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Siloxanes as Temporary Tethers in [2+2] Photocycloadditions

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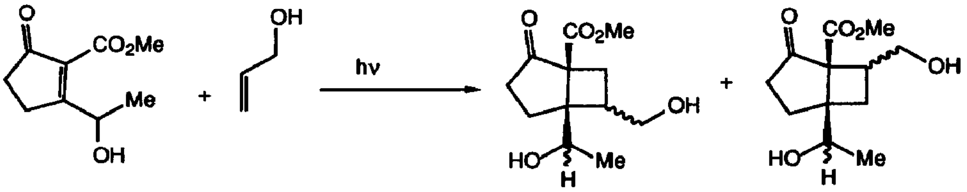
***Abstract:** Intramolecular [2+2] photocycloadditions utilizing siloxanes as temporary tethers between an enone and olefin results in the products of an intermolecular photocycloaddition with the selectivity of the intramolecular reaction after cleavage of the temporary tether.*

The [2 + 2] enone-alkene photocycloaddition has become an important reaction in the rapid construction of advanced intermediates for the synthesis of complex natural products.[1,2] There are, however, severe limitations on the use of the *intermolecular* variant of the reaction when the two partners are unsymmetrical and not highly polarized because the regioselectivity of the intermolecular photocycloaddition is determined by a combination of electrostatic[3] and steric interactions[4] between the enone and the olefin. These effects may be interpreted by a charge-transfer interaction in the excited state or more likely by a partitioning of the intermediate biradicals between products (by closure to the cyclobutane) and reactants (by β-sission of the biradical).[5] The result of such a combination is often a complex mixture of regioisomers with little or no stereoselectivity.[1] An example which illustrates this point is shown in Scheme 1. It would be predicted that the reaction will result in two regioisomers each with four possible stereoisomers. The reaction does, in fact, result in a mixture of all eight different products based on ^{1}H NMR analysis.

Scheme 1



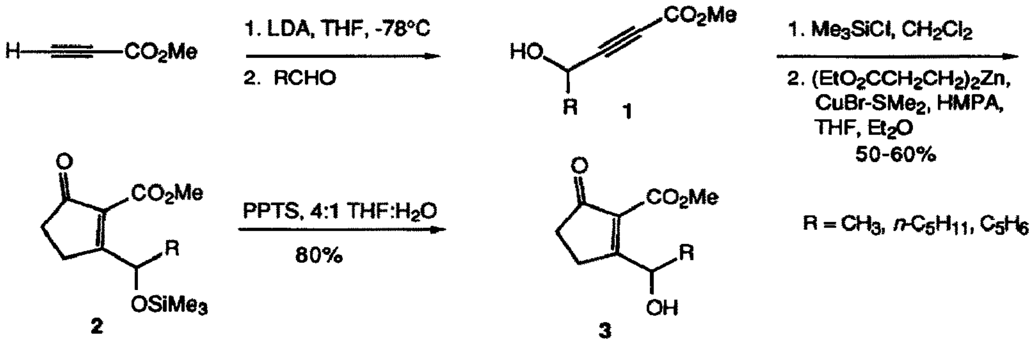
The *intramolecular* [2+2] photocycloaddition is a generally more regioselective and stereoselective process.[1] By incorporating the enone and olefin into one molecule, the regioselectivity is increased due to the geometric constraints in the transition state for ring closure. There is a general preference for the initial formation of five membered rings over six membered rings and a preference for the formation of six membered rings over seven membered rings. There is also usually a preference for straight versus crossed products. While most intramolecular photocycloadditions result in a *cis* ring fusion between five and four membered rings due to ring strain, the stereochemistry of the ring fusion between a six-membered ring and a four-membered ring is less predictable. The greater flexibility of six membered rings allow the formation of both *cis* and *trans* ring junctures.[1]

Because of the high levels of regioselectivity and stereoselectivity provided by ***intramolecular*** [2 + 2] photocycloaddition reactions, it was anticipated that the use of a temporary tether between the enone and olefin in the photocycloaddition reaction could provide the product of an *intermolecular* cycloaddition with high and predictable selectivity after removal of the temporary linker. Silicon was chosen as a removable linking atom for the initial studies since it can be oxidatively or reductively excised. Additionally, silicon has been used successfully as a temporary linker in other intramolecular reactions such as radical cyclizations,[6] Diels-Alder cycloadditions,[7] hydrosilylation reactions,[8] electrochemical reactions[9] and pyrone cycloadditions.[10] It has been shown that treatment of siloxanes with hydrogen peroxide will cleave the siloxane resulting in a diol with retention of stereochemistry.[11]

We report here the synthesis of a photosubstrate consisting of vinylic or allylic dialkylsiloxanes tethered *via* an alcohol moiety to a carboalkoxy cyclopentenone derived from a zinc homoenolate protocol.[12] Following irradiation of the substrate, the resultant silicon-oxygen bond can be cleaved by oxidation with retention of stereochemistry.[11]

Addition of the anion of methyl propiolate to the appropriate substituted aldehyde in THF at -78°C resulted in the formation of acetylenic ester **1** (Scheme 2).[13] The alcohol **1** was then protected using trimethylsilyl chloride, imidazole and catalytic 4-dimethyl-aminopyridine (DMAP) in methylene chloride (CH_2Cl_2). The protected acetylenic ester was then converted to the cyclopentenone **2** using the zinc homoenolate conjugate addition-cyclization on the acetylenic ester.[12] The protected acetylenic ester was added to the zinc homoenolate solution containing copper(I) bromide dimethylsulfide complex and hexamethylphosphoramide (HMPA). The resultant trimethylsilyl protected cyclopentenone was treated with pyridinium p-toluenesulfonate (PPTS) in a 4:1 THF:H_2O solution to give the alcohol **3**.

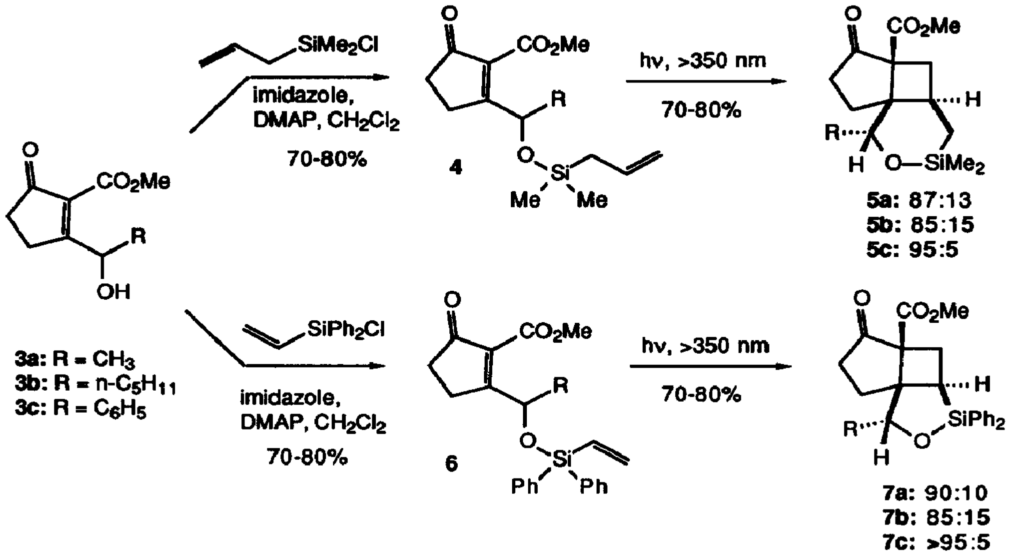
Scheme 2



Cyclopentenone **3** was then treated with allylchlorodimethylsilane, catalytic DMAP and imidazole in CH_2Cl_2 to give photosubstrate **4**. (Scheme 3) The photosubstrate **4a** was then irradiated in a 6:1 hexanes:methylene chloride mixture for 4 hours using a 450W Hanovia medium pressure mercury vapor lamp and uranium glass filter (>350 nm) yielding an 87:13 mixture of diastereomeric photoadducts with photoadduct **5a** as the major product. The minor product is epimeric at the carbinol center.

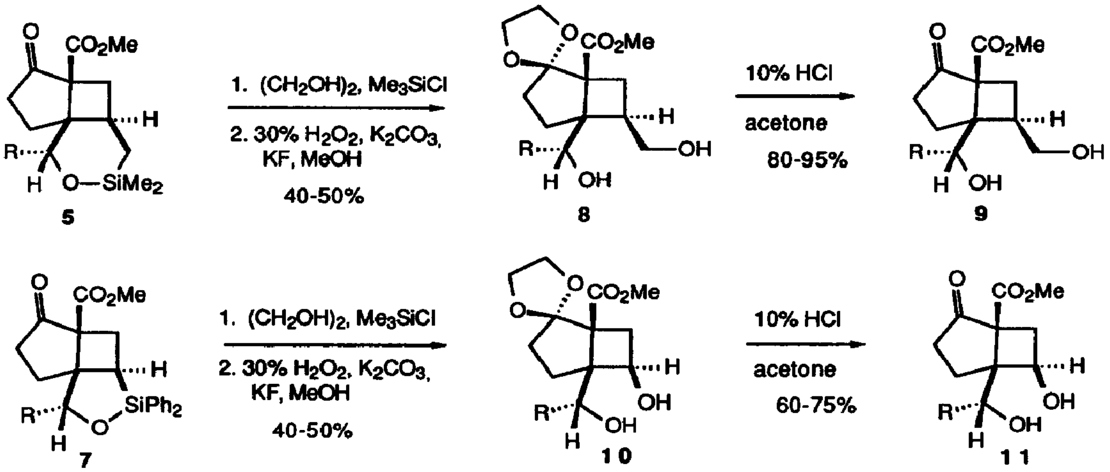
The stereochemistry of photoadduct **5a** (R = CH_3) was proven by single crystal x-ray crystallography of a similar photoadduct with an ethyl rather than methyl ester following inconclusive NOE studies. The crystal structure[14] showed a *cis*-5,4 ring juncture and a *cis*-6,4 ring juncture.

Scheme 3



Photoadduct **5** was then treated with ethylene glycol and trimethylsilylchloride in refluxing benzene. This was followed by treatment with 30% hydrogen peroxide, potassium fluoride and potassium carbonate in a 1:1 methanol:THF mixture yielding diol **8**.[15] The ketal protecting group was removed with 10% HCl in acetone to afford diol **9** as shown in Scheme 4.

Scheme 4



Protection of the ketone is necessary to prevent over oxidation of the photosubstrate upon treatment with H_2O_2. Direct oxidation of the photoadduct without protection of the ketone results in a Baeyer-Villiger oxidation of the cyclopentanone ring as determined by NMR. The ^1H NMR showed an additional CH_2 signal adjacent to an oxygen.

Cyclopentenone **3** was also treated with diphenylchlorovinylsilane in a similar manner to afford photosubstrate **6**. Irradiation of photosubstrate **6** afforded photoadduct **7**. The stereochemistry of **7a** is expected to be as shown due to the strain of the five-four ring juncture which does not allow for the formation of a *trans* ring juncture and from other precedented diastereocontrol when the allylic carbon of the enone is substituted (Scheme 3).[16] Photoadduct **7** was protected, oxidized, and deprotected yielding diol **11** (Scheme 4).

Thus, photoadducts **9** and **11** were prepared with complete regioselectivity and high stereoselectivity by utilizing an intramolecular [2 + 2] photocyclization. These specific photoadducts would either be produced with low selectivity or unavailable by simple intermolecular [2 + 2] photoadditions. The photosubstrates are readily available by the zinc homoenolate technology utilized to prepare them.

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