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Synthesis and Intramolecular Photocycloadditions of 2-Acyloxy-3-Hexenoyl Cyclohexenones: Diastereoselectivity in the Intramolecular [2+2] Photocycloadditions of Alkenes and Cyclohexenones Tethered by Four Atoms

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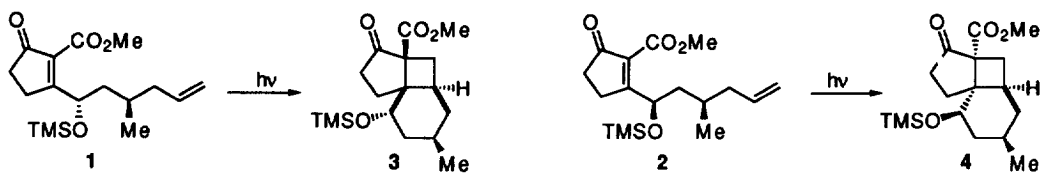
Abstract: *The intramolecular [2+2] photocycloaddition of 2-acyloxy-2-3-hexenoylcyclohexenones has been shown to be highly diastereoselective. The cycloadditions produce exclusively cis fused products and the sense and level of selectivity is consistent with a molecular mechanics model for initial bond formation in the stepwise cycloaddition.* © 1997 Elsevier Science Ltd.

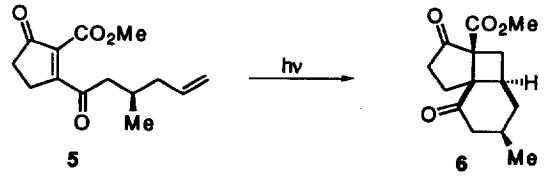
The stereocontrolled synthesis of polycyclic carbon skeleta continues to be an important area of organic synthesis because of the wealth of naturally occurring biologically active compounds which contain multiple carbocyclic rings. Control of stereogenicity of substituents on polycarbocyclic systems traditionally has been accomplished by taking advantage of the inherent steric bias of the ring system. In contrast, utilizing the influence of preexisting acyclic stereogenic centers during the formation of one or more of the rings of a polycyclic array has not been fully exploited. Photocycloadditions have been important reactions in the construction of polycarbocyclic ring systems[1,2] which could be further manipulated to give synthetically useful precursors to natural products.[3,4,5] The intramolecular [2+2] photocycloaddition has found wider application than the intermolecular version due to better regio and stereochemical control,[1] and to the ability to access polycyclic systems quickly and efficiently. Little, however, is understood as to how existing stereogenic centers on the tether between the enone and the olefin influence the stereochemical outcome of the intramolecular photocycloaddition particularly when the tether is longer than 3 atoms.[6,7] We report here our studies on the synthesis and stereoselective photocycloadditions of substituted 4-carbon tethered cyclohexenones.

Scheme 1



We had previously reported on the stereoselective photocycloadditions of 4-atom tethered cyclopentenones **1-2**.[6] The stereochemistry of the tricyclic photoadducts was controlled by the stereochemical relationship of the tether substituents. In particular, the *cis* fused cycloadduct **3** was favored when the tether substituents were *anti* and the *trans* fused cycloadduct **4** was formed when the tether substituents were *syn* (Scheme 1). The observed selectivity was attributed to the relative energetics of the competing transition states for the formation of the six membered ring. Interestingly, when the alcohol on the tether was oxidized to the corresponding ketone **5** (Scheme 2), only the *cis* fused adduct **6** was obtained.

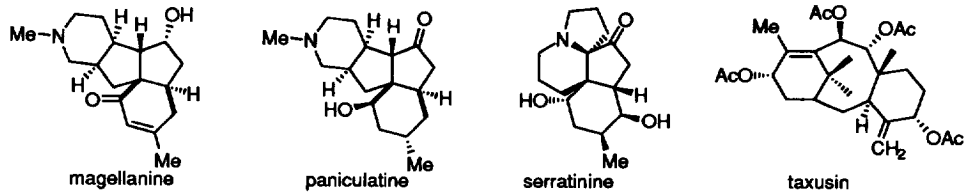
Scheme 2



Synthesis of the Photosubstrates.

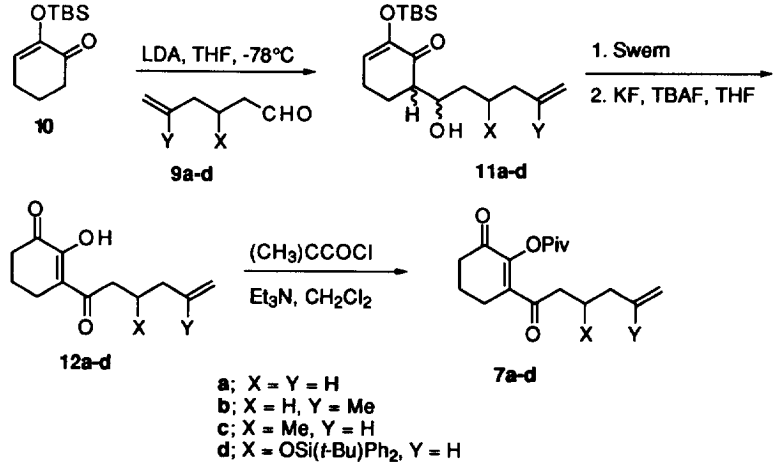
The synthesis of enediones **7a-d** (Scheme 4) and **8** (Scheme 5) was undertaken to evaluate the generality of the stereochemical effect of the carbonyl on the tether and to test the viability of the photoadducts in an approach to the lycopodium alkaloids magellanine,[8] serratinine,[9] and paniculatine[10] as well as the diterpene taxusin[11] (Scheme 3). A general procedure was developed which was amenable to the synthesis of all the required photosubstrates (Schemes 4 and 5).

Scheme 3



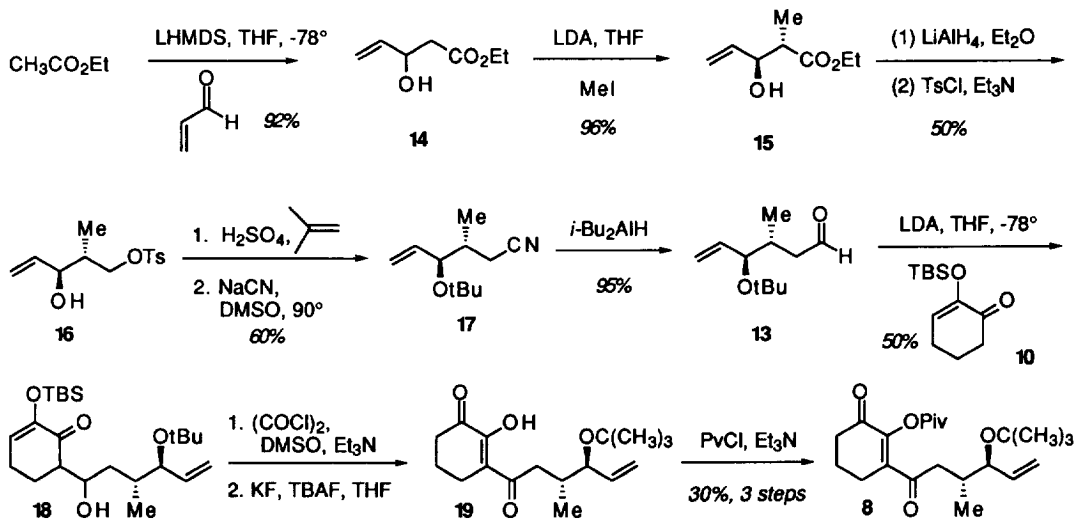
An aldol condensation between 5-hexenal **9a** and the lithium enolate of ketone **10**[12] produced a mixture of diastereomeric aldol products **11a** in good yield.[13] Oxidation of the secondary alcohol of **11a** followed by hydrolysis of the silyl enol ether by treatment with potassium fluoride and catalytic tetrabutylammonium fluoride provided the thermodynamic enol **12a**. Acylation of the enol by exposure to pivaloyl chloride and triethylamine gave enolpivalate **7a** in about 50% overall yield from the aldol product **11a**. The corresponding substituted photosubstrates **7b**, **7c**, and **7d** were prepared by the same sequence from the known aldehydes **9b**,[14] **9c**,[15] and **9d**,[16] respectively.

Scheme 4



Dienone **8** was prepared by the general procedure described above from aldehyde **13**. Aldehyde **13** was synthesized as illustrated in Scheme 5. Addition of the lithium enolate of ethyl acetate to acrolein in THF led to the formation of β-hydroxy ester **14** in 92% yield.[17] Diastereoselective alkylation with methyl iodide according to the Seebach procedure produced the desired *anti* relationship between the substituents in ester **15**.[18] Reduction of the ester with lithium aluminum hydride and tosylation of the resultant primary alcohol afforded 50% of tosylate **16**. Protection of the secondary alcohol as its *t*-butyl ether and displacement of the tosylate with sodium cyanide provided nitrile **17** in 60% overall yield. Diisobutylaluminum hydride reduction of the nitrile produced aldehyde **13** upon aqueous workup. An aldol condensation of aldehyde **13** with the lithium enolate of ketone **10** followed by the usual sequence gave photosubstrate **8**.

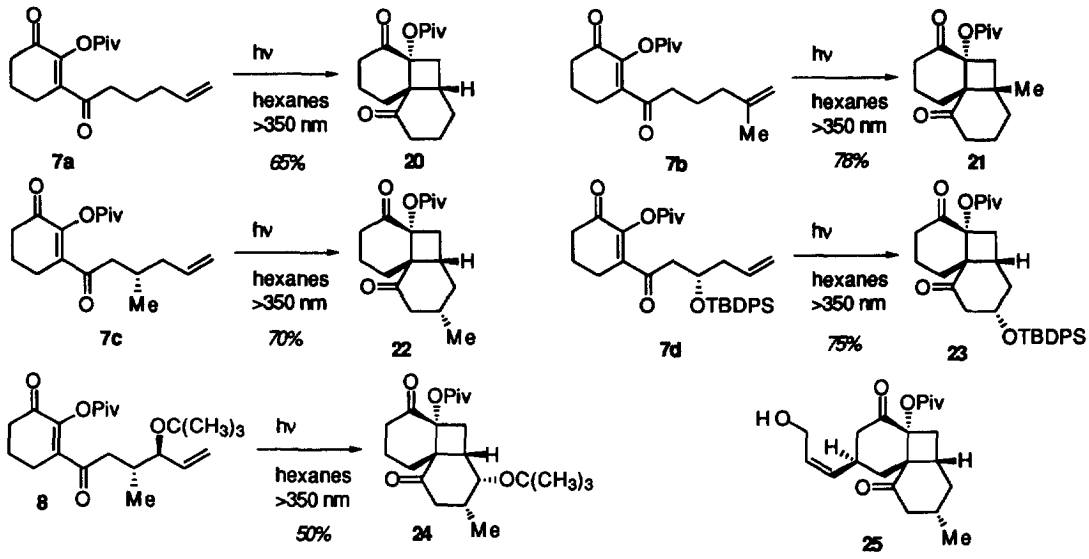
Scheme 5



Photocycloadditions of Enediones.

Each of the enediones **7a-d**, **8** was irradiated in a hexane solution with a Hanovia 450W mercury vapor lamp. The light was filtered through a uranium glass sleeve exposing the substrates to wavelengths greater than 350 nm. Irradiation of the simplest enedione **7a** produced a single *cis* fused photoadduct **20** in 65% yield (Scheme 6). When a methyl substituent was incorporated on the alkene in **7b**, the *cis* product **21** was again observed as the only product. Interestingly, when a stereogenic center was incorporated on the tether as in enediones **7c** and **7d** very high diastereoselectivity was observed in the photocycloaddition. Irradiation of photosubstrate **7c** in hexanes at >350 nm gave a single diastereomeric photoadduct **22** in 70% yield. That the ring juncture was *cis* and the methyl group and the ring juncture hydrogen were *trans* was determined by a combination of NOESY and COSY experiments. The assigned stereochemistry was unambiguously confirmed by a single crystal *X*-ray structure of the modified intermediate **25**. In an analogous manner photoadduct **23** was obtained as the sole product in 75 % yield after 6 hours of irradiation of enedione **7d**.

Scheme 6

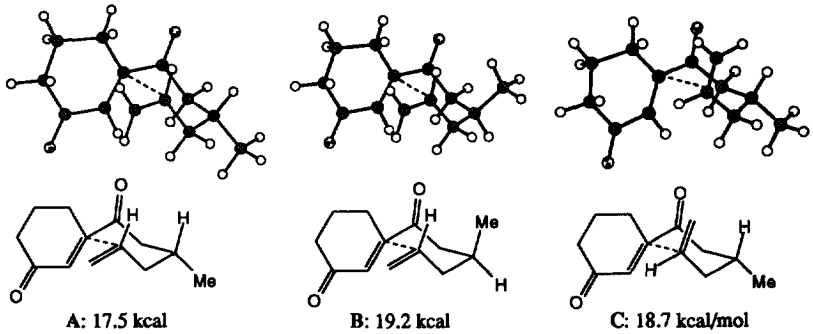


The exclusive formation of **22** and **23** can be rationalized by examination of the diastereomeric transition states shown in Scheme 7.[6,7] Initial bond formation of the photocycloaddition could occur through either 2,7 or 1,8 ring closure of the 1,7-diene, that is, through either a six membered or eight membered ring transition state. Weedon has recently demonstrated through trapping experiments that initial five membered ring formation is the exclusive pathway in 1,6-dienes.[19] On the other hand, Winkler has provided evidence that both 2,7 and 1,8 ring closure modes can occur in photocycloadditions between four atom tethered alkenes and the dioxinone chromophore.[7] If one assumes that the six membered ring should be favored for kinetic reasons, there are still 16 possible transition states for the first ring formation. Half the conformations are in the *s-cis* conformation of the tether carbonyl relative to the cyclohexenone and half are in the *s-trans* conformation. Based on dipolar effects the *s-trans* should be preferred and molecular mechanics calculations indicate that the three lowest energy conformations (and four of the five lowest) of the sixteen possible are all in the *s-trans* conformation.[20] The three lowest energy conformations are shown in Scheme 7. Transition state **A**, in which the substituent on the tether is oriented in a pseudo-equatorial position in a chair conformation of the six-membered ring, would predict the observed product. Transition state **A** is lower by 1.2 kcal/mol than transition state **C** which is the second lowest conformation, but would lead to a *trans* ring fusion. Molecular mechanics calculations also indicate that transition state **A** is lower in energy by about 1.7 kcal/mol than transition state **B**, the conformation closest in energy which would produce a *cis* fused product. Since *trans* 6-4 ring fusions are known to be obtained in intramolecular [2+2] photocycloadditions,[6] the high level of diastereoselectivity in these photocycloadditions is somewhat surprising. Nevertheless, the molecular mechanics model above fits reasonably well with the experimental results and predicts the observed major diastereomer. If one assumes initial 1,8 ring closure, once again, molecular mechanics calculations favor the transition state **D**, leading to the experimentally observed product, over transition state **E** but by approximately 1.7 kcal/mole. This value is more

in line with the experimentally observed ratio of >95:5. Note also that conformations **D** and **E** are both lower in energy than conformation A.

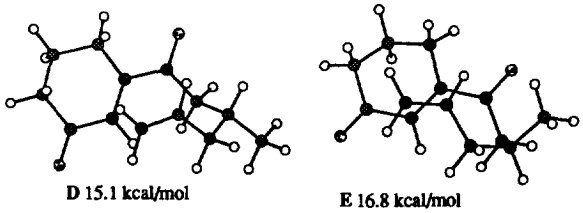
While the molecular mechanics correlation of the stereoselectivity of these photocycloaddditions provides a useful model for predicting the outcome of the reaction, the stereoselectivity may be controlled by different rates at which the various intermediate biradicals partition between product and ground state. In an effort to determine if other biradical intermediates are involved in these reactions, Weedon's method was investigated.[19] Unfortunately, attempted trapping of the intermediates in the photocycloaddition of enone **7c** by irradiating in the presence of H_2Se completely suppressed the photoaddition reaction resulting only in reduction of the C-C double bond of the enone.

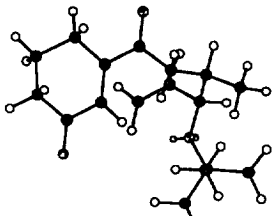
Scheme 7



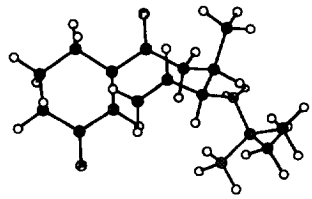
The disubstituted system **8** incorporated an *anti* relationship between a methyl group and a *t*-butyl ether on adjacent carbons. This orientation should force the molecule to adopt a conformation in which one of the substituents must be pseudo-axial in the photocycloaddition transition state. Irradiation of **8** in hexanes produced diketone **24** as the only identifiable product in 50% yield. The structural assignment of **24** was confirmed by a single crystal *X*-ray analysis. Molecular mechanics calculations of the transition states for the 2,7 ring closure in the photoaddition of **8** do not correlate with the observed product. However, the relative energy of the conformations **F** and **G** for 1,8 ring closure fit reasonably well with the experimental results. The overriding factor here for the observed selectivity appears to be the preference for the pseudo-equatorial disposition of the methyl group in the transition state. Finally, the lowest energy conformation **H** would appear to lead to a *trans* ring fusion. However, if initial 1,8 ring formation occurred through **H**, the intermediate 1,4 biradical could undergo a conformational change of the eight membered ring analogous in a similar manner to a case observed by Winkler.[7] This effectively inverts the stereogenicity of the ring fusion carbon to allow formation of a *cis* fused photoadduct which would be the observed product **24**.

Scheme 8

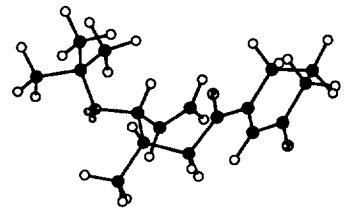




F 28.0 kcal/mol



G 29.6 kcal/mol



H 27.7 kcal/mol

Conclusion: We have demonstrated that high levels of stereocontrol are achievable in intramolecular enone - olefin photocycloadditions in which the enone and the alkene are connected by a four atom tether. While the order of formation and the exact source of the stereocontrol is still unclear, the molecular mechanics model presented here is a useful predictive tool since the diastereoselectivity correlates well with the energetics of conformations accessible during the first bond formation in the stepwise cycloaddition Studies are in progress to clarify the order of bond formation and the possibility that partitioning rates of intermediate radicals may be responsible for the stereocontrol in these photoadditions.

Experimental Section

General Procedures. Infrared (IR) spectra were obtained using a Mattson FT-IR 5000 Galaxy series infrared spectrometer. Proton and carbon nuclear magnetic resonance (^{1}H, ^{13}C NMR) spectra were recorded on the following instruments: Bruker Model AC-200 (1H at 200 MHz; ^{13}C at 50 MHz), Bruker Model WM-250 (^{1}H at 250 MHz) and Varian Model XL-400 (^{1}H at 400 MHz, ^{13}C at 100 MHz). Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, Georgia. High resolution mass spectral analysis were performed at the North Carolina State University Mass Spectrometry Facility, Raleigh, N.C. X-ray data was collected by Dr. Peter White at the *X*-ray Crystallography Laboratory, Department of Chemistry, UNC-Chapel Hill. Molecular mechanics calculations were performed on a Macintosh 9500 PowerPC using the MM2 force field in *Chem3D Pro*. The partially bonded atoms were restricted to a separated distance of 2.5Å. The calculations were performed until a divergence of 0.001 kcal was reached.

Ketone 10. To a solution of 1, 2-cyclohexanedione (24.6 g, 0.220 mole) in CH_2Cl_2 at 0°C was added imidazole (18.0 g, 0.264 mole), t-butyldimethylsilylchloride (32.2 g, 0.213 mole), and dimethylaminopyridine (2.68 g, 0.022 mole). After stirring for 3 hours, the reaction was quenched with sat. $NaHCO_3$. The layers were separated. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel to provide **ketone 10** (44.1 g, 91%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.11 (s, 6H), 0.91 (s, 9H), 1.94 (m, 2H), 2.36 (q, J=5.6 Hz, 2H), 2.45 (t, J=7.5Hz, 2H), 6.15 (t, J=4.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.59, 148.15, 127.65, 38.75, 25.71, 24.87, 23.21, 18.45, -4.68. IR (neat): 2920, 2860, 1680, 1630, 1260, 1200, 1150, 1110, 930, 830, 780 cm^{-1}.

General Procedure for the aldol reaction of ketone 10 with aldehydes 9a-d and 13.
To a solution of diisopropylamine (1.2 eq.) in THF at -78°C was added nBuLi (1.1 eq.) and the mixture was stirred for 15 min. Ketone **10** was diluted with THF and added dropwise to the reaction mixture. After stirring for 20-30 minutes, a solution of the aldehyde in THF was added dropwise to the enolate, and the resultant mixture stirred for 15-20 minutes. The reaction was then quenched with sat. NH_4Cl and warmed to room temperature. The volatiles were then removed under reduced pressure. The residue was taken up in ether and washed successively with 10% HCl, sat. $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel to provide the corresponding aldol products.

Alcohol 11a. Yield = 53%. ^1H NMR (200 MHz, $CDCl_3$) δ 0.65 (q, 6H), 0.93 (t, 9H), 1.30-1.79 (m, 6H), 1.87-2.13 (m, 3H), 2.21-2.46 (m, 3H), 3.78-3.93 (m, 1H), 4.87-5.05 (m, 2H), 5.67-5.90 (m, 1H), 6.10-6.19 (m, 1H). IR (neat): 3640-3180, 3080, 1670, 1630, 1260 cm^{-1}. Anal. Calcd for $C_{18}H_{32}O_3Si$: C, 66.62; H, 9.94. Found: C, 66.39; H, 9.88.

Alcohol 11b. Yield = 53%. ^1H NMR (250 MHz, $CDCl_3$) δ 0.10 (s, 6H), 0.90 (s, 9H), 1.55 (m, 4H), 1.70 (s, 3H), 2.00 (m, 4H), 2.40 (m, 4H), 3.85 (m, 1H), 4.70 (d, J=7.46 Hz, 2H), 6.15 (m, 1H). IR (neat): 3660-3240, 3085, 1680, 1635, 1255, 835 cm^{-1}. Anal. Calcd for $C_{19}H_{34}O_3Si$: C, 67.40; H, 10.12. Found: C, 67.33; H, 10.10.

Alcohol 11c. Yield = 65%. ^1H NMR (250 MHz, $CDCl_3$) δ 0.12 (s, 6H), 0.88 (d, J=7.17 Hz, 3H), 0.91 (s, 9H), 1.31-1.78 (m, 5H), 1.80-2.08 (m, 3H), 2.21-2.48 (m, 3H), 3.80-3.98 (m, 1H), 4.92-5.03 (m, 2H), 5.62-5.83 (m, 1H), 6.10-6.18 (m, 1H). IR (neat): 3480, 2920, 1720, 1630, 1250, 825 cm^{-1}. Anal. Calcd. for $C_{19}H_{34}O_3Si$: C, 67.40; H, 10.12. Found: C, 67.44; H, 10.22.

Alcohol 11d. Yield = 74%. ^1H NMR (200 MHz, $CDCl_3$) δ 0.09 (s, 6H), 0.89 (s, 9H), 1.02 (s, 9H), 1.48-1.71 (m, 3H), 1.89-2.55 (m, 7H), 4.00-4.35 (m, 2H), 4.72-4.98 (m, 2H), 5.46-5.80 (m, 1H), 6.06-6.16 (m, 1H), 7.28-7.48 (m, 6H), 7.59-7.72 (m, 4H). IR (neat): 3720-3160, 3080, 1680, 1635, 1260, 1110, 835 cm^{-1}. Anal. Calcd for $C_{34}H_{50}O_4Si_2$: C, 70.54; H, 8.71. Found: C, 70.63; H, 8.69.

Alcohol 18. Yield = 50%. ^1H NMR (200 MHz, $CDCl_3$) δ 0.10 (s, 6H), 0.89 (d, J=8.61 Hz, 3H), 0.91 (s, 9H), 1.18 (s, 9H), 1.40-1.90 (m, 5H), 1.99-2.15 (m, 1H), 2.30-2.48 (m, 3H), 3.91-4.10 (m, 2H), 5.01-5.18 (m, 2H), 5.68-5.89 (m, 1H), 6.09-6.19 (m, 1H). IR (neat): 3660-3200, 1680, 1630, 1250, 830 cm^{-1}. Anal. Calcd for $C_{23}H_{42}O_4Si$: C, 67.27; H, 10.31. Found: C, 67.41; H, 10.23.

General procedure for the conversion of alcohols 11a-d and 18 into enolpivalates 7a-d and 8.
A solution of oxalyl chloride (1.1 eq of a 2.0 M solution in CH_2Cl_2) in CH_2Cl_2 was cooled to -78°C. Dry dimethyl sulfoxide (2.2 eq) diluted with CH_2Cl_2 was added dropwise while maintaining a reaction temperature below -60°C. After stirring for 10 min, a solution of alcohol **11a-d** or **8** in CH_2Cl_2 was added dropwise at a rate to maintain the reaction temperature below -65°C. After stirring for 15 min at -78°C, triethylamine (5.0 eq)

was added dropwise, neat, while maintaining a reaction temperature below -65°C. The reaction was stirred for 5 min at -78°C, then allowed to warm to room temperature. The organic layer was washed successively with H_2O, 10% HCl, saturated $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude diketone was dissolved in a 3:1 mixture of THF/H_2O. Excess potassium fluoride was added followed by 10 mole% of tetrabutylammonium fluoride. The reaction was stirred at room temperature until all the silylenolether had disappeared by TLC. The volatiles were then removed under reduced pressure. The residue was taken up in ether and washed with saturated $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated to provide triketones **12a-d** and **19**. The triketones were found to be unstable and were immediately subjected to the next reaction. A solution of the triketone in CH_2Cl_2 was cooled to 0°C with an ice bath. Triethylamine (1.1 eq) was added dropwise followed by pivaloyl chloride (1.1 eq) and the reaction was stirred for 30-60 min. The reaction was quenched with 10% HCl and the layers were separated. The organic layer was washed with saturated $NaHCO_3$ and brine, then dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography to provide enolpivalates **7a-d** and **8**.

Enolpivalate 7a. Yield (from alcohol **11a**) = 38%. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.30 (s, 9H), 1.58-1.79 (m, 2H), 1.97-2.12 (m, 4H), 2.48-2.70 (m, 6H), 4.89-5.05 (m, 2H), 5.60-5.88 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.1, 192.5, 176.0, 143.7, 141.9, 137.6, 115.5, 42.26, 39.03, 37.81, 32.93, 27.13, 25.89, 22.48, 21.73. IR (neat): 1755, 1700, 1640, 1480, 1120, 1095, 905 cm^{-1}. Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.90; H, 8.33.

Enolpivalate 7b. Yield (from alcohol **11b**) = 45%. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.30 (s, 9H), 1.68 (s, 3H), 1.70-1.83 (m, 2H), 1.92-2.12 (m, 4H), 2.49-2.69 (m, 6H), 4.68 (d, J=12.4 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.2, 192.4, 176.0, 144.6, 143.6, 141.9, 110.8, 42.29, 38.97, 37.76, 36.92, 27.07, 25.89, 22.05, 21.70, 21.09. IR (neat): 1760, 1700, 1485, 1280, 1120, 1100 cm^{-1}. Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.66; H, 8.59.

Enolpivalate 7c. Yield (from ketone **11c**) = 50%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.89 (d, J=6.7 Hz, 3H), 1.30 (s, 9H), 1.94-2.12 (m, 4H), 2.17 (m, 1H), 2.37-2.74 (m, 6H), 4.98 (m, 2H), 5.70 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.19, 192.44, 176.03, 143.33, 142.31, 136.40, 116.75, 49.52, 41.10, 39.01, 37.80, 28.81, 27.15, 25.97, 21.78, 19.88. IR (neat): 2960, 1755, 1690, 1480, 1270, 1160, 1090 cm^{-1}. Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.41; H, 8.52.

Enolpivalate 7d. Yield (from alcohol **11d**) = 32%. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.00 (s, 9H), 1.29 (s, 9H), 1.86-2.07 (m, 2H), 2.13-2.28 (m, 2H), 2.35-2.59 (m, 4H), 2.81 (m, 2H), 4.38 (m, 1H), 4.81-5.02 (m, 2H), 5.50-5.78 (m, 1H), 7.29-7.48 (m, 6H), 7.58-7.72 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 200.1, 192.6, 175.9, 143.9, 141.7, 135.9, 133.9, 129.7, 127.6, 127.5, 118.0, 68.80, 49.48, 41.54, 38.97, 37.76, 27.13, 26.96, 25.60, 21.61, 19.24.

Enolpivalate 8. Yield (from alcohol **18**) = 30%. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (d, J=6.3 Hz, 3H), 1.11 (s, 9H), 1.29 (s, 9H), 1.95-2.19 (m, 3H), 2.38-2.68 (m, 5H), 2.78 (m, 1H), 3.75 (dd, J=4.47, 6.32 Hz,

1H), 4.99-5.15 (m, 2H), 5.60-5.80 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.3, 192.4, 175.9, 143.1, 142.4, 140.8, 115.3, 76.22, 74.03, 45.70, 38.91, 37.73, 34.35, 28.72, 27.13, 26.03, 21.73, 16.88. IR (neat): 1760, 1705, 1370, 1130, 1100, 920 cm^{-1}. Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.91; H, 9.12.

Ethyl 3-hydroxy-4-pentenoate (14). A solution of hexamethyldisilazane (0.545 mole, 115.1ml) in 500 ml of THF was cooled to -78°C. nBuLi (0.500 mole, 312.5 ml of a 1.6M solution in hexanes) was added dropwise and the solution stirred for 15 min. Freshly distilled ethyl acetate (0.455 mole, 44.3 ml) was diluted with an equal volume of THF and the solution was added dropwise to the reaction maintaining temperature below -65°C. After complete addition, the enolate was stirred for 15 min. Freshly distilled acrolein (0.682 mole, 45.6 ml) was added dropwise and the reaction stirred for 25-30 min. The reaction was quenched with sat. NH_4Cl and was allowed to warm to room temperature. The volatiles were removed under reduced pressure and the remaining residue was taken up in ether and filtered through celite. The filtrate was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography of the residue gave β-hydroxy ester **14** (60.3g, 92%). ^1H NMR (250 MHz, $CDCl_3$) δ 1.24 (t, J=7.2 Hz, 3H), 2.49 (dd, J=8.4, 16.0 Hz, 1H), 2.54 (dd, J=4.0, 16.0 Hz, 1H), 2.97 (m, 1H), 4.14 (q, J=7.2 Hz, 2H), 4.50 (m, 1H), 5.13 (m, 1H), 5.28 (m, 1H), 5.85 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 138.7, 115.4, 68.90, 60.77, 41.09, 14.13. IR (neat): 3450, 2980, 2930, 2900, 1730, 1430, 1365, 1270, 1170, 1120, 1020, 920 cm^{-1}.

Ethyl 3-hydroxy-2-methyl-4-pentenoate (15). To a solution of diisopropylamine (0.181 mole, 25.3 ml) in 70 ml of THF at -78°C was added nBuLi (0.174 mole, 108.4 ml of a 1.6M solution in hexanes) and the mixture was stirred for 15 min. β-hydroxy ester **14** was diluted with 10 ml of THF and was introduced to the reaction dropwise. The reaction was stirred for 1 hour to ensure complete formation of the alkoxyenolate. A solution of methyl iodide (0.174 mole, 10.8 ml) in 10 ml of THF was then added dropwise to the enolate. After stirring for 45 min at -78°C, the reaction was warmed to -10°C and stirred at this temperature for 3-4 hours. The reaction was quenched at -10°C with sat. NH_4Cl and allowed to warm to room temperature. The volatiles were removed under reduced pressure and the residue was diluted with ether. The organic layer was filtered through celite to remove the lithium salts and washed with H_2O and brine. The ether layer was dried over $MgSO_4$, filtered, and concentrated to provide ester **15** (10.6g, 96%) which was used without further purification. ^1H NMR (200 MHz, $CDCl_3$) δ 1.18 (d, J=6.3 Hz, 3H), 1.28 (t, J=5.0 Hz, 3H), 2.55 (m, 1H), 4.10-4.22 (m, 3H), 5.15-5.38 (m, 2H), 5.75-5.92 (m, 1H).

Tosylate 16. To a solution of lithium aluminum hydride (41.8 mmol, 1.59g) in 100 ml of dry ether at 0 °C was added ester **15** (34.8 mmol, 5.5g) in 15 ml of ether. The reaction was stirred for 30 min at 0°C, and then quenched by the sequential addition of 1.6 ml of H_2O, 1.6 ml of 10% NaOH solution, and 4.8 ml H_2O. The solution was filtered through celite and the salts that collected were washed with EtOAc. The solution was concentrated, then redissolved in ether and washed with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the diol (3.65 g, 90%) which was used without further purification. ^1H NMR (200 MHz, $CDCl_3$) δ 0.85 (d, J=6.0 Hz, 3H), 1.78 (m, 1H), 2.42-2.69 (m, 2H), 3.53-3.80 (m, 2H), 4.01 (m, 1H), 5.11-5.29 (m, 2H), 5.78-5.93 (m, 1H). To a solution of the diol (17.2 mmol,

2.0g) in 35 ml of CH_2Cl_2 at 0°C was added Et_3N (25.8 mmol, 3.60 ml). A solution of tosyl chloride (18.9 mmol, 3.61 g) in 10 ml of CH_2Cl_2 was added dropwise to the solution followed by the addition of DMAP (10 mole%). The reaction was stirred for 4 hours and monitored by TLC. The reaction was quenched with H_2O and the layers separated. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel to provide tosylate **16** (2.60 g, 56%). ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (d, J=6.3 Hz, 3H), 1.61 (d, J=3.8 Hz, 1H), 1.88 (m, 1H), 2.41 (s, 3H), 3.90-4.16 (m, 3H), 5.08-5.25 (m, 2H), 5.65-5.86 (m, 1H), 7.31 (d, J=7.58 Hz, 2H), 7.78 (d, J=7.58 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.7, 138.2, 132.8, 129.7, 127.8, 116.8, 73.79, 72.03, 38.42, 21.50, 12.81. IR (neat): 3740-3120, 2980, 1595, 1355, 1170 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_4S$: C, 57.76; H, 6.71. Found: C, 57.74; H, 6.67.

3-methyl-4-t-butoxy-5-hexenenitrile (17). To a solution of tosylate **16** (14.4 mmol, 3.88g) in 15 ml of CH_2Cl_2 in a sealed tube cooled to -78°C was condensed a large excess of isobutylene (approx. 30 ml). Catalytic sulfuric acid (1.4 mmol, 0.080 ml) was added and the tube was sealed tightly. The solution was allowed to warm to room temperature and stir overnight. The solution was again cooled to -78°C and the cap of the tube was removed. The solution was warmed to room temperature slowly allowing the excess isobutylene to boil off. The organic layer was washed with sat. $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to provide the t-butyl ether (2.95g, 63%) which was used without further purification. ^1H NMR (200 MHz, $CDCl_3$) δ 0.83 (d, J=6.31 Hz, 3H), 1.08 (s, 9H), 1.78 (m, 1H), 2.43 (s, 3H), 3.80 (m, 1H), 3.88-4.05 (m, 2H), 4.98-5.15 (m, 2H), 5.55-5.78 (m, 1H), 7.32 (d, J=7.8 Hz, 2H), 7.78 (d, J=7.8 Hz, 2H). To a solution of the t-butyl ether (8.3 mmol, 2.71g) in 40 ml of dry DMSO was added sodium cyanide (20.8 mmol, 1.02g). The solution was heated at 90°C for 5 hours. Upon cooling to room temperature, ether was added. The organic layer was washed with H_2O (8X) and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel to provide nitrile **17** (1.43g, 95%). ^1H NMR (200 MHz, $CDCl_3$) δ 1.03 (d, J=6.73 Hz, 3H), 1.17 (s, 9H), 1.81 (m, 1H), 2.40 (m, 2H), 3.75 (m, 1H), 5.10-5.23 (m, 2H), 5.61-5.82 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.3, 119.3, 116.4, 75.76, 74.43, 35.76, 28.77, 20.42, 15.92. IR (neat): 2980, 2240, 1460, 1420, 1390, 1365, 1190, 1060 cm^{-1}. Anal. Calcd for $C_{11}H_{19}ON$: C, 72.88; H, 10.56; N, 7.73. Found: C, 72.59; H, 10.45; N, 7.56.

3-methyl-4-t-butoxy-5-hexenal (13). To a solution of nitrile **17** (2.75 mmol, 0.498g) in 20 ml of dry ether at -78°C was added diisobutylaluminum hydride (5.49 mmol, 5.49 ml of a 1.0 M solution in hexanes). The reaction was stirred at -78°C for 1 hour, then warmed to 0°C and stirred for 2 hours. The reaction was quenched with 5% H_2SO_4. The layers were separated and the organic layer was washed further with 5% H_2SO_4 (2X), and brine. The ether layer was dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography on silica gel provided aldehyde **13** (0.481g, 95%). ^1H NMR (200 MHz, $CDCl_3$) δ 0.91 (d, J=5.05 Hz, 3H), 1.12 (s, 9H), 2.00-2.18 (m, 1H), 2.19-2.27 (m, 1H), 2.39-2.58 (m, 1H), 3.66 (m, 1H), 5.02-5.18 (m, 2H), 5.62-5.85 (m, 1H), 9.69 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.9, 141.3, 116.0, 77.64, 74.75, 48.00, 34.30, 28.92, 17.08. IR (neat): 2980, 2930, 2880, 2710, 1725, 1360, 1190 cm^{-1}.

General procedure for the [2+2] photocycloaddition reactions of enolpivalates 7a-d and 8. A hexane solution of enolpivalates **7a, 7b, 7c, 7d,** or **8** in a toroidal reactor was irradiated with a Hanovia 450W mercury vapor lamp. The light was filtered through a uranium glass sleeve exposing the substrates to wavelengths greater than 350 nm. The solvent was removed under reduced pressure and the residues purified by flash chromatography on silica gel to provide the corresponding photoadducts **19, 20, 21, 22,** or **23.**

Photoadduct 20. Yield = 65%. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.18 (s, 9H), 1.47-2.98 (band, 15H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.3, 207.0, 176.9, 76.83, 56.81, 40.27, 37.87, 31.72, 30.28, 29.70, 29.53, 26.78, 26.00, 18.87, 18.47. IR (neat): 2940, 1740, 1710, 1480, 1460, 1145 cm^{-1}. Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.73; H, 8.36.

Photoadduct 21. Yield = 78%. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.18 (s, 9H), 1.20 (s, 3H), 1.50-2.55 (band, 11H), 2.30 (d, J=18.4 Hz, 1H), 2.40 (d, J=18.4 Hz, 1H), 2.65 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.08, 205.41, 177.01, 79.27, 77.21, 58.74, 41.24, 39.59, 39.09, 38.34, 36.95, 27.28, 26.98, 23.18, 20.54, 19.62. Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.31; H, 8.49.

Photoadduct 22. Yield = 70%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.00 (d, J=6.3 Hz, 3H), 1.18 (s, 9H), 1.63 (m, 1H), 1.88-2.25 (band, 8H), 2.43-2.81 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.05, 205.37, 167.00, 80.04, 55.46, 48.63, 38.67, 38.10, 37.96, 35.72, 33.56, 32.24, 28.52, 26.99, 21.95, 19.23. IR (neat): 2960, 1710, 1480, 1230, 1140 cm^{-1}. Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.39; H, 8.64.

Photoadduct 23. Yield = 75%. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.03 (s, 9H), 1.22 (s, 9H), 1.50-1.63 (m, 1H), 1.73-1.82 (m, 2H), 1.94-2.17 (m, 3H), 2.27-2.65 (band, 5H), 2.81-3.05 (m, 2H), 4.27 (m, 1H), 7.30-7.49 (m, 6H), 7.57-7.69 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 208.6, 208.2, 177.9, 135.8, 135.7, 133.4, 133.1, 129.9, 127.7, 70.13, 57.22, 47.52, 37.84, 34.90, 32.70, 29.55, 28.54, 27.01, 26.90, 19.13, 19.04. IR (neat): 2960, 2930, 1730, 1710, 1425, 1155, 1135, 1110 cm^{-1}. Anal. Calcd for $C_{33}H_{42}O_5Si$: C, 72.49; H, 7.74. Found: C, 72.51; H, 7.74.

Photoadduct 24. Yield = 50%. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.02 (d, J=5.89 Hz, 3H), 1.11 (s, 9H), 1.14 (s, 9H), 1.53-1.69 (m, 1H), 1.83-2.28 (band, 6H), 2.43 (dd, J=10.52, 15.58, 1H), 2.49 (m, 1H), 2.61-3.02 (band, 3H), 3.75 (dd, J=3.79, 7.16 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.6, 208.4, 177.6, 77.17, 75.27, 73.51, 66.08, 56.41, 42.49, 37.99, 37.81, 34.67, 33.45, 30.62, 28.46, 26.87, 18.61, 17.43. IR (neat): 2970, 1740, 1710, 1390, 1365, 1190, 1150 cm^{-1}. Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.92; H, 9.02.

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