MODEL COMPOUNDS FOR THE PHOTOACTIVATION OF GLYCOSYL DONORS

BY

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“Lauren You Were Right. Haikus Explain Things Better”

\[ It \text{ is in the wits} \]
\[ of \text{ friend’s spirits I write this} \]
\[ within \text{ my two mits} \]
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<td>Description</td>
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<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Ac</td>
<td>Acetyl group</td>
</tr>
<tr>
<td>Alc</td>
<td>Generic Alcohol</td>
</tr>
<tr>
<td>BET</td>
<td>Back Electron Transfer</td>
</tr>
<tr>
<td>$^{13}$C NMR</td>
<td>Carbon Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>DCB</td>
<td>Dicyanobenzene</td>
</tr>
<tr>
<td>DCE</td>
<td>Dichloroethylene</td>
</tr>
<tr>
<td>DCQ</td>
<td>Dichlorobenzoquinone</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>E</td>
<td>Energy</td>
</tr>
<tr>
<td>equiv</td>
<td>Equivalent(s)</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl Group</td>
</tr>
<tr>
<td>FID</td>
<td>Flame Ionization Detector</td>
</tr>
<tr>
<td>GC</td>
<td>Gas Chromatography</td>
</tr>
<tr>
<td>H+</td>
<td>Proton</td>
</tr>
<tr>
<td>$^{1}$H NMR</td>
<td>Proton Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>HOMO</td>
<td>Highest Occupied Molecular Orbital</td>
</tr>
<tr>
<td>hr</td>
<td>Hour(s)</td>
</tr>
<tr>
<td>HRMS</td>
<td>High-Resolution Mass Spectrometry</td>
</tr>
<tr>
<td>hv</td>
<td>Light/Photons</td>
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<tr>
<td>ISC</td>
<td>Intersystem Crossing</td>
</tr>
<tr>
<td>J</td>
<td>Coupling Constant</td>
</tr>
<tr>
<td>LUMO</td>
<td>Lowest Unoccupied Molecular Orbital</td>
</tr>
<tr>
<td>m</td>
<td>Multiplet</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>min</td>
<td>Minute(s)</td>
</tr>
<tr>
<td>MS</td>
<td>Mass Spectrometry</td>
</tr>
<tr>
<td>NBS</td>
<td>N-Bromosuccinimide</td>
</tr>
<tr>
<td>nm</td>
<td>Nanometer</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>Nuc</td>
<td>Nucleophile</td>
</tr>
<tr>
<td>P</td>
<td>Protecting Group</td>
</tr>
<tr>
<td>PPTs</td>
<td>Pyridinium Para-toluenesulfonic Acid</td>
</tr>
<tr>
<td>PET</td>
<td>Photo-induced Electron Transfer</td>
</tr>
<tr>
<td>RT</td>
<td>Room Temperature</td>
</tr>
<tr>
<td>s</td>
<td>Singlet</td>
</tr>
<tr>
<td>Sens</td>
<td>Sensitizer</td>
</tr>
<tr>
<td>Sug</td>
<td>Sugar with a Free Hydroxyl Group</td>
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<td>TBDMS</td>
<td>Tertiarybutyldimethylsilyl</td>
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<td>TCQ</td>
<td>Tetrachlorobenzoquinone</td>
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<tr>
<td>TEA</td>
<td>Triethylamine</td>
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<td>THF</td>
<td>Tetrahydrofuran</td>
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<td>THP</td>
<td>Tetrahydropyran</td>
</tr>
<tr>
<td>Tf</td>
<td>Triflate</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
</tr>
<tr>
<td>Vis</td>
<td>Visible</td>
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ABSTRACT

MODEL COMPOUNDS FOR THE PHOTOACTIVATION OF GLYCOSYL DONORS

Nature exhibits complex arrays of carbohydrates in many different forms. Carbohydrate chemists still face many challenges in the synthesis of these complex substrates. This project aims to offer carbohydrate chemists a novel way of activating the anomeric position of a sugar by light to promote glycosylation. This involved photolyzing model pyran compounds, in the presence of various photosensitizers, to induce an intramolecular cyclization. This cyclization leads to the generation of an oxonium intermediate that may alkylate other nucleophiles, which should be analogous to a glycosylation reaction. It was determined that a moiety with an internal sensitizer could photochemically exchange a tetrahydropyran at 300 nm. It was also determined that 6-methylhex-5-en-1-ol-THP ether, 6-methylhept-5-en-2-ol-THP ether, and 3-methylbut-2-en-1-ol-THP ether will transfer a pyran to a nucleophile in the presence of stoichiometric tetrachloroquinone at 350 nm. THP-ethers such as 6-methylhex-5-en-1-ol-THP ether and 3-methylbut-2-en-1-ol-THP will transfer a pyran to a nucleophile in presence of catalytic dicyanobenzene at 350 nm. α-Terpineol-THP Ether will transfer a pyran at 419 nm, using catalytic amounts of dichloroquinone. A fast and efficient way to photochemically install a THP group on an alcohol was also discovered. The synthesis, characterization, and mechanistic principles of these compounds are discussed as potential candidates for glycosyl activation.
INTRODUCTION

Biological Relevance of Carbohydrates

Biosynthesis of complex carbohydrates is a process that has been conserved by nature over time. Carbohydrates are inextricably linked to the processes that comprise life and are as pervasive as they are versatile. Carbohydrates are found attached to lipids (glycolipids), proteins (glycoproteins), exist in monomeric forms as energy sources, and are present in polymeric form (as those found on cellular surfaces). While proteins and nucleic acids are assembled in a linear fashion, carbohydrates in their polymeric form may exist in a vast array of varying geometries. Their biosynthesis exhibits a wide range of complexity and in turn gives way to a wide range of function in living organisms.

Several themes have arisen in current glycobiology, two of which are: 1) How do carbohydrates interact and influence the proteins to which they are attached? 2) What roles do carbohydrates play in cellular recognition events?

Within the last decade there has been increased interest to determine the bioactivity of various glycosides, such the derivative of those shown in Figure 1.

\[
\alpha\text{-D-Glucoside}
\]

It is only within the last few decades that the biological function of naturally occurring glycosides, polysaccharides, and various glycoconjugates (glycoproteins and glycolipids) has been revealed. The inabilities to obtain pure samples from natural sources and obtaining well-defined oligosaccharides are limiting factors in current research to find therapeutic potentials of natural glycosides.

In order to assemble such versatile molecules, it has become pertinent to develop versatile methods for their construction. An ever increasing need for stereo and
regiospecificity in the preparation of glycosides has resulted in innovative methods for anomeric substitution, glycosylation, and protecting groups.

**Selective Activation of Carbohydrates**

Monosaccharides are subunits that are linked together by O-glycosidic bonds that result in oligosaccharides. In a biological setting, the chirality of polysaccharides is dictated by enzymatic processes that control specificity and stereoselectivity. Chemist’s attempts to control the stereoselectivity and regioselectivity of glycosylation reactions go back as far as the late 19th century. 7-9 One of the first glycosylation reactions, a nucleophilic attack on the anomeric position, is accredited to Knorr and Koenigs in 1901.9 The reaction, involving the use of anomeric halogens as glycosyl donors, has been used as a common synthetic approach in glycosylation reactions ever since. It has been known that stereo and regiospecific problems arise from these reactions and it has been a considerable challenge to synthetic chemists. Current research involves the convergence of synthetic strategies for preparation of oligosaccharides, in which there is a selective activation of one leaving group over another. In efforts to expand the scope of glycoside activating groups, considerable work has been focused on the selective activation of moieties at the reducing end of carbohydrates that are active during glycosylation but do not affect the protecting groups.10

Chemical synthesis of glycosides involves a glycosyl donor (1), which is a protected saccharide with some leaving group at the anomeric position, and an aglycone (R1OH, Scheme 1) typically containing a lone hydroxyl group. A leaving group at the anomeric position can be activated to generate an anomeric oxonium cation that can thus alkylate the aglycone.11

![Scheme 1-Glycosylation Reaction.](image-url)
Building complex oligosaccharides involves activating and deactivating substituents at the anomeric position to successively introduce other sugars. It has been reported that n-pentenyl glycosides undergo specific cleavage with N-Bromosuccinimide (NBS) under conditions that leave various other protecting groups unaffected. According to the mechanism proposed by Fraser-Reid (Scheme 2), the double bond of n-pentenyl is oxidized to form a bromonium cation (5). This should lead to an intramolecular cyclization (5→6) that affords an oxonium cation (7), thus allowing for exchange of another nucleophile at the anomeric position. (5-8 or 5-9).

Scheme 2- Proposed mechanism of n-pentenyl cleavage by NBS (Sug = saccharide with a free hydroxyl group, P = protecting group)

Activating the anomeric position by light would be beneficial to carbohydrate chemists, in that photons are cheap reagents and do not generate harmful waste. Such a moiety could serve the dual function of acting as a protecting group as well as an excellent leaving group when activated by light. When constructing a highly functionalized oligosaccharide, a photochemical method could conserve steps and material. Such a photochemical functionality could also be considered orthogonal to
other protecting groups. In order to provide a context for such a reaction, the basic photochemistry involved must be discussed.

**Photochemical Transformations**

Photochemical reactions have established their importance in organic chemistry yet their role is not as wide-ranging as thermal reactions. An ever-expanding interest in the facets of photochemistry has led to the production of a vast amount of literature. As a result, there have been many developments in the area of photochemistry that deal with organic synthesis. Photochemical reactions can give insight into the nature of reaction mechanisms as well as yield products that are not normally available to thermal reaction pathways.

Light (hv) is a form of energy that can be thought of as consisting of photons that carry specific energies. Photons have an inherent quantum of energy that a ground state molecule (M) may absorb upon interaction. When a molecule absorbs energy from a photon, it is said to be in an excited state (M*). This process is shown below in Scheme 3.

\[
\text{M} + \text{hv} \rightarrow \text{M}^* \\
\text{ground state} \quad \text{excited state}
\]

**Scheme 3 – Absorption of Light by a Ground State Molecule**

When a molecule absorbs a photon of a specific energy, the electronics of the molecule will have a corresponding transition. When a molecule is in its ground state, its electrons are in their lowest energy molecular orbitals (HOMO-Highest Occupied Molecular Orbital). When the molecule absorbs a photon, valence electrons of the molecule can be transferred to higher-energy orbitals (LUMO-Lowest Unoccupied Molecular Orbital). This process is shown below in Scheme 4.
According to the Stark-Einstein law, a molecule will only absorb light to produce a single electronic transition. The energy of the light absorbed must match the difference between the ground state and the excited state. Electrons also have an intrinsic property of spin and can be explained classically as a charge rotating about an axis. When a charge spins, a magnetic moment is associated with the direction of spin. Electrons can be envisaged to behave like small magnets, containing a north and south pole. In a closed shell orbital, in which the electrons are paired, one electron must be “spin-up” and the other “spin-down”.

This is represented in Scheme 5 by an upward arrow for spin-up and a downward arrow for spin-down. Valence electrons follow the Pauli Exclusion Principle in that they are “spin-paired” (also called a singlet state) because two electrons cannot occupy the same quantum state. The vast majority of ground states of organic molecules are in closed shells and in a singlet state. When a molecule is excited by a photon, an electron is transferred from the HOMO to the LUMO without changing its spin. A molecule in its excited state that has opposite (paired) spins is called a singlet excited state ($M_1^*$).

Another electronic arrangement is also possible for excited-state molecules. This is known as a triplet excited state ($^3M^*$) and the two electrons have unpaired spin. Direct
excitation to the triplet state is not quantum mechanically allowed, because it would be in
direct violation of the rules mentioned above. Direct excitation to the triplet state is said
to be spin-forbidden. The electron in the excited state must undergo a spin-flip to reach
the triplet excited state after it has been excited to its singlet state (Scheme 6). A non-
radiative transition between two electronically excited states is known as intersystem
crossing (ISC).\textsuperscript{14}

\begin{center}
\begin{tikzpicture}
\node (M) at (0,0) {$\text{M}$};
\node (HOMO) at (-1,1) {$\text{HOMO}$};
\node (LUMO) at (1,1) {$\text{LUMO}$};
\node (1M*) at (2,0) {$^{1}\text{M}^{*}$};
\node (3M*) at (2,-1) {$^{3}\text{M}^{*}$};
\node (hv) at (1,2) {$h\nu$};
\node (ISC) at (1,0) {$\text{ISC}$};
\draw[->] (M) -- (HOMO);
\draw[->] (HOMO) -- (LUMO);
\draw[->] (LUMO) -- (hv);
\draw[->] (hv) -- (1M*);
\draw[->] (1M*) -- (ISC);
\draw[->] (ISC) -- (3M*);
\end{tikzpicture}
\end{center}

\textbf{Scheme 6}

Electron spin is perturbed by external magnetic fields and are found to be either
oriented in the direction of the field or opposing it. Interactions with a magnetic field can
influence an electron’s spin by spin-orbit coupling or spin-spin coupling. Spin-orbit
coupling interactions involve the electron’s spin about its own axis relative to its orbit
about the nucleus. Spin-spin interactions involve the electron’s coupling of other
magnetic fields in the molecule.

An excited state molecule can transfer its excitation energy to another molecule.
A triplet sensitizer is a molecule that may transfer its triplet excitation energy to some
acceptor. The triplet sensitizer is excited to its singlet state (Sens\textsubscript{1}^{*}), undergoes
intersystem crossing to arrive at its excited triplet state (Sens\textsubscript{3}^{*}), and then imparts its
energy on a ground state molecule (Scheme 7). The ground state molecule (M) is thereby
excited by the triplet sensitizer into its excited triplet state (\textsuperscript{3}M^{*}).

\begin{align*}
\text{Sens} \quad h\nu \quad \text{Sens}_1^{*} \quad \text{ISC} \quad \text{Sens}_3^{*} \\
\text{Sens}_3^{*} + M \quad \text{E transfer} \quad \text{Sens} + \text{3M}^{*}
\end{align*}

\textbf{Scheme 7}
The molecule that has the energy imparted upon it, in this case M, is known as the quencher. When the molecule of interest is excited, in order to transfer its triplet excitation energy, it is called the sensitizer. Ideally, for energy transfer to take place, the triplet sensitizer and the quencher need to absorb light at different wavelengths so the sensitizer can be selectively excited. The triplet excitation energy of the sensitizer should be high relative to the triplet energy of the quencher. This allows for an exothermic energy transfer, which is thermodynamically favorable and will thus increase the rate of energy transfer to the quencher. The triplet lifetime of the sensitizer should also be long, so as to maximize the probability that energy transfer may occur.

**Photoinduced Electron Transfer**

Photoinduced electron transfer (PET) is a common process that may lead to quenching. An excited state molecule has an electron in an anti-bonding orbital (most likely the LUMO) and thus will have a different oxidation potential than its ground state. The excited state is easier to oxidize than its ground state because the electron that is to be removed is in an orbital that is higher in energy. This leaves a vacancy in the lower energy orbital and thus the molecule can accept an electron. This makes the molecule easier to reduce and also a better acceptor than its ground state counterpart. The excited state thus has lowered the potential energy required to oxidize or reduce it. This is commonly referred to as lower oxidation or reduction potential. Excited states therefore can undergo electron transfers and accept electrons from ground states that have occupied molecular orbitals that are slightly higher in energy than the HOMO of the excited state (Scheme 8, A.). Excited states may also transfer an electron that has been promoted to its LUMO to a LUMO that is slightly lower in energy in a ground state molecule (Scheme 8, B.).
Scheme 8 – Transfer of Electrons Between Donors and Acceptors

(A* = excited state of acceptor, D* = excited state of donor, A = acceptor, D = Donor)

The donor molecule’s HOMOs and LUMOs must be slightly higher in energy than the acceptors so that the reaction is exothermic, and thus thermodynamically favorable. If the reaction proceeds, the net result is that the donor molecule becomes a radical cation and the acceptor molecule a radical anion. These molecules may then further react to do other chemistry, such as the generation of photoacids.

Photoacids

Photoacids are light-absorbing molecules that are more acidic in the excited state than in the ground state. The pKₐ values of the excited state molecules differ considerably from those of the ground state.¹⁶ An example of enhanced acidity upon photo-excitation is seen in 2-naphthol, which is shown in Scheme 9. The excited singlet state (pKₐ = 3) is a much stronger acid than its ground state counterpart (pKₐ = 9).¹⁶ The excited state of 2-naphthol will ionize in a pH range between 3 and 9, when normally this compound will not ionize at this pH range.
It should also be noted that lifetimes of photoacids are quite short. This typically leaves only enough time for the photoacid to donate a proton to the surrounding solvent. A drawback to conventional ionic photoacids is that the mechanism of their action is based upon an irreversible reaction to generate them. Unwanted side products may arise due to interactions with the conjugate base of the photoacid.

Phenols are good candidates to generate photoacids because they can be produced from quinones and are known to undergo fast deprotonation once ionized. Flash photolysis studies have shown that if chloranil (2,3,5,6-tetrachloro-p-Benzoquinone) is irradiated in the presence of solvents that contain hydroxyl groups, then formation of the a semiquinone radical results (Scheme 10).

As shown above, irradiation of chloranil results in a semiquinone radical. The semiquinone radical lies in equilibrium with its radical anion which may donate a proton to the surrounding solvent.

An alternative approach involves the design of short-lived photoacids that are produced only for the duration of the photochemical event and return to their neutral form,
upon relaxing back to the ground state. Such a system might involve the use of anthraquinones, shown below in Scheme 11.

![Scheme 11 – Ionization of Dichloroanthraquinone in Polar Solvent](image)

The above scheme shows the same transformation as in the chloranil reaction, except the radical anion of the anthraquinone may react with oxygen to return the original neutral species. These types of molecules can provide insight into the latent reactivity of photoacids in general and in turn may allow for control of photoacid catalysis.

**Inter/Intramolecular Additions of Alcohols to Alkenes**

In developing a moiety that could be activated by light at the anomeric position, there are two ideas (one photochemical and intermolecular and the other thermal and intramolecular) that are complimentary to one another. A synthesis of these two ideas provides a starting point for development of the moiety in question. It has been shown that alcohols can be photochemically added to alkenes in an anti-Markownikoff fashion, via a photosensitized electron transfer reaction.\textsuperscript{18} This reaction (Scheme 12) involves the addition of various alcohols to 1,1-diphenylethylene. Upon irradiation of 10, alcohol, and the appropriate sensitizer, the reaction yields ether 11.
Scheme 12 – Photochemical Addition of Alcohol to 1,1-Diphenylethylene

A proposed mechanism is shown below in Scheme 13.

Scheme 13 – Mechanism of Photochemical Addition of Alcohol to an Alkene

Goal and Hypotheses

The goal of this project was to develop a molecule that could be selectively photo-activated at the anomeric position, in order to subsequently activate the anomeric position of a glycoside. If there is an O-linked aglycan at the anomeric position of the sugar containing an alkene that is four to five bonds away from the oxygen linked to the sugar, then this could lead to activation of the anomeric position (shown in Scheme 15). Our hypothesis is if the alkene of the moiety is photo-activated by a sensitizer, then the
oxygen may intramolecularly add to the activated alkene (13). The oxonium intermediate can be generated on sugar 14 by expelling the furanyl cation, leaving intermediate 15 to alkylate other nucleophiles. We began our study of such a photo-activated system by modeling it with a simple molecule that resembles the anomeric position of a sugar, an acetal of a pyran (Scheme 16).

![Scheme 15 – Proposed Mechanism of Photochemical Glycosyl Activation](image)

**Scheme 15** – Proposed Mechanism of Photochemical Glycosyl Activation

![Scheme 16 – Model Compound for Glycosyl Activation](image)

**Scheme 16** – Model Compound for Glycosyl Activation
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RESULTS AND DISCUSSION

Towards a Model for Glycosyl Activation

The acetals of 16, 17, and 18 were used as starting points towards model compounds for glycosyl donors. The tetrahydropyran (THP) ethers of 16, 17, and 18 were constructed by reaction of dihydropyran with their corresponding alcohols in a solution containing a catalytic amount of PPTs (pyridinium paratoluene sulfonate). The carbon of the acetal (indicated by * in Scheme 17) is a chiral center and thus the pyran exists as two different stereoisomers. The pyran of the 6-methylhepten-2-ol (18) has two stereocenters associated with it and may potentially exist as four stereoisomers, because the racemic mixture of 18 was used. Stereocenters tend to complicate splitting patterns in HNMR spectra, but the above alcohols were not chosen based upon potential spectral complexity. The alcohols were chosen because alcohols 17 and 18 are commercially available.

Scheme 17 – THP-ethers Synthesized for Photolysis Reactions

The THP ether of 6-methyl-5-hepten-2-ol (18) was photolyzed in CH₂Cl₂ with stoichiometric amounts of several electron accepting photosensitizers, with a non-photoactive nucleophile (pentanol), to test the reactivity of various commercially available sensitizers (Scheme 19). The reaction progress and percent conversion to
product were determined by gas-chromatography (GC). The results of the experiment are shown in Table 1.

![Reaction Scheme](image)

**Scheme 19** – Photolysis Reaction with Various Sensitziers

<table>
<thead>
<tr>
<th>Sensitizer</th>
<th>Irradiation time (350 nm)</th>
<th>Percent conversion to 19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracyanoethylene</td>
<td>1 hr</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>2 hr</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>3 hr</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>15 hr</td>
<td>83</td>
</tr>
<tr>
<td>tetracyanoquinodimethane</td>
<td>1 hr</td>
<td>0.05%</td>
</tr>
<tr>
<td></td>
<td>15 hr</td>
<td>1.7%</td>
</tr>
<tr>
<td>dicyanobenzene *</td>
<td>1 hr</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>2 hr</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>15 hr</td>
<td>95%</td>
</tr>
<tr>
<td>Tetrachloroquinone</td>
<td>1 hr</td>
<td>100%</td>
</tr>
<tr>
<td>Dicyanoanthracene</td>
<td>15 hr</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Table 1** – Results of Photolysis Reaction of Scheme 19

(* = biphenyl used as cosensitizer, irradiated at 300 nm)
Tetracyanoethylene did not show conversion past 83% despite the time of irradiation it was subjected to. This reaction was not investigated further. Tetracyanoquinodimethane and dicyanoanthracene provided low yields, most likely due to their low solubility. The reaction proceeded quickly and efficiently with 2, 3, 5, 6-tetrachloroquinone (TCQ) and proceeded efficiently yet slowly with dicyanobenzene (DCB). The reaction with DCB only proceeded at a wavelength of 300 nm. The transformation was repeated under a 350 nm lamp and no reaction was observed. Both the reaction of 18 with DCB and TCQ showed no unwanted side products, as observed by GC.

**Catalytic and Stoichiometric Sensitizers**

A separate experiment was then conducted to determine if the two sensitizers, TCQ and DCB, were catalytic or stoichiometric. Both sensitizers were subjected to the same conditions as the previous experiment mentioned above, except 0.2 equivalents were used. It was determined that the reaction is catalytic in DCB and stoichiometric in TCQ. The reaction with DCB is however quite slow, taking 24 hours or more for complete conversion to 19.

**Alkene Photochemistry with Tetrachloroquinone and Dicyanobenzene**

To ensure that the alkene in the molecule was necessary, in order for the photolysis to occur, the THP pyran of pentanol was irradiated at 350 nm with five equivalents of methanol and one equivalent of TCQ (Scheme 20). The reaction was irradiated for 14 hours at 350 nm and no reaction occurred.

![Scheme 20 - Control Photolysis of THP Ether](attachment:image.png)
Compounds 16 and 17 were then tested to determine if their reactivity was similar to that of 18. The results are shown below in Tables 2 and 3.

![Diagram](https://via.placeholder.com/150)

\[ 16 \xrightarrow{hv + Sens^*} \text{butanol} \]

<table>
<thead>
<tr>
<th>Sensitizer</th>
<th>Nuc.</th>
<th>Time Irradiated (350 nm)</th>
<th>% Conversion</th>
<th>Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCQ</td>
<td>n-butanol</td>
<td>1 hr</td>
<td>100</td>
<td>62</td>
</tr>
<tr>
<td>TCQ</td>
<td>2-butanol</td>
<td>1 hr</td>
<td>100</td>
<td>70</td>
</tr>
<tr>
<td>DCB</td>
<td>n-butanol</td>
<td>24 hrs</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 2 - Results of the Photolysis of 16**

The photolysis of 16 with TCQ proceeded to completion quickly and an isolated yield was obtained to determine if conversion matched isolated yields. One equivalent of sensitizer was used in both reactions with TCQ and DCB. Biphenyl (one equivalent) was used as a cosensitizer in the photolysis with DCB. The yields of these reactions may be slightly lower due to the volatility of the product. The product was obtained by column chromatography, concentrated *in vacuo*, and left under a vacuum for an extended period and some of the product was lost. However, the product was still obtained in good yield. To determine if the reaction could be extended to secondary alcohols, 2-butanol was used. The reaction with 2-butanol showed similar yields to that of n-butanol, so the reaction is therefore not limited to primary alcohols. The reaction with dicyanobenzene did not proceed at all. We believe this could be due to the decreased rate of cyclization exhibited by 16, when compared to that of 18.
Similar results were achieved upon irradiation of \(17\) with TCQ. A longer reaction time is observed for \(17\) than \(16\) or \(18\), but the reaction still proceeds in good conversion when TCQ is used as the sensitizer. The reaction with DCB may proceed to completion, but for practical purposes the reaction was not monitored past 24 hours. A proposed mechanism of this system is shown in Scheme 21.

**Table 3 – Results of the Photolysis of \(17\)**

<table>
<thead>
<tr>
<th>Sensitizer</th>
<th>Nucleophile</th>
<th>Time Irradiated</th>
<th>% Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCQ</td>
<td>n-butanol</td>
<td>3 hr</td>
<td>95</td>
</tr>
<tr>
<td>DCB</td>
<td>n-butanol</td>
<td>24 hr</td>
<td>22</td>
</tr>
</tbody>
</table>

**Scheme 21 – Mechanism of THP Transfer from \(18\) to a Nucleophile**

(Sens* = excited state of triplet sensitizer, Sens = radical anion of sensitizer)
As shown in the above mechanism, the THP ether of 6-methyl-2-heptenol reacts with a triplet sensitizer to form a radical ion pair (20). This may then cyclize to form intermediate 21. The furanyl cation can be displaced by the pyran oxygen in 21 thus generating an oxonium cation and a furanyl radical 22. The pyranyl oxonium intermediate may react with an external nucleophile to generate the desired product, shown at the very bottom right of Scheme 21. The furanyl radical may have two possible fates. The radical may couple with the sensitizer (23), which we believe is the case with TCQ. If TCQ ‘traps’ the furanyl intermediate, then the reaction pathway for back-electron transfer is no longer available and there is no competition between the anion of 6-methyl-2-heptenol (24) and an external nucleophile (ROH). This is reflected in the efficiency of this reaction with TCQ, as compared with DCB. With DCB, the reaction takes much longer to complete because 22 may react with the radical anion of the DCB in such a way that BET is favorable, which would generate 24 in a significant enough concentration to compete with an external nucleophile. If 24 recombines with the oxonium intermediate then the starting material is regenerated. This rationale may explain why the reaction proceeds catalytically in DCB and is stoichiometric with respect to TCQ.

All three systems (16, 17, and 18) selected are potential candidates to be used in the activation of a glycoside. According to the Thorpe-Ingold rules of cyclization, the rate of cyclization is determined by how restricted the bond angles of the compound in question are.20 So the more substituents (such as the methyl adjacent to the oxygen in 18, Scheme 17) added to a molecule, the faster the rate of intramolecular cyclization. The 5-methyl-hexenol moiety was chosen based upon the nucleophilicity of a primary alcohol and relative rate of cyclization. TCQ was chosen as the sensitizer based upon its relatively fast rate of reaction and because DCB does not react with the 5-methyl-hexenol system.

**Synthesis of 5-methyl-hexen-1-ol Substituted Tetraacetyl Glucose**

A synthesis of 5-methyl-5-hexen-1-ol (26) is shown in Scheme 22. The methyl ester was obtained via a Johnson-Claisen rearrangement in propionic acid. The methyl ester of 26 was then reduced with LiAlH₄ to give 5-methyl-5-hexen-1-ol.
Synthesis of 26 proved to be straightforward and was convenient, in that this methodology can be applied to large scales. The reaction of tetraacetyl-bromoglucose (25) with 5-methyl-5-hexen-1-ol (26) proved to be somewhat problematic. It was determined that a dual solvent system was needed in order to solubilize the silver(I)triflate. Silver triflate is not soluble in dichloromethane alone but is soluble in acetonitrile. The desired product was found to be minor (from 5-8%) and the acylated form of 5-methyl-5-hexen-1-ol was found to be the major product (40-50%). The identity of the major product of this reaction was unclear in the beginning because the \(^1\)H NMR spectra of 26 and its acylated form are very similar. A TLC analysis revealed that
the major product was significantly less polar than the starting hexenol. A $^{13}$C NMR spectrum revealed that a carbonyl carbon was present in the molecule (shown in Figure 2).

![Figure 2 – Crude $^{13}$C NMR of Acylated 5-methylhex-4-en-1-ol](image)

Along with the TLC analysis, the $^{13}$C NMR peak at 170 ppm suggests that the major product was the acylated form of 5-methyl hexenol. To determine the cause of the acylation, a control experiment was setup. It was first believed that 26 was reacting with acetonitrile and silver triflate to give the imino ether (shown in Scheme 24).

![Scheme 24](image)

The imino ether could then be hydrolyzed by any extraneous water in the reaction to give the ester. This control with acetonitrile was negative and so another rationale was envisaged, which is shown in Scheme 25.
Scheme 25 – Proposed Mechanism of Acylation
(Sug = sugar, Alc = alcohol, -OTf = triflate ion)

The anomeric position of tetraacetylbromoglucose is activated by precipitation of silver bromide to form the oxonium cation 27. It has been shown that acyl groups adjacent to the anomeric position may react with the oxonium intermediate. The π-electrons of the adjacent acyl group in 27 could act as a nucleophile to give 28. This leaves behind a cation on the adjacent protecting group, making available an alternate electrophile. The hexenol in solution may react with electrophiles 28 to give intermediate 29, the protonated form of an orthoester. The reaction may then proceed further, which is attributed to the weak basicity of the triflate ion. Intermediate 29 has made available a proton potentially acidic enough to protonate the triflate ion, another sugar, or unreacted alcohol. The triflate ion may become protonated to form triflic acid. Triflic acid is a strong acid that may further catalyze the acylation of the hexenol nucleophile, via the orthoester group in 30. After protonation of 30, 31 is setup to undergo an intramolecular
acylation of the hexenol. This leaves an undesired oxonium cation (32) with a free hydroxyl group. The free hydroxyl group also leaves another nucleophile in solution, which may further react with other oxonium intermediates to give unwanted side products. In order to neutralize any significant concentration of triflic acid, the reaction was attempted with the addition of triethylamine. With the addition of TEA, the reaction was completed in yields on the order of 45-56% (shown in Scheme 26).

![Scheme 26](image)

**Photolysis of 5-methyl-hexen-1-ol Substituted Tetraacetyl Glucose**

As a proof of principle experiment, a photolysis of 33 was carried out in methanol with TCQ (Scheme 27). This reaction was monitored by GC and gave 80% conversion after one hour. It should be noted that the compound begins to break down if irradiation is continued longer than one hour.

![Scheme 27](image)
If excess pentanol, in dichloromethane, is used as a nucleophile (in this case five equivalents) the reaction does not proceed to completion at all. $^1$H NMR evidence suggests that the protecting acetate groups of the tetraacetyl-hexenyl glucose are no longer present after one hour of irradiation under the conditions shown in Scheme 27. The product of the proposed coupling of the furan/sensitizer intermediates (23) was isolated and a crystal structure was obtained (shown in Figure 3).

![Figure 3 – X-Ray Crystal Structure of Tetrachlorobenzoquinone](image)

This suggests that TCQ is reduced before coupling with the cyclized furan. For the reaction to proceed, the furan intermediate must be ‘trapped’ to inhibit the formation of hexenol anion to prevent competition with the desired external nucleophile. If the anion is generated then it is probable that the anion may become acylated from the surrounding acetate groups. The possibility also exists that a photoacid is generated. As mentioned in the introduction, the irradiation of chloranil can generate a photoacid that may donate a proton to the solvent. This could in turn drive the cleavage of the acetate groups and generate many unwanted side reactions. The number of equivalents of nucleophile, necessary to drive the reaction forward, must be decreased for practical applications. This system proved to be problematic in a number of areas.

**Glycosyl Activation with Internal Sensitizer**

A reevaluation of 33 left us with an alternative approach in order to address some of the problems that were presented above. It was proposed that the moiety should still undergo an intramolecular cyclization, but it may be more effective if the molecule could
also undergo an intramolecular electron transfer. A proposed structure of such a molecule is shown in Scheme 28.

Scheme 28 – Proposed Photolysis Reaction of 34

Compound 34 (Scheme 28) was proposed based upon dicyanobenzene’s photochemical ability to accept an electron from the alkene and the fact that the cyano functionality is photochemically inert. Upon electron abstraction from the alkene, the photosensitized alcohol may cyclize into the furan radical. The idea was that the alkene could donate an electron to form the radical anion of the cyano-benzene so that it may subsequently couple with the furan radical intramolecularly. This could give a trapped intermediate (36) so that subsequent unwanted photoproducts could be eliminated.

In order to model the behavior of such a compound, the THP ether of a compound similar to compound 34 was envisaged. If the alkyl region of 34 was a bit more branched, the molecule would become more rigid, therefore the rate of cyclization should be quicker. Scheme 29 shows a proposed mechanism of how the new system would work. Target molecule 37 would initially undergo an intramolecular electron transfer to give the radical ion pair in 38.
The oxygen beside the pyran ring may then cyclize onto the carbon bearing the positive charge to give furanyl radical cation 39. The two radicals may then couple to give furanyl cation 40. The lone pairs on the oxygen of the pyran can fold down to give the coupled product 41. This would leave the oxonium intermediate to alkylate a free nucleophile in solution to give the desired product without an extraneous reactive intermediate in solution.
Synthesis of Compound 37

A synthetic strategy to obtain 37 is shown in Scheme 30. Compound 18 was synthesized previously in the lab and was chosen as a starting point for the synthesis (shown in Scheme 17). The alcohol portion of THP ether is commercially available as a racemic mixture and 18 is easily obtained in good yields. Molecule 18 was treated with selenium dioxide to oxidize the vinyl methyl group up to aldehyde 42. The reaction was followed by thin layer chromatography (TLC) and the starting material was determined to be consumed after 20 minutes reaction time. This reaction is problematic in that the extraction process involves using excessive amounts of water to rid the reaction of extraneous selenium dioxide, that is required to drive the reaction forward.

When water is added to the reaction, it produces selenous acids that may also hydrolyze the THP. Product 42 had to be vacuum distilled over potassium carbonate prior to reduction to alcohol 43. If 42 was not purified before reduction, then no product was obtained. Compound 42 had to be purified by distillation because it was not separable from various byproducts by column chromatography. An 8% yield over the selenium dioxide oxidation and sodium borohydride reduction steps was observed. The low yield was mostly attributed to the hydrolysis of the THP ether in the selenium dioxide oxidation step, which can be promoted by heat and extraneous selenous acids.
The reduction step was achieved in moderate yield and the addition of the acyl chloride, from 43 to 37, was achieved in 93% yield.

**Photoactivation of 37**

Compound 37 was irradiated at 300 nm for 20 hours to obtain wanted product (Scheme 31). The product of Scheme 31 was isolated in 85% yield. The expected ‘trapped intermediate’ 41 was not found, but alcohol 43 was isolated with 90% recovery by column chromatography. A mechanism for the transformation shown in Scheme 31 is proposed in Scheme 32.

![Scheme 31 – Photolysis Reaction of 37 with Pentanol as a Nucleophile](image)

In this mechanism, 37 undergoes a photoinduced electron transfer reaction. The electron rich alkene system donates an electron to the cyanobenzene in its excited state, which gives the same radical ion pair as before (38, Scheme 24). After the oxonium intermediate is produced, the furanyl and cyanobenzyl radicals may couple (39). This gives anion 44, which is stabilized due to resonance about the benzene ring and is also alpha to the carbonyl. Anion 44 may rearomatize to regenerate the alkene, to return the original alcohol 43 of the starting THP pyran 32. This reaction may also be reversible, in that 43 may recombine with the oxonium intermediate instead of an external nucleophile, to return the starting THP ether. This may contribute to the fact that this reaction takes close to a day to complete.
The above reaction is an excellent way to photochemically exchange a nucleophile from a modified THP ether. The expected product of this reaction was obtained in excellent yield and the only other side product was the ‘starting nucleophile’ 38. This reaction however does have a few drawbacks. The wavelength required to sensitize cyanobenzene is 300 nm or less. In general, it is preferable to sensitize reactions with light more towards the visible end of the electromagnetic spectrum (higher wavelength) because there is less energy in those photons. If too short a wavelength (higher energy) is used, then sigma bonds begin to absorb radiation and decomposition of the compound may result. The more effectively the molecule absorbs, the higher the
probability of some electronic excitation. If there are an increased number of electronic promotions to orbitals that are higher in energy, the more likely photochemical transformations involving sensitized processes are.

**Evaluation of Activation with Internal Sensitizer**

Molecule 37 is an excellent starting point for future work with this particular reaction. To increase its absorption wavelength, the π-system of cyanobenzene could be extended to increase its conjugation. A cyanoanthracene may be sufficient to sensitize this reaction at longer wavelengths, thus decreasing the time necessary to complete the reaction and preventing material from being by irradiation at lower/more energetic wavelengths.

Another consideration may be to modify the benzene ring in 37. If more photochemically inert electron-withdrawing groups are placed around the ring, then this may lower its overall reduction potential in its excited state. To increase its stability, an allylic amide linkage could be considered to replace the ester linkage in 37. The size of the carbon chain, stretching from alkene to the oxygen linked to the acetal, could also be shortened to determine if the rate of reaction is a function of chain length.

Shortening the alkyl region of 37 may also be beneficial to purification processes as well. As is, 37 is a liquid and shortening the chain may allow for a greater likelihood that it will be a solid. Solids are synthetically useful, in that they may be crystallized. If this system is applied to large scale synthesis, separation by column chromatography may prove difficult. The above modifications could yield a molecule that could be used for practical applications in exchanging nucleophiles at the anomeric position.

**Photochemical THP Transfer from α-Terpineol-THP Ether**

Based upon the above data and considerations above, another THP ether and sensitizer was investigated for their potential uses in our system. Dichloroquinone (DCQ) was used in conjunction with the THP ether of commercially available α-terpineol (40, Scheme 33).
The α-terpineol THP ether (45) was chosen based upon the commercial availability of α-terpineol and upon the observation discussed earlier that the restriction of the bond angles increases the rate of cyclization. α-Terpineol has very restricted bond angles in that the alkene is contained within a cyclohexene ring and there are two methyl groups adjacent to the oxygen. The synthesis of 45 is shown below in Scheme 34. Dichloroquinone was chosen on the basis that it absorbs in the visible region of the electromagnetic spectrum.

An experiment was setup in order to determine the relative rate of reaction of DCQ, compared with TCQ. As shown in Scheme 33, 40 was irradiated at 419 nm for one hour with one equivalent of pentanol used as the nucleophile.
Table 4 – Results from Photolysis of 45

(Percent conversion obtained by GC analysis)

It was determined from the results, shown below in Table 4, that the reaction is faster when DCQ is used as the sensitizer. A second nucleophile (benzyl alcohol), which is also a primary alcohol, was used to check the reproducibility of the reaction. Upon further analysis of this system, it was discovered that the reaction is catalytic with respect to DCQ (as low as 5% catalyst loading).

Photolysis of Model Compounds with DCQ

A competition experiment was setup to determine if the system extends to the THP ethers that were constructed earlier (Scheme 35).

![Scheme 35 – Photolysis of Various THP Ethers at 419 nm](image)
Table 5 – Results of Photolysis of Various THP Ethers at 419 nm
(R group abbreviations shown in Scheme 35)

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>R</th>
<th>Irradiation Time</th>
<th>% Conversion</th>
<th>Sensitizer</th>
<th>Equiv. of nucleophile</th>
</tr>
</thead>
<tbody>
<tr>
<td>pentanol</td>
<td>hept</td>
<td>10 min</td>
<td>46%</td>
<td>DCQ</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25 min</td>
<td>73%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 hr</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pentanol</td>
<td>hex</td>
<td>10 min</td>
<td>33%</td>
<td>DCQ</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 hr</td>
<td>90%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pentanol</td>
<td>terp</td>
<td>10 min</td>
<td>100%</td>
<td>DCQ</td>
<td>1</td>
</tr>
</tbody>
</table>

The results are shown above in Table 5. It was determined that when the R-group was α-terpineol, the rate of conversion was extremely efficient in that it took only a few minutes to convert starting material to product. These results are also a good illustration of the Thorpe-Ingold rules of cyclization, in that the system with the least restricted bond angles has the slowest rate of conversion.

**Photolysis of α-Terpineol-THP Ether**

After determining that the α-terpineol THP system was catalytic in DCQ, various nucleophiles were chosen to determine the scope of the reaction (shown in Scheme 31, results in Table 6).
<table>
<thead>
<tr>
<th>Nucleophile (R)</th>
<th>Time irradiated 419 nm (hrs)</th>
<th>% isolated yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentanol</td>
<td>1</td>
<td>95</td>
</tr>
<tr>
<td>2-pentanol</td>
<td>1</td>
<td>94</td>
</tr>
<tr>
<td>Benzyl alcohol</td>
<td>0.5</td>
<td>99</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>1.5</td>
<td>91</td>
</tr>
<tr>
<td>Allyl alcohol</td>
<td>0.5</td>
<td>92</td>
</tr>
<tr>
<td>Methyl-thiopropanol</td>
<td>2</td>
<td>75</td>
</tr>
<tr>
<td>pentanol (bicarbonate added)</td>
<td>4</td>
<td>90</td>
</tr>
</tbody>
</table>

**Table 6** – Results of Photolysis of α-Terpineol THP Ether with Various Nucleophiles

The results in Table 6 showed that this system is tolerant of alcohols that contain alkenes as well as thioethers. The last entry, in Table 6, shows the results of the reaction when a base (sodium bicarbonate) was added. The reaction was tested with base in solution to determine if there was a possibility that the reaction was photoacid catalyzed. The reaction was slowed by the addition of base but was not prevented it from going to completion. If the photolysis was carried out in the presence of a base that is soluble in CH₂Cl₂, no reaction was observed after 6 hours of irradiation. This suggests that this reaction may be due to a photochemically generated acid. It should also be noted that some bases that are soluble in CH₂Cl₂, such as tertiary amines, contain a lone pair of electrons and may also undergo PET reactions. This could also prevent the electron transfer from the alkene to the triplet sensitizer in the excited state.

**Activation of THP with TCQ**

The addition of a THP group to free hydroxyl groups was also accomplished with 3,4-dihydroxyran (DHP) (Scheme 37).
Scheme 37 – Activation of DHP with Various Nucleophiles and DCQ

<table>
<thead>
<tr>
<th>Nucleophile (R)</th>
<th>Time irradiated (419 nm)</th>
<th>% isolated yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-C₅H₉OH (46)</td>
<td>30 min</td>
<td>99</td>
</tr>
<tr>
<td>2-C₅H₉OH (47)</td>
<td>30 min</td>
<td>91</td>
</tr>
<tr>
<td>PhCH₂OH (48)</td>
<td>30 min</td>
<td>89</td>
</tr>
<tr>
<td>Cholesterol (49)</td>
<td>40 min</td>
<td>94</td>
</tr>
<tr>
<td>Allyl alcohol (50)</td>
<td>30 min</td>
<td>98</td>
</tr>
<tr>
<td>CH₃S(CH₂)₃OH (51)</td>
<td>1 hr</td>
<td>90</td>
</tr>
<tr>
<td>CH₂=CHC(CH₃)₂OH (52)</td>
<td>30 min</td>
<td>99</td>
</tr>
<tr>
<td>BOCNH(CH₂)₃OH (53)</td>
<td>2 hr</td>
<td>94</td>
</tr>
<tr>
<td>(CH₃)₂N(CH₂)₂OH (54)</td>
<td>12 hr</td>
<td>0</td>
</tr>
<tr>
<td>1-nonanol (55)</td>
<td>30 min</td>
<td>96</td>
</tr>
<tr>
<td>TBDMSOCH₂CH₂OH (56)</td>
<td>20 min</td>
<td>48</td>
</tr>
<tr>
<td>Benzyl alcohol (sunlight) (57)</td>
<td>30 min</td>
<td>98</td>
</tr>
<tr>
<td>α-terpineol (58)</td>
<td>2 hrs</td>
<td>20</td>
</tr>
<tr>
<td>6-methyl-5-hepten-2-ol (59)</td>
<td>2 hrs</td>
<td>0</td>
</tr>
<tr>
<td>5-methyl-5-hexen-1-ol (60)</td>
<td>45 min</td>
<td>92</td>
</tr>
<tr>
<td>Methyl p-hydroxybenzoate (61)</td>
<td>1 hr</td>
<td>90</td>
</tr>
</tbody>
</table>

Table 7 – Results of Photolysis of 3,4-Dihydropyran with Various Nucleophiles

The above reaction proved to be an efficient photochemical method to install a THP protecting group on free hydroxyls. Table 7 shows the results of tetrahydropyranylation of various alcohols with dihydropyran (DHP), dichloromethane, and visible light.

Evaluation of Tetrahydropyranylation Using DCQ

This is an excellent way to introduce a THP to a free hydroxyl in that it is ‘clean and green’, takes little time to complete, little workup is needed to purify, is insensitive to the presence of oxygen, little catalyst is needed (using just 5 mol % DCQ), and may even be carried out in ambient fluorescent light or sunlight (even during winter months).
DCQ was added to a solution of DHP and alcohol in dichloromethane and then irradiated. The reaction was monitored by GC until the reaction was found to be complete. After solvent removal, the desired THP ether could be isolated by column chromatography or an analytically pure sample could be obtained by distillation. In most cases it was possible to dissolve the crude product in cold diethyl-ether and filter out the solid DCQ. The desired THP would thus be left in the cold ether layer and was found to be better than 95% pure. A sample $^1$H NMR spectra is shown in Figure 4 of the pentanol THP ether (obtained without any other purification besides the filtration technique mentioned above).

![Figure 4 – Crude $^1$HNMR of Pentanol-THP Ether](image)

**Mechanistic Evaluation of Photochemical Tetrahydropyranylation**

This method also tolerated many functional groups and 3° alcohols even gave good yields, as shown by entry 52. $\alpha$-Terpineol is a more hindered nucleophile than 2-methyl-3-buten-2-ol, in that it contains a cyclohexene ring. The steric of $\alpha$-terpineol may explain observation of decreased yield. Another explanation is that there is an
alternate mechanistic pathway involved. Both \( \textbf{52} \) and \( \textbf{58} \) are 3°alcohols that contain alkenes, but \( \alpha \)-terpineol contains an alkene that is between the 4\(^{th}\) and 5\(^{th}\) carbons from the oxygen. The alkene may interact with the sensitizer as illustrated by Scheme 15. Entry \( \textbf{59} \) contains the same alkene distance from the oxygen as \( \alpha \)-terpineol, yet is a secondary alcohol. Both cases exhibit low yields and in the case of \( \textbf{59} \), no reaction was observed after 2 hrs of irradiation.

Entries \( \textbf{58} \) and \( \textbf{59} \) indicate that this reaction may involve a mechanism that has both electron transfer and photoacid characteristics. The THP group may be introduced by way of a photoacid to the terpineol and heptenol, but then may be photolyzed off by a PET reaction and subsequent cyclization. An equilibrium between the two mechanisms may have been reached with entry \( \textbf{58} \). This is consistent with the observation that a 20\% yield was maintained over 2 hrs of irradiation with DCQ.

The question, of whether the above sensitized reactions were initiated by photoinduced electron transfer or photogenerated acid, still remains. Further evidence for the electron transfer mechanism was probed with a competition experiment (Scheme 38) between two secondary alcohols, one unsaturated (6-methyl-5-hepten-2-ol) and the other saturated (2-pentanol). The results are summarized in Table 8.

\[
\begin{array}{c}
\text{O} \\
\text{R} \quad \begin{array}{c}
\text{O} \\
\text{R} \quad \begin{array}{c}
\text{OH} \\
\text{OH} \\
\end{array}
\end{array}
\end{array}
\begin{array}{c}
0.05 \text{M CH}_2\text{Cl}_2 \\
0.05 \text{ DCQ} \\
419 \text{ nm}
\end{array}
\]

\textbf{Scheme 38} – Photolysis of 3,4-Dihydropyran with Secondary Alcohols
Table 8 – Results of Photolysis of 3,4-Dihydropyran with Secondary Alcohols

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Irradiation time</th>
<th>% conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-pentanol</td>
<td>10 min</td>
<td>100</td>
</tr>
<tr>
<td>6-methyl-5-hepten-2-ol</td>
<td>10 min</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>20 min</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1 hr</td>
<td>0</td>
</tr>
</tbody>
</table>

A stock solution of DCQ in dichloromethane was used to ensure that the concentration of sensitizer was kept constant. As shown, the reaction with the saturated alcohol proceeded quickly and to full conversion while the unsaturated secondary alcohol did not react after an 1 hr of irradiation. This experiment is a good illustration of the fact that sterics are not the only factor in obtaining full conversion for this reaction. The answer may be that both photoacid generation and PET are operating simultaneously. Further investigation of the mechanism may be beneficial to future generations of these types of compounds.

Acid-sensitive species were also tolerated, such as BOC and TBDMS protecting groups. No cleavage of the TBDMS nor BOC groups was observed upon photolysis. Irradiation of the BOC protected amide required a longer irradiation time and needed more DCQ to drive the reaction to completion (up to 50 mol%). This may be due to the slight neutralization of the photogenerated acid by the amide. No reaction was observed when N,N-dimethylaminopropanol (47) was used. Either DCQ is quenched by the presence of the amine, because it may participate in electron transfer reactions, or the photoacid is prevented from forming in any appreciable concentrations due to the basic character of amines.

Several possibilities exist for the identity of a photogenerated acid. Photogenerated HCl, which is formed from either CH₂Cl₂ or DCQ, was ruled out. Photolysis of DCQ with visible light does not result in dechlorination and no HCl was generated. No hydrolysis of the BOC group was observed so this also argues against generation of HCl. However, photoreduction of dichlorquinone in CH₂Cl₂ with a small amount of methanol leads to an increase in acidity.

When acetic acid (pKₐ = 4.75) was used to catalyze the reaction (10 mol % AcOH), no conversion was observed after 20 minutes, while the same reaction sensitized by DCQ
undergoes 80% conversion in the same amount of time. So the source of acid is likely an acid that has a $pK_a$ less than 4.75 in its excited state. Possible structures for catalytic species are shown in Figure 5.

![Possible Photoacids Responsible for THP Activation](image)

**Figure 5** – Possible Photoacids Responsible for THP Activation

**Conclusion**

The basis for a new method of glycosylation has been successfully demonstrated through THP-ether prototypes. Activation of the acetal of these pyran systems by a PET mechanism is possible at 300 nm. This allowed pentanol to be exchanged at the acetal position of the pyran, with a yield of 85%. (E)-6-hydroxy-2-methylhept-2-enyl 4-cyanobenzoate was recovered in up to 90% yield and did not decompose at 300 nm of 20 hours. It was also shown that the introduction of a THP to alcohols can be accomplished by a catalytic amount of DCQ in visible light. The yields for THP installation were found to be up to 99% and pure samples (up to 95%) may be obtained by purifying via cold filtration. There is evidence that suggests the installation of a THP group is photoacid catalyzed. However, in situations in which an alkene is located between the 4th and 5th carbons from an oxygen, a PET mechanism may also be operating simultaneously.
REFERENCES
EXPERIMENTAL

General

Proton nuclear magnetic resonance spectra were obtained using a Bruker Avance 300 MHz spectrometer or a Bruker 500 MHz spectrometer. $^{13}$C NMR spectra were obtained using a 500 MHz Bruker spectrometer at 125 MHz. Thin-layer chromatography was carried out on silica gel (250 μm thickness with fluorescein). The chromatograms were visualized with UV light (254 nm). The chromatograms that could not be visualized by UV light were stained with phosphomolybdic acid solution. The solution was prepared by dissolving 10 g of phosphomolybdic acid in 250 mL of 95% ethanol. Column chromatography was performed using silica gel (60 Å) unless otherwise noted. GC analyses were carried out on an Agilent 6890 GC and analytes were detected by FID following elution from a 0.25-0.60 micron Agilent Inc.column (30m x 0.032mm, 325/350C, SN US1415761H). GC-MS analyses were carried out on an Agilent 6850 GC system coupled to an Agilent 5973 mass spectrometer. All elemental analyses were carried out by Atlantic Microlabs, Inc. in Norcross, GA. High-resolution mass spectrometry (HRMS) analyses were performed at Old Dominion University, Norfolk, VA. The samples were dissolved in 1:1:1 THF:MeOH:MeCN with NaCl and were analyzed by positive ion electrospray on a Bruker 12T Apex-Qe FTICR-MS with an Apollo II source. The X-Ray crystallographic analysis was performed at Wake Forest University by Dr. Cynthia Day. All reagents were obtained from commercial sources or synthesized as shown on the following pages. Dichloromethane was dried via an alumina column and dry acetonitrile was obtained by distillation over sodium. Photolyses were carried out in a Rayonet reactor and utilized 419 nm unless otherwise stated. All photolyses were irradiated through Pyrex glass while immersed in a water bath (temperature never reached over 35°C for 419 lamps). For all photochemical transformations dark controls were run, by placing an identical reaction wrapped in aluminum foil in the Rayonet reactor alongside the photoreactions being irradiated, to conclude that the photochemistry involved was not due to thermal processes. All reactions were carried out at ambient temperature under an argon atmosphere unless otherwise stated.
Model Pyrans for Photolysis

\[
\text{\textbullet} + \text{OH} \quad \rightarrow \quad \text{\textbullet} \quad \text{\textbullet}
\]

2-(6-methylhept-5-en-2-yloxy)tetrahydro-2H-pyran (18) (Representative Procedure for THP Ether Formation by Catalytic PPTs). 3,4-dihydro-2H-pyran (1.97 g, 0.023 mol) was placed in dry CH₂Cl₂ (0.1M, 156 mL) and stirred for 5 minutes under an inert atmosphere. (R/S) 6-methylhept-5-en-2-ol (2.00 g, 0.016 mol) was then added to the solution along with pyridinium-p-toluenesulfonate (0.58 g, 0.0016 mol). The reaction was allowed to stir at room temperature for 6 hours. The solution was then washed with 2 x 30-mL portions of saturated NaCO₃ and 20 mL of brine. The resultant CH₂Cl₂ layer was then dried with MgSO₄ and concentrated under reduced pressure. The yellow liquid was then purified by column chromatography (8:1 hexane/ethylacetate, 1% acetone) to give 2-(6-methylhept-5-en-2-yloxy)tetrahydro-2H-pyran (2.01 g, 60.6%). ¹H NMR (500 MHz, CDCl₃) δ 5.14 (m, 2H), δ 4.73 (m, 1H), δ 4.62 (m, 1H), δ 3.91 (m, 2H), δ 3.80 (m, 1H), δ 3.73 (m, 1H), δ 3.49 (m, 2H), δ 2.01 (m, 4H), δ 1.83 (m, 2H), δ 1.68 (m, 8H), δ 1.64 (m, 1H), δ 1.61 (m, 6H), δ 1.56 (m, 11H), δ 1.24 (d, 3H), δ 1.12 (d, 3H).

\[
\text{\textbullet} + \text{OH} \quad \rightarrow \quad \text{\textbullet} \quad \text{\textbullet}
\]

2-(5-methylhex-4-enyloxy)tetrahydro-2H-pyran (16). The crude oil, obtained as described by the representative procedure for the formation of THP ether by catalytic PPTs, could be further purified by flash column chromatography (7/1 hexane/ethyl acetate) to yield a clear oil (1.44 g, 7.3 mmol, 66%). ¹H NMR (300 MHz, CDCl₃) δ 5.15 (m, 1H), δ 4.60 (m, 1H), δ 3.90 (m, 1H), δ 3.75 (m, 1H), δ 3.52 (m, 1H), δ 3.36 (m, 1H), δ 2.05 (m, 2H), δ 1.72 (m, 14H). ¹³C NMR (125 MHz, CDCl₃) δ 130.5, 121.2, 105.8, 66.3, 63.0, 31.1, 30.1, 25.9, 23.9, 23.0, 19.7, 17.6.

The crude oil, obtained as described by the representative procedure for the formation of THP ether by catalytic PPTs, could be further purified by flash column chromatography (7/1 hexane/ethyl acetate) to yield a clear oil (2.42 g, 14 mmol, 62%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.3 (m, 1H), $\delta$ 4.63 (m, 1H), $\delta$ 4.23 (m, 1H), $\delta$ 3.96 (m, 1H), $\delta$ 3.50 (m, 1H), $\delta$ 1.65 (m, 12 H).

2-(pentyloxy)tetrahydro-2H-pyran (19). Zhou, Jingyao; Lu, Guodi; Huang, Xin; Wu, Shihui. *Synthetic Communications*, **1991**, 21(3), 435-441. The crude oil, obtained as described above by the representative procedure for the formation of THP ether by catalytic PPTs, could be further purified by flash column chromatography (7/1 hexane/ethyl acetate) to yield a clear oil (500 mg, 2.9 mmol, 71%). The sample was determined to be analytically pure based upon an $^1$H NMR spectrum and that it yielded one peak by GC analysis. (Batch used as GC standard to determine percent composition for photochemical transformations). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.57 (m, 1H), $\delta$ 3.87 (m, 1H), $\delta$ 3.71 (m, 1H), $\delta$ 3.51 (m, 1H), $\delta$ 3.39 (m, 1H), $\delta$ 1.81 (m, 2H), $\delta$ 1.57 (m, 6H), $\delta$ 1.34 (m, 4H), $\delta$ 0.90 (m, 3H).
Photolyses of Model Pyrans

2-(pentyloxy)tetrahydro-2H-pyran (19) (Representative Procedure for Photochemical Pyran Transfer from 6-methylhept-5-en-2-ol-THP Ether). To a solution of 18 (0.20 g, 0.96 mmol) in 12 mL of CH₂Cl₂, pentanol (0.13 g, 1.4 mmol) was added. Biphenyl (0.15 g, 0.96 mmol) and dicyanoanthracene (0.15 g, 0.96 mmol) were then added to the reaction mixture and allowed to stir for 20 minutes so that the dicyanoanthracene would dissolve. The reaction mixture was then purged with argon for 20 minutes to rid the solution of oxygen. The reaction flask was immersed in a water bath to dissipate excess heat while in the photoreactor. The solution was then irradiated at 350 nm for 12 hours and followed by GC analysis to determine the percent conversion.

The following commercially available triplet-sensitizers were used to determine which one gave the highest conversion at the quickest rate: dicyanobenzene, tetracyanoethylene, tetrachlorobenzoquinone, and 2,2’-(cyclohexa-2,5-diene-1,4-diylidene)dimalononitrile.

2-butoxytetrahydro-2H-pyran (Photochemical Pyran Transfer from 6-methylhex-5-en-1-ol-THP Ether). To a solution of 16 (0.10 g, 0.51 mmol) in 6 mL of CH₂Cl₂, n-butanol (52 mg, 0.76 mmol) was added. Tetrachlorobenzoquinone (0.12 g, 0.51 mmol) was then added to the reaction mixture and the solution was purged with argon for 10 minutes. The solution was irradiated at 350 nm for 1 hour to achieve complete conversion, as determined by TLC. The reaction mixture was then concentrated in vacuo. A purple precipitate formed as the solution cooled while it was being concentrated. The reaction mixture was then gravity filtered to remove the purple precipitate. The crude yellow oil was then purified by flash column chromatography (6/1 petroleum ether/ethyl
acetate, 1% TEA) to give 2-butoxytetrahydro-2H-pyran (45 mg, 0.31 mmol, 62%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.87 (m, 1H), $\delta$ 3.94 (m, 1H), $\delta$ 3.80 (m, 1H), $\delta$ 3.51 (m, 2H), $\delta$ 1.67 (m, 12H), $\delta$ 0.96 (m, 3H).

2-sec-butoxytetrahydro-2H-pyran (Photochemical Pyran Transfer from 2-(3-methylbut-2-enyloxy)tetrahydro-2H-pyran). Wang, Min; Song, Zhi Guo; Gong, Hong; Jiang, Heng. *Chinese Chemical Letters*, 2007, 18(7), 799-802. To a solution of 16 (0.10 g, 0.51 mmol) in 6 mL of CH$_2$Cl$_2$, 2-butanol (56 mg, 0.76 mmol) was added. Tetrachlorobenzoquinone (0.12 g, 0.51 mmol) was then added to the reaction mixture and the solution was purged with argon for 10 minutes. The solution was irradiated at 350 nm for 1 hour to achieve complete conversion, as determined by TLC. The reaction mixture was then concentrated in vacuo. A purple precipitate formed as the solution cooled while it was being concentrated. The reaction mixture was then gravity filtered to remove the purple precipitate. The crude yellow oil was then purified by flash column chromatography (6/1 petroleum ether/ethyl acetate, 1% TEA) to give 2-sec-butoxytetrahydro-2H-pyran (56 mg, 0.35 mmol, 70%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.94 (m, 1H), $\delta$ 3.94 (m, 1H), $\delta$ 3.80 (m, 1H), $\delta$ 3.14 (m, 1H), $\delta$ 1.67 (m, 8H), $\delta$ 1.23 (m, 3H), $\delta$ 0.98 (m, 3H).
2-butoxytetrahydro-2H-pyran (Photochemical Pyran Transfer from 3-methylbut-2-en-1-ol-THP Ether). To a solution of 17 (0.10 g, 0.59 mmol) in 7 mL of CH₂Cl₂, n-butanol (65 mg, 0.88 mmol) was added. Dicyanobenzene (0.75 mg, 0.59 mmol) and biphenyl (90 mg, 0.59 mmol) was then added to the reaction mixture and allowed to stir for 15 minutes to allow full dissolution. The solution was purged with argon for 10 minutes. The solution was irradiated at 350 nm for 24 hour to achieve 22% conversion, as determined by TLC. The reaction mixture was then concentrated in vacuo. The crude mixture was dissolved in cold hexanes and then gravity filtered to remove excess dicyanobenzene. The crude yellow oil was then purified by flash column chromatography (6/1 petroleum ether/ethyl acetate, 1% TEA) to give 2-butoxytetrahydro-2H-pyran (14 mg, 0.09 mmol, 15%). 

\[ \begin{align*} &\text{O} \quad \text{O} \\
&\text{O} \quad \text{O} \\
&+ \quad \text{OH} \\
&\text{CN} \quad \text{CN} \\
&\Rightarrow \text{O} \quad \text{O} \\
&\text{O} \quad \text{O} \\
\end{align*} \]

1H NMR (300 MHz, CDCl₃) δ 4.87 (m, 1H), δ 3.94 (m, 1H), δ 3.80 (m, 1H), δ 3.51 (m, 2H), δ 1.67 (m, 12H), δ 0.96 (m, 3H).

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2-butoxytetrahydro-2H-pyran (Photochemical Pyran Transfer from 6-methylhex-5-en-1-ol-THP Ether). Edelson-Averbukh, M.; Mandelbaum, A. International Journal of Mass Spectrometry, 2001 210/211(1-3), 545-556. To a solution of 17 (0.10 g, 0.59 mmol) in 7 mL of CH₂Cl₂, n-butanol (65 mg, 0.88 mmol) was added. Tetrachloroquinone (145 mg, 0.59 mmol) was then added to the reaction mixture and purged with argon for 10 minutes. The solution was irradiated at 350 nm for 1 hour to achieve 95% conversion, as determined by TLC. The reaction mixture was then
concentrated in vacuo. A purple precipitate formed as the solution cooled while it was being concentrated. The crude mixture was then dissolved in cold hexanes and gravity filtered to remove the purple precipitate. The crude yellow oil was then purified by flash column chromatography (6/1 petroleum ether/ethyl acetate, 1% TEA) to give 2-butoxytetrahydro-2H-pyran (72 mg, 0.47 mmol, 80%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.87 (m, 1H), $\delta$ 3.94 (m, 1H), $\delta$ 3.80 (m, 1H), $\delta$ 3.51 (m, 2H), $\delta$ 1.67 (m, 12H), $\delta$ 0.96 (m, 3H).

**Synthesis of 33**

![Chemical structure](image)

ethyl 5-methylhex-4-enoate. Marcotullio, Maria Carla; Campagna, Valerio; Sternativo, Silvia; Costantino, Ferdinando; Curini, Massimo. *Synthesis*, 2006, 16, 2760-2766. 41.0 g of 2-methyl-3-buten-2-ol (0.48 mol) and 2 mL of propionic acid were refluxed in 400 mL of tetramethylorthoacetate for 36 hours. The resulting mixture was concentrated under vacuum to remove the extraneous tetramethylorthooacetate. The clear liquid was slowly added to 300 mL of 1N HCl and extracted with diethyl ether. The ether layer was then dried with MgSO$_4$ and concentrated under reduced pressure. The liquid was then subjected to vacuum distillation which yielded 41.0 g of ethyl 5-methylhex-4-enoate (59.6%). $^1$HNMR (300 MHz, CDCl$_3$) $\delta$ 5.05 (m, 1H), $\delta$ 4.10 (q, 2 H, J=7.16 Hz), $\delta$ 2.28 (m, 4H), $\delta$ 1.65 (s, 3H), $\delta$ 1.58 (s, 3H), $\delta$ 1.22 (t, 3H, 7.12 Hz).
5-methylhex-4-en-1-ol (26). Cocker, Wesley. *Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry* **1984**, *10*, 2245-2254. To a solution of dry ether, 1.48 g of LiAlH₄ (0.039 mol) was added. The solution was then cooled to 0°C. Ethyl 5-methylhex-4-enoate (8.5 g, 0.056 mol) was then added drop wise over a period of 20 minutes. The reaction was then monitored by TLC and was found to be complete after 45 minutes. The solution was then quenched with 1N HCl (added very slowly) and extracted with diethyl ether. The ether layer was then dried with MgSO₄ and concentrated under reduced pressure. The resultant clear liquid was found to be 5-methylhex-4-en-1-ol (4.06 g, 67%). ¹HNMR (300 MHz, CDCl₃) δ 5.14 (m, 1H), δ 3.64 (t, 2 H, J=6.41 Hz), δ 2.05 (q, 2H, J=7.25 Hz), δ 1.69 (s, 3H), δ 1.62 (m, 6H).

α/β-5-methylhex-4-en-1-ol-tetraacetyl glucose (33). α-β-bromo-tetraacetyl-glucopyranoside (2.00 g, 4.9 mmol) and 5-methyl-4-en-1-ol (0.58 g, 5.4 mmol) were added to 50mL of 20% CH₃CN in CH₂Cl₂ (CH₃CN distilled, dry condition, argon atmosphere), which was allowed to stir for 15 minutes at room temperature. The solution was then cooled to 78°C and allowed to equilibrate for 10 minutes. Triethyl amine (0.54 g, 5.4 mmol) was then added to the solution in order to prevent formation of triflic acid. Silver triflate (1.2 g, 4.9 mmol) was then added to the solution slowly. The solution was then placed in an icebath and allowed to stir for 3 hours. The resulting solution was then concentrated under reduced pressure to remove excess solvent and was subjected to column chromatography (7/1 Hex/EtOAc→3/1 Hex/EtOAc). The resulting clear, viscous liquid was found to be α-β-5-methylhex-4-en-1-ol-tetraacetyl glucose (0.87 g, 40% yield).
\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 5.69\) (d, 1H, \(J=5.27\) Hz), \(\delta 5.16\) (m, 1H), \(\delta 5.05\) (m, 1H), \(\delta 4.88\) (m, 1H), \(\delta 4.28\) (m, 1H), \(\delta 4.17\) (m, 2H), \(\delta 3.91\) (m, 1H), \(\delta 3.43\) (t, 2H, \(J=6.46\) Hz), \(\delta 2.08\) (m, 12H), \(\delta 1.71\) (m, 6H), \(\delta 1.57\) (m, 4H).

**Photolysis of 33**

\(\alpha/\beta\)-methoxy-tetraacetyl glucose (Photolysis of \(\alpha/\beta\)-5-methylhex-4-en-1-ol-tetraacetyl glucose). To a solution of \(\alpha/\beta\)-5-methylhex-4-en-1-ol-tetraacetyl glucose (44 mg, 0.099 mmol) in methanol (6 mL), tetrachlorobenzoquinone (24 mg, 0.099 mmol) was added. The solution was purged with argon for 10 minutes to rid the system of oxygen. The solution was then irradiated at 350 nm for 1 hour to achieve 80\% conversion (monitored by GC). If the solution was irradiated for longer than 1 hr the product began to break down, as determined by GC analysis. The resulting solution was then concentrated under reduced pressure to remove methanol and was subjected to column chromatography (7/1 hexane/ethyl acetate\(\rightarrow\)2/1 hexane/ethyl acetate) to give a clear oil \(\alpha/\beta\)-methoxy-tetraacetyl glucose (13 mg, 0.035 mmol, 35\%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 5.61\) (m, 1H), \(\delta 5.25\) (m, 1H), \(\delta 5.11\) (m, 1H), \(\delta 4.67\) (m, 2H), \(\delta 3.78\) (s, 3H), \(\delta 2.05\) (m, 12H).

**Synthesis of Pyran with Internal Sensitizer**

\((E)-2\text{-methyl-6-(tetrahydro-2H-pyran-2-yloxy)hept-2-en-1-ol (43).}\) 2-(6-methylhept-5-en-2-yloxy)tetrahydro-2H-pyran (4.49 g, 0.021 mol) was placed in 45 mL of THF. Selenium dioxide (4.7 g, 0.042 mol) was then added and the solution was allowed to reflux for 20 minutes. An orange solution results and the reaction was determined to be
The solution may then be dissolved in cold methanol to precipitate the insoluble selenium impurities. The solution was then gravity filtered and the filtrate was then dissolved in diethyl ether and washed with H₂O (2-100 mL portions). The ether layer was then dried over MgSO₄ and concentrated under reduced pressure to remove excess solvent. The crude oil was then further purified by vacuum distillation over K₂CO₃ (head temperature of 135 °C (0.5 Torr). The ¹H NMR (300 MHz, CDCl₃) showed a characteristic aldehyde peak at 9.24 ppm. The spectrum however still showed impurities. The crude, clear, aldehyde distillate was then dissolved in 200 mL of ethanol, in which was placed NaBH₄ (0.96 g, 0.021 mol). The solution was allowed to stir for 3 hours at room temperature. The reaction was then slowly quenched with H₂O. The solution was then dissolved in diethyl ether and washed with H₂O (2-30 mL portions). The ether layer was then dried with MgSO₄ and concentrated under reduced pressure to remove excess solvent. The crude, yellow oil was then purified by column chromatography (10/1 Hex/EtOAc → 3/1 Hex/EtOAc). The resulting clear liquid was found to be (E)-2-methyl-6-(tetrahydro-2H-pyran-2-yloxy)hept-2-en-1-ol (0.43 g, 8% yield). ¹H NMR (300 MHz, CDCl₃) δ 5.42 (m, 1H), δ 4.62 (m, 1H), δ 4.13 (m, 1H), δ 3.99 (s, 2H), δ 3.81 (m, 3H), δ 3.48 (m, 2H), δ 1.54 (m, 6H), δ 1.43 (m, 4H), δ 1.22 (m, 4H).

(E)-2-methyl-6-(tetrahydro-2H-pyran-2-yloxy)hept-2-enyl 4-cyanobenzoate (37).

(E)-2-methyl-6-(tetrahydro-2H-pyran-2-yloxy)hept-2-en-1-ol (68.8 mg, 0.30 mmol) and triethyl amine (0.1 mL, 0.90 mmol) were added to 3 mL of dry dichloromethane. Cyanobenzoyl chloride (50 mg, 0.30 mmol) was then added to the solution and was allowed to stir at room temperature. By TLC analysis the reaction was determined to be complete after 30 minutes. The resultant mixture was diluted with CH₂Cl₂ and washed.
with 1N HCl (2-5 mL portions). The organic layer was washed with brine, dried with 
MgSO₄, and concentrated under reduced pressure. The white solid was subjected to 
column chromatography (7/1 Hex/EtOAc) which resulted in (E)-2-methyl-6-(tetrahydro-
2H-pyran-2-yloxy)hept-2-enyl 4-cyanobenzoate (90 mg, 91% yield). ¹H NMR (300 MHz, 
CDCl₃) δ 8.09 (d, 2H, J=8.38 Hz), δ 7.69 (d, 2H, J=8.38 Hz), δ 5.60 (m, 1H), δ 4.73 (s, 2 
H), δ 3.46 (m, 2H), δ 3.35 (m, 1H), δ 1.8 (m, 2H), δ 1.65 (m, 12 H), δ 1.13 (m, 2H), δ 
1.10 (m, 1H).

![Chemical Structure](image)

2-butoxytetrahydro-2H-pyran (Photochemical THP Transfer from 37). (E)-2-
methyl-6-(tetrahydro-2H-pyran-2-yloxy)hept-2-enyl 4-cyanobenzoate (9.8 mg, 0.03 
mmol) was added to 10 mL of dichloromethane, along with pentanol (12.1 mg, 0.14 
mmol). The solution was irradiated for at 300 nm in a rayonet reactor. GC analysis 
showed that the pentanyl-THP ether was formed with 94% conversion after irradiation 
for 20 hours. The solution was then concentrated under reduced pressure and then further 
concentrated in vacuo to remove any excess pentanol. A TLC analysis showed that two 
products were present. The products were separated by column chromatography (7/1 
Hex/EtOAc → 3/1 Hex/EtOAc). The expected pentanyl-THP ether was found, while the 
unexpected (E)-2-methyl-6-(tetrahydro-2H-pyran-2-yloxy)hept-2-en-1-ol was obtained 
with 93% recovery. The pentanyl-THP ether was found in 91% yield (4.3 mg). ¹H NMR 
(300 MHz, CDCl₃) δ 4.57 (m, 1H), δ 3.87 (m, 1H), δ 3.74 (m, 1H), δ 3.5 (m, 1H), δ 3.4 
(m, 1H), δ 1.82 (m, 2H), δ 1.53 (m, 7H), δ 1.34 (m, 3H), δ 0.84 (m, 3H).
**α-Terpineol-THP Ether**

![Chemical Structure](image)

**α-Terpineol-THP Ether (45).** Wagner, A.; Heitz, M. P.; Mioskowski, C; *Tetrahedron Letters*, **1989**, *30*(15), 1971-4. 3,4-dihydro-2H-pyran (2.00 g, 0.013 mol) was placed in dry CH₂Cl₂ (0.1M, 130 mL) and stirred for 5 minutes under an inert atmosphere. α-terpineol (2.18 g, 0.026 mol) was then added to the solution along with pyridinium-p-toluenesulfonate (0.32 g, 1.32 mmol). The reaction was allowed to stir at room temperature for 16 hours. The solution was then washed with 2 x 30-mL portions of saturated Na₂CO₃ and 20 mL of brine. The resultant CH₂Cl₂ layer was then dried with MgSO₄ and concentrated under reduced pressure. The yellow liquid was then purified by column chromatography (8:1 hexane/ethylacetate, 1% acetone) to give α-terpineol-THP ether (1.5 g, 6.4 mmol, 50%). ¹H NMR (300 MHz, CDCl₃) δ 5.38 (m, 1H), δ 4.77 (m, 1H), δ 3.95 (m, 1H), δ 3.42 (m, 1H), δ 1.84 (m, 5H), δ 1.64 (m, 9H), δ 1.27 (m, 1H), δ 1.16 (m, 7H).

**Photolyses of α-Terpineol-THP Ether**

![Chemical Structure](image)

**Representative Procedure for Photochemical Exchange of THP from α-Terpineol to Pentanol.** To a solution of 2-(2-(4-methylcyclohex-3-enyl)propan-2-yloxy)tetrahydro-2H-pyran (133 mg, 0.56 mmol) in dry CH₂Cl₂, pentanol (68 mg, 0.62 mmol) was added. The solution was then purged with argon for 15 minutes prior to the addition of 1,5-
dichloroanthraquinone (155 mg, 0.56 mmol) to the reaction mixture. The solution was irradiated at 419 nm for 1 hr until the α-terpineol-THP ether was shown to be consumed by GC analysis. The reaction was neutralized with TEA and concentrated in vacuo to afford a yellow oil. The crude product was then dissolved in cold diethyl ether and the insoluble material was removed by gravity filtration. The oil could be further purified by flash column chromatography (7/1 petroleum ether/ethyl acetate → 6/1 petroleum ether/ethyl acetate) to afford a clear oil (96 mg, 53 mmol, 95%). 

$^{1}$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.57 (m, 1H), $\delta$ 3.87 (m, 1H), $\delta$ 3.71 (m, 1H), $\delta$ 3.51 (m, 1H), $\delta$ 3.39 (m, 1H), $\delta$ 1.81 (m, 2H), $\delta$ 1.57 (m, 6H), $\delta$ 1.34 (m, 4H), $\delta$ 0.90 (m, 3H).


The crude yellow oil, obtained as described by the representative procedure for photochemical exchange of a THP from α-terpineol, was further purified by flash column chromatography (7/1 hexane/ethyl acetate, 1% TEA) to give a clear oil (0.14 g, 0.79 mmol, 94%). $^{1}$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.70 (m, 1H), $\delta$ 3.91 (m, 1H), $\delta$ 3.73 (m, 1H), $\delta$ 3.46 (m, 1H), $\delta$ 1.82 (m, 1H), $\delta$ 1.70 (m, 2H), $\delta$ 1.53 (m, 5H), $\delta$ 0.95 (m, 4H).
2-(benzyloxy)tetrahydro-2H-pyran (Photochemical Exchange of THP). Duan, Zhiying; Gu, Yanlong; Deng, Youquan. *Synthetic Communications* **2005**, *35*(14), P1939-1945. The crude yellow oil, obtained as described by the representative procedure for photochemical exchange of a THP from α-terpineol α-terpineol (except only 30 minutes of irradiation at 419 nm was required for full conversion), was further purified by flash column chromatography (7/1 hexane/ethyl acetate, 1% TEA) to give a clear oil (0.16 g, 0.83 mmol, 99%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.18 (m, 5H), $\delta$ 4.71 (d, 1H, J = 12.0 Hz), $\delta$ 4.61 (d, 1H, J = 3.54 Hz), $\delta$ 4.42 (d, 1H, J = 12.0 Hz), $\delta$ 3.82 (m, 1H), $\delta$ 3.45 (m, 1H), $\delta$ 1.45 (m, 6H).

cholesterol-THP ether (Photochemical Exchange THP). Choucair, Bassima; Dherbomez, Michel; Roussakis, Cristos; El Kihel, Laila. *Tetrahedron*, **2004**, *60*(50), 11477-11486. The white solid, obtained as described by the representative procedure for photochemical exchange of a THP from α-terpineol (except only 1.5 hours of irradiation at 419 nm was required for full conversion), was further purified by flash column chromatography (7/1 hexane/ethyl acetate, 1% TEA) to give a clear oil (0.26 g, 0.55 mmol, 91%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.34 (m, 1H), $\delta$ 4.71 (m, 1H), $\delta$ 3.90 (m, 1H), $\delta$ 3.51 (m, 1H), $\delta$ 2.34 (m, 2H), $\delta$ 1.83 (m, 5H), $\delta$ 1.41 (m, 15H), $\delta$ 1.14 (m, 7H), $\delta$ 0.92 (m, 13H), $\delta$ 0.67 (m, 2H).
2-(allyloxy)tetrahydro-2H-pyran. Menicagli, R.; Malanga, C.; Dell'Innocenti, M.; Lardicci, L. Journal of Organic Chemistry, 1987, 52(26), 5700-5704. The crude oil, obtained as described by the representative procedure for photochemical exchange of a THP from α-terpineol (except only 30 minutes of irradiation at 419 nm was required for full conversion), was further purified by flash column chromatography (7/1 hexane/ethyl acetate, 1% TEA) to give a clear oil (0.12 g, 0.85 mmol, 92%). $^1$H NMR (300 MHz, CDCl$_3$) δ 5.96 (m, 1H), δ 5.29 (m, 2H), δ 4.602 (m, 1H), δ 4.23 (m, 1H), δ 3.98 (m, 1H), δ 3.83 (m, 1H), δ 3.50 (m, 1H), 1.57 (m, 6H).

2-(allyloxy)tetrahydro-2H-pyran. The crude oil, obtained as described by the representative procedure for photochemical exchange of a THP from α-terpineol (except 2 hours of irradiation at 419 nm was required), was further purified by flash column chromatography (7/1 hexane/ethyl acetate, 1% TEA) to give a clear oil (0.12 g, 0.85 mmol, 92%). $^1$H NMR (500 MHz, CDCl$_3$) δ 4.56 (m, 1H), 3.81 (m, 2H), 3.47 (m, 2H), 2.59 (m, 2H), 2.09 (s, 3H), 1.86 (m, 3H), 1.57 (m, 1H), 1.50 (m, 4H).
Photochemical Activation of THP

Representative Procedure for Photochemical THP Ether Formation. 3-Thiomethyl-1-propanol THP Ether (51). To a solution of 3-(methylthio)-1-propanol (128 mg, 1.21 mmol) in dry CH₂Cl₂ was added 3,4-dihydro-2H-pyran (111 mg, 1.32 mmol, 1.1 equiv). 1,5-Dichloroanthraquinone (16 mg, 0.06 mmol) was then added to the reaction mixture. The solution was irradiated at 419 nm for 1 h until the 3-(methylthio)-1-propanol was shown to be consumed by GC analysis. The reaction was neutralized with TEA and concentrated in vacuo to afford a yellow oil. The crude product was then dissolved in cold Et₂O and insoluble material removed by gravity filtration. 1H NMR indicated that the crude product thus obtained was quite pure (see the Supporting Information). The oil could be further purified by flash column chromatography (7/1 petroleum ether/ethyl acetate → 6/1 petroleum ether/ethyl acetate) to afford a yellow oil (220 mg, 1.17 mmol, 97%). An analytically pure sample was obtained by vacuum distillation over K₂CO₃ (head temperature of 110 °C (0.5 Torr)). 1H NMR (500 MHz, CDCl₃) δ 4.56 (m, 1H), 3.81 (m, 2H), 3.47 (m, 2H), 2.59 (m, 2H), 2.09 (s, 3H), 1.86 (m, 1H), 1.57 (m, 1H), 1.50 1H NMR (125 MHz, CDCl₃) δ 99.2, 66.3, 62.7, 31.3, 31.0, 29.7, 25.8, 19.9, 15.8. HRMS (ESI+) calcd for C₉H₁₈O₂SNa⁺ 213.0919, found 213.0910. Anal. Caled for C₉H₁₈O₂S: C, 56.80; H, 9.53; S, 16.85. Found: C, 56.83; H, 9.53; S, 16.58.

2-(pentyloxy)tetrahydro-2H-pyran (46) (Photochemical Pyranylation of Pentanol). The crude oil, obtained as described by the representative procedure for photochemical introduction of THP (except for a 30 min irradiation time was required for full conversion), was further purified by flash column chromatography (5/1 petroleum
ether/ethyl acetate) to give a clear oil (0.18 g, 1.04 mmol, 99%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.57 (m, 1H), $\delta$ 3.87 (m, 1H), $\delta$ 3.71 (m, 1H), $\delta$ 3.51 (m, 1H), $\delta$ 3.39 (m, 1H), $\delta$ 1.81 (m, 2H), $\delta$ 1.57 (m, 6H), $\delta$ 1.34 (m, 4H), $\delta$ 0.90 (m, 3H).

\[ \text{O} + \text{CH}_2\text{OH} \rightarrow \text{O} \text{O} \text{CH}_2\text{CH}_2\text{CH}_3 \]

**2-(pentan-2-yloxy)tetrahydro-2H-pyran (47).** The crude oil, obtained as described by the representative procedure for photochemical introduction of THP (except for a 30 min irradiation time was required for full conversion), was further purified by flash column chromatography (7/1 petroleum ether/ethyl acetate, 1% TEA) to give a clear oil (0.18 g, 1.04 mmol, 92%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.70 (m, 1H), $\delta$ 3.91 (m, 1H), $\delta$ 3.73 (m, 1H), $\delta$ 3.46 (m, 1H), $\delta$ 1.82 (m, 1H), $\delta$ 1.70 (m, 2H), $\delta$ 1.53 (m, 5H), $\delta$ 0.95 (m, 4H).

\[ \text{O} + \text{C}_6\text{H}_5\text{CH}_2\text{OH} \rightarrow \text{O} \text{O} \text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CH}_3 \]

**2-(benzyloxy)tetrahydro-2H-pyran (48).** The crude oil, obtained as described by the representative procedure for photochemical introduction of THP, except for a 30 min irradiation time at 419 nm was required for full conversion. This reaction was also carried out in sunlight (45 min irradiation time) on a sunny day in January at a temperature of 14.3°C. Both products were further purified by flash column chromatography (7/1 petroleum ether/ethyl acetate, 1% TEA) to give a clear oils (0.24 g, 1.2 mmol, 99% in sunlight at 14.3°C on a sunny day in January and 40 mg, 0.21 mmol, 89% when irradiated at 419 nm Rayonet lamps). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.18 (m,
5H), δ 4.71 (d, 1H, J = 12.0 Hz), δ 4.61 (d, 1H, J = 3.54 Hz), δ 4.42 (d, 1H, J = 12.0 Hz), δ 3.82 (m, 1H), δ 3.45 (m, 1H), δ 1.45 (m, 6H).

**cholesterol-THP ether (49).** The white solid, obtained as described by the representative procedure for photochemical introduction of THP (except for a 40 min irradiation time was required for full conversion), was further purified by flash column chromatography (7/1 petroleum ether/ethyl acetate → 5/1 petroleum ether/ethyl acetate, 1% TEA) to give white solid (0.13 g, 0.28 mmol, 96%). $^1$H NMR (300 MHz, CDCl$_3$) δ 5.34 (m, 1H), δ 4.71 (m, 1H), δ 3.90 (m, 1H), δ 3.51 (m, 1H), δ 2.34 (m, 2H), δ 1.83 (m, 5H), δ 1.41 (m, 15H), δ 1.14 (m, 7H), δ 0.92 (m, 13H), δ 0.67 (m, 2H).

2-(allyloxy)tetrahydro-2H-pyran (50). The crude oil, obtained as described by the representative procedure for photochemical introduction of THP (except for a 30 min irradiation time was required for full conversion), was further purified by flash column chromatography (7/1 petroleum ether/ethyl acetate, 1% TEA) to give a clear oil (0.17 g, 0.75 mmol, 96%). $^1$H NMR (300 MHz, CDCl$_3$) δ 5.96 (m, 1H), δ 5.29 (m, 2H), δ 4.602 (m, 1H), δ 4.23 (m, 1H), δ 3.98 (m, 1H), δ 3.83 (m, 1H), δ 3.50 (m, 1H), 1.57 (m, 6H).
2-(2-methylbut-3-en-2-yloxy)tetrahydro-2H-pyran (52). Hegedues, Vigh, Hell; *Synthetic Communications*, **2004**, *34*(22), 4145-4152. The crude oil, obtained as described by the representative procedure for photochemical introduction of THP (except for a 30 min irradiation time was required for full conversion), was further purified by flash column chromatography (7/1 petroleum ether/ethyl acetate, 1% TEA) to give a clear oil (0.17 g, 0.75 mmol, 96%). 1H NMR (300 MHz, CDCl3) δ 5.94 (m, 1H), δ 5.10 (m, 2H), δ 4.60 (m, 1H), δ 3.92 (m, 1H), δ 3.42 (m, 1H), δ 1.82 (m, 1H), δ 1.63 (m, 1H), δ 1.40 (m, 4H), δ 1.34 (s, 3H), δ 1.24 (s, 3H).

N-tert-Butoxycarbonyl-3-amino-1-propanol THP Ether (53). The crude oil, obtained as described by the representative procedure for photochemical introduction of THP, could be further purified by flash column chromatography (3/1 petroleum ether/ethyl acetate → 2/1 petroleum ether/ethyl acetate) to yield a yellow oil (200 mg, 0.76 mmol, 94%). An analytically pure sample was obtained by vacuum distillation over K2CO3 (head temperature of 130 °C (0.5 Torr)). 1H NMR (500 MHz, CDCl3) δ 4.91 (s, 1H), 4.57 (m, 1H), 3.62 (m, 2H), 3.47 (m, 2H), 3.24 (m, 2H), 1.71 (m, 4H), 1.55 (m, 4H), 1.41 (s, 9H). 13C NMR (125 MHz, CDCl3) δ 156.2, 99.0, 78.6, 65.9, 62.0, 39.2, 31.3, 30.4, 28.9, 26.2, 20.0. HRMS (ESI+) calcd for C13H25NO4Na+ 282.1676, found 282.1666. Anal. Calcd for C13H25NO4: C, 60.21; H, 9.72; N, 5.40. Found: C, 60.24; H, 9.77; N, 5.20.
2-(nonyloxy)tetrahydro-2H-pyran (55). Olah, George A.; Husain, Altaf; Singh, Brij P. *Synthesis*, 1983, 11, 892-895. The crude oil, obtained as described by the representative procedure for photochemical introduction of THP (except for a 30 min irradiation time required for full conversion), was further purified by flash column chromatography (7/1 petroleum ether/ethyl acetate, 1% TEA) to give a clear oil (0.17 g, 0.75 mmol, 96%).

$^1$H NMR (300 MHz, CDCl$_3$) δ 4.61 (m, 1H), δ 3.86 (m, 2H), δ 3.35 (m, 2H), δ 1.79 (m, 4H), δ 1.39 (m, 3H), δ 1.24 (m, 13H), δ 0.89 (m, 3H).

2-(tert-Butyldimethylsiloxy)ethanol THP Ether (56). The crude oil, obtained as described by the representative procedure for photochemical introduction of THP (except for a 2 hr irradiation time required for full conversion), was further purified by flash column chromatography (7/1 petroleum ether/ethyl acetate) to give a yellow oil (80 mg, 0.31 mmol, 48%). An analytically pure sample was obtained by vacuum distillation over K$_2$CO$_3$ (head temperature of 82 °C (0.5 Torr)). $^1$H NMR (500 MHz, CDCl$_3$) δ 4.64 (m, 1H), 3.87 (m, 1H), 3.75 (m, 3H), 3.49 (m, 2H), 1.70 (m, 1H), 1.60 (m, 1H), 1.52 (m, 4H), 0.87 (s, 9 H), 0.08 (s, 6H). 13C NMR (75 MHz,CDCl$_3$) δ 98.9, 68.7, 62.7, 62.0, 30.6, 25.9, 19.4, 18.4, -5.22, -5.25. HRMS (ESI+) calcd for C$_{13}$H$_{28}$O$_3$SiNa$^+$ 283.1699, found 283.1691. Anal. Calcd for C$_{13}$H$_{28}$O$_3$Si: C, 59.95; H, 10.84. Found: C, 60.16; H, 10.98.
α-Terpineol THP Ether (58). The crude oil, obtained as described by the representative procedure for photochemical introduction of THP (except for a 2 hours irradiation time was required for 20% conversion). It should be noted that more irradiation time did not yield a higher conversion, as determined by GC analysis. The reaction mixture was further purified by flash column chromatography (7/1 petroleum ether/ethyl acetate, 1% TEA) to give a clear oil (12 mg, 0.05 mmol, 20%). $^1$H NMR (300 MHz, CDCl3) δ 5.38 (m, 1H), δ 4.77 (m, 1H), δ 3.95 (m, 1H), δ 3.42 (m, 1H), δ 1.84 (m, 5H), δ 1.64 (m, 9H), δ 1.27 (m, 1H), δ 1.16 (m, 7H).

2-(5-methylhex-4-enyloxy)tetrahydro-2H-pyran (60). The crude oil, obtained as described by the representative procedure for photochemical introduction of THP (except for a 45 min irradiation time was required for full conversion), was further purified by flash column chromatography (7/1 petroleum ether/ethyl acetate, 1% TEA) to give a clear oil (0.10 g, 0.34 mmol, 92%). $^1$H NMR (300 MHz, CDCl3) δ 5.15 (m, 1H), δ 4.60 (m, 1H), δ 3.90 (m, 1H), δ 3.75 (m, 1H), δ 3.52 (m, 1H), δ 3.36 (m, 1H), δ 2.05 (m, 2H), δ 1.72 (m, 14H).
methyl 4-(tetrahydro-2H-pyran-2-yloxy)benzoate (61). The crude oil, obtained as described by the representative procedure for photochemical introduction of THP (except for a 1 hr irradiation time was required for full conversion), was further purified by flash column chromatography (7/1 petroleum ether/ethyl acetate, 1% TEA) to give a clear oil (0.25 g, 1.1 mmol, 90%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.00 (d, 2H, $J = 8.95$ Hz), $\delta$ 8.00 (d, 2H, $J = 9.02$ Hz), $\delta$ 5.50 (t, 1H, $J = 3.01$ Hz), $\delta$ 3.88 (m, 4H), $\delta$ 3.04 (m, 1H), $\delta$ 2.01 (m, 3H), $\delta$ 1.59 (m, 3H).
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