Silicon-Controlled Intramolecular Thermal H-Ene Reaction – A New Access to a Key Intermediate of (±)-*cis*-γ-Irone

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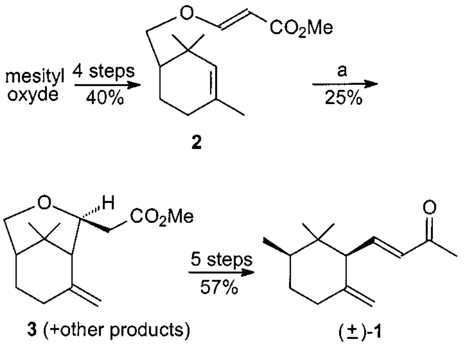
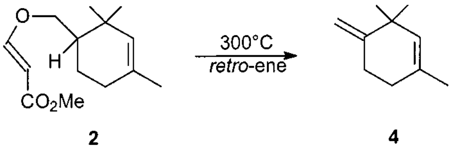
The primordial influence of the silyl group in an intramolecular thermal H-ene reaction is reported. The silyl group lowered the energy of the transition state and allowed the reaction to proceed at a lower temperature than that of the simple all-carbon analog, thereby excluding the formation of undesirable by-products. This sequence has been applied for new access to a key intermediate in the diastereoselective synthesis of (±)-*cis*-γ-irone with high chemocontrol and significantly improved overall yield.

The intramolecular ene reaction has recently received considerable attention and offers a valuable method for the formation of the C−C bond in natural-product synthesis.[1][2] As an example, in an elegant approach,[3] *cis*-γ-irone (**1**) has been stereoselectively synthesized by a thermal H-ene reaction of β-(alkenyloxy)acrylate **2**, yielding the 3-oxabicyclo[3.3.1]nonane derivative **3** as a key intermediate (Scheme 1).



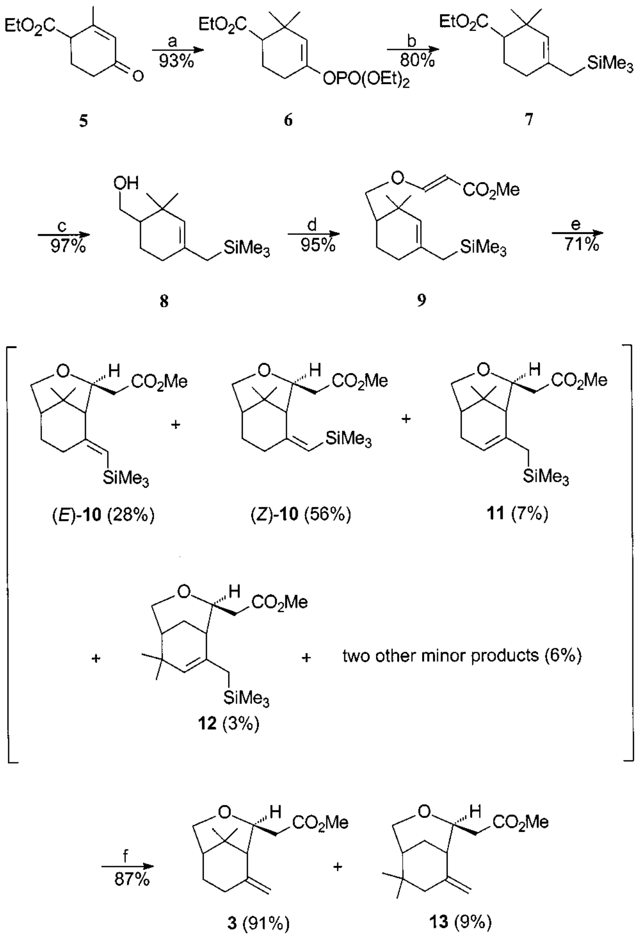
Scheme 1. Reagents: (a) toluene, sealed tube at 300°C for 9 h

This step, however, suffers from a modest yield of 25% of the expected cyclized compound **3** and this has a significant adverse effect, at this crucial stage, on the overall yield of the synthesis. The major drawback is the formation of a side-product, 1,3,3-trimethyl-4-methylidene-1-cyclohexene (**4**) (ca. 40%, Scheme 2), by a competitive *retro*-ene reaction.[4]



Scheme 2

As part of our interest in the ene reaction of allylsilanes,[5][6] we report herein a significant improvement in the diastereoselective synthesis of **3** starting from Hagemann's ester and based on an allylsilane chemo-controlled intramolecular thermal H-ene reaction (Scheme 3).



Scheme 3. Reagents and conditions: (a) Me_2CuLi, Et_2O, 0°C then $ClPO(OEt)_2$/HMPA, THF, room temp.; (b) Me_3SiCH_2MgCl, $Cl_2Ni(dppp)$, THF reflux; (c) $LiAlH_4$, Et_2O, −5°C; (d) methyl propiolate, *N*-methylmorpholine, Et_2O, room temp.; (e) decalin, sealed tube previously washed with Sylon CT, 250°C for 96 h; (f) sulfinic acid, CH_3CN, reflux

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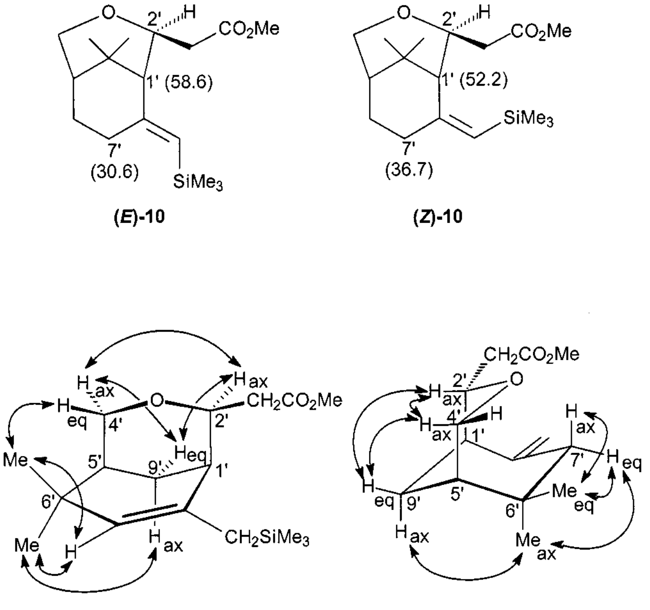
The commercially available Hagemann's ester (**5**) was converted into the cyclic diethyl enol phosphate **6** by the 1,4-addition of dimethylcuprate (Me_2CuLi), followed by quenching with chlorodiethylphosphate in hexamethylphosphoric triamide.[7] The dichloro[1,3-bis(diphenylphosphanyl)propane]nickel(II)-catalyzed coupling reaction of **6** with 1-(trimethylsilyl)methylmagnesium chloride[7] gave trimethyl-(4-ethoxycarbonyl-3,3-dimethylcyclohex-1-enylmethyl)silane (**7**), and $LiAlH_4$ reduction of **7** furnished the desired alcohol **8**. Addition of alcohol **8** to methyl propiolate in the presence of *N*-methylmorpholine[8] afforded the (*E*)-β-alkoxyacrylate **9**. Heating a solution of **9** in decalin (sealed tube previously washed with 5% dichlorodimethylsilane in toluene: Sylon CT) at 250 °C for 96 h produced unreacted **9** (see Experimental Section) and, in 71% yield, a mixture of vinylsilanes **10** [(*E*)/(*Z*) = 1:2] and four minor products (GC ratio 84:7:3:3:3). Among these minor products, two have been characterized as allylsilane **11** (7%) and transposed skeleton allylsilane **12** (3%) (Scheme 3). Desilylation of this mixture with sulfinic acid,[9] which led to **3** (from **10** + **11**) and **13** (from **12**) as the sole products in 87% overall yield (ratio 91:9), allowed us to propose a transposed vinylsilane skeleton for the two unidentified minor products.

The structural assignments of the different products were established by means of careful ^1H, ^{13}C, COSY and NOESY studies. In the ^{13}C-NMR spectra, regioisomers **10** and **11** were identified by the chemical shifts of the quaternary sp^2-hybridized carbon atom, which differed significantly. The signals of the vinyl isomers (*E*)-**10** ($\delta = 157.3$) and (*Z*)-**10** ($\delta = 157.4$) appeared at lower field than that of allylic isomer **11** ($\delta = 131.9$). For vinylsilanes **10**, the configuration of the double bond is assigned as (*E*)/(*Z*) on the basis of the comparison of the observed ^{13}C chemical shifts of carbon atoms 1′ and 7′ (Figure 1).



(*E*)-10 **(*Z*)-10**

12 **13**

Figure 1. ^{13}C-NMR and NOESY experiment assignments

NOESY experiments established that the structures of **12** and **13** are as shown (Figure 1). The plots were characterized by strong cross-peaks between $H_{2'ax}$, $H_{4'ax}$, $H_{9'eq}$, as well as between the $H_{4'ax}$ and $H_{9'eq}$ combination. Accordingly, these pairs of protons must reside in close proximity in a favored chair-like conformation of the tetrahydropyran ring.[10] Moreover, in vinylsilane **12**, an NOE effect was observed between the olefinic hydrogen atom and both methyl groups of the *gem*-dimethyl moiety, as well as between the methyl group in close proximity with $H_{4'eq}$ and the one in close proximity with $H_{9'ax}$. In the same way, in **13**, $Me_{6'eq}$ displayed a significant NOE with $H_{7'ax}$ and $H_{7'eq}$ whereas $Me_{6'ax}$ displayed a significant NOE with $H_{7'eq}$ and $H_{9'ax}$.

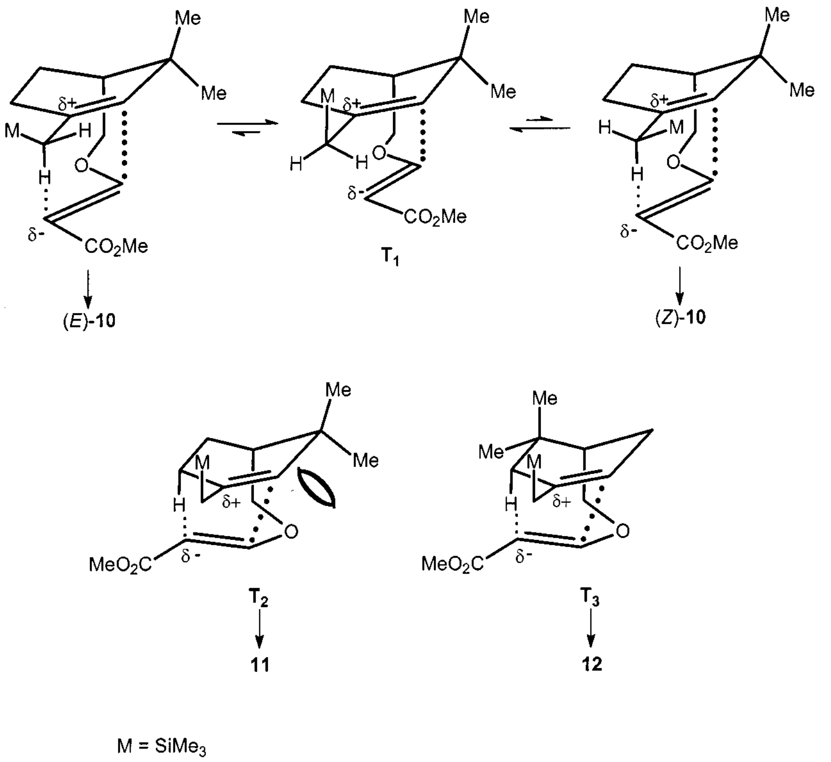
From the classical mechanistic standpoint, it is generally agreed that the concerted ene reaction involves a highly asynchronous transition state featuring a well-developed C−C bond prior to a relatively late proton transfer towards the incipient carbocation.[1,4a,6b] Consequently, a reasonable explanation for this reactivity is that the ene transition state has dipolar character and the silyl group, which enhances the nucleophilicity of the endocyclic double bond,[11] is also a powerful force for stabilization of the partial positive charge at the β-carbon atom (β-effect).[12] These effects lower the energy of the transition state and allow the reaction to proceed smoothly at a lower temperature than the simple all-carbon analog. The formation of the undesirable *retro*-ene by-product **4** (Scheme 2) is thus excluded. Inspection of Dreiding models[3] showed that two possible transition states, T_1 and T_2, could be visualized for the H-ene reaction (Scheme 4).

The relatively slow rate of cyclization may be ascribed to the fact that in the energetically favored transition state T_1, which yielded the major vinylic compounds **10**, an exocyclic α-silylated methylene C−H bond needs to be broken and must turn to be coplanar with the potentially empty carbon p-orbital[13] and, consequently, must perturb the σ-C−Si bond hyperconjugation. Moreover, the formation of the major product (*Z*)-**10** could be explained by the fact that when this rotation occurs the main transferred hydrogen atom is the one in close proximity with the negative part of the enophile.

The transition state T_2 is disfavored in comparison to T_1 because of a 1,4-steric interaction between the O atom and the *gem*-dimethyl group in the boat-like tetrahydropyran moiety to be formed. However, in this transition state a *pseudo*-axial *endo*-hydrogen atom is well positioned and the σ-C−Si bond hyperconjugation is not perturbed. This yielded by far the minor allylsilane **11**.

On the other hand, the formation of the transposed skeleton compounds could be reasonably explained by the partial isomerization of the starting allylsilane **9** under the conditions of the thermolysis.[14] In this case, the formation of the allylsilane **12** arose from the transition state T_3 (Scheme 4) in which the unfavorable steric interactions with the *gem*-dimethyl group, as in T_2, are absent.

In summary, the intramolecular thermal H-ene reaction of an allylsilane has been studied in terms of chemo- and regioselectivity. This has been developed into a strategy for



Scheme 4. Possible transition states for the H-ene reaction

a new access to a key intermediate in the diastereoselective synthesis of (±)-*cis*-γ-irone with total chemocontrol and 56% overall yield.

Experimental Section

General Remarks: ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution with Bruker AM-400 or Bruker AM-200 spectrometers (Bruker AM-400 for COSY and NOESY experiments). Infrared spectra were obtained from films using a Perkin-Elmer 257 Infrared Spectrophotometer. Routine monitoring of reactions was performed using Merck 60F 254 silica gel, aluminium-supported TLC plates. Column chromatography was performed using silica gel 60 (230−400 mesh) and gradients of pentane/ether as eluent unless otherwise stated. GC analyses were carried out with a Chrompack 9001 using a WCOT fused silica column (25 m × 0.32 mm i.d.; CP-Wax-52 CB stationary phase; N_2 carrier gas: 50 KPa). Microanalyses were performed with a Technicon CHN analyzer at our University. Solutions were dried with magnesium sulfate and the solvents evaporated using a rotary evaporator under reduced pressure.

Enol Phosphate 6: To a stirred suspension of copper(I) iodide (1.04 g, 5.48 mmol) in dry ether (30 mL) at −5 °C was added dropwise MeLi (1.5 M in ether, 7.3 mL, 10.96 mmol) under Ar. The mixture was stirred for 1 h at 0 °C and then a solution of **5** (500 mg, 2.74 mmol) in ether (10 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h, and then a mixture of $ClPO(OEt)_2$ (1.2 mL, 8.22 mmol) and HMPA (1.4 mL, 8.22 mmol) in THF (10 mL) was added dropwise. The solution was allowed to warm up to room temp., stirred for 12 h and then poured into a saturated aqueous NH_4Cl/NH_4OH solution (40 mL) and extracted with ether (3 × 30 mL). The organic layers were combined, washed with 30 mL of brine, dried, and the solvent was evaporated. The oily residue was subjected to silica gel column chromatography to afford 851 mg (93%) of **6**. − IR (neat): nu (tilde) = 1740 cm^{-1} (C=O), 1280 (P=O), 1050 (C−O). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.22 (s, 1 H), 4.12 (m, 6 H), 2.38−2.08 (m, 3 H), 2.08−1.77 (m, 2 H), 1.32 (t, 6 H, *J* = 7 Hz), 1.25 (t, 3 H, *J* = 7.2 Hz), 1.17 (s, 3 H), 0.97 (s, 3 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.7 (C), 145.6 (C, *J* = −8.9 Hz), 120.7 (CH, *J* = 5.4 Hz), 64.0 (2 CH_2, *J* = −6.1 Hz), 59.9 (CH_2), 49.2 (CH), 34.3 (C), 29.8 (CH_3), 26.7 (CH_2, *J* = 3.9 Hz), 24.5 (CH_3), 22.0 (CH_2), 15.9 (2 CH_3, *J* = 6.6 Hz), 14.1 (CH_3). − $C_{15}H_{27}O_6P$ (334.3): calcd. C 53.88, H 8.14; found C 53.84, H 8.16.

Allylsilane 7: To a stirred solution of enol phosphate **6** (500 mg, 1.49 mmol) and $NiCl_2$(dppp) (81 mg, 0.149 mmol) in dry THF (30 mL) was added a 1 M ethereal solution of (trimethylsilyl)methylmagnesium chloride (3.8 mL, 3.8 mmol) at room temp. under Ar. The reaction mixture was refluxed for 36 h and then quenched with 20 mL of saturated aqueous NH_4Cl and stirred for 45 min. After extraction with ether (3 × 30 mL), the organic layers were combined, washed with 30 mL of brine, dried, and the solvent was evaporated. Purification by silica gel column chromatography (pentane) afforded 320 mg (80%) of **7**. − IR (neat): nu (tilde) = 1740 cm^{-1} (C=O), 1660 (C=C), 1250 ($SiCH_3$), 1150 (C−O), 850 (Si−C). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.86 (s, 1 H), 4.12 (m, 2 H), 2.32−2.21 (m, 1 H), 2.01−1.60 (m, 4 H), 1.45 (s, 2 H), 1.24 (t, 3 H, *J* = 7.1 Hz), 1.10 (s, 3 H), 0.90 (s, 3 H), −0.02 (s, 9 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.9 (C), 132.4 (C), 130.0 (CH), 59.7 (CH_2), 50.1 (CH), 34.5 (C), 30.4 (CH_3), 30.2 (CH_2), 27.2 (CH_2), 24.8 (CH_3), 22.6 (CH_2), 14.3 (CH_3), −1.4 (3 CH_3). − $C_{15}H_{28}O_2Si$ (268.5): calcd. C 67.09, H 10.51; found C 67.15, H 10.49.

Alcohol 8: To a stirred suspension of $LiAlH_4$ (570 mg, 15 mmol) in dry ether (40 mL) at −10 °C was added dropwise an ethereal solution of ester **7** (1.25 g, 4.66 mmol). After being stirred for 30 min at room temp., the reaction mixture was diluted with ether (50 mL) and cooled in an ice bath. Celite (20 g), $Na_2SO_4 \cdot 10\ H_2O$ (20 g) and 1 mL of 10% NaOH were added. After 30 min, the mixture was filtered through a pad of $MgSO_4$ and concentrated to give 1.20 g (97%) of pure **8**. − IR (neat): nu (tilde) = 3300 cm^{-1} (OH), 1660 (C=C), 1250 ($SiCH_3$), 1020 (C−O), 850 (Si−C). − ^1H NMR (200 MHz, $CDCl_3$): δ = 4.82 (s, 1 H), 3.82 and 3.36 (ABX, 2 H, *J* = −10.5, 8.7, 3.3 Hz), 2.04−1.75 (m, 4 H), 1.49−1.22 (m, 1 H partially overlapped), 1.34 (s, 2 H), 1.02 (s, 3 H), 0.79 (s, 3 H), −0.02 (s, 9 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 132.8 (C), 131.0 (CH), 63.8 (CH_2), 46.3 (CH), 33.8 (C), 30.6 (CH_2), 30.0 (CH_3), 27.3 (CH_2), 23.9 (CH_3), 22.5 (CH_2), −1.3 (3 CH_3). − $C_{13}H_{26}OSi$ (226.4): calcd. C 68.96, H 11.58; found C 68.87, H 11.52.

β-(Alkenyloxy)acrylate 9: To a solution of methyl propiolate (930 mg, 11.06 mmol) in 20 mL of dry ether was added *N*-methylmorpholine (1.11 g, 11.06 mmol) followed by a solution of **8** (1.25 g, 5.53 mmol) in 10 mL of dry ether. The resulting mixture was stirred at room temp. under Ar for 48 h, poured into 100 mL of water, then extracted with ether (3 × 30 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried and concentrated. Silica gel column chromatography of the residual oil gave 1.630 g (95%) of **9**. − IR (neat): nu (tilde) = 1720 cm^{-1} (C=O), 1640 (C=C), 1625 (C=C), 1250 ($SiCH_3$), 1150 (C−O), 850 (Si−C). − ^1H NMR (200 MHz, $CDCl_3$): δ = 7.61 (d, 1 H, *J* = 12.7 Hz), 5.20 (d, 1 H, *J* = 12.7 Hz), 4.85 (s, 1 H), 3.97 and 3.54 (ABX, 2 H, *J* = −10.3, 9.8, 4.3 Hz), 3.69 (s, 3 H), 2.30−1.58 (m, 5 H), 1.37 (s, 2 H), 1.03 (s, 3 H), 0.82 (s, 3 H), −0.02 (s, 9 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 168.3 (C), 162.9 (CH), 132.9 (C), 130.2 (CH), 95.8 (CH), 72.5 (CH_2), 50.9 (CH_3), 42.8 (CH), 33.7 (C), 30.1 (CH_3), 29.9 (CH_2), 27.2 (CH_2), 23.9 (CH_3), 22.6 (CH_2), −1.4 (3 CH_3). − $C_{17}H_{30}O_3Si$ (310.5): calcd. C 65.76, H 9.74; found C 65.79, H 9.69.

Thermal H-Ene Reaction Procedure: A solution of 800 mg (2.57 mmol) of **9** in 2 mL of decalin (previously filtered through basic alumina) was heated in a glass tube (previously washed with Sylon CT and sealed under vacuum) at 250°C for 96 h. After cooling, the tube was opened and capillary GC analysis (150−220°C; 6°C/min) of the crude mixture revealed 6 peaks with t_R [min] = 9.9, 10.03, 10.15, 10.3, 11.3, 11.7 in a ratio of 28:3:3:3:56:7. These peaks correspond to (*E*)-**10**, uncharacterized, **12**, uncharacterized, (*Z*)-**10** and **11**, respectively (correlation with later NMR spectra allowed the assignments of the GC peaks). A seventh peak, with t_R = 13.5 min, corresponds to unreacted **9**. This mixture was then rapidly chromatographed on a silica gel column and afforded 157 mg (20%) of **9** and 569 mg (71%) of products whose ratios agree with the previous GC analysis. For characterization, a portion (250 mg) of these H-ene reaction compounds was subjected to a second, more painstaking purification by silica gel column chromatography, which led to the separation of pure **12**, different ratios of inseparable (*E*)-**10** + (*Z*)-**10** and pure **11**.

Vinylsilanes (*Z*)-10 and (*E*)-10: ^1H NMR (200 MHz, $CDCl_3$): δ = 5.34 [br. s, 1 H, (*Z*)-**10**], 5.02 [br. s, 1 H, (*E*)-**10**], 4.55−4.37 [m, 1 H, (*Z*)-**10**], 4.45−4.35 [m, 1 H, (*E*)-**10**], 4.17 (d, 2 H, *J* = 11.5 Hz), 3.72 (d, 2 H, *J* = 11.5 Hz), 3.68 (s, 6 H), 3.05−2.78 [m, 1 H, (*Z*)-**10**], 2.70−2.51 [m, 1 H, (*E*)-**10**], 2.50−1.80 (m, 12 H), 1.75−1.52 (m, 2 H), 1.22 [s, 3 H, (*Z*)-**10**], 1.19 [s, 3 H, (*E*)-**10**], 0.96 [s, 3 H, (*Z*)-**10**], 0.92 [s, 3 H, (*E*)-**10**], 0.08 [s, 9 H, (*E*)-**10**], 0.06 [s, 9 H, (*Z*)-**10**]. − ^{13}C NMR (50 MHz, $CDCl_3$): **(*Z*)-10:** δ = 173.2 (C), 157.4 (C), 125.6 (CH), 71.3 (CH), 70.3 (CH_2), 52.2 (CH), 51.9 (CH_3), 40.5 (CH_2), 38.5 (CH), 36.7 (CH_2), 34.0 (C), 29.0 (CH_3), 28.4 (CH_2), 26.1 (CH_3), 1.5 (3 CH_3); **(*E*)-10:** δ = 173.2 (C), 157.3 (C), 126.5 (CH), 71.2 (CH), 70.4 (CH_2), 58.6 (CH), 52.1 (CH_3), 40.3 (CH_2), 38.4 (CH), 33.7 (C), 30.6 (CH_2), 28.9 (CH_3), 27.9 (CH_2), 25.8 (CH_3), 0.6 (3 CH_3). − **Allylsilane 11:** ^1H NMR (200 MHz, $CDCl_3$): δ = 5.47 (m, 1 H), 4.35 (m, 1 H), 4.04 (br. d, 1 H, *J* = 11.5 Hz), 3.68 (s, 3 H), 3.58 (d, 1 H, *J* = 11.5 Hz), 2.51 (dd, 1 H, *J* = 15.1, 8.8 Hz), 2.39 (dd, 1 H, *J* = 15.1, 4.7 Hz), 2.28−2.38 (m, 1 H), 2.10 (br. d, 1 H, *J* = 17.6 Hz), 1.71 and 1.12 (AB, 2 H, *J* = −13.8 Hz), m (1 H) overlapped by 1.21 (s, 3 H), 1.02 (s, 3 H), 0.01 (s, 9 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.1 (C), 131.9 (C), 122.0 (CH), 71.0 (CH_2), 70.1 (CH), 51.4 (CH_3), 49.2 (CH), 39.8 (CH_2), 36.7 (CH), 32.5 (C), 31.2 (CH_2), 29.4 (CH_2), 28.3 (CH_3), 24.8 (CH_3), −1.1 (3 CH_3). − **Transposed-Skeleton Allylsilane 12:** ^1H NMR (400 MHz, $CDCl_3$): δ = 5.09 (br. s, 1 H, =CH), 4.04 (dt, 1 H, *J* = 11.7, 2.0 Hz, $H_{4'eq}$), 3.92 (ddd, 1 H, *J* = 7.5, 5.5, 1.8 Hz, $H_{2'ax}$), 3.65 (s, 3 H, OCH_3), 3.48 (dd, 1 H, *J* = 11.6, 2.1 Hz, $H_{4'ax}$), 2.46 (dd, 1 H, *J* = 15.5, 8.4 Hz, C*H*HCO_2Me), 2.38 (dd, 1 H, *J* = 15.5, 5.5 Hz, CH*H*CO_2Me), 2.00 (dq, 1 H, *J* = 12.2, 3.2, 3.2, 3.2 Hz, $H_{9'ax}$), 1.86 (m, 1 H, $H_{1'}$), 1.71 (dt, 1 H, *J* = 12.8, 2.8, 2.8 Hz, $H_{9'eq}$), 1.58 (dd, 1 H, *J* = 13.6, 0.8 Hz, C*H*$HSiMe_3$), 1.19 (m, 1 H, $H_{5'}$), 1.15 (br. d, 1 H, *J* = 13.6 Hz, CH*H*$SiMe_3$), 1.05 (s, 3 H, $Me_{6'eq}$), 0.94 (s, 3 H, $Me_{6'ax}$), −0.04 (s, 9 H, $SiMe_3$). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.22 (C), 133.88 (CH), 130.69 (C), 76.79 (CH), 70.99 (CH_2), 51.66 (CH_3), 39.61 (CH_2), 38.89 (CH), 38.01 (CH), 35.69 (C), 31.20 (CH_3), 30.21 (CH_2), 28.31 (CH_2), 26.78 (CH_3), −1.30 (3 CH_3).

Key Intermediate 3 and Transposed-Skeleton Compound 13: The crude H-ene reaction products (319 mg, 1.03 mmol) and *p*-toluenesulfinic acid (31 mg, 0.2 mmol) in 10 mL of CH_2Cl_2 was added one drop of water, and the reaction mixture was refluxed for 3 h. After cooling to room temp., the reaction mixture was quenched with H_2O (15 mL) and extracted with CH_2Cl_2 (2 × 20 mL). Capillary GC analysis showed the presence of only two products (ratio 91:9). The residue was then chromatographed on a silica gel column and yielded 201 mg (87%) of **3** and **13**. − **Key Intermediate 3:**[3] IR (neat): nu (tilde) = 3055 cm^{-1} (=CH), 1730 (C=O), 1640 (C=C), 1165 (C−O), 890 (=CH_2). − ^1H NMR (200 MHz, $CDCl_3$): δ = 4.80 (t, 1 H, *J* = 2.5 Hz), 4.50 (t, 1 H, *J* = 2.5 Hz), 4.39 (ddd, 1 H, *J* = 8.5, 5.0, 2.0 Hz), 4.16 (dt, 1 H, *J* = 11.5, 2.5 Hz), 3.72 (dd, 1 H, *J* = 11.4, 1.5 Hz), 3.66 (s, 3 H), 2.74−2.62 (m, 1 H), 2.40 (dd, 1 H, *J* = 15.5, 8.5 Hz), 2.25 (dd, 1 H, *J* = 15.5, 5.0 Hz), 2.22−2.14 (m, 1 H), 2.02−1.90 (m, 1 H), 1.71 (m, 1 H), 1.66−1.58 (m, 1 H), m (1 H) overlapped by 1.19 (s, 3 H), 0.92 (s, 3 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.3 (C), 147.3 (C), 111.2 (CH_2), 70.7 (CH_2), 69.8 (CH), 53.4 (CH_2), 51.6 (CH_3), 39.8 (CH), 38.1 (CH_2), 32.9 (C), 30.5 (CH), 28.4 (CH_3), 27.3 (CH), 25.3 (CH_3). − $C_{14}H_{22}O_3$ (238.3): calcd. C 70.56, H 9.31; found C 70.51, H 9.27. − **Transposed-Skeleton Compound 13:** IR (neat): nu (tilde) = 3050 cm^{-1} (=CH), 1730 (C=O), 1640 (C=C), 1160 (C−O), 890 (=CH_2). − ^1H NMR (400 MHz, $CDCl_3$): δ = 4.73 (t, 1 H, *J* = 2.4 Hz, =CH_2), 4.61 (t, 1 H, *J* = 2.4 Hz, =CH_2), 4.18 (dt, 1 H, *J* = 11.7, 2.1, 2.1 Hz, $H_{4'eq}$), 4.01 (ddd, 1 H, *J* = 8.1, 5.2, 2.1 Hz, $H_{2'ax}$), 3.66 (s, 3 H, OCH_3), 3.64 (dd, 1 H, *J* = 11.8, 2.3 Hz, $H_{4'ax}$), 2.67 (br. d, 1 H, *J* = 14 Hz, $H_{7'ax}$), 2.41 (dd, 1 H, *J* = 15.8, 8.1 Hz, C*H*HCO_2Me), 2.29 (dd, 1 H, *J* = 15.8, 5.2 Hz, CH*H*CO_2Me), 2.16 (m, 1 H, $H_{1'}$), 2.11 (dq, 1 H, *J* = 12.7, 3.3, 3.3, 3.3 Hz, $H_{9'ax}$), 1.86 (d, 1 H, *J* = 14 Hz, $H_{7'eq}$), 1.77 (dt, 1 H, *J* = 12.8, 2.8, 2.8 Hz, $H_{9'eq}$), 1.15 (m, 1 H, $H_{5'}$), 1.03 (s, 3 H, $Me_{6'eq}$), 0.94 (s, 3 H, $Me_{6'ax}$). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.20 (C), 147.28 (C), 110.85 (CH_2), 76.56 (CH), 70.10 (CH_2), 51.68 (CH_3), 46.34 (CH_2), 42.83 (CH), 39.55 (CH), 39.22 (CH_2), 34.48 (C), 31.51 (CH_2), 28.92 (CH_3), 28.38 (CH_3). − $C_{14}H_{22}O_3$ (238.3): calcd. C 70.56, H 9.31; found C 70.60, H 9.26.

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