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The Stereochemical Course of Intramolecular Michael Reactions

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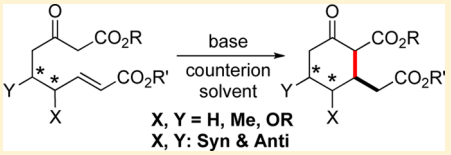
Supporting Information

ABSTRACT: We present a general model for understanding the stereochemical course of intramolecular Michael reactions. We show that the addition of β-ketoester enolates to α,β-unsaturated esters and imides bearing adjacent stereocenters (X, Y = H, Me, OR) leads to high levels of asymmetric induction. Reinforcing and nonreinforcing stereochemical relationships are evaluated from the syn and anti reactant diastereomers. On the basis of synthetic, spectroscopic, and computational studies, we propose that the outcomes of these reactions can be rationalized by a dipole-minimized chair transition-state model.



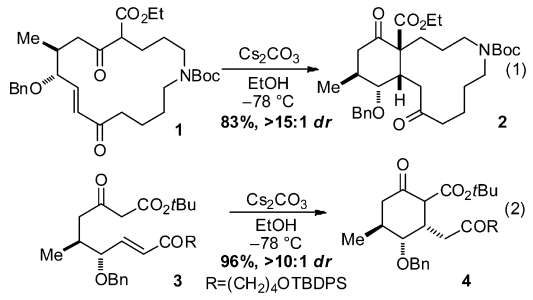
INTRODUCTION

In 1887, Arthur Michael showed that the intermolecular conjugate addition of stabilized carbanions to electron-deficient olefins is an efficient method for the mild formation of C−C bonds.[1−3] Since then, intramolecular Michael reactions have seen extensive use in the construction of polycyclic natural products.[4−8] For example, en route to a synthesis of adrenosterone, Stork and co-workers formed the requisite trans-hydrindane systems by adding aldehyde and β-ketoester enolates to α,β-unsaturated ketones and esters.[9−11] In this paper, we demonstrate that high levels of diastereoselection can be achieved in the intramolecular addition of β-ketoester enolates to α,β-unsaturated carbonyl groups bearing allylic and homoallylic stereocenters.

In certain cases, the sense of asymmetric induction is significantly influenced by counterion structure and solvent. In others, reinforcing and non-reinforcing stereochemical relationships between the allylic and homoallylic centers are clearly present. Based on synthetic, spectroscopic, and computational studies, we propose a dipole-minimized chair transition-state model that accounts for the bulk of our observations.

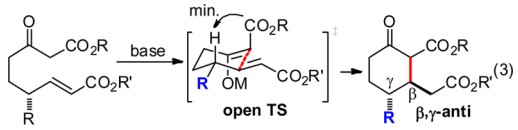
Our interest in this area arose during the course of our total syntheses of clavolonine[12] and salvinorin A.[13] These efforts revealed that Michael acceptors bearing adjacent stereocenters can engage pendant β-carboxyester enolates in highly diastereoselective bond formations (Scheme 1). Interestingly, the observed facial selectivity was independent of whether the reaction was conducted in a transannular (eq 1) or intramolecular (eq 2) format. To disentangle the local perturbations introduced by the substituents adjacent to the acceptor from the global conformational demands of macrocycle **1**, we decided to consider the behavior of intramolecular Michael additions in more detail.

Scheme 1. Transannular vs. intramolecular Michael additions



RESULTS AND DISCUSSION

If the reactions proceed via chair transition states, then two plausible scenarios can be envisioned. With a dipole-minimized enolate (eq 3), avoidance of a 1,3-diaxial interaction and an open



transition state would lead to β,γ-anti selectivity. Alternatively, a more chelating metal might enforce a closed transition state in which the acceptor occupies an axial position, leading to β,γ-syn selectivity (eq 4).

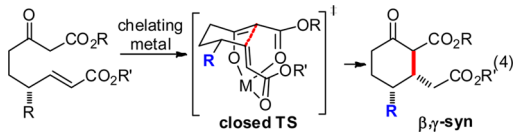


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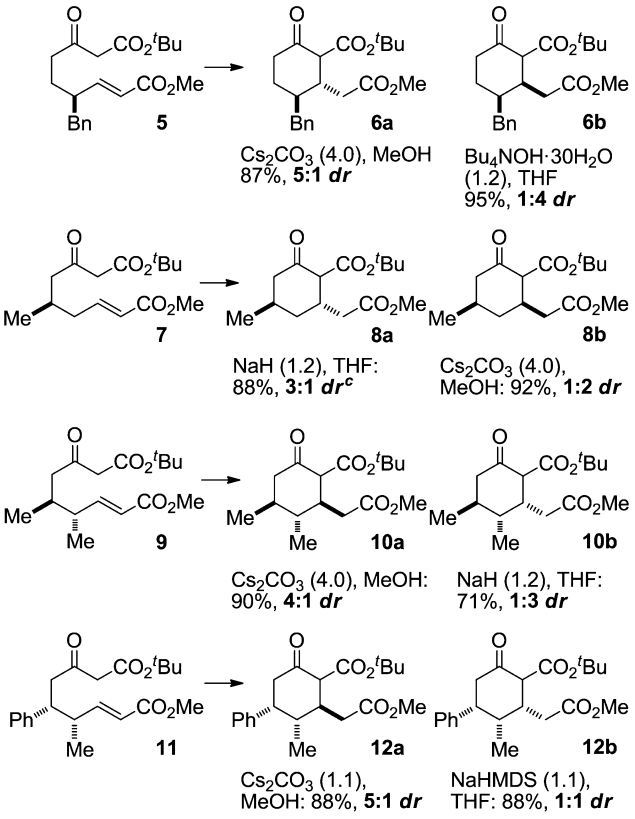
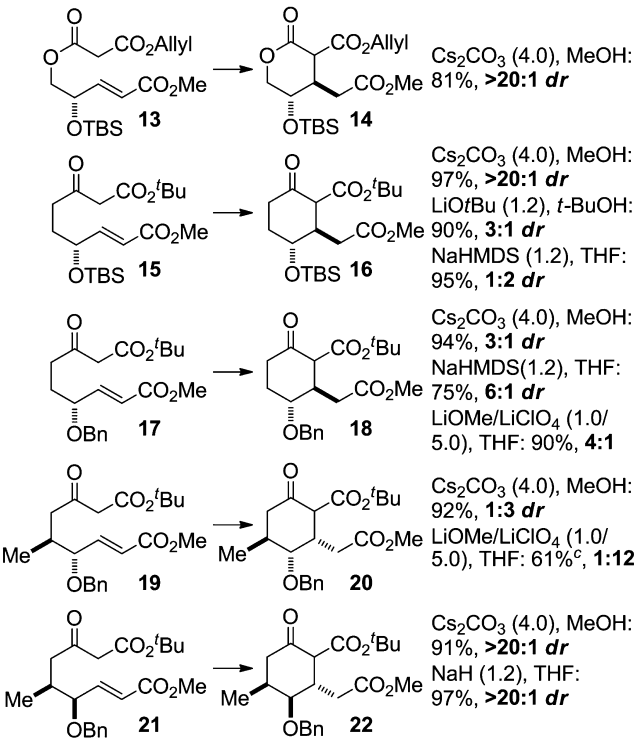
Table 1. Alkyl Substituents[a] (*E*-Configured Acceptors)[19]



[a]Conditions: base (equiv), −78 °C to rt, 18 h; dr refers to anti/syn ratio.

Table 2. Alkoxy Substituents[a] (*E*-Configured Acceptors)



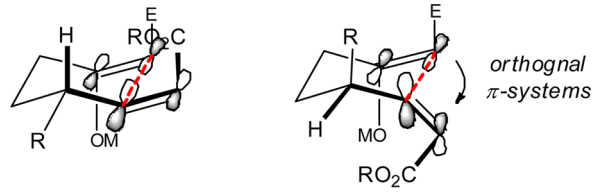
[a]Conditions: base (equiv), −78 °C to rt, 18 h; dr refers to anti/syn. [b]Remainder was recovered starting material.

In accordance with this hypothesis, Table 1 demonstrates that alkyl-substituted substrates can lead to either diastereomer, depending on the conditions.[14] These findings echo the results of our previous studies[12] and those of Keck[15] and Gung.[16,17] In contrast, β,γ-anti products predominate for alkoxy-substituted substrates (Table 2). Changing the enolization conditions generally allowed us to perturb the level, but not overall sense, of diastereoselection. Although one provocative explanation for this marked β,γ-anti preference might be that it is stereoelectronically favorable to position the forming bond anti to the C−O σ^* orbital, in analogy to the polar Felkin−Anh model for carbonyl additions,[18] we will suggest below that more mundane steric and electrostatic factors are responsible.

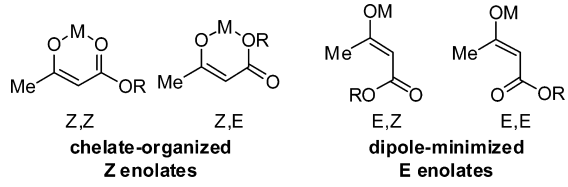
We hypothesized that an alternative means of enforcing β,γ-anti selectivity might be to use the 1,3-allylic strain induced by a combination of *Z*-acceptors and γ-substituents. In such arrangements, there are two conformations that place the acceptor and its allylic hydrogen in the same plane (Scheme 2). For a reaction to occur, there must be sufficient orbital overlap between the π-system of the enolate and the π^*-system of the acceptor. Therefore, only **23**‡ should be reactive and β,γ-anti selectivity should be observed.

An examination of Table 3 shows that *Z*-acceptors are indeed uniformly β,γ-anti selective, regardless of γ-alkyl or γ-alkoxy substitution. Similar to the results of Table 2, changing the enolization conditions sometimes decreased the magnitude of selectivity, but never overturned it completely. Notably, the use of β,β-disubstituted acceptors allowed the formation of quaternary stereocenters. However, this required the increased electrophilicity of imide acceptors.[20]

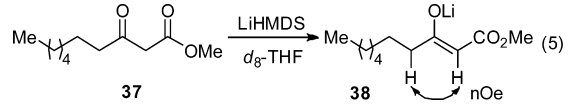
Scheme 2. Minimization of 1,3-Allylic Strain for *Z*-Acceptors



Although keto−enol tautomerism ultimately erases any memory of the reactive configuration at the enolate, it is clear that enolate geometry plays an important role in determining stereoselectivity. In general, β-ketoester enolates can exist as chelated (*Z*) or dipole-minimized (*E*) forms:[21−25]



Variable-temperature ^{1}H and ^{13}C NMR studies show that when methyl 3-oxodecanoate (**37**) is treated with 1 equiv of LiHMDS in THF-d_8, it is converted to *Z* enolate **38**:



(The *Z,Z* and *Z,E* forms were not distinguishable.) Similar behavior was observed in THF-d_8 with LiOMe (with and without

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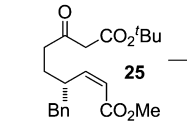
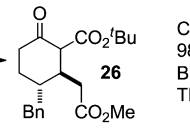
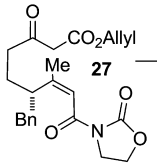
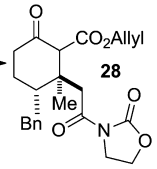
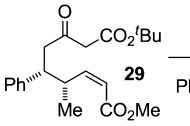
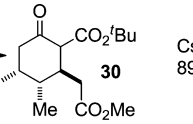
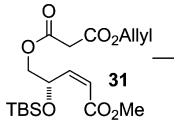
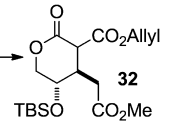
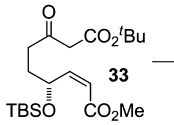
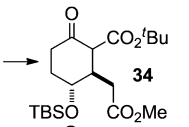
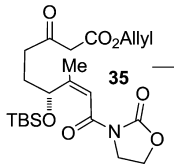
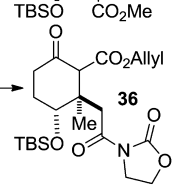
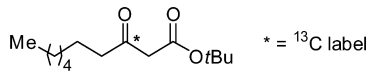
Table 3. Alkyl and Alkoxy Substituents (*Z* Acceptors)

substrate	product	conditions[a]
		Cs_2CO_3 (4.0), MeOH: 98%, **>20:1 *dr*** $Bu_4NOH{\cdot}30H_2O$ (1.2), THF: 84%, **>20:1 *dr***
		Cs_2CO_3 (1.1), THF: 85%, **>20:1 *dr***
		Cs_2CO_3 (1.1), MeOH: 89%, **>20:1 *dr***
		Cs_2CO_3 (1.1), DMF: 85%, **>20:1 *dr***
		Cs_2CO_3 (4.0), MeOH: 91%, **>20:1 *dr*** NaHMDS (1.2), THF: 71%, **4:1 dr**
		Cs_2CO_3 (1.05), THF: 89%, **>20:1 *dr***

[a]Base (equiv); −78 °C to rt; *β*,*γ*-anti/*β*,*γ*-syn.

$LiClO_4$), NaHMDS, and NaH. No evidence of the E enolate was found and the lineshapes were unchanged with temperature. In MeOH-d_4, deuterium exchange with solvent complicates NMR observations.[26] Instead, the enolates of [3-^{13}C]-*tert*-butyl 3-oxodecanoate (**39**) were directly observed in standard protio-solvents via ^{13}C NMR with inverse-gated decoupling.



39

Upon the addition of 1 equiv of LiHMDS to **39** in THF, the carbonyl resonance shifted from 201.6 ppm to 188.6 ppm, indicating enolization. Similar experiments in methanol with NaHMDS, KHMDS, and Cs_2CO_3 revealed two singlets at ca. 190 ppm (*Z* isomer) and 182 ppm (*E* isomer) in ratios of 5:1, 1:1, 1:2, and 1:3, respectively. These assignments were confirmed by the addition of one equivalent of LiOMe to the cesium enolate; the ratio was reversed from 1:3 to 3:1.

The possibility that these enolate isomers are in rapid equilibrium was confirmed by selective inversion experiments.[27−29] We made the unusual choice of performing the experiments in the ^{13}C domain not only to avoid the interference of water, but also to take advantage of the relatively long T_1 relaxation times of carbonyl carbons. An equimolar mixture of **39** and $Bu_4NOH{\cdot}30H_2O$ gave a ca. 2:1 ratio of isomers (no assignments made). When one of the resulting singlets was selectively inverted, the magnetization of its counterpart experienced a transient decrease (Figure 1). This observation is a classic hallmark of a chemical exchange process.

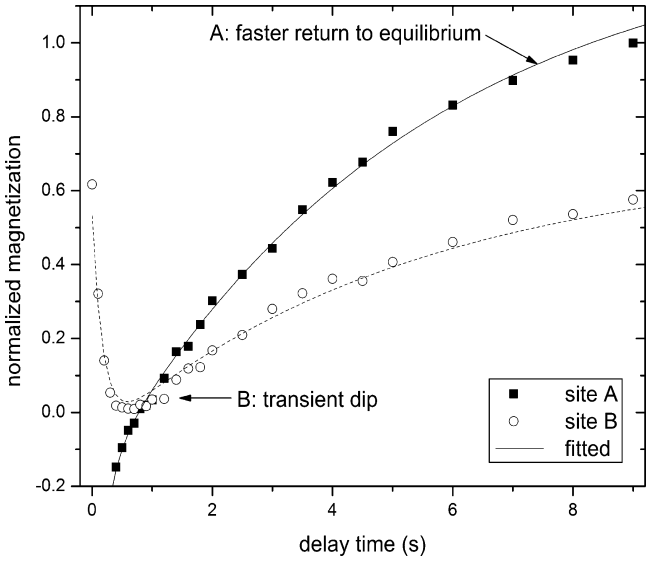


Figure 1. Selective inversion data for the tetrabutylammonium enolate of **39** (0.12 M in THF at 318 K). The unequal asymptotes reflect the ca. 2:1 equilibrium ratio of enolate isomers.

Fitting the data to a two-site model and subsequent Eyring analysis places the activation enthalpy of enolate isomerization at ca. 14 kcal/mol (see the Supporting Information). This is significantly lower than the >20 kcal/mol barriers that would be expected for these Michael reactions, which are unimolecular reactions with half-lives of hours. Similar experiments with Cs_2CO_3/MeOH gave broad signals also indicative of rapid enolate geometry equilibration.

This behavior contrasts with that of more conventional ester enolates, which do not easily isomerize. This can be readily explained. In ethereal solutions, enolate isomerization must occur through a high barrier C=C *π*-bond rotation process. In hydroxylic solutions, the acidity of the solvent allows small amounts of *β*-ketoester to exist and undergo facile C−C *σ*-bond rotation. Additionally, these Michael reactions are irreversible: re-exposure of diastereomeric mixtures of Michael products to the reaction conditions gave no change in the product ratio. Together, these observations suggest that the sensitivity of the diastereoselectivity to the enolization conditions results from differentially selective *E* and *Z* enolate pathways that can compete via a Curtin−Hammett scenario in hydroxylic solvents.

How is stereochemical information relayed in these reactions? Although modeling the subtle effects of ion-pairing with metals like cesium is still challenging,[30] we have previously shown that the stereochemical outcomes of Michael additions can be successfully predicted by treating lithium enolates as explicitly ether-solvated contact ion pairs.[31] Such an analysis of simplified system **40** at M05-2X/6-311+g(d,p)//M05-2X/6-31g(d) reproduces the irreversibility noted above (Scheme 3): the forward free energy barrier is somewhat underestimated (18.6 kcal/mol) but significantly smaller than the reverse barrier (33.8 kcal/mol).[32] This difference largely reflects the favorability of replacing a less stable C=C bond with a more stable C−C bond. While this is initially countered by the conversion of a more stable *β*-ketoester enolate (**40**, pK_a in DMSO ∼ 14) into a less stable ester enolate (**45**, pK_a ∼ 30), eventual proton transfer to form a new *β*-ketoester enolate (**46**) compensates for this.

A search for transition structures revealed that chair conformations (**41**‡ and **42**‡) are considerably favored over

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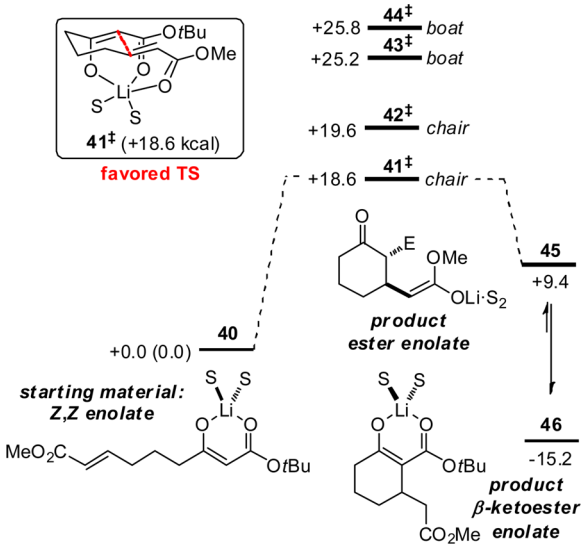
Scheme 3. Energetics of Intramolecular Michael Additions



boat ones (**43**‡ and **44**‡). Interestingly, the acceptor prefers to occupy an axial orientation (by 1 kcal/mol). Although this may be somewhat surprising, the disfavored equatorial orientation incurs a steric interaction between the enolate and the acceptor (Figure 2). This is reflected in the elongated distance for the

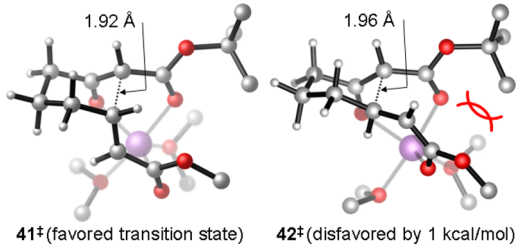
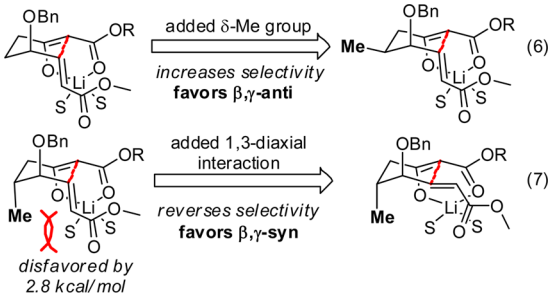


Figure 2. Preferred acceptor orientation.

forming C−C bond (1.96 Å for **42**‡ vs 1.92 Å for **41**‡). In turn, this appears to decrease the favorability of lithium ion transfer; for example, the distance from the lithium ion to the acceptor carbonyl oxygen increases from 1.98 Å in **41**‡ to 2.15 Å for **42**‡).

For a truncated version of γ-silyloxy-substituted substrate **15**, the lowest energy chair transition state also orients its substituents in a trans-1,2-diaxial fashion (**47**‡, Scheme 4). In this case, **47**‡ avoids both an analogous enolate−acceptor interaction and a new acceptor−substituent interaction (Figure 3). The minimization of the acceptor−substituent interaction accounts for the increase in selectivity with protecting group size

Scheme 4. Influence of the δ-Stereocenter



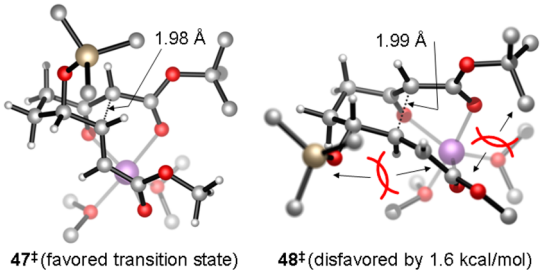


Figure 3. Diaxial preference in transition states.

(**15** vs **17**). Additionally, the axial orientation of the γ-silyloxy substituent minimizes its dipole interactions with the enolate and acceptor carbonyl groups.

This 1,2-diaxial model also accounts for the increase in β,γ-anti selectivity (**17** vs **21**) observed when an equatorial δ-methyl group is added (Scheme 4, eq 6).[33] Reinforcing stereocontrol results from the unfavorable 1,3-interactions that would be incurred by placing the δ-methyl group in a pseudoaxial position. In contrast, adding an axial δ-methyl completely reverses the selectivity to β,γ-syn (**17** vs **19**). The normally favored diaxial geometry now suffers from a destabilizing 1,3-interaction (eq 7). As a consequence, the substituents adopt a more stable 1,2-diequatorial conformation, while the acceptor remains axial to facilitate lithium ion transfer.

CONCLUSIONS

Intramolecular Michael reactions are kinetically controlled transformations whose product distributions reflect a complex interplay between the intrinsic stereochemical preferences of the substituents present and the enolate geometry. If the lithium enolates are treated as geometrically pure contact ion pairs, the predicted dipole-minimized chair transition states are in qualitative agreement with experiment. This analysis should provide a basis for greater sophistication in the design of future Michael additions.

EXPERIMENTAL SECTION

Computations. All structures were optimized at M05-2X/6-31g(d) in the gas phase using the ultrafine grid. Single point energies were obtained at M05-2X/6-311+g(d,p) and the free energy corrections from M05-2X/6-31g(d) were added to obtain the final energies. Frequency analyses were performed to verify that each structure actually corresponds to a local minimum or first-order saddle point. Computations were performed using Gaussian 09, Revision A.02.

Selective Inversion Analysis. Selective 180° inversions were achieved with shaped IBURP2 pulses and used in a standard selective-inversion recovery experiment as described by Bain and co-workers.[27] A delay of 60 s was used in between delay time increments.

General Experimental Details. All reactions were carried out under an atmosphere of nitrogen in flame-dried or oven-dried glassware with magnetic stirring. Flash chromatography was carried out with 230−400 mesh silica gel. Analytical thin-layer chromatography was performed with 0.25 mm silica gel plates. Visualization was accomplished with UV light, aqueous ceric ammonium molybdate (CAM) solution, anisaldehyde, potassium permanganate, or potassium iodoplatinate (PIP) staining followed by heating. Melting points are uncorrected. Optical rotations were measured on a digital polarimeter with a sodium lamp. Infrared spectra were recorded on an FT-IR spectrometer. NMR spectra are reported in ppm using residual solvent as the internal standard. High-resolution mass spectrometry data were obtained generally obtained via electrospray ionizartion with a quadrupole detector. Semipreparative HPLC was performed using an a 21.2 mm normal

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phase silica column. Unless otherwise noted, the synthesized compounds were judged to be >95% pure.

Tetrahydrofuran, dichloromethane, ethyl ether, and toluene were purified by filtration through a column of activated alumina under an argon atmosphere. Triethylamine, diisopropylethylamine, and diisopropylamine were distilled from calcium hydride immediately before use. Benzyl bromide and allyl bromide were purified by passage through a column of basic alumina before use.

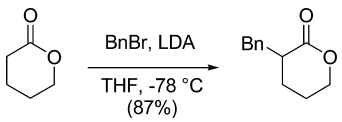
General Procedure for Michael Additions. A solution of substrate (ca. 20 mg) in 1 mL of solvent was prepared under an argon atmosphere and chilled to −78 °C. A solution of base in 1 mL of solvent was prepared at room temperature and added dropwise. The clear and colorless or slightly yellow solution generally became vivid yellow in color. The reaction was allowed to proceed at −78 °C for 1 h and allowed to warm to room temperature slowly over several hours. After 18 h, the mixture was diluted with 30 mL of dichloromethane and extracted with 30 mL of 0.1 M HCl. The layers were separated and the aqueous layer was back-extracted four times with 10 mL portions of dichloromethane. The combined organic layers were washed with 10 mL of brine, dried over sodium sulfate, filtered, and concentrated. The crude Michael adduct was purified by silica gel chromatography to yield a yellow oil. Typically, the ^{1}H NMR spectra of these adducts were very complex due to the presence of keto−enol tautomers and diastereomers. As a result, only characterization data for their decarboxylated counterparts are given (see the Supporting Information; diastereomer ratios were assessed on the crude material). These cyclohexanones were typically isolated as yellow oils and were further purified by semipreparative HPLC to separate any diastereomers for detailed stereochemical analysis.

Decarboxylation Procedures. *A. Krapcho Method.* A solution of Michael adduct (10 mg) in 1 mL of DMSO was prepared in a sealed tube. Lithium chloride (approximately 10 mg) and water (approximately 0.1 mL) were added. The mixture was heated at 135 °C for 3.5 h.

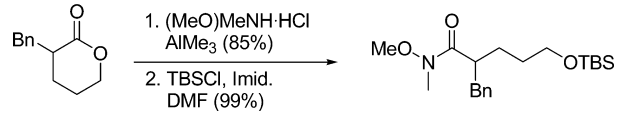
B. TFA Method. A solution of *tert*-butyl β-ketoester (10 mg) was dissolved in 0.8 mL of $CDCl_3$ at room temperature. Trifluoroacetic acid (0.2 mL) was added. The yellow solution was allowed to stand at room temperature for 2 h. The solvent was removed by passing a gentle stream of nitrogen over the solution. The oil was then thoroughly evacuated under high vacuum for 5 min. The oil was suspended in 1 mL of $CDCl_3$ and heated at 80 °C for 1 h. The ratio of diastereomers was assessed by ^{1}H NMR analysis. The crude cyclohexanone was purified by silica gel chromatography.

C. Pd Method. A solution of allyl β-ketoester (10 mg) was dissolved in 5 mL of CH_2Cl_2 at room temperature under an argon atmosphere. Morpholine (20 equivalents) was added, followed by palladium tetrakis(triphenylphosphine) (10 mol %). The yellow solution was allowed to stand at room temperature for 1 h. The mixture was diluted with 50 mL of 3:1 hexanes/ethyl acetate and 50 mL of 0.1 M HCl. The layers were separated, and the aqueous layer was back-extracted four times with 10 mL portions of 3:1 hexanes/ethyl acetate. The combined organic layers were washed with 50 mL of water and 10 mL of brine, dried over sodium sulfate, and concentrated. The crude cyclohexanone was purified by silica gel chromatography. The ratio of diastereomers was assessed by ^{1}H NMR analysis.

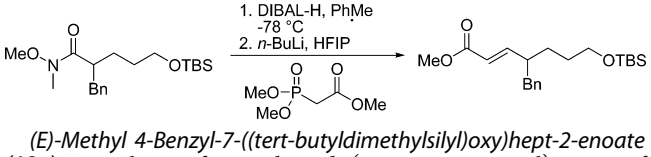
Substrate Preparation and Compound Characterization Data.



*3-Benzyltetrahydropyran-2-one (**S-017**).* To a solution of diisopropylamine (8.7 mL, 62.1 mmol) in 50 mL of THF at −10 °C was added freshly titrated *n*-butyllithium (22.2 mL of a 2.68 M solution in hexane, 59.4 mmol). The solution was stirred for 30 min and cooled to −78 °C. A solution of recently distilled δ-valerolactone (5.0 mL, 54 mmol) in 50 mL of THF was added dropwise over 1.5 h, followed by a solution of benzyl bromide (12.8 mL in 25 mL THF, 108 mmol). The benzyl bromide was filtered through a neutral alumina plug before use. The solution was stirred at −78 °C for 3 h. The solution was warmed to −40 °C over 1 h while stirring. The reaction was quenched with 5 mL of 2-propanol and 25 mL of saturated aqueous ammonium chloride. The mixture was extracted with 100 mL of diethyl ether three times, diluted with hexanes, dried over sodium sulfate, and concentrated to yield a brown oil. The oil was purified by silica gel chromatography (5, 10% 2-propanol/hexanes) to afford the desired alkylated lactone as a clear yellow oil (8.98 g, 87%): TLC R_f = 0.60 (20% 2-propanol/hexanes, $KMnO_4$ stain); IR ($CHCl_3$ film) 3028, 2950, 2874, 1956, 1747, 1604, 1496, 1454, 1392, 1344, 1248, 1150, 1072, 977, 747, 702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.75−1.83 (1 H, m), 1.84−1.95 (2 H, m), 2.66−2.78 (2 H, m), 3.36 (2 H, dd, J = 18.56, 8.79 Hz), 4.21−4.33 (2 H, m), 7.18−7.24 (3 H, m), 7.25−7.32 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 24.2, 37.3, 41.6, 68.6, 126.6, 129.3, 139.1, 174.2; HRMS (CI) calcd for $C_{12}H_{18}O_2N$ [M + NH_4]$^+$ 208.1338, found 208.1328.



*2-Benzyl-5-(tert-butyldimethylsilanyloxy)pentanoic Acid Methoxymethylamide (**S-018**).* To a solution of *N,O*-dimethylhydroxylamine hydrochloride (dried azeotropically with benzene immediately prior to use) (3.07 g, 31.5 mmol) in dichloromethane (17.5 mL, to make a 1.8 M solution) at 0 °C was added trimethylaluminum (3.02 mL, 31.5 mmol) dropwise over 5 min. The solution was stirred for 45 min. Valerolactone (2.00 g, 10.5 mmol in 20 mL of dichloromethane) was added dropwise over 5 min. The solution was stirred for 3 h. The reaction was quenched with a solution of Rochelle's salt (3.60 g, 12.6 mmol) in water (5.0 mL, 280 mmol). The mixture was filtered over a Celite plug and rinsed with 10 mL of dichloromethane. The mixture was concentrated to yield the desired Weinreb amide as a clear oil (2.61 g, 99%). The oil was dissolved in 20 mL of DMF, and *tert*-butyldimethylsilyl chloride (1.58 g, 10.5 mmol) and imidazole (1.70 g, 25.0 mmol) were added. The mixture was stirred overnight. The mixture was diluted with 100 mL 3:1 hexanes/ethyl acetate and 100 mL of 1 M HCl. The layers were separated, and the aqueous layer was washed three times with 20 mL portions of 3:1 hexanes/ethyl acetate. The combined organic layers were washed with 50 mL of water and 50 mL of brine, dried over sodium sulfate, concentrated, and purified by silica gel chromatography (3, 5, 7% 2-propanol/hexanes) to yield the desired protected alcohol as a clear oil (3.26 g, 85%): TLC R_f = 0.30 (30% 2-propanol/hexanes, $KMnO_4$ stain); IR ($CHCl_3$ film) 2930, 2857, 1662, 1468, 1387, 1255, 1175, 1101, 992, 836, 776, 700, 668 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.02 (6 H, s), 0.83−0.94 (9 H, s), 1.39−1.75 (5 H, m), 2.67 (1 H, dd, J = 12.9, 5.6 Hz), 2.97 (1 H, dd, J = 13.2, 8.8 Hz), 3.10 (3 H, s), 3.30 (3 H, s), 3.48−3.66 (2 H, m), 7.07−7.33 (5 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3, 18.3, 25.9, 28.8, 30.6, 38.9, 43.1, 61.1, 62.9, 126.1, 128.2, 129.1, 140.2; HRMS (ESI) calcd for $C_{20}H_{36}NO_3Si$ [M + H]$^+$ 366.2464, found 366.2459.



*(E)-Methyl 4-Benzyl-7-((tert-butyldimethylsilyl)oxy)hept-2-enoate (**18a**).* To a solution of Weinreb amide (210 mg, 0.574 mmol) in 5 mL of toluene at −78 °C was added a solution of DIBAL-H (1.72 mL, 1.72 mmol, 1.0 M in toluene) dropwise. The solution was stirred for 4 h at −78 °C and quenched by the addition of ethyl acetate followed by water. The solution was diluted with 100 mL of dichloromethane and 100 mL of 1 M HCl. The emulsion was stirred vigorously for 20 min. The layers were separated, and the aqueous layer was washed three times with 20 mL of dichloromethane. The combined organic layers were washed with 50 mL of brine and concentrated to yield a clear oil. The oil was purified by silica gel chromatography (3% EtOAc/hexanes) to yield the desired alcohol as a clear oil (114 mg, 70%). *n*-BuLi in hexanes (0.15 mL, 0.42 mmol, 2.89 M) and trimethyl phosphonoacetate (70 uL, 0.43 mmol) were added in sequence to a solution of 1,1,1,3,3,3-hexafluoro-2-propanol (47 uL, 0.44 mmol) in 3 mL of DME at −15 °C. Aldehyde (100 mg, 0.36 mmol) was added, and the reaction was stirred for 4 h. The reaction was allowed to warm to room temperature and was stirred

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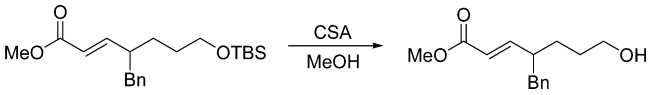
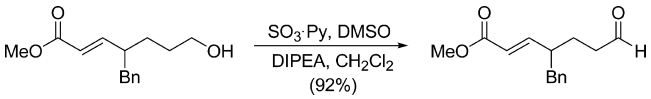
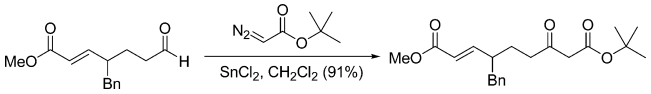
for an additional 20 h. The mixture was diluted with 50 mL of dichloromethane and quenched with 10 mL of saturated aqueous ammonium chloride and 50 mL of water. The aqueous layer was separated and extracted three times with dichloromethane. The combined organic layers were washed with sodium sulfate and concentrated to yield a white suspension. The mixture was purified by silica gel chromatography (5% EtOAc/hexanes) to yield the desired protected olefin as a clear oil (99 mg, 70%, 34:1 *E*:*Z*).



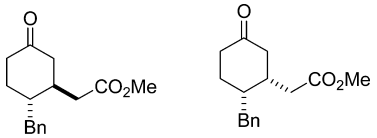
*(E)-Methyl 4-Benzyl-7-hydroxyhept-2-enoate (**S-019**).* The olefin (99 mg) was dissolved in 5 mL of methanol, and 10-camphorsulfonic acid (63 mg, 0.27 mmol) was added. The solution was stirred at room temperature for 30 min, after which TLC analysis indicated full consumption of starting material. Ten milliliters of sodium bicarbonate solution was added, and the bulk of the methanol was removed by rotary evaporation. The mixture was resuspended in 50 mL of dichloromethane and 50 mL of sodium bicarbonate. The layers were separated, and the aqueous layer was back-extracted three times with 10 mL portions of dichloromethane. The combined organic layers were washed with 20 mL of brine, dried over sodium sulfate, concentrated, and purified by silica gel chromatography (30, 60% EtOAc/hexanes) to yield the desired olefin−alcohol as a clear oil (54 mg, 73%): TLC R_f 0.3 (50% EtOAc/hexanes); IR ($CHCl_3$ film) 3422 (br), 3026, 2931, 2358, 1718, 1654, 1496, 1436, 1271, 1210, 1157, 1053, 983, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 1.36−1.44 (1H, m), 1.44−1.53 (1H, m), 1.54−1.65 (2H, m), 2.44−2.54 (1H, m), 2.65−2.76 (2H, m), 3.55−3.64 (2H, m), 3.71 (3H, s), 5.70 (1H, dd, J = 15.6, 1.0 Hz), 6.80 (1H, dd, J = 15.6, 9.3 Hz), 7.12 (2H, d, J = 6.8 Hz), 7.19 (1H, t, J = 7.3 Hz), 7.27 (2H, dd, J = 10.3, 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, and via spectrally edited gHSQC, 500 MHz in $CDCl_3$, 4 transients per increment, 2 × 128 increments with linear prediction to 1024, ^1H spectral window of 4015 Hz, ^{13}C spectral window of 21384 Hz) δ 167.1 (C), 152.5 (6.81, CH), 139.5 (C), 129.3 (7.28, CH), 128.6 (7.21, CH), 126.4 (7.12, CH), 121.6 (5.70, CH), 62.9 (3.59, CH_2), 51.7 (3.71, CH_3), 44.5 (2.49, CH), 41.3 (2.71, CH_2), 30.6 (1.48, 1.58, CH_2), 30.1 (1.41, 1.58, CH_2); HRMS (ESI) calcd for $C_{15}H_{21}O_3$ $[M + H]^+$ 249.1491, found 249.1481.



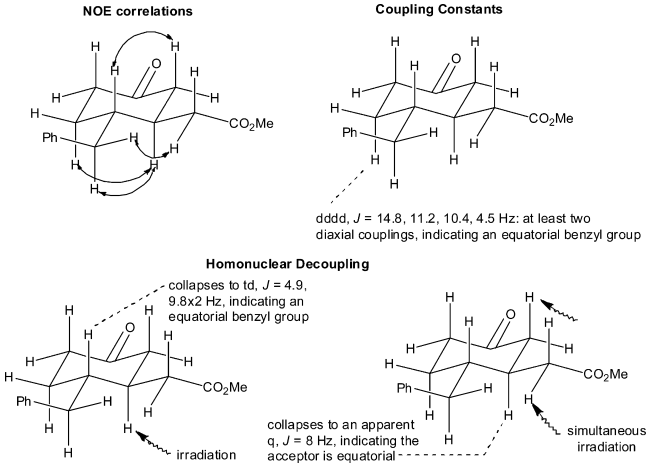
*4-Benzyl-7-oxo-hept-2-enoic Acid Methyl Ester (**S-020**).* To a stirring solution of alcohol (36 mg, 0.145 mmol) in 4 mL of CH_2Cl_2 at 0 °C was added freshly distilled *N*,*N*-diisopropylethylamine (0.18 mL, 1.01 mmol) dropwise via syringe. After 10 min, dimethyl sulfoxide (0.10 mL, 1.45 mmol) was added to the reaction mixture via syringe and the solution was allowed to stir for an additional 10 min. Sulfur trioxide pyridine complex (0.122 g, 11.7 mmol) was then added in one portion. The reaction was allowed to proceed for 4 h at 0 °C, after which TLC analysis indicated complete consumption of starting material. The reaction was quenched by transfer into an 125 mL Erlenmeyer flask that contained a stirring saturated aqueous $NaHCO_3$ solution. The aqueous layer was back-extracted three times with 3:1 hexanes/ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, and concentrated. The yellow oil was purified by silica gel chromatography (5% 2-propanol/hexanes) to yield the desired aldehyde as a clear, colorless oil (33 mg, 92%): TLC R_f 0.5 (20% 2-propanol/hexanes, $KMnO_4$ stain); IR ($CHCl_3$ film) 2341, 1722, 1654, 1457, 1435, 1362, 1317, 1273, 1213, 1161, 1031, 986, 857 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.55−1.69 (1H, m), 1.82−1.95 (1H, m), 2.31−2.45 (2H, m), 2.44−2.57 (1H, m), 2.72 (2 H, d, J = 7.0 Hz), 3.71 (3H, s), 5.70 (1H, dd, J = 15.7, 0.7 Hz), 6.74 (1H, dd, J = 15.7, 9.3 Hz), 7.10−7.13 (2H, m), 7.16−7.23 (1H, m), 7.23−7.31 (2H, m), 9.71 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.7, 41.1, 41.5, 43.7, 51.5, 122.0, 126.4, 128.3, 129.1, 138.7, 151.1, 166.6, 201.5; HRMS (CI) calcd for $C_{15}H_{18}O_3$ $[M + H^+]$ 246.1256, found 246.1271.



*(E)-9-tert-Butyl 1-Methyl 4-benzyl-7-oxonon-2-enedioate Ester (**5**).* To a dry vial were added tin(II) chloride (76 mg, 0.4 mmol) and dichloromethane (3 mL). *tert*-Butyl diazoacetate (1.12 mL, 8.12 mmol) was added dropwise to the vial with vigorous stirring. After gas evolution ceased, aldehyde (1.00 g, 4.06 mmol) was added, and the yellow solution was stirred overnight. The solution was diluted with 100 mL of dichloromethane and 100 mL of saturated sodium bicarbonate solution. The layers were separated, and the aqueous layer was back-extracted three times with 10 mL portions of dichloromethane. The combined organic layers were washed with 50 mL of water and 50 mL of brine, dried over sodium sulfate, and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (5% 2-propanol/hexanes). The remaining *tert*-butyl diazoacetate was removed by high vacuum evaporation to yield the desired ketoester as a yellow oil (1.32 g, 91%): TLC R_f 0.65 (20% 2-propanol/hexanes, red, anisaldehyde stain); IR ($CHCl_3$ film) 3429, 2963, 2932, 1720, 1654, 1496, 1456, 1436, 1369, 1317, 1272, 1215, 1160, 985, 851, 749, 701, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.34−1.36 (9 H, s), 1.43−1.56 (1 H, m), 1.71−1.83 (1 H, m), 2.30−2.48 (3 H, m), 2.56−2.67 (2 H, m), 3.18 (2 H, s), 3.60 (3 H, s), 5.59 (1 H, d, J = 16.5 Hz), 6.64 (1 H, dd, J = 15.6, 9.2 Hz), 7.01 (2 H, d, J = 6.9 Hz), 7.09 (1 H, t, J = 7.3 Hz), 7.16 (2 H, t, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.0, 27.9, 40.3, 41.1, 43.5, 50.6, 51.4, 81.9, 121.8, 126.2, 128.3, 128.1, 129.0, 138.8, 151.3, 166.2, 166.5, 202.4; HRMS (ESI) calcd for $C_{21}H_{32}O_5N$ $[M + NH_4]^+$ 378.2280, found 378.2282.



*1,2-trans-(2-Benzyl-5-oxocyclohexyl)acetic acid methyl ester (**S-021-anti**):* TLC R_f 0.30 (30% EtOAc/hexanes, CAM stain); HRMS (ESI) calcd for $C_{16}H_{21}O_3$ $[M + H]^+$ 261.1491, found 261.1486. The compound was characterized by extensive NMR analysis (Table 4). While data are given in $CDCl_3$, good separation of peaks was observed in 1:1 $C_6D_6/CDCl_3$.



*1,2-cis-(2-Benzyl-5-oxocyclohexyl)acetic acid methyl ester (**S-021-syn**):* TLC R_f = 0.30 (30% EtOAc/hexanes, CAM stain); ^1H NMR (500 MHz, $CDCl_3$) δ 1.63 (1 H, m, J = 14.1, 8.8 × 2, 5.5), 1.80, 1 H, ddd, J = 13.7, 6.9, 3.8), 2.33 (1 H, m), 2.26 (1 H, m), 2.34 (1 H, m), 2.52 (1 H, m), 2.62 (1 H, m), 2.65 (1 H, m), 2.77 (dd, J = 13.5, 5.5), 3.70 (3 H, s), 7.17 (2 H, m), 7.23 (1 H, m), 7.32 (2 H, m); ^{13}C NMR (125 MHz, $CDCl_3$, obtained by HSQC/HMBC) δ 27.3, 34.6, 36.2, 37.6, 40.1, 51.9, 126.5, 128.8, 129.1, 140.3, 172.0, 211.0; HRMS (ESI) calcd for $C_{16}H_{21}O_3$ $[M + H]^+$ 261.1491, found 261.1500.

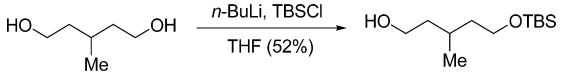


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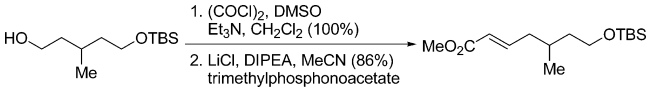
Table 4. NMR Data for S-021-anti (500 MHz, $CDCl_3$)

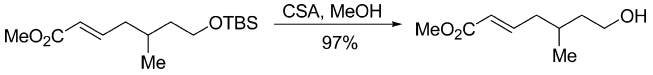
ID	δ ^{1}H	δ ^{13}C	Hs	type	couplings (Hz)
1	7.31	128.7	2	m	
2	7.23	126.5	1	m	
3	7.17	129.3	2	m	
4	3.70	51.9	3	s	
5	3.06	39.0	1	dd	13.6, 4.1
6	2.62	38.8	1	dd	15.3, 4.8
7	2.50	45.9	1	td	8.7, 3.2
8	2.41	38.8	1	m	
9	2.34	39.0	1	m	
10	2.33	40.2	1	m	
11	2.27	45.9	1	m	
12	2.21	40.2	1	m	
13	2.19	39.6	1	m	
14	1.90	29.6	1	m	
15	1.89	41.3	1	m	
16	1.42	29.6	1	dddd	14.8, 11.2, 10.4, 4.5
quaternary carbons: 170.0, 140.3, 211.0					

*3-((tert-Butyldimethylsilyl)oxy)-2-methylpropan-1-ol (**S-022**).* *n*-BuLi (2.74 M in hexane, 36.5 mL, 100 mmol) was added dropwise to a solution of 3-methyl-1,5-pentanediol (12.1 mL, 100 mmol, dried azeotropically with benzene immediately prior to use) in 250 mL of THF at 0 °C. The solution was stirred for 30 min and warmed to room temperature. The solution was stirred for another 1 h, after which *tert*-butyldimethylsilyl chloride (15.1 g, 100 mmol) was added in one portion. The mixture was stirred at room temperature overnight. The cloudy yellow solution was concentrated and resuspended in 200 mL of ether and 200 mL of 1 M HCl. The layers were separated, and the aqueous layer was back-extracted three times with 30 mL portions of ether. The combined organic extracts were washed with 100 mL of water and 100 mL of brine, diluted with 300 mL hexanes, dried over sodium sulfate, and concentrated to give a yellow oil. The oil was purified by dry column vacuum chromatography (0, 1, 2, 3, 4, 5, 10, 15, 20, 25, 30% EtOAc/hexanes) to yield the desired monoprotected diol as a clear oil (12 g, 52%): TLC R_f 0.5 (30% EtOAc/hexanes); IR 3339, 2929, 2859, 1463, 1388, 1362, 1256, 1097, 1006, 898, 836, 775, 663 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (6 H, s), 0.83−0.93 (12 H, m), 1.32−1.47 (2 H, m), 1.52−1.64 (2 H, m), 1.66−1.75 (1 H, m), 1.82 (1 H, br s), 3.55−3.77 (4 H, m); ^{13}C NMR (500 MHz, $CDCl_3$) δ −5.3, 18.2, 19.9, 25.9, 26.4, 39.6, 39.8, 60.9, 61.3; HRMS (ESI) calcd for $[C_{12}H_{29}O_2Si]^+$ 233.1937, found 233.1935.

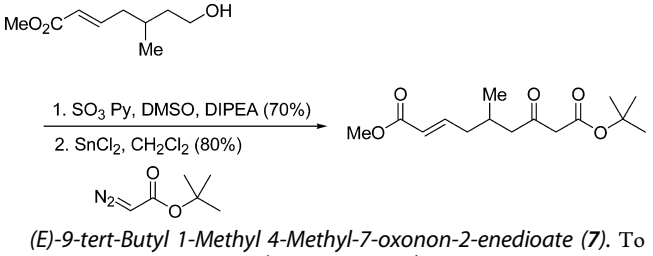


*7-(tert-Butyldimethylsilanyloxy)-5-methylhept-2-enoic Acid Methyl Ester (**S-023**).* To a solution of distilled oxalyl chloride (2.58 mL, 30.1 mmol) in 40 mL of dichloromethane at −78 °C was added DMSO (4.28 mL, 60.2 mmol) dropwise via syringe. After the solution was stirred at −78 °C for 0.5 h, a precooled (−78 °C) solution of alcohol (5.0 g, 21.5 mmol) in 40 mL of dichloromethane was added dropwise via cannula. The resulting solution was stirred for 0.5 h at −78 °C. Freshly distilled triethylamine (13.2 mL, 94.6 mmol) was added over 5 min. The reaction was allowed to proceed at −78 °C for 30 min and then at 0 °C for 1.5 h, after which ^{1}H NMR indicated complete consumption of starting material. The reaction was quenched with 20 mL pH 7 phosphate buffer and stirred for 5 min while warming to room temperature. HCl (1 M, 100 mL) was added, and the layers were separated. The aqueous layer was back-extracted three times with 50 mL portions of dichloromethane. The combined organic extracts were washed with 50 mL of water followed by 50 mL of brine. The solution was dried over sodium sulfate and concentrated to yield the desired aldehyde as a yellow oil (5.1 g, 100%): TLC R_f = 0.7 (30% EtOAc/hexanes, CAM stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03−0.06 (6 H, m), 0.87−0.90 (9 H, m), 0.98 (6 H, d, J = 6.3 Hz), 1.05−1.19 (1 H, m), 1.46 (1 H, td, J = 13.4, 6.3 Hz), 1.52−1.61 (1 H, m, J = 13.2, 13.2, 6.3 Hz), 2.25 (1 H, ddd, J = 18.1, 7.8, 2.9 Hz), 2.42−2.49 (1 H, m, J = 12.0, 8.5, 6.0, 2.0 Hz), 3.59−3.72 (4 H, m), 9.75 (1 H, t, J = 2.2 Hz).

To a suspension of lithium chloride (4.56 g, 108 mmol) in 30 mL of acetonitrile was added trimethyl phosphonoacetate (5.2 mL, 32.3 mmol) followed by diisopropylethylamine (11.2 mL, 64.5 mmol). A solution of aldehyde (4.95 g, 21.5 mmol) in 30 mL of acetonitrile as added, and the solution was heated at 60 C for 2 h. The solution was cooled, and the bulk of the lithium chloride was removed by decanting. The solution was concentrated, and transferred to a separatory funnel with successive washes with diethyl ether and water. 100 mL 1 M HCl was added, and the layers were separated. The aqueous layer was back-extracted three times with 50 mL portion of diethyl ether. The combined organic layers were washed with 50 mL of water and 50 mL of brine, diluted with 100 mL of hexanes, and dried over sodium sulfate. The solution was filtered through a combined Celite (2 × 15 cm) and silica plug (5 × 15 cm). 250 mL of 30% v/v ethyl acetate in hexanes was poured through the plug. The combined solution was concentrated to yield the desired enoate as a yellow oil (5.3 g, 86%): TLC R_f = 0.8 (30% EtOAc/hexanes, $KMnO_4$); IR ($CHCl_3$ film) 2929, 1726, 1657, 1437, 1323, 1272, 1204, 1171, 1093, 1045, 983, 837, 777 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm −0.04−0.08 (6 H, m), 0.78−0.98 (12 H, m), 1.28−1.47 (1 H, m), 1.47−1.69 (1 H, m), 1.72−1.86 (1 H, m), 1.89−2.13 (2 H, m), 2.15−2.28 (1 H, m), 3.55−3.75 (5 H, m), 5.74−5.87 (1 H, m), 6.92 (1 H, ddd, J = 15.4, 7.7, 7.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.4, −3.6, −3.0, 17.9, 18.0, 18.2, 19.4, 25.5, 25.6, 25.8, 29.1, 39.1, 39.3, 39.6, 51.3, 51.3, 60.5, 60.9, 122.0, 122.2, 147.9, 148.3, 166.9; HRMS (ESI) calcd for $[C_{15}H_{31}O_3Si]^+$ 287.2042, found 287.2046.



*7-Hydroxy-5-methyl-hept-2-enoic Acid Methyl Ester (**S-024**).* 10-Camphorsulfonic acid (4.23 g, 18.2 mmol) was added to a room-temperature solution of enoate (5.22 g, 18.2 mmol) in 30 mL of anhydrous methanol. The solution was stirred vigorously for 20 min. Dichloromethane (50 mL) followed by 50 mL of saturated sodium bicarbonate solution was added slowly. The suspension was stirred vigorously for 5 min, after which the bulk of the organic solvent was evaporated. Dichloromethane (100 mL) and 50 mL of sodium bicarbonate solution were added, and the layers were separated. The aqueous layer was back-extracted five times with 20 mL portions of dichloromethane. The combined organic extracts were washed with 50 mL of brine and dried over sodium sulfate. Two thirds of the solvent was evaporated, and roughly 25 g of Celite were added. The suspension was evaporated to dryness and purified by dry column flash chromatography (5 × 15 cm) using a gradient elution: 0, 5, 10, 15, 20, 30, 40% EtOAc/hexanes to yield the desired alcohol as a yellow oil (3.04 g, 97%): TLC R_f = 0.4 (30% EtOAc/hexanes, CAM stain); IR ($CHCl_3$ film) 3436, 2929, 1727, 1656, 1437, 1324, 1274, 1203, 1168, 1046, 984, 851, 720 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.88 (3 H, d, J = 6.4 Hz), 1.36 (1 H, td, J = 14.0, 6.4 Hz), 1.56 (1 H, td, J = 13.2, 7.1 Hz), 1.76 (1 H, app td, J = 13.3, 6.9 Hz), 2.00−2.07 (1 H, m, J = 15.1, 7.3, 7.3, 1.4 Hz), 2.14−2.23 (1 H, m, J = 14.2, 7.2, 5.8, 1.6 Hz), 2.28 (1 H, br s), 3.53−3.70 (5 H, m), 5.78 (1 H, d, J = 15.6 Hz), 6.89 (1 H, ddd, J = 15.5, 7.7, 7.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3, 29.0, 39.1, 39.5, 51.2, 60.3, 122.0, 148.0, 166.9; HRMS (ESI) calcd for $[C_9H_{17}O_3]^+$ 173.1177, found 173.1171.



*(E)-9-tert-Butyl 1-Methyl 4-Methyl-7-oxonon-2-enedioate (**7**).* To a stirring solution of alcohol (1.72 g, 10 mmol) in 50 mL of CH_2Cl_2 at 0 °C was added freshly distilled *N,N*-diisopropylethylamine (12.2 mL, 70 mmol) followed by dimethyl sulfoxide (7.1 mL, 100 mmol). Sulfur

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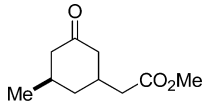
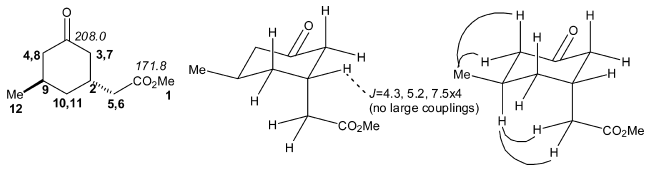
trioxide pyridine complex (8.41 g, 40 mmol) was then added in one portion. The reaction was allowed to proceed for 3 h at 0 °C, after which time TLC indicated consumption of starting material. A 100 mL saturated sodium bicarbonate solution was added, and the solution was stirred vigorously. Dichloromethane (50 mL) was added, and the layers were separated. The aqueous layer was washed three times with 20 mL portions of dichloromethane. The combined organic extracts were washed with 50 mL of 1 M HCl and 50 mL of brine. The organic extract was dried over sodium sulfate and purified by flash chromatography (10, 20, 30% EtOAc/hexanes) to yield the desired aldehyde as a clear oil (1.27 g, 75%): TLC R_f = 0.7 (30% EtOAc/hexanes, CAM stain); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (3 H, d, J = 5.5 Hz), 2.09−2.52 (5 H, m), 3.73 (3 H, s), 5.85 (1 H, d, J = 15.7 Hz), 6.91 (1 H, ddd, J = 15.2, 7.5, 7.3 Hz), 9.76 (1 H, s). To a dry vial were added tin(II) chloride (80 mg, 0.80 mmol) and dichloromethane (5 mL). *tert*-Butyl diazoacetate (2.06 mL, 14.9 mmol) was added dropwise to the vial with vigorous stirring. After gas evolution ceased, aldehyde (1.27 g, 7.46 mmol) was added and the yellow solution was stirred overnight. The solution was diluted with 100 mL of dichloromethane and 100 mL of saturated sodium bicarbonate solution. The layers were separated, and the aqueous layer was back-extracted three times with 10 mL portions of dichloromethane. The combined organic layers were washed with 50 mL of water and 50 mL of brine, dried over sodium sulfate, and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (5% 2-propanol/hexanes). The remaining *tert*-butyl diazoacetate was removed by high vacuum evaporation to yield the desired ketoester as a yellow oil (1.71 g, 80%): TLC R_f = 0.40 (30% EtOAc/hexanes, CAM stain); IR ($CHCl_3$ film) 2957, 1726, 1657, 1437, 1369, 1323, 1273, 1154, 1042, 985, 844, 720 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45−1.51 (12 H, m), 2.07−2.16 (1 H, m), 2.18−2.29 (2 H, m), 2.37−2.44 (1 H, app dd, J = 17.1, 7.3 Hz), 2.52 (1 H, app dd, J = 17.1, 5.4 Hz), 3.32 (2 H, s), 3.73 (3 H, s), 5.74−5.92 (1 H, m), 6.82−6.96 (1 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.6, 27.8, 27.9, 28.0, 28.1, 28.2, 38.9, 49.1, 51.0, 51.3, 81.9, 122.7, 146.9, 166.2, 166.6, 202.1; HRMS (ESI) calcd for $[C_{15}H_{28}O_5N]^+$ 302.1967, found 302.1955.



The compound was formed as a mixture of diastereomers. Separation via silica gel chromatography (gradient elution: 10, 20, 30, 50% EtOAc/hexanes) yielded a yellow oil. The mixture was further purified by semipreparative HPLC (Zorbax RX-SIL column, 0.5% 2-propanol/hexanes, 215 nm, 20 mL/min) to yield the 1,3-*cis* (26.2 min) and 1,3-*trans* (34.3 min) adducts.

*1,3-trans-(3-Methyl-5-oxocyclohexyl)acetic acid methyl ester (**S-025-anti**):* TLC R_f = 0.35 (30% EtOAc/hexanes, CAM stain); IR (film) 2938, 2874, 1734, 1713, 1440, 1370, 1323, 1259, 1226, 1164, 1105, 1063, 1014 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{17}O_3$ $[M + H]^+$: 185.1177, found 185.1178; NMR data, see Table 5.



*1,3-cis-(3-Methyl-5-oxocyclohexyl)acetic acid methyl ester (**S-025-syn**):* TLC R_f = 0.35 (30% EtOAc/hexanes, CAM stain); IR ($CHCl_3$ film) 2939, 2848, 1734, 1715, 1652, 1558, 1436, 1235, 1168, 1110, 1021 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 0.38−0.45 (2 H, m), 0.53 (3 H, d, J = 6.3 Hz), 1.20−1.32 (1 H, m), 1.31−1.51 (3 H, m), 1.74−1.91 (3 H, m), 2.13 (1 H, ddd, J = 13.4, 2.0, 1.7 Hz), 2.26 (1 H, dt, J = 13.2, 1.5 Hz), 3.26 (3 H, s); HRMS (ESI) calcd for $C_{10}H_{17}O_3$ $[M + H]^+$ 185.1177, found 185.1185.

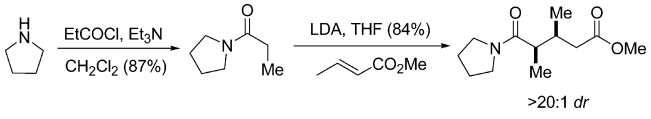
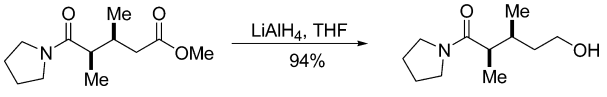


Table 5. NMR Data for S-05-anti (500 MHz, C_6D_6)

ID	δ ^{1}H	δ ^{13}C	Hs	type	couplings (Hz)
1	3.24	51.0	3	s	
2	2.30	31.3	1	dddddd	4.3, 5.2, 7.5 × 4
3	2.08	46.4	1	dddd	0.9, 1.3, 5.2, 13.8
4	1.98	48.5	1	ddd	8.6, 1.6, 0.9
5/6	1.87	38.7	2	dd	1.7, 7.3
7	1.78	46.4	1	dddd	13.8, 7.7, 1.6, 0.8
8	1.63	48.5	1	m	
9	1.62	29.3	1	m	
10/11	1.10	36.6	2	m	
12	0.58	20.8	3	d	6.6
quaternary carbons: 208.0, 171.8					

*3,4-Dimethyl-5-oxo-5-pyrrolidin-1-ylpentanoic Acid Methyl Ester (**S-026**).* Propionyl chloride (20.8 mL, 240 mmol) was added dropwise to a solution of pyrrolidine (20.0 mL, 240 mmol) and triethylamine (83.6 mL, 600 mmol) in 500 mL of dichloromethane at 0 °C. The large amount of evolved HCl gas was carefully purged during the addition with a stream of nitrogen gas. The solution became viscous. The cooling bath was removed, and the less viscous yellow suspension was allowed to stir overnight. The mixture was diluted with 200 mL of dichloromethane and washed with 250 mL of 1 M HCl. The aqueous layer was separated and back-extracted three times with 50 mL portions of dichloromethane. The combined organic layers were washed with 250 mL of 1 M NaOH and 50 mL of brine. The organic extracts were filtered through a combined pad of Celite (5 × 10 cm) and silica (10 × 10 cm). The pad was washed with 150 mL of ethyl acetate. The yellow solution was concentrated to yield *N*-propionoylpyrrolidine as a yellow oil (26.6 g, 87%). This amide was surprisingly unstable, proving unsuitable for the subsequent Michael addition if not prepared immediately before use. Old samples of amide were suitable if purified by the above aqueous workup immediately before use.

The following procedure is adapted from that of Yamaguchi.[34] To a solution of freshly distilled diispropylamine (12.2 mL, 87 mmol) in 250 mL of THF at 0 °C was added *n*-butyllithium (29.3 mL, 78.6 mmol, 2.68 M in hexane) dropwise. The solution was stirred for 30 min and cooled to −78 °C. *N*-Propionylpyrrolidine (10.0 g, 78.6 mmol) was added dropwise, after which the solution turned yellow. The solution was stirred for 30 min. Methyl crotonate (8.34 mL, 78.6 mmol) was added dropwise. The solution became a vivid yellow color. The solution was stirred at −78 °C for 1.5 h, after which ^{1}H NMR analysis indicated complete consumption of starting materials. Methanol (5 mL) was added, and the solution was warmed to room temperature (the addition of 2-propanol causes immediate transesterification). The solution was washed with 300 mL of 1 M HCl. The aqueous layer was back-extracted three times with diethyl ether. The combined organic layers were washed twice with 50 mL portions of 1 M HCl and 200 mL of 1 M NaOH and 100 mL of brine. The combined organic extracts were diluted with 100 mL hexanes and dried over sodium sulfate. The dried extract was filtered through a pad of Celite (5 × 10 cm) and silica (10 × 10 cm). The pad was washed with 200 mL of ethyl acetate. The combined organic extracts were concentrated to yield the desired Michael adduct as a yellow oil (15.02 g, 84%, >20:1 *syn*:*anti*): TLC R_f = 0.4 (20% *i*-PrOH/hexanes, PIP stain); IR ($CHCl_3$ film) 2971, 2877, 1734, 1635, 1435, 1372, 1343, 1313, 1254, 1193, 1089, 1005 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (3 H, d, J = 6.9 Hz), 1.04 (3 H, d, J = 6.9 Hz), 1.80 (2 H, ddd, J = 13.6, 6.8, 6.6 Hz), 1.85−1.95 (2 H, m), 2.13−2.19 (1 H, m, J = 15.1, 7.8 Hz), 2.20−2.27 (1 H, m, J = 7.3 Hz), 2.32−2.40 (1 H, m, J = 14.6, 5.0 Hz), 2.49 (1 H, ddd, J = 14.1, 7.0, 6.9 Hz), 3.34−3.47 (3 H, m), 3.50 (1 H, ddd, J = 9.8, 7.1, 6.9 Hz), 3.58−3.63 (3 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 16.1, 24.2, 26.1, 32.4, 39.1, 41.8, 45.6, 46.4, 51.3, 173.2, 174.1; HRMS (ESI) calcd for $C_{12}H_{22}NO_3$ $[M + H]^+$ 228.1599, found 228.1596.



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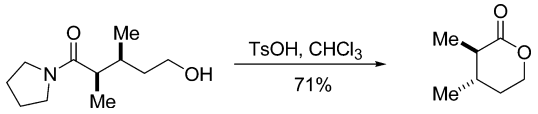
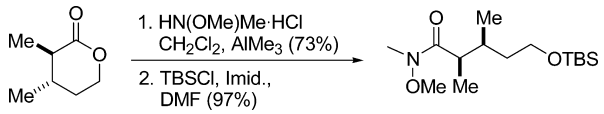
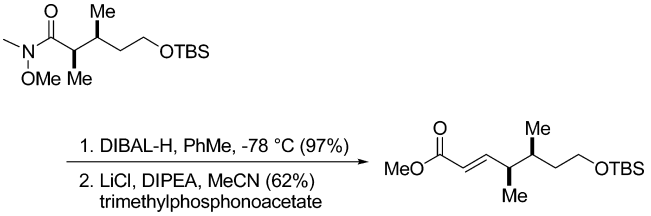
5-Hydroxy-2,3-dimethyl-1-pyrrolidin-1-ylpentan-1-one (***S-027***). Dry THF (225 mL) was carefully and slowly added to lithium aluminum hydride (2.23 g, 58.8 mmol) (caution! gas evolution!). The gray suspension was cooled to −40 °C and stirred for 10 min. A solution of ester (5.34 g, 23.5 mmol) in 10 mL of THF was added slowly to the rapidly stirring suspension of lithium aluminum hydride. The solution was allowed to warm to −30 °C over 45 min. A 1:1 by weight mixture of sodium sulfate decahydrate and Celite was added portionwise until gas evolution ceased. The suspension was warmed to room temperature and filtered. The gray cake was washed with 250 mL 10% 2-propanol/ethyl acetate. The solution was concentrated to yield the desired alcohol as a yellow oil (4.38 g, 94%): TLC R_f = 0.1 (30% *i*-PrOH/hexanes, PIP stain); IR ($CHCl_3$ film) 3407, 2968, 2875, 1620, 1436, 1378, 1341, 1228, 1191, 1060, 916, 854 cm^{-1}; 1H NMR (500 MHz, $CDCl_3$) δ ppm 0.91 (3 H, d, J = 6.9 Hz), 1.06 (3 H, d, J = 6.9 Hz), 1.33−1.44 (1 H, m), 1.45−1.57 (1 H, m), 1.77−1.87 (2 H, m), 1.88−2.04 (3 H, m), 2.23−2.37 (1 H, m), 3.38−3.51 (4 H, m), 3.58 (2 H, t, J = 6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 14.5, 16.7, 24.2, 26.0, 31.7, 38.8, 43.6, 45.6, 45.7, 46.5, 60.5, 175.5; HRMS (ESI) calcd for $[C_{11}H_{22}NO_2]^+$ 200.1650, found 200.1643.



3,4-Dimethyltetrahydropyran-2-one (***S-028***). To a solution of amide (4.1 g, 20.6 mmol) in 25 mL of chloroform was added *p*-toluenesulfonic acid monohydrate (4.32 g, 22.7 mmol). The solution was heated at 40 °C for 1.5 h. The solution was diluted with 50 mL of dichloromethane and extracted with 75 mL of 1 M HCl. The layers were separated, and the aqueous layer was back-extracted three times with 20 mL portions of dichloromethane. The combined organic layers were washed with 75 mL of 1 M NaOH and 50 mL of brine. The solution was filtered through a pad of silica (5 × 5 cm), and the pad was washed with 100 mL of 20% 2-propanol/hexanes. The solution was concentrated to yield the desired valerolactone as a clear oil (1.87 g, 71%): TLC R_f = 0.50 (30% EtOAc/hexanes, $KMnO_4$ stain); IR ($CHCl_3$ film) 2967, 2891, 1732, 1458, 1401, 1315, 1258, 1228, 1193, 1137, 1106, 1044, 992 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 (3 H, d, J = 6.3 Hz), 1.28 (3 H, d, J = 7.3 Hz), 1.53−1.63 (2 H, m), 1.66−1.76 (1 H, m), 1.91−1.99 (2 H, m), 2.08−2.16 (1 H, m), 4.21−4.29 (1 H, m), 4.30−4.40 (1 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.5, 16.7, 24.2, 26.0, 31.7, 38.8, 43.6, 45.6, 45.7, 46.5, 60.5, 175.5; HRMS (ESI) calcd for $[C_7H_{12}O_2$ + MeCN + H$]^+$ 170.1181, found 170.1187.



(2,3-erythro)-5-((tert-Butyldimethylsilyl)oxy)-N-methoxy-N,2,3-trimethylpentanamide (***S-029***). To a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (4.01 g, 41.1 mmol, freshly dried by iterative azeotropic drying with benzene) in dichloromethane (22.8 mL, to make a 1.8 M solution) at 0 °C was added trimethylaluminum (3.94 mL, 41.1 mmol) dropwise over 15 min under vigorous purging with argon. The solution was stirred for 1 h. A solution of valerolactone (1.76 g, 13.7 mmol) in 25 mL of dichloromethane was added dropwise over 5 min. The solution was stirred for 3 h. The reaction was carefully quenched dropwise with a solution of Rochelle's salt (4.64 g, 16.4 mmol) in water (6.86 mL, 381 mmol). The evolved methane was carefully removed during quenching with a continuous stream of argon. The mixture was filtered over a Celite plug (2 × 10 cm) and rinsed with 50 mL of dichloromethane. The mixture was concentrated to yield the desired alcohol as a yellow oil (1.89 g, 73%): TLC R_f 0.1 (30% EtOAc/hexanes, PIP stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (3 H, t, J = 6.1 Hz), 1.08 (3 H, d, J = 6.8 Hz), 1.43 (1 H, td, J = 14.2, 6.3 Hz), 1.53 (1 H, td, J = 12.9, 6.8 Hz), 1.58−1.64 (1 H, m), 1.72 (1 H, s), 1.81−1.88 (1 H, m), 1.89−2.01 (1 H, m), 2.70 (1 H, s), 3.18 (3 H, s), 3.46 (1 H, td, J = 6.6, 2.9 Hz), 3.58−3.66 (2 H, m), 3.66−3.70 (3 H, m). To a solution of alcohol (1.8 g, 9.51 mmol) in 10 mL of DMF were added imidazole (1.63 g, 24 mmol) and *tert*-butyl-dimethylsilyl chloride (1.43 g, 9.51 mmol). The reaction was stirred overnight. The mixture was diluted with 100 mL of 3:1 hexanes/EtOAc and 100 mL of 1 M HCl. The layers were separated, and the aqueous layer was back-extracted three times with 20 mL portions of 3:1 hexanes/EtOAc. The combined organic layers were washed with 100 mL of water and 50 mL of brine, dried over sodium sulfate, and concentrated to yield the desired silyl ether as a clear oil (2.78 g, 97%): TLC R_f = 0.4 (30% EtOAc/hexanes, PIP stain); IR ($CHCl_3$ film) 2932, 2858, 1668, 1463, 1385, 1256, 1095, 996, 901, 836, 776, 662; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03 (6 H, s), 0.82−0.94 (12 H, m), 1.04 (3 H, t, J = 6.6 Hz), 1.07−1.13 (1 H, m), 1.30−1.41 (1 H, m), 1.59 (1 H, ddd, J = 20.6, 7.6, 4.3 Hz), 1.82−1.98 (1 H, m), 2.70−2.83 (1 H, m), 3.17 (3 H, s), 3.57−3.69 (2 H, m), 3.67 (3 H, s); 13C NMR (100 MHz, $CDCl_3$) δ −5.3, 13.2, 15.8, 18.3, 25.9, 32.0, 38.2, 40.0, 61.3, 61.6; HRMS (ESI) calcd for $C_9H_{20}NO_3$ $[M + H]^+$ 190.1443, found 190.1434.



(4,5-erythro,E)-Methyl 7-((tert-Butyldimethylsilyl)oxy)-4,5-dimethylhept-2-enoate (***S-030***). To a solution of Weinreb amide (2.42 g, 7.97 mmol) in 100 mL of toluene at −78 °C was added diisobutylaluminum hydride (2.5 mL, 19.9 mmol) dropwise over 5 min. The solution was stirred for 2 h and then quenched cold with 2 mL of 2-propanol. The solution was diluted with 200 mL of dichloromethane and stirred with 200 mL of 1 M HCl. The organic layer was washed with 100 mL of 1 M NaOH. The combined aqueous layers were back-extracted three times with 20 mL portions of dichloromethane. The combined organic layers were diluted with 100 mL hexanes, dried over sodium sulfate, and filtered through a Celite plug (10 × 10 cm). The cloudy white solution was concentrated to yield the desired aldehyde as a cloudy white oil (1.89 g, 97%): TLC R_f = 0.8 (30% EtOAc/hexanes, CAM stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.00−0.05 (6 H, m), 0.82−0.91 (12 H, m), 1.00 (3 H, d, J = 6.8 Hz), 1.40−1.51 (1 H, m, J = 13.8, 8.2, 5.9, 5.9 Hz), 1.60 (1 H, td, J = 13.2, 6.3 Hz), 2.18−2.29 (1 H, m), 2.32−2.43 (1 H, m), 3.59−3.74 (2 H, m), 9.65 (1 H, s).

To 20 mL of freshly distilled acetonitrile were added lithium chloride (1.64 g, 38.7 mmol), freshly distilled diisopropylethylamine (4.02 mL, 23.1 mmol), and trimethyl phosphonoacetate (1.48 mL, 9.2 mmol). Aldehyde (1.89 g, 7.73 mmol) was then added. The yellow suspension was heated at 60 °C for 1 h. The suspension was cooled and poured into a separatory funnel. One hundred milliliters of 25% EtOAc/hexanes followed by 200 mL of 1 M HCl were carefully poured in. The triphasic mixture became biphasic upon gentle agitation. The layers were separated, and the aqueous layer was back-extracted five times with 30 mL portions of 25% EtOAc/hexanes. The combined organic layers were washed twice with 75 mL portions of 1 M NaOH, followed by 100 mL of brine. The combined organic extracts were dried over sodium sulfate and filtered through a silica plug (5 × 10 cm). The plug was washed with 250 mL 40% EtOAc/hexanes. The solution was concentrated to yield the desired a yellow oil. The oil was purified by silica gel chromatography (10, 20% EtOAc/hexanes) to give the desired enoate (1.44 g, 62%, >20:1 *E*/*Z*): TLC R_f = 0.8 (30% EtOAc/hexanes); IR ($CHCl_3$ film) 2943, 2858, 1728, 1654, 1472, 1436, 1386, 1256, 1177, 1098, 988, 899, 836, 776, 728, 667 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03−0.05 (6 H, m), 0.85 (6 H, d, J = 6.9 Hz), 0.89 (9 H, t), 0.99 (3 H, t, J = 7.6 Hz), 1.23−1.32 (1 H, m), 1.59−1.75 (2 H, m), 2.23−2.34 (1 H, m), 3.56−3.70 (2 H, m), 3.73 (3 H, s), 5.78 (1 H, d, J = 16.9 Hz), 6.93 (1 H, dd, J = 15.8, 7.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.39, −5.35, 14.7, 15.9, 18.2, 25.8, 33.8, 36.9, 41.1, 51.3, 61.2, 119.9, 153.9, 167.1; HRMS (ESI) calcd for $C_{16}H_{33}O_3Si$ $[M + H]^+$ 301.2199, found 301.2190.

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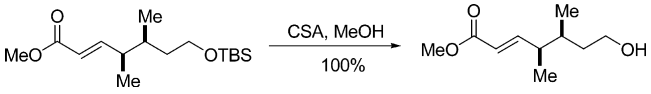
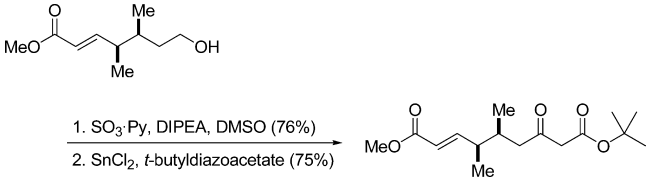
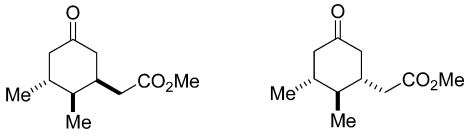


*7-Hydroxy-4,5-dimethylhept-2-enoic Acid Methyl Ester (**S-031**).* The olefin (1.44 g, 4.79 mmol) was dissolved in 10 mL of methanol, and 10-camphorsulfonic acid (1.11 g, 4.79 mmol) was added. The solution was stirred at room temperature for 30 min, after which TLC analysis indicated full consumption of starting material. Ten mL of sodium bicarbonate solution was added, and the bulk of the methanol was removed by rotary evaporation. The mixture was resuspended in 50 mL of dichloromethane and 50 mL of sodium bicarbonate. The layers were separated, and the aqueous layer was back-extracted three times with 10 mL portions of dichloromethane. The combined organic layers were washed with 20 mL of brine, dried over sodium sulfate, concentrated, and purified by silica gel chromatography (30% EtOAc/hexanes) to yield the desired olefin−alcohol as a clear oil (0.90 g, 100%): TLC R_f = 0.3 (30% EtOAc/hexanes, CAM stain); IR ($CHCl_3$ film) 3435, 2943, 2878, 1724, 1653, 1436, 1272, 1178, 1047, 988, 864 cm^{-1}; 1H NMR (500 MHz, $CDCl_3$) δ ppm 0.87 (3 H, d, J = 6.9 Hz), 1.01 (3 H, d, J = 6.9 Hz), 1.28−1.37 (1 H, m), 1.42−1.49 (1 H, br s), 1.63−1.73 (2 H, m), 2.21−2.32 (1 H, m, J = 13.2, 13.2, 6.8, 1.1 Hz), 3.59−3.72 (2 H, m), 3.72 (3 H, s), 5.78 (1 H, d, J = 16.9 Hz), 6.91 (1 H, dd, J = 15.8, 7.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) d 15.00, 16.00, 33.87, 36.91, 41.30, 51.38, 61.00, 120.13, 153.60, 167.17; HRMS (ESI) calcd for $C_{10}H_{19}O_3$ $[M + H]^+$ 187.1334, found 187.1339.



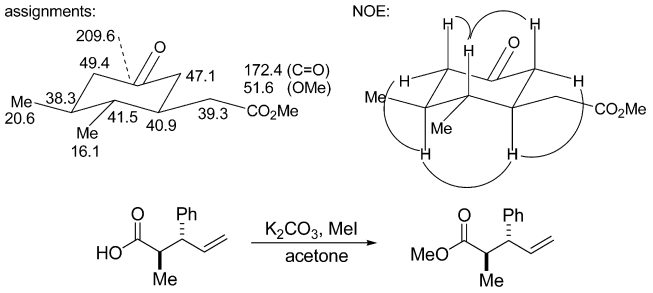
*(4,5-erythro,E)-9-tert-Butyl 1-Methyl 4,5-Dimethyl-7-oxonon-2-enedioate (**9**).* To a stirring solution of alcohol (0.88 g, 4.72 mmol) in 20 mL of CH_2Cl_2 at −5 °C was added freshly distilled *N,N*-diisopropylethylamine (5.75 mL, 33 mmol) dropwise via syringe. After 10 min at −5 °C, dimethyl sulfoxide (3.34 mL, 47 mmol) was added to the reaction mixture via syringe, and the solution was allowed to stir for an additional 10 min. Sulfur trioxide pyridine complex (3.98 g, 18.9 mmol) was then added in one portion. The reaction was allowed to proceed for 4 h at −5 °C, after which time TLC analysis indicated complete consumption of starting material. The reaction was quenched by transfer into a 125 mL Erlenmeyer flask that contained 50 mL of saturated aqueous $NaHCO_3$ solution. The mixture was stirred for 5 min. The layers were separated, and the aqueous phase was back-extracted three times with 20 mL portions of dichloromethane. The reaction mixture was then concentrated under reduced pressure to yield a yellow oil which was immediately purified by silica gel chromatography (15, 30% EtOAc/hexanes) to yield the aldehyde as a clear yellow oil (0.67 g, 76%): TLC R_f = 0.65 (30% EtOAc/hexanes, $KMnO_4$ stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (3 H, d, J = 6.8 Hz), 1.05 (3 H, d, J = 6.8 Hz), 2.13−2.21 (1 H, m), 2.21−2.27 (1 H, m), 2.26−2.34 (1 H, m), 2.49 (1 H, dd, J = 16.4, 4.2 Hz), 3.74 (3 H, s), 5.82 (1 H, d, J = 16.1 Hz), 6.87 (1 H, dd, J = 15.6, 8.3 Hz), 9.75 (1 H, s).

To a dry vial were added tin(II) chloride (66 mg, 0.35 mmol) and dichloromethane (2 mL). *tert*-Butyl diazoacetate (0.99 mL, 7.2 mmol) was added dropwise to the vial with vigorous stirring. After gas evolution ceased, aldehyde (0.66 g, 3.58 mmol) was added, and the yellow solution was stirred overnight. The solution was diluted with 100 mL of dichloromethane and 100 mL of saturated sodium bicarbonate solution. The layers were separated, and the aqueous layer was back-extracted three times with 10 mL portions of dichloromethane. The combined organic layers were washed with 50 mL of water and 50 mL of brine, dried over sodium sulfate, and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (15% EtOAc/hexanes). The remaining *tert*-butyl diazoacetate was removed by high vacuum evaporation to yield the desired ketoester as a yellow oil (0.80 g, 75%): TLC R_f 0.6 (30% EtOAc/hexanes, CAM stain); IR ($CHCl_3$ film) 2976, 1720, 1654, 1457, 1436, 1369, 1319, 1275, 1151, 846 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (3 H, d, J = 6.4 Hz), 1.41−1.50 (12 H, m), 2.01−2.15 (1 H, m), 2.17−2.27 (1 H, m), 2.34−2.43 (1 H, m, J = 17.4, 7.3 Hz), 2.46−2.55 (1 H, m, J = 17.4, 5.5 Hz), 3.29 (2 H, s), 3.63−3.76 (3 H, m), 5.81 (1 H, d, J = 15.6 Hz), 6.81−6.97 (1 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.6, 27.9, 28.0, 28.1, 28.2, 38.9, 49.1, 51.0, 51.3, 81.9, 122.7, 146.9, 166.2, 166.6, 202.1; HRMS (ESI) calcd For $C_{16}H_{30}O_5N$ $[M + NH_4]^+$ 316.2124, found 316.2125.

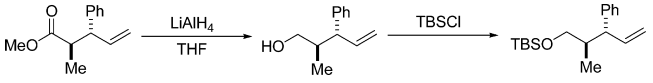


*Methyl 2-((1,2-syn)-(2,3-anti)-2,3-dimethyl-5-oxocyclohexyl)-acetate (**S-032-syn**):* TLC R_f = 0.4 (30% EtOAc/hexanes, CAM stain); IR ($CHCl_3$ film) 2956, 2882, 1731, 1714, 1698, 1434, 1381, 1270, 1240, 1166, 1112, 1072, 1015, 894 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ = 3.26 (s, 3 H), 2.26 (dt, J = 1.5, 13.2 Hz, 1 H), 2.13 (ddd, J = 1.7, 2.0, 13.4 Hz, 1 H), 1.91−1.74 (m, 3 H), 1.51−1.31 (m, 3 H), 1.32−1.20 (m, 1 H), 0.53 (d, J = 6.3 Hz, 3 H), 0.45−0.38 (m, 2 H); HRMS (ESI) calcd for $C_{11}H_{19}O_3$ $[M + H]^+$ 199.1334, found 199.1325.

*Methyl 2-((1,2-anti)-(2,3-anti)-2,3-dimethyl-5-oxocyclohexyl)-acetate (**S-032-anti**):* TLC R_f = 0.4 (30% EtOAc/hexanes, CAM stain); IR ($CHCl_3$ film) 2956, 2882, 1738, 1716, 1434, 1373, 1328, 1284, 1260, 1240, 1169, 1147 cm^{-1}; ^{1}H NMR (500 MHz, ca. 10% C_6D_6 in $CDCl_3$) (^{13}C NMR, 125 MHz, via gHSQC/gHMBC correlations) δ 0.82−16.1 (3 H, d, J = 6.3 Hz), 0.85 (3 H, d, J = 6.3 Hz), 1.02−1.10 − 41.5 (1 H, m), 1.29−1.39 − 38.3 (1 H, m), 1.68−1.78 − 40.9 (1 H, m), 1.88−49.4 (1 H, t, J = 13.4 × 2 Hz), 2.01−2.05 − 39.3 (1 H, m), 2.06−2.09 − 47.1 (1 H, m), 2.18−49.4 (1 H, ddd, J = 14.0, 4.3, 2.2 Hz), 2.26−47.1 (1 H, ddd, J = 13.9, 4.2, 2.4 Hz), 2.39−39.3 (1 H, dd, J = 15.1, 4.4 Hz), 3.48−51.6 (3 H, s), quaternary carbons: 172.4, 209.6; HRMS (ESI) calcd for $C_{11}H_{19}O_3$ $[M + H]^+$ 199.1334, found 199.1340.



*(2,3-erythro)-Methyl 2-Methyl-3-phenylpent-4-enoate (**S-033**).* This sequence commences with a carboxylic acid, which was obtained in racemic form using a known procedure.[35] To a stirring solution of acid (3.11 g, 16.3 mmol) in 32 mL of acetone at room temperature was added potassium carbonate (2.71 g, 19.6 mmol). The white suspension was stirred vigorously for 30 min. Methyl iodide (1.22 mL, 19.6 mmol) was added, and the suspension was stirred overnight. The bulk of the acetone was removed by rotary evaporation at 20 °C and 200 Torr. The white slurry was dissolved in 100 mL of saturated sodium bicarbonate and 50 mL of diethyl ether. The layers were separated, and the aqueous layer was back-extracted five times with 20 mL portions of ether. Pentane was added, and the yellow solution was dried over sodium sulfate, filtered, and concentrated at 20 °C and 200 Torr to yield the desired methyl ester as a yellow oil (3.29 g, 99%). TLC R_f 0.7 (30% EtOAc/hexanes, anisaldehyde stain, yellow). The properties of this compound matched those known in the literature.[35]



*tert-Butyldimethyl(((2,3-threo)-2-methyl-3-phenylpent-4-en-1-yl)oxy)silane (**S-034**).* To a solution of methyl ester (5.08 g, 24.9 mmol) in 100 mL of tetrahydrofuran at −20 °C was added lithium aluminum hydride (4.06 g, 107 mmol) in several portions over 5 min. Some gas evolution was observed. The gray suspension was allowed to stir for 30 min at −20 °C, after which TLC analysis indicated complete consumption of starting material. Celite and sodium sulfate decahydrate

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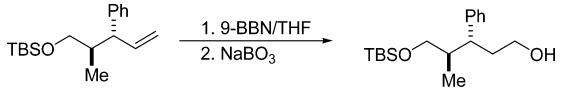
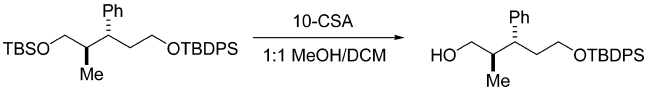
were added slowly. After the cessation of gas evolution, a small amount of water was added to completely quench any remaining lithium aluminum hydride. The gray suspension was filtered over Celite, and the filter cake was washed with 250 mL of ether. Hexanes (100 mL) was added, and the clear and colorless solution was dried over sodium sulfate, filtered over paper, and concentrated to yield the desired alcohol as a clear and colorless oil (2.84 g, 65%): TLC R_f 0.5 (30% EtOAc/hexanes, anisaldehyde stain, blue); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.36−7.29 (m, 2 H), 7.26−7.16 (m, 3 H), 6.10−5.97 (m, 1 H), 5.13−5.05 (m, 2 H), 3.76 (s, 1 H), 3.53−3.44 (m, 1 H), 3.39−3.30 (m, 1 H), 3.24 (t, J = 9.0 Hz, 1 H), 2.09−1.98 (m, 1 H), 1.87 (s, 1 H), 1.17 (t, J = 5.9 Hz, 1 H), 1.02 (d, J = 6.8 Hz, 3 H).

To a solution of primary alcohol (2.84 g, 16.1 mmol) in 20 mL of DMF at room temperature was added imidazole (2.74 g, 40.3 mmol) followed by *tert*-butyldiphenylsilyl chloride (2.67 g, 17.7 mmol). After 30 min, TLC indicated complete consumption of starting material. Methanol (5 mL) was added, and the clear and colorless solution was stirred for 10 min. The mixture was diluted with 50 mL of 0.1 M HCl and 50 mL of 1:1 hexanes/ether. The layers were separated, and the aqueous layer was back-extracted three times with 15 mL portions of 1:1 hexanes/ether. The combined organic extracts were washed twice with 50 mL portions of water and once with 10 mL of brine. The clear and colorless solution was dried over sodium sulfate, filtered over paper, and concentrated to yield the desired silyl ether as a clear and colorless oil (4.30 g, 92%): TLC R_f 0.7 (30% EtOAc/hexanes, anisaldehyde stain, green); IR (ATR) 3078, 3029, 2956, 2929, 2857, 1684, 1601, 1472, 1389, 1361, 1331, 1089, 1023, 913, 837, 776, 671 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.38−7.29 (m, 2 H), 7.26−7.19 (m, 3 H), 6.11−6.01 (m, 1 H), 5.16−5.05 (m, 2 H), 3.47−3.38 (m, 1 H), 3.32 (s, 2 H), 2.06−1.96 (m, 1 H), 1.06−0.98 (m, 3 H), 0.95−0.89 (m, 9 H), 0.01 (d, J = 6.9 Hz, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 144.0, 139.9, 128.3, 127.9, 126.0, 115.6, 65.8, 52.4, 40.4, 25.9, 18.3, 14.6, −5.5, −5.5; HRMS (ESI) calcd for $C_{18}H_{31}OSi$ [M + H]$^+$: 291.2139, found 291.2140.



*(3,4-threo)-5-((tert-Butyldimethylsilyl)oxy)-4-methyl-3-phenylpentan-1-ol (**S-035**).* 9-BBN dimer (2.58 g, 10.6 mmol, carefully prepared[36] and stored at −20 °C in a nitrogen glovebox; commercial material gave poor results) was dissolved in 120 mL of THF at room temperature. The clear and colorless solution was stirred for 1 h. A solution of olefin (4.1 g, 14.1 mmol) in 20 mL of THF was added dropwise via cannula over 20 min. The clear and colorless solution was stirred for 3 h at room temperature. At this point, TLC analysis indicated complete consumption of starting material. The solution was cooled to 0 °C, and water (120 mL) was added (gas evolution!), followed by sodium perborate tetrahydrate (10.8 g, 70.5 mmol). The white suspension was allowed to warm to room temperature and stirred overnight. The white suspension was diluted with 100 mL of ether and decanted into a separatory funnel. The remaining white particulates were alternately washed three times with 50 mL portions of 1:1 ether/water. The layers were separated, and the aqueous phase was back-extracted three times with 50 mL portions of ether. The combined organic phases were washed twice with 50 mL of water and once with 25 mL of brine. The clear and colorless solution was diluted with 200 mL of hexanes, dried thoroughly over sodium sulfate, and concentrated to yield a clear and colorless oil. The oil was purified by silica gel chromatography (gradient elution 5, 10, 20% EtOAc/hexanes) to yield the desired alcohol as a clear and colorless oil (4.20 g, 96%): TLC R_f 0.4 (borane)/0.5 (alcohol) (30% EtOAc/hexanes, CAM stain; a number of other spots visible above and below); IR (ATR) 3343, 2954, 2929, 2857, 1471, 1388, 1361, 1220, 1070, 1029, 833, 773, 735, 667 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.28 (d, J = 7.6 Hz, 2 H), 7.23−7.15 (m, 3 H), 3.50−3.44 (m, 1 H), 3.41−3.33 (m, 2 H), 3.23−3.16 (m, 1 H), 2.75−2.66 (m, 1 H), 2.12−2.02 (m, 1 H), 1.92−1.79 (m, 2 H), 1.01 (d, J = 6.6 Hz, 3 H), 0.90−0.85 (m, 9 H), −0.04 (d, J = 5.7 Hz, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 143.8, 128.2, 128.2, 126.1, 66.1, 61.5, 44.3, 41.3, 34.8, 25.9, 18.2, 14.7, −5.5, −5.6; HRMS (ESI) calcd for $C_{18}H_{32}O_2SiNa$ [M + Na]$^+$ 331.2064, found 331.2060.

*(6,7-threo)-2,2,3,3,6,12,12-Heptamethyl-7,11,11-triphenyl-4,10-dioxa-3,11-disilatridecane (**S-036**).* To a solution of alcohol (3.04 g, 9.85 mmol) in 10 mL of DMF were added imidazole (1.68 g, 24.6 mmol) and *tert*-butyldiphenylsilyl chloride (2.65 mL, 10.3 mmol). The reaction was stirred overnight. The reaction was diluted with 50 mL 3:1 hexanes/ethyl acetate and 100 mL of 1 M HCl. The layers were separated, and the aqueous layer was back-extracted three times with 20 mL portions of 3:1 hexanes/ethyl acetate. The combined organic layers were washed with 50 mL of water and 50 mL of brine, dried over sodium sulfate, and concentrated to yield a clear oil. The oil was purified by silica gel chromatography (5, 10% EtOAc/hexanes) to yield the desired protected alcohol as a clear and colorless oil (4.01 g, 94%): TLC R_f 0.8 (30% EtOAc/hexanes, CAM stain); IR (ATR) 3071, 3028, 2955, 2929, 2856, 1589, 1492, 1472, 1427, 1389, 1361, 1251, 1188, 1105, 1085, 1056, 1027, 1006, 938, 833, 774, 761, 738, 699, 668; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.71−7.63 (m, 2 H), 7.62−7.54 (m, 2 H), 7.48−7.31 (m, 6 H), 7.26 (d, J = 7.3 Hz, 2 H), 7.24−7.15 (m, 1 H), 7.16−7.06 (m, 2 H), 3.58−3.50 (m, 1 H), 3.49−3.36 (m, 2 H), 3.27−3.17 (m, 1 H), 2.90−2.80 (m, 1 H), 2.17−2.07 (m, 1 H), 1.87−1.71 (m, 2 H), 1.07 (s, 12 H), 0.95−0.86 (m, 12 H), 0.00 (d, J = 6.8 Hz, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 143.9, 135.5, 135.5, 134.8, 134.0, 134.0, 129.4, 129.3, 128.4, 128.0, 127.7, 127.5, 127.5, 125.8, 66.3, 62.1, 43.7, 41.4, 34.7, 26.8, 26.5, 25.9, 19.1, 18.2, 14.9, −5.5, −5.5; HRMS (ESI) calcd for $C_{34}H_{50}O_2Si_2Na$ [M + Na]$^+$ 569.3242, found 569.3237.



*5-(tert-Butyldiphenylsilanyloxy)-2-methyl-3-phenylpentan-1-ol (**S-037**).* To a solution of disilyl ether (1.12 g, 2.05 mmol) in 5 mL of methanol and 5 mL of dichloromethane at 0 °C was added 10-camphorsulfonic acid (72 mg, 0.31 mmol). The clear and colorless solution was stirred for 1 h at 0 °C. The mixture was poured into 50 mL of saturated sodium bicarbonate solution and 50 mL of dichloromethane. The layers were separated, and the aqueous layer was back-extracted four times with 10 mL portions of dichloromethane. The combined organic extracts were washed once with 10 mL of brine, dried over sodium sulfate, filtered, and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (gradient elution: 5, 10, 20, 25% EtOAc/hexanes) to yield the desired alcohol as a clear and colorless oil (0.72 g, 81%): TLC R_f 0.65 (30% EtOAc/hexanes, CAM stain); IR (ATR) 3341, 3070, 3027, 2956, 2930, 2857, 1589, 1492, 1472, 1453, 1427, 1389, 1361, 1189, 1107, 1028, 982, 938, 822, 782, 72, 739, 629 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.74 (d, J = 6.9 Hz, 2 H), 7.67 (d, J = 6.9 Hz, 2 H), 7.54−7.38 (m, 6 H), 7.33 (d, J = 7.6 Hz, 2 H), 7.27 (s, 1 H), 7.19 (d, J = 7.3 Hz, 2 H), 3.67−3.59 (m, 1 H), 3.58−3.47 (m, 2 H), 3.37−3.26 (m, 1 H), 2.91−2.80 (m, 1 H), 2.28−2.14 (m, 1 H), 2.01−1.82 (m, 2 H), 1.80−1.67 (m, 1 H), 1.16 (s, 9 H), 1.11 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 143.4, 135.4, 135.4, 133.8, 133.8, 129.4, 129.4, 128.2, 128.2, 127.5, 127.4, 126.0, 66.4, 61.9, 44.3, 41.2, 34.8, 26.8, 19.1, 14.8; HRMS (ESI) calcd for $C_{28}H_{37}O_2Si$ [M + H]$^+$ 433.2563, found 433.2563.

*(2,3-erythro)-5-((tert-Butyldiphenylsilyl)oxy)-2-methyl-3-phenylpentanal (**S-038a**).* To a suspension of Dess−Martin periodinane (1.96 g, 4.62 mmol) in 6 mL of dichloromethane at room temperature was added sodium bicarbonate (0.78 g, 9.24 mmol). A solution of alcohol (1.00 g, 2.31 mmol) in 6 mL of dichloromethane was added. The white suspension was stirred for 2.5 h. Twelve mL of 1:1 hexanes/ether was added, followed by 12 mL of saturated sodium thiosulfate solution and 6 mL of saturated sodium bicarbonate solution. The mixture was stirred vigorously for 10 min. At this point, the solution became mostly clear, with a few remaining particulates. The mixture was poured into 20 mL of saturated sodium bicarbonate solution, 20 mL of saturated sodium

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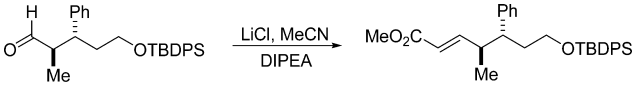
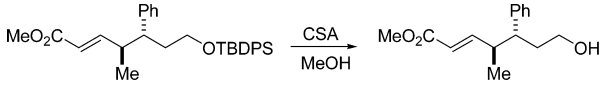
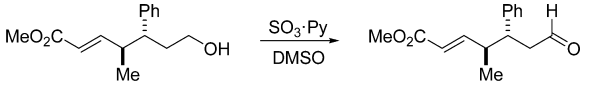
thiosulfate solution, and 50 mL of 1:1 hexanes/ether. The layers were separated, and the aqueous layer was back-extracted four times with 10 mL portions of 1:1 hexanes/ether. The clear and colorless solution was washed with 10 mL of brine, dried over sodium sulfate, filtered, and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (gradient elution: 4, 8% EtOAc/hexanes) to yield the desired aldehyde as a clear and colorless oil (0.78 g, 78%): TLC R_f 0.7 (30% EtOAc/hexanes, CAM stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.61−9.53 (m, 1 H), 7.66−7.59 (m, 2 H), 7.57−7.48 (m, 2 H), 7.28 (s, 3 H), 3.63−3.52 (m, 1 H), 3.52−3.38 (m, 1 H), 3.30−3.23 (m, 1 H), 2.65−2.57 (m, 1 H), 2.05−1.96 (m, 1 H), 1.91−1.81 (m, 1 H), 1.04 (s, 9 H).



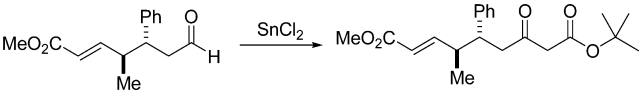
*(4,5-erythro,E)-Methyl 7-(tert-Butyldiphenylsilyloxy)-4-methyl-5-phenylhept-2-enoate (**S-038b**).* To a solution of aldehyde (0.6 g, 1.39 mmol) in 10 mL of acetonitrile were added lithium chloride (0.12 g, 2.8 mmol) and trimethylphosphonoacetate (0.27 mL, 1.67 mmol). Diisopropylethylamine (0.24 mL, 1.39 mmol) was added. The clear white suspension became brown within minutes. The mixture was stirred overnight at room temperature. The brown solution was poured into 50 mL of dichloromethane and 50 mL of 0.1 M HCl. The layers were separated, and the aqueous phase was back-extracted three times with 10 mL portions of dichloromethane. The combined organic extracts were washed with 10 mL of brine, dried over sodium sulfate, and concentrated to yield a yellow oil (>20:1 *E*/*Z*). The oil was purified by silica gel chromatography (gradient elution: 2, 4, 10% EtOAc/hexanes) to yield the desired *E*-ester (0.04 g, 18%) as a clear and colorless oil: TLC R_f = 0.75 (30% EtOAc/hexanes, $KMnO_4$ stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.66−7.57 (m, 2 H), 7.58−7.48 (m, 2 H), 7.28 (s, 10 H), 7.08−7.00 (m, 1 H), 6.90−6.78 (m, 1 H), 5.73−5.63 (m, 1 H), 3.71 (s, 3 H), 3.61−3.52 (m, 1 H), 3.52−3.43 (m, 1 H), 2.95−2.88 (m, 1 H), 2.65−2.52 (m, 1 H), 2.05−1.96 (m, 1 H), 1.92−1.81 (m, 1 H), 1.05−1.00 (m, 15 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 167.1, 152.9, 135.5, 133.9, 129.5, 127.6, 120.4, 120.0, 77.2, 77.0, 76.7, 62.1, 61.9, 51.3, 41.0, 36.7, 34.1, 33.8, 26.8, 19.2, 16.5, 16.1, 14.8.



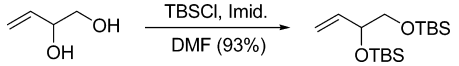
*(4,5-erythro,E)-Methyl 7-Hydroxy-4-methyl-5-phenylhept-2-enoate (**S-039a**).* To a solution of silyl ether (0.48 g, 0.99 mmol) in 10 mL of methanol at room temperature was added 10-camphorsulfonic acid (0.46 g, 1.97 mmol). The mixture was stirred for 1 h, after which TLC analysis indicated complete consumption of starting material. The mixture was diluted with 50 mL of saturated sodium bicarbonate solution and 50 mL of dichloromethane. The layers were separated, and the aqueous layer was back-extracted three times with 15 mL portions of dichloromethane. The combined organic layers were washed with 20 mL of brine, dried over sodium sulfate, filtered, and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (gradient elution: 15, 40% EtOAc/hexanes) to yield the desired alcohol as a clear and colorless oil (0.14 g, 58%): TLC R_f = 0.2 (30% EtOAc/hexanes, $KMnO_4$ stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.34−7.09 (m, 15 H), 6.85 (dd, *J* = 8.3, 15.6 Hz, 1 H), 5.70 (dd, *J* = 1.2, 15.9 Hz, 1 H), 4.13 (s, 1 H), 3.71 (s, 3 H), 3.59−3.51 (m, 1 H), 3.46 (s, 1 H), 2.87−2.77 (m, 1 H), 2.65−2.58 (m, 1 H), 2.05−1.85 (m, 2 H), 1.32−1.23 (m, 2 H), 1.06 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 167.2, 167.1, 153.7, 152.6, 120.4, 120.0, 60.8, 60.7, 51.3, 41.2, 41.1, 36.8, 36.8, 34.0, 33.8, 16.3, 15.9, 15.9, 14.9.



*(4,5-erythro,E)-Methyl 4-Methyl-7-oxo-5-phenylhept-2-enoate (**S-039b**).* To a stirring solution of alcohol (130 mg, 0.52 mmol) in 5 mL of CH_2Cl_2 at 0 °C was added freshly distilled *N*,*N*-diisopropylethylamine (0.69 mL, 4.0 mmol) dropwise via syringe. After 10 min, dimethyl sulfoxide (0.40 mL, 5.6 mmol) was added to the reaction mixture via syringe, and the solution was allowed to stir for an additional 10 min. Sulfur trioxide−pyridine complex (0.48 g, 2.3 mmol) was then added in one portion. The reaction was allowed to proceed for 1 h at 0 °C, after which TLC analysis indicated complete consumption of starting material. The reaction was diluted with 50 mL of dichloromethane and 50 mL of 0.1 M HCl. The layers were separated, and the aqueous phase was back-extracted four times with 15 mL portions of dichloromethane. The combined organic layers were washed with 25 mL of saturated sodium bicarbonate solution followed by 25 mL of brine. The clear and colorless solution was washed with brine, dried over sodium sulfate, and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography to yield the desired aldehyde as a clear, colorless oil (115 mg, 89%): TLC R_f 0.5 (30% EtOAc/hexanes, $KMnO_4$ stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.66 (t, *J* = 1.7 Hz, 1 H), 7.43−7.09 (m, 5 H), 6.81 (dd, *J* = 8.3, 15.6 Hz, 1 H), 5.74 (dd, *J* = 1.2, 15.9 Hz, 1 H), 3.72 (s, 3 H), 3.37−3.30 (m, 1 H), 2.93−2.74 (m, 3 H), 2.71−2.61 (m, 1 H), 1.05 (d, *J* = 6.3 Hz, 3 H).



*(4S,5R,E)-9-tert-Butyl 1-Methyl 4-Methyl-7-oxo-5-phenylnon-2-enedioate (**11**).* To a dry vial were added tin(II) chloride (4.7 mg, 0.03 mmol) and 1 mL of deuterochloroform. *tert*-Butyl diazoacetate (0.12 mL, 0.9 mmol) was added dropwise to the vial with vigorous stirring. After gas evolution ceased, aldehyde (115 mg, 0.47 mmol) was added, and the yellow solution was stirred overnight. The solution was diluted with 50 mL of dichloromethane and 50 mL of saturated sodium bicarbonate solution. The layers were separated, and the aqueous layer was back-extracted four times with 10 mL portions of dichloromethane. The combined organic layers were washed consecutively with 50 mL of water and 50 mL of brine, dried over sodium sulfate, and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (gradient elution: 10, 20% EtOAc/hexanes) to yield the desired ketoester as a yellow oil (150 mg, 90%): TLC R_f 0.5 (30% EtOAc/hexanes, anisaldehyde stain, brown); IR (ATR) 2977, 1717, 1653, 1495, 1455, 1435, 1394, 1368, 1316, 11258, 1145, 1071, 1032, 984, 845, 757, 729, 702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.33−7.08 (m, 5 H), 6.79 (dd, *J* = 8.4, 15.7 Hz, 1 H), 5.73 (dd, *J* = 1.1, 15.8 Hz, 1 H), 3.71 (s, 2 H), 3.36−3.27 (m, 1 H), 3.23 (s, 2 H), 2.98−2.92 (m, 1 H), 1.44 (s, 9 H), 1.02 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 201.5, 166.7, 166.1, 151.2, 140.6, 128.6, 128.4, 128.4, 128.3, 128.1, 127.9, 126.9, 126.8, 121.2, 82.0, 77.2, 77.0, 76.7, 51.4, 51.1, 45.9, 45.1, 45.1, 43.1, 41.1, 28.3, 27.9, 17.3; HRMS (ESI) calcd for $C_{21}H_{28}O_5Na$ [M + Na]$^+$ 383.1829, found 383.1827.



*3,4-Bis(tert-butyldimethylsilanyloxy)but-1-ene (**S-040**).* To a solution of 3,4-dihydroxy-1-butene (1.68 mL, 20 mmol) in 20 mL of DMF were added imidazole (8.17 g) and *tert*-butyldimethylsilyl chloride (9.04 g, 60 mmol). The reaction was stirred overnight. The reaction was diluted with 100 mL of diethyl ether and 100 mL of saturated ammonium chloride solution. The layers were separated, and the aqueous phase was back-extracted three times with 20 mL portions of ether. The combined organic extracts were washed with 50 mL of brine, diluted with 100 mL of hexanes, dried over sodium sulfate, and concentrated under reduced pressure to afford the crude product as a yellow oil. The oil was purified by silica gel chromatography (5% EtOAc/hexanes) to give the desired bis-silyl ether as a clear and colorless oil (5.87 g, 92%): TLC R_f 0.9 (30% EtOAc/hexanes, $KMnO_4$ stain); IR ($CHCl_3$ film) 2945, 2858, 1472, 1256, 1123, 1095, 836, 776 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04−0.07 (12 H, m), 0.91 (18 H, d, *J* = 4.6 Hz), 3.46 (1 H, dd, *J* = 10.1, 6.0 Hz), 3.55 (1 H, dd, *J* = 10.1, 6.4 Hz), 4.13−4.19 (1 H, m), 5.25 (1 H, t, *J* = 1.6 Hz), 5.29 (1 H, t, *J* = 1.8 Hz), 5.87 (1 H, ddd, *J* = 17.2, 10.5, 5.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.3, −5.2, −4.6, −2.9, 18.3, 18.4, 25.7, 25.9, 26.0, 68.0, 74.5, 114.8, 138.8; HRMS (ESI) calcd for $[C_{16}H_{37}O_2Si_2]^+$ 317.2332, found 317.2322.

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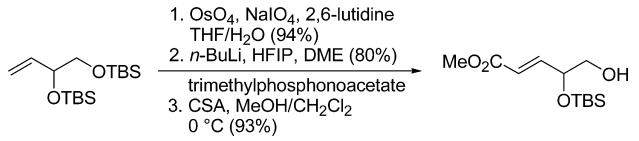
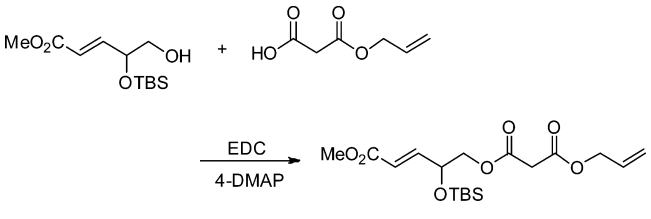


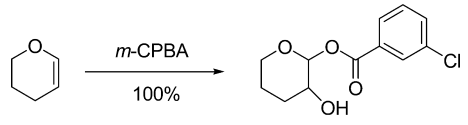
*4-(tert-Butyldimethylsilanyloxy)-5-hydroxypent-2-enoic Acid Methyl Ester (**S-041**).* To a solution of bis-silyl ether (1.58 g, 5.0 mmol) in 40 mL of 3:1 THF/pH 7 buffer were added 2,6-lutidine (1.16 mL, 10.0 mmol), osmium tetraoxide (1.0 mL, 0.1 mmol, as a 2.5% by weight solution in *t*-BuOH), and sodium periodate (4.28 g, 20 mmol). The reaction was stirred at room temperature for 3 h. The reaction was diluted with 150 mL of diethyl ether and 100 mL of saturated ammonium chloride solution. The layers were separated, and the aqueous phase was back-extracted three times with 20 mL portions of ether. The combined organic extracts were washed with 100 mL of brine, diluted with 100 mL of hexanes, dried over sodium sulfate, and concentrated under reduced pressure to afford the crude product as a yellow oil. The oil was purified by silica gel chromatography (5% EtOAc/hexanes) to give the desired aldehyde as a clear and colorless oil (5.87 g, 92%): TLC R_f 0.2 (20% EtOAc/hexanes, CAM stain); ^{1}H NMR (500 MHz, $CDCl_3$) d −0.01−0.16 (12 H, m), 0.79−0.97 (18 H, m), 3.81 (3 H, d, J = 4.9 Hz), 4.06 (1 H, t, J = 4.6 Hz), 9.66 (1 H, s).

A solution of *n*-butyllithium (3.89 mL, 9.81 mmol, 2.52 M in hexane) and trimethyl phosphonoacetate (1.61 mL, 9.98 mmol) were added in sequence to a solution of 1,1,1,2,2,2-hexafluoro2-propanol (1.08 mL, 10.3 mmol) in 25 mL of DME at −15 °C. The aldehyde (2.65 g, 8.32 mmol) was then added. The white suspension was stirred for 2 h, after which the reaction was diluted with 100 mL of dichloromethane and 100 mL of saturated ammonium chloride solution. The layers were separated, and the aqueous phase was back-extracted three times with 20 mL portions of dichloromethane. The combined organic extracts were washed with 75 mL of brine, dried over sodium sulfate, and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (5% EtOAc/hexanes) to yield the desired olefin as a yellow oil (2.5 g, 80%, 10:1 *E*:*Z*): TLC R_f 0.8 (30% EtOAc/hexanes, $KMnO_4$ stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03−0.11 (12 H, m), 0.84−0.97 (18 H, m), 3.44−3.53 (1 H, m), 3.55−3.61 (1 H, m), 3.74 (3 H, s), 4.26−4.40 (1 H, m), 6.07 (1 H, d, J = 15.6 Hz), 7.03 (1 H, dd, J = 15.6, 4.4 Hz); LRMS (CI) calcd for $C_{18}H_{39}O_4Si_2$ $[M + H]^+$ 375.2, found 375.4.

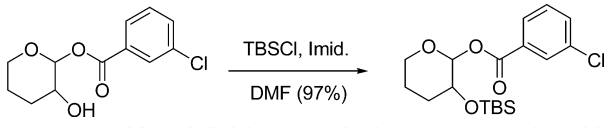
The olefin (1.66 g, 4.43 mmol) was dissolved in 25 mL of methanol and 25 mL of dichloromethane at 0 °C. 10-Camphorsulfonic acid (1.03 g, 4.43 mmol) was added slowly over 2 min, and the reaction was allowed to proceed at 0 °C for 1 h and 50 min. The reaction was quenched by the addition of 50 mL of saturated sodium bicarbonate solution. The mixture was partially evaporated to remove the bulk of the organic solvent. The mixture was resuspended in 100 mL of dichloromethane, and the layers were separated. The aqueous phase was back-extracted three times with 20 mL portions of dichloromethane. The combined organic layers were washed with 50 mL of brine, dried over sodium sulfate, and concentrated to yield a clear oil. The oil was purified by silica gel chromatography (15% EtOAc/hexanes) to afford the desired alcohol (1.06 g, 93%): TLC R_f = 0.5 (30% EtOAc/hexanes, $KMnO_4$ stain); IR ($CHCl_3$ film) 3468, 2943, 2858, 1729, 1662, 1468, 1437, 1362, 1294, 1259, 1167, 1135, 1062, 1135, 1062, 978, 837, 779, 669 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.09 (6 H, d, J = 10.1 Hz), 0.92 (9 H, s), 1.65 (1 H, s), 1.90−2.00 (1 H, m), 3.44−3.56 (1 H, m), 3.63 (1 H, ddd, J = 11.2, 7.1, 4.1 Hz), 3.74 (3 H, s), 4.34−4.46 (1 H, m), 6.06 (1 H, dd, J = 15.6, 1.8 Hz), 6.92 (1 H, dd, J = 15.6, 5.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.9, −4.6, 18.1, 25.7, 51.6, 66.1, 72.5, 121.5, 147.3, 166.5; HRMS (ESI) calcd for $C_{12}H_{25}O_4Si$ $[M + H]^+$ 261.1522, found 261.1520.



*(E)-Allyl (2-((tert-Butyldimethylsilyl)oxy)-5-methoxy-5-oxopent-3-en-1-yl) Malonate (**13**).* To a solution of alcohol (350 mg, 1.34 mmol) in 10 mL of dichloromethane were added 3-dimethylaminopropylcarbodiimide hydrochloride (0.51 g, 2.7 mmol) and 4-dimethylaminopyridine (82 mg, 0.67 mmol) followed by allyl malonic half acid (0.39 g, 2.7 mmol). The white suspension became a clear dark yellow solution. After 4 h, TLC analysis indicated the complete consumption of starting material. The solution was diluted with 50 mL of dichloromethane and 50 mL of 1 M HCl, and the layers were separated. The aqueous phase was back-extracted three times with 20 mL portions of dichloromethane. The combined organic layers were washed with 30 mL of sodium bicarbonate solution followed by 30 mL of brine. The mixture was concentrated under reduced pressure to yield a yellow oil. The oil was passed through a silica gel plug (10 × 10 cm) with 200 mL of 30% EtOAc/hexanes) to yield the desired allyl malonate as a yellow oil (450 mg, 87%): TLC R_f = 0.8 (50% EtOAc/hexanes, KMnO4 stain); IR ($CHCl_3$ film) 2955, 2942, 2858, 1735, 1664, 1437, 1275, 1146, 1026, 981, 838, 780 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.96−6.84 (m, 1 H), 6.15−6.05 (m, 1 H), 5.98−5.82 (m, 1 H), 5.39−5.29 (m, 1 H), 5.29−5.19 (m, 1 H), 4.69−4.58 (m, 2 H), 4.58−4.47 (m, 1 H), 4.16−4.03 (m, 2 H), 3.74 (d, J = 1.4 Hz, 3 H), 3.41 (d, J = 0.9 Hz, 2 H), 0.90 (d, J = 0.9 Hz, 9 H), 0.06 (d, J = 10.1 Hz, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.5, 166.0, 165.8, 146.3, 131.4, 121.8, 118.8, 69.5, 67.9, 66.1, 51.6, 41.3, 25.6, 18.1, −4.9, −5.0; HRMS (ESI) calcd for $C_{18}H_{30}O_7SiNa$ $[M + Na]^+$ 409.1658, found 409.1660.



*3-Hydroxytetrahydro-2H-pyran-2-yl 3-chlorobenzoate (**S-042**).* *m*-Chloroperoxybenzoic acid (mCPBA) (15.0 g, 86 mmol) was dissolved in 300 mL of dichloromethane at 0 °C and stirred for 5 min. 3,4-Dihydro-2*H*-pyran (6.82 mL, 74.8 mmol) was added over 5 min. The mixture was stirred at 0 °C for 1 h. The mixture was washed three times with 50 mL of portions of 1 M NaOH. The combined organic extracts were washed with brine, dried over sodium sulfate, and concentrated to yield the desired *cis*-pyran benzoate as a white solid (21.0 g, 100%): TLC R_f 0.60 (20% 2-propanol/hexanes); IR ($CHCl_3$ film) 3437, 2949, 2881, 1734, 1576, 1427, 1288, 1256, 1209, 1131, 1068, 1031, 991, 930, 748 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.57−1.68 (1 H, m), 1.76−1.84 (1 H, m), 1.90−2.01 (1 H, m), 2.10−2.21 (1 H, m), 3.67−3.85 (2 H, m), 3.93−4.03 (1 H, m), 5.93 (1 H, d, J = 4.4 Hz), 7.26 (1 H, s), 7.41 (1 H, dd, J = 8.1 Hz), 7.56 (1 H, d, J = 5.9 Hz), 7.89−8.13 (1 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 27.3, 63.9, 66.5, 95.6, 128.0, 129.8, 131.3, 133.4, 133.6, 134.6, 163.8; HRMS (ESI) calcd for $C_{12}H_{17}O_4ClN$ $[M + NH_4^+]$ 274.0846, found 274.0837.



*3-((tert-Butyldimethylsilyl)oxy)tetrahydro-2H-pyran-2-yl 3-Chlorobenzoate (**S-043**).* To a solution of lactol benzoate (17.5 g, 68.2 mmol) in 70 mL of DMF were added imidazole (13.6 g, 200 mmol) and *tert*-butyldimethylsilyl chloride (15.1 g, 100 mmol). The solution was stirred overnight. The mixture was diluted with 200 mL of ether and 200 mL of 1 M HCl. The layers were separated, and the aqueous layer was washed three times with 20 mL portions of ether. The combined organic extracts were washed with 100 mL of brine, diluted with 200 mL of hexanes, dried over sodium sulfate, and concentrated to yield the crude silyl ether as a yellow oil. The oil was purified by silica gel chromatography (10, 15, 30% EtOAc/hexanes) to yield the desired *cis*-silyl ether as a clear oil (24.5 g, 97%): TLC R_f 0.70 (30% EtOAc/hexanes); IR ($CHCl_3$ film) 2942, 2857, 1736, 1576, 1472, 1427, 1361, 1286, 1256, 1212, 1133, 1078, 928, 835, 778, 748, 673 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.09 (6 H, d), 0.76−0.97 (9 H, m), 1.51−1.60 (1 H, m), 1.66−1.75 (1 H, m), 1.92−2.10 (2 H, m), 3.68−3.81 (2 H, m), 3.91−4.01 (1 H, m), 5.85 (1 H, t, J = 4.2 Hz), 7.40 (1 H, t, J = 7.8 Hz), 7.55 (1 H, d, J = 6.8 Hz), 7.94−7.99 (1 H, m), 8.05 (1 H, s); ^{13}C

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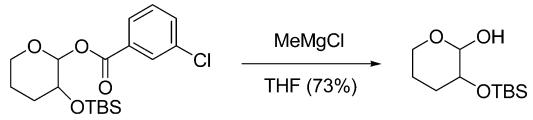
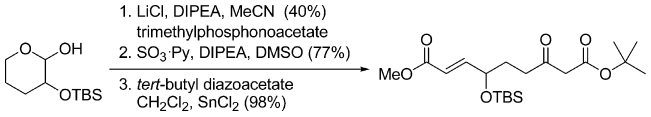
NMR (125 MHz, $CDCl_3$) −4.8, −4.7, 17.9, 21.5, 25.6, 28.98, 64.2, 67.1, 96.2, 127.9, 129.7, 129.8, 131.6, 133.2, 134.5, 163.8; HRMS (ESI) calcd for $C_{18}H_{31}O_4SiClN$ $[M + NH_4]^+$ 388.1711, found 388.1713.



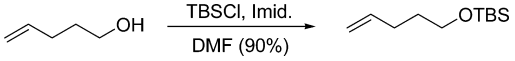
*3-((tert-Butyldimethylsilyl)oxy)tetrahydro-2H-pyran-2-ol (**S-044**).* To a solution of lactol benzoate (1.11 g, 3.0 mmol) in 50 mL of THF at −20 °C was added methylmagnesium chloride (3.0 mL, 9.0 mmol, 3.0 M in THF) dropwise via syringe. The dark brown solution was stirred for 5 h. The reaction was quenched with the addition of 5 mL of water. The mixture was diluted with 100 mL of diethyl ether and 100 mL of saturated ammonium chloride solution. The layers were separated, and the aqueous phase was back-extracted three times with 20 mL portions of ether. The solution was diluted with 200 mL of hexanes, dried over sodium sulfate, and concentrated under reduced pressure to yield the crude lactol as a yellow oil. The oil was purified by silica gel chromatography (10, 20% EtOAc/hexanes) to yield the desired *cis*-lactol as a clear oil (0.52 g, 73%): TLC R_f 0.5 (30% EtOAc/hexanes, CAM stain); IR ($CHCl_3$ film) 3475, 2943, 2858, 1464, 1390, 1362, 1255, 1209, 1143, 1082, 1011, 924, 838, 782, 678 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.13 (6 H, d, J = 9.3 Hz), 0.92 (9 H, s), 1.53−1.72 (3 H, m), 1.73−1.84 (1 H, m), 3.40−3.49 (1 H, m), 3.50−3.57 (1 H, m), 3.68−3.78 (1 H, m), 4.99 (1 H, d, J = 2.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.5, −4.4, 18.0, 23.7, 25.6, 27.2, 59.8, 68.4, 93.6; HRMS (ESI) calcd for $C_{11}H_{25}O_3Si$ $[M + H]^+$ 233.1573, found 233.1571.



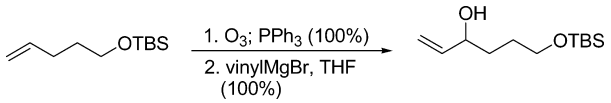
*(E)-9-tert-Butyl 1-Methyl 4-((tert-Butyldimethylsilyl)oxy)-7-oxo-non-2-enedioate (**15**).* To a suspension of lithium chloride (0.47 g, 11 mmol) in 20 mL of acetonitrile were added diisopropylethylamine (1.22 mL, 7.0 mmol) and trimethyl phosphonoacetate (0.81 mL, 5.0 mmol). A solution of lactol (0.52 g, 2.26 mmol) in 2 mL of acetonitrile was added, and the suspension was heated to reflux for 5 h. The mixture was cooled and diluted with 100 mL of diethyl ether and 100 mL of 1 M HCl. The layers were separated, and the aqueous layer was back-extracted three times with 20 mL portions of diethyl ether. The combined organic extracts were washed with 50 mL of brine, diluted with 100 mL of hexanes, dried over sodium sulfate, and concentrated to yield a dark yellow oil. The oil was purified by silica gel chromatography (10, 20, 50% EtOAc/hexanes) to yield the desired unstable unsaturated ester as a yellow oil (0.25 g, 40%): TLC R_f 0.1 (30% EtOAc/hexanes, $KMnO_4$ stain); ^1H NMR (500 MHz, $CDCl_3$) δ 0.06 (6 H, d, J = 12.2 Hz), 1.21 (9 H, d, J = 5.9 Hz), 1.55−1.70 (2 H, m), 3.59−3.67 (1 H, m), 3.73−3.76 (3 H, m), 3.96−4.10 (2 H, m), 4.40 (1 H, dd, J = 3.4 Hz), 6.00 (1 H, dd, J = 15.6, 2.0 Hz), 6.93 (1 H, dd, J = 15.6, 4.4 Hz).

The olefin−alcohol (0.11 g, 0.39 mmol) was immediately dissolved in 10 mL of dichloromethane at 0 °C. Freshly distilled *N,N*-diisopropylethylamine (0.47 mL, 2.72 mmol) was added dropwise via syringe. After 10 min of stirring at 0 °C, dimethyl sulfoxide (0.28 mL, 3.9 mmol) was added to the reaction mixture via syringe, and the solution was allowed to stir for an additional 10 min. Sulfur trioxide pyridine complex (0.33 g, 1.56 mmol) was then added in one portion. The reaction was allowed to proceed for 2 h at −0 °C, after which TLC analysis indicated complete consumption of starting material. The reaction was quenched by transfer into an 125 mL Erlenmeyer flask that contained a stirring solution of saturated sodium bicarbonate solution (50 mL). Dichloromethane (50 mL) was added, and the layers were separated. The aqueous layer was back-extracted three times with three 20 mL portions of dichloromethane. The combined organic extracts were washed with 50 mL of brine, dried over sodium sulfate, and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (15% EtOAc/hexanes) to yield the desired unstable aldehyde as a clear oil (80 mg, 77%): TLC R_f 0.5 (30% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 0.02 (6 H, d, J = 9.8 Hz), 0.89 (9 H, s), 1.78−1.86 (1 H, m), 1.95 (1 H, td, J = 13.7, 6.8 Hz), 2.37−2.57 (2 H, m), 3.73 (3 H, s), 4.35−4.51 (1 H, m), 5.99 (1 H, dd, J = 15.6, 2.0 Hz), 6.86 (1 H, dd, J = 15.6, 4.4 Hz), 9.76 (1 H, s).

To a dry vial were added tin(II) chloride (53 mg, 0.28 mmol) and dichloromethane (5 mL). *tert*-Butyl diazoacetate (0.14 mL, 1.0 mmol) was added dropwise to the vial with vigorous stirring. After gas evolution ceased, aldehyde (80 mg, 0.28 mmol) was added, and the yellow solution was stirred overnight. The solution was diluted with 100 mL of dichloromethane and 100 mL of saturated sodium bicarbonate solution. The layers were separated, and the aqueous layer was back-extracted three times with 10 mL portions of dichloromethane. The combined organic layers were washed with 50 mL of water and 50 mL of brine, dried over sodium sulfate, and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (5% 2-propanol/hexanes). The remaining *tert*-butyl diazoacetate was removed by high vacuum evaporation to yield the desired ketoester as a yellow oil (110 mg, 98%): TLC R_f = 0.70 (30% EtOAc/hexanes, CAM stain); IR ($CHCl_3$ film) 2931, 2858, 1727, 1650, 1468, 1436, 1369, 1268, 1165, 983, 838, 778, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.04 (6 H, d, J = 8.8 Hz), 0.90 (9 H, s), 1.45 (9 H, s), 1.53−1.65 (1 H, m), 1.75−1.83 (1 H, m, J = 14.2, 8.9, 5.6, 5.5 Hz), 1.88−1.96 (1 H, m, J = 14.0, 9.3, 5.9, 5.9 Hz), 2.44−2.68 (2 H, m), 3.33 (2 H, s), 3.74 (3 H, s), 4.38−4.47 (1 H, m), 6.00 (1 H, dd, J = 15.6, 2.0 Hz), 6.87 (1 H, dd, J = 15.1, 4.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) −5.0, −4.7, 18.1, 25.7, 27.9, 30.1, 37.2, 50.7, 51.5, 69.9, 81.9, 120.1, 150.2, 166.3, 166.7, 202.7; HRMS (ESI) calcd for $C_{20}H_{40}O_6SiN$ $[M + NH_4]^+$ 418.2625, found 418.2614.



*tert-Butyldimethyl-pent-4-enyloxysilane (**S-045**).* To a solution of 4-penten-1-ol (26.1 mL, 0.26 mol) in 200 mL of DMF were added imidazole (43.7 g, 0.64 mol) and *tert*-butyldimethylsilyl chloride (39.2 g, 0.26 mol) at 0 °C. The reaction was stirred overnight. The reaction was diluted with 300 mL of diethyl ether and 300 mL of saturated ammonium chloride solution. The layers were separated, and the aqueous phase was back-extracted three times with 50 mL portions of ether. The combined organic extracts were washed with 150 mL of brine, diluted with 300 mL of hexanes, dried over sodium sulfate, and concentrated under reduced pressure to afford the desired silyl ether as a clear and colorless oil (46.2 g, 90%): TLC R_f = 0.9 (30% EtOAc/hexanes, $KMnO_4$ stain); IR ($CHCl_3$ film) 3080, 2931, 2859, 1642, 1468, 1388, 1256, 1102, 1006, 912, 836, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.05 (6 H, s), 0.90 (9 H, s), 1.55−1.67 (2 H, m), 2.02−2.18 (2 H, m), 3.62 (2 H, t, J = 6.4 Hz), 4.89−5.10 (2 H, m), 5.82 (1 H, dd, J = 16.9, 10.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.3, 18.3, 25.9, 30.0, 32.02, 62.5, 114.4, 138.5; HRMS (ESI) calcd for $[C_{11}H_{25}OSi]^+$ 201.1675, found 201.1674.



*6-((tert-Butyldimethylsilyl)oxy)hex-1-en-3-ol (**S-046**).* Ozone was bubbled through a solution of olefin (20 g, 100 mmol) in 200 mL of dichloromethane at −78 °C until the solution turned blue. The solution was sparged with nitrogen for 5 min, after which triphenylphosphine (26.2 g, 100 mmol) was added in one portion. The solution was stirred for 15 min, after which the cooling bath was removed. The suspension was stirred for 6 h, after which NMR analysis indicated complete consumption of ozonide. The bulk of the solvent was removed by rotary evaporation. The yellow-brown slurry was resuspended in 200 mL of 5% EtOAc/hexanes and filtered through a silica plug (10 × 10 cm). The plug was rinsed with 100 mL of 15% EtOAc/hexanes. The solution was concentrated to yield the desired aldehyde as a clear oil (20.2 g, 100%): TLC R_f = 0.8 (30% EtOAc/hexanes, CAM stain); ^1H NMR (500 MHz, $CDCl_3$) δ 0.04 (6 H, s), 0.88 (9 H, s), 1.86 (2 H, ddd, J = 12.8, 6.6, 6.5 Hz), 2.50 (2 H, s), 3.65 (2 H, t, J = 6.1 Hz), 9.79 (1 H, s). A solution of aldehyde (20.2 g, 100 mmol) in 100 mL of THF was added dropwise to a 1.0 M solution of vinylmagnesium bromide in THF (125 mL, 125 mmol) over 15 min at −78 °C. The solution was stirred for 5 min and warmed to 0 °C. The solution was stirred for 15 min and warmed to

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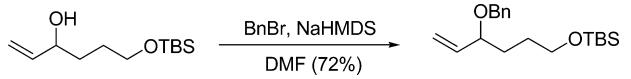
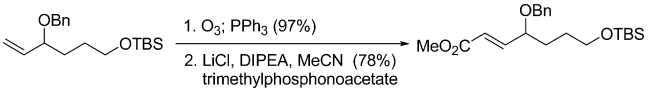
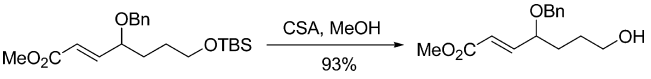
room temperature. 2-Propanol (5 mL) was added, and the mixture was diluted with 200 mL of diethyl ether and 200 mL of saturated ammonium chloride. The layers were separated, and the aqueous layer was back-extracted three times with 50 mL portions of diethyl ether. The combined organic extracts were washed with 100 mL of brine, diluted with 200 mL of hexanes, dried over sodium sulfate, and concentrated to yield the desired allylic alcohol as a yellow oil (23.1 g, 100%): TLC R_f = 0.6 (30% EtOAc/hexanes); IR ($CHCl_3$ film) 3364, 2930, 2858, 1472, 1256, 1100, 992, 920, 835, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.05 (9 H, s), 0.89 (9 H, s), 1.51−1.70 (4 H, m), 3.64 (2 H, t, J = 5.7 Hz), 4.05−4.17 (1 H, m), 5.07 (1 H, d, J = 10.5 Hz), 5.22 (1 H, d, J = 17.4 Hz), 5.79−5.94 (1 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.4, 18.2, 25.5, 25.6, 25.8, 28.6, 34.3, 63.3, 67.8, 72.5, 114.2, 128.3, 128.4, 128.4, 128.6, 132.0, 133.5, 133.7, 141.2; HRMS (ESI) calcd for $[C_{12}H_{27}O_2Si]^+$ 231.1780, found 231.1779.



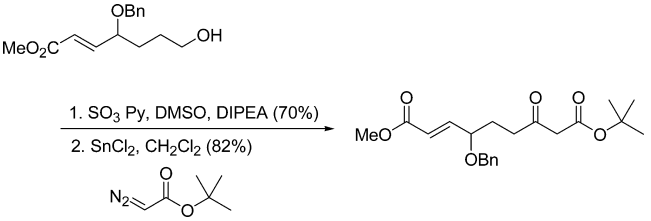
*((4-(Benzyloxy)hex-5-en-1-yl)oxy)(tert-butyl)dimethylsilane (**S-047**).* To a solution of allylic alcohol (1.38 g, 6.0 mmol) in 10 mL of DMF at 0 °C was added sodium bis(trimethylsilyl)silazane (1.32 g, 7.2 mmol) in one portion. The solution was stirred vigorously for 10 min. Benzyl bromide (0.71 mL, 6.0 mmol), freshly prepurified by passage over neutral alumina, was added. The solution was stirred for 10 min and warmed to room temperature. The solution was stirred for 1 h. Water (5 mL) was added, and the solution was diluted with 75 mL of 1 M HCl and 30 mL of diethyl ether. The layers were separated, and the aqueous layer was back-extracted three times with 20 mL portions of diethyl ether. The combined organic extracts were washed with 100 mL of water and 50 mL of brine. The solution was diluted with 50 mL of hexanes, dried over sodium sulfate, and concentrated to yield an orange oil. The oil was purified by silica gel chromatography (0,3,10% EtOAc/hexanes) to yield the desired benzyl ether as a clear yellow oil (1.38 g, 72%): TLC R_f = 0.8 (30% EtOAc/hexanes, $KMnO_4$ stain); IR ($CHCl_3$ film) 3065, 3016, 2930, 2859, 1721, 1460, 1445, 1389, 1361, 1256, 1096, 993, 926, 836, 776, 735, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.05 (6 H, s), 0.90 (9 H, s), 1.47−1.81 (4 H, m), 3.57−3.87 (3 H, m), 4.37 (1 H, d, J = 11.9 Hz), 4.60 (1 H, d, J = 11.9 Hz), 5.18−5.31 (2 H, m), 5.71−5.80 (1 H, m), 7.12−8.11 (5 H, m); ^{13}C NMR (500 MHz, $CDCl_3$) δ −5.3, −3.6, 18.2, 25.6, 25.9, 28.6, 31.7, 62.9, 69.9, 70.1, 80.3, 117.0, 117.3, 127.3, 127.6, 128.2, 128.9, 129.6, 129.9, 130.0, 130.1, 131.9, 132.0, 132.1, 134.0, 134.1, 138.5, 138.7, 138.9; HRMS (ESI) calcd for $[C_{19}H_{33}O_2Si]^+$ 321.2250, found 321.2253.



*4-Benzyloxy-7-(tert-butyldimethylsilanyloxy)hept-2-enoic Acid Methyl Ester (**S-048**).* Ozone was bubbled through a solution of olefin (12.5 g, 38.5 mmol) in 200 mL of dichloromethane at −78 °C until the solution turned blue. The solution was sparged with nitrogen gas for 2 min. Triphenylphosphine (9.59 g, 36.6 mmol) was added. The cooling bath was removed after 15 min. The solution was stirred vigorously for 3 h. The bulk of the dichloromethane was removed by rotary evaporation until approximately 50 mL of solution remained. The solution was passed through a silica plug (10 × 10 cm). The plug was rinsed with 400 mL of 15% EtOAc/hexanes. The light yellow filtrate was concentrated to yield the desired aldehyde as a yellow oil (12.1 g, 97%): TLC R_f 0.75 (30% EtOAc/hexanes); ^1H NMR (600 MHz, $CDCl_3$) δ ppm 0.07 (6 H, s), 0.92 (9 H, s), 1.61−1.97 (4 H, m), 3.57−3.69 (2 H, m), 3.79−3.88 (1 H, m), 4.58 (1 H, d, J = 11.7 Hz), 4.72 (1 H, d, J = 11.7 Hz), 7.26−7.44 (5 H, m), 9.69 (1 H, d, J = 2.0 Hz). To 50 mL of freshly distilled acetonitrile were added lithium chloride (7.93 g, 187 mmol), freshly distilled diisopropylethylamine (19.6 mL, 113 mmol), and trimethylphosphonoacetate (7.25 mL, 45 mmol). Aldehyde (12.1 g, 37.5 mmol) was then added. The yellow suspension was heated at 60 °C for 1 h. The suspension was cooled and poured into a separatory funnel. One hundred milliliters of 25% EtOAc/hexanes followed by 200 mL of 1 M HCl were carefully poured in. The triphasic mixture became biphasic upon gentle agitation. The layers were separated, and the aqueous layer was back-extracted five times with 30 mL portions of 25% EtOAc/hexanes. The combined organic layers were washed twice with 75 mL portions of 1 M NaOH, followed by 100 mL of brine. The combined organic extracts were dried over sodium sulfate and filtered through a silica plug (5 × 10 cm). The plug was washed with 250 mL of 40% EtOAc/hexanes. The solution was concentrated to yield the desired enoate as a yellow oil (11.01 g, 78%): TLC R_f = 0.3 (30% EtOAc/hexanes, $KMnO_4$ stain) ; IR ($CHCl_3$ film) 2941, 2857, 1727, 1660, 1467, 1436, 1361, 1257, 1203, 1168, 1096, 1028, 936, 777, 740, 697, 663 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.04 (6 H, s), 0.89 (9 H, s), 1.56−1.74 (4 H, m), 3.57−3.75 (2 H, m), 3.77 (3 H, s), 3.99 (1 H, q, J = 6.4 Hz), 4.39 (1 H, d, J = 11.9 Hz), 4.59 (1 H, d, J = 11.9 Hz), 6.04 (2 H, d, J = 16.9 Hz), 6.89 (2 H, dd, J = 16.0, 6.4 Hz), 7.21−7.75 (5 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.3, 18.2, 25.9, 28.2, 31.2, 51.5, 62.7, 70.9, 121.6, 127.4, 127.6, 127.6, 128.2, 128.3, 128.3, 128.4, 128.4, 128.4, 128.6, 132.0, 133.6, 138.0, 148.5, 166.6; HRMS (ESI) calcd for $[C_{21}H_{35}O_4Si]^+$ 379.2304, found 379.2297.



*4-Benzyloxy-7-hydroxy-hept-2-enoic Acid Methyl Ester (**S-049**).* To a solution of silyl ether (3.03 g, 8 mmol) in 10 mL of methanol was added 10-camphorsulfonic acid (1.86 g, 8 mmol). The solution was stirred for 20 min. Dichloromethane (50 mL) and 50 mL of saturated sodium bicarbonate were added. The solution was gently agitated until gas evolution stopped. The layers were separated, and the aqueous layer was back-extracted three times with 20 mL portions of dichloromethane. The combined aqueous extracts were washed with 50 mL of brine, dried over sodium sulfate, and concentrated to yield a dark yellow oil. The oil was purified by silica gel chromatography (10,20,30,50,[100]% EtOAc/hexanes) to yield the desired alcohol as a clear yellow oil (1.96 g, 93%): TLC R_f = 0.2 (30% EtOAc/hexanes); IR ($CHCl_3$ film) 3421, 3014, 2950, 2868, 1724, 1659, 1497, 1437, 1275, 1169, 1062, 985, 738, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.58−1.79 (4 H, m), 3.61 (1 H, q, J = 5.9 Hz), 3.75 (3 H, s), 4.00 (1 H, q, J = 4.9 Hz), 4.11 (2 H, q, J = 7.0 Hz), 4.37 (1 H, d, J = 11.7 Hz), 4.59 (1 H, d, J = 11.7 Hz), 6.03 (1 H, d, J = 17.1 Hz), 6.87 (1 H, dd, J = 16.1, 6.8 Hz), 7.26−7.38 (5 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.2, 31.2, 31.3, 51.6, 62.4, 71.0, 77.7, 121.8, 127.7, 127.8, 128.3, 128.4, 137.7, 148.1, 166.5; HRMS (ESI) calcd for $[C_{15}H_{21}O_4]^+$ 265.1440, found 265.1435.



*(E)-9-tert-Butyl 1-Methyl 4-(benzyloxy)-7-oxonon-2-enedioate (**17**).* The olefin−alcohol (1.25 g, 4.73 mmol) was dissolved in 50 mL of dichloromethane at 0 °C. Freshly distilled *N,N*-diisopropylethylamine (5.8 mL, 33.1 mmol) was added dropwise via syringe. After 10 min of stirring at 0 °C, dimethyl sulfoxide (3.34 mL, 47 mmol) was added to the reaction mixture via syringe, and the solution was allowed to stir for an additional 10 min. Sulfur trioxide pyridine complex (3.98 g, 18.9 mmol) was then added in one portion. The reaction was allowed to proceed for 2.5 h at 0 °C, after which TLC analysis indicated complete consumption of starting material. The reaction was quenched by transfer into an 125 mL Erlenmeyer flask that contained a stirring solution of saturated sodium bicarbonate solution (50 mL). Dichloromethane (50 mL) was added, and the layers were separated. The aqueous layer was back-extracted three times with three 20 mL portions of dichloromethane. The combined organic extracts were washed with 50 mL of brine, dried over sodium sulfate, and concentrated to yield a yellow oil. Excess pyridine was removed azeotropically with heptane. The oil was purified by silica gel chromatography (**15**, 30% EtOAc/hexanes) to yield the desired aldehyde as a clear oil (0.87 g, 70%): TLC R_f = 0.50 (30% EtOAc/hexanes, CAM stain); ^1H NMR (500 MHz, $CDCl_3$) δ 1.17−1.33 (1 H, m), 1.84−2.00 (2 H, m), 2.49−2.56 (1 H, m, J = 7.3, 6.3, 4.4,

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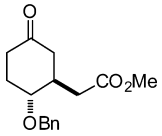
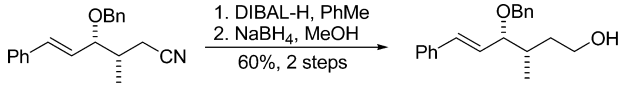
1.5 Hz), 3.73−3.78 (3 H, m), 3.99−4.04 (1 H, m, J = 7.3, 5.9, 4.4, 1.0 Hz), 4.33 (1 H, d, J = 11.7 Hz), 4.56 (1 H, d, J = 11.7 Hz), 6.05 (1 H, d, J = 17.1 Hz), 6.74−6.89 (1 H, m, J = 15.6, 5.9 Hz), 7.25−7.39 (5 H, m), 9.72 (1 H, s). To a dry vial were added tin(II) chloride (57 mg, 0.3 mmol) and dichloromethane (5 mL). *tert*-Butyl diazoacetate (0.97 mL, 7.0 mmol) was added dropwise to the vial with vigorous stirring. After gas evolution ceased, aldehyde (0.86 g, 3.28 mmol) was added, and the yellow solution was stirred overnight. The solution was diluted with 100 mL of dichloromethane and 100 mL of saturated sodium bicarbonate solution. The layers were separated, and the aqueous layer was back-extracted three times with 10 mL portions of dichloromethane. The combined organic layers were washed with 50 mL of water, 50 mL of brine, dried over sodium sulfate, and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (2% 2-propanol/hexanes). The remaining *tert*-butyl diazoacetate was removed by high vacuum evaporation to yield the desired ketoester as a yellow oil (1.00 g, 82%): TLC R_f = 0.50 (30% EtOAc/hexanes, purple, anisaldehyde stain); IR ($CHCl_3$ film) 2980, 2886, 1726, 1660, 1456, 1369, 1309, 1275, 1168, 1097, 843, 738, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.40−1.50 (9 H, m), 1.83 (1 H, td, J = 13.9, 7.8 Hz), 1.91−2.01 (1 H, m, J = 14.8, 7.3, 7.2, 4.9 Hz), 2.53−2.67 (2 H, m), 3.28 (2 H, d, J = 4.4 Hz), 3.73−3.78 (3 H, m), 3.97−4.05 (3 H, m, J = 7.6, 6.1, 4.9, 1.0 Hz), 4.33 (1 H, d, J = 11.7 Hz), 4.55 (1 H, d, J = 11.7 Hz), 6.04 (1 H, d, J = 14.6 Hz), 6.77−6.89 (1 H, m, J = 15.6, 6.3 Hz), 7.23−7.37 (5 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.9, 27.9, 28.2, 28.3, 37.9, 50.5, 51.6, 71.0, 76.4, 81.9, 122.0, 127.7, 128.4, 137.7, 147.6, 166.3, 166.4, 202.5; HRMS (ESI) calcd for $[C_{21}H_{32}O_6N]^+$ 394.2230, found 394.2240.

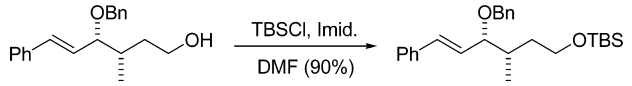


*Methyl 2-((1,2-erythro)-2-(Benzyloxy)-5-oxocyclohexyl)acetate (**S-049a**).* The properties of this compound matched those of a known compound.[37]

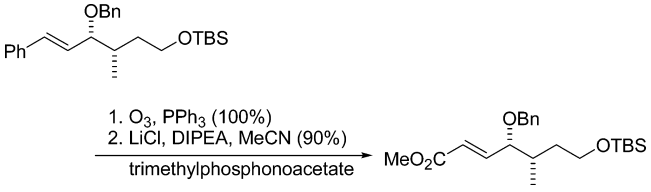


*(3S,4R,E)-4-(Benzyloxy)-3-methyl-6-phenylhex-5-en-1-ol (**S-050**).* The starting material was prepared by previously published procedures.[12] To a solution of cyanide (3.67 g, 12.6 mmol, azeotropically dried with benzene immediately prior to use) in 50 mL of dry toluene at −78 °C was added diisobutylaluminum hydride (2.37 mL, 18.9 mmol) dropwise over 10 min. The solution was warmed to −55 °C over 1 h and then stirred at −55 °C for 24 h. The reaction was quenched with the careful dropwise addition of 5 mL of 2-propanol. The solution was diluted with 300 mL of 1 M HCl and 300 mL of dichloromethane and stirred vigorously for 10 min. The layers were separated, and the aqueous phase was back-extracted four times with 50 mL portions of dichloromethane. The combined organic layers were washed with 200 mL of 1 M NaOH and 200 mL of brine. The solution was dried over sodium sulfate, and concentrated to yield the desired aldehyde as a clear oil (2.60 g, 70%).

The aldehyde (2.60 g, 8.82 mmol) was immediately dissolved in 30 mL of methanol and cooled to 0 °C. Sodium borohydride (0.95 g, 25 mmol) was added. The solution bubbled vigorously. After 10 min, the solution was warmed to room temperature and stirred for 50 min. The mixture was concentrated and resuspended in 100 mL of dichloromethane and 100 mL of 1 M HCl. The layers were separated, and the aqueous phase was back-extracted three times with dichloromethane. The combined organic extracts were washed with 50 mL of pH 7 buffer and 50 mL of brine. The solution was dried over sodium sulfate and concentrated to yield a clear oil. The oil was purified by silica gel chromatography (10, 30, 50% EtOAc/hexanes) to yield the desired alcohol as a clear oil (2.25 g, 60%): TLC R_f = 0.1 (20% EtOAc/hexanes, CAM stain); IR ($CHCl_3$ film) 3028, 2931, 2875, 1951, 1878, 1810, 1495, 1453, 1372, 1354, 1204, 1064, 970, 747, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.00 (3 H, d, J = 6.9 Hz), 1.42−1.54 (1 H, m, J = 12.8, 12.8, 6.9 Hz), 1.82 (1 H, td, J = 14.0, 6.4 Hz), 2.02 (1 H, ddd, J = 13.7, 6.9, 4.6 Hz), 2.29 (1 H, br s), 3.61−3.69 (1 H, m), 3.70−3.79 (1 H, m), 3.85 (1 H, dd, J = 8.0, 4.3 Hz), 4.42 (1 H, d, J = 11.9 Hz), 4.68 (1 H, d, J = 11.9 Hz), 6.21 (1 H, dd, J = 16.0, 8.2 Hz), 6.56 (1 H, d, J = 16.0 Hz), 7.25−7.32 (4 H, m), 7.33−7.39 (4 H, m), 7.43 (2 H, d, J = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.6, 35.7, 35.8, 61.3, 70.3, 84.2, 126.5, 127.5, 127.6, 127.6, 127.7, 128.3, 128.6, 133.8, 136.4, 138.3; $[\alpha]^{25}_D$ +88.8 (c = 3.81, $CDCl_3$); HRMS (ESI) calcd for $C_{20}H_{28}NO_2$ $[M + H]^+$ 314.2120, found 314.2131.



*(((3S,4R,E)-4-(Benzyloxy)-3-methyl-6-phenylhex-5-en-1-yl)oxy)-(tert-butyl)dimethylsilane (**S-051**).* To a solution of alcohol (2.25 g, 7.59 mmol) in 10 mL of DMF were added *tert*-butyldimethylsilyl chloride (1.20 g, 7.97 mmol) and imidazole (1.09 g, 16.0 mmol). The reaction was stirred overnight. The reaction was diluted with 100 mL of diethyl ether and 100 mL of saturated ammonium chloride solution. The layers were separated, and the aqueous phase was back-extracted three times with 20 mL portions of ether. The combined organic extracts were washed with 50 mL of brine, diluted with 100 mL of hexanes, dried over sodium sulfate, and concentrated under reduced pressure to afford the desired silyl ether as a clear and colorless oil (2.77 g, 90%): TLC R_f = 0.8 (20% EtOAc/hexanes, $KMnO_4$); IR ($CHCl_3$ film) 3028, 2929, 2857, 1944, 1870, 1801, 1496, 1467, 1388, 1360, 1300, 1255, 1206, 1094, 1038, 979, 970, 899, 836, 775, 746, 694, 665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 0.02−0.04 (6 H, m), 0.87−0.90 (9 H, m), 1.01 (3 H, d, J = 6.9 Hz), 1.35 (1 H, ddd, J = 19.5, 8.7, 6.2 Hz), 1.78−1.85 (3 H, m, J = 13.9, 7.1, 7.1, 4.6 Hz), 1.87−1.97 (1 H, m), 3.57−3.71 (2 H, m), 3.75 (1 H, dd, J = 7.8, 6.0 Hz), 4.39 (1 H, d, J = 11.9 Hz), 4.64 (1 H, d, J = 11.9 Hz), 6.16 (1 H, dd, J = 16.0, 7.8 Hz), 6.53 (1 H, d, J = 16.0 Hz), 7.23−7.30 (4 H, m), 7.31−7.37 (4 H, m), 7.41 (2 H, d, J = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.3, 15.4, 18.3, 25.9, 34.9, 35.8, 61.3, 70.2, 84.0, 126.4, 127.3, 127.6, 128.2, 128.5, 129.1, 132.9, 136.7, 138.9; $[\alpha]^{25}_D$ +90.3 (c = 0.64, $CDCl_3$); HRMS (ESI) calcd for $C_{26}H_{42}O_2SiN$ $[M + NH_4]^+$ 428.2985, found 428.2999.



*(4R,5S,E)-Methyl 4-(Benzyloxy)-7-((tert-butyldimethylsilyl)oxy)-5-methylhept-2-enoate (**S-052**).* To a solution of silyl ether (2.70 g, 6.57 mmol) in 15 mL of dichloromethane at −78 °C was added ozone until the solution turned blue. The solution was then sparged with nitrogen for 5 min. Triphenylphosphine (1.72 g, 6.57 mmol) was then added. The solution was allowed to warm to room temperature. The reaction was stirred for 3 h. The bulk of the solvent was removed, and the mixture was dissolved in 50 mL of 30% EtOAc/hexanes. The solution was filtered through a silica plug (5 × 5 cm). The plug was washed with 50 mL of 30% EtOAc/hexanes. The solution was concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (5, 10% EtOAc/hexanes) to yield the desired aldehyde as a yellow oil (2.21 g, 100%): TLC R_f = 0.8 (20% EtOAc/hexanes); ^1H NMR (600 MHz, $CDCl_3$) δ 0.04−0.08 (6 H, m), 0.89−0.94 (9 H, m), 0.98−1.05 (3 H, m), 1.49 (1 H, ddd, J = 19.6, 7.9, 5.9 Hz), 1.75 (1 H, td, J = 13.3, 6.6 Hz), 2.20−2.32 (1 H, m), 4.52 (1 H, d, J = 12.0 Hz), 4.76 (1 H, d, J = 12.0 Hz), 7.30−7.42 (5 H, m), 9.73 (1 H, d, J = 2.1 Hz).

To 50 mL of freshly distilled acetonitrile were added lithium chloride (2.79 g, 65.7 mmol), freshly distilled diisopropylethylamine (3.43 mL, 19.7 mmol), and trimethyl phosphonoacetate (1.59 mL, 9.86 mmol). Aldehyde (2.21 g, 6.57 mmol) was then added. The yellow suspension was heated at 60 °C for 1.5 h after which ^1H NMR analysis indicated complete consumption of starting material. The suspension was cooled and poured into a separatory funnel. One hundred milliliters of 25% EtOAc/hexanes followed by 100 mL of 1 M HCl were carefully poured in. The layers were separated, and the aqueous layer was back-extracted five times with 20 mL portions of 25% EtOAc/hexanes. The combined

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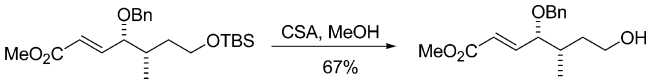
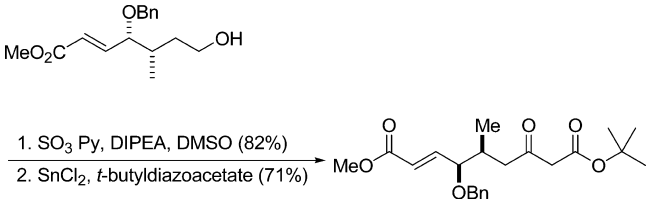
organic layers were washed twice with 75 mL portions of 1 M NaOH, followed by 100 mL of brine. The combined organic extracts were dried over sodium sulfate and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (10% EtOAc/hexanes) to afford the desired enoate as a yellow oil (2.3 g, 90%, >20:1 *E*:*Z*): TLC R_f = 0.7 (20% EtOAc/hexanes, $KMnO_4$ stain); IR ($CHCl_3$ film) 3060, 2952, 2929, 2857, 1959, 1888, 1810, 1725, 1658, 1638, 1582, 1496, 1472, 1458, 1435, 1388, 1360, 1312, 1273, 1257, 1202, 1170, 1094, 1034, 987, 900, 836, 775, 744, 721, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.01−0.04 (6 H, m), 0.86−0.91 (9 H, m), 0.94 (3 H, d, *J* = 6.9 Hz), 1.29−1.39 (1 H, m), 1.68−1.76 (1 H, m), 1.87−1.97 (1 H, m), 3.55−3.65 (2 H, m), 3.76 (3 H, s), 3.86 (1 H, t, *J* = 5.0 Hz), 4.35 (1 H, d, *J* = 11.9 Hz), 4.59 (1 H, d, *J* = 11.9 Hz), 6.03 (1 H, d, *J* = 14.6 Hz), 6.90 (1 H, dd, *J* = 16.0, 6.4 Hz), 7.22−7.40 (5 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.3, −5.3, 14.8, 18.2, 25.9, 30.9, 34.0, 35.5, 51.5, 60.9, 71.1, 81.5, 122.3, 127.5, 127.6, 128.0, 128.3, 128.4, 128.4, 128.5, 128.6, 128.8, 130.2, 131.9, 132.0, 132.1, 133.6, 133.7, 138.2, 147.5, 167.4; $[\alpha]^{25}_D$ +14.0 (*c* = 0.64, $CDCl_3$); HRMS (ESI) calcd for $C_{22}H_{40}NO_4Si$ $[M + NH_4]^+$ 410.2727, found 410.2722.

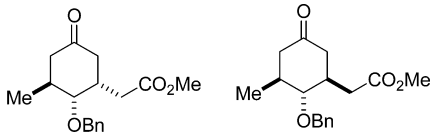


*(4R,5S,E)-Methyl 4-(Benzyloxy)-7-hydroxy-5-methylhept-2-enoate (**S-053**).* To a solution of silyl ether (2.30 g, 5.86 mmol) in 20 mL of methanol was added 10-camphorsulfonic acid (1.36 g, 5.86 mmol). The solution was stirred for 45 min. Dichloromethane (50 mL) and 50 mL of saturated sodium bicarbonate was added. The solution was gently agitated until gas evolution stopped. The layers were separated, and the aqueous layer was back-extracted three times with 20 mL portions of dichloromethane. The combined aqueous extracts were washed with 50 mL of brine, dried over sodium sulfate, and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (10, 20, 50% EtOAc/hexanes) to yield the desired alcohol as a clear yellow oil (1.08 g, 67%): TLC R_f = 0.1 (20% EtOAc/hexanes, CAM stain); IR ($CHCl_3$ film) 3417, 2936, 2876, 1724, 1657, 1436, 1277, 1196, 1171, 1066, 987, 866, 738, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.95 (3 H, d, *J* = 6.9 Hz), 1.44 (1 H, td, *J* = 13.7, 6.0 Hz), 1.73 (1 H, td, *J* = 13.8, 6.2 Hz), 2.00 (1 H, ddd, *J* = 13.5, 7.1, 4.6 Hz), 3.58−3.64 (1 H, m, *J* = 11.0, 7.8, 6.0 Hz), 3.66−3.74 (1 H, m), 3.77 (3 H, s), 3.90 (1 H, ddd, *J* = 6.3, 4.7, 1.4 Hz), 4.37 (1 H, d, *J* = 11.9 Hz), 4.61 (1 H, d, *J* = 11.9 Hz), 6.05 (1 H, d, *J* = 16.9 Hz), 6.91 (1 H, dd, *J* = 16.0, 6.4 Hz), 7.31 (5 H, d); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.7, 34.7, 35.5, 51.6, 61.0, 71.2, 81.8, 122.9, 127.6, 127.7, 128.4, 137.8, 146.4, 166.4; $[\alpha]^{25}_D$ +36.1 (*c* = 0.81, $CDCl_3$); HRMS (ESI) calcd for $C_{16}H_{23}O_4$ $[M + H]^+$ 279.1596, found 279.1606.

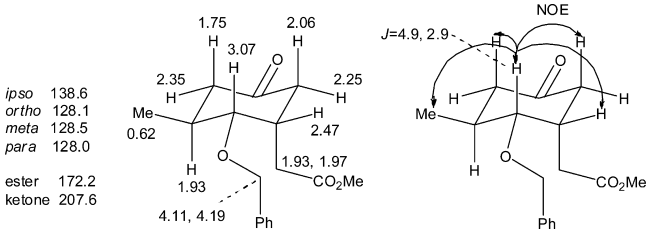


*(4R,5S,E)-9-tert-Butyl 1-Methyl 4-(benzyloxy)-5-methyl-7-oxonon-2-enedioate (**19**).* The olefin−alcohol (1.05 g, 3.77 mmol) was dissolved in 10 mL of dichloromethane at 0 °C. Freshly distilled *N*,*N*-diisopropylethylamine (4.88 mL, 28.0 mmol) was added dropwise via syringe. After 10 min of stirring at 0 °C, dimethyl sulfoxide (2.70 mL, 38.0 mmol) was added to the reaction mixture via syringe, and the solution was allowed to stir for an additional 10 min. Sulfur trioxide−pyridine complex (3.36 g, 16.0 mmol) was then added in one portion. The reaction was allowed to proceed for 2 h at 0 °C, after which TLC analysis indicated complete consumption of starting material. The reaction was quenched by transfer into an 125 mL Erlenmeyer flask that contained a stirring solution of saturated sodium bicarbonate solution (50 mL). Dichloromethane (50 mL) was added, and the layers were separated. The aqueous layer was back-extracted three times with three 20 mL portions of dichloromethane. The combined organic extracts were washed with 50 mL of brine, dried over sodium sulfate, and concentrated to yield a yellow oil. Excess pyridine was removed azeotropically with heptane. The oil was purified by silica gel chromatography (5, 10, 20% EtOAc/hexanes) to yield the desired aldehyde as a clear oil (0.86 g, 82%): TLC R_f = 0.40 (20% EtOAc/hexanes, CAM stain); ^1H NMR (500 MHz, $CDCl_3$) δ ppm 0.98 (3 H, d, *J* = 6.8 Hz), 2.19−2.32 (1 H, m), 2.39−2.51 (1 H, m), 2.61 (1 H, dd, *J* = 17.1, 5.9 Hz), 3.95 (1 H, ddd, *J* = 6.0, 4.5, 1.2 Hz), 4.33 (2 H, d, *J* = 11.7 Hz), 4.59 (2 H, d, *J* = 12.2 Hz), 6.83−6.91 (4 H, m, *J* = 22.0, 6.3 Hz), 7.20−7.44 (5 H, m), 9.71 (1 H, s).

To a dry vial were added tin(II) chloride (57 mg, 0.3 mmol) and dichloromethane (5 mL). *tert*-Butyl diazoacetate (0.46 mL, 3.3 mmol) was added dropwise to the vial with vigorous stirring. After gas evolution ceased, aldehyde (0.34 g, 1.22 mmol) was added, and the yellow solution was stirred overnight. The solution was diluted with 100 mL of dichloromethane and 100 mL of saturated sodium bicarbonate solution. The layers were separated, and the aqueous layer was back-extracted three times with 10 mL portions of dichloromethane. The combined organic layers were washed with 50 mL of water and 50 mL of brine, dried over sodium sulfate, and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (0, 10, 20, 50% EtOAc/hexanes). The remaining *tert*-butyl diazoacetate was removed by high vacuum evaporation to yield the desired β-ketoester as a yellow oil (0.42 g, 90%): TLC R_f = 0.3 (20% EtOAc/hexanes, $KMnO_4$ stain); IR ($CHCl_3$ film) 2978, 2879, 1726, 1654, 1456, 1436, 1369, 1307, 1275, 1159, 1070, 987, 843, 738, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ ppm 0.93 (3 H, d, *J* = 6.9 Hz), 1.42−1.51 (9 H, m), 2.31−2.38 (1 H, m, *J* = 16.9, 7.8 Hz), 2.40−2.47 (1 H, m), 2.70 (1 H, dd, *J* = 17.2, 5.3 Hz), 3.25 (2 H, d, *J* = 6.4 Hz), 3.77 (3 H, s), 3.94 (1 H, ddd, *J* = 5.8, 4.2, 1.4 Hz), 4.33 (1 H, d, *J* = 11.9 Hz), 4.57 (1 H, d, *J* = 11.9 Hz), 6.06 (1 H, d, *J* = 14.2 Hz), 6.87 (1 H, dd, *J* = 15.6, 6.0 Hz), 7.24−7.37 (5 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) 15.1, 27.9, 32.8, 45.3, 51.0, 51.6, 71.1, 80.2, 81.9, 122.8, 127.7, 127.7, 128.4, 137.9, 146.2, 166.3, 166.4, 202.3; $[\alpha]^{25}_D$ +116 (*c* = 1.38, CH_2Cl_2); HRMS (ESI) calcd for $C_{22}H_{34}O_6N$ $[M + NH_4]^+$ 408.2386, found 408.2373.



*Methyl 2-((1R,2R,3S)-2-(Benzyloxy)-3-methyl-5-oxocyclohexyl)-acetate (**S-054-syn**).* The crude decarboxylated adduct was purified by silica gel chromatography (gradient elution: 5, 10, 15, 25% EtOAc/hexanes) to yield the desired decarboxylated adduct as a mixture of diastereomers. The yellow oil was purified by preparative HPLC (Zorbax RX-SIL, 0.7% 2-propanol/hexanes, 215 nm, 20 mL/min). This separated the desired 1,2-*cis* (**S-65**, 19 min) and 1,2-*trans* (**S-66**, 31 min) isomers: TLC R_f = 0.20 (20% EtOAc/hexanes, CAM stain); ^1H NMR (500 MHz, C_6D_6) (^{13}C NMR, 125 MHz, via gHSQC/gHMBC correlations) δ 0.62−17.1 (3 H, d, *J* = 7.3 Hz), 1.75−43.5 (1 H, dd, *J* = 13.5, 5.1), 1.88−1.97 − 32.5 (1 H, m), 1.97−35.6 (1 H, dd, *J* = 16.0, 7.1 Hz), 2.06−43.2 (1 H, dd, *J* = 14.0, 4.9 Hz), 2.25−43.2 (1 H, dd, *J* = 14.0, 10.7 Hz), 2.35−43.5 (1 H, dd, *J* = 13.5, 4.6 Hz), 2.37−2.43 − 35.6 (1 H, m, *J* = 16.0, 7.3 Hz), 2.43−2.52 − 34.1 (1 H, m), 3.07−79.8 (1 H, dd, *J* = 4.9, 2.9), 3.23−50.9 (3 H, s), 4.11−71.1 (1 H, d, *J* = 11.4), 4.19−71.1 (1 H, d, *J* = 11.4), 7.04−7.21 − 128.03−128.08−128.48, quaternary carbons: 138.5, 172.2, 207.6; HRMS calcd for $C_{17}H_{23}O_4$ $[M + H]^+$ 291.1596, found 291.1606.



*Methyl 2-((1S,2R,3S)-2-(benzyloxy)-3-methyl-5-oxocyclohexyl)-acetate (**S-054-anti**):* TLC R_f = 0.20 (20% EtOAc/hexanes, CAM stain); ^1H NMR (500 MHz, $CDCl_3$) 1.18 (3 H, d, *J* = 7.0 Hz), 2.05−2.52

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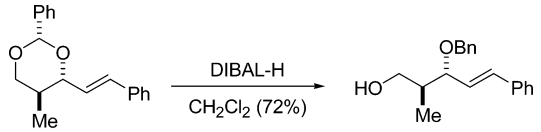
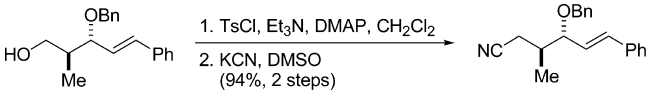
(7 H, m), 2.69 (1 H, dd, J = 5.4, 15.4 Hz), 3.34 (1 H, t, J = 9.6 Hz), 3.62 (3 H, s), 4.63 (2 H, dd, J = 11.4 Hz), 7.26−7.39 (5 H, m); HRMS calcd for $C_{17}H_{23}O_4$ $[M + H]^+$ 291.1596, found 291.1606.

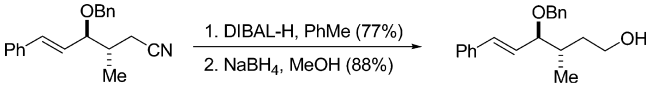
(2S,4R,5S)-5-Methyl-2-phenyl-4-((E)-styryl)-1,3-dioxane (***S-055***). The starting material oxazolidinone was obtained from our previously reported magnesium-catalyzed antialdol procedures.[38] To a solution of oxazolidinone (25.0 g, 68.4 mmol) in 600 mL of diethyl ether at −10 °C was added lithium borohydride (34.2 mL, 68.4 mmol, as a 2.0 M solution in THF). The reaction was stirred for 1.5 h and quenched with 150 mL of 1 M NaOH and 200 mL of water. The layers were separated and the aqueous layer was back-extracted three times with 100 mL portions of ether. The combined organic extracts were washed with 100 mL of brine, diluted with 300 mL of hexanes, dried over sodium sulfate, and concentrated to give a yellow oil. The oil was dissolved in dichloromethane and filtered through a silica plug (5 × 2 cm). The plug was rinsed with 20% EtOAc/dichloromethane, and the combined filtrate was concentrated to give the desired diol as a crude yellow oil. TLC R_f = 0.2 (50% EtOAc/hexanes, CAM stain). The diol was dissolved in 400 mL of benzene, and dimethoxymethylbenzene (13.3 mL, 88.9 mmol) and p-toluenesulfonic acid monohydrate (17.0 g, 88.9 mmol) were added. The reaction was stirred overnight. The reaction was diluted with 500 mL of saturated sodium bicarbonate solution. The layers were separated, and the aqueous layer was back-extracted with three 100 mL portions of dichloromethane. The combined organic layers were washed with 200 mL of brine, dried over sodium sulfate, and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (10% EtOAc/hexanes) to yield the desired benzylidene acetal (13.0 g, 63%). NOESY measurements (1D PFGSE) confirmed the proposed all-equatorial stereochemistry at the benzylidene acetal: TLC R_f = 0.5 (50% EtOAc/hexaenes); IR ($CHCl_3$ film) 3029, 2562, 2896, 2842, 1494, 1451, 1396, 1370, 1300, 1162, 1147, 1107, 1086, 1071, 1026, 974, 926, 747, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (3 H, d, J = 7.0 Hz), 1.92−2.11 (1 H, m), 3.61 (1 H, t, J = 11.4 Hz), 4.08 (1 H, dd, J = 9.7, 7.5 Hz), 4.22 (1 H, dd, J = 11.4, 4.8 Hz), 5.61 (1 H, s), 6.27 (1 H, dd, J = 15.9, 7.5 Hz), 6.70 (1 H, d, J = 15.7 Hz), 7.20−7.58 (10 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 34.3, 73.0, 84.5, 101.2, 126.1, 126.6, 127.2, 127.8, 128.2, 128.5, 128.8, 133.1, 136.5, 138.4; $[\alpha]^{25}_D$ +12.5 (c = 2.63, CH_2Cl_2); HRMS (ESI) calcd for $[C_{19}H_{24}O_2N]^+$ 298.1807, found 298.1817.



(2S,3R,E)-3-(Benzyloxy)-2-methyl-5-phenylpent-4-en-1-ol (***S-056***). To a solution of benzylidene acetal (19.3 g, 68.8 mmol) in 275 mL of dichloromethane at −78 °C was added DIBAL-H (36.7 mL, 206 mmol) dropwise via syringe. The reaction was stirred for 1 h and then warmed to −10 °C. The reaction was allowed to proceed for 48 h. The reaction was slowly quenched with methanol and diluted with 500 mL of 1 M HCl. The mixture was stirred vigorously, and the layers were separated. The aqueous layer was back-extracted three times with 50 mL portions of dichloromethane. The combined organic extracts were washed three times with 100 mL portions of brine, dried over sodium sulfate, and concentrated to yield a yellow oil. The oil was purifed by silica gel chromatography (10, 20, 30, 40% EtOAc/hexanes) to yield the desired alcohol as a clear oil (13.9 g, 72%; also recovered 3% of the incorrect regioisomer). TLC R_f = 0.2 (20% EtOAc/hexanes); IR ($CHCl_3$ film) 3414, 3028, 2962, 2875, 1599, 1494, 1454, 1378, 1660, 1206, 1085, 1066, 1028, 970, 912, 748, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.89 (3 H, dd, J = 7.0, 1.5 Hz), 1.91−2.09 (2 H, m), 3.01 (1 H, dd, J = 7.0, 3.3 Hz), 3.62−3.75 (2 H, m), 3.86 (1 H, t, J = 8.2 Hz), 4.41 (1 H, d, J = 11.7 Hz), 4.68 (1 H, d, J = 11.7 Hz), 6.14 (1 H, ddd, J = 15.9, 8.4, 1.6 Hz), 6.57 (1 H, d, J = 15.7 Hz), 7.22−7.50 (10 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 40.2, 67.2, 70.2, 85.7, 126.5, 127.7, 127.8, 127.9, 128.3, 128.4, 128.4, 128.6, 134.0, 136.1, 137.9; $[\alpha]^{25}_D$ −84.2° (c = 1.93, CH_2Cl_2); HRMS (ESI) calcd for $[C_{19}H_{26}O_2N]^+$ 300.1964, found 300.1966.



4-Benzyloxy-3-methyl-6-phenylhex-5-enenitrile (***S-057***). To a solution of alcohol (13.8 g, 48.9 mmol) in 63 mL of dichloromethane were added p-toluenesulfonyl chloride (10.2 g, 53.7 mmol), 4-dimethylaminopyridine (0.60 mg, 4.89 mmol), and triethylamine (8.5 mL, 91.1 mmol). The reaction was stirred for 6 h and then diluted with 100 mL of 1 M HCl. The layers were separated, and the aqueous layer was back-extracted with three 25 mL portions of dichloromethane. The combined organic extracts were washed with 100 mL of brine, dried over sodium sulfate, and concentrated to yield the desired tosylate as a yellow oil. TLC R_f = 0.35 (20% EtOAc/hexanes, $KMnO_4$ stain). The oil was immediately dissolved in 50 mL of DMSO. Potassium cyanide (6.37 g, 48.9 mmol) was added (caution: highly toxic!), and the mixture was heated at 50 °C for 20 h. The mixture was diluted with 250 mL of 1 M NaOH. The layers were separated and the aqueous layer was back-extracted three times with 200 mL portions of diethyl ether. The combined organic layers were diluted with 400 mL of hexanes, washed with 200 mL of brine, dried over sodium sulfate, and concentrated to yield the desired cyanide (13.4 g, 94%) as a yellow oil, which did not require further purification: TLC R_f = 0.5 (20% EtOAc/hexanes, $KMnO_4$ stain); IR ($CHCl_3$ film) 3061, 2968, 2931, 2864, 2245, 1652, 1600, 1578, 1495, 1454, 1420, 1385, 1348, 1206, 1109, 1086, 1028, 971, 748, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.12 (3 H, d, J = 7.0 Hz), 2.04−2.19 (1 H, m), 2.58 (2 H, d, J = 5.5 Hz), 3.76 (1 H, t, J = 8.2 Hz), 4.40 (1 H, d, J = 11.4 Hz), 4.66 (1 H, d, J = 11.7 Hz), 6.08 (1 H, dd, J = 15.9, 8.2 Hz), 6.64 (1 H, d, J = 16.1 Hz), 7.26−7.48 (10 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) 16.0, 20.9, 35.3, 70.5, 82.7, 118.8, 126.5, 127.3, 127.7, 127.8, 128.1, 128.4, 128.6, 134.9, 135.9, 137.9; $[\alpha]^{25}_D$ −61.6 (c = 3.05, CH_2Cl_2); HRMS (ESI) calcd for $[C_{20}H_{25}ON_2]^+$ 309.1967, found 309.1971.



4-Benzyloxy-3-methyl-6-phenylhex-5-en-1-ol (***S-058***). To a solution of cyanide (1.40 g, 4.8 mmol, azeotropically dried with benzene immediately prior to use) in 100 mL of dry toluene at −40 °C was added diisobutylaluminum hydride (0.90 mL, 7.2 mmol) dropwise over 10 min. The solution was warmed to −20 °C over 1 h and then stirred at −20 °C for 10 h. The reaction was quenched with the careful dropwise addition of 2 mL of 2-propanol. The solution was diluted with 200 mL of 1 M HCl and stirred vigorously for 10 min. The layers were separated and the aqueous phase was back-extracted three times with 20 mL portions of ethyl acetate. The combined organic layers were washed with 200 mL of pH 7 phosphate buffer and 200 mL of brine. The solution was dried over sodium sulfate and concentrated to yield the desired aldehyde as a clear oil (1.10 g, 77%): TLC R_f = 0.45 (20% EtOAc/hexanes, CAM stain); ^1H NMR (500 MHz, $CDCl_3$) δ 0.98 (3 H, d, J = 6.9 Hz), 2.26−2.46 (3 H, m), 2.64 (1 H, ddd, J = 16.0, 6.2, 2.5 Hz), 3.65 (1 H, t, J = 8.0 Hz), 4.36 (1 H, d, J = 11.4 Hz), 4.61 (1 H, d, J = 11.4 Hz), 6.09 (1 H, dd, J = 16.0, 8.2 Hz), 6.56 (1 H, d, J = 15.6 Hz), 7.11−7.49 (10 H, m), 9.76 (1 H, s).

The aldehyde (1.04 g, 3.53 mmol) was immediately dissolved in 10 mL of methanol and cooled to 0 °C. Sodium borohydride (0.40 g, 10.5 mmol) was added. The solution bubbled vigorously. After 10 min, the solution was warmed to room temperature and stirred for 30 min. The mixture was concentrated and resuspended in 100 mL of dichloromethane and 100 mL of 1 M HCl. The layers were separated, and the aqueous phase was back-extracted three times with dichloromethane. The combined organic extracts were washed with 50 mL of pH 7 buffer and 50 mL of brine. The solution was dried over sodium sulfate and concentrated to yield a clear oil. The oil was purified by silica gel chromatography (20, 30, 50% EtOAc/hexanes) to yield the desired

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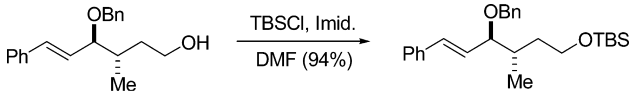
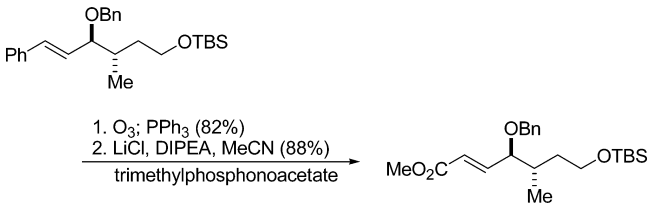
alcohol as a clear oil (0.92 g, 88%): TLC R_f = 0.1 (20% EtOAc/hexanes, CAM stain); IR ($CHCl_3$ film) 3349, 3027, 2960, 2927, 2871, 1598, 1494, 1452, 1380, 1065, 970, 892, 748, 693 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.96 (3 H, d, J = 7.3 Hz), 1.79−1.88 (1 H, m), 1.90−1.98 (1 H, m), 1.99−2.08 (1 H, m), 3.61−3.78 (3 H, m), 4.40 (1 H, d, J = 11.9 Hz), 4.66 (1 H, d, J = 11.9 Hz), 6.14 (1 H, dd, J = 16.0, 8.7 Hz), 6.54 (1 H, d, J = 16.0 Hz), 7.23−7.47 (10 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.5, 30.9, 35.6, 36.3, 61.0, 70.3, 84.6, 126.5, 127.5, 127.8, 127.9, 128.3, 128.6, 128.7, 133.6, 136.4, 138.3; $[\alpha]^{25}_D$ −69.2 (c = 0.48, $CDCl_3$); HRMS calcd for $C_{20}H_{28}O_2N$ $[M + NH_4]^+$ 314.2120, found 314.2124.

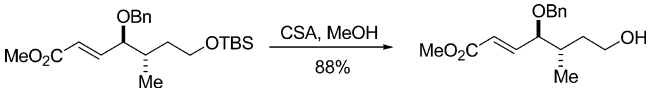


*(4-Benzyloxy-3-methyl-6-phenylhex-5-enyloxy)-tert-butyldimethylsilane (**S-059**).* To a solution of alcohol (0.90 g, 3.04 mmol) in 5 mL of DMF were added *tert*-butyldimethylsilyl chloride (0.50 g, 3.3 mmol) and imidazole (0.48 g, 7.0 mmol). The reaction was stirred overnight. The reaction was diluted with 100 mL of diethyl ether and 100 mL of saturated ammonium chloride solution. The layers were separated, and the aqueous phase was back-extracted three times with 20 mL portions of ether. The combined organic extracts were washed with 50 mL of brine, diluted with 100 mL of hexanes, dried over sodium sulfate, and concentrated under reduced pressure to afford the desired silyl ether as a clear and colorless oil (1.28 g, 94%): TLC R_f = 0.8 (20% EtOAc/hexanes, $KMnO_4$); IR ($CHCl_3$ film) 3028, 2928, 2856, 1945, 1874, 1806, 1726, 1658, 1600, 1495, 1462, 1388, 1360, 1301, 1255, 1206, 1094, 1028, 1005, 970, 898, 835, 775, 747, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.01−0.07 (6 H, m), 0.86−0.91 (9 H, m), 0.94−0.98 (3 H, m, J = 6.4, 6.4 Hz), 1.32−1.41 (3 H, m, J = 13.7, 8.7, 6.9, 5.5 Hz), 1.82−1.90 (1 H, m), 1.96 (1 H, ddd, J = 12.9, 6.6, 6.5 Hz), 3.63−3.72 (2 H, m), 3.75 (1 H, dd, J = 7.8, 6.0 Hz), 4.37−4.44 (1 H, m, J = 12.4 Hz), 4.64 (1 H, d, J = 11.9 Hz), 6.15 (1 H, dd, J = 15.8, 8.0 Hz), 6.54 (1 H, d, J = 16.0 Hz), 7.24−7.29 (2 H, m), 7.31−7.37 (6 H, m), 7.40−7.43 (4 H, m, J = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.28, −5.25, 15.6, 18.3, 25.9, 34.8, 36.0, 61.5, 70.2, 84.3, 126.4, 127.3, 127.6, 128.2, 128.5, 133.2, 136.7, 138.9; $[\alpha]^{25}_D$ −41.3° (c = 1.68, $CDCl_3$); HRMS (ESI) calcd for $C_{26}H_{42}O_2SiN$ $[M + NH_4]^+$ 428.2985, found 428.2968.

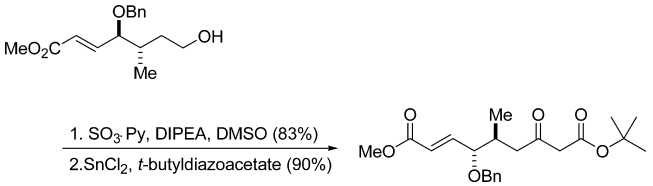


*4-Benzyloxy-7-(tert-butyldimethylsilanyloxy)-5-methylhept-2-enoic Acid Methyl Ester (**S-060**).* To a solution of silyl ether (1.53 g, 1.22 mmol) in 15 mL of dichloromethane at −78 °C was added ozone until the solution turned blue. The solution was then sparged with nitrogen for 5 min. Triphenylphosphine (1.00 g, 3.8 mmol) was then added. The solution was allowed to warm to room temperature. The reaction was stirred for 3 h. The bulk of the solvent was removed, and the mixture was dissolved in 50 mL of 30% EtOAc/hexanes. The solution was filtered through a silica plug (5 × 5 cm). The plug was washed with 50 mL of 30% EtOAc/hexanes. The solution was concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (5, 10% EtOAc/hexanes) to yield the desired aldehyde as a yellow oil (1.03 g, 82%): TLC R_f = 0.8 (20% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 0.03 (9 H, s), 0.84−0.90 (9 H, m), 1.00 (3 H, d, J = 6.8 Hz), 1.40−1.50 (1 H, m, J = 14.1, 8.6, 5.6, 5.4 Hz), 1.71−1.81 (2 H, m, J = 14.2, 14.2, 6.8 Hz), 2.16−2.26 (1 H, m), 3.55−3.72 (3 H, m), 4.51 (1 H, d, J = 12.2 Hz), 4.69 (1 H, d, J = 11.7 Hz), 7.28−7.41 (10 H, m), 9.62−9.72 (1 H, m, J = 2.4 Hz).

To 50 mL of freshly distilled acetonitrile were added lithium chloride (1.06 g, 25 mmol), freshly distilled diisopropylethylamine (1.31 mL, 7.5 mmol), and trimethylphosphonoacetate (0.60 mL, 3.75 mmol). Aldehyde (0.84 g, 2.5 mmol) was then added. The yellow suspension was heated at 60 °C for 3 h. The suspension was cooled and poured into a separatory funnel. One hundred milliliters of 25% EtOAc/hexanes followed by 100 mL of 1 M HCl were carefully poured in. The layers were separated, and the aqueous layer was back-extracted five times with 20 mL portions of 25% EtOAc/hexanes. The combined organic layers were washed twice with 75 mL portions of 1 M NaOH, followed by 100 mL of brine. The combined organic extracts were dried over sodium sulfate and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (10% EtOAc/hexanes) to afford the desired enoate as a yellow oil (0.87 g, 88%, >20:1 E:Z): TLC R_f = 0.7 (20% EtOAc/hexanes, $KMnO_4$ stain); IR ($CHCl_3$ film) 2942, 2857, 1728, 1658, 1462, 1435, 1388, 1360, 1256, 1169, 1095, 988, 900, 836, 776, 734, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.01−0.05 (6 H, m), 0.87−0.90 (9 H, m), 0.90−0.93 (3 H, m, J = 6.9 Hz), 1.29−1.37 (1 H, m), 1.70−1.78 (1 H, m, J = 14.0, 7.3, 7.1, 4.6 Hz), 1.93−2.02 (1 H, m), 3.57−3.72 (2 H, m), 3.76 (3 H, s), 3.82−3.86 (1 H, m, J = 6.4, 6.4, 1.4 Hz), 4.38 (1 H, d, J = 11.9 Hz), 4.57 (1 H, d, J = 11.9 Hz), 6.03 (1 H, d, J = 15.6 Hz), 6.81−6.93 (1 H, m), 7.22−7.41 (5 H, m) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.3, −5.3, 15.2, 18.2, 25.8, 25.9, 34.2, 35.4, 51.5, 61.1, 71.0, 82.1, 122.7, 127.5, 128.3, 138.2, 147.0, 166.5; $[\alpha]^{25}_D$ −7.8° (c = 2.03, $CDCl_3$); HRMS calcd for $C_{22}H_{40}O_4SiN$ $[M + NH_4]^+$ 410.2727, found 410.2722.



*4-Benzyloxy-7-hydroxy-5-methylhept-2-enoic Acid Methyl Ester (**S-061**).* To a solution of silyl ether (0.70 g, 1.78 mmol) in 10 mL of methanol was added 10-camphorsulfonic acid (0.47 g, 2.0 mmol). The solution was stirred for 30 min. Dichloromethane (50 mL) and 50 mL of saturated sodium bicarbonate were added. The solution was gently agitated until gas evolution stopped. The layers were separated, and the aqueous layer was back-extracted three times with 20 mL portions of dichloromethane. The combined aqueous extracts were washed with 50 mL of brine, dried over sodium sulfate, and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (10, 20, 50% EtOAc/hexanes) to yield the desired alcohol as a clear yellow oil (0.44 g, 88%): TLC R_f = 0.1 (20% EtOAc/hexanes, CAM stain); IR ($CHCl_3$ film) 3427, 2953, 2876, 1725, 1656, 1455, 1437, 1277, 1196, 1171, 1066, 988, 868, 737, 699 cm^{-1}; ^{13}C NMR (500 MHz, $CDCl_3$) δ 0.93 (3 H, d, J = 6.9 Hz), 1.44−1.52 (1 H, m), 1.70 (1 H, br s, J = 2.8 Hz), 1.72−1.80 (1 H, m), 1.91−1.98 (1 H, m), 3.58−3.66 (1 H, m), 3.69−3.74 (1 H, m), 3.76−3.83 (4 H, m), 4.36 (1 H, d, J = 11.4 Hz), 4.60 (1 H, d, J = 11.9 Hz), 6.03 (1 H, d, J = 14.6 Hz), 6.87 (1 H, dd, J = 15.8, 6.6 Hz), 7.22−7.39 (5 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.9, 30.9, 34.7, 35.6, 51.6, 60.7, 71.2, 82.3, 110.6, 123.0, 127.8, 128.4, 137.7, 146.8, 166.4; $[\alpha]^{25}_D$ −32.7 (c = 0.60, $CDCl_3$); HRMS (ESI) calcd for $C_{16}H_{26}O_4N$ $[M + NH_4]^+$ 296.1862, found 296.1868.



*(4S,5S,E)-9-tert-Butyl 1-Methyl 4-(Benzyloxy)-5-methyl-7-oxonon-2-enedioate (**21**).* The olefin−alcohol (0.37 g, 1.33 mmol) was dissolved in 10 mL of dichloromethane at 0 °C. Freshly distilled *N,N*-diisopropylethylamine (1.62 mL, 9.31 mmol) was added dropwise via syringe. After 10 min of stirring at 0 °C, dimethyl sulfoxide (0.94 mL, 13.3 mmol) was added to the reaction mixture via syringe and the solution was allowed to stir for an additional 10 min. Sulfur trioxide−pyridine complex (1.11 g, 5.3 mmol) was then added in one portion. The reaction was allowed to proceed for 2 h at 0 °C, after which TLC analysis indicated complete consumption of starting material. The reaction was quenched by transfer into an 125 mL Erlenmeyer flask that contained a stirring solution of saturated sodium bicarbonate solution (50 mL). Dichloromethane (50 mL) was added, and the layers were separated. The aqueous layer was back-extracted three times with three 20 mL portions of dichloromethane. The combined organic extracts were washed with 50 mL of brine, dried over sodium sulfate, and concentrated to yield a yellow oil. Excess pyridine was removed

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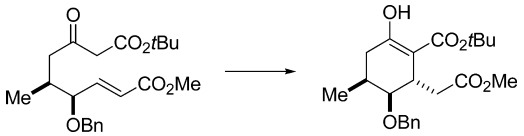
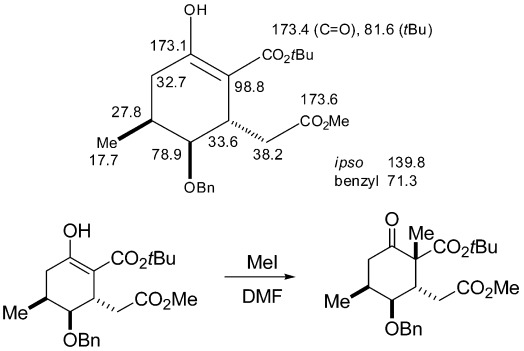
azeotropically with heptane. The oil was purified by silica gel chromatography (5, 10, 20% EtOAc/hexanes) to yield the desired aldehyde as a clear oil (0.29 g, 83%): TLC R_f = 0.40 (20% EtOAc/hexanes, CAM stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (3 H, d, J = 6.3 Hz), 2.27−2.39 (2 H, m), 2.51−2.63 (2 H, m), 3.68−3.75 (1 H, m), 3.78 (3 H, s), 4.31 (1 H, d, J = 11.7 Hz), 4.56 (1 H, d, J = 11.7 Hz), 6.04 (1 H, d, J = 14.6 Hz), 6.83 (1 H, dd, J = 15.9, 7.1 Hz), 7.20−7.41 (5 H, m), 9.72 (1 H, s).

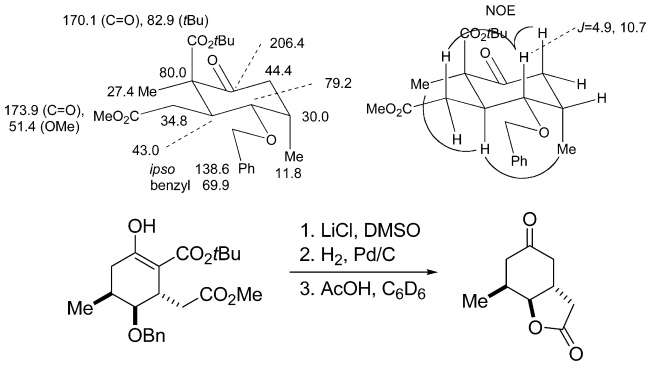
To a dry vial was added tin(II) chloride (57 mg, 0.3 mmol) and dichloromethane (5 mL). *tert*-Butyl diazoacetate (0.46 mL, 3.3 mmol) was added dropwise to the vial with vigorous stirring. After gas evolution ceased, aldehyde (0.34 g, 1.22 mmol) was added, and the yellow solution was stirred overnight. The solution was diluted with 100 mL of dichloromethane and 100 mL of saturated sodium bicarbonate solution. The layers were separated, and the aqueous layer was back-extracted three times with 10 mL portions of dichloromethane. The combined organic layers were washed with 50 mL of water, 50 mL of brine, dried over sodium sulfate, and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (0, 10, 20, 50% EtOAc/hexanes). The remaining *tert*-butyl diazoacetate was removed by high vacuum evaporation to yield the desired ketoester as a yellow oil (0.42 g, 90%): TLC R_f = 0.3 (20% EtOAc/hexanes, $KMnO_4$ stain); IR ($CHCl_3$ film) 2979, 1736, 1718, 1659, 1456, 1436, 1369, 1276, 1155, 1070, 988, 844, 783 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92−0.94 (3 H, m), 1.43−1.52 (9 H, m), 2.29−2.38 (1 H, m, J = 13.0, 11.2, 8.2, 6.4 Hz), 2.43 (1 H, dd), 2.68 (1 H, dd, J = 17.4, 4.6 Hz), 3.29 (2 H, d, J = 3.2 Hz), 3.70−3.79 (1 H, m), 3.76 (3 H, s), 4.31 (1 H, d, J = 11.4 Hz), 4.56 (1 H, d, J = 11.4 Hz), 6.03 (1 H, d, J = 14.6 Hz), 6.81 (1 H, dd, J = 15.6, 6.9 Hz), 7.23−7.38 (5 H, m); ^{13}C NMR (125 MHz, CDCl3) δ 16.3, 27.9, 33.4, 45.5, 50.9, 51.6, 71.3, 81.6, 81.8, 123.2, 127.6, 127.7, 127.7, 128.3, 137.7, 146.5, 166.2, 166.3, 202.2; $[\alpha]^{25}_D$ −64.5 (c = 1.97, $CDCl_3$); HRMS (ESI) calcd for $C_{22}H_{34}O_6N$ $[M + NH_4]^+$ 408.2386, found 408.2389.



*3-Benzyloxy-2-methoxycarbonylmethyl-4-methyl-6-oxocyclohexanecarboxylic Acid tert-Butyl Ester (**S-062**).* The β-ketoester adduct was purified by silica gel chromatography (gradient elution: 5, 10% EtOAc/hexanes) to yield a yellow oil. It adduct was unusual in that it was formed primarily as the enol tautomer and could be characterized by NMR spectroscopy: TLC R_f = 0.5 (20% EtOAc/hexanes, CAM stain); ^{1}H NMR (500 MHz, $CDCl_3$) (^{13}C NMR, 125 MHz, via gHSQC/gHMBC correlations) δ 0.99−17.58 (3 H, d, J = 6.6 Hz), 1.49−28.25 (9 H, s), 1.94−27.80 (1 H, ddd, J = 12.5, 6.1, 5.9), 2.08−38.25 (1 H, m), 2.11−32.74 (1 H, m), 2.31−32.74 (1 H, dd, J = 18.1, 12.0), 2.64−38.25 (1 H, dd, J = 16.1, 2.4), 3.27 (1 H, d, J = 10.7 Hz), 3.33−3.37 − 78.94 (1 H, m), 3.69−51.43 (3 H, s), 4.52−71.28 (1 H, d, J = 12.2 Hz), 4.73 (1 H, d, J = 12.2 Hz), 7.23−7.39 − 128.1 (unresolved aromatic carbons, 5 H, m), 12.56 (1 H, br s), quaternary carbons: 98.81, 139.78, 173.1, 173.4, 173.6; LRMS (ESI) calcd for $C_{22}H_{31}O_6$ $[M + H]^+$ 391.2121, found 391.2148. Although 2D NMR allowed structural assignments to be established, the stereochemistry could not be determined definitively.



*3-Benzyloxy-2-methoxycarbonylmethyl-1,4-dimethyl-6-oxocyclohexanecarboxylic Acid tert-Butyl Ester (**S-063**).* To a solution of enol (15 mg, 0.038 mmol) in 1 mL of DMF at room temperature were added cesium carbonate (0.098 g, 0.3 mmol) and methyl iodide (19 uL, 0.3 mmol). The yellow solution was stirred for 24 h and diluted with 25 mL of 3:1 hexanes/EtOAc and 25 mL of pH 7 buffer. The layers were separated, and the aqueous layer was back-extracted three times with 10 mL portions of 3:1 hexanes/ethyl acetate. The combined organic layers were washed with 25 mL of brine, dried over sodium sulfate, and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (5, 15% EtOAc/hexanes) to yield the desired methylated ketoester as a yellow oil (15 mg, 97%): TLC R_f = 0.5 (20% EtOAc/hexanes, CAM stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95−11.8 (3 H, d, J = 7.1 Hz), 1.37−27.3 (9 H, s), 2.37−44.0 (1 H, dd, J = 14.2, 2.9 Hz), 2.46−34.8 (1 H, m), 2.52−42.9 (1 H, m), 2.58 (1 H, dd, J = 16.4, 8.2 Hz), 2.60−30.0 (1 H, m), 2.91−44.3 (1 H, dd, J = 14.2, 5.4 Hz), 3.44−51.3 (3 H, s), 4.02−79.2 (1 H, dd, J = 10.9, 4.9 Hz), 4.41−69.8 (1 H, d, J = 11.2 Hz), 4.63−69.8 (1 H, d, J = 11.2 Hz), 7.34−128.3 (5 H, m), quaternary carbons: 79.9, 82.8, 138.5, 170.1, 173.8, 206.4; HRMS (ESI) calcd for $C_{23}H_{33}O_6$ $[M + H]^+$ 405.2277, found 405.2281.



*7-Methyltetrahydrobenzofuran-2,5-dione (**S-064**).* Under standard Krapcho conditions, the ketoester was converted to its corresponding ketone. The ketone was purified by silica gel chromatography (gradient elution: 5, 10, 25% EtOAc/hexanes) to yield a yellow oil: TLC R_f = 0.3 (20% EtOAc/hexanes, CAM stain); ^{1}H NMR (600 MHz, C_6D_6) δ 0.84 (3 H, d, J = 6.9 Hz), 1.80−1.87 (1 H, m), 1.98−2.08 (3 H, m), 2.19 (1 H, dd, J = 15.8, 6.2 Hz), 2.27 (1 H, ddd, J = 13.9, 8.9, 1.3 Hz), 2.59 (1 H, ddd, J = 14.2, 5.7, 1.4 Hz), 2.75 (1 H, ddd, J = 20.2, 6.3, 6.2 Hz), 3.16 (1 H, dd, J = 6.0, 3.2 Hz), 3.35 (3 H, s), 4.29 (1 H, d, J = 11.7 Hz), 4.35 (1 H, d, J = 11.7 Hz), 7.05−7.42 (5 H, m); LRMS (ESI) calcd for $C_{17}H_{23}O_4$ $[M + H]^+$ 291.2, found 291.3. Although 2D NMR studies allowed the structural assignments to be established, the stereochemistry could not be determined definitively due to presumed conformational lability; therefore, the compound was converted to its corresponding lactone to definitively establish its stereochemistry.

Ketone (30 mg, 0.1 mmol) was dissolved in 1 mL of ethanol, and palladium on carbon (10 mg) was added. The black suspension was stirred overnight under a hydrogen atmosphere (balloon pressure). The suspension was purged with nitrogen and filtered through a Celite plug. The plug was rinsed with ethyl acetate. The yellow solution was concentrated and purified by silica gel chromatography (5% 2-propanol/hexanes) to yield the desired alcohol as a yellow oil (18 mg, 90%): TLC R_f = 0.3 (30% 2-propanol/hexanes, CAM stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (3 H, d, J = 6.8 Hz), 2.04−2.08 (1 H, m, J = 3.4 Hz), 2.12 (1 H, dd, J = 14.2, 6.8 Hz), 2.18−2.24 (1 H, m), 2.25−2.40 (3 H, m), 2.43 (1 H, dd, J = 15.9, 6.6 Hz), 2.57−2.69 (2 H, m), 3.67 (3 H, s), 3.78−3.84 (1 H, m); LRMS (ESI) calcd for $C_{10}H_{17}O_4$ $[M + H]^+$ 201.1, found 201.4.

The lactone (18 mg, 0.09 mmol) was dissolved in 1 mL of benzene-d_6, and two drops of glacial acetic acid were added. After 8 h at room temperature, ^{1}H NMR analysis indicated near-complete consumption of starting material. The mixture was diluted with 20 mL of dichloromethane, and 20 mL of saturated sodium bicarbonate solution was added. The layers were separated, and the aqueous layer was back-extracted three times with 10 mL portions of dichloromethane. The combined organic layers were dried over sodium sulfate, concentrated, and purified by silica gel chromatography (10, 20% 2-propanol/hexanes) to yield the desired lactone as a clear oil (12 mg, 72%): TLC R_f

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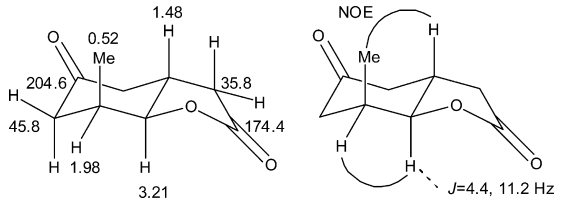
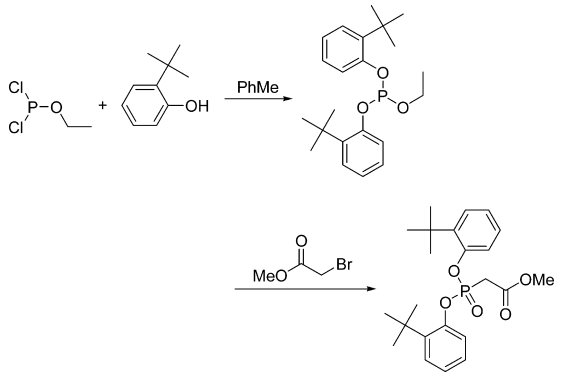
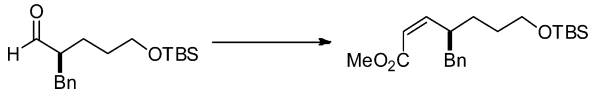
= 0.25 (30% 2-propanol/hexanes, CAM stain); ^{1}H NMR (500 MHz, C_6D_6) (^{13}C NMR, 125 MHz, by gHSQC/gHMBC correlations) δ 0.52−11.7 (3 H, d, J = 7.0 Hz), 1.25−43.2 (1 H, m), 1.35−35.8 (1 H, dd, J = 12.7, 15.4 Hz), 1.48−29.8 (1 H, ddddd, partial J = 3.9, 6.4, 11.7 Hz), 1.69−45.8 (1 H, dd, J = 6.8, 15.7 Hz), 1.79−35.8 (1 H, m), 1.85−45.8 (1 H, m), 1.87−43.2 (1 H, m), 1.98−30.3 (1 H, m), 2.31−82.9 (1 H, dd, J = 4.4, 11.2 Hz), quaternary carbons: 174.4, 204.5; HRMS (CI) calcd for $C_9H_{13}O_3$ $[M + H]^+$ 169.0865, found 169.0870.

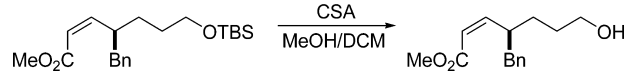




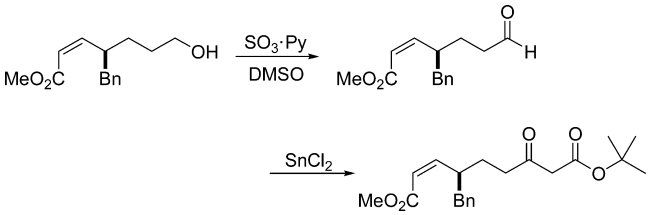
*[Bis-(2-tert-butylphenoxy)phosphoryl]acetic Acid Methyl Ester (**S-065a**).*[39] This reagent was synthesized according to the following modified literature procedure. To a solution of 2-*tert*-butylphenol (15.0 mL, 97.5 mmol, freshly distilled) and triethylamine (14.3 mL, 103 mmol) in 300 mL of toluene at 0 °C was added a solution of ethyl dichlorophosphite (5.7 mL, 50 mmol) in 50 mL of diethyl ether slowly over 30 min. The viscous white suspension was warmed to room temperature and stirred for 3 h. The mixture was then vacuum filtered over paper. The remaining white salts were washed with two 50 mL portions of toluene. The yellow filtrate was passed over a pad of alumina (10 × 10 cm), and the pad was rinsed with two 50 mL portions of toluene. The solution was concentrated to yield the desired diarylethoxyphosphite as a slightly yellow oil (18.8 g, 100%). Methyl bromoacetate (7.13 mL, 75.5 mmol) was added to the diarylethoxyphosphite, and the yellow solution was stirred for 15 h at 130 °C. The yellow solution was cooled to 80 °C and concentrated under high vacuum with vigorous stirring to yield a viscous yellow oil (caution, toxic volatiles). The oil was purified by dry column vacuum chromatography (20 × 10 cm, 250 mL fractions, gradient elution: 0 to 14% EtOAc/hexanes in 1% steps) to yield a clear and colorless solution. The solution was concentrated to yield desired phosphonate reagent **S-3** as a white crystalline solid (15.00 g, 72%). If desired, the phosphonate was easily recrystallized from hot heptane (4−5 mL/g). TLC R_f 0.8 (starting materials and other impurities)/0.5 (product and a related impurity)/0.3 (impurity) (30% EtOAc/hexanes, UV). The properties of this compound matched those known in the literature.



*(Z)-Methyl 4-Benzyl-7-((tert-butyldimethylsilyl)oxy)hept-2-enoate (**S-065b**).* To a suspension of phosphonate **S-065** (0.53 g, 1.27 mmol) and cesium carbonate (0.41 g, 1.27 mmol) in 7 mL of acetonitrile and 2 mL of THF at 0 °C was added a solution of aldehyde (0.39 g, 1.27 mmol) in 1 mL of THF. The suspension was stirred overnight, during which time it warmed to room temperature. The mixture was purified directly by silica gel chromatography (10% EtOAc/hexanes) to yield the desired olefin as a ca. 5:1 mixture of Z/E isomers: TLC R_f 0.8 (30% EtOAc/hexanes, $KMnO_4$ stain); IR (film) 2995, 2930, 2857, 2359, 2342, 1724, 1645, 1437, 1256, 1171, 1100, 833, 775, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.31−7.15 (m, 5 H), 6.03−5.94 (m, 1 H), 5.80−5.72 (m, 1 H), 3.67 (s, 3 H), 3.62−3.53 (m, 2 H), 2.71−2.64 (m, 2 H), 1.62−1.40 (m, 4 H), 0.90−0.84 (m, 9 H), 0.06−−0.01 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 166.8, 154,3, 139.9, 129.5, 128.3, 126.2, 119.9, 63.2, 51.2, 41.8, 39.5, 30.8, 30.7, 26.2, 18.6, −5.05, −5.06; HRMS (ESI) calcd for $C_{21}H_{35}O_3Si$ $[M + H]^+$ 363.2355, found 363.2345.



*(Z)-Methyl 4-Benzyl-7-hydroxyhept-2-enoate (**S-066**).* To a solution of olefin (0.36 g, 0.99 mmol) in 2 mL of methanol and 2 mL of dichloromethane at 0 °C was added 10-camphorsulfonic acid (35 mg, 0.15 mmol). The solution was stirred at 0 °C for 1.5 h, after which TLC analysis indicated full consumption of starting material. Ten mL of sodium bicarbonate solution were added, and the bulk of the methanol was removed by rotary evaporation. The mixture was resuspended in 50 mL of dichloromethane and 50 mL of sodium bicarbonate. The layers were separated and the aqueous layer was back-extracted three times with 10 mL portions of dichloromethane. The combined organic layers were washed with 20 mL of brine, dried over sodium sulfate, concentrated, and purified by silica gel chromatography (gradient elution: 5, 10, 20, 30, 50% EtOAc/hexanes) to yield the desired *Z*-olefin-alcohol as a clear oil (0.17 g, 69%): TLC R_f 0.45 (desired *Z* isomer)/0.50 (*E* isomer) (30% EtOAc/hexanes, $KMnO_4$ stain); IR (film) 3374, 2944, 1719, 1646, 1496, 1437, 1408, 1205, 1172, 1060, 911, 826, 751, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.29−7.13 (m, 5 H), 6.00 (dd, J = 10.3, 11.4 Hz, 1 H), 5.77 (dd, J = 0.8, 11.6 Hz, 1 H), 3.89−3.78 (m, 1 H), 3.66−3.64 (m, 3 H), 3.61 (d, J = 8.9 Hz, 2 H), 2.75−2.68 (m, 1 H), 2.64 (d, J = 7.3 Hz, 1 H), 1.63−1.49 (m, 4 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.7, 154.0, 139.5, 129.2, 128.1, 126.0, 119.7, 62.6, 51.0, 41.4, 39.0, 30.4, 30.2; HRMS (ESI) calcd for $C_{15}H_{21}O_3$ $[M + H]^+$ 249.1485, found 249.1492.



*(2-Z)-4-Benzyl-7-oxonon-2-enedioic Acid 9-tert-Butyl Ester 1-Methyl Ester (**25**).* To a stirring solution of alcohol (0.15 g, 0.60 mmol) in 5 mL of CH_2Cl_2 at 0 °C was added freshly distilled *N,N*-diisopropylethylamine (0.79 mL, 4.5 mmol) via syringe. After 10 min, dimethyl sulfoxide (0.46 mL, 6.4 mmol) was added to the reaction mixture via syringe, and the solution was allowed to stir for an additional 10 min. Sulfur trioxide−pyridine complex (0.54 g, 2.6 mmol) was then added in one portion. The reaction was allowed to proceed for 1 h at 0 °C, after which TLC analysis indicated complete consumption of starting material. The reaction was diluted with 50 mL of 0.1 M HCl and 50 mL of dichloromethane. The aqueous layer was back-extracted three times with dichloromethane. The organic layers were combined, washed with brine, dried over sodium sulfate, and concentrated to yield the desired aldehyde as a yellow oil (106 mg, 71%): TLC R_f = 0.6 (30% EtOAc/hexanes, $KMnO_4$ stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.74 (s, 1 H), 7.30−7.15 (m, 5 H), 5.95 (s, 1 H), 5.82 (d, J = 11.7 Hz, 1 H), 3.92−3.76 (m, 1 H), 3.69 (s, 3 H), 2.71 (d, J = 6.8 Hz, 2 H), 2.45 (s, 2 H), 1.97−1.83 (m, 2 H).

To a dry vial were added tin(II) chloride (5.7 mg, 0.03 mmol) and deuterochloroform (1 mL). *tert*-Butyl diazoacetate (0.11 mL, 0.8 mmol) was added dropwise to the vial with vigorous stirring. After gas evolution ceased, aldehyde (106 mg, 0.43 mmol) was added, and the yellow solution was stirred overnight. The solution was diluted with 50 mL of dichloromethane and 50 mL of saturated sodium bicarbonate solution. The layers were separated, and the aqueous layer was back-extracted three times with 20 mL portions of dichloromethane. The combined organic layers were washed with 50 mL of water and 50 mL of brine, dried over sodium sulfate, and concentrated to yield a yellow oil. The oil

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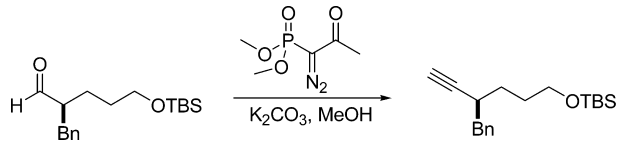
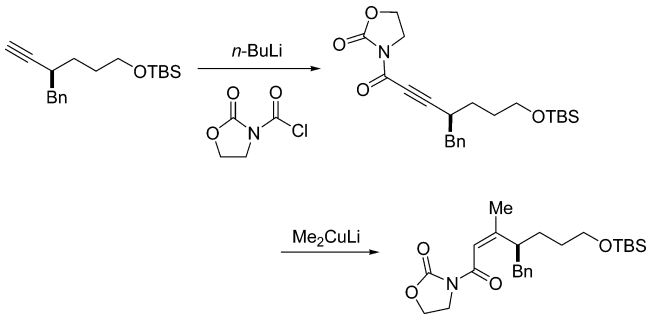
was purified by silica gel chromatography (gradient elution: 3, 5, 20% EtOAc/hexanes) to yield the desired ketoester as a yellow oil (120 mg, 77%): TLC R_f 0.65 (30% EtOAc/hexanes, $KMnO_4$) stain; IR (film) 3028, 2980, 2951, 2361, 1715, 1643, 1437, 1368, 1203, 1165, 827, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.30−7.11 (m, 5 H), 5.96−5.87 (m, 1 H), 5.81−5.73 (m, 1 H), 3.84−3.72 (m, 1 H), 3.66 (s, 3 H), 3.28 (s, 2 H), 2.67 (s, 2 H), 2.56−2.43 (m, 2 H), 1.92−1.79 (m, 2 H), 1.48−1.38 (m, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 202.9, 166.5, 166.4, 152.8, 139.0, 129.1, 128.1, 126.1, 120.3, 90.4, 81.8, 51.0, 50.6, 41.6, 41.4, 40.6, 39.1, 38.8, 33.0, 28.2, 27.9, 27.6; HRMS (ESI) calcd for $C_{21}H_{32}O_5N$ $[M + NH_4]^+$ 378.2280, found 378.2272.

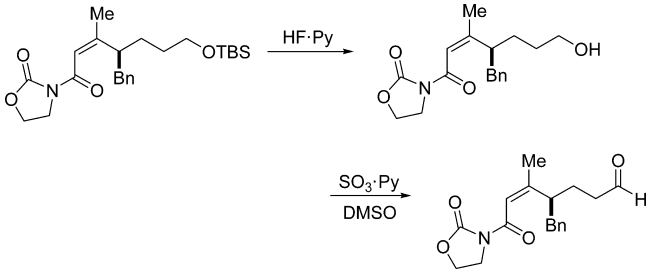


*(4-Benzylhex-5-ynyloxy)-tert-butyldimethylsilane (**S-067**).* To a solution of aldehyde (2.10 g, 6.85 mmol) in 30 mL of methanol at 0 °C was added a solution of Bestmann−Ohira reagent (1.58 g, 8.22 mmol) in 5 mL of methanol. Potassium carbonate (1.80 g, 13.0 mmol) was added in one portion. The bright yellow suspension was stirred vigorously for 90 min at 0 °C. The mixture was poured slowly into a mixture of 3:1 hexanes/ether and 1 M HCl (gas evolution!). The layers were separated and the aqueous phase was back-extracted three times with 20 mL of portions of ether. The combined organic extracts were washed with brine, dried over sodium sulfate, and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (gradient elution: 3, 5% EtOAc/hexanes) to yield the desired alkyne as a clear and colorless oil (1.31 g, 63%): TLC R_f 0.80 (30% EtOAc/hexanes); IR (film) 3311, 2930, 2858, 1472, 1389, 1361, 1256, 1101, 1006, 836, 775, 699, 630 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.35−7.20 (m, 5 H), 3.65 (d, J = 1.0 Hz, 2 H), 2.89−2.81 (m, 1 H), 2.81−2.75 (m, 1 H), 2.70−2.61 (m, 1 H), 2.09 (d, J = 2.4 Hz, 1 H), 1.90−1.75 (m, 1 H), 1.72−1.62 (m, 2 H), 1.54−1.43 (m, 1 H), 0.97−0.84 (m, 9 H), 0.06 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 139.6, 129.5, 128.4, 126.6, 87.3, 70.5, 63.1, 41.6, 33.5, 30.9, 30.6, 26.2, 18.6, −5.0; HRMS (ESI) calcd for $C_{19}H_{30}OSiNa$ $[M + Na]^+$ 325.1958, found 325.1951.



*(2-Z)-3-[4-Benzyl-7-(tert-butyldimethylsilanyloxy)-3-methylhept-2-enoyl]oxazolidin-2-one (**S-068**).* To a solution of alkyne (0.923 g, 3.05 mmol) in 9 mL of THF at −78 °C was added *n*-butyllithium (1.25 mL, 3.20 mmol, 2.57 M in hexanes) dropwise via syringe. The solution became brown within a few moments. The solution was stirred for 20 min and then transferred dropwise via cannula to a solution of acyl chloride (0.91 g, 6.1 mmol) in 9 mL of THF at −78 °C over 15 min. The yellow solution was allowed to warm to 0 °C over 1 h and then allowed to react at room temperature over the next 2 h. The reaction was diluted with 40 mL of 50% ammonium chloride and 40 mL of ether. The layers were separated, and the aqueous phase was back-extracted three times with 20 mL portions of ether. The combined organic extracts were washed twice with sodium bicarbonate solution, once with brine, diluted with hexanes, dried over sodium sulfate, and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (10, 20, 30, 50% EtOAc/hexanes) to yield the desired unsaturated oxazolidinone as a clear and colorless oil (0.95 g, 75%): TLC R_f 0.45 (30% EtOAc/hexanes, $KMnO_4$ stain); ^1H NMR (500 MHz, $CDCl_3$) δ = 7.34−7.18 (m, 5 H), 4.40 (d, J = 8.3 Hz, 2 H), 4.03 (d, J = 8.3 Hz, 2 H), 3.68−3.55 (m, 2 H), 3.03−2.95 (m, 1 H), 2.92−2.79 (m, 2 H), 1.88−1.77 (m, 1 H), 1.75−1.61 (m, 2 H), 1.35−1.21 (m, 1 H), 0.92−0.82 (m, 9 H), 0.03 (s, 6 H).

To a finely crushed, argon-purged suspension of copper(I) iodide (309 mg, 1.62 mmol) in 12 mL of THF at 0 °C was added salt-free methyllithium (2.42 mL, 3.24 mmol, 1.34 M in ether) dropwise via syringe. Upon addition, a yellow color appeared, but the solution became colorless within a few moments. After 30 min, the turbidity of the suspension lessened greatly to the point where the mixture was mostly homogeneous. The mixture was cooled to −78 °C, and an argon-purged solution of alkyne (675 mg, 1.62 mmol) in 3 mL of THF was added dropwise. Upon addition, a vivid yellow color appeared. The mixture was stirred at −78 °C for 1 h. Ammonium chloride solution (0.5 mL) was added dropwise. The mixture was stirred for 5 min at −78 °C and then warmed to room temperature. The mixture was diluted with 150 mL of 50% ammonium hydroxide solution, 50 mL of hexanes, and 50 mL of ether. The layers were separated and the aqueous phase was back-extracted three times with 30 mL portions of ether. The combined organic extracts were washed with brine, diluted with hexanes, dried over sodium sulfate, and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (gradient elution: 10, 20, 30, 50% EtOAc/hexanes) to yield the desired olefin a yellow oil (0.49 g, 70%, undesired isomer dominates at 2:1 *E*:*Z*). The oil was purified by semipreparative HPLC (ZORBAX RX-Sil, 0.6% IPA/HX, 225 nm, 15 mL/min, 25−50 min): TLC R_f 0.45 (desired *Z*)/0.50 (undesired *E*) (30% EtOAc/hexanes, UV visualization); IR (film) 2929, 2857, 1778, 1681, 1622, 1472, 1454, 1385, 1360, 1256, 1202, 1107, 1043, 1006, 972, 836, 776, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.36−7.08 (m, 5 H), 4.41−4.24 (m, 2 H), 4.08−3.98 (m, 1 H), 3.98−3.91 (m, 1 H), 3.91−3.83 (m, 1 H), 3.64−3.51 (m, 2 H), 2.74−2.63 (m, 2 H), 1.91 (d, J = 1.0 Hz, 3 H), 1.56−1.49 (m, 2 H), 1.49−1.40 (m, 2 H), 0.95−0.79 (m, 9 H), 0.03 (d, J = 1.0 Hz, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 164.7, 161.9, 153.0, 140.1, 129.2, 128.9, 128.0, 125.7, 118.4, 63.0, 61.6, 42.4, 42.1, 40.3, 30.8, 28.4, 25.9, 19.7, 18.3, −5.3; HRMS (ESI) calcd for $C_{24}H_{38}NO_4Si$ $[M + H]^+$ 432.2570, found 432.2583.



*(7-Z)-6-Benzyl-7-methyl-3,9-dioxo-9-(2-oxo-oxazolidin-3-yl)non-7-enoic Acid Allyl Ester (**S-068b**).* To a solution of disilyl ether (126 mg, 0.29 mmol) in 10 mL of THF and 0.5 mL of pyridine at 0 °C was added HF−pyridine (110 drops). The solution was stirred for 30 min at 0 °C. The mixture was diluted with 10 mL of dichloromethane and 10 mL of saturated sodium bicarbonate solution (slowly, gas evolution!). The mixture was poured into a separatory funnel and diluted with a further 40 mL of dichloromethane and 40 mL of saturated sodium bicarbonate solution. The layers were separated and the aqueous phase was back-extracted four times with 20 mL portions of dichloromethane. The combined organic extracts were washed with 30 mL of 0.1 M HCl and 30 mL of brine. The clear and colorless solution was dried over sodium sulfate and concentrated to yield the desired alcohol as a clear and colorless oil (91 mg, 98%): TLC R_f 0.05 (30% EtOAc/hexanes, $KMnO_4$ stain); ^1H NMR (500 MHz, $CDCl_3$) δ = 7.30−7.23 (m, 2 H), 7.21−7.12 (m, 3 H), 6.82 (d, J = 1.5 Hz, 1 H), 4.34 (ddd, J = 4.6, 7.1, 8.8 Hz, 2 H), 4.10−4.00 (m, 1 H), 3.99−3.91 (m, 1 H), 3.91−3.82 (m, 1 H), 3.72−3.57 (m, 2 H), 2.78−2.70 (m, 1 H), 2.70−2.61 (m, 1 H), 1.92 (d, J = 1.5 Hz, 3 H), 1.61−1.50 (m, 4 H).

To a stirring solution of alcohol (91 mg, 0.29 mmol) in 6 mL of CH_2Cl_2 at 0 °C was added freshly distilled *N*,*N*-diisopropylethylamine (0.35 mL, 2.0 mmol) via syringe. After 10 min, dimethyl sulfoxide (0.20 mL, 2.9 mmol) was added to the reaction mixture via syringe, and the solution was allowed to stir for an additional 10 min. Sulfur trioxide−pyridine complex (0.24 g, 1.1 mmol) was then added in one portion.

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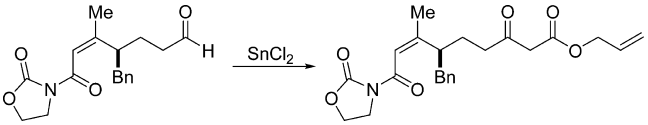
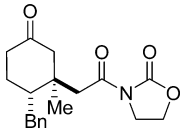
The reaction was allowed to proceed for 30 min at 0 °C, after which TLC analysis indicated complete consumption of starting material. The reaction was diluted with 50 mL of 0.1 M HCl and 50 mL of dichloromethane. The aqueous layer was back-extracted three times with dichloromethane. The organic layers were combined, washed with brine, dried over sodium sulfate, and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (gradient elution: 40, 60% EtOAc/hexanes) to yield the desired aldehyde as a yellow oil (89 mg, 98%): TLC R_f 0.5 (65% EtOAc/hexanes, CAM stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.73 (s, 1 H), 7.32−7.13 (m, 5 H), 6.90−6.80 (m, 1 H), 4.36 (d, J = 8.8 Hz, 2 H), 4.05−3.81 (m, 3 H), 2.73 (d, J = 7.3 Hz, 2 H), 2.49−2.35 (m, 2 H), 2.06 (s, 1 H), 1.91 (d, J = 1.0 Hz, 3 H).



*(Z)-Allyl 6-Benzyl-7-methyl-3,9-dioxo-9-(2-oxooxazolidin-3-yl)-non-7-enoate (**27**).* To a dry vial were added tin(II) chloride (2.7 mg, 0.01 mmol) and deuterochloroform (0.5 mL). Allyl diazoacetate (0.10 mL, 0.84 mmol) was added dropwise to the vial with vigorous stirring. After gas evolution ceased, aldehyde (89 mg, 0.28 mmol) was added, and the yellow solution was stirred overnight. The solution was diluted with 50 mL of dichloromethane and 50 mL of saturated sodium bicarbonate solution. The layers were separated, and the aqueous layer was back-extracted three times with 20 mL portions of dichloromethane. The combined organic layers were washed with 50 mL of water, 50 mL of brine, dried over sodium sulfate, and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (gradient elution: 20, 50% EtOAc/hexanes) to yield the desired ketoester as a yellow oil (71 mg, 61%): TLC R_f 0.60 (65% EtOAc/hexanes, $KMnO_4$) stain; IR (film) 2927, 1772, 1716, 1674, 1623, 1479, 1455, 1387, 1200, 1111, 1043, 936, 843, 760, 703 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.32−7.11 (m, 5 H), 6.79 (d, J = 1.1 Hz, 1 H), 5.90 (dd, J = 10.5, 17.2 Hz, 1 H), 5.33 (dd, J = 1.4, 17.2 Hz, 1 H), 5.25 (dd, J = 1.3, 10.4 Hz, 1 H), 4.61 (dt, J = 1.3, 5.8 Hz, 2 H), 4.42−4.27 (m, 2 H), 4.01−3.83 (m, 2 H), 3.80−3.69 (m, 1 H), 3.42 (d, J = 1.1 Hz, 2 H), 2.71 (d, J = 7.6 Hz, 2 H), 2.60−2.38 (m, 2 H), 1.90−1.86 (m, 3 H), 1.94−1.68 (m, 4 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 202.1, 166.8, 164.8, 159.6, 153.0, 139.6, 131.6, 129.0, 128.1, 125.9, 119.5, 118.8, 67.9, 65.8, 61.7, 49.1, 42.4, 41.6, 40.8, 40.0, 25.6, 25.6, 19.4; HRMS (ESI) calcd for $C_{23}H_{28}NO_6$ $[M + H]^+$ 414.1811, found 414.1808.



*3-[2-(2-Benzyl-1-methyl-5-oxocyclohexyl)acetyl]oxazolidin-2-one (**S-069**):* TLC R_f = 0.40 (50% EtOAc/hexanes, yellow, anisaldehyde stain); IR (film) 3026, 2956, 1778, 1723, 1692, 1603, 1480, 1452, 1383, 1209, 1110, 1043, 973, 917, 702 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{23}NO_4Na$ $[M + Na]^+$ 352.1525, found 352.1530; NMR data, see Table 6.

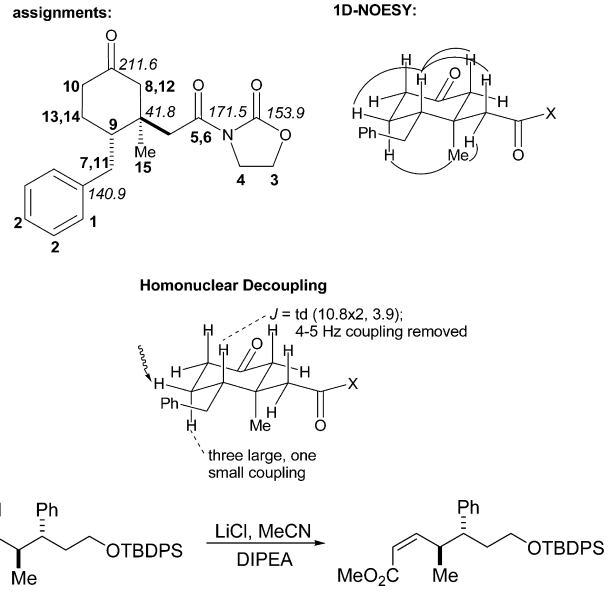
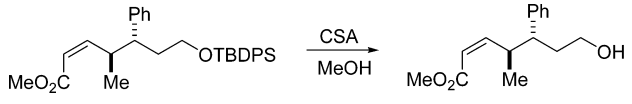


Table 6. NMR Data for S-069 (500 MHz, $CDCl_3$)

ID	δ ^{1}H	δ ^{13}C	Hs	type	couplings (Hz)
1	7.29	128.6	2	m	
2	7.19	129.6	3	m	
3	4.38	62.2	2	ddd	16.6, 12.2, 8.7
4	3.99	43.0	2	m	
5	3.32	43.6	1	d	16.1
6	2.97	43.6	1	d	16.1
7	2.96	36.8	1	dd	13.4, 3.7
8	2.88	52.7	1	d	13.7
9	2.49	43.8	1	m	
10	2.27	41.1	2	m	
11	2.26	36.8	1	m	
12	2.20	52.7	1	m	
13	1.84	27.8	1	m	
14	1.57	27.8	1	m	
15	1.04	20.4	3	s	

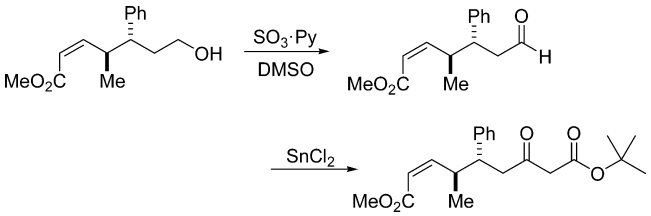
quaternary carbons: 211.6, 171.5, 153.9, 140.9, 41.8

(4,5-erythro,Z)-methyl 7-(tert-butyldiphenylsilyloxy)-4-methyl-5-phenylhept-2-enoate. To a suspension of lithium chloride (39 mg, 0.93 mmol) in 4 mL of acetonitrile at room temperature was added phosphonate **S-065** (0.23 g, 0.56 mmol) and diisopropylethylamine (0.16 mL, 0.46 mL). A solution of aldehyde (200 mg, 0.46 mmol) in 2 mL of acetonitrile was added. The solution was stirred overnight at room temperature. The brown solution was poured into 50 mL of dichloromethane and 50 mL of 0.1 M HCl. The layers were separated and the aqueous phase was back-extracted three times with 10 mL portions of dichloromethane. The combined organic extracts were washed with 10 mL of brine, dried over sodium sulfate, and concentrated to yield a yellow oil (4:1 Z/E mixture). The oil was purified by silica gel chromatography (gradient elution: 2, 4, 10% EtOAc/hexanes) to yield the desired Z-ester (0.17 g, 75%) and the undesired E-ester (0.04 g, 18%) as clear and colorless oils. TLC R_f 0.77 (Z)/0.75 (E)/0.70 (aldehyde)/0.40 (phosphonate) (30% EtOAc/hexanes, $KMnO_4$ stain); ^{1}H NMR (500 MHz, CDCl3) δ = 7.64 (dd, J = 1.5, 7.8 Hz, 2 H), 7.58−7.53 (m, 2 H), 7.46−7.30 (m, 6 H), 7.24 (d, J = 7.3 Hz, 3 H), 7.13−7.08 (m, 2 H), 5.94 (t, J = 11.0 Hz, 1 H), 5.61 (d, J = 10.7 Hz, 1 H), 3.91−3.83 (m, 1 H), 3.70 (s, 3 H), 3.62−3.53 (m, 1 H), 3.50−3.41 (m, 1 H), 2.20−2.06 (m, 1 H), 1.83−1.76 (m, 1 H), 1.07−1.02 (m, 12 H).



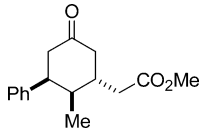
dx.doi.org/10.1021/jo302138z | J. Org. Chem. 2013, 78, 175−203

*(4,5-erythro,Z)-methyl 7-hydroxy-4-methyl-5-phenylhept-2-enoate (**S-070**).* To a solution of silyl ether (0.28 g, 0.58 mmol) in 5 mL of methanol at room temperature was added 10-camphorsulfonic acid (0.28 g, 1.15 mmol). The mixture was stirred for 1 h, after which TLC analysis indicated complete consumption of starting material. The mixture was diluted with 50 mL of saturated sodium bicarbonate solution and 50 mL of dichloromethane. The layers were separated and the aqueous layer was back-extracted three times with 15 mL portions of dichloromethane. The combined organic layers were washed with 20 mL of brine, dried over sodium sulfate, filtered, and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (gradient elution: 15, 40% EtOAc/hexanes) to yield the desired alcohol as a clear and colorless oil (0.12 g, 81%). TLC R_f 0.2 (30% EtOAc/hexanes, $KMnO_4$ stain); IR (ATR) 3362, 3028, 2950, 2874, 1719, 1642, 1494, 1453, 1437, 1409, 1372, 1195, 1174, 1125, 1042, 920, 824, 764, 730, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.30−7.23 (m, 3 H), 7.22−7.11 (m, 3 H), 5.90 (dd, J = 10.6, 11.6 Hz, 1 H), 5.60 (dd, J = 0.9, 11.7 Hz, 1 H), 3.96−3.86 (m, 1 H), 3.68 (s, 3 H), 3.56−3.49 (m, 1 H), 3.45−3.36 (m, 1 H), 2.74−2.66 (m, 1 H), 2.16−2.06 (m, 1 H), 1.92−1.77 (m, 1 H), 1.56−1.49 (m, 1 H), 1.06 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.7, 154.0, 142.1, 128.5, 128.1, 126.4, 118.1, 61.0, 50.9, 48.0, 37.1, 35.6, 18.5, 14.1; HRMS (ESI) calcd for $C_{15}H_{21}O_3$ $[M + H]^+$: 249.1491, found 249.1495.



*(2Z)-4-Methyl-7-oxo-5-phenyl-non-2-enedioic acid 9-tert-butyl ester 1-methyl ester (**29**).* To a stirring solution of alcohol (116 mg, 0.47 mmol) in 5 mL of CH_2Cl_2 at 0 °C was added freshly distilled *N,N*-diisopropylethylamine (0.29 mL, 1.67 mmol) dropwise via syringe. After 10 min, dimethyl sulfoxide (0.17 mL, 2.38 mmol) was added to the reaction mixture via syringe and the solution was allowed to stir for an additional 10 min. Sulfur trioxide pyridine complex (0.20 g, 0.95 mmol) was then added in one portion. The reaction was allowed to proceed for 1 h at 0 °C, after which TLC analysis indicated complete consumption of starting material. The reaction was diluted with 50 mL of dichloromethane and 50 mL of 0.1 M HCl. The layers were separated and the aqueous phase was back-extracted four times with 15 mL portions of dichloromethane. The combined organic layers were washed with 25 mL of saturated sodium bicarbonate solution followed by 25 mL of brine. The clear and colorless solution was washed with brine, dried over sodium sulfate, and concentrated to yield the desired aldehyde as a clear, colorless oil (48 mg, 42%). TLC R_f 0.6 (30% EtOAc/hexanes, anisaldehyde stain, brown); ^1H NMR (500 MHz, CDCl3) δ = 9.66 (t, J = 1.7 Hz, 1 H), 7.35−7.09 (m, 5 H), 5.86 (dd, J = 10.5, 11.5 Hz, 1 H), 5.71 (d, J = 11.7 Hz, 1 H), 4.00−3.87 (m, 1 H), 3.71 (s, 3 H), 3.35−3.27 (m, 1 H), 2.90 (dd, J = 1.5, 5.9 Hz, 1 H), 2.86−2.73 (m, 1 H), 1.04 (d, J = 6.8 Hz, 3 H).

To a dry vial was added tin(II) chloride (3.8 mg, 0.02 mmol) and 1 mL of deuterochloroform. *tert*-Butyl diazoacetate (0.06 mL, 0.4 mmol) was added dropwise to the vial with vigorous stirring. After gas evolution ceased, aldehyde (48 mg, 0.20 mmol) was added and the yellow solution was stirred overnight. The solution was diluted with 50 mL of dichloromethane and 50 mL of saturated sodium bicarbonate solution. The layers were separated and the aqueous layer was back-extracted four times with 10 mL portions of dichloromethane. The combined organic layers were washed consecutively with 50 mL of water, 50 mL of brine, dried over sodium sulfate, and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (gradient elution: 10, 20% EtOAc/hexanes) to yield **29** as a yellow oil (62 mg, 89%). TLC R_f 0.5 (30% EtOAc/hexanes, anisaldehyde stain, brown); IR (ATR) 2977, 1716, 1642, 1454, 1437, 1408, 1368, 1317, 1253, 1174, 1003, 920, 826, 761, 732, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.30−7.11 (m, 5 H), 5.83 (dd, J = 10.8, 11.4 Hz, 1 H), 5.67 (dd, J = 0.7, 11.7 Hz, 1 H), 3.94−3.81 (m, 1 H), 3.69 (s, 3 H), 3.33−3.23 (m, 1 H), 3.21 (d, J = 1.8 Hz, 2 H), 3.03 (dd, J = 6.0 Hz, 1 H), 2.90 (dd, J = 8.2 Hz, 1 H), 1.43 (s, 9 H), 1.03 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (126 MHz, CDCl3) δ = 201.8, 166.6, 166.3, 152.8, 141.2, 128.5, 128.2, 128.1, 126.6, 118.9, 81.7, 51.2, 51.0, 46.5, 45.7, 36.4, 27.9, 18.6; HRMS (ESI) calcd for $C_{21}H_{28}O_5Na$ $[M + Na]^+$: 383.1829, found 383.1833.



*(2-Methyl-5-oxo-3-phenyl-cyclohexyl)-acetic acid methyl ester (**S-071**).* TLC R_f 0.6 (substrate, brown)/0.65 (cyclized β-ketoester, pink)/0.4 (cyclohexanone, pink) (30% EtOAc/hexanes, anisaldehyde stain); HRMS (ESI) calcd for $C_{16}H_{20}O_3Na$ $[M + Na]^+$ 283.1310, found 283.1311; NMR data, see Table 7.

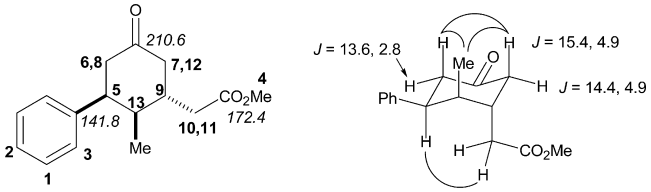


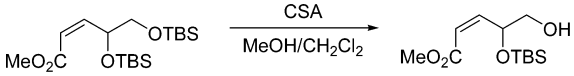
Table 7. NMR Data for S-071 (500 MHz, 40% C_6D_6 in $CDCl_3$)

ID	δ ^1H	δ ^{13}C	Hs	type	couplings (Hz)
1	7.15	128.4	2	t	7.3 × 2
2	7.08	128.1	1	t	7.3 × 2
3	6.90	126.8	2	d	7.8
4	3.47	51.6	3	s	
5	3.13	43.3	1	m	
6	2.55	42.5	1	dd	14.0, 10.0
7	2.46	43.0	1	dd	15.4, 4.9
8	2.31	42.5	1	m	13.6, 2.9 [TOCSY1D]
9	2.26	*38.2	1	m	
10	2.24	38.8	1	m	
11	2.16	38.8	1	m	14.6, 8.1
12	2.08	43.0	1	dd	14.6, 4.4
13	1.81	*38.2	1	m	
14	0.67	14.4	3	d	6.8

quaternary carbons: 210.6, 172.4, 141.8

*coincidental overlap

(Z)-Methyl 4,5-Bis(tert-butyldimethylsilyloxy)pent-2-enoate. To a solution of phosphonate (1.34 g, 3.2 mmol) in 15 mL of acetonitrile and 8 mL of THF was added cesium carbonate (1.04 g, 3.2 mmol) followed by aldehyde (1.00 g, 3.14 mmol). After 18 h, the solution was diluted with 50 mL of dichloromethane and 50 mL of 1 M HCl (gas evolution!), and the layers were separated. The aqueous phase was back-extracted three times with 20 mL portions of dichloromethane. The combined organic layers were washed with 30 mL of sodium bicarbonate solution followed by 30 mL of brine. The mixture was concentrated under reduced pressure to yield a yellow oil. NMR analysis indicated a crude olefin isomer ratio of 8:1 (*Z*:*E*). The oil was purified by silica gel chromatography (15% EtOAc/heaxnes) to yield the desired olefin as a yellow oil (8:1 *Z*/*E* mixture, 0.67 g, 57%): TLC R_f = 0.7 (30% EtOAc/hexanes, $KMnO_4$ stain); ^1H NMR (500 MHz, $CDCl_3$) δ = 6.14 (dd, J = 8.3, 11.7 Hz, 1 H), 5.81 (dd, J = 1.5, 11.7 Hz, 1 H), 3.73 (s, 3 H), 3.66−3.52 (m, 2 H), 0.91−0.86 (m, 18 H), 0.11−0.02 (m, 12 H).



(Z)-Methyl 4-(tert-Butyldimethylsilyloxy)-5-hydroxypent-2-enoate. The olefin (500 mg, 1.33 mmol) was dissolved in 5 mL of methanol and 5 mL of dichloromethane at 0 °C. 10-Camphorsulfonic

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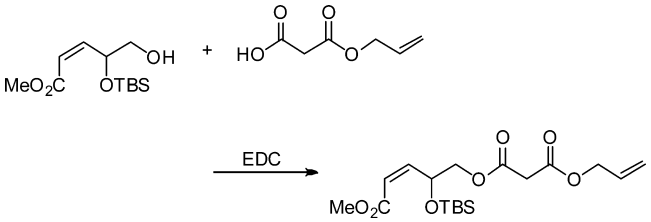
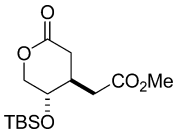
acid (0.06 g, 0.26 mmol) was added. The reaction was allowed to proceed at 0 °C for approximately 2 h with frequent monitoring by TLC. The reaction was stopped when the spot corresponding to the diol became significant; this occurred before the complete consumption of starting material. The reaction was quenched by the addition of 50 mL of saturated sodium bicarbonate solution and 50 mL of dichloromethane. The aqueous phase was back-extracted three times with 20 mL portions of dichloromethane. The combined organic extracts were washed with 30 mL of sodium bicarbonate solution and 30 mL of brine. The solution was concentrated under reduced pressure to yield a yellow oil. The oil was purified by silica gel chromatography (gradient elution: 10, 20, 25% EtOAc/hexanes) to afford the desired alcohol as a yellow oil (235 mg, 68%): TLC R_f = 0.65 (50% EtOAc/hexanes, $KMnO_4$ stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.23 (dd, J = 7.8, 11.7 Hz, 1 H), 5.86 (dd, J = 1.2, 12.0 Hz, 1 H), 5.44−5.35 (m, 1 H), 3.75 (s, 3 H), 3.70−3.53 (m, 2 H), 0.97−0.85 (m, 9 H), 0.09 (d, J = 17.6 Hz, 6 H).



*(Z)-Allyl 2-(tert-Butyldimethylsilyloxy)-5-methoxy-5-oxopent-3-enyl malonate (**31**).* To a solution of alcohol (114 mg, 0.44 mmol) in 5 mL of dichloromethane was added 3-dimethylaminopropylcarbodiimide hydrochloride (0.51 g, 2.7 mmol) followed by allylmalonic half acid (0.39 g, 2.7 mmol). The white suspension became a clear yellow solution. After 3 h, TLC analysis indicated the complete consumption of starting material. The solution was diluted with 50 mL of dichloromethane and 50 mL of 1 M HCl, and the layers were separated. The aqueous phase was back-extracted three times with 20 mL portions of dichloromethane. The combined organic layers were washed with 30 mL of sodium bicarbonate solution followed by 30 mL of brine. The mixture was concentrated under reduced pressure to yield a yellow oil. The oil was passed through a silica gel plug (10 × 10 cm) with 200 mL of 30% EtOAc/hexanes) to yield the desired allyl malonate as a yellow oil (5:1 Z/E mixture, 165 mg, 98%). The oil was further purified by semipreparative HPLC (Zorbax RX-Sil column, 0.5% i-PrOH/hexanes, retention times: 10 min (Z) and 20 min (E), 225 nm): TLC R_f = 0.5 (30% EtOAc/hexanes, KMnO4 stain); IR ($CHCl_3$ film) 2957, 2857, 1759, 1738, 1725, 1650, 1463, 1439, 1406, 1330, 1254, 1202, 1148, 1113, 997, 938, 890, 838 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.19−6.07 (m, 1 H), 5.97−5.85 (m, 1 H), 5.85−5.78 (m, 1 H), 5.60−5.49 (m, 1 H), 5.40−5.27 (m, 1 H), 5.28−5.18 (m, 1 H), 4.63 (dd, J = 1.3, 5.8 Hz, 2 H), 4.22−4.15 (m, 1 H), 4.14−4.07 (m, 1 H), 3.72 (s, 3 H), 3.40 (s, 2 H), 0.93−0.80 (m, 9 H), 0.05 (d, J = 14.4 Hz, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.1, 165.9, 165.8, 149.0, 131.5, 120.1, 118.7, 68.0, 67.0, 66.0, 51.5, 41.3, 25.6, 18.0, −4.9, −4.9; HRMS (ESI) calcd for $C_{18}H_{31}O_7Si$ $[M + H]^+$ 387.1834, found 387.1828.



*Methyl 2-((4,5-anti)-5-(tert-Butyldimethylsilyloxy)-2-oxo-tetrahydro-2H-pyran-4-yl)acetate (**S-072**).* The crude malonate product was decarboxylated directly using $Pd(PPh_3)_4$ to yield a yellow oil. The oil was purified by silica gel chromatography (15% EtOAc/hexanes) to yield **S-072** as a yellow oil: TLC R_f = 0.6 (30% EtOAc/hexanes, anisaldehyde stain); IR ($CHCl_3$ film) 2943, 2858, 1738, 1712, 1442, 1370, 1253, 1153, 1121, 1085, 838, 776 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{26}O_5SiNa$ $[M + Na]^+$: 325.1447, found 325.1443; NMR data, see Table 8.

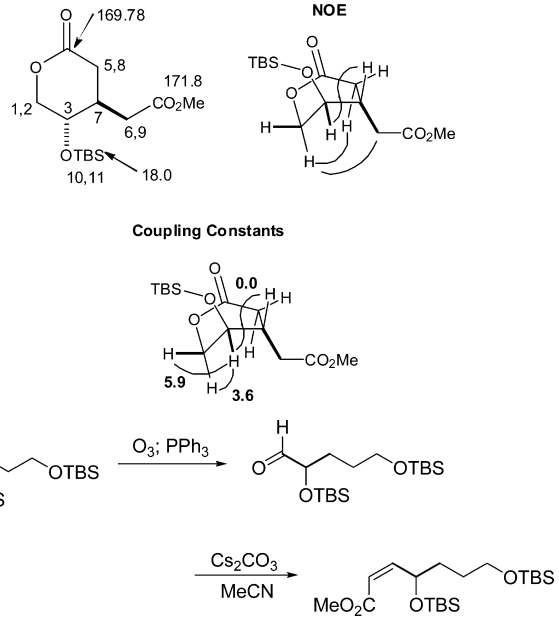


Table 8. NMR Data for S-072 (500 MHz, $CDCl_3$)

ID	δ ^{1}H	δ ^{13}C	Hs	type	couplings (Hz)
1	4.30	71.9	1	dd	11.7, 3.9
2	4.07	71.9	1	dd	11.7, 6.3
3	3.84	67.5	1	td	6.6, 3.9
4	3.69	52.1	3	s	
5	2.93	32.9	1	dd	17.3, 5.6
6	2.57	36.5	1	dd	16.1, 5.6
7	2.43	36.1	1	m	
8	2.35	32.9	1	dd	17.3, 7.8
9	2.29	36.5	1	dd	15.6, 7.8
10	0.88	25.8	9	s	
11	0.09	−4.5	6	d	2.4

quaternary carbons: 169.7, 171.8, 18.0

*(Z)-Methyl 4,7-Bis(tert-butyldimethylsilyloxy)hept-2-enoate (**S-073**).* The olefin (2.60 g, 7.54 mmol) was dissolved in 50 mL of dichloromethane and cooled to −78 °C. Ozone was bubbled through the solution until it turned blue. Nitrogen was bubbled through to purge the solution. Triphenylphosphine (1.94 g, 7.39 mmol) was added, and the solution was allowed to warm to room temperature. The cloudy white suspension was stirred for 3 h to give a yellow solution, after which NMR indicated near complete consumption of ozonide. The bulk of the solvent was removed by rotary evaporation. The white suspension was loaded onto a silica plug (10 × 5 cm) and eluted with 600 mL of 20% EtOAc in hexanes. The solution was concentrated to yield the desired aldehyde as a slightly yellow oil (2.00 g, 77%): TLC R_f 0.7 (20% EtOAc/hexanes, anisaldehyde stain, red); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.60 (d, J = 1.5 Hz, 1 H), 4.02−3.97 (m, 1 H), 3.62 (d, J = 2.0 Hz, 2 H), 1.56 (s, 4 H), 0.98−0.83 (m, 18 H), 0.09 (s, 2 H), 0.04 (s, 9 H).

To a suspension of cesium carbonate (1.86 g, 5.72 mmol) in 45 mL of acetonitrile and 15 mL of THF was added (2.39 g, 5.72 mmol). The white suspension was vigorously stirred at room temperature for 5 min. The suspension was cooled to 0 °C, and a solution of aldehyde (1.80 g, 5.19 mmol) in 5 mL of acetonitrile as added. The white suspension was stirred for 15 min and then warmed to room temperature. The reaction was stirred for a further 4 h. The mixture was diluted with 100 mL of water and 75 mL of ether. The layers were separated and the aqueous layer was back-extracted three times with 30 mL portions of ether. The combined organic extracts were washed with 50 mL of 0.1 M HCl, 50 mL of 0.1 M NaOH, and 25 mL of brine. The clear solution was diluted with hexanes, dried over sodium sulfate, and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (gradient

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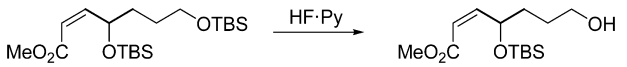
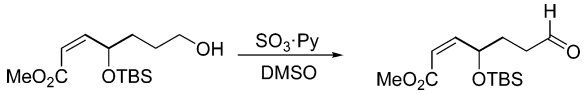
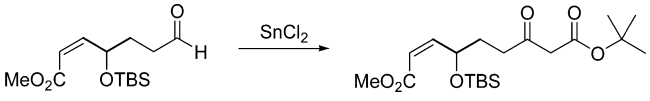
elution: 1, 2, 3, 5% EtOAc/hexanes) to yield the desired ester as a clear and colorless oil (1.10 g, 53%): TLC R_f = 0.80 (20% EtOAc/hexanes, anisaldehyde stain, blue); IR ($CHCl_3$ film) 2952, 2856, 1726, 1650, 1472, 1438, 1403, 1362, 1255, 1199, 1100, 1006, 939, 837, 778, 710, 663 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 6.15 (dd, J = 8.2, 11.7 Hz, 1 H), 5.69 (d, J = 11.9 Hz, 1 H), 5.36−5.25 (m, 1 H), 3.73−3.65 (m, 3 H), 3.60 (t, J = 6.0 Hz, 3 H), 1.73−1.44 (m, 6 H), 0.94−0.82 (m, 18 H), 0.06−−0.03 (m, 12 H); ^{13}C NMR (126 MHz, CDCl3) δ = 166.4, 154.1, 117.4, 68.8, 63.4, 51.4, 34.0, 28.8, 26.2, 26.1, 26.1, 26.0, 26.0, 18.5, 18.3, −4.4, −4.7, −5.0, −5.1.



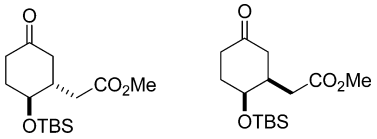
*(Z)-Methyl 4-(tert-Butyldimethylsilyloxy)-7-hydroxyhept-2-enoate (**S-073b**).* To a solution of disilyl ether (50 mg, 0.12 mmol) in 2 mL of THF and 0.2 mL of pyridine at 0 °C was added HF−pyridine (8 drops). The reaction was stirred for 3 h at 0 °C. The reaction was quenched with 25 mL of saturated sodium bicarbonate solution and diluted with 25 mL of ether. The layers were separated, and the aqueous layer was back-extracted three times with 20 mL portions of ether. The combined organic extracts were washed with 20 mL of brine, dried over sodium sulfate, and concentrated to give a clear oil. The oil was purified by silica gel chromatgraphy to yield the desired alcohol as a clear oil (15 mg, 42%): TLC R_f = 0.2 (60% EtOAc/hexanes); IR ($CHCl_3$ film) 3430, 2954, 2858, 1725, 1652, 1540, 1473, 1438, 1404, 1362, 1255, 1199, 1092, 1005, 836, 777, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 6.26 (dd, J = 7.8, 11.7 Hz, 1 H), 5.74 (dd, J = 1.5, 11.7 Hz, 1 H), 5.42−5.34 (m, 1 H), 5.29 (q, J = 5.4 Hz, 1 H), 3.76−3.71 (m, 3 H), 3.71−3.61 (m, 2 H), 1.76−1.58 (m, 2 H), 1.43 (d, J = 5.9 Hz, 2 H), 0.96−0.81 (m, 9 H), 0.10−−0.02 (m, 6 H); HRMS (ESI) calcd for $C_{14}H_{28}O_4SiNa$ $[M + Na]^+$ 311.1649, found 311.1640.



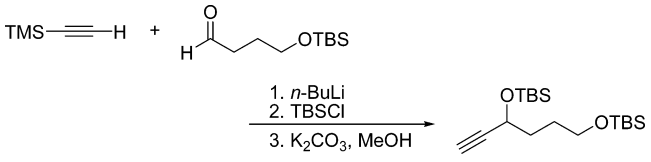
*(Z)-Methyl 4-(tert-Butyldimethylsilyloxy)-7-oxohept-2-enoate (**S-073c**).* The olefin-alcohol (100 mg, 0.35 mmol) was immediately dissolved in 3 mL of dichloromethane at 0 °C. Freshly distilled *N,N*-diisopropylethylamine (0.17 mL mL, 1.0 mmol) was added dropwise via syringe. After 10 min of stirring at 0 °C, dimethyl sulfoxide (0.25 mL, 3.5 mmol) was added to the reaction mixture via syringe and the solution was allowed to stir for an additional 10 min. Sulfur trioxide pyridine complex (0.29 g, 1.4 mmol) was then added in one portion. The reaction was allowed to proceed for 15 min at 0 °C, after which TLC analysis indicated complete consumption of starting material. The reaction was quenched by transfer into an 125 mL Erlenmeyer flask that contained a stirring solution of saturated sodium bicarbonate solution (50 mL). 50 mL of dichloromethane were added and the layers were separated. The aqueous layer was back-extracted three times with three 20 mL portions of dichloromethane. The combined organic extracts were washed with 50 mL of brine, dried over sodium sulfate, and concentrated to yield a yellow oil. The oil was eluted through a silica plug (2 × 5 cm) with 150 mL of 30% EtOAc/hexanes to yield the desired aldehyde as a clear oil (80 mg, 87%): TLC R_f 0.7 (30% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ = 9.80 (s, 1 H), 6.19 (dd, J = 7.8, 11.7 Hz, 1 H), 5.77 (dd, J = 1.5, 11.7 Hz, 1 H), 5.34 (dddd, J = 1.5, 5.5, 6.7, 7.9 Hz, 1 H), 3.74 (s, 3 H), 2.60−2.42 (m, 2 H), 1.98−1.83 (m, 2 H), 0.89 (s, 9 H), 0.04 (d, J = 20.5 Hz, 6 H).



*(Z)-9-tert-Butyl 1-Methyl 4-(tert-butyldimethylsilyloxy)-7-oxonon-2-enedioate (**33**).* To a dry vial were added tin(II) chloride (5.7 mg, 0.03 mmol) and dichloromethane (5 mL). *tert*-Butyl diazoacetate (0.07 mL, 0.5 mmol) was added dropwise to the vial with vigorous stirring. After gas evolution ceased, aldehyde (121 mg, 0.42 mmol) was added, and the yellow solution was stirred overnight. The solution was diluted with 100 mL of dichloromethane and 100 mL of saturated sodium bicarbonate solution. The layers were separated and the aqueous layer was back-extracted three times with 10 mL portions of dichloromethane. The combined organic layers were washed with 50 mL of water and 50 mL of brine, dried over sodium sulfate, and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (gradient elution: 15, 30% EtOAc/hexanes). The remaining *tert*-butyl diazoacetate was removed by high vacuum evaporation to yield the desired ketoester as a yellow oil (119 mg, 71%): TLC R_f = 0.70 (30% EtOAc/hexanes, CAM stain); IR ($CHCl_3$ film) 2956, 2858, 1723, 1652, 1473, 1438, 1404, 1369, 1321, 1254, 1201, 1179, 1085, 1005, 837, 778, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 6.12 (dd, J = 8.0, 11.7 Hz, 1 H), 5.72 (d, J = 11.9 Hz, 1 H), 5.36−5.23 (m, 1 H), 3.70 (d, J = 0.5 Hz, 3 H), 3.33 (s, 2 H), 2.72−2.42 (m, 2 H), 1.94−1.71 (m, 2 H), 1.54−1.36 (m, 9 H), 0.98−0.71 (m, 9 H), 0.11−0.10 (m, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 202.8, 166.4, 166.1, 153.0, 117.9, 81.8, 68.2, 67.8, 51.3, 50.7, 38.5, 30.9, 28.3, 27.9, 25.8, 18.0, −4.6, −4.9; HRMS (ESI) calcd for $C_{20}H_{36}O_6SiNa$ $[M + Na]^+$ 423.2179, found 423.2183.



*1,2-[2-(tert-Butyldimethylsilanyloxy)-5-oxocyclohexyl]acetic Acid Methyl Ester (**S-074**).* The properties of the *cis* and *trans* isomers were identical to those known in the literature.[37]



*5-Ethynyl-2,2,3,3,10,10,11,11-octamethyl-4,9-dioxa-3,10-disiladodecane (**S-075a**).* To a solution of (trimethylsilyl) acetylene (2.48 g, 25.3 mmol) in 50 mL of THF at −78 °C was added a solution of *n*-butyllithium (8.91 mL, 24.1 mmol, 2.71 M in hexanes) dropwise. The solution was stirred for 30 min. A solution of aldehyde (4.65 g, 23.0 mmol) in 12 mL of THF was added dropwise via cannula. The solution was stirred at −78 °C for 45 min. The reaction was quenched with 1 mL of pH 7 phosphate buffer and diluted with 75 mL of ether and 75 mL of saturated ammonium chloride solution. The layers were separated, and the aqueous layer was back-extracted three times with 20 mL portions of ether. The combined organic extracts were washed with 50 mL of brine, diluted with 100 mL of hexanes, dried over sodium sulfate, and concentrated to yield a dark oil. The oil was purified by silica gel chromatography (gradient elution: 0, 5, 10, 15% EtOAc/hexanes) to yield the desired propargylic alcohol as a yellow oil (4.54 g, 66%): TLC R_f = 0.4 (10% THF/hexanes, $KMnO_4$ stain); ^1H NMR (500 MHz, $CDCl_3$) δ = 4.43−4.29 (m, 1 H), 3.63 (s, 2 H), 1.69 (m, 4 H), 0.94−0.82 (m, 9 H), 0.19−0.02 (m, 15 H).

To a solution of alcohol (4.54 g, 15.1 mmol) in 15 mL of DMF were added *tert*-butyldimethylsilyl chloride (2.55 g, 16.9 mmol) and imidazole (2.57 g, 37.8 mmol). The mixture was stirred overnight. The mixture was quenched with 5 mL of MeOH and stirred for 15 min. The mixture was diluted with 100 mL of 25% EtOAc/hexanes and 100 mL of 0.1 M HCl. The layers were separated, and the aqueous layer was back-extracted three times with 20 mL portions of 25% EtOAc/hexanes. The combined organic layers were washed twice with 30 mL of water and once with 30 mL of brine. The solution was dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield the desired silyl ether as a pale yellow oil (5.82 g, 93%): TLC R_f = 0.8 (10% THF/hexanes, $KMnO_4$ stain); ^1H NMR (500 MHz, $CDCl_3$) δ = 4.41−4.34 (m, 1 H), 3.67−3.61 (m, 2 H), 1.76−1.58 (m, 4 H), 0.95−0.85 (m, 18 H), 0.22−0.00 (m, 21 H).

To a solution of silylalkyne (6.40 g, 15.4 mmol) in 100 mL of methanol was added potassium carbonate (4.26 g, 30.8 mmol). The white suspension was stirred for 2 h. The mixture was diluted with 75 mL of pH 7 phosphate buffer and 75 mL of hexanes. The layers were separated and the aqueous phase was back-extracted three times with 30 mL portions of hexanes. The combined organic extracts were washed with 30 mL of brine, dried over sodium sulfate, and concentrated to yield

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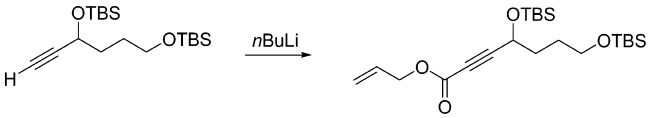
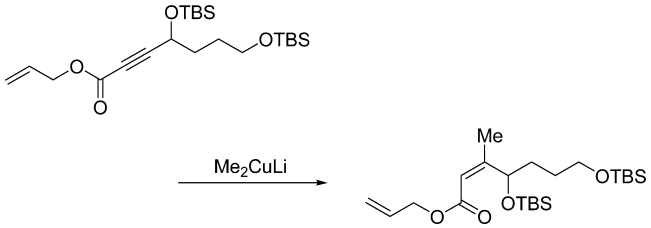
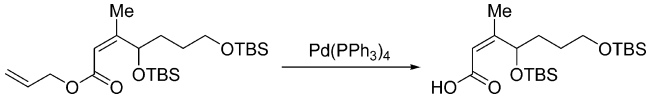
the desired alkyne as a clear and colorless oil (4.89 g, 93%): TLC R_f = 0.75 (10% THF/hexanes, $KMnO_4$ stain); ^1H NMR (500 MHz, $CDCl_3$) δ = 4.4.0 (m, 1 H), 3.63 (t, 2 H), 2.39 (s, 1 H), 1.78−1.62 (m, 4 H), 0.96 (m, 18 H), 1.18−1.04 (m, 12 H).



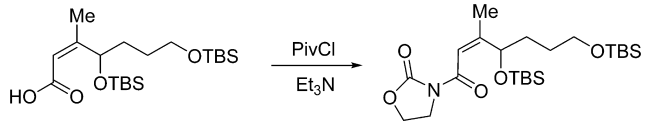
*Allyl 4,7-Bis(tert-butyldimethylsilyloxy)hept-2-ynoate (**S-075b**).* To a solution of alkyne (4.23 g, 12.3 mmol) in 80 mL of THF at −78 °C was added *n*-butyllithium (4.52 mL, 12.3 mmol, 2.72 M in hexanes). The light yellow solution was stirred for 30 min. Allyl chloroformate (1.44 mL, 13.5 mmol) was added dropwise. The yellow solution was stirred for 2 h at −78 °C. pH 7 phosphate buffer (1 mL) was added dropwise, and the suspension was allowed to warm slowly to room temperature. The mixture was diluted with 50 mL of ether and 100 mL of 50% ammonium chloride solution. The layers were separated, and the aqueous phase was back-extracted three times with 30 mL portions of ether. The combined organic layers were diluted with 75 mL of hexanes and washed with 50 mL of brine. The mixture dried over sodium sulfate and concentrated to yield the desired allyl ester as a clear and colorless oil (5.16 g, 98%): TLC R_f = 0.75 (10% THF/hexanes, $KMnO_4$ stain); TLC R_f = 0.60 (5% EtOAc/hexanes, $KMnO_4$ stain); ^1H NMR (500 MHz, $CDCl_3$) δ = 6.01−5.85 (m, 1 H), 5.42−5.33 (m, 1 H), 5.33−5.26 (m, 1 H), 4.68 (d, J = 5.4 Hz, 2 H), 4.57−4.50 (m, 1 H), 3.65 (s, 2 H), 1.84−1.73 (m, 2 H), 1.73−1.62 (m, 2 H), 0.93−0.87 (m, 18 H), 0.20−0.09 (m, 6 H), 0.08−0.03 (m, 6 H).



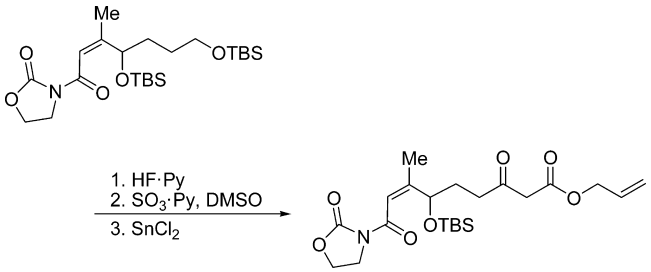
*(Z)-Allyl 4,7-Bis(tert-butyldimethylsilyloxy)-3-methylhept-2-enoate (**S-076**).* To a suspension of copper(I) iodide (257 mg, 1.35 mmol) in 8 mL of THF at −20 °C was added methyllithium (1.81 mL, 2.71 mmol, 1.5 M in ether as a complex with lithium bromide) dropwise. The clear light yellow solution was stirred vigorously for 15 min. The solution turned yellow upon the initial addition of methyllithium but became mostly clear and colorless afterward. A few undissolved yellow solids remained. The solution was cooled to −78 °C, and a solution of the alkyne (0.55 g, 1.29 mmol) in 7 mL of THF was added dropwise. The solution was stirred at −78 °C for 2 h. pH 7 phosphate buffer (1.0 mL) was added dropwise, and the mixture was allowed to warm slowly to room temperature. The mixture was diluted with 50 mL of ether and 50 mL of 10% (v/v) ammonium hydroxide solution. The aqueous phase became a deep blue color. The layers were separated and the aqueous layer was back-extracted three times with 20 mL portions of ether. The combined organic extracts were washed with 50 mL of brine and diluted with hexanes. The mixture was dried over sodium sulfate and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (2, 10%) to yield the desired olefin as a yellow oil (0.43 g, 75%, only *Z* isomer): TLC R_f = 0.60 (5% EtOAc/hexanes, $KMnO_4$ stain); ^1H NMR (500 MHz, $CDCl_3$) δ = 6.02−5.88 (m, 1 H), 5.71−5.63 (m, 1 H), 5.63−5.56 (m, 1 H), 5.37−5.31 (m, 1 H), 5.31−5.21 (m, 1 H), 4.64−4.56 (m, 2 H), 3.68−3.57 (m, 2 H), 1.71−1.58 (m, 2 H), 1.55−1.40 (m, 2 H), 0.99−0.80 (m, 18 H), 0.09−0.01 (m, 12 H).



*(Z)-4,7-Bis(tert-butyldimethylsilyloxy)-3-methylhept-2-enoic Acid (**S-076b**).* To a solution of allyl ester (1.50 g, 3.39 mmol) in 15 mL of dichloromethane at 0 °C were added morpholine (3.0 mL, 34 mmol) and palladium tetrakis(triphenylphosphine) (73 mg, 0.14 mmol). The mixture was stirred for 40 min and then allowed to warm to room temperature over 30 min. The yellow solution was diluted with 30 mL of dichloromethane, 10 mL of brine, and 10 mL of 1 M HCl. The layers were separated, and the aqueous phase was washed four times with 10 mL portions of dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (gradient elution: 10, 20% EtOAc/hexanes) to yield the desired acid as a yellow oil (1.22 g, 89%). The oil solidified upon standing to form yellow crystals: TLC R_f = 0.7 (30% EtOAc/hexanes, $KMnO_4$ stain); ^1H NMR (500 MHz, $CDCl_3$) δ = 5.69 (s, 1 H), 5.45−5.24 (m, 1 H), 3.61 (s, 2 H), 1.92 (s, 3 H), 1.71−1.41 (m, 4 H), 0.89 (d, J = 5.4 Hz, 18 H), 0.11−−0.01 (m, 12 H).



*(Z)-3-(4,7-Bis(tert-butyldimethylsilyloxy)-3-methylhept-2-enoyl)-oxazolidin-2-one (**S-077**).* To a solution of carboxylic acid (0.25 g, 0.62 mmol) in 5 mL of THF at 0 °C were added triethylamine (0.26 mL, 1.86 mmol) and pivaloyl chloride (76 uL, 0.62 mmol). The clear and colorless solution quickly became a white suspension upon addition of the acid chloride. In a separate flask, *n*-butyllithium (0.61 mL, 1.86 mmol, 3.05 M in hexanes) was added to a suspension of 2-oxazolidinone (162 mg, 1.86 mmol) in 10 mL of THF at −78 °C. Both mixtures were stirred for 30 min. The mixed anhydride was added to the lithiated oxazolidinone via syringe, and the mixture was stirred for 30 min at −78 °C. The mixture was warmed to 0 °C and stirred for 1 h and then to room temperature for 1 h. The mixture was diluted with 30 mL of ether and 50 mL of 1 M HCl. The layers were separateed and the aqueous layer was back-extracted three times with 15 mL portions of ether. The combined organic extracts were washed with 30 mL of brine, diluted with hexanes, dried over sodium sulfate, and concentrated to yield a yellow oil. The oil was purified by preparative HPLC (ZORBAX RX-Sil, 0.7% IPA/hexanes (20 min) followed by 1.0% IPA/hexanes (20 min), 225 nm, 15 mL/min) to yield the desired oxazolidinone as a clear and colorless oil (elutes at approximately 25 min, 130 mg, 44%): TLC R_f = 0.3 (15% EtOAc/hexanes, $KMnO_4$ stain); IR ($CHCl_3$ film) 2956, 2858, 1782, 1679, 1627, 1472, 1444, 1386, 1361, 1274, 1252, 1222, 1200, 1180, 1101, 1004, 970, 837, 776, 708, 665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 6.94−6.86 (m, 1 H), 5.48−5.38 (m, 1 H), 4.39 (s, 2 H), 4.08−3.99 (m, 2 H), 3.61 (s, 2 H), 1.96 (d, J = 1.1 Hz, 3 H), 1.70−1.56 (m, 2 H), 1.55−1.45 (m, 2 H), 0.93−0.79 (m, 18 H), 0.07−−0.06 (m, 12 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.2, 164.4, 153.5, 114.5, 70.8, 63.4, 61.9, 42.9, 33.1, 29.4, 26.2, 26.0, 19.9, 18.5, 18.3, −4.7, −4.8, −5.0; HRMS (ESI) calcd for $C_{23}H_{45}NO_5SiNa$ $[M + Na]^+$ 494.2729, found 494.2726.



*(Z)-Allyl 6-(tert-Butyldimethylsilyloxy)-7-methyl-3,9-dioxo-9-(2-oxooxazolidin-3-yl)non-7-enoate (**35**).* To a solution of disilyl ether (70 mg, 0.15 mmol) in 5 mL of THF and 0.5 mL of pyridine at 0 °C was added HF−pyridine (60 drops). The solution was stirred for 45 min at 0 °C. The mixture was diluted with 5 mL of dichloromethane and 5 mL of saturated sodium bicarbonate solution (slowly, gas evolution!). The mixture was poured into a separatory funnel and diluted with a further 40 mL of dichloromethane and 40 mL of saturated sodium bicarbonate solution. The layers were separated, and the aqueous phase was back-extracted three times with 20 mL portions of dichloromethane. The combined organic extracts were washed with 30 mL of 0.1 M HCl and 30 mL of brine. The clear and colorless solution was dried over sodium sulfate and concentrated to yield a clear and colorless oil. The oil was

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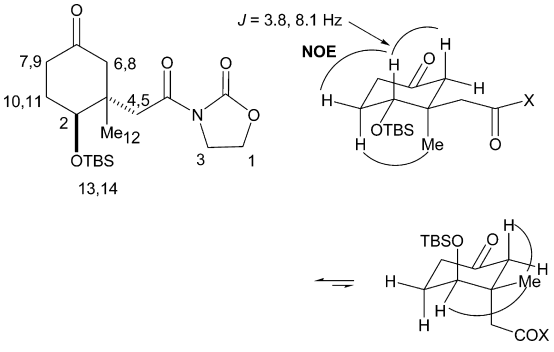
purified by silica gel chromatography (50, [70%] EtOAc/hexanes) to yield the desired alcohol as a clear and colorless oil (40 mg, 76%). The oil crystallized upon standing to a white solid: TLC R_f = 0.4 (70% EtOAc/hexanes, CAM stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.99−6.89 (m, 1 H), 5.48−5.39 (m, 1 H), 4.48−4.35 (m, 2 H), 4.13−3.99 (m, 2 H), 3.83−3.61 (m, 2 H), 2.01 (d, J = 1.5 Hz, 3 H), 1.79−1.59 (m, 4 H), 0.91 (s, 9 H), 0.08−0.05 (m, 6 H).

The alcohol (159 mg, 0.35 mmol) was immediately dissolved in 3 mL of dichloromethane at 0 °C. Freshly distilled *N,N*-diisopropylethylamine (0.54 mL, 3.1 mmol) was added dropwise via syringe. After 10 min of stirring at 0 °C, dimethyl sulfoxide (0.32 mL, 4.4 mmol) was added to the reaction mixture via syringe, and the solution was allowed to stir for an additional 10 min. Sulfur trioxide−pyridine complex (0.37 g, 1.8 mmol) was then added in one portion. The reaction was allowed to proceed for 20 min at 0 °C, after which TLC analysis indicated complete consumption of starting material. The reaction was quenched by transfer into an 125 mL Erlenmeyer flask that contained a stirring solution of saturated sodium bicarbonate solution (50 mL). Dichloromethane (50 mL) was added, and the layers were separated. The aqueous layer was back-extracted three times with three 20 mL portions of dichloromethane. The combined organic extracts were washed with 50 mL of brine, dried over sodium sulfate, and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (40% EtOAc/hexanes) to yield the desired aldehyde as a clear oil (134 mg, 85%): TLC R_f = 0.65 (70% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.89−9.72 (m, 1 H), 7.02−6.88 (m, 1 H), 5.49−5.36 (m, 1 H), 4.53−4.32 (m, 2 H), 4.11−3.98 (m, 2 H), 2.67−2.41 (m, 2 H), 2.00 (d, J = 1.5 Hz, 3 H), 1.98−1.90 (m, 1 H), 1.90−1.79 (m, 1 H), 0.90 (s, 9 H), 0.14−0.08 (m, 6 H).

To a dry vial was added tin(II) chloride (7.2 mg, 0.04 mmol) and dichloromethane (0.5 mL). Allyl diazoacetate (0.07 mL, 0.6 mmol) was added dropwise to the vial with vigorous stirring. After gas evolution ceased, aldehyde (134 mg, 0.38 mmol) was added, and the yellow solution was stirred overnight. The solution was diluted with 100 mL of dichloromethane and 100 mL of saturated sodium bicarbonate solution. The layers were separated, and the aqueous layer was back-extracted three times with 10 mL portions of dichloromethane. The combined organic layers were washed with 50 mL of water, 50 mL of brine, dried over sodium sulfate, and concentrated to yield a yellow oil. The oil was purified by silica gel chromatography (gradient elution: 10, 30, 50% EtOAc/hexanes). The remaining allyl diazoacetate was removed by high vacuum evaporation to yield the desired ketoester as a yellow oil (136 mg, 80%): TLC R_f = 0.65 (30% EtOAc/hexanes, $KMnO_4$ stain); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.93 (s, 1 H), 6.00−5.82 (m, 1 H), 5.40−5.30 (m, 2 H), 5.29−5.22 (m, 1 H), 4.63 (dt, J = 1.3, 5.7 Hz, 2 H), 4.41 (t, J = 8.1 Hz, 2 H), 4.04 (t, J = 8.1 Hz, 2 H), 3.49 (s, 2 H), 2.77−2.63 (m, 1 H), 2.63−2.50 (m, 1 H), 1.97 (d, J = 1.5 Hz, 7 H), 0.94−0.82 (m, 9 H), 0.08−−0.06 (m, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 202.0, 166.8, 164.3, 164.2, 153.2, 131.6, 118.8, 115.2, 106.8, 69.6, 65.9, 61.8, 49.1, 42.6, 39.4, 29.8, 25.7, 19.4, 18.0, −5.0, −5.1; HRMS (ESI) calcd for $C_{22}H_{36}NO_7Si$ [M + H]$^+$ 454.2256, found 454.2254.

*3-(2-((1,2-anti)-2-(tert-Butyldimethylsilyloxy)-1-methyl-5-oxocyclohexyl)acetyl)oxazolidin-2-one (**S-078**):* TLC R_f 0.45 (35% EtOAc/hexanes, CAM stain); HRMS (ESI) calcd for $C_{18}H_{31}O_5SiNNa$ [M + Na]$^+$ 392.1869, found 392.1854; NMR data, see Table 9.



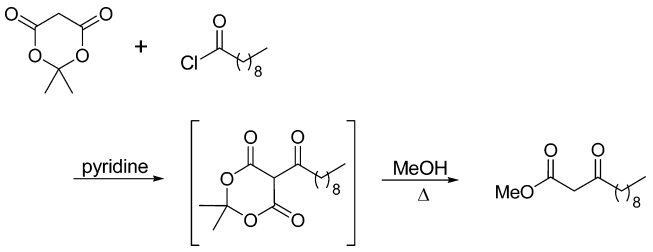
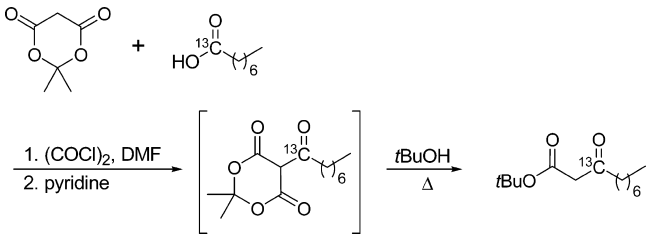


Table 9. NMR Data for S-078 (500 MHz, $CDCl_3$)

ID	δ ^{1}H	δ ^{13}C	Hs	type	couplings (Hz)
1	4.40	61.8	2	t	8.1
2	4.15	72.4	1	dd	3.8, 8.1
3	4.00	42.5	2	t	8.1
4	3.09	41.8	1	d	16.4
5	2.88	41.8	1	d	16.4
6	2.57	48.7	1	d	14.0
7	2.45	37.5	1	m	
8	2.43	48.7	1	d	14.0
9	2.32	37.5	1	m	
10	2.02	29.5	1	m	
11	1.90	29.5	1	m	
12	1.06	20.3	3	s	
13	0.91	25.8	6	s	
14	0.10	−4.2, −5.0	9	d	8.1

quaternary carbons: 210.4 (ketone), 171.1 (acyl), 153.4 (oxazolidinone), 37.5 (quaternary center), 18.0 (silyl *t*-butyl)

*3-Oxodecanoic Acid Methyl Ester (**37**).* To a solution of Meldrum's acid (4.45 g, 30.9 mmol, freshly recrystallized from hot acetone) in 50 mL of dichloromethane at 0 °C was added pyridine (6.07 mL, 75 mmol). To this clear and colorless solution was added decanoyl chloride (6.23 mL, 30 mmol). The solution became an orange suspension. The mixture was stirred for 30 min and then warmed to room temperature for 1 h. The mixture was washed with 100 mL of 1 M HCl. The layers were separated and the aqueous phase was back-extracted three times with 20 mL portions of dichloromethane. The combined organic layers were washed with 50 mL of 1 M HCl followed by 30 mL of brine. The orange solution was dried over sodium sulfate, filtered, and concentrated to give the desired adduct as an orange oil (mixture of keto−enol isomers in $CDCl_3$). The oil was suspended in 50 mL of methanol and heated at 70 °C for 2 h. The solvent was evaporated and the resulting orange oil was purified by silica gel chromatography (gradient elution: 10, 15, 30% EtOAc/hexanes) to yield the desired ketoester as yellow oil (4.8 g, 70%, about 90% pure): TLC R_f 0.70 (30% EtOAc/hexanes, anisaldehyde stain, purple); IR (ATR) 2925, 2855, 1747, 1716, 1654, 1629, 1437, 1407, 1318, 1235, 1152, 1087, 1008, 840, 801, 722 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 12.05−12.02 (m, 1 H), 5.01−5.00 (m, 1 H), 3.76 (s, 3 H), 3.46 (s, 3 H), 2.54 (t, J = 7.6 Hz, 2 H), 2.39−2.34 (m, 2 H), 2.37 (t, J = 7.6 Hz, 1 H), 2.21 (s, 1 H), 1.60 (br. s., 2 H), 1.42−1.18 (m, 8 H), 0.89 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 202.7, 167.6, 88.5, 52.1, 48.9, 42.9, 34.9, 33.8, 31.7, 29.3, 29.2, 29.1, 29.0, 28.9, 28.9, 26.1, 24.6, 23.3, 22.5, 14.0; HRMS (ESI) calcd for $C_{13}H_{25}O_3$ [M + H]$^+$ 229.1804, found 229.1800.



*[3-^{13}C]-3-Oxodecanoic Acid tert-Butyl Ester (**39**).* To a solution of oxalyl chloride (0.60 mL, 7.0 mmol) in 7 mL of dichloromethane was

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added [1-^{13}C]-*n*-octanoic acid (1.0 mL, 6.3 mmol, obtained from Cambridge Isotope Laboratories, 99% labeled). *N*,*N*-Dimethylformamide (0.1 mL) was added dropwise. This initiated vigorous gas evolution. The reaction was allowed to proceed at room temperature for 1 h. The slightly yellow solution was concentrated to yield [1-^{13}C]-octanoyl chloride as a yellow oil. The oil was dissolved in 5 mL of dichloromethane. To a solution of Meldrum's acid (0.91 g, 6.3 mmol, freshly recrystallized from hot acetone) in 5 mL of dichloromethane was added pyridine (1.3 mL, 16 mmol) followed by the above solution of labeled *n*-octanoyl chloride slowly over 30 s at 0 °C. The resulting orange suspension was warmed to room temperature. After 1 h, the orange mixture was diluted with 25 mL of dichloromethane and 50 mL of 0.1 M HCl. The mixture was separated, and the aqueous layer was back-extracted three times with 15 mL portions of dichloromethane. The combined organic extracts were washed with 30 mL of brine, dried over sodium sulfate, and concentrated to yield the desired acyl Meldrum's acid as an orange oil (1.56 g, 92%).

The oil was dissolved in 10 mL of benzene, and 2-methyl-2-propanol (2.7 mL, 16.5 mmol) was added. The dark mixture was heated at 60 °C for 4 h. The solvent was evaporated, and the mixture was purified by silica gel chromatography (gradient elution: 2, 5, 10% EtOAc/hexanes) to yield the desired ketoester as a yellow oil (0.86 g, 78%): TLC R_f 0.70 (30% EtOAc/hexanes, anisaldehyde stain, purple); IR (ATR) 2956, 2928, 2857, 1732, 1679, 1604, 1458, 1409, 1394, 1368, 1315, 1248, 1143, 1015, 953, 840, 725 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.32 (d, J = 6.2 Hz, 2 H), 2.50 (td, J = 5.7, 7.3 Hz, 2 H), 2.42 (q, J = 7.3 Hz, 1 H), 1.69−1.52 (m, 2 H), 1.45 (s, 9 H), 1.35−1.18 (m, 4 H), 0.89−0.83 (m, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 203.4 (s), 178.3 (d, J = 27 Hz), 173.6 (d, J = 85 Hz), 169.5 (s), 81.7 (s), 50.5 (s, J = 38 Hz), 42.8 (d, J = 40 Hz), 31.6 (s), 28.9 (s), 28.9 (s), 27.9 (s), 23.4 (d, J = 2 Hz), 22.5 (s), 14.0 (s); HRMS (ESI) calcd for $^{12}C_{13}{}^{13}C_1H_{26}O_3$ [M + Na]$^+$ 266.1814, found 266.1807.

■ ASSOCIATED CONTENT

Supporting Information

Computational details, Eyring analysis of selective inversion data, and NMR spectra. This information is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to the Late Professor Robert E. Ireland for his unconditional support, and longstanding friendship.

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