CH_4) for [MNH$_4$]$^+$ 367.2305, mes. 367.2307.

*4.4.2. 2-[5-(Tetrahydro-pyran-2-yloxy)-3-triethylsilanyl-pent-3-enyl]-malonic acid dimethyl ester (**17**) and 2-[5-(tetrahydro-pyran-2-yloxy)-4-triethylsilanyl-pent-3-enyl]-malonic acid dimethyl ester (**18**).* These compounds were prepared according to the general procedure A from 2-[5-(tetrahydro-pyran-2-yloxy)-pent-3-ynyl]-malonic acid dimethyl ester **16**[18] (13.13 g, 44 mmol). After completion of the reaction, a 2/3 mixture of two regioisomers **17** and **18** was obtained (16.18 g, 39 mmol). **17**: TLC (PE/EA=7:3): R_f=0.70. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.83 (t, J=5.6 Hz, 1H, =C*H*); 4.53 (m, 1H, OC*H*O); 4.26 (dd, part of AB system, J=13.0 and 5.6 Hz, 1H, =CHCH$_2$O); 4.06 (dd, part of AB system, J=13.0 and 6.6 Hz, 1H, =CHC*H*$_2$O); 3.68 (s, 6H, CO$_2$C*H*$_3$); 3.45 (m, 2H, CH$_2$C*H*$_2$O); 3.30 (t, J=7.6 Hz, 1H, C*H*CO$_2$CH$_3$); 2.12 (m, 2H, C*H*$_2$CH$_2$CSi); 1.93 (m, 2H, C*H*$_2$CSi); 1.9–1.4 (m, 6H, C*H*$_2$C*H*$_2$C*H*$_2$CH); 0.91 (t, J=7.6 Hz, 9H, CH$_2$C*H*$_3$); 0.56 (q, J=7.6 Hz, 6H, C*H*$_2$CH$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.6 (*C*O$_2$CH$_3$); 141.4 (=*C*Si); 139.3 (=*C*H); 98.1 (O*C*HO); 66.1 (=CH*C*H$_2$O); 62.4 (CH$_2$*C*H$_2$O); 52.5 (CO$_2$*C*H$_3$); 51.8 (*C*HCO$_2$Me); 41.1 (OCH*C*H$_2$); 30.7 (*C*H$_2$CH$_2$OCHO); 28.7 (*C*H$_2$CHCO$_2$Me); 25.6 (*C*H$_2$CH$_2$CHCO$_2$Me); 19.6 (*C*H$_2$CH$_2$CHO); 6.6 (SiCH$_2$*C*H$_3$); 2.9 (Si*C*H$_2$CH$_3$). IR (ATR), cm^{-1}: 2953; 2923; 1739; 1436; 1228; 1151; 1070; 1003; 733. **18**: TLC (PE/EA=7:3): R_f=0.70. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.83 (t, J=5.6 Hz, 1H, =C*H*); 4.53 (m, 1H, OC*H*O); 4.30 (d, 1H, J=11.7 Hz, 1H, part of C*H*$_2$O); 3.92 (d, J=11.7 Hz, 1H, part of C*H*$_2$O); 3.68 (s, 6H, CO$_2$C*H*$_3$); 3.45 (m, 2H, CH$_2$C*H*$_2$O); 3.30 (t, J=7.6 Hz, 1H, C*H*CO$_2$CH$_3$); 2.13 (m, 2H, =CHCH$_2$C*H*$_2$); 1.95 (m, 2H, =CHC*H*$_2$); 1.9–1.4 (m, 6H, C*H*$_2$C*H*$_2$C*H*$_2$CH); 0.83 (t, J=7.8 Hz, 9H, CH$_2$C*H*$_3$); 0.55 (q, J=7.8 Hz, 6H, C*H*$_2$CH$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.8 (*C*O$_2$CH$_3$); 139.6 (=*C*Si); 137.1 (=*C*H); 98.1 (OCHO); 62.4 (CH$_2$*C*H$_2$O); 61.7 (SiC*C*H$_2$O); 52.5 (CO$_2$*C*H$_3$); 51.1 (*C*HCO$_2$Me); 41.1 (OCH*C*H$_2$); 30.7 (*C*H$_2$CH$_2$OCHO); 30.6 (*C*H$_2$CH$_2$CHCO$_2$Me); 26.8 (*C*H$_2$CHCO$_2$Me); 19.3 (*C*H$_2$CH$_2$CHO); 7.5 (SiCH$_2$*C*H$_3$); 3.3 (Si*C*H$_2$CH$_3$).

4.5. General procedure D

*4.5.1. 2-(5-Hydroxy-pent-3-ynyl)-malonic acid dimethyl ester (**19**).* To a solution of **16** (1.49 g, 5.0 mmol) in MeOH (10 mL) was added at rt *p*-TSA (95 mg, 0.5 mmol, 10 mol %) and the mixture was stirred overnight. Then, the solution was diluted in Et_2O and a saturated aqueous solution of $NaHCO_3$ was added. The aqueous phase was extracted with Et_2O. Combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude compound was purified by flash chromatography to give **19** (1.07 g, 5.0 mmol, quant.) as a pale yellow oil. NMR spectrum were identical to the described molecule. TLC (PE/EA=7:3): R_f=0.20. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.18 (s, 2H, C*H*$_2$OH); 3.70 (s, 6H, CO$_2$C*H*$_3$); 3.54 (t, J=7.1 Hz, 1H, C*H*CO$_2$CH$_3$); 2.42 (s, 1H, O*H*); 2.27 (t, J=7.1 Hz, 2H, CCC*H*$_2$CH$_2$); 2.05 (dt, J=7.1 and 7.1 Hz, 2H, C*H*$_2$CHCO$_2$Me). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.6 (*C*O$_2$CH$_3$); 83.9 (CCCH$_2$OH); 80.1 (CCCH$_2$OH); 52.7 (CO$_2$*C*H$_3$); 51.1 (*C*H$_2$OH); 50.4 (*C*HCO$_2$CH$_3$); 27.6 (CCC*H*$_2$CH$_2$); 16.8 (CC*C*H$_2$CH$_2$). IR (ATR), cm^{-1}: 3419; 2955; 1728; 1435; 1248; 1154; 1047; 1010.

*4.5.2. 2-(5-Hydroxy-3-triethylsilanyl-pent-3-enyl)-malonic acid dimethyl ester (19) and 2-(5-hydroxy-4-triethylsilanyl-pent-3-enyl)-malonic acid dimethyl ester (**20**).* Following general procedure D, a 2/3 mixture of **17** and **18** (53.9 g, 130 mmol) delivered two regioisomers **19** (16.8 g, 50.8 mmol) and **20** (26.0 g, 78.7 mmol), which were separated on silica gel.

19: TLC (PE/EA=6:4): R_f=0.65. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.89 (t, J=6.1 Hz, 1H, =C*H*); 4.21 (d, J=6.1 Hz, 2H, C*H*$_2$OH); 3.70 (s, 6H, CO$_2$C*H*$_3$); 3.31 (t, J=7.6 Hz, 1H, C*H*(CO$_2$CH$_3$)$_2$); 2.05 (m, 2H, C*H*$_2$CH$_2$CSi); 2.02 (s, 1H, O*H*); 1.81 (m, 2H, C*H*$_2$CSi); 0.87 (t, J=8.1 Hz, 9H, CH$_2$C*H*$_3$); 0.55 (q, J=8.1 Hz, 6H, C*H*$_2$CH$_3$). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.7 (*C*O$_2$CH$_3$); 141.8 (=*C*H); 139.1 (=*C*Si); 59.3 (*C*H$_2$OH); 52.6 (CO$_2$*C*H$_3$); 51.6 (*C*H(CO$_2$CH$_3$)$_2$); 29.1 (*C*H$_2$CH$_2$CSi); 27.9 (*C*H$_2$CSi); 7.4 (CH$_2$*C*H$_3$); 2.9 (*C*H$_2$CH$_3$). IR (neat), cm^{-1}: 3446; 2954; 2911; 2874; 1736; 1437; 1268; 1158; 1005; 737. Anal. for $C_{16}H_{30}O_5Si$ (M=330.49 g mol^{-1}): calcd (%) : C=58.15; H=9.15. Found (%): C=58.01; H=9.16.

20: TLC (PE/EA=6:4): R_f=0.85. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.73 (t, J=7.1 Hz, 1H, =C*H*); 4.15 (s, 2H, C*H*$_2$OH); 3.71 (s, 6H, CO$_2$C*H*$_3$); 3.34 (t, J=7.6 Hz, 1H, C*H*(CO$_2$CH$_3$)$_2$); 2.21 (dt, J=7.6 and 7.1 Hz, 2H, C*H*$_2$CH$_2$CH=); 1.97 (dt, J=7.6 and 7.1 Hz, 2H, CH$_2$C*H*$_2$CH=); 1.53 (s, 1H, O*H*); 0.89 (t, J=8.2 Hz, 9H, CH$_2$C*H*$_3$); 0.60 (q, J=8.2 Hz, 6H, C*H*$_2$CH$_3$). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.9 (*C*O$_2$CH$_3$); 142.1 (=*C*H); 139.9 (=*C*Si); 60.4 (*C*H$_2$OH); 52.7 (CO$_2$*C*H$_3$); 51.0 (*C*H(CO$_2$CH$_3$)$_2$); 28.5 (CH$_2$*C*H$_2$CH=); 26.3 (CH$_2$*C*H$_2$CH=); 7.5 (CH$_2$*C*H$_3$); 3.2 (*C*H$_2$CH$_3$). IR (neat), cm^{-1}: 3474; 2953; 2877; 2361; 1733; 1437; 1229 (br); 1156; 1005; 716. Anal. for $C_{16}H_{30}O_5Si$ (M=330.49 g mol^{-1}): calcd (%): C=58.15; H=9.15. Found (%): C=58.10; H=9.10.

*4.5.3. 2-(5-Acetoxy-3-triethylsilanyl-pent-3-enyl)-malonic acid dimethyl ester (**21**)*

4.5.3.1. Method A. Following general procedure B, from allylic alcohol **19** (350 mg, 1.06 mmol). The product **21** (395 mg, 1.06 mmol) was quantitatively obtained as a colorless oil.

4.5.3.2. Method B.[19] Acetic anhydride (0.45 mL, 4.8 mmol, 1.2 equiv) was added dropwise to a solution of pyranyl protected compound **17** (1.66 g, 4 mmol) and $Cu(OTf)_2$ (72.3 mg, 0.2 mmol, 5 mol %) in CH_2Cl_2 (20 mL) and was stirred at rt overnight. The reaction mixture was diluted with CH_2Cl_2 and washed with sodium bicarbonate and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated on a rotary evaporator. The crude product was purified over silica gel by flash chromatography to provide the pure acetate **21** (863 mg, 2.32 mmol, 58%) as a pale yellow oil. TLC (=PE/EA): R_f=0.95. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.80 (t, J=6.1 Hz, 1H, =C*H*); 4.63 (d, J=6.1 Hz, 2H, CH$_2$O); 3.71 (s, 6H, CO$_2$C*H*$_3$); 3.33 (t, J=7.6 Hz, 1H, C*H*(CO$_2$CH$_3$)$_2$); 2.11 (m, 2H, C*H*$_2$CSi); 2.03 (s, 3H, COC*H*$_3$); 1.83 (m, 2H, C*H*$_2$CH$_2$CSi); 0.91 (t, J=7.6 Hz, 9H, CH$_2$C*H*$_3$); 0.60 (q, J=7.6 Hz, 6H, CH$_2$C*H*$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0 (*C*OCH$_3$); 169.6 (*C*O$_2$CH$_3$); 142.0 (=*C*H); 136.0 (=*C*Si); 61.0

(CH_2O); 52.6 (CO_2CH_3); 51.6 ($CH(CO_2CH_3)_2$); 29.0 (CH_2CH_2CSi); 28.0 (CH_2CSi); 21.1 ($COCH_3$); 7.4 (CH_2CH_3); 2.8 (CH_2CH_3). IR (ATR), cm^{-1}: 2954; 2875; 1735; 1435; 1225; 1154; 1017; 717.

*4.5.4. 4-Triethylsilanyl-cyclohex-3-ene-1,1-dicarboxylic acid dimethyl ester (**22**).* To a solution of NaH (80 mg, 2 mmol, 1 equiv, 60% in mineral oil) in freshly distilled and degassed DMF (0.5 mL), was added, at 0 °C, a solution of allylic acetate **21** (745 mg, 2 mmol) in DMF (0.5 mL). The mixture was warmed to rt and stirred 15 min. In a second flask, $Pd(OAc)_2$ (44.9 mg, 0.2 mmol, 10 mol %) was dissolved in DMF (1 mL). Distilled $P(Oi\text{-}Pr)_3$ (0.2 mL, 0.8 mmol, 40 mol %) was added dropwise. After the first drop of phosphite, the mixture become dark but at the end of the addition it took on a pale yellow color. The catalyst was stirred 5 min and added onto the first mixture. The mixture was immediately warmed to 90 °C (in a beforehand warmed oil bath). The completion of the reaction was followed by TLC (revealed by $KMnO_4$). After 2 h, the mixture was filtered over Celite and silica then the DMF was evaporated under reduced pressure (30 °C under 0.5 mmHg) and the crude product was purified by flash chromatography to give **22** (413 mg, 1.32 mmol) as a colorless oil. TLC (PE/EA=9:1): R_f=0.90. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.89 (tt, J=3.6 and 2.0 Hz, 1H, =C*H*); 3.69 (s, 6H, CO_2CH_3); 2.58 (d, J=3.6 Hz, 2H, =CHCH_2); 2.09 (m, 2H, CH_2CH$_2$CSi); 2.07 (m, 2H, CH_2CSi); 0.86 (t, J=7.6 Hz, 9H, CH$_2$CH_3); 0.52 (q, J=7.6 Hz, 6H, CH_2CH$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.3 (CO_2CH_3); 135.0 (=*C*Si); 133.4 (=*C*H); 53.1 (CCO_2CH_3); 52.6 (CO_2CH_3); 32.2 (=CH*C*H$_2$); 28.1 (=CSiCH$_2$*C*H$_2$); 24.8 (=CSiCH_2); 7.4 (CH$_2$*C*H$_3$); 2.5 (*C*H$_2$CH$_3$). IR (neat), cm^{-1}: 2952; 2874; 1736; 1619; 1238; 716. Anal. for $C_{16}H_{28}O_4Si$ (M=312.48 g mol^{-1}): calcd (%): C=61.50; H=9.03. Found (%): C=61.32; H=9.11.

*4.5.5. 2-(5-Acetoxy-3-triethylsilanyl-pent-3-enyl)-malonic acid diisopropyl ester (**23**).* To a solution of **19** (330.5 mg, 1 mmol) in *i*-PrOH (3 mL), was added distilled $Ti(Oi\text{-}Pr)_4$ (0.3 mL, 1 mmol, 1 equiv) and the mixture was warmed to 80 °C overnight. After completion of the reaction, Et_2O and a saturated aqueous solution of Na_2SO_4 were added. Ti salts were filtered and the crude allylic alcohol (351 mg, 0.9 mmol) was obtained as a translucent oil pure enough for direct conversion into the corresponding acetate. To a solution of allylic alcohol (187 mg, 0.48 mmol), in dry CH_2Cl_2 (2.5 mL), distilled Et_3N (0.25 mL, 1.78 mmol, 3.7 equiv) was added and the resulting suspension was allowed to stir at room temperature until dissolution was completed. Acetic anhydride (70 L, 0.75 mmol, 1.5 equiv) was added dropwise at 0 °C and the reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was treated with a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with CH_2Cl_2. The collected organic layers were washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The crude product was purified by flash chromatography to give **23** (199 mg, 0.48 mmol, 96%) as a colorless oil. TLC (PE/EA=7:3): R_f=0.95. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.80 (t, J=6.1 Hz, 1H, =C*H*); 5.05 (sept, J=6.2 Hz, 2× 1H, $CO_2CH(CH_3)_2$); 4.67 (d, J=6.1 Hz, 2H, CH_2O); 3.22 (t, J=7.6 Hz, 1H, C$H(CO_2i\text{-}Pr)_2$); 2.13 (m, 2H, CH_2CSi); 2.05 (s, 3H, COCH_3); 1.82 (m, 2H, CH_2CH$_2$CSi); 1.23 (d, J=6.2 Hz, 2× 6H, $CO_2CH(CH_3)_2$); 0.89 (t, J=7.5 Hz, 9H, CH$_2$CH_3); 0.60 (q, J=7.5 Hz, 6H, CH_2CH$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0 ($COCH_3$); 168.9 (CO_2i-Pr); 142.2 (=*C*Si); 136.0 (=*C*H); 69.0 ($CO_2CH(CH_3)_2$); 61.2 (*C*H$_2$O); 52.5 (*C*H$(CO_2i\text{-}Pr)_2$); 28.8 (*C*H$_2$CH$_2$CSi); 28.1 (*C*H$_2$CSi); 21.8 ($CO_2CH(CH_3)_2$); 21.2 ($COCH_3$); 7.5 (CH_2CH_3); 2.9 (*C*H$_2$CH$_3$). IR (neat), cm^{-1}: 2953; 2876; 1727; 1466; 1374; 1227; 1102; 717. Anal. for $C_{22}H_{40}O_6Si$ (M=428.63 g mol^{-1}): calcd (%): C=61.65; H=9.41. Found (%): C=61.67; H=9.49.

*4.5.6. 4-Triethylsilanyl-cyclohex-3-ene-1,1-dicarboxylic acid diisopropyl ester (**24**).* This compound was prepared following the general procedure C. From **23** (215 mg, 0.5 mmol), pure compound **24** (84 mg, 0.23 mmol, 45%) was obtained as a colorless oil. TLC (PE/EA=9:1): R_f=0.90. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.90 (t, J=3.6 Hz, 1H, =C*H*); 4.99 (sept, J=6.1 Hz, 2× 1H, $CO_2CH(CH_3)_2$); 2.54 (d, J=3.6 Hz, 2H,=CHCH_2); 2.05 (s, 2× 2H, =CSiCH_2CH$_2$); 1.19 (2× d, J=6.1 Hz, 12H, $CO_2CH(CH_3)_2$); 0.86 (t, J=7.6 Hz, 9H, SiCH$_2$CH_3); 0.51 (q, J=7.6 Hz, 6H, SiCH_2CH$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.4 ($CO_2CH(CH_3)_2$); 134.8 (=*C*Si); 133.7 (=*C*H); 68.6 ($CO_2CH(CH_3)_2$); 53.0 ($C(CO_2i\text{-}Pr)_2$); 32.0 (=CHCH$_2$); 27.8 (SiCCH$_2$CH$_2$); 24.7 (SiCCH$_2$); 21.7 ($CO_2CH(CH_3)_2$); 7.5 (CH_2CH_3); 2.5 (*C*H$_2$CH$_3$). IR (neat), cm^{-1}: 2952; 2875; 1727; 1619; 1466; 1285; 1172; 1145; 715. Anal. for $C_{20}H_{36}O_4Si$ (M=368.58 g mol^{-1}): calcd (%): C=65.17; H=9.84. Found (%): C=65.21; H=9.69.

*4.5.7. 2-(5-Acetoxy-4-triethylsilanyl-pent-3-enyl)-malonic acid dimethyl ester (**25**).* This compound was prepared quantitatively following the general procedure B, from **20** (330 mg, 1 mmol). TLC (PE/EA=7:3): R_f=0.95. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.87 (t, J=7.1 Hz, 1H, =C*H*); 4.67 (s, 2H, CH_2O); 3.76 (s, 6H, CO_2CH_3); 3.39 (t, J=7.6 Hz, 1H, C$H(CO_2CH_3)_2$); 2.23 (dd, J=15.3 and 7.1 Hz, 2H, =CHCH_2); 2.06 (s, 3H, COCH_3); 2.02 (dd, J=15.3 and 7.6 Hz, 2H, CH_2CH$_2$CH=); 0.93 (t, J=7.6 Hz, 9H, CH$_2$CH_3); 0.62 (q, J=7.6 Hz, 6H, CH_2CH$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.9 ($OCOCH_3$); 169.7 (CO_2CH_3); 143.8 (=*C*H); 134.4 (=*C*Si); 62.9 (*C*H$_2$O); 52.6 (CO_2CH_3); 51.0 ($CH(CO_2CH_3)_2$); 28.5 (*C*H$_2$CH$_2$CH=); 26.7 (*C*H$_2$CH=); 21.0 ($COCH_3$); 7.3 (CH_2CH_3); 3.1 (*C*H$_2$CH$_3$). IR (neat), cm^{-1}: 3459; 2954; 2911; 2875; 1739; 1436; 1231; 1156; 1021; 736. Anal. for $C_{18}H_{32}O_6Si$ (M=372.53 g mol^{-1}): calcd (%): C=58.03; H=8.66. Found (%): C=57.98; H=8.77.

*4.5.8. 2-(4-Triethylsilanyl-penta-2,4-dienyl)-malonic acid dimethyl ester (**26**).* The formation of this compound occurs when compound **25** was submitted to the palladium-catalyzed general procedure C. TLC (PE/EA=7:3): R_f=0.80. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.18 (d, J=15.2 Hz, 1H, CH=*C*HCSi); 5.70 (d, J=3.1 Hz, 1H, SiC=CH_{trans}); 5.59 (dt, J=15.2 and 7.1 Hz, 1H, C*H*=CHC=CH$_2$); 5.29 (d, J=3.1 Hz, 1H, SiC=CH_{cis}); 3.69 (s, 6H, CO_2CH_3); 3.42 (t, J=7.6 Hz, 1H, C*H*CO_2Me); 2.63 (dd, J=7.6 and 7.1 Hz, 2H, CH_2CHCO$_2$Me); 0.88 (t, J=7.6 Hz, 9H, SiCH$_2$CH_3); 0.61 (q, J=7.6 Hz, 6H, SiCH_2CH$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.3 (CO_2CH_3); 145.5 (=*C*Si); 138.4 (CH=*C*HCSi); 128.8 (SiC=*C*H$_2$); 125.9 (*C*H=CHCSi); 52.5 (CO_2CH_3); 51.9 (*C*HCO$_2$Me); 32.5 (*C*H$_2$CHCO$_2$Me); 7.3 (SiCH$_2$*C*H$_3$); 2.0 (SiC*H*$_2$CH$_3$). IR (ATR), cm^{-1}: 2952; 2924; 2874; 1737; 1435; 1228; 1151; 1003; 967.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.08.080.

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