STEREOCONTROLLED RHENIUM(VII) OXIDE-MEDIATED N-CONTAINING HETEROCYCLE FORMATION

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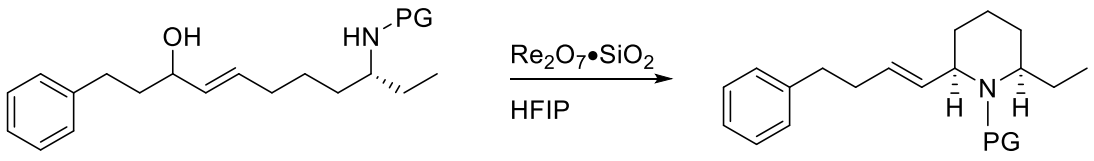
Piperidines are worthy synthetic targets because they are widely represented amongst pharmaceuticals and biologically active molecules in general. Rhenium(VII) oxide has been previously used by the Floreancig group for the ionization of allylic alcohols, followed by oxygen nucleophile attack to form tetrahydropyrans. This work further expands that methodology by utilizing protected nitrogen nucleophiles to form piperidines. Solvent studies determined that 1,1,1,3,3,3-hexafluoroisopropanol was the most suitable solvent for these reactions. An array of protecting groups were tested to determine viable protecting group conditions and in an attempt to develop orthogonal strategies for multiple functional group tolerance. Time course studies elucidated the mechanism of the reaction, and the role of product equilibration. Stereochemical assignments were complicated by the NMR peak distortion associated with the barrier to rotation in amides, which was a consequence of using protected nitrogen nucleophiles as starting materials. This problem was overcome by using an easily cleavable protecting group, assigning the stereochemistry of the deprotected piperidine, then reprotecting the molecule with a protecting group of interest to obtain reference spectra for comparison with piperidine products obtained by cyclization of starting materials with various protecting groups of interest installed. Several substrates were prepared, including an oxazinone which produced a bicyclic product.



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LIST OF ABBREVIATIONS

9-BBN	9-Borabicyclo[3.3.1]nonane
Alloc	Allyloxycarbonyl
Cbz	Carboxybenzyloxy
C-C	Carbon-Carbon
C-H	Carbon-Hydrogen
C-N	Carbon-Nitrogen
COSY	Correlation Spectroscopy
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
d.r.	Diastereomeric ratio
ESI	Electrospray ionization
Et	Ethyl
Fmoc	Fluorenylmethyloxycarbonyl
g	Gram
h	Hour(s)

HRMS	High resolution mass spectrometry
HFIP	1,1,1,3,3,3-Hexafluoroisopropanol
Hz	Hertz
IR	Infrared
J	Coupling constant
M	Molar
Me	Methyl
MeCN	Acetonitrile
mol	Mole
NCS	N-Chlorosuccinimide
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser enhancement spectroscopy
Nosyl	2-Nitrobenzenesulfonyl or 4-nitrobenzenesulfonyl
PG	Protecting group
Ph	Phenyl
rt	Room temperature
SiO_2	Silica gel
TBAF	Tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl

THF	Tetrahydrofuran
Tosyl	*p*-toluenesulfonyl

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I would first like to thank my advisor, Dr. Paul Floreancig, for accepting me into his group and giving me interesting research to conduct. His leadership has made me a better scientist, and helped me acquire the technical laboratory and problem solving skills necessary for a productive career as a chemist. I would like to thank my committee members, Dr. Islam and Dr. Wang, for their guidance in this process. I also would like to thank all the Floreancig group members, with whom I've shared lab space and ideas, for their assistance and comradery.

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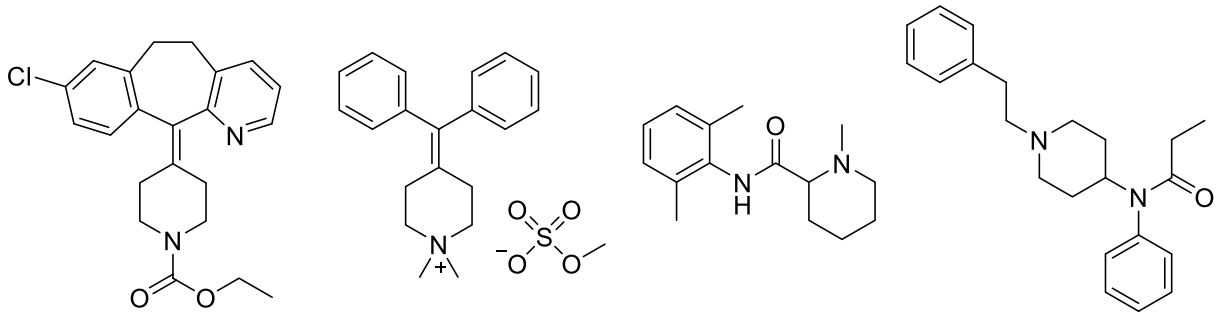
Additionally, I owe a great deal of thanks to my parents, for years of patience, and to my fiancée, Lauren, for tolerating me. Finally, I would like to thank my son, Jackson, the reason I felt I needed a graduate degree to begin with.

1.0 PIPERIDINES

Nitrogen-containing heterocycles are prominent motifs in biologically active and medicinally-relevant molecules.[1] 59% of unique small molecule drugs contain a nitrogen heterocycle. Moreover, among all FDA approved drugs, piperidines occur more frequently than any other nitrogen-containing heterocycle, often with substitutions variously at the 1, 2, and 4 positions of the ring. Piperidine structures are represented among antihistamines, antimuscarinic agents, antidepressants, local anesthetics, and analgesics.[2] Several examples are presented in Figure 1. Given the predominance of this motif in drug molecules, it is of great importance to develop new methods for their synthesis, especially methods that proceed in high yield with a great degree of stereocontrol.

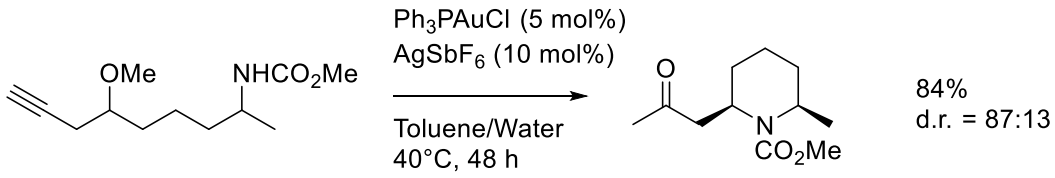


Loratadine Diphemanil methylsulfate Mepivacaine Fentanyl

Figure 1 Examples of Piperidine-Containing Pharmaceuticals

1.1 SYNTHESIS OF PIPERIDINES

1.1.1 Existing Methods for Piperidine Synthesis



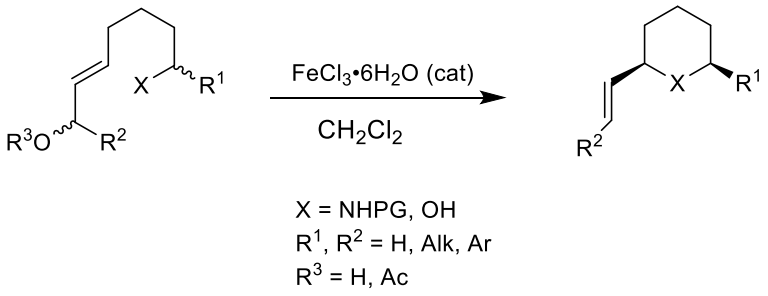
Scheme 1 Gold-Catalyzed Piperidine Formation From Homopropargyllic Ether

Diverse methods exist for the synthesis of piperidines.[3] Pyridine molecules can be reduced by catalytic hydrogenation[4] or sodium metal and ethanol[5] to yield the piperidine derivatives. Nucleophilic substitution is another common method for the construction of these heterocycles. Nitrogen nucleophiles have been used to intramolecularly displace halides[6] or activated alcohols such as triflates[7] and tosylates.[8,9] The Floreancig group previously reported a method whereby a gold catalyst in water-saturated toluene in the presence of silver promoted the conversion of homopropargylic ethers with pendent nitrogen nucleophiles into piperidines[10] (Scheme 1). This method tolerated sulfonamides and many carbamates.

1.1.2 Dehydrative Cyclization

Catalytic dehydrative cyclization reactions are an important method for the creation of heterocycles. These reactions proceed mainly through two possible mechanisms. Catalysis using soft electrophilic transition metals such as palladium[11,12], gold[13], and ruthenium[14] proceeds by a mechanism of the metal coordinating to the alkene in an allylic alcohol. This promotes the cyclization, and elimination of the elements of water. Hard Lewis acids such as BF_3•OEt_2[15], aryl boronic acids[16], $Bi(OTf)_3$[17], and hot water[18] react with an alcohol to form a stabilized carbocation. That carbocation can then be attacked by a nucleophile on the same molecule, forming a heterocycle. The soft electrophilic

transition metal catalysts enable kinetic control of the reaction through substrate control or ligand selection. The hard Lewis acid catalysts permit the products to equilibrate, thereby establishing thermodynamic control for the reaction.



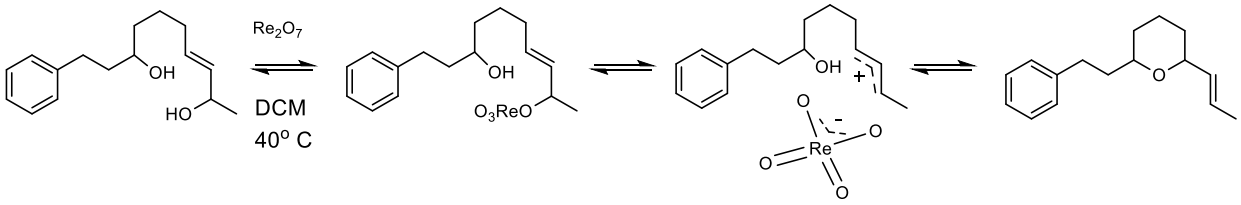
Scheme 2 Dehydrative Cyclization With Catalytic $FeCl_3$•$6H_2O$

The Cossy group reported the use of catalytic $FeCl_3$•$6H_2O$, a hard Lewis acid, to synthesize nitrogen and oxygen heterocycles from allylic alcohols quickly and at room temperature, with a high degree of diastereoselectivity (Scheme 2).[19] Regarding piperidine formation, the group found that their methodology worked best when the nitrogen was protected with a tosyl protecting group.

1.1.3 Rhenium Oxide-Mediated Dehydrative Cyclization

[1,3]-Transposition of allylic alcohols by transition metals is well-documented, and synthetically quite useful. This transformation was first reported by Chabardes in the late 1960's[20], and was initially developed and used by the fragrance industry. Efforts towards using [1,3]-allylic alcohol transposition as a synthetic method were traditionally hampered by a lack of control of regio- and stereoselectivity in the reaction. Our group has conducted several previous studies where Re_2O_7 was used to transpose an allylic alcohol, beginning with using this method to complete the ring-closing step in the synthesis of the leucascandrolide A macrolactone.[21] Regioselectivity issues were addressed by the use of substrates with appended electrophiles, which direct the reaction. Stereoselectivity was achieved by taking advantage of the tendency of these systems to equilibrate under thermodynamic control, thus leading to an excess of

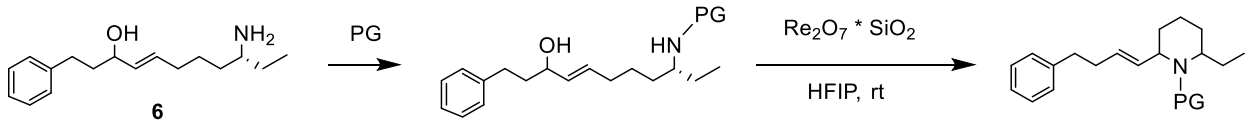
the more stable product. While pursuing this research, it was observed that allylic alcohols could also act as precursors to allylic cations in the presence of Re catalyst.[22] This observation led to the use of Re_2O_7 for dehydrative cyclization reactions.[23]



Scheme 3 Re_2O_7-Mediated Dehydrative Cyclizations, Previous Examples All Oxygen Nucleophiles

Previous studies from the Floreancig group explored the use of Re_2O_7 to promote oxygen-containing heterocycle formation in several ways.[22,24,25] In one reported method, Re_2O_7 immobilized on silica gel promotes the formation of allylic cations, which are then attacked by pendent oxygen nucleophiles to form tetrahydropyrans (Scheme 3).[23] These dehydrative cyclizations, in which an equivalent of water is eliminated during the cyclization step, are the focus of this work and are attractive for several reasons. They proceed under mild conditions, and water is the sole waste product. Deposition of the catalyst on silica gel is simple and allows for easy handling of even very small quantities of catalyst. Furthermore, the Re_2O_7 catalyst is easily removed by filtration at the reaction's completion. Finally, these reactions proceed in good yield and with good to excellent levels of stereocontrol. Whereas previous examples of this method utilized oxygen nucleophiles to form tetrahydropyrans and tetrahydrofurans, the object of the studies reported in this thesis was to use protected amines as nucleophiles for the development of analogous high yielding and stereocontrolled methods for the synthesis of piperidines. Nitrogen nucleophiles present unique challenges because although they are suitably nucleophilic, the amine functionality is quite basic, and therefore unprotected amines are

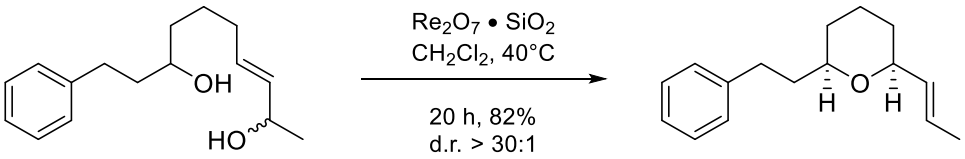
incompatible with rhenium oxide chemistry. The protecting group chemistry of amines is well-developed and numerous choices are available to modulate the reactivity of nitrogen-containing functional groups in organic synthesis.[26] We found that several N-carbamate and N-sulfonyl protected amino allylic alcohols readily cyclize to cis-2,6-substitued piperidines in the presence of a catalytic amount of Re_2O_7, as generalized in Scheme 4. Moreover these cyclization reactions proceed rapidly at room temperature with good to excellent levels of stereocontrol.



Scheme 4 Dehydrative Cyclization With Protected Amine Nucleophiles

2.0 PIPERIDINE CONSTRUCTION THROUGH DEHYDRATIVE CYCLIZATION

The Floreancig group has previously reported the use of Re_2O_7•SiO_2 to transpose allylic alcohols.[21,22,24,25] Recently, they reported the use of this methodology to ionize an allylic alcohol and then attack the resulting allylic cation with a pendant oxygen nucleophile, forming a tetrahydropyran (Scheme 5).[23] These reactions proceed in good yield and with a high degree of diastereoselectivity. Several examples were presented, and the methodology was used to construct the tetrahydropyran subunit of the natural product herboxidiene. It was a natural progression to proceed to using nitrogen nucleophiles with this methodology to produce piperidines.



Scheme 5 Previous Work By Floreancig Group Using Oxygen Nucleophiles

2.1 INITIAL WORK

2.1.1 Ellman's Chiral Auxiliary

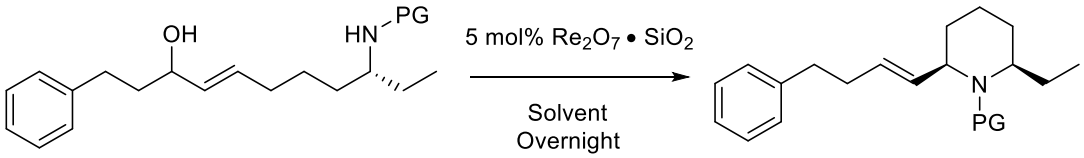
In order to install an ethyl group with absolute stereocontrol at what would become the 6-position of the piperidine product, a diastereoselective Grignard reaction with a chiral sulfinyl imide auxiliary was utilized. The Ellman group has amply explored this chemistry, which uses a *tert*-butylsulfinylimine as a single enantiomer to direct the Grignard reagent to add from only one side of the aldimine. Initially, we hoped that the resulting sulfonamide could serve as a protecting group for the nitrogen, permitting the Re_2O_7-mediated cyclization to proceed. Unfortunately, after several experiments with varying solvent and temperature, it became apparent that the sulfonamide-protected amine was

unsuitable for the cyclization reaction. We attributed this to a strong electron withdrawing effect from the sulfonamide, which dampened the nucleophilicity of the nitrogen, or possibly interference from the lone pair on the sulfur. The auxiliary was, however, easily cleaved with HCl in dioxane, allowing for reprotection with various suitable protecting groups.

2.1.2 Solvent Screen

Nitrogen nucleophiles present several distinct challenges compared to their oxygen counterparts. Amines are much more basic than alcohols, which we presumed would be a problem, as rhenium oxide is a Lewis acid. This problem could easily be overcome by using protecting group chemistry to modify the amine basicity, but in turn this lowered the nucleophilicity of the group. The lowered nucleophilicity meant that dichloromethane was no longer a viable solvent choice. Dichloromethane was not polar enough to sufficiently stabilize the allylic cation and provide opportunity for attack from the weaker nucleophile. Therefore, the first challenge was to find a suitable solvent for this reaction. Table 1 presents a collection of solvent that was screened to improve reactivity.

Table 1 Exploration Of Solvent Conditions

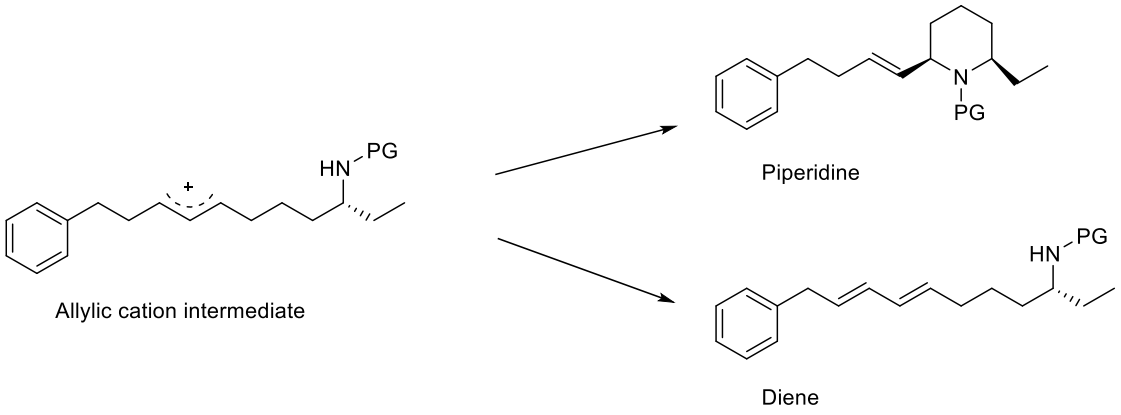


Entry	Protecting Group	Solvent	Temperature	% Yield
1	Cbz	DCM	rt	47
2	Cbz	DCM	40	27
3	Cbz	MeCN	rt	46
4	*t*-Butylsulfinamide	DCE	80	TO*
5	Cbz	HFIP	rt	63
6	Methyl carbamate	HFIP	rt	65
7	Methyl carbamate	Isopropanol	rt	TO

rt = room temperature TO = Transposed only, no cyclization
* Transposed and dehydrated
All reactions were purified by filtering through silica and removal of solvent

Dichloromethane was the first solvent tested, because it worked well during previous work by our group making tetrahydropyrans in this manner. However, for reactions with a nitrogen nucleophile, dichloromethane did not give satisfactory yields. While some desired product was formed, a significant amount of material instead simply dehydrated to the undesired diene product (Scheme 6). This result is consistent with the formation of an allylic cation, which can cyclize if attacked by a suitable nucleophile, but could also undergo competitive elimination to form the diene. These poorer nucleophiles are unable to attack the allylic carbocation strongly enough to outcompete the elimination reaction when dichloromethane is the solvent. This was observed even more markedly as temperature increased, with higher temperature resulting in less desired piperidine product and more diene. Additionally, the

cyclization product did not form with a high degree of stereoselectivity, with a diastereomeric ratio typically of 1:2. Changing the solvent to dichloroethane and further heating the reaction resulted in no desired product being formed. Acetonitrile failed to show any improvement as well. Happily, using 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as the solvent improved yield. The last 2 entries in Table 1 demonstrate that while HFIP is a suitable solvent for this methodology, using isopropanol did not promote the desired transformation. This observation is consistent with the idea that a more stable allylic cation should enhance the ability of the nucleophile to attack, delaying the alternative collapse to the undesirable diene product. Isopropanol fails as a solvent for this system because the non-fluorinated alcohol is nucleophilic enough to attack the cation as it forms, and does so faster than the cyclization reaction can occur, forming the isopropyl ether.



Scheme 6 Competing Pathways From Allylic Cation

2.1.3 HFIP as an Ideal Solvent

1,1,1,3,3,3-Hexafluoroisopropanol (HFIP) is the perfluorinated analog of isopropanol. Whereas isopropanol is a typical alcohol solvent, HFIP exhibits some strong solvent characteristics which are absent in the parent alcohol and unique to fluorinated alcohols. The trifluoromethyl groups create a

strong electron withdrawing effect, which is chiefly responsible for the unique properties of HFIP[27] (Figure 2). This withdrawal of electrons increases the acidity of the hydroxy functionality, with a pKa of 9.3[28], a substantial increase in acidity from isopropanol's pka of 17.1. A further consequence of the strong electron withdrawal is that HFIP is extremely polar. Out of 360 solvents tested, HFIP was the most polar.[29,30] HFIP is also a very strong hydrogen bond donor, and a very weak hydrogen bond acceptor.[31] Importantly, HFIP is not nucleophilic, which is vital in a system where a cation is formed. For example, isopropanol fails as a solvent for the dehydrative cyclization reaction (Table 1) because it simply adds to the cation, forming the allylic isopropyl ether. These properties allow HFIP to stabilize the allylic cation formed by Re_2O_7, giving the weakly nucleophilic protected nitrogen more opportunity to attack and form the desired piperidine product.

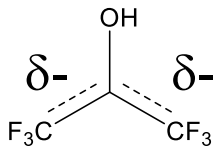


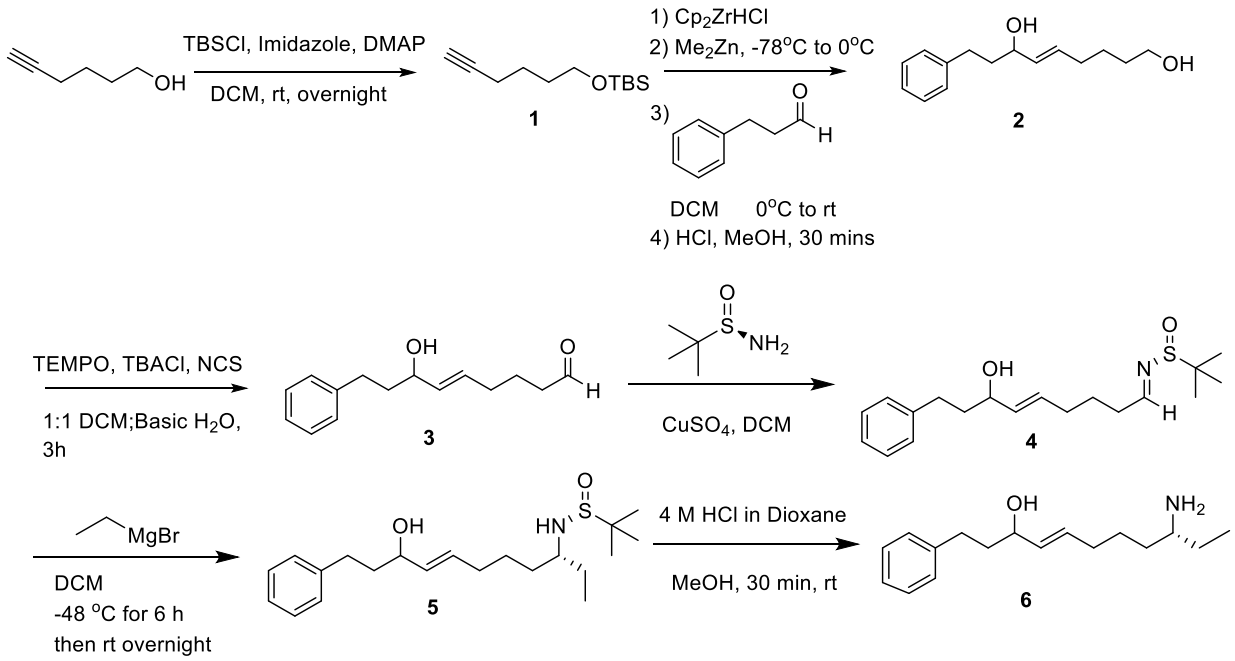
Figure 2 Unique Properties of HFIP Are Due To Strong Inductive Effect

2.2 SYNTHESIS OF SUBSTRATES

2.2.1 Synthesis of Molecule 6

The first substrate, molecule **6**, was synthesized starting from hex-5-yn-1-ol. The alcohol was protected with the TBS-group by reaction with TBSCl in the presence of imidazole and DMAP. The Schwartz reagent was used to complete a hydrozirconation, then transmetallation to zinc using dimethyl zinc, followed by addition to hydrocinnamaldehyde[32] and treatment with HCL in methanol to yield molecule **2**. A TEMPO oxidation with *N*-chlorosuccinimide as the stochiometric oxidant [33] selectively oxidized only the primary alcohol to yield molecule **3**. Reaction with Ellman's chiral auxiliary followed

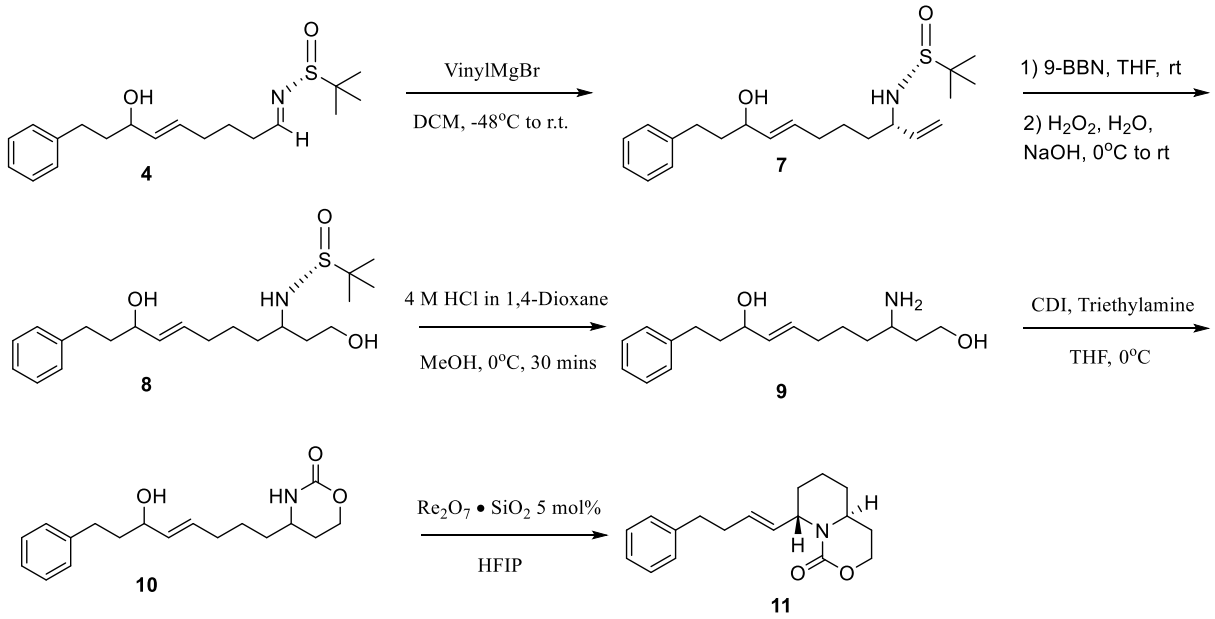
by Grignard addition into the imine and removal of the auxiliary[34] finally yielded molecule **6**. Molecule **6** was protected with various protecting groups and used for initial studies on solvent and the suitability of different protecting groups in this system.



Scheme 7 Synthesis of Molecule 6 From Hex-5-yn-1-ol

2.2.2 Synthesis of Molecule 10

The same synthetic route was followed for molecule **10**, starting from hex-5-yn-1-ol and proceeding as above until the point of the Grignard addition into the chiral *tert*-butanesulfinyl amide. Addition of vinyl magnesium bromide provided a handle for further functionalization. 9-BBN hydroboration/oxidation of the newly installed alkene[35] led to molecule **8**, and the chiral auxiliary was removed as above. The deprotected amino-monoallylic diol **9** was then treated with *N*,*N*,-carbonyldiimidazole in order to form a cyclic carbamate.[36] This nitrogen of the cyclic carbamate was expected to act as the nucleophile for this substrate in the Re_2O_7-catalyzed allylic alcohol transposition-cyclization sequence.



Scheme 8 Synthesis Of Molecule 10

2.3 CYCLIZATION OF MOLECULE 10 TO MOLECULE 11

Exposure of molecule **10** to the typical cyclization conditions produced an interesting result. While in all other cases with HFIP as the solvent these conditions preferentially produced the 2,6-*cis* piperidine, the piperidine ring in molecule **11** exhibited 2,6-*trans* stereochemistry. We theorized that this result was due to the necessary geometry of the molecule during the transition state of the cyclization reaction (Figure 3). In order for the lone pair of electrons on the nitrogen to attack the allylic cation, the cyclic carbamate must assume the axial position. This geometry permits the nitrogen to be in position to form the new bond which makes the piperidine. If the side chain on carbon 2 were to assume equatorial geometry, as one might expect, the lone pair of electrons on the nitrogen is unable to successfully interact with the allylic cation and form this bond. The alkene side chain on carbon 6 maintains the equatorial position because that minimizes steric interactions between the side chain and the protons of the ring, as

would be expected in a typical six-membered ring. Therefore, the resulting piperidine product molecule **11** has 2,6-*trans* stereochemistry.

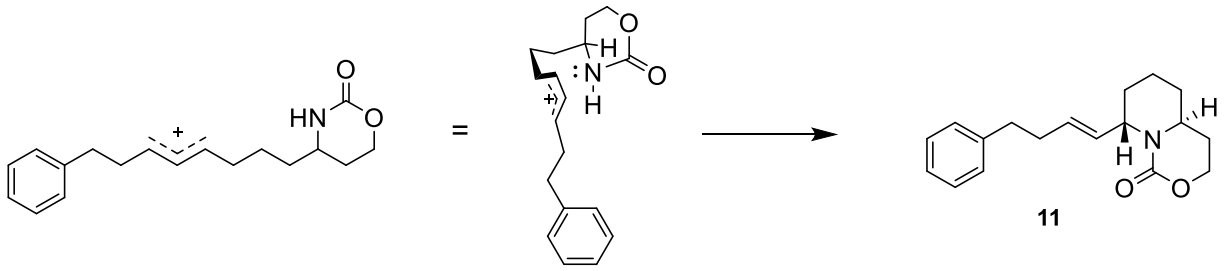
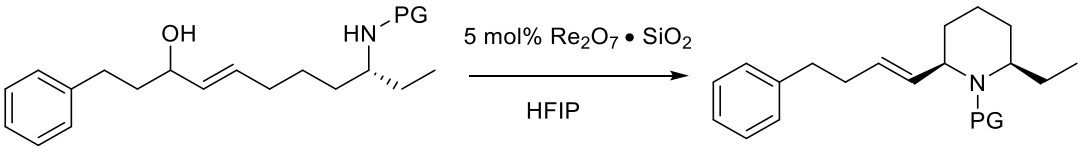


Figure 3 Basis of the Observed Stereochemistry of Molecule 11

2.4 SCOPE OF PROTECTING GROUPS

A variety of protecting groups were explored (Table 2). As mentioned above, the sulfonamide derived from Ellman's chiral auxiliary was ineffective. TLC showed that the allylic alcohol transposed under these conditions, but there was no cyclization. Heating the reaction still produced no cyclization, but did induce dehydration to the diene. The next protecting group to be explored was Cbz. We were pleased to find that when the amine was protected with a Cbz group, the desired cyclization proceeded in 63% yield. The Tosyl protecting group worked, although at reduced yield. Substrates bearing the 2-, and 4-nosyl protecting groups both did not work, presumably because the electron withdrawing effect of the nitro group further reduced the nucleophilicity of the nitrogen compared to the N-tosyl derivative, rendering the nitrogen unable to trap the cation. Alloc and acetamide protection still allowed the reaction to proceed, but at greatly reduced yields. Methyl carbamate protection of the nitrogen gave results comparable to Cbz protection. Fmoc proved to be the best choice for this system, with a yield of 83%. Importantly, entry 7 is in line with our initial hypothesis that unprotected nitrogen atoms are incompatible with the rhenium catalyst due to the formation of a Lewis acid-Lewis base complex.

Table 2 Exploration of Protecting Groups



Entry	Protecting Group	Temperature	Yield
1	*t*-Butylsulfinamide	rt	0%
2	*t*-Butylsulfinamide	55°C	0%
3	Cbz	rt	63%
4	Tosyl	rt	33%
5	2-Nosyl	rt	0%
6	4-Nosyl	rt	0%
7	None	rt	0%
8	Alloc	rt	40%
9	Acetamide	rt	14%
10	Methyl carbamate	rt	65%
11	Fmoc	rt	83%

2.5 STEREOCHEMICAL OUTCOMES

2.5.1 Consequences Of Amide Barrier To Rotation In ^{1}H NMR

Assigning stereochemistry to the protected piperidine was complicated by the amide barrier to rotation, which causes signal broadening on ^{1}H NMR. The lone pair of electrons on the nitrogen of the amide delocalizes into the C-N bond, which means that there is a partial double bond between the two atoms. These delocalized electrons are responsible for the high barrier to internal rotation in a carbamate, generally ca. 21 kcal/mol. [37] Since this stronger bond hinders rotation, the two substituents on the amide nitrogen are fixed into either of two conformations whose interconversion is a slow process. In the case

of piperidine rings, where the substituents on the nitrogen are in fixed positions because of incorporation in the ring, it is the carbamate group which can potentially rotate (Figure 4). With regard to the protected piperidine products described in this work, the carbonyl group is on one side of the ring or the other, with rotation about the carbamate C-N bond hindered by the partial double bond character of the bond. The carbonyl oxygen therefore has a defined stereochemical relationship to the protons on carbons 2 and 6 of the piperidine ring, but this relationship is fluid, as there is still limited rotation about the C-N bond. A consequence of this high barrier to rotation is that on a ^{1}H NMR spectrum of an N-protected piperidine, the protons on carbons 2 and 6 of the piperidine do not split as normally expected, making splitting pattern analysis and coupling constant determination impossible. The averaging of the signals generated by the protons on carbons 2 and 6 instead produce broad singlets with chemical shifts in the expected ranges, but no observable splitting. Since coupling constant analysis would typically be used to determine stereochemistry, this presents a challenge.

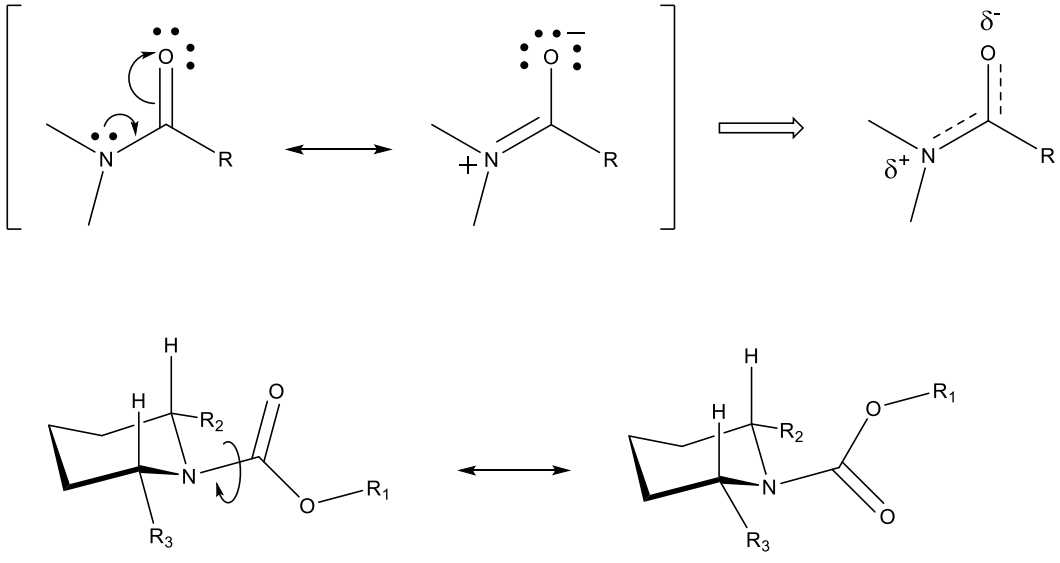
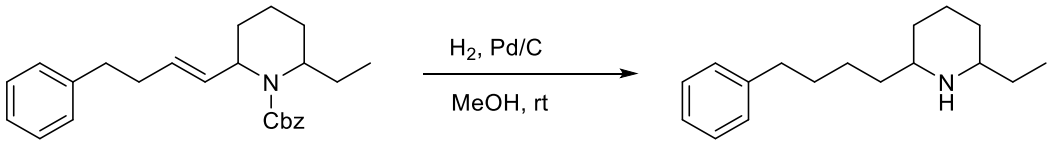


Figure 4 Amide Barrier to Rotation and Consequences in Carbamate-Protected Piperidines

Furthermore, this signal distortion prevents the use of 2-D NOESY spectroscopy to determine the stereochemical relationship between the substituents at the 2 and 6 positions. Typically, the presence of a through-space correlation is easily determined by 2-D NOESY. If the protons at carbons 2 and 6 of a 2,6-substituted piperidine have a *cis* relationship, there should be a strong interaction between them on the 2-D NOESY spectrograph. If these protons have a *trans* relationship, that should be identifiable by an interaction between the proton on carbon 2 and the protons on the side chain of carbon 6, as well as an interaction between the proton on carbon 6 and the protons of the substituent on carbon 2. In the case of piperidines made from protected molecule **6**, this would mean the proton on carbon 2 would show a through-space correlation with the alkenyl protons from the substituent on carbon 6, and the proton on carbon 6 would show a through-space interaction with the ethyl group on carbon 2 (Figure 5, below). None of these interactions, whether to confirm *cis* or *trans* stereochemistry, was observed. An alternative strategy had to be developed.

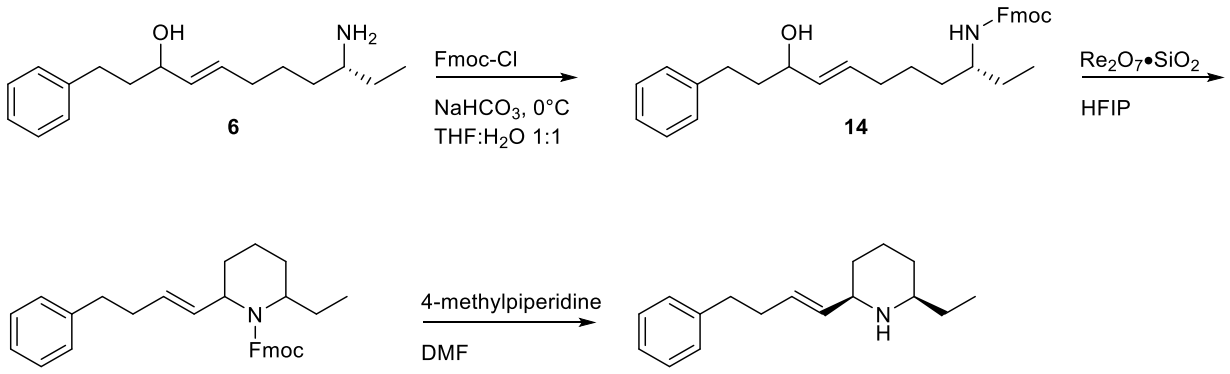
2.5.2 Strategy For Assigning Stereochemistry

In order to determine the stereochemistry of the products of these Re_2O_7-mediated cyclizations, the protecting groups had to be removed from the nitrogen. The first attempt was made with a Cbz-protected piperidine. After cyclization, the *N*-protected piperidine product was subjected to hydrogenolysis by palladium on carbon in an atmosphere of hydrogen gas. While this did remove the Cbz group, it also reduced the double bond in the side chain branching from piperidine carbon 6 (Scheme 9). The loss of this alkene made distinguishing between the protons at carbons 2 and 6 impossible, even by Correlation Spectroscopy (COSY). Since the two sidechains could not be differentiated in the ^1H NMR spectrum, it was still impossible to determine their stereochemical relationship.



Scheme 9 Removal Of Cbz Protecting Group By Hydrogenolysis And Resulting Loss Of Alkene

The solution to this problem was to use the 9-fluorenylmethyloxy (Fmoc) protecting group. Fmoc protection is achieved easily in minutes under Schotten-Baumann[38] conditions. The Fmoc protecting group proved to be amenable to the Re_2O_7 cyclization, and was then easily removed by treatment with 4-methylpiperidine in DMF (Scheme 10). The resulting product could then be analyzed by ^1H NMR, COSY, and NOESY, and the stereochemistry of the protons on the carbons at positions 2 and 6 assigned. Reprotection of this piperidine product with various protecting groups allowed for comparison to the products of cyclizations performed with Cbz and Tosyl N-protections. In all cases where HFIP was the solvent, the 2,6-*cis* piperidine was the major product.



Scheme 10 Fmoc Protection, Cyclization, Deprotection

Stereochemical assignment of the protons on carbons 2 and 6 in the deprotected piperidine product was made by 2-D NOESY (Figure 5). The key interactions which we hoped the 2-D NOESY would provide were either a correlation between the protons on carbons 2 and 6, or a correlation between each of those protons and the protons of the substituent on the opposite carbon (Figure 6). For example,

if the proton on carbon 2 showed an interaction through space with the alkenyl protons from the substituent on carbon 6, that would indicate a *trans* relationship between the protons of carbons 2 and 6. There was a strong correlation between the signal at 2.58 ppm, and the signal at 3.19 ppm. The signal at 2.58 ppm represents the proton on carbon 2, and the one at 3.19 ppm represents the proton on carbon 6. Since they have a through-space correlation by 2-D NOESY, they are near one another in space, and thus they must have a *cis* relationship. Additionally, no interaction was observed between either of the protons on carbons 2 and 6 and the alkyl substituent on the opposite carbon, as would be expected in the case of a *trans* relationship between those alkyl substituents. While the absence of these crosspeaks can not be taken as absolute proof of the *cis* stereochemistry on its own, it does serve to further corroborate other evidence that the stereochemistry is *cis*, as described above.

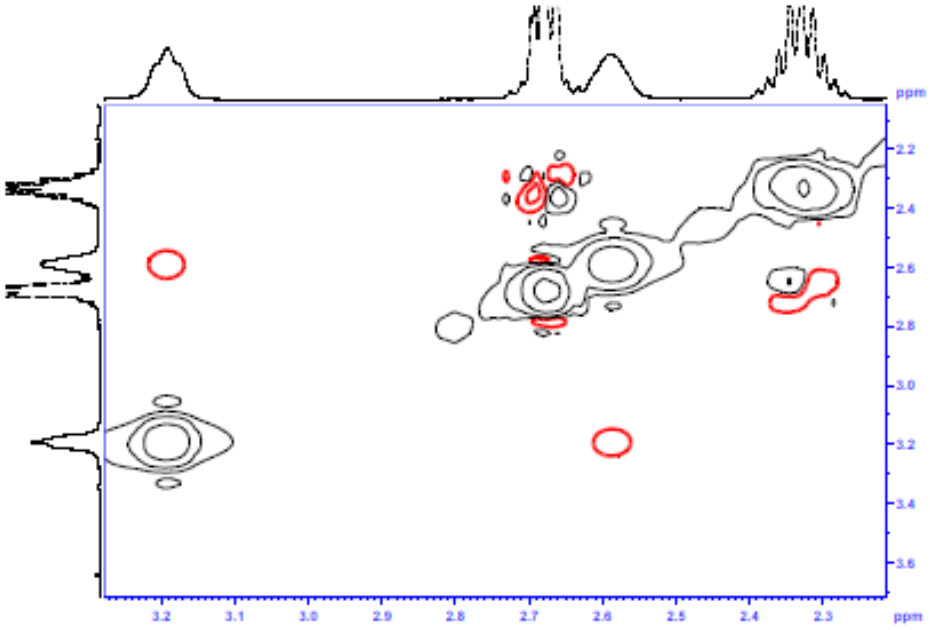
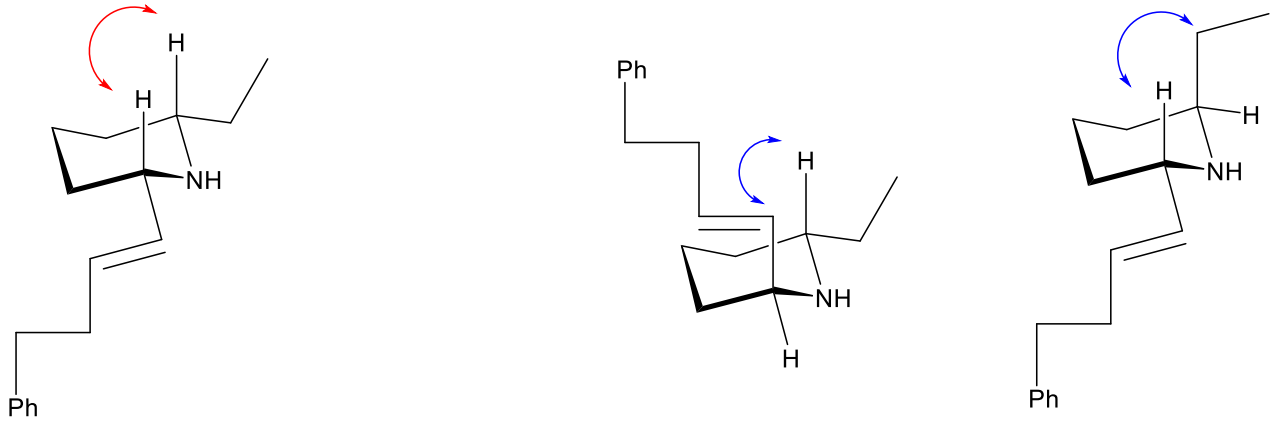


Figure 5 2-D NOESY of Deprotected Piperidine

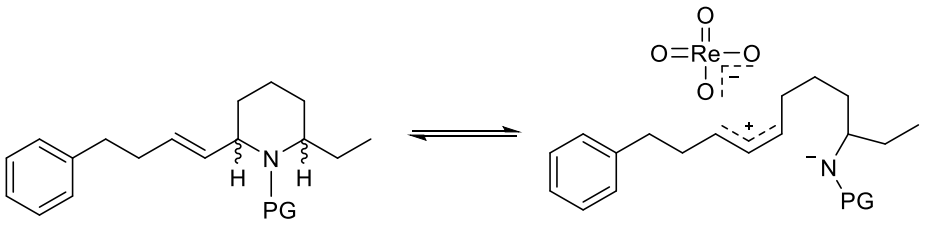


2,6-*cis* 2,6-*trans*

Figure 6 Anticipated NOESY Interactions to Establish Stereochemistry

The Floreancig group previously demonstrated Re_2O_7-mediated cyclization reactions to form tetrahydropyrans, and noted that these molecules equilibrated to yield the more thermodynamically stable product over time.[23] The formation of the piperidines described in this work was expected to proceed similarly, and indeed did so. Since the 2,6-*cis* piperidine was the major product, as determined above by 2-D NOESY spectroscopy, we assumed this to be the thermodynamically more stable of the two diastereomers. Resubjection studies, solvent studies, and kinetic experiments provide proof of this equilibration.

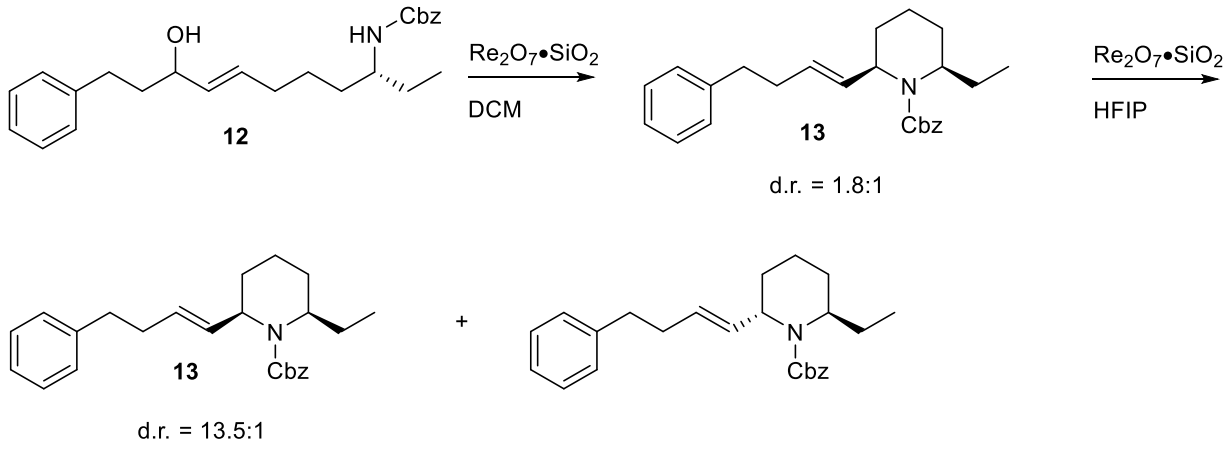
As mentioned previously, HFIP is an extremely polar solvent. Since the key transition state in this method involves an allylic cation, it is reasonable to propose that the highly polar nature of HFIP stabilizes this transition state. With the cation thus stabilized, the piperidine product can more readily reopen and then close to the ring again. Over time, this opening and closing will lead to an excess of the more thermodynamically stable product, as the more stable product is less likely to reopen once formed.



Scheme 11 Equilibration

2.5.3 Resubjection Study

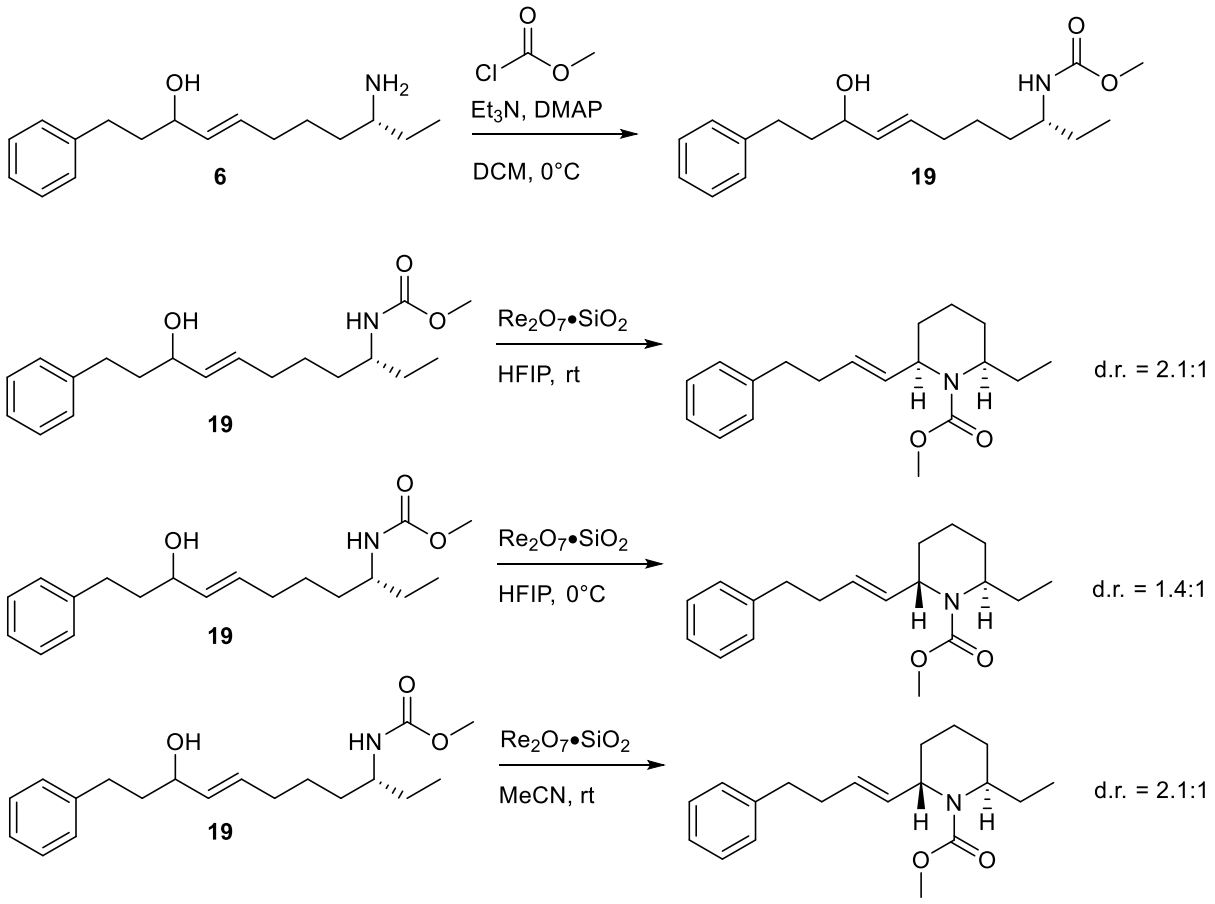
Resubjection studies confirm that the 2,6-*cis* product is the thermodynamic product, and that the system equilibrates under thermodynamic control. Essentially, these studies consisted of performing the Re_2O_7-mediated cyclization reaction in methylene chloride and recording the diastereomeric ratio in the product by ^1H NMR. The product was then treated with Re_2O_7 again, this time in HFIP, and the change in diastereomeric ratio calculated (Scheme 12). The cyclization reaction performed in methylene chloride yielded a mixture of diastereomers in which the *cis* isomer predominated, but only by a factor of 1.8:1. When this mixture of diastereomers was exposed to Re_2O_7 on silica gel a second time, using HFIP as the solvent, the ratio of *cis* to *trans* diastereomers increased to 13.5:1. Since the proportion of the product with 2,6-*cis* configuration increased substantially, this is the thermodynamic product, and the system clearly equilibrates.



Scheme 12 Resubjection Study

2.5.4 Time Course Experiments

To further validate these assertions, a study on the time course of this reaction was also performed. Molecule **6** was N-protected by forming the methyl carbamate, using methyl chloroformate, triethylamine, and DMAP[39] to yield molecule **19**. Molecule **19** was then used to assess the reaction's time course. The initial experiment was to perform the Re_2O_7-mediated cyclization under typical conditions, removing samples every 2.5 minutes, filtering through silica to stop the reaction, and monitoring the reaction's progress by ^1H NMR. To our surprise, the reaction was complete after only the initial 2.5 minutes. However, the diastereomeric ratio at 2.5 minutes was 2.1:1, in favor of the thermodynamic 2,6-*cis* product. In order to further confirm that the 2,6-*cis* product was the thermodynamic product, and to prove equilibration, the Re_2O_7-mediated cyclization was performed again on molecule **19**, but at 0 °C in an ice bath. Gratifyingly, the diastereomeric ratio after 2.5 minutes at 0 °C was 1.4:1 in favor of the 2,6-*trans* product. As a further proof of thermodynamic control, and a further exploration of the role of HFIP, molecule **19** was also subjected to Re_2O_7•SiO_2 at room temperature in acetonitrile. The diastereomeric ratio after 4 hours was 2.1:1 in favor of the 2,6-*trans* product (Scheme 13). Taken together, these results strongly indicate that the products of Re_2O_7-mediated cyclization of protected amines to piperidines equilibrate under thermodynamic control, and that the 2,6-*cis* product is the more thermodynamically stable product. These conclusions agree with expectations based on previous work with Re_2O_7 to form tetrahydropyrans.



Scheme 13 Time Course Experiments

2.5.5 Effects of Solvent on Stereochemistry

To further explore the role that HFIP plays in stabilizing the allylic carbocation, a series of experiments were performed using less optimal solvents that we had explored earlier. These solvents were less polar than HFIP to varying degrees. The effects of solvent polarity on the diastereomeric ratio of the reaction products could thus be determined. Additionally, we hoped to find solvent conditions which would permit the selective formation of the *trans*-2,6-piperidine, as a complementary method to *cis*-2,6-piperidine formation in HFIP. Ultimately, this proved impossible, as non-HFIP solvents resulted in very poor yields for the cyclization reaction, with dehydration to the diene outcompeting the

cyclization. A comparison of the solvent effects did, however, further elucidate the need for polar solvent in this system. A more polar solvent should enable the intermediate allylic cation to survive for longer, thus promoting formation of an excess of the thermodynamic 2,6-*cis* product. As Figure 5 demonstrates, that was the observed solvent effect. With HFIP as the solvent, the 2,6-*cis* piperidine predominated by a ratio of 21:1, but this ratio decreased to 1:1 in acetonitrile. When the solvent was dichloromethane, the 2,6-*trans* product was the predominant diastereomer by a ratio of 2:1. This solvent effect conformed to our expectations. Unfortunately, use of even less polar solvents caused the reaction to fail completely, making it impossible to develop a complimentary methodology with which to produce the 2,6-*trans* product in a synthetically useful excess.

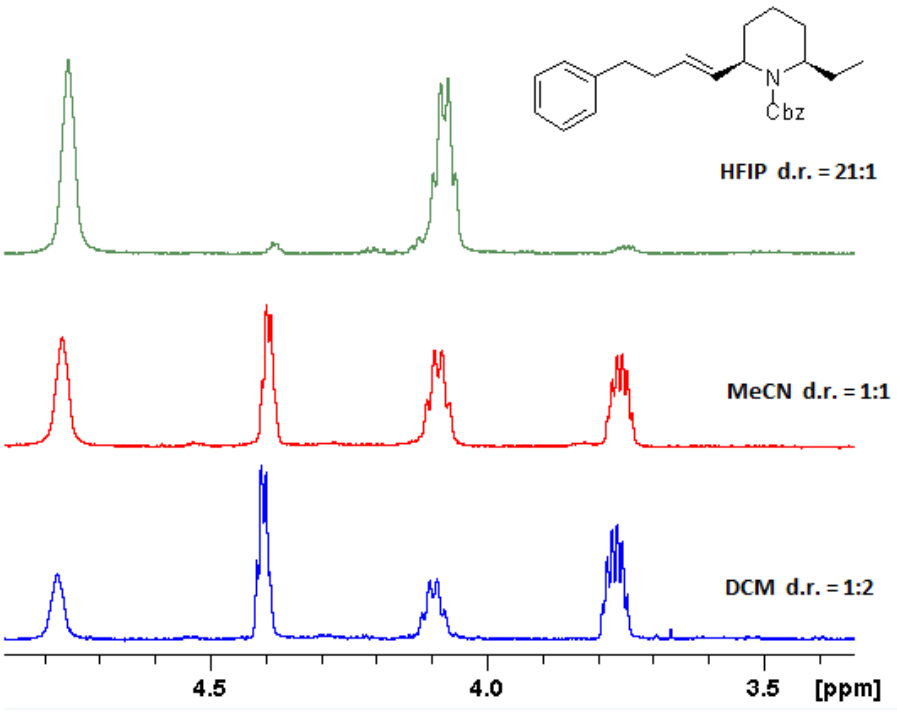


Figure 7 Comparison of Stereochemical Outcomes in Different Solvents

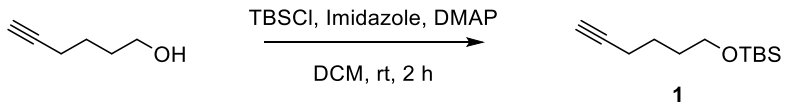
2.6 CONCLUSIONS

Herein, we have reported a method of using Re_2O_7 supported on silica gel to ionize an allylic alcohol, forming an allylic cation. This allylic cation is then attacked by a pendant protected nitrogen nucleophile, forming a piperidine. This method allows for the construction of N-heterocycles from open chain molecules quickly and with ease. Furthermore, use of the Fmoc protecting group results in high yields, and a high degree of diastereocontrol in the product. Studies on solvent suitability, protecting group suitability, and a limited substrate scope were described. A method of determining the diastereomeric ratios of the products was described, and an explanation given for why ^{1}H NMR of the protected piperidines was so difficult. We also discussed the results of studies that led to the conclusion that the system equilibrates under thermodynamic control. This method has the potential to be synthetically useful in the construction of complex molecules.

A good direction to proceed with this research would be to further explore the scope of potential substrates. Substitutions at various positions around the ring other than the 2 and 6 carbons of the piperidines could be explored. It might also be worthwhile to determine whether HFIP must be the sole solvent, or whether the system could still function well with HFIP as an additive in a more traditional organic solvent. Ultimately, this methodology could be showcased as the key step to form the piperidine subunit of a natural product.

APPENDIX A SUPPORTING INFORMATION

General Experimental: Proton (^{1}HNMR) and carbon (^{13}CNMR) nuclear magnetic resonance spectra were recorded on Bruker Avance 300 spectrometer at 300 MHz and 75 MHz, Bruker Avance 400 spectrometer at 400 MHz and 100 MHz, and Bruker Avance 500 spectrometer at 500 MHz and 125 MHz. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak was used as a reference value, for ^{1}H NMR: $CDCl_3$ = 7.26 ppm, for ^{13}C NMR: $CDCl_3$ = 77.2 ppm. Data are reported as follows: (m = multiplet; s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; ddd = doublet of doublet of doublets; dt = doublet of triplets; br = broad; app = apparently). High resolution mass spectra were recorded on either a Q-Exactive, Thermo Scientific or Q-Tof Ultima API, Micromass UK limited spectrometer. Infrared (IR) spectra were collected on a Perkin Elmer Spectrum Two FT-IR spectrometer. Analytical TLC was performed on E. Merck pre-coated (25 mm) silica gel 60 F_{254} plates. Visualization was done under UV (254 nm) or by staining (135 mL absolute ethanol, 5 mL concentrated sulfuric acid, 1.5 mL glacial acetic acid, 3.7 mL *p*-anisaldehyde or 1.5 g ninhydrin, 100 mL absolute ethanol, 3.0 mL glacial acetic acid). Flash chromatography was done using SiliCycle SiliaFlash P60 40-63 μm 60 Å silica gel. Hexafluoroisopropanol was purchased from Oakwood Chemicals and used directly. Reagent grade ethyl acetate, diethyl ether, acetone, dichloromethane, methanol, pentane, and hexanes (commercial mixture) were purchased from Fisher Scientific and were used as-is for chromatography. Dichloromethane was distilled under N_2 from CaH_2. Diethyl ether and tetrahydrofuran were distilled under N_2 from sodium/benzophenone ketyl. All reactions were performed in oven or flame-dried glassware under positive pressure of inert gas (Ar or N_2) with magnetic stirring unless otherwise noted.

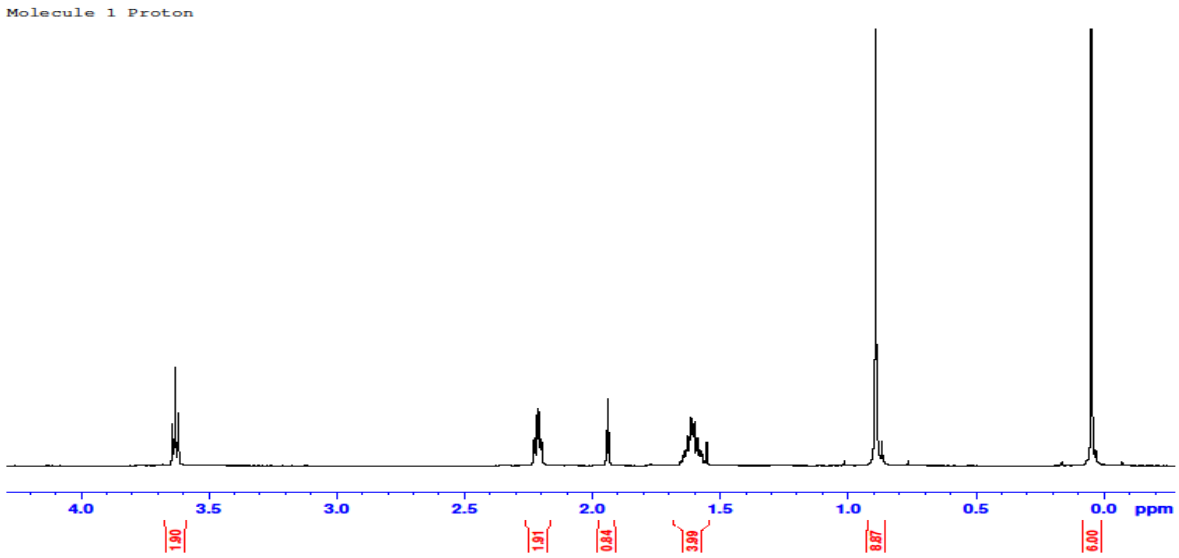


1

***Tert*-butyl(hex-5-yn-1-yloxy)dimethylsilane (Molecule 1)**

To a flame-dried flask with a stir bar was added 5-hexyn-1-ol (2.50 mL, 22.7 mmol), *tert*-butyldimethylsilyl chloride (1.2 eq, 4.100 g, 27.2 mmol), imidazole (2 eq, 3.087 g, 45.3 mmol), dimethylamino pyridine (0.05 eq, 0.139 mg, 1.1 mmol), and anhydrous dichloromethane (75.0 mL, 0.3 M). At 2 hours, TLC indicated reaction completion. The reaction was quenched with 30 mL H_2O, the aqueous and organic layers were separated, and the aqueous was extracted with 3 30 mL portions of EtOAc. The combined organic portions were washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The crude residue was purified by column chromatography on silica gel (10% EtOAc in hexanes) to afford a golden oil. 4.703 g, 97.6%.

^{1}H NMR (500 MHz $CDCl_3$): δ 3.63 (t, *J* = 6 Hz, 2H), 2.21 (td, *J* = 6.8, 2.6 Hz, 2H), 1.94 (t, *J* = 2.7 Hz, 1H), 1.55-1.65 (m, 4H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz $CDCl_3$): δ 84.7, 68.4, 62.7, 32.0, 26.1, 25.1, 18.5, 18.4, -5.2; HRMS (ESI+) *m/z* calcd for $C_{12}H_{25}OSi$ $[M+H]^+$ 213.1669, found 213.1668.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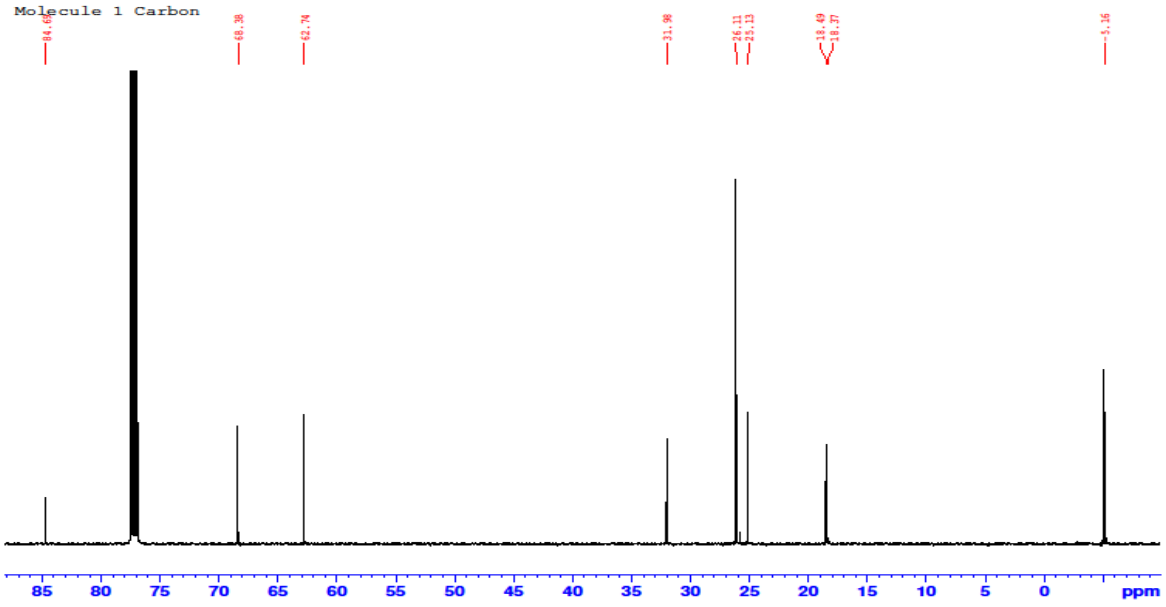
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.90
1.91
0.84
3.99
8.87
6.00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62.74
31.98
26.11
25.13
18.49
18.37
-5.16
85
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50
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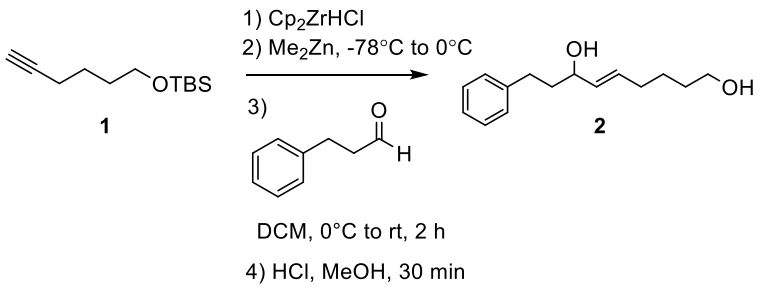
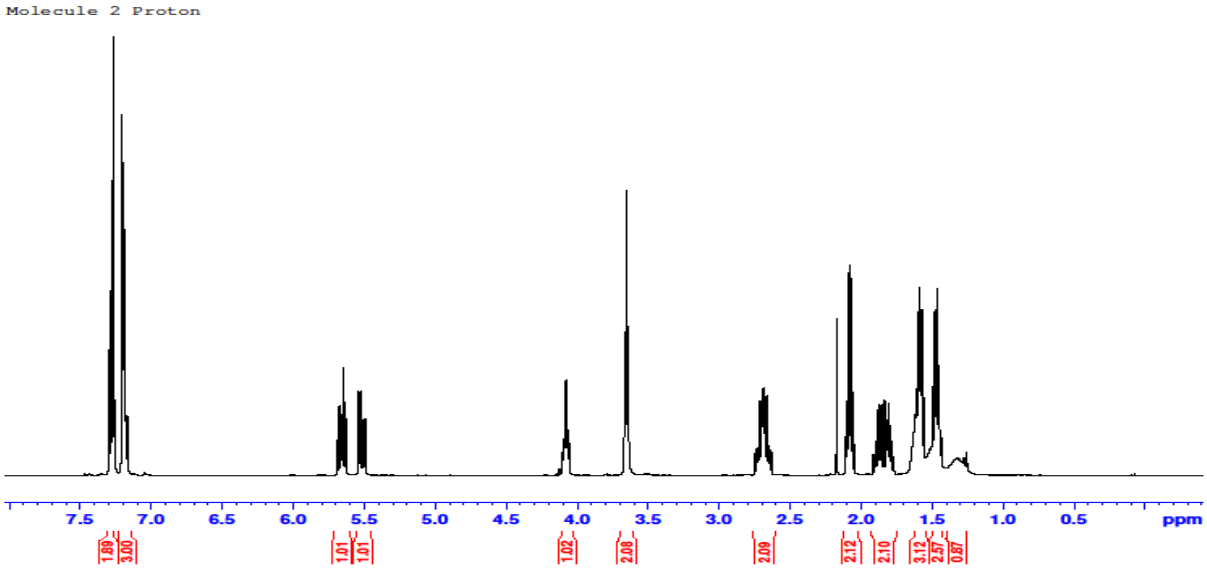
35
30
25
20
15
10
5
0
ppm

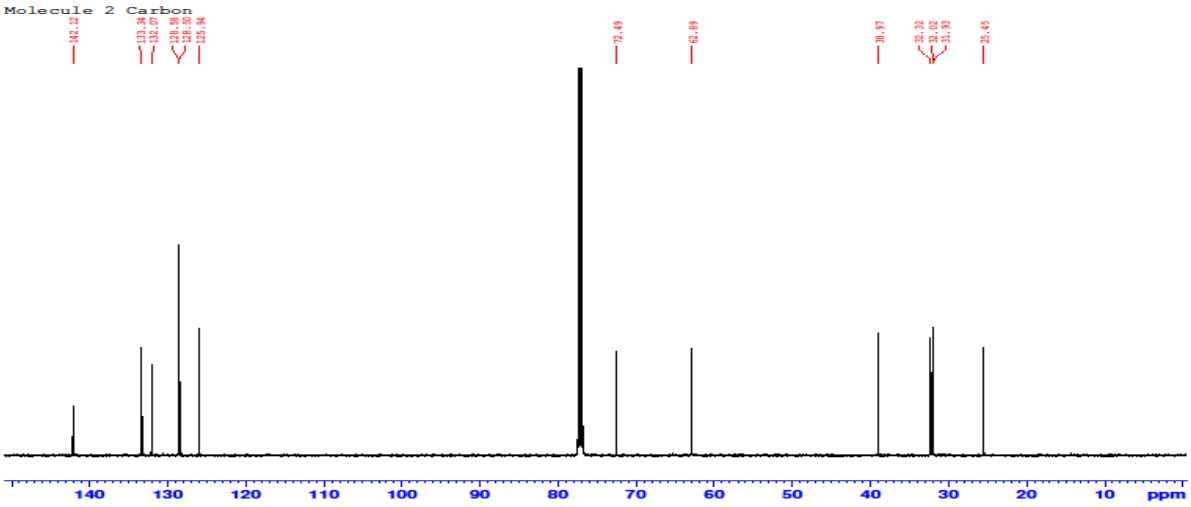


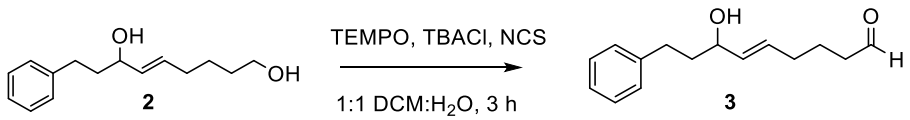
(E)-9-phenylnon-5-ene-1,7-diol (Molecule 2)

To a flame-dried flask with a stir bar was added zirconocene chloride hydride (1.1 eq, 18.6 mmol). The flask was sealed with a septum, purged of atmosphere and backfilled with argon. *Tert*-butyl(hex-5-yn-1-yloxy)dimethylsilane (16.9 mmol), then anhydrous methylene chloride (52.0 mL) were added via syringe. The reaction was stirred at room temperature until the solution became homogenous. Once homogenous, the flask was cooled to -78 °C (dry ice/acetone bath), and dimethyl zinc (1 eq, 16.9 mmol) was added dropwise with stirring. The dry ice/acetone bath was replaced with an ice bath, and the reaction was allowed to warm to 0 °C. 3-Phenylpropanal (1.2 eq, 20.3 mmol, distilled under vacuum prior to use) was added dropwise with stirring, the reaction was allowed to warm to room temperature and stirred. After 2 hours TLC indicated reaction completion. 20 mL saturated aqueous ammonium chloride was added, and stirred until gas evolution ceased, then the mixture was filtered through a pad of Celite. The layers were separated, and the aqueous was extracted 3 times with 20 mL portions of diethyl ether. Combined organic portions were concentrated under vacuum, and the residue redissolved in methanol, cooled to 0 °C, and acidified to pH ~ 3. After stirring 10 min, TLC indicated reaction completion. 30 mL methylene chloride and 30 mL H_2O were added, the layers were separated, and the aqueous layer was extracted with 3 15 mL portions of methylene chloride. The combined organic portions were washed with brine, dried over sodium sulfate, and concentrated under vacuum. Purification by column chromatography on silica gel (1:1 EtOAc:hexanes then 100% EtOAc) yielded the product as a yellow oil. 65.5%.

^{1}H NMR (500 MHz $CDCl_3$): δ 7.26-7.29 (m, 2H), 7.17-7.20 (m, 3H), 5.63-5.69 (m, 1H), 5.51 (dd, 7, *J* = 15.4, 7 Hz, 1H), 4.08 (dd, *J* = 6.64 Hz, 1H), 3.65 (t, *J* = 6.5 Hz, 2H), 2.63-2.74 (m, 2H), 2.08 (dd, *J* = 7.1 Hz, 2), 1.77-1.91 (m, 2H), 1.43-1.61 (m, 4H); ^{13}C NMR (125 MHz $CDCl_3$): δ 142.1, 133.3, 132.1, 128.6, 128.5, 125.9, 72.5, 62.9, 39.0, 32.3, 32.0, 31.9, 25.4; IR (neat) 3309, 2930, 2859, 1496, 1454, 1057, 1031, 970, 747, 699; HRMS (ESI+) *m/z* calcd for $C_{15}H_{22}O_2Na$ $[M+Na]^+$ 257.1512, found 257.1530.



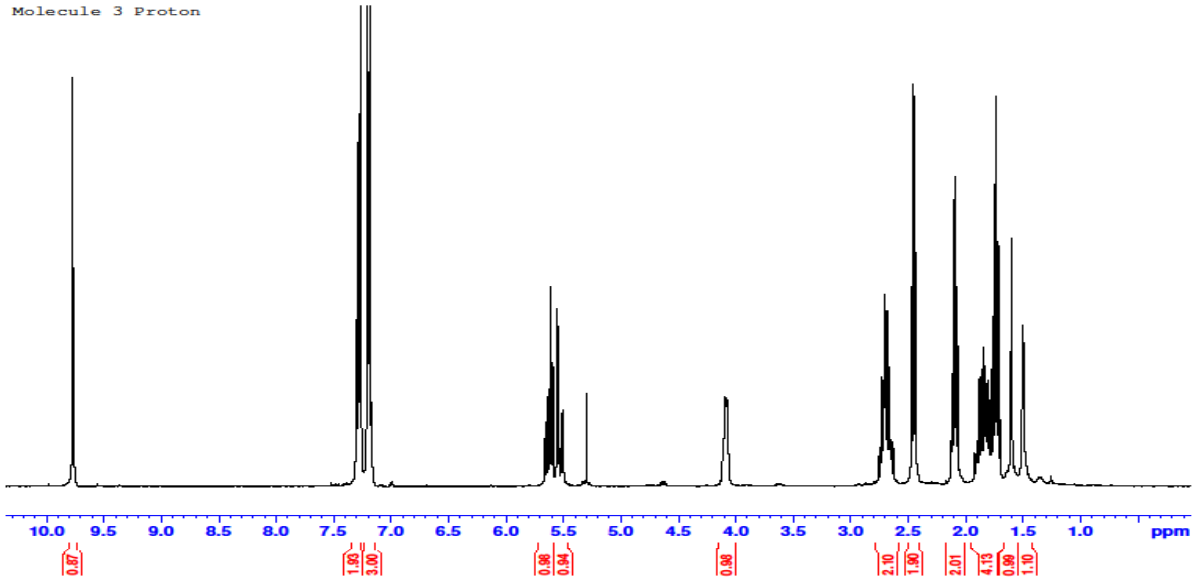




(E)-7-hydroxy-9-phenylnon-5-enal (Molecule 3)

To a round-bottom flask with a stir bar was added 86 mL methylene chloride, 86 mL aqueous solution (0.5 M $NaHCO_3$, 0.05 M K_2CO_3), (E)-9-phenylnon-5-ene-1,7-diol (11.0 mmol), (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (0.1 eq, 1.1 mmol), and tetra-*n*-butylammonium chloride (0.1 eq, 1.1 mmol). N-chlorosuccinimide (recrystallized from toluene, 1.8 eq, 19.9 mmol) was added as a single portion. The mixture was stirred at room temperature for 3 hours, at which point TLC indicated completion. The aqueous and organic layers were separated, and the aqueous was extracted with 3 25 mL portions of methylene chloride. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. Purification by silica gel column chromatography (1:1 EtOAc:hexanes) yielded a dark yellow oil. 79.6%.

^{1}H NMR (500 MHz $CDCl_3$): δ 9.77 (t, *J* = 1.6 Hz, 1H), 7.26-7.30 (m, 2H), 7.17-7.20 (m, 3H), 5.60-5.65 (m, 1H), 5.53 (dd, *J* = 15.4, 6.7 Hz, 1H), 4.09 (dd, *J* = 6.5 Hz, 1H), 2.63-2.75 (m, 2H), 2.45 (td, *J* = 1.6, 7.3 Hz, 2H), 2.09 (dd, *J* = 7 Hz, 2H), 1.78-1.91 (m, 2H), 1.73 (p, *J* = 7.4 Hz, 2H); ^{13}C NMR (125 MHz $CDCl_3$): δ 202.5, 142.0, 134.2, 130.9, 128.6, 128.5, 126.0, 72.3, 43.3, 38.9, 31.9, 31.6, 21.6; IR (neat) 3422, 2925, 2859, 1715, 1496, 1454, 1391, 1360, 1179, 972, 748, 700; HRMS (ESI+) *m/z* calcd for $C_{15}H_{21}O_2$ $[M+H]^+$ 233.1536, found 233.1540.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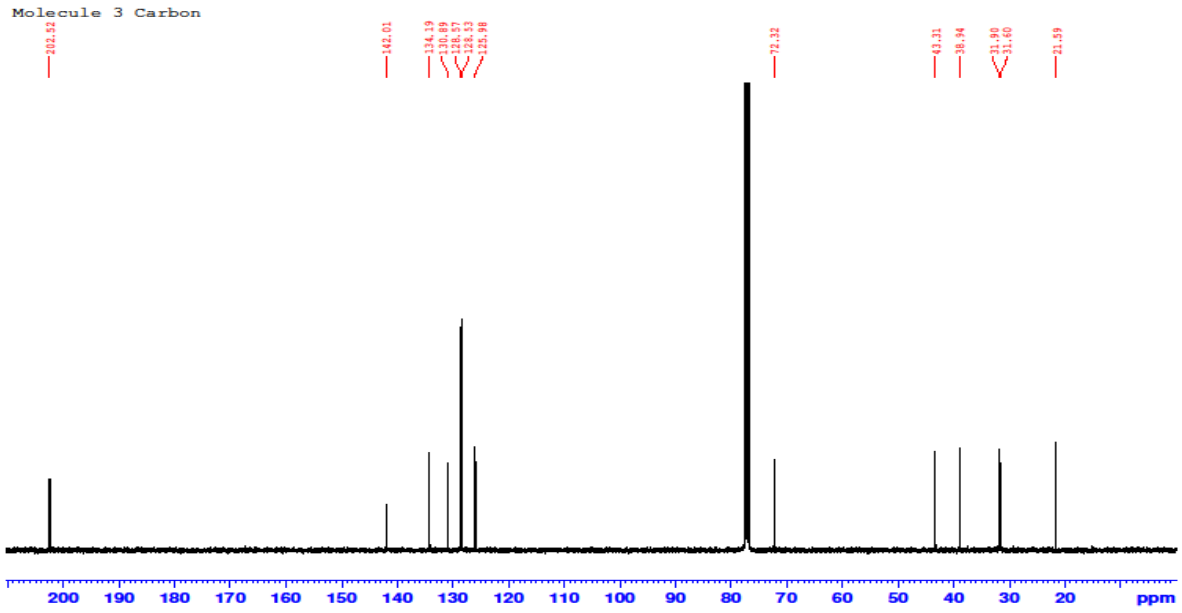
3.00
0.98
0.94
0.98
2.10
1.90
2.01
4.13
0.99
1.10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128.57
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43.31
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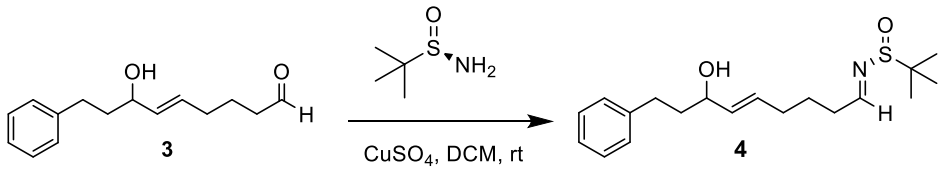
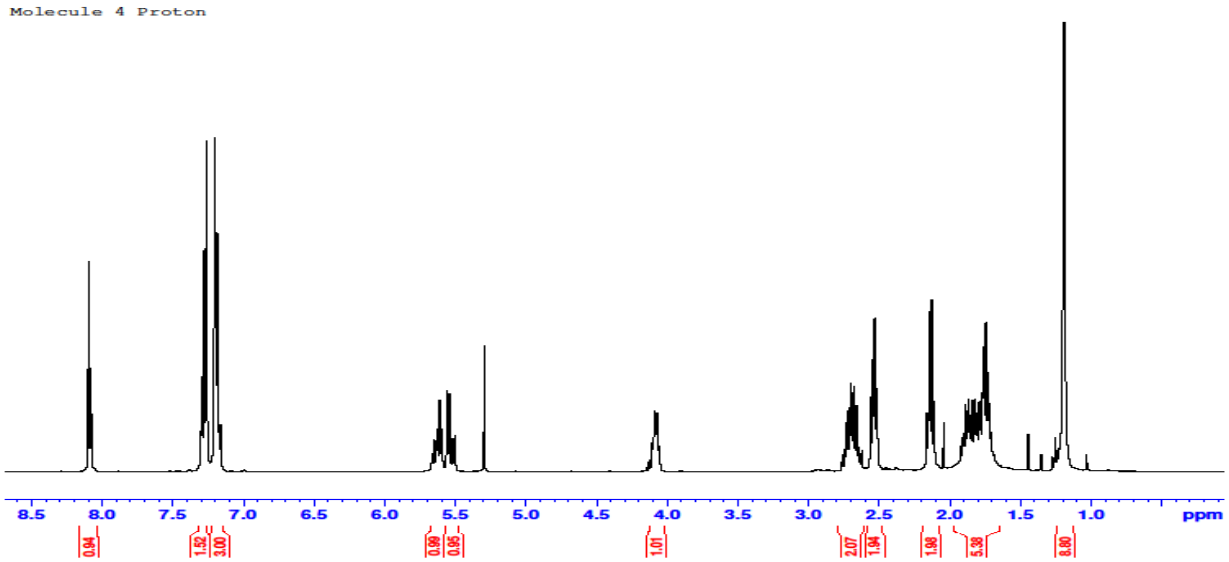


(R)-N-((1E,5E)-7-hydroxy-9-phenylnon-5-en-1-ylidene)-2-methylpropane-2-sulfinamide (Molecule 4)

To a flame-dried flask with a stir bar was added 2-methyl-2-propanesulfinamide (11.6 mmol), copper (II) sulfate (2.2 eq, 25.5 mmol), and 20 mL anhydrous methylene chloride. Separately, (E)-7-hydroxy-9-phenylnon-5-enal (1.05 eq, 12.2 mmol) was dissolved into 5 ml anhydrous methylene chloride, and this solution was added to the reaction mixture dropwise with stirring. After stirring overnight at room temperature, TLC indicated reaction completion. The reaction was filtered through a pad of Celite, and the filtrate concentrated under vacuum. The residue was purified by column chromatography on silica gel (1:1 EtOAc:hexanes) to yield a yellow oil. 64.4%.

^{1}H NMR (400 MHz $CDCl_3$): δ 8.09 (t, *J* = 4.7 Hz, 1H), 7.26-7.30 (m, 2H), 7.16-7.20 (m, 3H), 5.59-5.67 (m, 1H), 5.50-5.56 (m, 1H), 4.07-4.09 (m, 1H), 2.62-2.76 (m, 2H), 2.54 (dt, *J* = 7.1, 14.4 Hz, 2H), 2.14 (dd, *J* = 6.9 Hz, 2H), 1.63-1.92 (m, 6H), 1.19 (s, 9H); ^{13}C NMR (100 MHz $CDCl_3$): δ 169.7, 142.1, 134.2, 131.2, 131.1, 128.6, 128.5, 125.9, 72.3, 56.7, 38.9, 35.7, 31.8, 25.3, 22.5; IR (neat) 3412, 2926, 2862, 1622, 1496, 1475, 1454, 1363, 1182, 1062, 970, 748, 700, 584; HRMS (ESI+) *m/z* calcd for $C_{19}H_{30}NO_2S$ $[M+H]^+$ 336.1992, found 336.2010.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3.0
2.5
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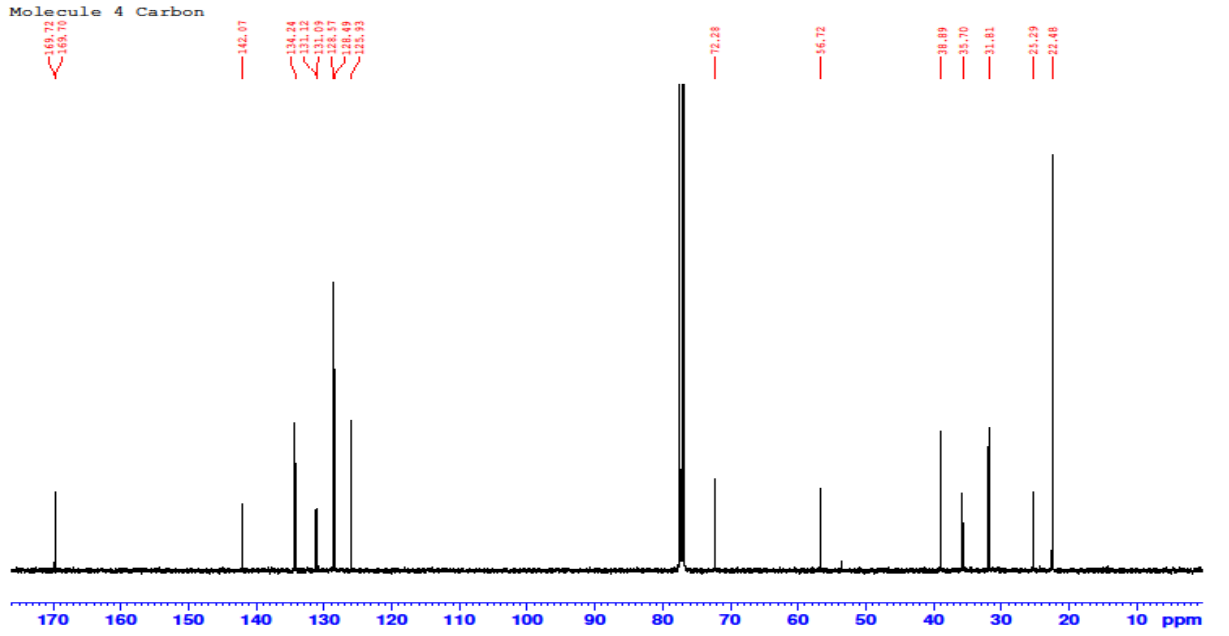
8.80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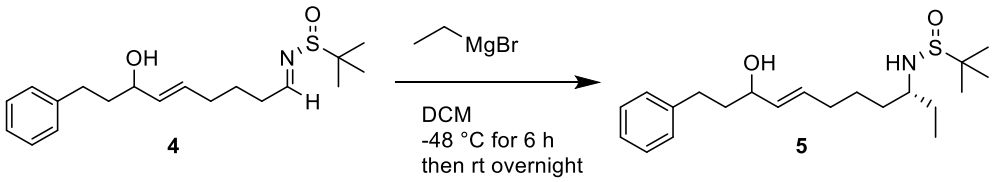
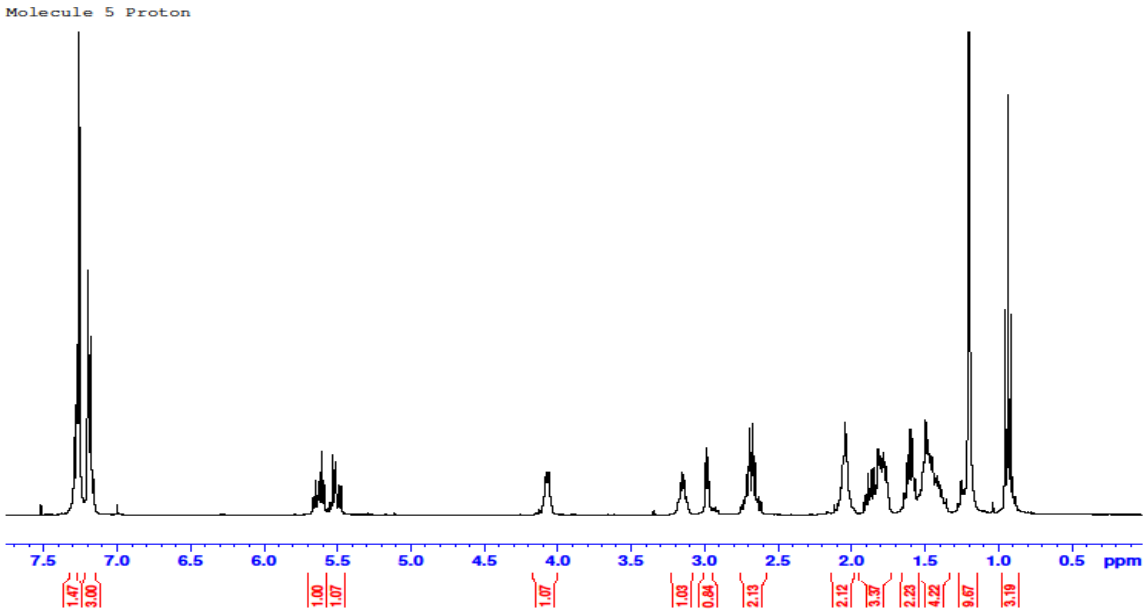


(R)-N-((1E,5E)-7-hydroxy-9-phenylnon-5-en-1-ylidene)-2-methylpropane-2-sulfinamide (Molecule 5)

To a flame-dried flask with a stir bar was added (R)-N-((1E,5E)-7-hydroxy-9-phenylnon-5-en-1-ylidene)-2-methylpropane-2-sulfinamide (5.4 mmol). The flask was sealed with a septum and flushed with argon. 32.5 mL anhydrous methylene chloride was added and the flask was cooled to -48 °C (dry ice and 1:1 ethylene glycol:ethanol bath). 3.0 M solution of ethyl magnesium bromide in THF (2.5 eq, 13.4 mmol, 4.48 mL) was added dropwise with stirring. The mixture was stirred 6 hours at -48 °C, then warmed to rt and stirred overnight, after which TLC indicated reaction completion. The reaction was quenched by dropwise addition of saturated aqueous ammonium chloride. The aqueous and organic layers were separated, and the aqueous extracted with 3 15 mL portions of EtOAc. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated under vacuum. Purification by silica gel column chromatography yielded a dark yellow oil. 75.7%.

^{1}H NMR (400 MHz $CDCl_3$): δ 7.26-7.30 (m, 2H), 7.16-7.20 (m, 3H), 5.57-5.66 (m, 1H), 5.47-5.55 (m, 1H), 4.07 (q, *J* = 6.6 Hz, 1H), 3.15 (p, J = 11.2 Hz, 1H), 3.00 (d, *J* = 6.4 Hz, 1H), 2.62-2.75 (m, 2H), 1.98-2.11 (m, 2H), 1.75-1.92 (m, 3H), 1.55-1.64 (m, 2H), 1.34-1.54 (m, 4H), 1.20 (s, 9H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz $CDCl_3$): δ 142.2, 133.6, 131.9, 128.6, 128.5, 125.9, 72.4, 57.8, 57.6, 55.8, 39.0, 34.5, 32.0, 29.1, 25.1, 22.8, 10.1; IR (neat) 3244, 2928, 2860, 1603, 1496, 1455, 1363, 1043, 969, 745, 699, 600, 493; HRMS (ESI+) *m/z* calcd for $C_{21}H_{36}NO_2S$ $[M+H]^+$ 366.2461, found 366.2471.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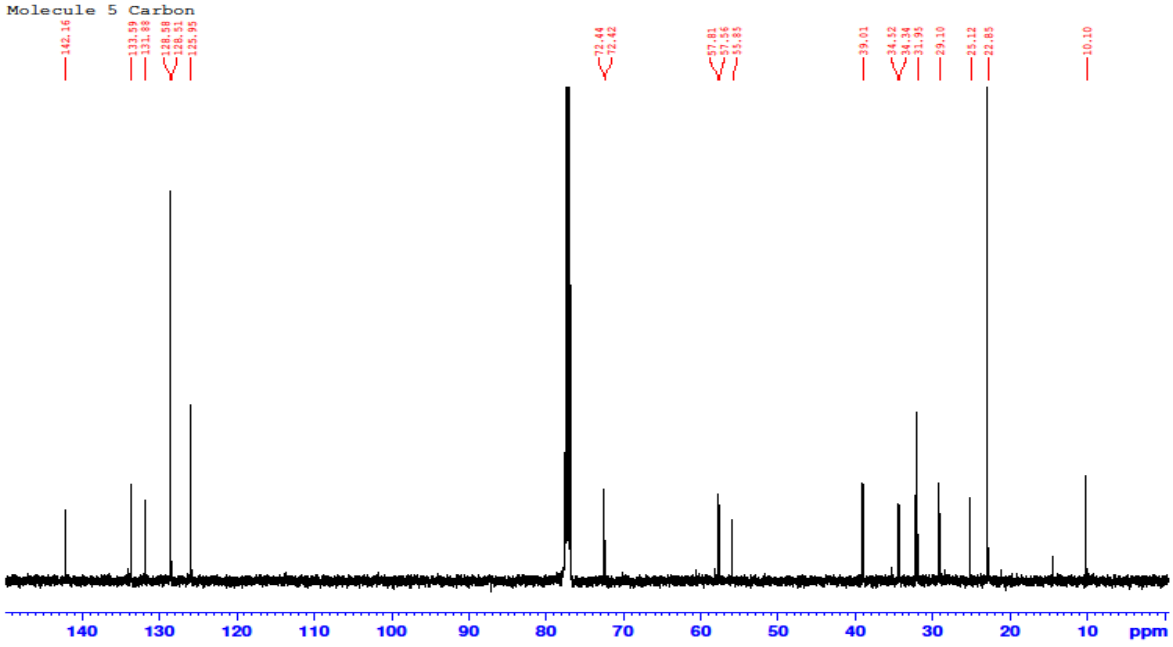
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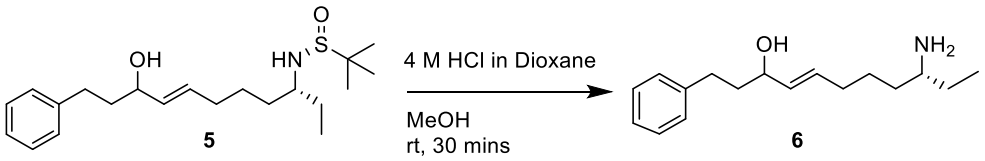
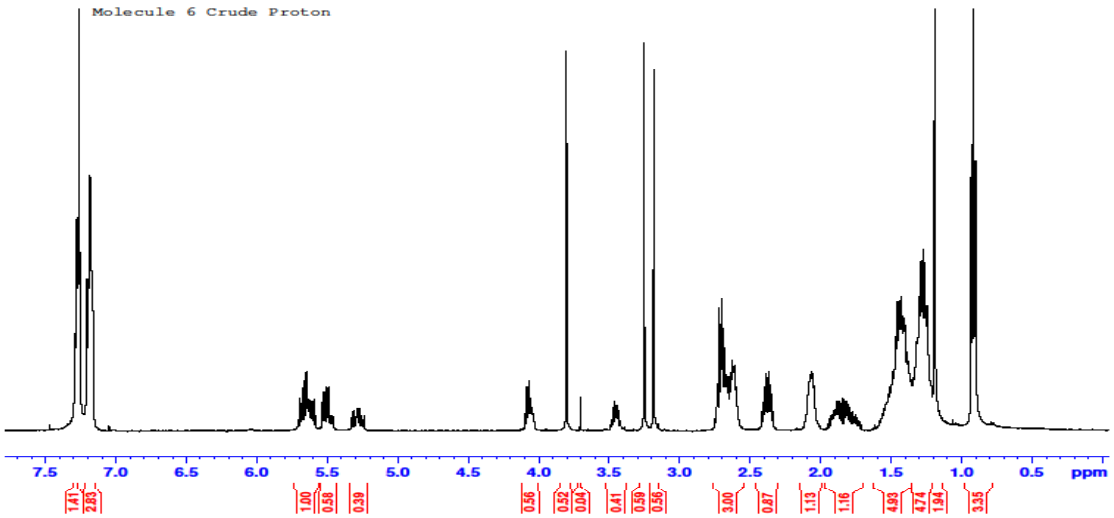
10
ppm



(9R,E)-9-amino-1-phenylundec-4-en-3-ol (Molecule 6)

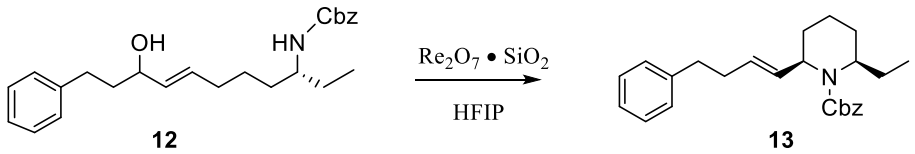
To a flame-dried flask with a stir bar was added (R)-N-((1E,5E)-7-hydroxy-9-phenylnon-5-en-1-ylidene)-2-methylpropane-2-sulfinamide (4.1 mmol), and 4.1 mL methanol. The flask was cooled to 0 °C (ice bath). 4 M HCl solution in 1,4-dioxane (2 eq, 8.1 mmol, 2.0 mL) was added to reaction dropwise with stirring. The mixture was stirred at 0 °C for 10 min, at which time TLC indicated reaction completion. The reaction was diluted with 4.1 ml H_2O, and then made basic (pH 12) to pH paper by dropwise addition of 5 M NaOH with stirring. The reaction was then extracted 4 times with 8 mL portions of methylene chloride. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated under vacuum to yield a dark yellow oil. This crude was used without further purification.

^{1}H NMR (500 MHz $CDCl_3$): δ 7.26-7.29 (m, 2H), 7.16-7.20 (m, 3H), 5.58-5.71 (m, 1H), 5.24-5.53 (m, 1H), 2.58-2.75 (m, 3H), 2.34-2.41 (m, 1H), 2.01-2.11 (m, 1H), 1.71-1.95 (m, 1H), 1.17-1.58 (m, 7H), 0.91 (t, J = 7.4 Hz, 3H); HRMS (ESI+) *m/z* calcd for $C_{17}H_{28}ON$ $[M+H]^+$ 262.2165, found 262.2169.



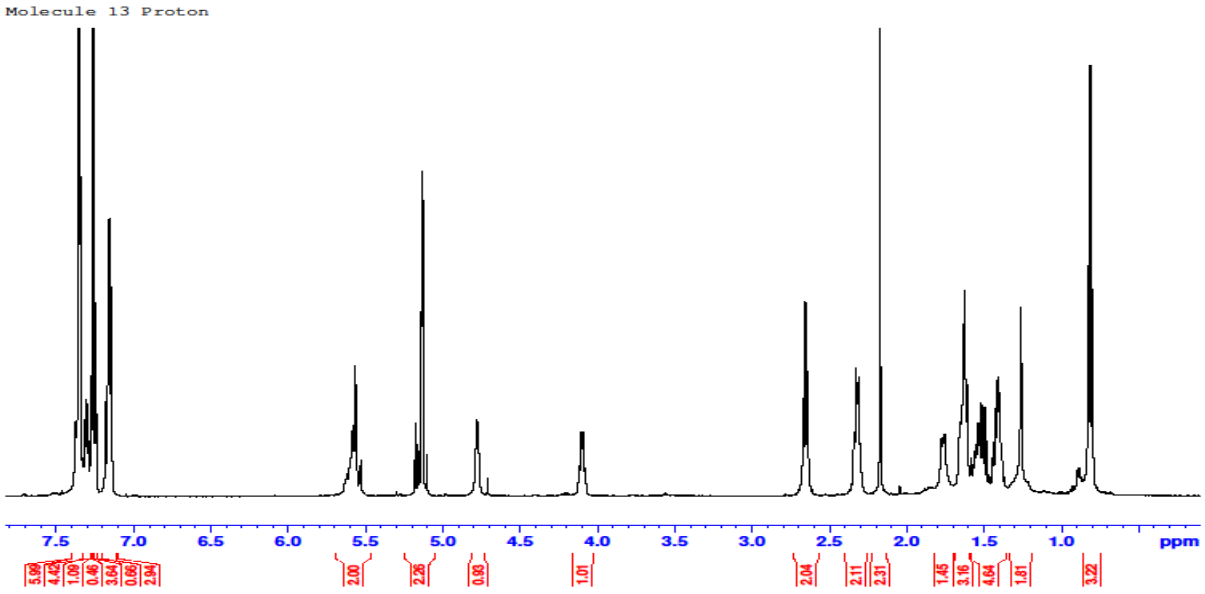
A.1 GENERAL EXPERIMENTAL FOR RE_2O_7

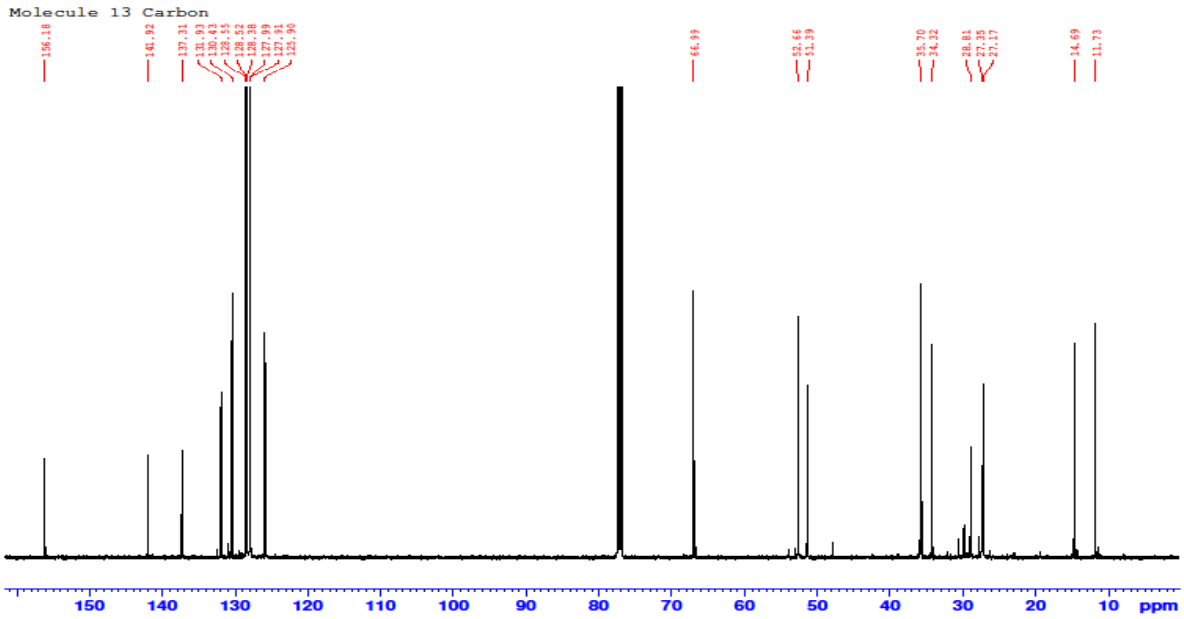
To a flame-dried flask with a stir bar was added 0.1 M solution of substrate (1 eq) in 1,1,1,3,3,3-hexafluoroisopropanol. $Re_2O_7 \cdot SiO_2$ (0.05 eq) was added as a single portion with stirring. The flask was sealed with a septum, and the reaction stirred for the indicated time. Once complete by TLC, reactions were filtered through a plug of silica gel, eluted with EtOAc and methylene chloride, and the filtrate was concentrated under vacuum. Crude products were purified by silica gel column chromatography (20% EtOAc in hexanes), and characterized by NMR and HRMS.



Benzyl (2R,6R)-2-ethyl-6-((E)-4-phenylbut-1-en-1-yl)piperidine-1-carboxylate (Molecule 13)

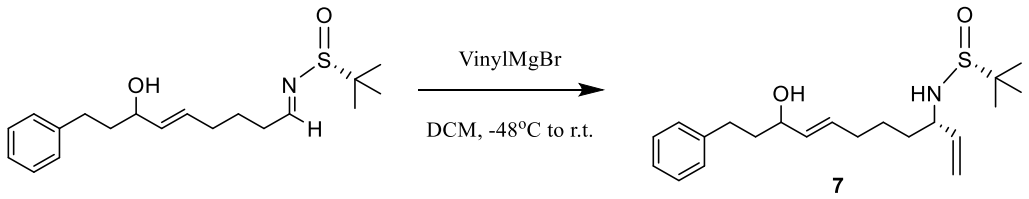
^{1}H NMR (500 MHz $CDCl_3$): δ 7.25-7.36 (m, 6H), 7.13-7.19 (m, 4H), 5.50-5.68 (m, 2H), 5.10-5.16 (m, 2H), 4.76 (s, 1H), 4.06-4.14 (m, 1H), 2.65 (t, *J* = 7.2 Hz, 2H), 2.28-2.36 (m, 2H), 1.18-1.79 (m, 8H), 0.81 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz $CDCl_3$): δ 156.2, 141.9, 137.3, 131.9, 130.4, 128.6, 128.5, 128.4, 128.3, 127.9, 125.9, 67.0, 52.7, 51.4, 35.7, 34.3, 28.8, 27.3, 27.2, 14.7, 11.7; HRMS (ESI+) *m/z* calcd for $C_{25}H_{32}O_2N$ $[M+H]^+$ 378.2428, found 378.2444.





Procedure For Supporting Re_2O_7 On Silica Gel: To a flame-dried 500 mL round-bottom flask with a stir bar was added 9.0011 g silica gel. The flask was sealed with a septum and flushed with argon. 200 mL anhydrous diethyl ether was added via syringe, and the mixture was stirred 5 min at room temperature. 1.00 g Re_2O_7 was added as a single portion under positive pressure of argon. The flask was resealed and wrapped in aluminum foil, and the mixture was stirred at room temperature for 3 hours. The diethyl ether was then removed by rotary evaporation, and the foil-wrapped flask was dried under high vacuum overnight to yield the catalyst. Catalytic activity was determined by comparison between two identical reactions, with one catalyzed by previously prepared catalyst of known activity and the other by the silica gel-supported catalyst.

A.2 SYNTHESIS OF MOLECULES 10 AND 11



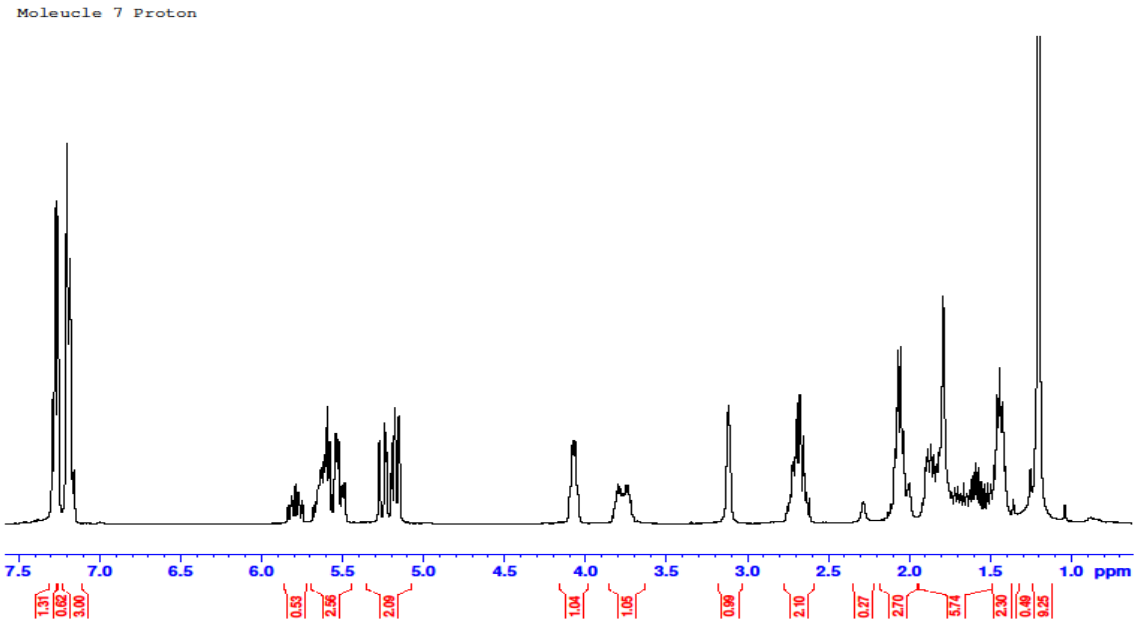
7

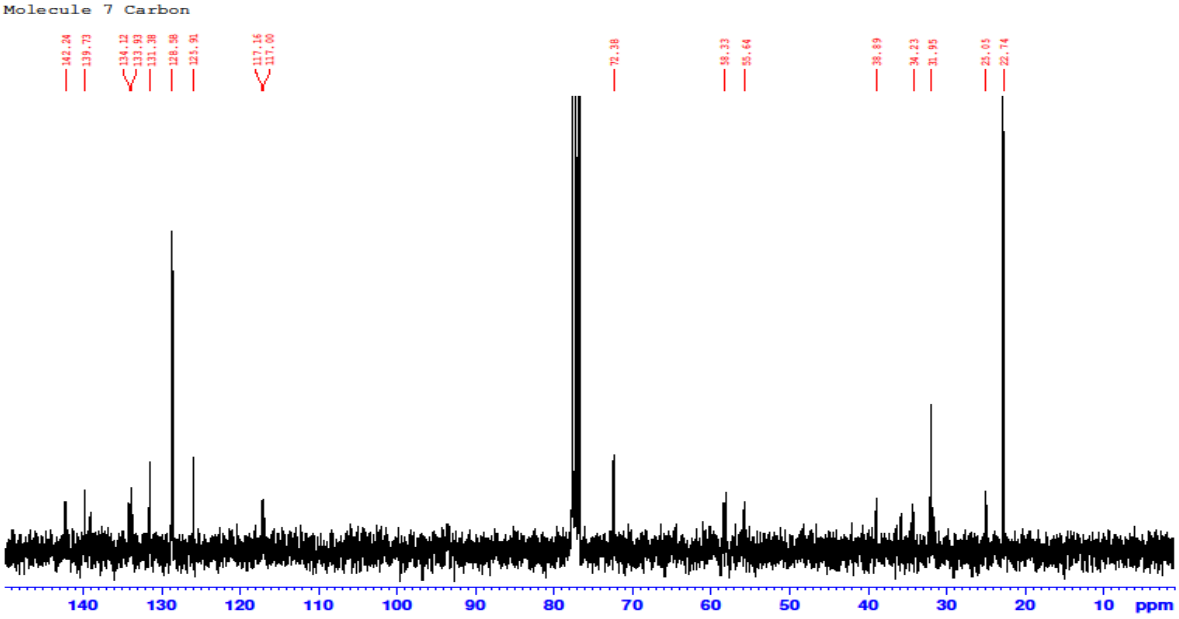
(R)-N-((E)-9-hydroxy-11-phenylundeca-1,7-dien-3-yl)-2-methylpropane-2-sulfinamide (Molecule 7)

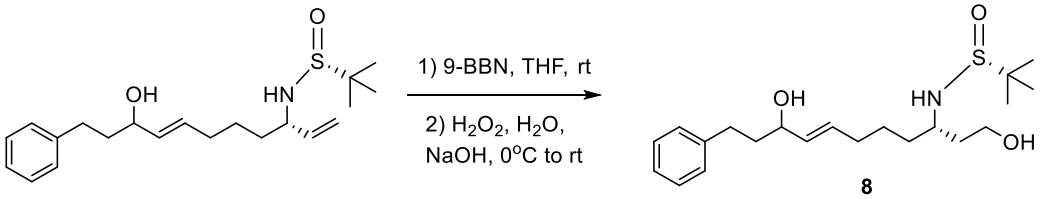
To a flame-dried flask with a stir bar was added (R)-N-((1E,5E)-7-hydroxy-9-phenylnon-5-en-1-ylidene)-2-methylpropane-2-sulfinamide (4.48 mmol). The flask was sealed with a septum and flushed with argon. 27.0 mL anhydrous methylene chloride was added via syringe, and the flask was then cooled to -48 °C (dry ice and 1:1 ethylene glycol:ethanol bath). 0.7 M solution of vinyl magnesium bromide in THF (2.5 eq, 11.19 mmol, 16.0 mL) was added dropwise with stirring. The mixture was stirred at -48 °C for 6 hours, then warmed to room temperature and stirred overnight, after which time TLC indicated reaction completion. The reaction was cooled to 0 °C and quenched by dropwise addition of saturated aqueous ammonium chloride, warmed to room temperature, and stirred for 10 min. The aqueous and organic layers were separated, and the aqueous was extracted with 3 10 mL portions of EtOAc. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated under vacuum. Purification by silica gel column chromatography (1:1 EtOAc:hexanes, then 100% EtOAc) yielded a pale yellow oil. 80.8%

^{1}H NMR (400 MHz $CDCl_3$): δ 7.25-7.29 (m, 2H), 7.16-7.20 (m, 3H), 5.48-5.84 (m, 3H), 5.15-5.27 (m, 2H), 4.07 (d, *J* = 6.2Hz, 1H), 3.70-3.83 (m, 1H), 3.11 (s, 1H), 2.62-2.75 (m, 2H), 1.40-2.15 (m, 9H), 1.20 (s, 9H); ^{13}C NMR (75 MHz $CDCl_3$): δ 142.2, 139.7, 134.1, 133.9, 131.4, 128.6, 125.9, 117.2, 117.0, 72.4, 58.3, 55.6, 38.9, 34.2, 32.0, 25.1, 22.7; IR (neat) 3352, 2924, 2859, 1454, 1363, 1176, 1046,

969, 918, 747, 699, 598, 490; HRMS (ESI+) *m/z* calcd for $C_{21}H_{34}O_2NS$ $[M+H]^+$ 364.2305, found 364.2318.



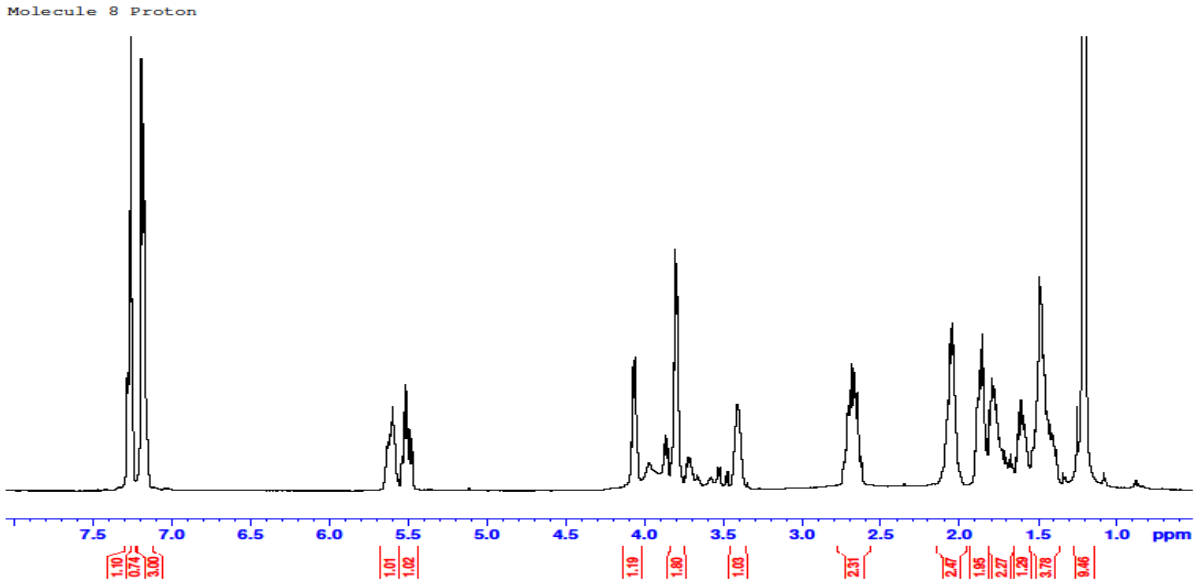




(R)-N-((E)-1,9-dihydroxy-11-phenylundec-7-en-3-yl)-2-methylpropane-2-sulfinamide (Molecule 8)

To a flame-dried flask with a stir bar was added (R)-N-((E)-9-hydroxy-11-phenylundeca-1,7-dien-3-yl)-2-methylpropane-2-sulfinamide (2.06 mmol). The flask was sealed with a septum and flushed with argon. Anhydrous THF (5.67 mL) was added via syringe, then 0.5 M 9-borabicyclo[3.3.1]nonane solution in THF (4 eq, 8.24 mmol, 16.49 mL) was added via syringe dropwise with stirring. The mixture was stirred at room temperature 2 hours, at which time TLC indicated complete consumption of starting material. The flask was cooled to 0 °C (ice bath), and 3 M aqueous sodium hydroxide (1.5 eq, 3.09 mmol, 1.03 mL), then 30% aqueous hydrogen peroxide (5 eq, 10.30 mmol, 1.04 mL) was added dropwise with stirring. The reaction was allowed to warm to room temperature and stirred overnight, after which time TLC indicated reaction completion. The reaction was quenched by dropwise addition of saturated aqueous sodium chloride and extracted with 3 10 mL portions of EtOAc. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude residue was purified by short (~4 inch) silica gel column chromatography (1:1 EtOAc:hexanes, then 100% EtOAc, then 10% MeOH in EtOAc) to yield a pale golden oil. 94.9 %

^{1}H NMR (400 MHz $CDCl_3$): δ 7.24-7.30 (m, 2H), 7.15-7.22 (m, 3H), 5.40-5.68 (m, 2H), 4.08 (q, *J* = 6.5 Hz, 1H), 3.82 (t, *J* = 5.04 Hz, 1H), 3.58-3.75 (m, 1H), 3.29-3.47 (m, 1H), 2.57-2.75 (m, 2H), 1.73-1.93 (m, 4H), 1.55-1.72 (m, 4H), 1.34-1.53 (m, 4H), 1.22 (s, 9H); ^{13}C NMR (75 MHz $CDCl_3$): δ 142.1, 133.6, 131.6, 128.5, 125.9, 72.3, 60.2, 56.1, 54.9, 54.6, 39.0, 38.3, 36.5, 35.5, 31.9, 25.3, 22.9; IR (neat) 3325, 2924, 2856, 1706, 1447, 1366, 1217, 1055, 1004, 735, 700, 598; HRMS (ESI+) *m/z* calcd for $C_{21}H_{36}O_3NS$ $[M+H]^+$ 382.2410, found 382.2416.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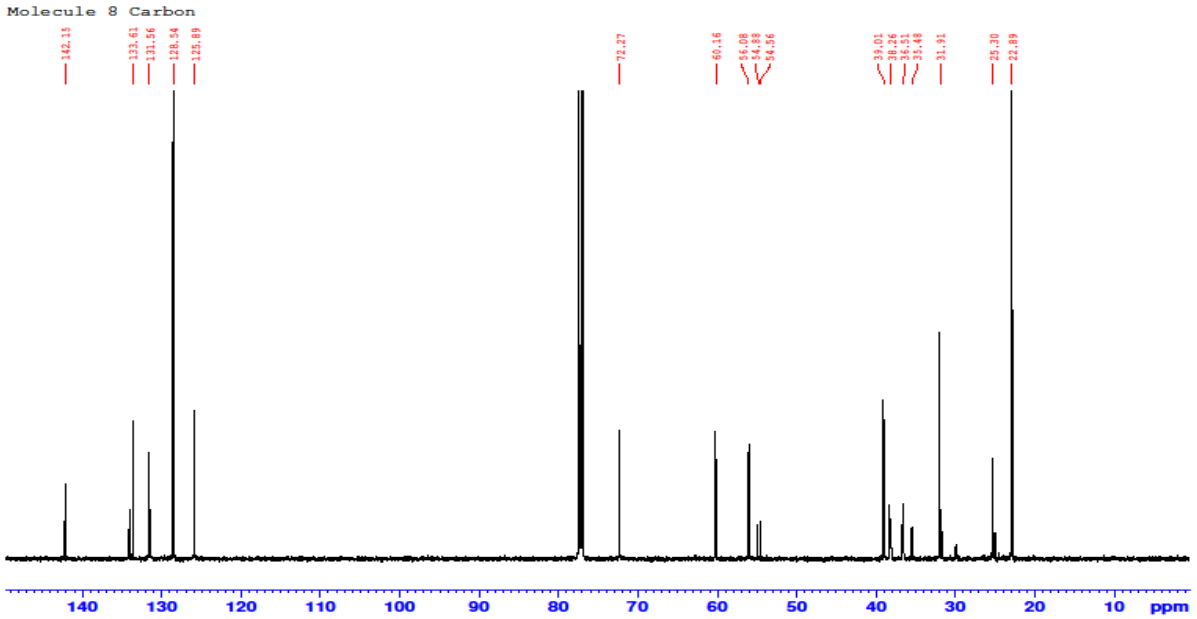
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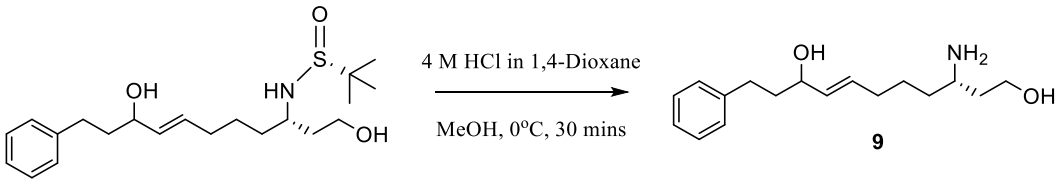
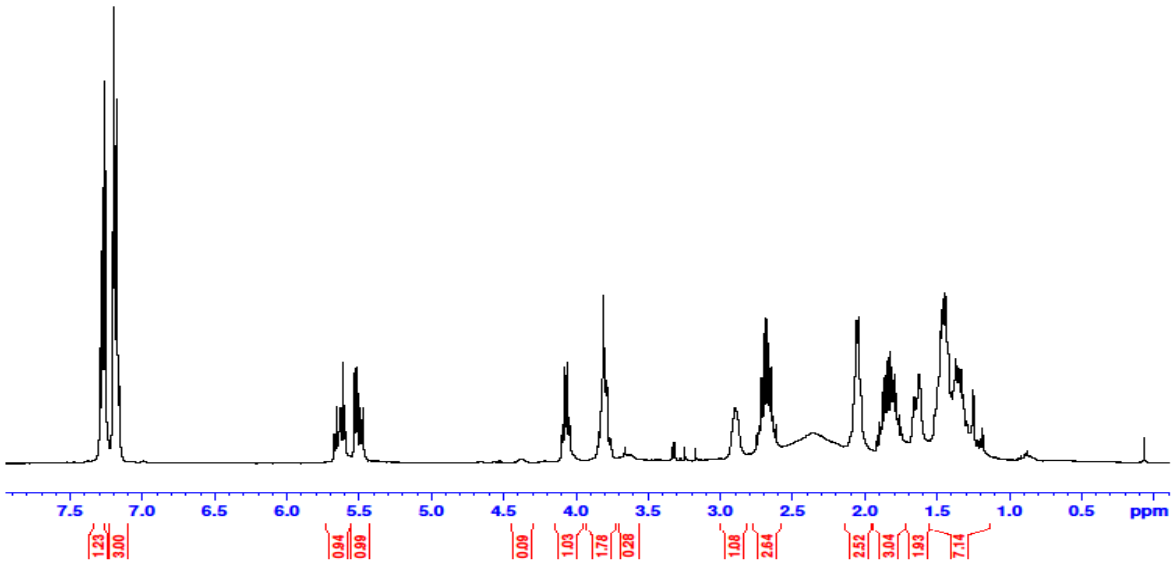


(E)-3-amino-11-phenylundec-7-ene-1,9-diol (Molecule 9)

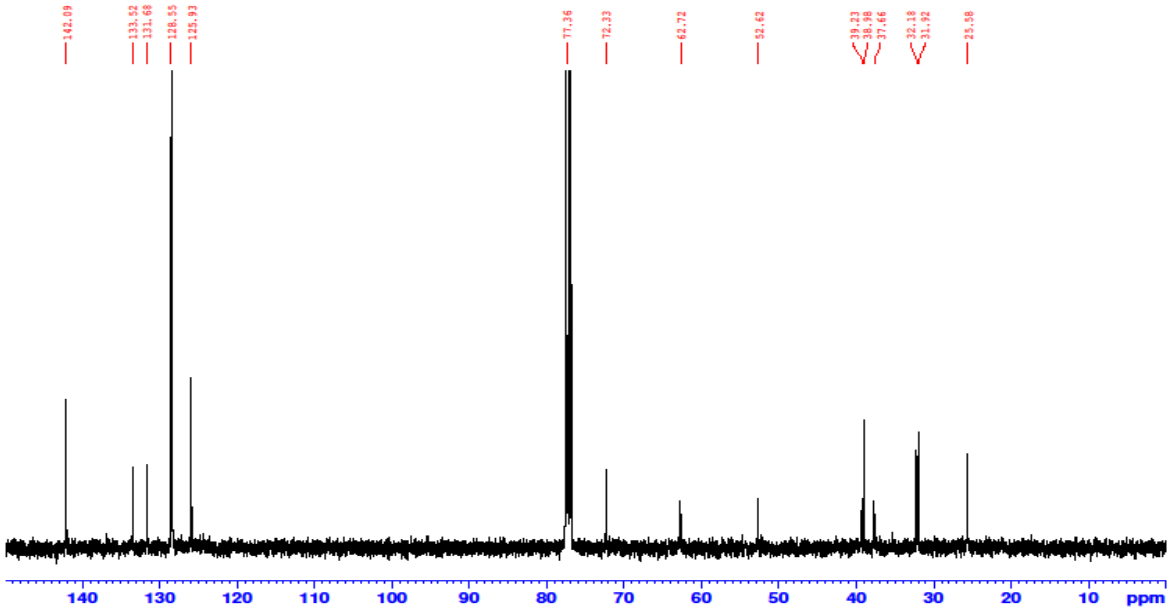
To a flame-dried flask with a stir bar was added (R)-N-((E)-1,9-dihydroxy-11-phenylundec-7-en-3-yl)-2-methylpropane-2-sulfinamide (0.96 mmol), 1.0 mL MeOH. The flask was cooled to 0 °C (ice bath), and 4 M HCl in 1,4-dioxane (2 eq, 1.91 mmol, 0.48 mL) was added dropwise with stirring. The mixture was stirred at 0 °C for 10 min, at which time TLC indicated reaction completion. The reaction was diluted with 1.0 mL H_2O and made basic (pH 12) to pH paper by dropwise addition of 5 M aqueous sodium hydroxide with stirring, then extracted with 4 3 mL portions of methylene chloride. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated under vacuum to yield a yellow oil. This crude product was used without further purification.

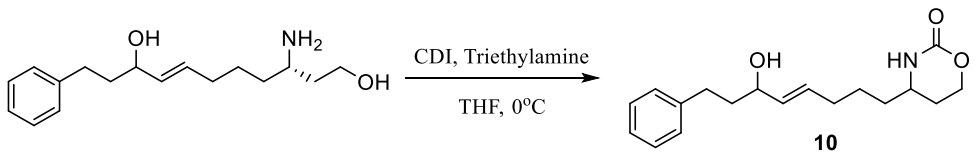
^{1}H NMR (400 MHz $CDCl_3$): δ 7.26-7.31 (m, 2H), 7.15-7.21 (m, 3H), 5.59-5.68 (m, 1H), 5.50 (dd, *J* = 6.8, 7.4 Hz, 1H), 4.07 (q, *J* = 6.6 Hz, 1H), 3.75-3.85 (m, 2H), 2.90 (s, 1H), 2.61-2.76 (m, 2H), 2.00-2.11 (m, 2H), 1.75-1.92 (m, 3H), 1.18-1.68 (m, 9H); ^{13}C NMR (100 MHz $CDCl_3$): δ 142.1, 133.5, 131.7, 128.5, 125.9, 77.4, 72.3, 62.7, 52.6, 39.2, 39.0, 37.7, 32.2, 31.9, 25.6; IR (neat) 3284, 2923, 2855, 1602, 1495, 1454, 1060, 969, 748, 700; HRMS (ESI+) *m/z* calcd for $C_{17}H_{28}NO_2$ $[M+H]^+$ 278.2115, found 278.2123.

Molecule 9 Crude Proton



Molecule 9 Crude Carbon

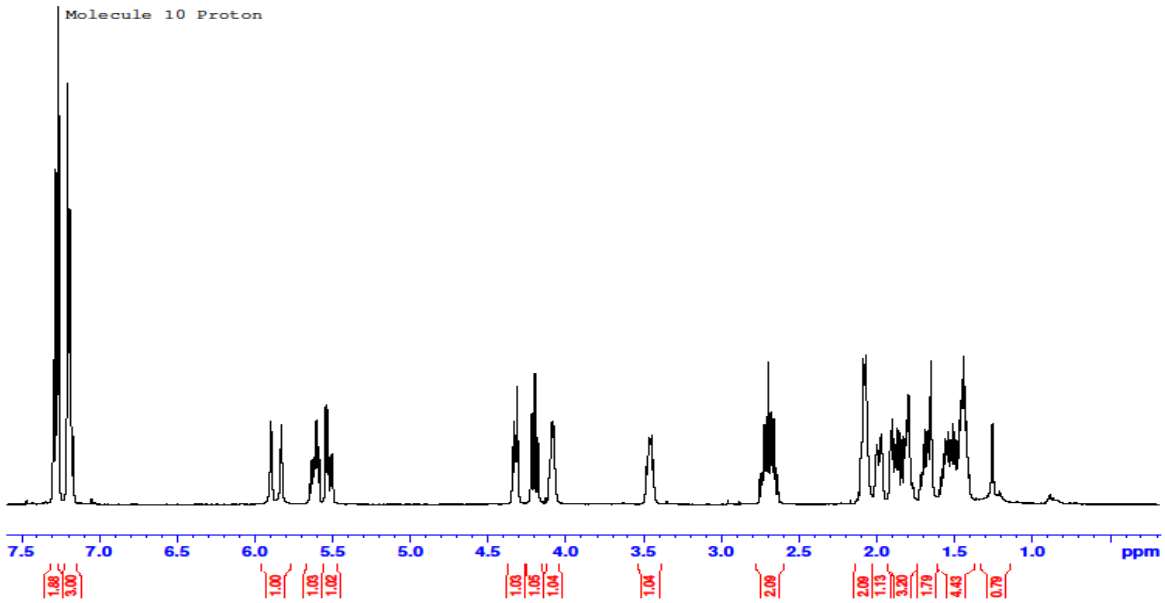




(E)-4-(6-hydroxy-8-phenyloct-4-en-1-yl)-1,3-oxazinan-2-one (Molecule 10)

To a flame-dried flask with a stir bar was added (E)-3-amino-11-phenylundec-7-ene-1,9-diol (0.96 mmol), 9.6 mL anhydrous THF. The flask was cooled to 0 °C (ice bath) and 1,1'-carbonyldiimidazole (1 eq, 0.96 mmol) was added as a single portion with stirring. Separately, triethylamine (1 eq, 0.96 mmol, 0.13 mL) was dissolved into 2.0 mL anhydrous THF and this was added to the reaction dropwise with stirring. The mixture was stirred at 0 °C for 15 min, at which point TLC indicated reaction completion. The reaction was diluted with 10.0 mL H_2O, and 10.0 mL methylene chloride, the layers were separated, and the aqueous was extracted with 3 10.0 mL portions of methylene chloride. Purification by silica gel column chromatography yielded a pale yellow oil. 78.5%.

^{1}H NMR (400 MHz $CDCl_3$): δ 7.26-7.30 (m, 2H), 7.16-7.20 (m, 3H), 5.78 (d, *J* = 23.1 Hz, 1H), 5.58-5.66 (m, 1H), 5.49-5.55 (dddd, *J* = 5.6, 7.4, 1.0 Hz, 1H), 4.31 (dt, *J* = 4.2 Hz, 1H), 4.20 (td, *J* = 2.8, 10.7 Hz, 1H), 4.08 (dd, *J* = 6.5 Hz, 1H), 3.42-3.49 (m, 1H), 2.62-2.76 (m, 2H), 2.08 (q, *J* = 6.7 Hz, 2H), 1.38-2.03 (m, 13H); ^{13}C NMR (100 MHz $CDCl_3$): δ 154.5, 142.1, 134.3, 131.0, 128.5, 126.0, 77.4, 72.3, 65.8, 51.0, 39.0, 35.8, 35.6, 32.0, 27.4, 24.7; IR (neat) 3260, 2925, 2858, 1694, 1481, 1428, 1367, 1291, 1097, 970, 767, 749, 700; HRMS (ESI+) *m/z* calcd for $C_{18}H_{26}NO_3$ $[M+H]^+$ 304.1907, found 304.1916.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1.0
ppm
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1.00
1.03
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1.03
1.06
1.04
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2.00
1.13
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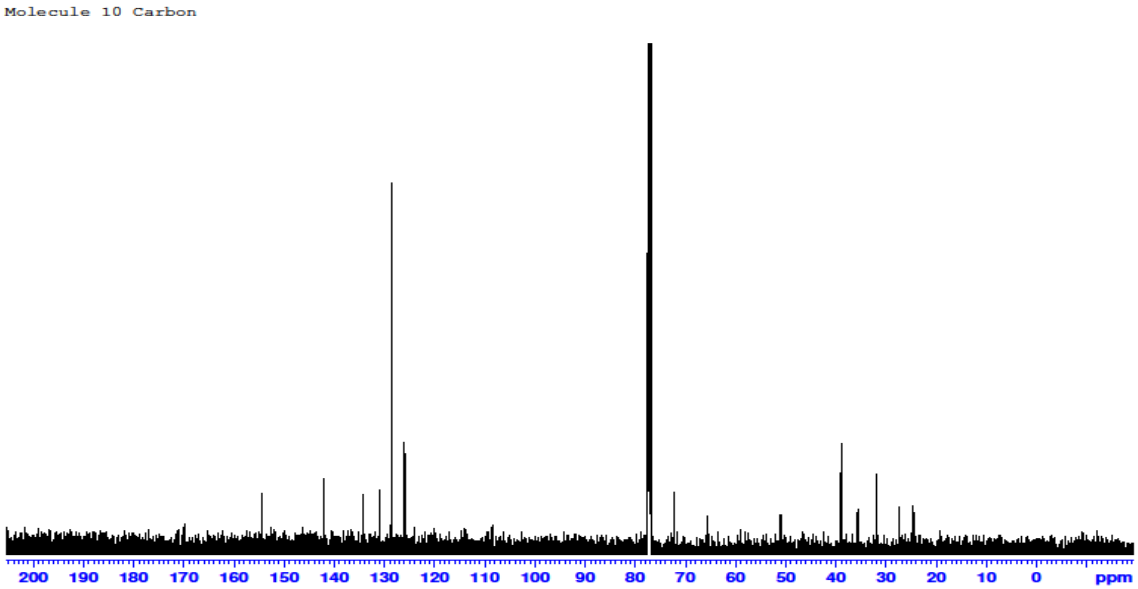
0.76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60
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20
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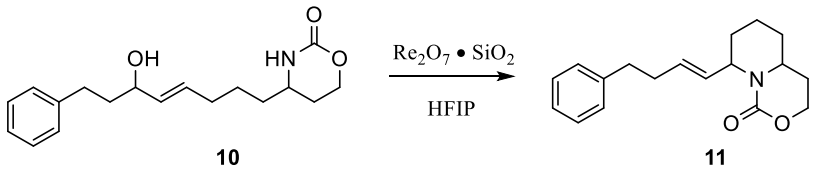
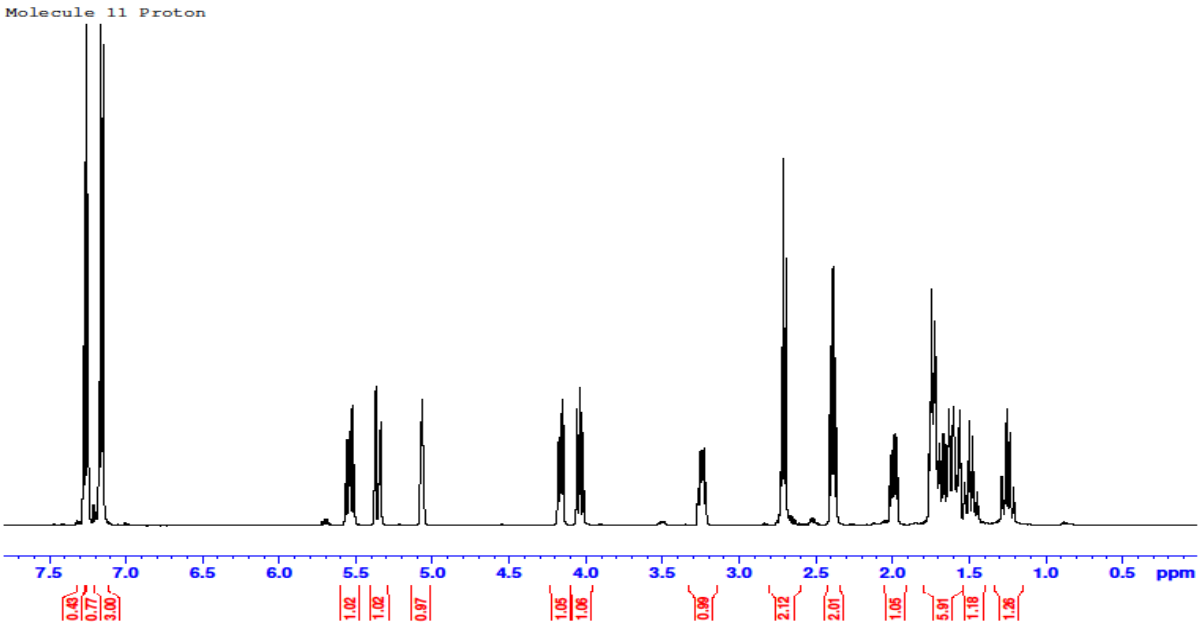
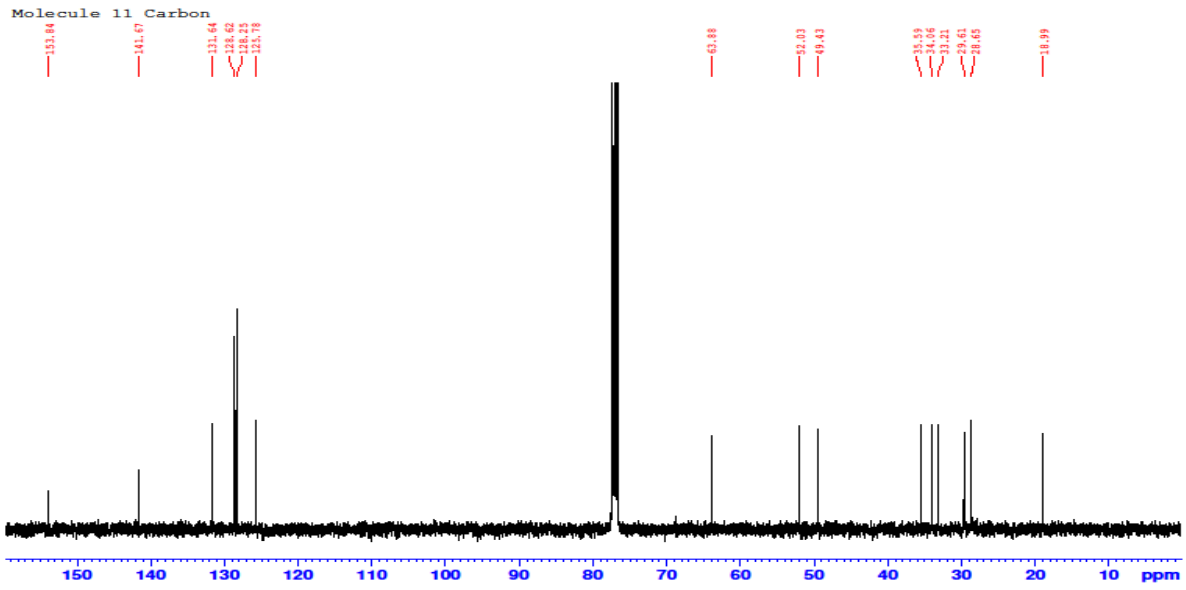
0
ppm



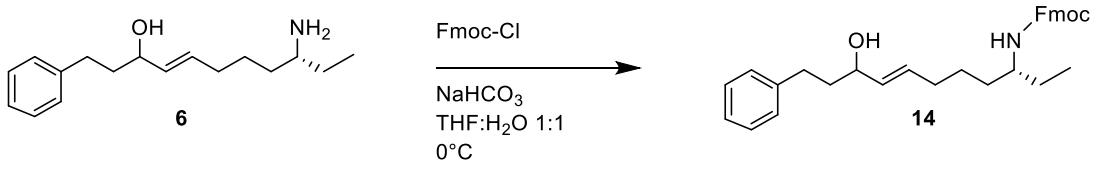
(E)-8-(4-phenylbut-1-en-1-yl)hexahydro-1*H*,3*H*-pyrido[1,2-*c*][1,3]oxazin-1-one (Molecule 11)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.24-7.29 (m, 2H), 7.14-7.19 (m, 3H), 5.50-5.59 (m, 1H), 5.36 (dd, *J* = 6.7 Hz, 1H), 5.07 (s, 1H), 4.14-4.20 (m, 1H), 4.00-4.08 (m, 1H), 3.20-3.29 (m, 1H), 2.71 (t, *J* = 7.5Hz, 2H), 2.39 (q, *J* = 7.2 Hz, 2H), 1.96-2.04 (m, 1H), 1.42-1.78 (m, 10H), 1.19-1.31 (m, 3H); ^{13}C NMR (100 MHz $CDCl_3$): δ 153.8, 141.7, 131.6, 128.6, 128.3, 125.8, 63.9, 52.0, 49.4, 35.6, 34.0, 33.2, 29.7, 28.6, 19.0; HRMS (ESI+) *m/z* calcd for $C_{18}H_{24}NO_2$ $[M+H]^+$ 286.1802, found 286.1811.





A.3 EXPERIMENTAL FOR PROTECTIONS

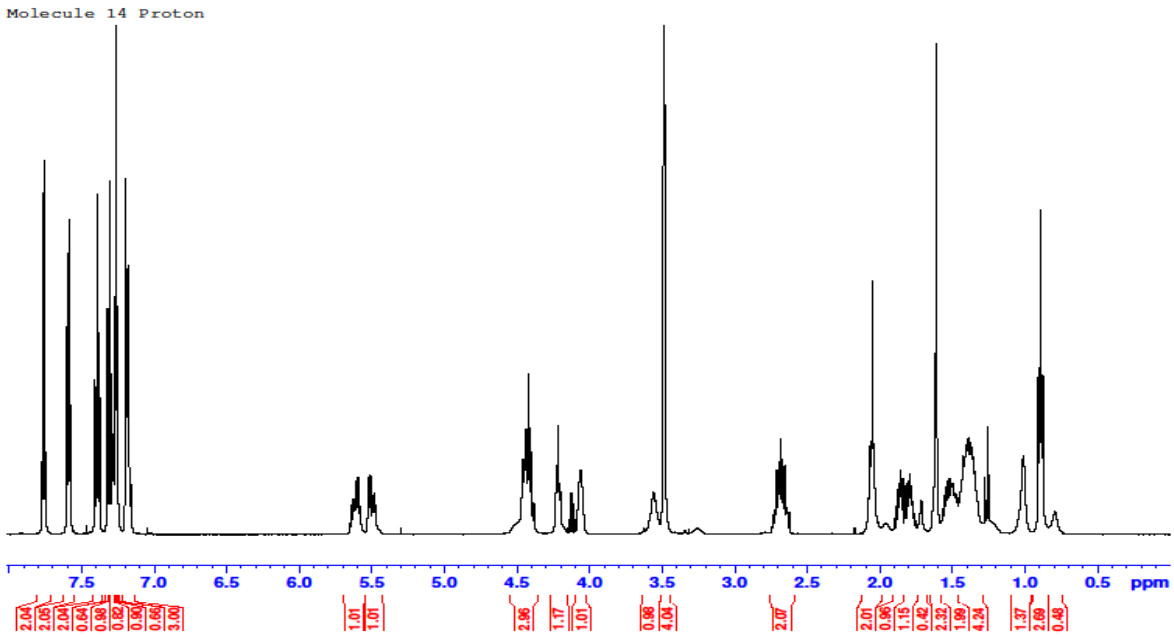


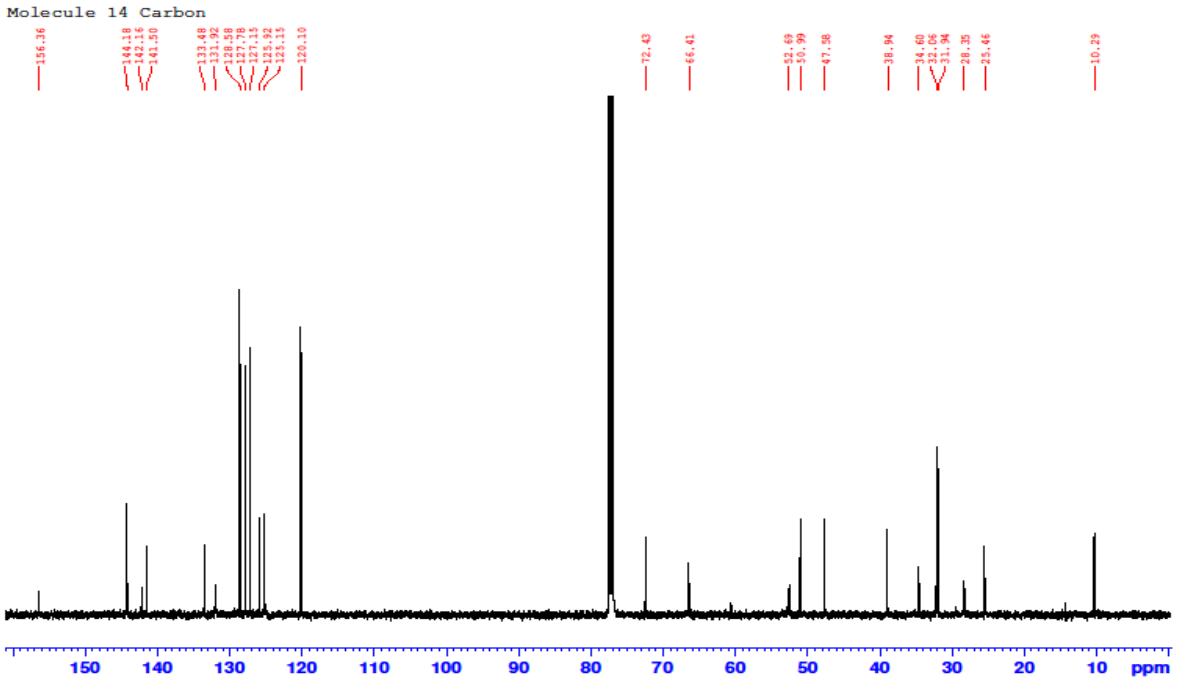
(9*H*-fluoren-9-yl)methyl ((3R, E)-9-hydroxy-11-phenylundec-7-en-3-yl) carbamate (Molecule 14)

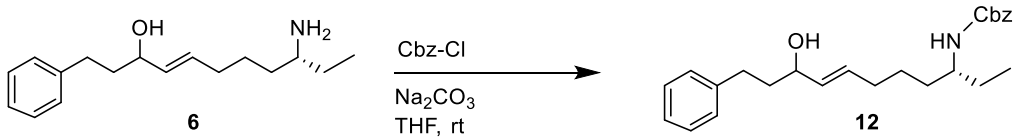
To a flame-dried flask with a stir bar was added (9R,E)-9-amino-1-phenylundec-4-en-3-ol (3.869 mmol), 15.0 mL THF. The flask was cooled to 0 °C (ice bath). 9-Fluorenylmethoxycarbonyl chloride (1 eq, 3.869 mmol) was dissolved separately into 5.0 mL THF. $NaHCO_3$ (1.3 eq, 5.030 mmol) was dissolved separately into 20.0 mL H_2O. The 9-fluorenylmethoxycarbonyl chloride solution was added to the reaction vessel dropwise with stirring at 0 °C, followed by the $NaHCO_3$ solution dropwise with

stirring at 0 °C. The reaction was stirred at 0 °C for 10 min, at which time TLC indicated the reaction was complete. 40.0 mL dichloromethane and 20.0 mL H_2O were added to the reaction, and the layers were separated. The aqueous layer was extracted with 5 30 mL portions of dichloromethane. The organic portions were combined, washed with brine, dried over sodium sulfate, and concentrated under vacuum. The residue was purified by column chromatography on silica gel (10% then 20% then 35% EtOAc in hexanes). 80.3%.

^{1}H NMR (500 MHz $CDCl_3$): δ 7.76 (d, *J* = 7.6 Hz, 2H), 7.59 (d, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 3H), 7.25-7.28 (m, 2H), 7.15-7.21 (m, 3H), 5.57-5.66 (m, 1H), 5.50 (dd, *J* = 6.8 Hz, 1H), 4.38-4.48 (m, 3H), 4.21 (t, *J* = 6.7 Hz, 1H), 4.06 (s, 1H), 3.51-3.62 (m, 1H), 3.49 (s, 4H), 2.61-2.74 (m, 2H), 2.0-2.1 (m, 2H), 1.75-1.90 (m, 2H), 1.01 (s, 1H), 0.89 (t, *J* = 7.4, 3H); ^{13}C NMR (126 MHz $CDCl_3$): δ 156.4, 144.2, 142.2, 141.5, 133.5, 131.9, 128.5, 127.8, 127.2, 125.9, 125.1, 120.1, 72.4, 66.4, 52.7, 51.0, 47.6, 38.9, 34.6, 32.1, 31.9, 28.3, 25.4, 10.3.



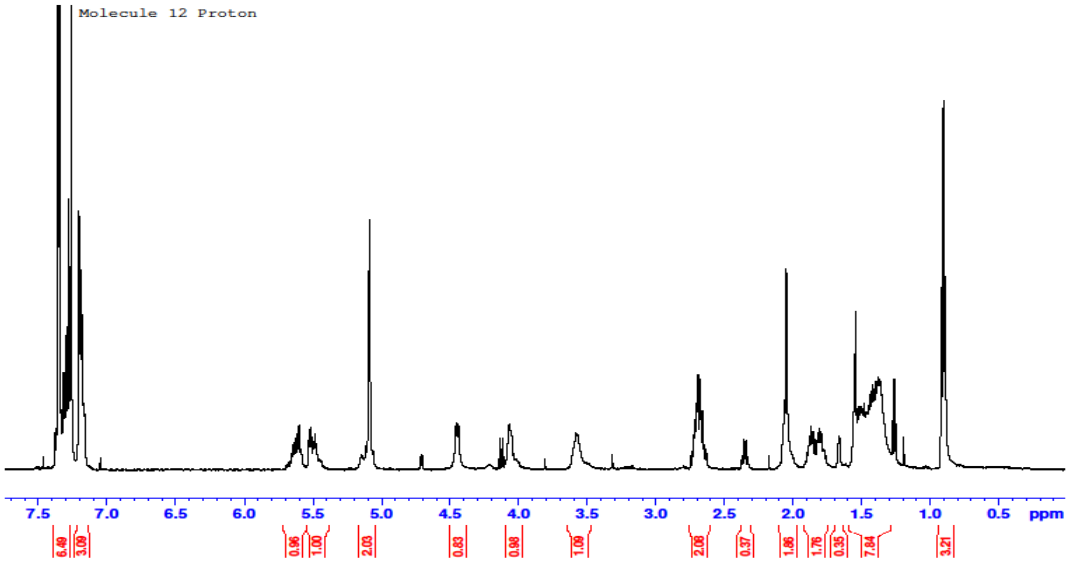


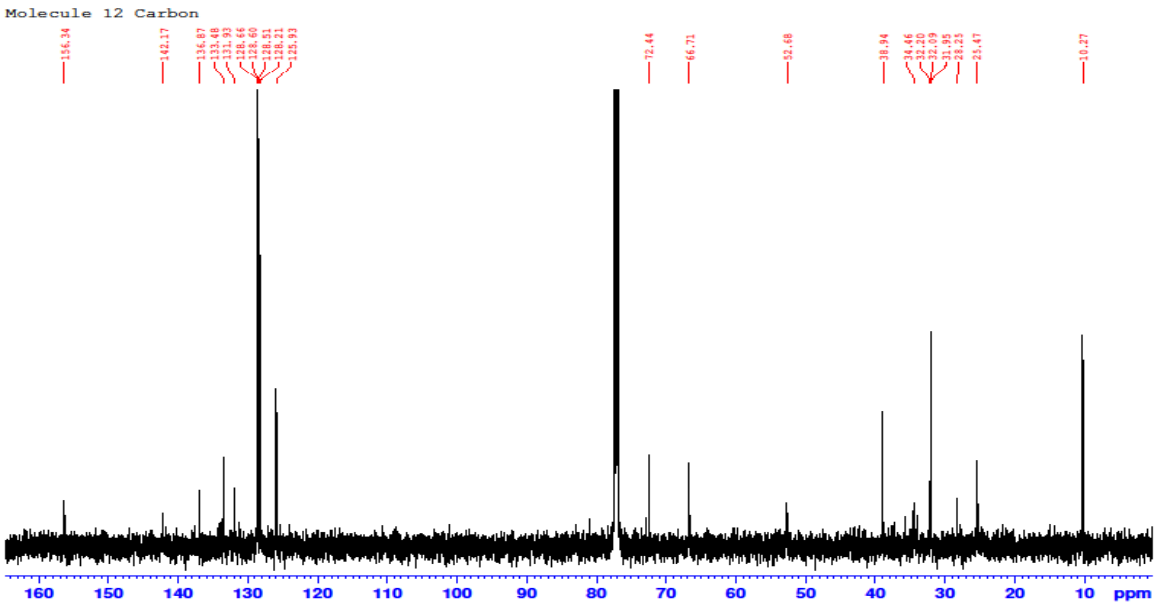


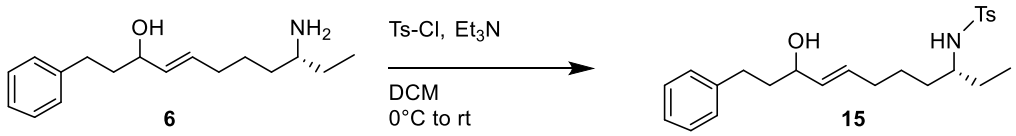
Benzyl ((3R, E)-9-hydroxy-11-phenylundec-7-en-3-yl) carbamate (Molecule 12)

To a flame-dried flask with a stir bar was added (9R,E)-9-amino-1-phenylundec-4-en-3-ol (0.765 mmol), 3.1 mL dry THF, and Na_2CO_3 (1.5 eq, 1.148 mmol). Benzyl chloroformate (0.95 eq, 0.727 mmol, 0.10 mL) was added dropwise with stirring over 5 min at room temperature. The reaction was stirred overnight at room temperature, until TLC indicated reaction completion. The reaction mixture was filtered through a pad of Celite and concentrated under vacuum. The residue was purified by column chromatography on silica gel (20% EtOAc in hexanes then 1:1 EtOAc:hexanes). 63.8%.

^{1}H NMR (500 MHz $CDCl_3$): δ 7.25-7.38 (m, 7H), 7.15-7.22 (m, 3H), 5.56-5.70 (m, 1H), 5.40-5.54 (m, 1H), 5.05-5.16 (m, 2H), 4.45 (d, *J* = 8.5 Hz, 1H), 3.99-4.09 (m, 1H), 3.51-3.64 (m, 1H), 2.62-2.75 (m, 2H), 1.75-1.92 (m, 2H), 1.28-1.59 (m, 8H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz $CDCl_3$): δ 156.3, 142.2, 136.9, 133.5, 131.9, 128.7, 128.6, 128.5, 128.2, 125.9, 72.4, 66.7, 52.6, 38.9, 34.5, 32.2, 32.1, 32.0, 28.3, 25.5, 10.3.





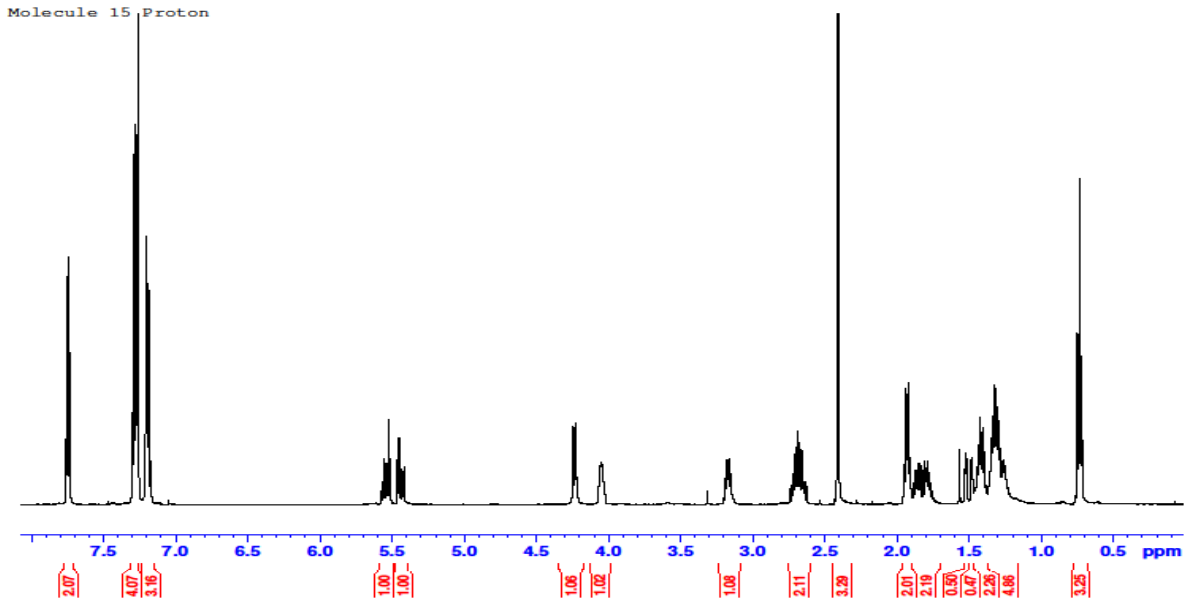


6 15

Benzyl ((3R, E)-9-hydroxy-11-phenylundec-7-en-3-yl) carbamate (Molecule 15)

To a flame-dried flask with a stir bar was added (9R,E)-9-amino-1-phenylundec-4-en-3-ol (0.574 mmol), triethylamine (1.1 eq, 0.631 mmol, 0.088 mL), and 2.0 mL dry methylene chloride. The flask was cooled to 0 °C (ice bath). Tosyl chloride (1 eq, 0.574 mmol) was dissolved separately into 0.8 mL dry methylene chloride. The tosyl chloride solution was added dropwise with stirring to reaction flask at 0 °C. The ice bath was removed and the reaction was allowed to warm to room temperature with stirring. After 15 minutes, TLC indicated completion. The reaction was quenched by addition of 3.0 mL of saturated aqueous ammonium chloride, the layers were separated, and the aqueous layer was extracted with 3 3.0 mL portions of methylene chloride. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated under vacuum. Purified by silica gel column chromatography (10% to 35% EtOAc in hexanes gradient). 54.5%

^{1}H NMR (500 MHz $CDCl_3$): δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.26-7.30 (m, 4H), 7.17-7.21 (m, 3H), 5.51-5.57 (m, 1H), 5.44 (dd *J* = 6.8 Hz, 1H), 4.24 (d, *J* = 8.4 Hz, 1H), 4.02-4.08 (m, 1H), 3.13-3.21 (m, 1H), 2.63-2.74 (m, 2H), 2.41 (s, 3H), 1.93 (q, *J* = 6.8 Hz, 2H), 1.75-1.88 (m, 2H), 1.50 (d, *J* = 3.7 Hz, 1H), 1.16-1.46 (m, 7H), 0.73 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz $CDCl_3$): δ 143.3, 142.1, 138.6, 133.5, 131.6, 129.7, 128.6, 127.2, 126.0, 72.4, 55.4, 39.0, 34.2, 32.0, 31.9, 27.9, 24.9, 24.8, 21.6, 9.7; HRMS (ESI+) *m/z* calcd for $C_{24}H_{32}NO_2S$ $[M+H]^+$ 398.2148, found 398.2155.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ppm
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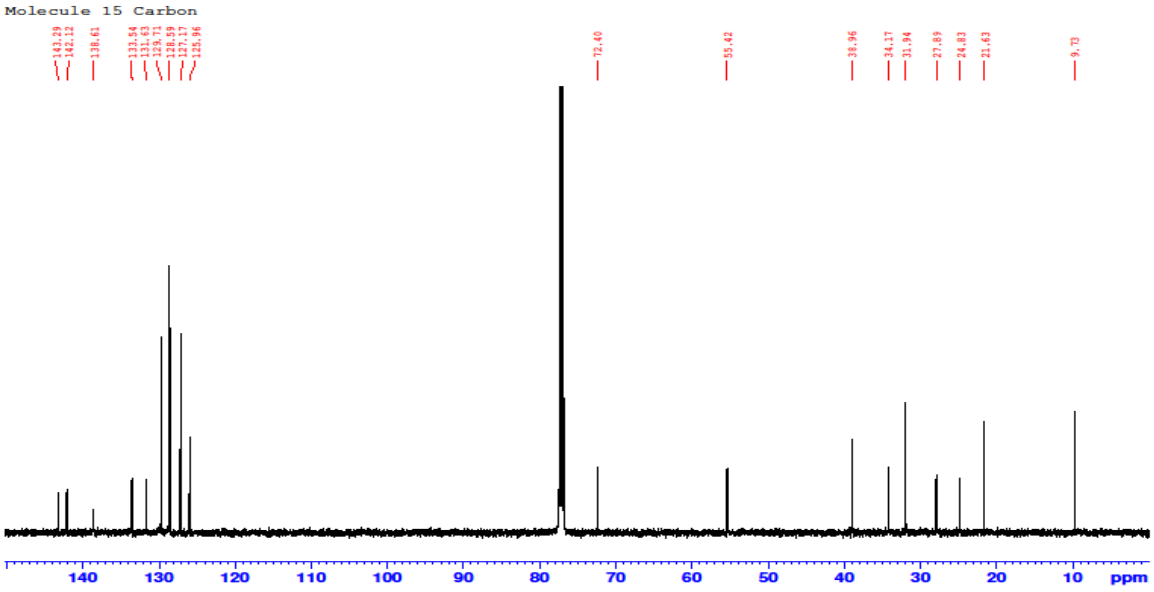
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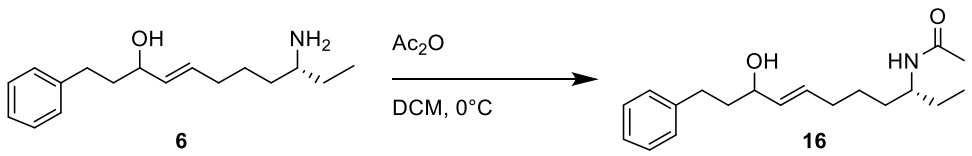
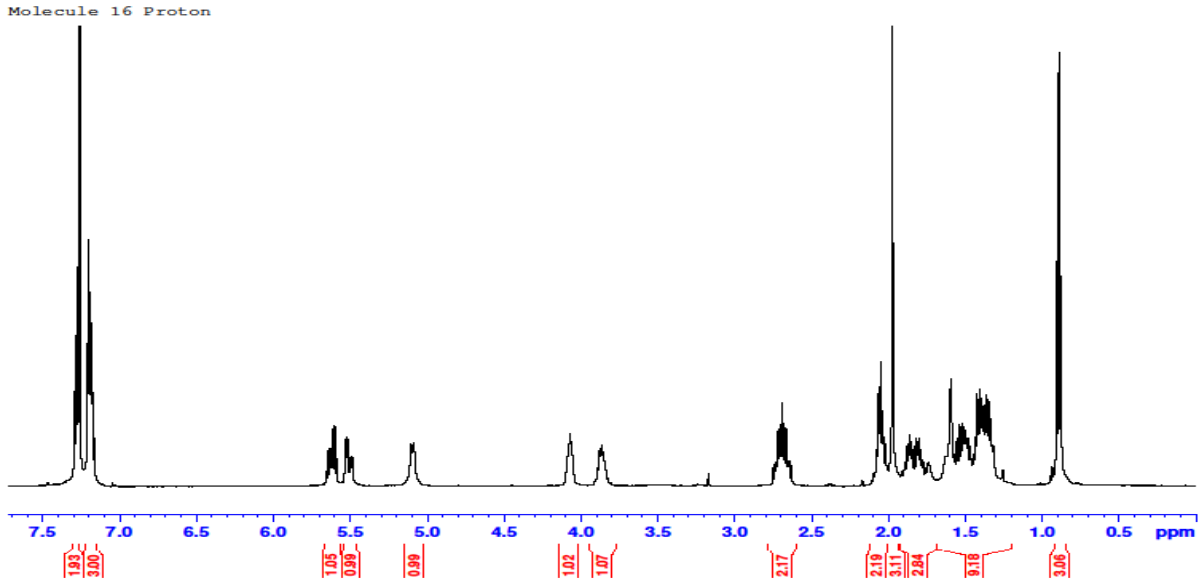


6 16

***N*-((3R,E)-9-Hydroxy-11-phenylundec-7-en-3-yl) acetamide (Molecule 16)**

To a flame-dried flask with a stir bar was added (9R,E)-9-amino-1-phenylundec-4-en-3-ol (0.383 mmol) and 3.83 mL dry methylene chloride. The flask was cooled to 0 °C (ice bath). Acetic anhydride (1 eq, 0.383 mmol, 0.036 mL) was added dropwise with stirring at 0 °C, and the reaction was stirred at 0 °C. After 30 min, TLC indicated reaction completion. The reaction was quenched with 2.0 mL H_2O and the layers were separated. The aqueous layer was extracted with 3 3.0 mL portions of methylene chloride and the combined organics were washed with saturated aqueous $NaHCO_3$, then brine, dried over sodium sulfate, and concentrated under vacuum. Purified by silica gel column chromatography (100% EtOAc). 48.7%.

^{1}H NMR (500 MHz $CDCl_3$): δ 7.26-7.30 (m, 2H), 7.16-7.20 (m, 3H), 5.59-5.66 (m, 1H), 5.48-5.53 (m, 1H), 5.10 (d, *J* = 8.2 Hz, 1H), 4.05-4.10 (m, 1H), 3.80-3.91 (m, 1H), 2.63-2.75 (m, 2H), 2.01-2.10 (m, 2H), 1.97 (s, 3H), 1.69-1.91 (m, 3H), 1.26-1.66 (m, 9H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz $CDCl_3$): δ 169.7, 142.2, 133.6, 131.9, 128.6, 125.9, 72.4, 50.7, 50.5, 39.0, 34.3, 32.2, 32.0, 28.0, 25.4, 23.7, 10.3; HRMS (ESI+) *m/z* calcd for $C_{19}H_{30}NO_2$ $[M+H]^+$ 304.2271, found 304.2267.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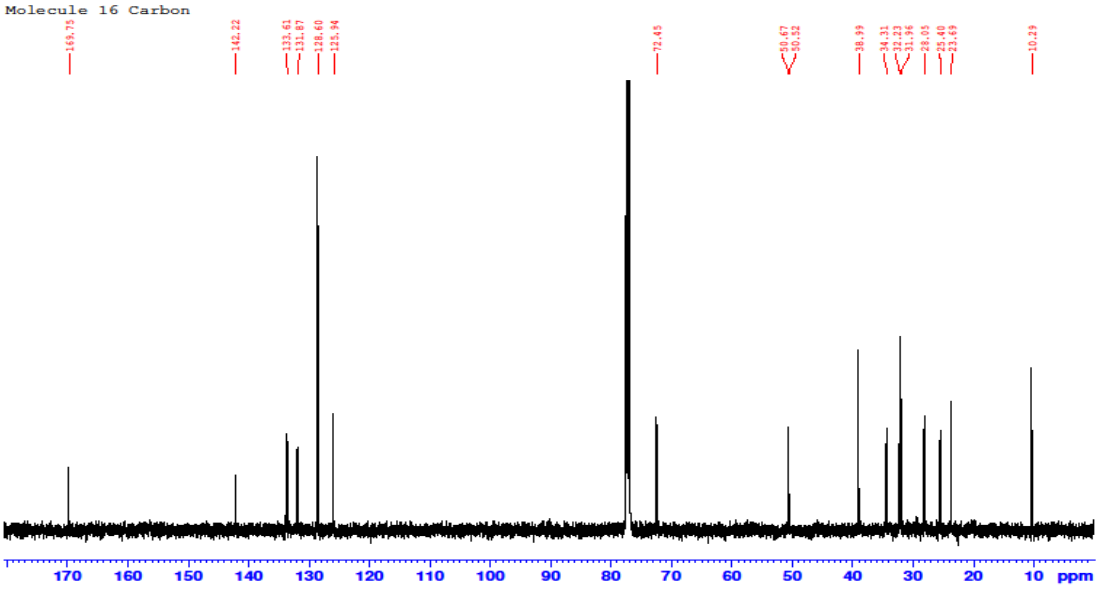
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32.23
31.96
28.05
25.40
23.69
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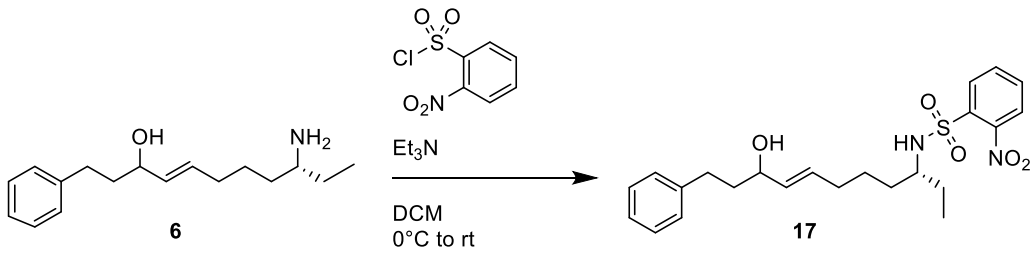
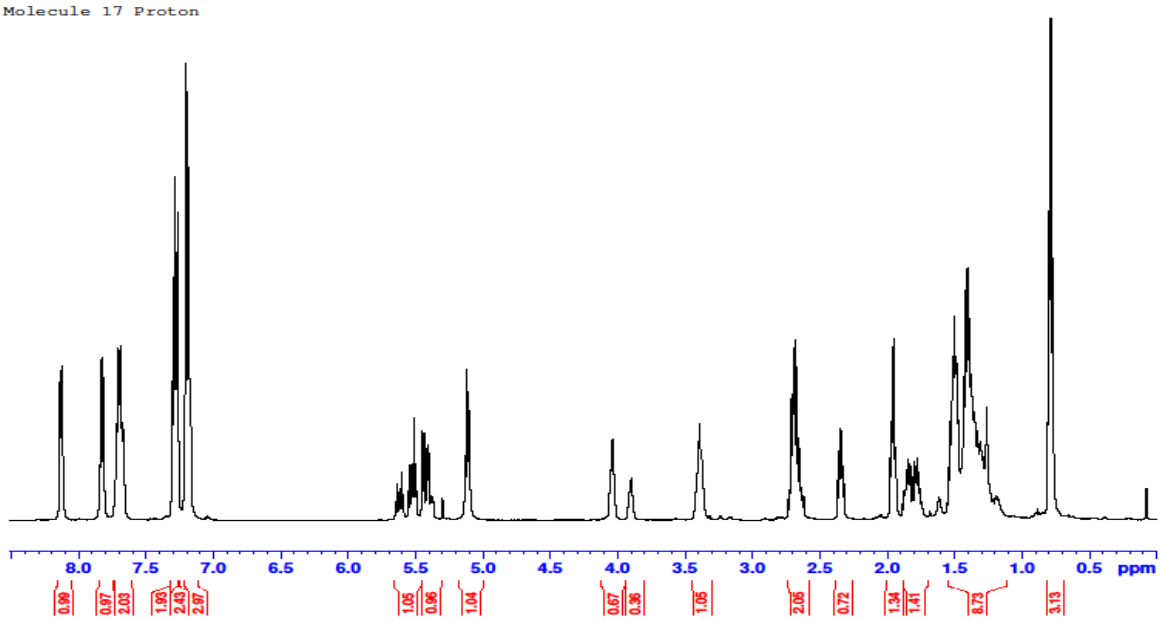
ppm

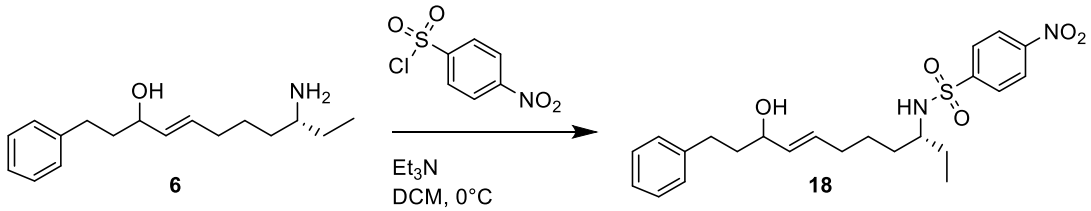


***N*-((3R, E)-9-Hydroxy-11-phenylundec-7-en-3-yl)-2-nitrobenzenesulfonamide (Molecule 17)**

To a flame-dried flask with a stir bar was added (9R,E)-9-amino-1-phenylundec-4-en-3-ol (0.459 mmol), triethylamine (1 eq, 0.459 mmol, 0.064 mL), and 0.93 mL dry methylene chloride. The flask was cooled to 0 °C (ice bath). 2-Nitrobenzenesulfonyl chloride (0.91 eq, 0.417 mmol) was added in equal portions at 1 min intervals over 5 min with stirring at 0 °C. Allowed to warm to room temperature and stirred for 15 min, at which time TLC indicated reaction completion. The reaction was quenched by addition of 0.93 mL of 1M aqueous HCL, and the aqueous and organic layers were separated. The aqueous was extracted with 3 1 mL portions of methylene chloride, and the combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under vacuum. Purified by silica gel column chromatography (100% hexanes then 1:1 hexanes:EtOAc). 27.8%.

^{1}H NMR (500 MHz $CDCl_3$): δ 8.13 (d, *J* = 7.6, 1H), 7.81-7.85 (m, 1 H), 7.65-7.74 (m, 2H), 7.27-7.31 (m, 2H), 7.16-7.22 (m, 3H), 5.50-5.65 (m, 1H), 5.36-5.46 (m, 1H), 5.12 (t, *J* = 7.7 Hz, 1H), 4.04 (q, *J* = 6.4 Hz, 1H), 3.35-3.43 (m, 1H), 2.62-2.73 (m, 2H), 2.34 (q, *J* = 7.3 Hz, 1H), 1.95 (q, *J* = 6.9 Hz, 1H), 1.73-1.89 (m, 1H), 1.14-1.56 (m, 9H), 0.78 (t, *J* = 7.3 Hz, 3H).



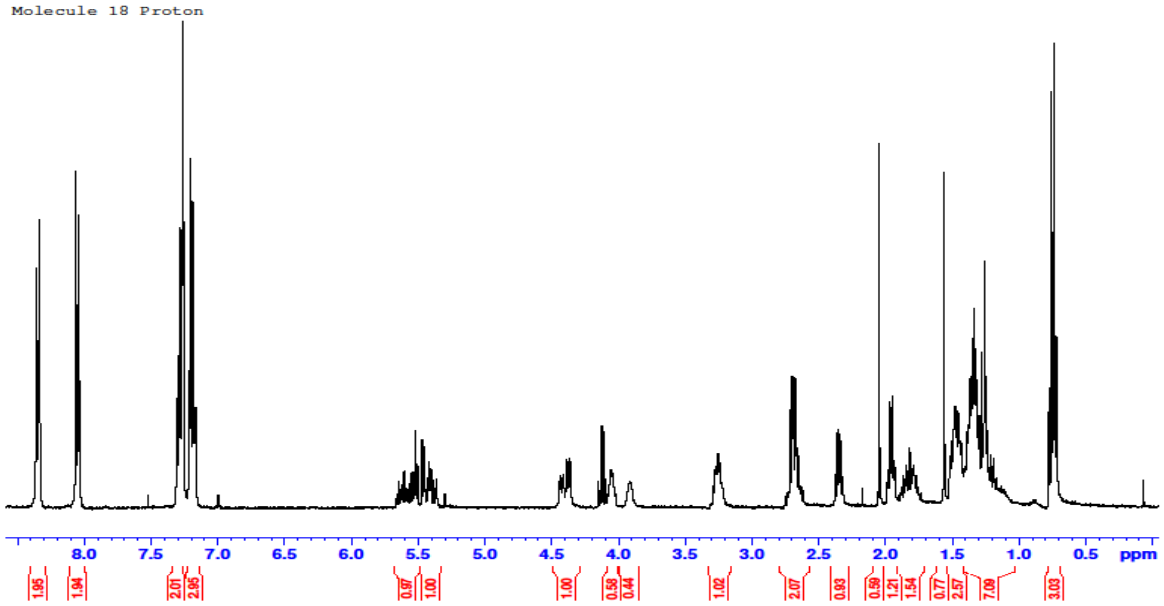


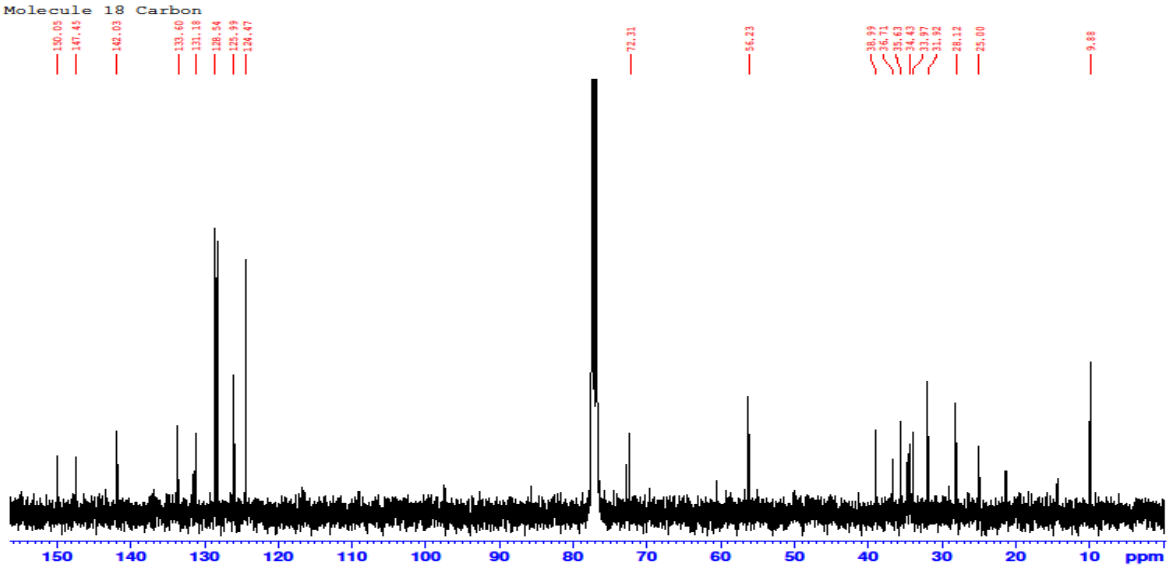
***N*-((3R, E)-9-Hydroxy-11-phenylundec-7-en-3-yl)-4-nitrobenzenesulfonamide (Molecule 18)**

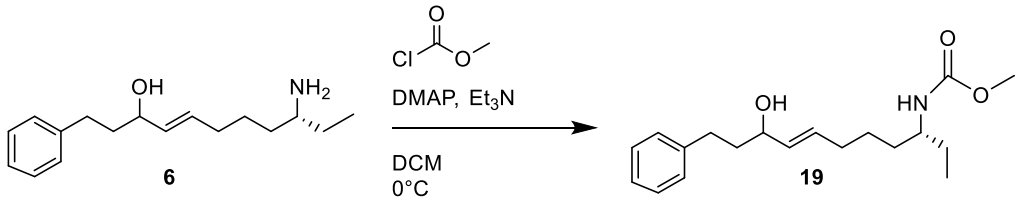
To a flame-dried flask with a stir bar was added (9R,E)-9-amino-1-phenylundec-4-en-3-ol (0.287 mmol), 0.7 mL dry methylene chloride, and triethylamine (1.1 eq, 0.316 mmol, 0.044 mL). The flask was cooled to 0 °C (ice bath). 4-Nitrobenzenesulfonyl chloride (1 eq, 0.287 mmol) was dissolved separately into 0.7 mL dry methylene chloride, and added dropwise with stirring over 5 min to the reaction flask at 0 °C. Immediately after addition ceased, TLC indicated reaction completion. The reaction was quenched with 1.0 mL saturated aqueous ammonium chloride and the layers were separated. The aqueous layer was extracted with 3 1 mL portions of methylene chloride. The combined organic layers were washed with

brine, dried over sodium sulfate, and concentrated under vacuum. Purified by silica gel column chromatography (10% then 35% EtOAc in hexanes). 44.9%.

^{1}H NMR (400 MHz $CDCl_3$): δ 8.35 (d, *J* = 8.8 Hz, 2H), 8.05 (d, *J* = 8.7 Hz, 2H), 7.27-7.31 (m, 2H), 7.16-7.22 (m, 3H), 5.51-5.66 (m, 1H), 5.36-5.48 (m, 1H), 4.37 (d, *J* = 9.0 Hz, 1H), 4.05 (p, *J* = 5.6 Hz, 1H), 3.20-3.31 (m, 1H), 2.61-2.75 (m, 2H), 2.35 (q, *J* = 7.2 Hz, 1H), 1.96 (q, *J* = 6.8 Hz, 1H), 1.74-1.90 (m, 2H), 1.10-152 (m, 9H), 0.74 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz $CDCl_3$): δ 150.0, 147.5, 142.0, 133.6, 131.2, 128.5, 126.0, 124.5, 72.3, 56.2, 39.0, 36.7, 35.6, 34.4, 34.0, 31.9, 28.1, 25.0, 9.9; HRMS (ESI-) *m/z* calcd for $C_{23}H_{29}N_2O_5S$ $[M]^-$ 445.1792, found 445.1770.



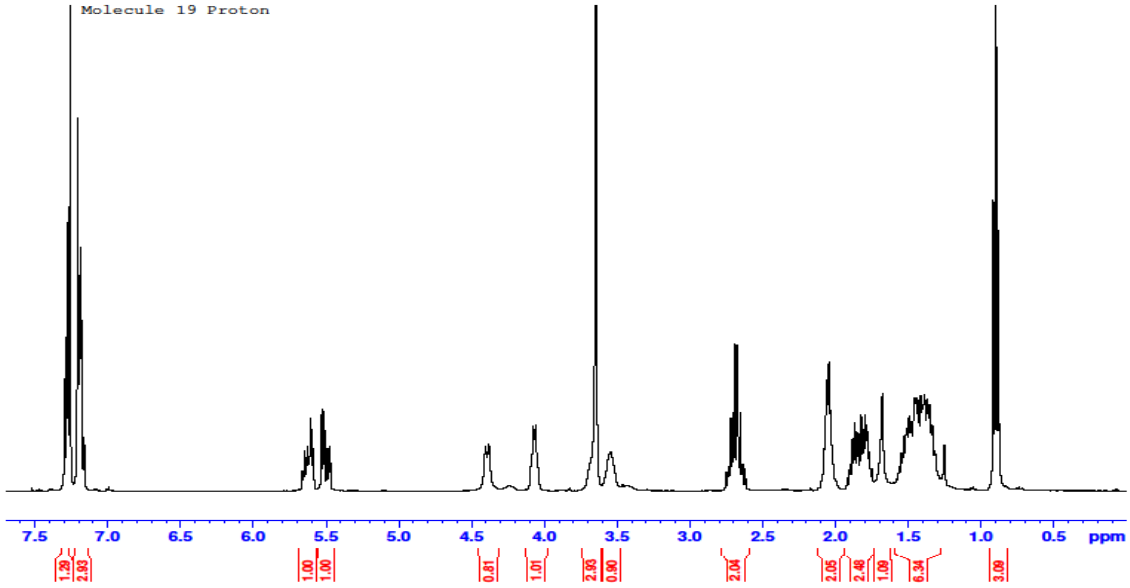


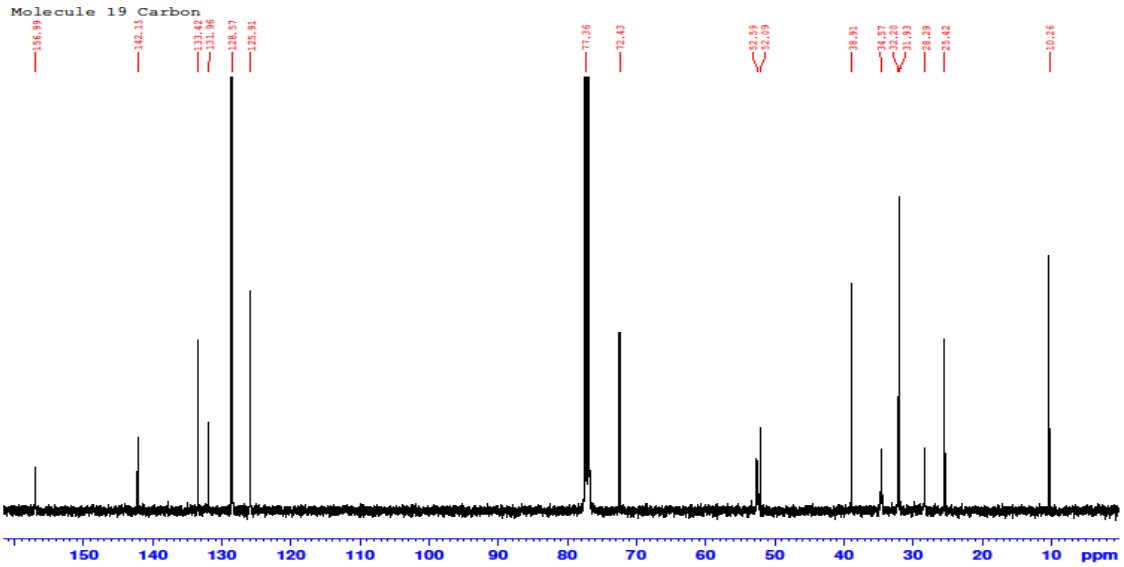


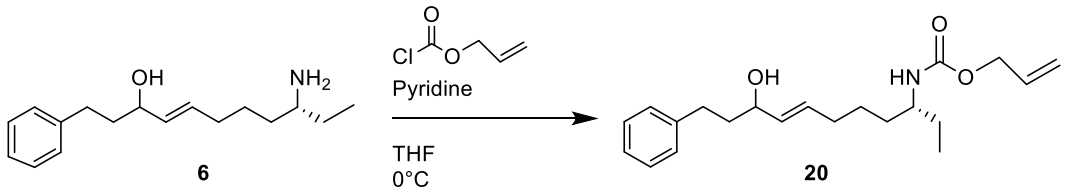
Methyl ((3R, E)-9-hydroxy-11-phenylundec-7-en-3-yl) carbamate (Molecule 19)

To a flame-dried flask with a stir bar was added (9R,E)-9-amino-1-phenylundec-4-en-3-ol (0.383 mmol) and 7.66 mL dry methylene chloride. The flask was cooled to 0 °C (ice bath). Triethylamine (1.1 eq, 0.421 mmol, 0.059 mL) was added dropwise with stirring at 0 °C. 4-Dimethylaminopyridine (0.1 eq, 0.0383 mmol) was added as a single portion with stirring at 0 °C. Methyl chloroformate (0.95 eq, 0.363 mmol, 0.028 mL) was added dropwise with stirring at 0 °C. The reaction was stirred at 0 °C for 15 min, at which time TLC indicated reaction completion. The reaction was quenched by addition of 5 mL of saturated aqueous ammonium chloride, the layers were separated, and the aqueous layer was extracted with 3 5 mL portions of methylene chloride. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated under vacuum. Purified by silica gel column chromatography (10% to 35% EtOAc in hexanes, gradient). 57.1%.

^{1}H NMR (400 MHz $CDCl_3$): δ 7.26-7.30 (m, 2H), 7.15-7.22 (m, 3H), 5.58-5.67 (m, 1H), 5.47-5.54 (m, 1H), 4.39 (d, *J* = 8.6 Hz, 1H), 4.07 (m, 1H), 3.65 (s, 3H), 3.50-3.59 (m, 1H), 2.626-2.75 (m, 2H), 1.99-2.10 (m, 2H), 1.74-1.92 (m, 2H), 1.68 (s, 1H), 1.25-1.56 (m, 7H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz $CDCl_3$): δ 157.0, 142.1, 133.4, 132.0, 128.6, 125.9, 77.4, 72.4, 52.6, 52.1, 38.9, 34.6, 32.2, 31.9, 28.3, 25.4, 10.3; HRMS (ESI+) *m/z* calcd for $C_{19}H_{30}NO_3$ $[M+H]^+$ 320.2220, found 320.2235.



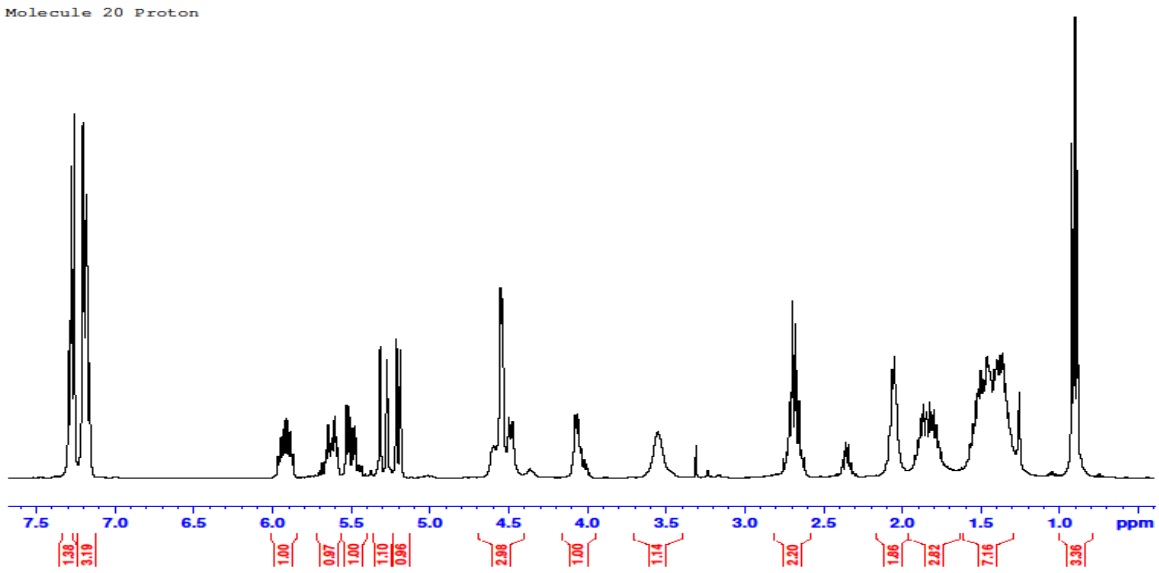




Allyl ((3R, E)-9-hydroxy-11-phenylundec-7-en-3-yl) carbamate (Molecule 20)

To a flame-dried flask with a stir bar was added (9R,E)-9-amino-1-phenylundec-4-en-3-ol (0.765 mmol) and 2.8 mL dry THF. The flask was cooled to 0 °C. Pyridine (0.95 eq, 0.727 mmol, 0.059 mL), then alloc chloride (0.95 eq, 0.727 mmol, 0.077 mL) were added dropwise with stirring at 0 °C. The reaction was stirred at 0 °C for 90 min, at which time TLC indicated completion. The reaction mixture was filtered through a pad of Celite, the filtrate was concentrated under vacuum, resuspended in diethyl ether, and filtered through a pad of Celite a second time. The filtrate was washed with deionized water, then brine, dried over magnesium sulfate, and concentrated under vacuum. The residue was purified by silica gel column chromatography (10% to 35% EtOAc in hexanes, gradient). 15.1%.

^{1}H NMR (400 MHz $CDCl_3$): δ 7.26-7.30 (m, 2H), 7.15-7.22 (m, 3H), 5.86-5.98 (m, 1H), 5.57-5.71 (m, 1H), 5.43-5.54 (m, 1H), 5.29 (dd, *J* = 17.2, 1.3 Hz, 1H), 5.20 (d, *J* = 10.4 Hz, 1H), 4.45-4.63 (m, 3H), 3.98-4.10 (m, 1H), 3.55 (s, 1H), 2.61-2.76 (m, 2H), 1.99-2.10 (m, 2H), 1.72-1.93 (m, 3H), 1.28-1.58 (m, 7H), 0.90 (t, *J* = 7.4 Hz, 3H).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2.20
1.86
2.62
7.16
3.36

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