SILVER (I) CATALYZED CYCLOISOMERIZATIONS OF ENESULFONAMIDES AND ENECARBAMATES

by

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Abstract

Eight substrates with the general structure 11.0 were synthesized. The substrates differed with respect to the heteroatom tether ($X = \text{oxygen or nitrogen}$), nitrogen protecting group ($PG = p$-toluenesulfonamid, tert-butylcarbamate, methyl carbamate), and substitution on the ring ($Y = \text{H or Ph}$). Silver (I)-catalyzed cycloisomerizations of the enesulfonamide and enecarbamate substrates successfully gave eight diene products 11.1a-h in poor to good yields (36-81%). Diene 11.1a was also further subjected to the Diels Alder reaction, with acrolein and methacrolein to give tricyclic cycloadducts 11.21a and 11.22a.
# Table of Contents

Abstract.................................................................................................................................................. ii
Table of Contents....................................................................................................................................... iii
List of Tables............................................................................................................................................ iv
List of Figures........................................................................................................................................... v
List of Schemes......................................................................................................................................... vi
List of Abbreviations and Symbols........................................................................................................ viii
Acknowledgements............................................................................................................................... xi

I. Introduction........................................................................................................................................... 1
II. Results and Discussion......................................................................................................................... 10
   A. Synthesis of Substrates....................................................................................................................... 10
      1. Synthesis of Oxygen-Tethered Substrates 11.0a-d................................................................. 10
      2. Synthesis of Nitrogen-Tethered Substrates 11.0e-h........................................................... 16
   B. Cycloisomerization Reactions......................................................................................................... 29
   C. Further Results................................................................................................................................. 33
III. Conclusion and Future Research...................................................................................................... 35
IV. Experimental....................................................................................................................................... 36
   A. General .......................................................................................................................................... 36
   B. Synthesis of Substrates.................................................................................................................... 37
   C. Cycloisomerization Reactions......................................................................................................... 71
   D. Diels Alder Reactions...................................................................................................................... 77
V. References........................................................................................................................................... 81
VI. Appendix: Selected Spectra................................................................................................................ 84
List of Tables

Table 1: Attempted Allylic Aminations to Introduce Nitrogen Tether..........................17
Table 2: Attempted Mitsunobu Reaction Conditions to
    Introduce Nitrogen Tether.................................................19
Table 3: Reaction Conditions attempted for Alkylation of
    Carbamates 26.1f and 26.2g..................................................26
Table 4: Reaction Conditions attempted for Alkylation of Carbamates 26.2..................28
Table 5: Reaction Conditions attempted for Alkylation of Carbamate 28.2 ..................29
Table 6: AgOTf-Catalyzed Cycloisomerizations of 11.0a-h.................................30
Table 7: NMR data for 11.0a.........................................................125
Table 8: NMR data for 11.0b.........................................................127
Table 9: ^H Selective NOE Data for 11.0b.............................................128
Table 10: NMR data for 11.0c.........................................................131
Table 11: NMR data for 11.0d.........................................................133
Table 12: ^H Selective NOE Data for 11.0d.............................................134
Table 13: NMR data for 11.0e.........................................................136
Table 14: ^H Selective NOE Data for 11.0e.............................................137
Table 15: NMR data for 11.0g.........................................................140
Table 16: NMR data for 11.0h.........................................................143
Table 17: X-Ray Crystallographic Experimental Data.........................................147
List of Figures

Figure 1: Silver (I) complexes with alkenes and 3-hexyne........................................2
Figure 2: General structure of required substrates.......................................................10
Figure 3: Analysis of Stereochemistry and $^1$H Selective NOE Data 
for Alcohol 13.5........................................................................................................13
Figure 4: $^1$H Selective NOE Data for Azides 25.3f and 25.3g ....................................24
Figure 5: $^1$H Selective NOE Correlation between alkenyl protons in 11.1 .............31
List of Schemes

Scheme 1: Palladium-Catalyzed Cycloisomerizations of 1,6-Enynes ..................................1
Scheme 2: Churchill’s Molecular Structure and Solid State Molecular Structure of Tris(triphenylphosphine)pentakis (pentafluorophenylethynyl)rhodiumdisilver ......................................3
Scheme 3: Scott’s Silver (I) complexes with Cyclic Polyacetylenes ..................................4
Scheme 4: 12-Membered Macrocycle Sandwich Complexes of Tribenzocyclododeca-1,5,9-triene-3,7,11-triyne (TCB) and the Solid State Molecular Structures .....................................................4
Scheme 5: Silver (I) Complexes and their Solid State Molecular Structures ..........................5
Scheme 6: Early silver(I)-catalyzed cycloisomerizations afforded butenolides .........................6
Scheme 7: Marshall’s synthesis of trisubstituted furans from alkynyl allylic alcohols ..................7
Scheme 8: Syntheses of prolines and pyrroles using Silver (I) Catalyzed Isomerizations ............7
Scheme 9: Dake’s Synthesis of 1,3-Dienes through Cycloisomerizations of Enesulfonamides and Enecarbamates ..........................................................8
Scheme 10: Diels Alder Reaction on Diene 9.1e .................................................................8
Scheme 11: Proposed transformation for research project ....................................................9
Scheme 12: Synthesis of Oxygen-Tethered Enesulfonamide 11.0a .......................................11
Scheme 13: Synthesis of Oxygen-Tethered, Phenyl-Substituted Enesulfonamide 11.0b ............12
Scheme 14: Synthesis of Oxygen-Tethered Enecarbamate 11.0c .........................................13
Scheme 15: Mechanism of Bromoketalization .....................................................................14
Scheme 16: Synthesis of Oxygen-Tethered tert-Butyl Carbamate 11.0d ...............................15
Scheme 17: Proposed Retrosynthesis of Nitrogen-Tethered Enesulfonamide 11.0e, using an Allylic Amination ..................................................................................16
Scheme 18: Proposed Synthesis for the Nitrogen Tether of Enesulfonamide 11.0e, using a Mitsunobu reaction .................................................................17
Scheme 19: Mechanism of the Mitsunobu Reaction ................................................. 18
Scheme 20: Proposed Synthesis for the Nitrogen Tether of
Enesulfonamide 11.0e, through Conversion to an Azide ......................... 20
Scheme 21: Mechanism of Conversion from Alcohol to Azide
using Diphenylphosphorylazide ............................................................. 20
Scheme 22: Experimentally Observed Products,
Based on the Order of Reagent Addition ............................................. 21
Scheme 23: Formation of unwanted side product, through
Two possible reaction pathways ................................................................. 22
Scheme 24: Synthesis of Nitrogen-Tethered Enesulfonamide 11.0e .................. 23
Scheme 25: Mechanism for the Formation of diastereomers 25.3f and 25.3g .......... 23
Scheme 26: Synthesis of Diastereomeric Enesulfonamides 11.0f and 11.0g ........ 25
Scheme 27: Synthesis of Nitrogen-Tethered Enecarbamate 11.0h ..................... 27
Scheme 28: Attempted Synthesis of tert-Butyl carbamate Cyclization Precursor .... 28
Scheme 29: Proposed Mechanism of Cycloisomerization Reaction .................... 32
Scheme 30: Solid State Molecular Structure of Dimer 11.1D ............................ 32
Scheme 31: Diels Alder Reaction of Diene 11.1a with Acrolein ...................... 33
Scheme 32: Transition State Depiction for Diels Alder Reaction of
Diene 11.1a with Acrolein .......................................................... 33
Scheme 33: Transition State Depiction for Diels Alder Reaction of
Diene 11.11a ..................................................................................... 34
Scheme 34: Diels Alder Reaction of Diene 11.1a with Methacrolein ................. 34
Scheme 35: Key silver (I)-catalyzed cycloisomerization ................................... 35
Scheme 36: Alkene Migration for Formation of Furans and Pyroles ................. 36
<table>
<thead>
<tr>
<th>Abbreviation</th>
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</tr>
<tr>
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</tr>
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</tr>
<tr>
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</tr>
<tr>
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</tr>
<tr>
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</tr>
<tr>
<td>brsm</td>
<td>based on recovered starting materials</td>
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<tr>
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<tr>
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</tr>
<tr>
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<td>dibenzylideneacetone</td>
</tr>
<tr>
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<td>1,8-diazabicyclo[5,4,0]undec-7-ene</td>
</tr>
<tr>
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</tr>
<tr>
<td>DEAD</td>
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</tr>
<tr>
<td>DIAD</td>
<td>diisopropyl azodicarboxylate</td>
</tr>
<tr>
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<tr>
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<td>N,N-(dimethylamino)pyridine</td>
</tr>
<tr>
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<td>N,N-dimethylformamide</td>
</tr>
<tr>
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</tr>
<tr>
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</tr>
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equiv equivalent(s)
ESI electrospray ionization
et. al et alii (Latin)
g gram(s)
h hour(s)
HMQC Heteronuclear Multiple-Quantum Correlation
HRMS high resolution mass spectroscopy
Hz Hertz
IR infrared
J coupling constant
m multiplet
mCPBA meta-chloroperoxybenzoic acid
Me methyl
mg milligram(s)
MHz MegaHertz
min minute(s)
ml milliliter(s)
μL microliter(s)
mmol millimole(s)
mp melting point
Ms methanesulfonate
MS mass spectroscopy, molecular sieves
N Normal
NEt₃ triethylamine
NMR Nuclear Magnetic Resonance
NOE Nuclear Overhauser Effect
OEt₂ diethyl ether
OMe methoxy
OTf trifluoromethanesulfonate
P protecting group
PCy₃ tricyclohexylphosphine
Ph phenyl
PPh₃ triphenylphosphine
ppm parts per million
^Pr isopropyl
q quartet
rt room temperature
s singlet
S_N1 unimolecular nucleophilic substitution
S_N2 bimolecular nucleophilic substitution
t triplet
TBDPS tert-butyldiphenylsilyl
td triplet of doublets
temp. temperature
TFA trifluoroacetic acid
THF tetrahydrofuran
TLC thin layer chromatography
TMS trimethylsilyl
Ts, tosyl para-toluenesulfonamide
UV Ultraviolet
Z zusammem (configuration)
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I. Introduction

Transition metal catalyzed reactions allow the transformation of relatively simple starting materials into interesting and more complex structures, using relatively simple reaction conditions. Cycloisomerization reactions catalyzed by palladium, platinum, and gold have been widely studied and reviewed in the past 20 years. Scheme 1 shows some cycloisomerizations of 1,6-enynes that can be achieved using transition metal catalysis. In each example, the reaction is typically initiated by coordination of the transition metal to a site of unsaturation (i.e. alkenes or alkynes) in the substrate. Compared with platinum and palladium catalysis, silver catalysis has been studied to a lesser extent; however, more examples have been appearing in the literature.

Scheme 1: Palladium-Catalyzed Cycloisomerizations of 1,6-Enynes
The ability of silver (I) to complex to alkenes was first demonstrated by Lucas et al. in 1937, through the formation of a water soluble isobutene-silver complex. Winstead and Lucas expanded the scope of these studies in 1938, when they showed that silver (I) could rapidly and reversibly complex to a variety of alkenes, such as 1-hexene, cyclohexene, dimethylbutadiene, and allyl alcohol as shown in Figure 1. Their research was based on a distribution method, which involved distributing the olefin between carbon tetrachloride and aqueous silver nitrate, then determining the quantity of alkene in the aqueous layer. When the olefin was distributed between carbon tetrachloride and various mixtures of aqueous silver nitrate/potassium nitrate, the quantity of olefin in the aqueous layer was again determined. The changes in the quantity of olefin in the aqueous layer could be compared to the changes in concentration of Ag⁺ in the aqueous layer. Applying the same distribution method, Dorsey and Lucas found in 1956 that silver (I) also complexes with alkynes such as 3-hexyne.

In 1976, Lewandos et al. further studied silver (I) π-complexes with olefins and alkynes using NMR spectroscopy and IR spectroscopy. In the ¹H NMR spectrum of cyclohexene the signals at 5.65 ppm and 1.97 ppm, due to the vinylic and allylic protons respectively, were shifted downfield to 5.87 ppm and 2.05 ppm respectively after 0.36 equiv of silver trifluoromethanesulfonate were added. The α and β protons in 3-hexyne were shifted downfield from 2.14 ppm to 2.23 ppm and from 1.04 ppm to 1.08 ppm, respectively, after the addition of 0.36 equiv of silver trifluoromethanesulfonate. The signals in the ¹³C NMR spectra of various internal alkynes were all shifted downfield by 0.8 to 1.6 ppm, upon coordination to silver trifluoromethanesulfonate. IR spectroscopy showed the stretching frequency of the carbon-carbon double bond in cyclohexene.

![Figure 1: Silver (I) complexes with alkenes and 3-hexyne.](image-url)
decrease from 1651 cm$^{-1}$ to 1577 cm$^{-1}$.\textsuperscript{10} The stretching frequency of the carbon-carbon triple bond in 2-hexyne decreased from 2210 cm$^{-1}$ to 2181 cm$^{-1}$ after the coordination of silver trifluoromethanesulfonate.\textsuperscript{10} Finally, formation of the silver (I) $\pi$-complexes were also confirmed by elemental analysis.\textsuperscript{10}

In 1974, Churchill and DeBoer reported solid state molecular structure 2.1S in Scheme 2, that contained two silver atoms asymmetrically $\pi$-coordinated to three alkynes.\textsuperscript{12} Complex 2.1 was synthesized from the reaction of Wilkinson's catalyst and silver acetylide 2.0. The silver-carbon bond distances in the complex ranged from 2.33 – 3.12Å. The acetylene bond lengths ranged from 1.20 – 1.23Å, which is typical for a carbon-carbon triple bond.\textsuperscript{13} In 1985, Scott \textit{et al.} isolated two stable silver (I) complexes when polyacetylenes 3.0 and 3.2 in Scheme 3 were treated with silver trifluoromethanesulfonate and heated at 65 °C.\textsuperscript{14} In 1988, Youngs \textit{et al.} also isolated sandwich complexes of silver (I) with polyacetylene 1,2:5,6:9,10-tribenzocyclododec-1,5,9,-triene-3,7,11-triyne 4.0 (TBC).\textsuperscript{15} In Scheme 4, both the staggered conformation (4.1) and the eclipsed conformation (4.2) of the complexes were isolated. The reported silver-carbon bond lengths ranged from 2.67 – 2.81Å for 4.1S, while the silver-carbon bond lengths for 5.2S ranged from 2.47 – 2.94Å. These are consistent with the silver-carbon bond lengths of 2.33 – 3.12Å previously reported by Churchill.\textsuperscript{16}
Scheme 3: Scott's Silver (I) complexes with Cyclic Polyacetylenes.\textsuperscript{14}

Scheme 5 shows other examples of silver (I) alkyne complexes and their solid state molecular structures that have been reported in the literature.\textsuperscript{17-19} Solid state molecular structures $5.1S$, $5.3S$, and $5.5S$ show that the triflate anion remains coordinated
to silver while it coordinates to the alkyne. The silver-carbon bond lengths in all the complexes range from 2.26 - 2.48 Å and the acetylene bond lengths range from 1.20 Å to 1.24 Å. Gleiter et. al compared the acetylene bond lengths in biscyclooctyne derivative 5.4 before and after formation of the silver (I) complex. They found that the acetylene bond length increased from 1.202 Å to 1.224 Å after silver (I) was complexed to the alkyne. This lengthening of the acetylene bond, upon complexation of silver(I), suggests that complexation might weaken the carbon-carbon triple bond and perhaps make it reactive enough to act as an electrophile.
In 1958, Castaner and Pascual discovered that when an alkyne tethered to a weak nucleophile was treated with silver (I), the substrate isomerized to produce a ring and a newly formed carbon-oxygen bond. Scheme 6 shows this cycloisomerization of phenylpropargylidenemalonic acid 6.0 into butenolide 6.1 after treatment with aqueous silver nitrate. Similar conditions were later used to synthesize aurone 6.3 from arylpropynone 6.2. In 1984, Willard et al. used a silver(I)-catalyzed cycloisomerization to form the butenolide in the last step of the total synthesis of cyanobacterin 6.5. In each of these examples, silver (I) presumably coordinates to the acetylene, activating it for intramolecular nucleophilic attack by adjacent alcohols and carboxylic acids.

Scheme 6: Early silver(I)-catalyzed cycloisomerizations afforded butenolides.

1995, Marshall and Sehon demonstrated that the treatment of β-alkynyl allylic alcohol 7.0 with catalytic silver trifluoromethanesulfonate would result in the formation of trisubstituted furan 7.1 (Scheme 7).
Scheme 7: Marshall’s synthesis of trisubstituted furans from alkynyl allylic alcohols.\(^{23}\)

Several years later, Rutjes et al showed that silver (I) salts could also catalyze the intramolecular addition of an amide to a carbon-carbon triple bond, to form a new carbon-nitrogen bond. In Scheme 8, propargyl glycine derivative 8.0 is treated with silver trifluoromethanesulfonate to afford pyrrole 8.1, which can then be hydrogenated to give 2,5-disubstituted proline derivative 8.2.\(^{24}\) In 2006, Dake et al. found that β-alkynylimine 8.4, formed \textit{in situ} from β-alkynylketone 8.3, would cyclize to produce trisubstituted benzyl-protected pyrrole 8.5 upon treatment with silver trifluoromethanesulfonate in 1,2-dichloroethane.\(^{25}\)

Scheme 8: Syntheses of prolines and pyrroles using Ag (I) Catalyzed Isomerizations.\(^{24,25}\)

In 2004, Dake and Harrison presented examples of silver (I)-catalyzed cycloisomerization reactions in which intramolecular attack of enesulfonamide or enecarbamate onto an alkyne moiety resulted in a newly formed carbon-carbon bond, as
shown in Scheme 9. Treatment of enesulfonamides 9.0 with 2 mol % silver trifluoromethanesulfonate in refluxing THF/CH₂Cl₂ afforded 1,3-dienes 9.1. Several R groups attached to the alkyne in enesulfonamide 9.0 were tested. While alkyne substrates attached to alkyl groups (9.0a-b) showed no reaction, reactions using substrates containing conjugating electron-withdrawing groups such as ketones and esters (9.0c-e) were more successful. The electron-withdrawing groups served both to activate the alkyne and stabilize the reaction products. Enecarbamate 9.0f also reacted under the same conditions to give diene 9.1f. Diene 9.1e was then used for a Diels Alder reaction with acrolein, in the presence of boron trifluoride diethyl etherate at -78 °C, to afford cycloadduct 10.1 in Scheme 10.
The results from the silver (I) catalyzed cycloisomerizations of enesulfonamides and enecarbamate 9.0 were the inspiration of my research project. The reactions of these substrates resulted in the formation of a new carbon-carbon bond and a fused five-membered ring. If one carbon in substrate 9.0 could be substituted by a heteroatom (X = oxygen or nitrogen), as shown in Scheme 11, then perhaps the cycloisomerization of such a substrate 11.0 would result in the formation of a fused heterocycle 11.1. Different protecting groups on nitrogen could also be varied and tested. Dienes such as 11.1 could then be subjected to further reactions such as the Diels Alder reaction, similar to reactions performed previously.

The next section will discuss the synthesis of the various substrates 11.0, their reactions under silver (I) catalysis, and further reactivity that was studied.
II. Results and Discussion

A. Synthesis of Substrates

Eight cyclization substrates were synthesized in total; each substrate shares the same general structure shown in Figure 2. The substrates differ from one another by the heteroatom tethered to the ring (X = oxygen or nitrogen), the protecting group on nitrogen (P = Ts, CO$_2$Bu, or CO$_2$Me), and the substitution pattern at position Y in the ring (Y = H or Ph). The synthesis of the oxygen-tethered substrates will first be discussed, followed by a discussion of the nitrogen-tethered substrates.

\[ CO_2CH_3 \]

\[ P \]

\[ X = O, N \]

\[ PG = Ts, CO_2Bu, CO_2Me \]

\[ Y = H, Ph \]

Figure 2: General structure of required substrates

1. Synthesis of Oxygen-Tethered Substrates 11.0a-d

The synthesis of enesulfonamide 11.0a in Scheme 12 began with the tosylation of \( \delta \)-valerolactam 12.0.\(^{27} \) Reduction of amide 12.1 to aminol 12.2 using diisobutylaluminum hydride, followed by elimination gave enesulfonamide 12.3.\(^{28} \) Methoxybromination, followed by elimination of the bromide ion using 1,8-diazabicyclo[5,4,0]undec-7-ene afforded allylic methyl ether 12.5.\(^{29} \) \( S_n1' \) reaction with propargyl alcohol in the presence of ytterbium (III) trifluoromethanesulfonate introduced the oxygen tether onto the ring of propargyl ether 12.6.\(^{30} \) Formation of 12.6 was confirmed by the disappearance of a 3-proton singlet in the $^1$H NMR spectrum of
Scheme 12: Synthesis of Oxygen-Tethered Enesulfonamide 11.0a

12.5 and the appearance of a 2-proton doublet in the $^1$H NMR spectrum of 12.6. The 4-proton multiplet at 2.37 – 2.41 ppm in the $^1$H NMR spectrum of 12.6 is evidence of the presence of the terminal alkynyl proton, which overlaps with the 3-proton signal from the methyl group of the toluenesulfonamide functionality. Additionally, the 2-proton multiplet at 5.71 - 5.85 ppm, which corresponded to the alkene protons in the $^1$H NMR spectrum of 12.5, was replaced with two signals at 6.81 and 5.10 ppm that are characteristic of the newly formed double bond of the enesulfonamide moiety in 12.6. The combination of these spectral data assists in differentiation between 12.5 and 12.6. The presence of the enesulfonamide moiety in 12.6 means that the oxygen tether is no longer attached to the carbon adjacent to the nitrogen as in 12.5, but rather is attached to the carbon allylic to the enesulfonamide, as in 12.6. Functionalization of the terminal alkyne was accomplished by deprotonation of the alkyne with n-butyllithium at -78 °C, followed by quenching with methyl chloroformate to afford alkynyl ester 11.0a. The formation of 11.0a was confirmed by the disappearance of the one proton singlet at 2.41 ppm, which corresponds to the terminal alkyne in the $^1$H NMR spectrum 12.6, and by the appearance of a 3-proton singlet at 3.75 ppm which corresponds to the methyl ester in 11.0a.

The oxygen tether and enesulfonamide functionalities of alkynyl ester 11.0b were constructed from an aza-Diels Alder reaction, as shown in Scheme 13. Danishefsky's
diene 13.1 was synthesized from the reaction of methoxybutenone 13.0 with triethylamine-zinc chloride, followed by subsequent trapping with trimethylchlorosilane.\textsuperscript{31-32} Condensation of benzaldehyde 13.2 with N-toluensulfonamide in the presence of an ion-exchange resin afforded N-tosylated aldimine 13.3.\textsuperscript{33} Copper (I)-catalyzed aza-Diels Alder reaction of diene 13.1 with aldimine 13.3, followed by treatment with trifluoroacetic acid afforded enesulfonamide 13.4 as a racemic mixture.\textsuperscript{34} Luche reduction of enesulfonamide 13.4 afforded alcohol

\[
\begin{align*}
\text{O} & \quad \text{TMSCl, NEt}_3, \text{ZnCl}_2 \\
\text{13.0} & \quad \text{C}_6\text{H}_6, 43^{\circ}\text{C} \\
& \quad (87\%) \\
\text{OTMS} & \quad \text{13.1} \\
\end{align*}
\]

\[
\begin{align*}
\text{TsNH}_2, 5\ \text{A MS,} & \quad \text{Amberlyst 15} \\
\text{H} & \quad \text{C}_6\text{H}_5\text{CH}_3, 142^\circ\text{C} \\
& \quad (35\%) \\
\text{H} & \quad \text{N} \\
\text{Ts} & \quad \text{13.3} \\
1) & \quad 10\text{ mol}\%\ \text{CuOTf} \\
& \quad \text{PPPh}_3, \text{13.1} \\
& \quad \text{CH}_2\text{Cl}_2 \\
& \quad (63\%) \\
\text{NaBH}_4 & \quad \text{CeCl}_3, 7\text{H}_2\text{O} \\
& \quad \text{CH}_2\text{OH} \\
& \quad (92\%) \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{Br, NaH} \\
\text{THF} & \quad (54\%) \\
\text{O} & \quad \text{13.6} \\
& \quad \text{Cl} \\
& \quad \text{O} & \quad \text{O} \\
\text{CO}_2\text{CH}_3 & \quad \text{11.0b} \\
\end{align*}
\]

Scheme 13: Synthesis of Oxygen-Tethered, Phenyl-Substituted Enesulfonamide 11.0b

13.5 with a relative trans stereochemistry.\textsuperscript{35} The analysis for the assigned stereochemistry of 13.5 is shown in Figure 3. Due to A\textsuperscript{1,3} strain, the phenyl ring is expected to adopt a pseudo-axial orientation. Luche reduction of dihydropyridones is known to preferentially occur through axial attack, to give equatorial alcohols.\textsuperscript{36} Consequently, the hydride approaches enesulfonamide 13.4 from the pseudo-axial position, to give trans-alcohol 13.5. \textsuperscript{1}H selective NOE data in Figure 3 also support the
assigned trans stereochemistry. Selective irradiation of H-3a shows an NOE to the phenyl ring as well as to H-6a and H-7, supporting the assigned stereochemistry. Alkylation of alcohol 13.5 with propargyl bromide afforded propargyl ether 13.6, which was finally functionalized with methyl chloroformate to give alkynyl ester 11.0b.

Figure 3: Analysis of Stereochemistry and $^1$H Selective NOE Data for Alcohol 13.5

The synthesis of methyl carbamate 11.0c in Scheme 14 was adapted from Kozikowski$^{37}$ and Schell,$^{38}$ with some modifications. Starting with piperidone hydrochloride 14.0, the amine was protected using methyl chloroformate to afford methyl carbamate 14.1. Using Garbisch’s bromoketalization procedure, treatment of the

Scheme 14: Synthesis of Oxygen-Tethered Enecarbamate 11.0c
resulting carbamate with bromine and ethylene glycol served to α-brominate and protect the ketone in one step.\textsuperscript{39} The mechanism of bromoketalization begins with the bromination of enol of 14.1, as shown in Scheme 15. Protonated bromoketone 15.2 is activated for ketal formation with ethylene glycol. After proton transfer and production of water, bromoketal 14.2 is formed. With bromoketal 14.2 in hand, the synthesis of enecarbamate 11.0c continued with the elimination of the bromide ion of bromoketal 14.2 followed by ketal deprotection to afford enecarbamate 14.4. Evidence for the formation of 14.4 is provided by the appearance of two doublets at 7.60 and 5.06 ppm in the \textsuperscript{1}H NMR spectrum of 14.4, which correspond to the double bond of the enecarbamate moiety. Luche reduction of enone 14.4 afforded alcohol 14.5 which was alkylated to give propargyl ether 14.6.\textsuperscript{40} Functionalization of 14.6 using methyl chloroformate afforded alkynyl ester 11.0c.
Following a modified procedure of Oediger and Joop, the synthesis of tert-butyl carbamate 11.0d began with the quaternization of pyridine 16.0 with di-tert-butyl-dicarbonate, followed by reduction with sodium borohydride to give tert-butyl carbamate 16.2. Treatment of tert-butyl carbamate 16.2 with meta-chloroperoxidebenzoic acid gave epoxide 16.3. Lithium diisopropylamine, formed in situ from diisopropylamine and n-butyllithium at -78 °C, was used to open epoxide 16.3 and consequently introduce both the enecarbamate moiety and the alcohol at position 4 of enecarbamate 16.4. Again, the appearance of two multiplets 6.70 – 6.99 ppm and 4.79 – 5.08 ppm in the $^1$H NMR spectrum of 16.4, which correspond to the double bond of the enecarbamate moiety, confirm the formation of the enecarbamate. Finally, alkylation with propargyl bromide and functionalization with methyl chloroformate gave alkyl ester 11.0d.
2. Synthesis of Nitrogen-Tethered Substrates 11.0e-h

Substrates 11.0a-d contain an oxygen-tether, with variations in the nitrogen protecting group and substitution pattern on the ring. The following substrates 11.0e-h contain a nitrogen-tether, and also vary with respect to the nitrogen protecting group and the substitution pattern on the ring.

Retrosynthetically, the nitrogen tether of 11.0e was envisioned to stem from amine 17.1, which could be installed through an allylic amination of acetate 17.2 in Scheme 17. As a result, acetate 17.2 was synthesized from an $S_{N2}'$ reaction of acetic acid and methyl ether 12.5. Unfortunately, the proposed allylic amination was unsuccessful under the conditions that were tested. Allylic aminations of enesulfonamide acetates such as 17.2 have not been reported previously; however, they have been reported on cyclohexene rings. In Table 1, reaction conditions using tetrakistriphenylphosphine palladium (0), triphenylphosphine, and sodium toluenesulfonamide, $p$-toluenesulfonamide gave no reaction (entry 1). $[\text{Pd(C}_3\text{H}_5\text{Cl)]}_2$ and triphenylphosphine also gave no reaction (entry 2). Changing the nitrogen nucleophile to benzylamine (entries 3-6) or substituting triphenylphosphine for a bulkier ligand, such as

![Scheme 17: Proposed Retrosynthesis of Nitrogen-Tethered Enesulfonamide 11.0e, using an Allylic Amination](image-url)
Table 1: Attempted Allylic Aminations to Introduce Nitrogen Tether

OAc

\[
\text{catalyst, nucleophile}\text{solvent}
\]
\[\text{Z = Bn, Ts}\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalytic system</th>
<th>Nucleophile</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Result *</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 mol % (\text{Pd(PPh}_3)<em>4), 5 mol % (\text{PP}</em>{3})</td>
<td>TsNH(_2), NaNHTs</td>
<td>THF/DMSO (4:1)</td>
<td>50</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>5 mol % ([\text{Pd(C}_3\text{H}_5\text{Cl})<em>2]), 5 mol % (\text{PP}</em>{3})</td>
<td>TsNH(_2), NaNHTs</td>
<td>THF/DMSO (4:1)</td>
<td>50</td>
<td>NR</td>
</tr>
<tr>
<td>3</td>
<td>5 mol % ([\text{Pd(C}_3\text{H}_5\text{Cl})<em>2]), 5 mol % (\text{PP}</em>{3})</td>
<td>BnNH(_2)</td>
<td>CH(_2)Cl(_2)</td>
<td>45</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>5 mol % ([\text{Pd(C}_3\text{H}_5\text{Cl})_2]), 5 mol % dppe</td>
<td>BnNH(_2)</td>
<td>CH(_2)Cl(_2)</td>
<td>45</td>
<td>NR</td>
</tr>
<tr>
<td>5</td>
<td>5 mol % (\text{Pd}_2(\text{dba})<em>3), 5 mol % (\text{PP}</em>{3})</td>
<td>BnNH(_2)</td>
<td>THF</td>
<td>80</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>5 mol % (\text{Pd}_2(\text{dba})_3), 5 mol % (\text{PCy}_3)</td>
<td>BnNH(_2)</td>
<td>THF</td>
<td>80</td>
<td>NR</td>
</tr>
</tbody>
</table>

\*NR = no reaction.

1,2-bis(diphenylphosphino)ethane (entry 4), did not give the desired product. Reactions using \(\text{Pd}_2(\text{dba})_3\) with triphenylphosphine (entry 5) or \(\text{Pd}_2(\text{dba})_3\) with electron-rich tricyclohexylphosphine (entry 6) were also unsuccessful.

Another means of attaching the nitrogen tether could be through a Mitsunobu reaction from alcohol 18.1, as shown in Scheme 18. With this in mind, alcohol 18.1

Scheme 18: Proposed Synthesis for the Nitrogen Tether of Enesulfonamide 11.0e, using a Mitsunobu reaction
was synthesized from the saponification of acetate 17.2. The mechanism of the ensuing Mitsunobu reaction is outlined in Scheme 19. The nitrogen-nitrogen double bond of diethyl azodicarboxylate (DEAD) 19.0 is attacked by triphenylphosphine. Amine or amide 19.2 must be sufficiently acidic in order to protonate dicarboxylate 19.1, to yield phosphonium cation 19.3. Nucleophilic attack of alcohol 18.1 on phosphonium 19.3 forms phosphonium 19.4, where alcohol 18.1 has been activated for nucleophilic attack by a nitrogen nucleophile. The result of the Mitsunobu reaction is the conversion of an alcohol to an amine or an amide in one step, with inversion of configuration.

Unfortunately, the desired nitrogen-tethered products were not produced when alcohols 18.2 and 13.5 were treated under Mitsunobu conditions shown in Table 2. Reaction using 4-Methyl-N-prop-2-ynyl-benzenesulfonamide and DEAD (entry 1) gave no desired product. Nitrogen nucleophiles such as tert-butyl-4-toluenesulfonyl carbamate (entry 2), p-toluenesulfonamide (entry 3), and phthalimide (entry 4) are more commonly used for Mitsunobu reactions because they are more acidic than 4-methyl-N-prop-2-ynyl-benzenesulfonamide (entry 1). Phthalimide and p-toluenesulfonamide were used in hopes that these nucleophiles were less sterically hindered and could more
Table 2: Attempted Mitsunobu Reaction Conditions to Introduce Nitrogen Tether

<table>
<thead>
<tr>
<th>Entry</th>
<th>Y</th>
<th>Reaction Conditions</th>
<th>&quot;N&quot;</th>
<th>Result&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>1.3 equiv. DEAD, 1.35 equiv. PPh₃</td>
<td><img src="image" alt="Ts-N-Ph" /></td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>1.0 equiv. DIAD, 1.0 equiv. PPh₃</td>
<td><img src="image" alt="Ts-N-Boc" /></td>
<td>NR</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>1.0 equiv. DIAD, 1.0 equiv. PPh₃</td>
<td><img src="image" alt="Ts-N-H" /></td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>1.3 equiv. DIAD, 1.35 equiv. PPh₃</td>
<td><img src="image" alt="Ts-N-H" /></td>
<td>NR</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>1.0 equiv. DIAD, 1.0 equiv. PPh₃</td>
<td><img src="image" alt="Ph" /></td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>3.0 equiv. DIAD, 3.0 equiv. PPh₃</td>
<td><img src="image" alt="O-N-O" /></td>
<td>NR</td>
</tr>
</tbody>
</table>

<sup>a</sup>NR = no reaction.

effectively attack the substrate. However, these reactions were also unsuccessful. Even the replacement of DEAD with the more reactive DIAD (diisopropyl azodicarboxylate), did not give the desired results.

With the failure of the Mitsunobu reaction, another approach was investigated. The nitrogen tether of enesulfonamide 11.0e was envisioned to come from azide 20.1, as shown in Scheme 20. Unfortunately, mesylation of alcohol 18.1 followed by treatment with sodium azide, did not give azide 20.1. Gratifyingly, treatment of alcohol 18.1 with
Scheme 20: Proposed Synthesis for the Nitrogen Tether of Enesulfonamide $^{11.0e}$, Through Conversion to an Azide.

diphenylphosphorylazide (DPPA) and 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) in toluene afford the desired azide $^{20.1}$. In the mechanism of this reaction, shown in Scheme 21, the alcohol attacks diphenylphosphorylazide and generates an azide anion. Phosphate $^{21.1}$ is deprotonated by DBU to give salt $^{21.2}$ and phosphate $^{21.3}$. The azide anion, produced in situ, attacks phosphate $^{21.3}$ in an $S_N2$ fashion to give azide $^{20.1}$

Scheme 21: Mechanism of Conversion from Alcohol to Azide using Diphenylphosphorylazide.
typically with inversion of configuration. Azidination using diphenylphosphorylazide can be considered an alternative to the Mitsunobu reaction. Scheme 21 shows a competing S_N1 reaction pathway, in which phosphate 21.1 can dissociate into diphenylphosphate 21.4 and cation 21.5. Addition of DBU to the reaction serves to deprotonate phosphate 21.1, which prevents dissociation of phosphate 21.1 into diphenylphosphate 21.4 and cation 21.5, and therefore suppresses the S_N1 reaction pathway.

Consequently, the order in which the reagents were added to the reaction affected the experimentally observed products. When DPPA was added in the presence of DBU, as shown in Scheme 22, azide 20.1 was formed as the sole product. Presumably, the addition of DBU first allows phosphate 21.1 in Scheme 21 to be deprotonated as soon as it is formed, so that its reactivity towards other possible reaction pathways is inhibited. On the other hand, when DPPA is added before the addition of DBU, as shown in Scheme 22, azide 22.2 is observed alongside azide 20.1. Scheme 23 shows two possible mechanistic pathways for the formation of azide 22.2. Following Path A, the enesulfonamide moiety of phosphate 21.1 can displace the phosphate to give iminium ion 23.1. Nucleophilic attack at position $\alpha$ would give the desired azide 20.1, while

![Scheme 22: Experimentally Observed Products, based on the Order of Reagent Addition](image-url)
Scheme 23: Formation of unwanted side product, through two possible reaction pathways.

nucleophilic attack at position $b$ would produce azide 22.2. Alternatively, Path B shows formation of azide 22.2 through an $S_N2'$ reaction mechanism. Since the addition of DPPA in the presence of DBU appeared to inhibit the formation of azide 22.2, it is possible that Paths A and B are less likely to occur when phosphate 21.1 can be deprotonated as soon as it is formed.

The conversion to azide 20.1 from alcohol 18.1 is apparent from both the disappearance of the broad alcohol stretch at 3387 cm$^{-1}$ in the IR spectrum of 18.1 and the appearance of an azide stretch at 2095 cm$^{-1}$ in the IR spectrum of 20.1. The formation of the desired azide 20.1 as opposed to azide 22.2 is confirmed by the signals at 6.93 and 5.02 ppm in the $^1$H NMR spectrum of 20.1 which are characteristic of the polarized double bond of the enesulfonamide functionality.

With azide 20.1 in hand, the synthesis of enesulfonamide 11.0e in Scheme 24 continues with the reduction of azide 20.1 using the Staudinger reaction.$^{57}$ The resulting crude primary amine is immediately trapped with di-tert-butyl-dicarbonate to afford
Scheme 24: Synthesis of Nitrogen-Tethered Enesulfonamide 11.0e

carbamate 24.1. Alkylation with propargyl bromide followed by functionalization with methyl chloroformate afforded alkyl ester 11.0e.

Alcohol 13.5 can also be converted into an azide, as shown in Scheme 25. As previously discussed, when DPPA is added before DBU, the enesulfonamide moiety of phosphate 25.1 can displace the phosphate to give iminium ion 25.2. Nucleophilic attack of the azide anion on the nearly planar iminium ion generates two diastereomeric azides 25.3f and 25.3g. Azide 25.4 was not observed, perhaps due to steric bulk from the phenyl group and the tosyl group. The cis diastereomer 25.3g is formed preferentially.

Scheme 25: Mechanism for the Formation of diastereomers 25.3f and 25.3g
over the trans diastereomer 25.3f. Since the phenyl ring prefers to be oriented in the axial orientation, the slight preference for the formation of the cis diastereomer can be rationalized by the stereoelectronic preference of axial attack of the azide anion. The stereochemistries of the diastereomers were assigned using $^1$H selective NOE data, as illustrated in Figure 4. Selective irradiation of H-3a in azide 25.3f shows an NOE to H-6e, H-7, and the phenyl ring. Irradiation of H-3e in azide 25.3g shows an NOE to H-6e, H-6a, and H-7, but does not show an NOE to the phenyl ring. This suggests that azide 25.3f is the trans diastereomer and azide 25.3g is the cis diastereomer. Furthermore, it is known that axial protons typically resonate more upfield than equatorial protons, due to diamagnetic anisotropy. The pseudo-axial proton H-3a in azide 25.3f has a chemical shift of 3.50-3.57 ppm which is, as expected, more upfield than the pseudo-equatorial proton H-3e in azide 25.3g whose chemical shift is 3.86 ppm.

Figure 4: $^1$H Selective NOE Data for Azides 25.3f and 25.3g

The diastereomeric azides can then be separated and independently transformed into substrates 11.0f and 11.0g through the sequence of reactions previously discussed. In Scheme 26, azides 25.3f and 25.3g are subjected to the Staudinger reduction followed by trapping with di-tert-butyl-dicarbonate to give carbamates 26.1f and 26.1g.
Scheme 26: Synthesis of Diastereomeric Enesulfonamides 11.0f and 11.0g.

* based on recovered starting material

The ensuing alkylation of tert-butyl carbamates 26.2f and 26.2g with propargyl bromide proved to be challenging, possibly due to the steric bulk of the phenyl ring, in addition to the steric bulk of the tert-butyl carbamate functionality. Table 3 outlines some conditions that were tested for the alkylation reaction for both carbamate 26.2f and carbamate 26.2g. Reactions performed in THF returned only starting material (entries 1-3). Reactions using 1.1 equiv NaH and 1.1 equiv propargyl bromide in DMF showed some product formation, from carbamate 26.1f (entry 4). Increasing the equivalents of base and bromide used (2 equiv NaH and 6 equiv propargyl bromide) gave a slightly better yield (entry 5). This was also true for carbamate 26.2g (entries 6 and 7). Further increasing the amount of base used or leaving the reaction longer did not improve reaction conditions (entry 8). Heating the reaction caused the formation of other products and therefore decreased product yield (entry 9). As expected, alkylation of 26.2g (the cis diastereomer) gave lower yielding reactions compared with 26.2f (the trans diastereomer). This difference in reactivity can be attributed to steric hindrance caused by the phenyl ring, in the cis diastereomer. Once terminal alkynes 26.2f and 26.2g were in hand, functionalization of with methyl chloroformate afforded enesulfonamides 11.0f and 11.0g.
Table 3: Reaction Conditions attempted for Alkylation of Carbamates 26.1f and 26.2g

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diastereomer</th>
<th>Equiv NaH</th>
<th>Equiv Propargyl bromide</th>
<th>Solvent</th>
<th>Temp (°C), Reaction time(^a)</th>
<th>Yield (%)(^{bc})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26.1f</td>
<td>1.2</td>
<td>1.2</td>
<td>THF</td>
<td>rt, ON</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>26.1g</td>
<td>1.2</td>
<td>1.2</td>
<td>THF</td>
<td>rt, ON</td>
<td>NR</td>
</tr>
<tr>
<td>3</td>
<td>26.1g</td>
<td>1.1</td>
<td>12</td>
<td>THF</td>
<td>rt, ON</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>26.1f</td>
<td>1.1</td>
<td>1.1</td>
<td>DMF</td>
<td>rt, ON</td>
<td>31 (35 brsm)</td>
</tr>
<tr>
<td>5</td>
<td>26.1f</td>
<td>2.0</td>
<td>6</td>
<td>DMF</td>
<td>rt, ON</td>
<td>48 (68 brsm)</td>
</tr>
<tr>
<td>6</td>
<td>26.1g</td>
<td>1.6</td>
<td>7</td>
<td>DMF</td>
<td>rt, ON</td>
<td>17 (31 brsm)</td>
</tr>
<tr>
<td>7</td>
<td>26.1g</td>
<td>2</td>
<td>6</td>
<td>DMF</td>
<td>rt, ON</td>
<td>31 (46 brsm)</td>
</tr>
<tr>
<td>8</td>
<td>26.1f</td>
<td>5</td>
<td>5</td>
<td>DMF</td>
<td>rt, 2 days</td>
<td>25 (30 brsm)</td>
</tr>
<tr>
<td>9</td>
<td>26.1g</td>
<td>5</td>
<td>5</td>
<td>DMF</td>
<td>50°C, ON</td>
<td>7</td>
</tr>
</tbody>
</table>

\(^a\)ON = overnight, \(^b\)NR = no reaction, \(^c\)brsm = based on recovered starting material

Enecarbamate 11.0h was synthesized according to Scheme 27. Azidination of alcohol 14.5 using diphenylphosphorylazide, followed by Staudinger reduction and trapping with di-tert-butyl-dicarbonate gave carbamate 27.2. Alkylation with propargyl bromide and functionalization of the terminal alkyne with methyl chloroformate gave enecarbamate 11.0h.
The alkylation of 27.2 was again, more difficult than expected. This is most likely due to sterics from the tert-butyl carbamate. Table 4 shows some conditions that were tested. Reactions were unsuccessful when performed in THF, even when the base was changed to KH (entry 2) or when KI was used as an additive (entry 3). Reactions heated at 80 °C in DMSO or DMF showed decomposition (entries 4 and 5). Of the conditions that were tested, reaction at room temperature in DMF gave the best results, although the yield was still poor (entry 6). Heating the reaction at 50 °C in DMF did not produce more product (entry 7).
Table 4: Reaction Conditions attempted for Alkylation of Carbamates 26.2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv)</th>
<th>Additives (equiv)</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Yield (%)<strong>a,b</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaH (2)</td>
<td></td>
<td>THF</td>
<td>80</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>NaH (2)</td>
<td>KI (0.5)</td>
<td>THF</td>
<td>80</td>
<td>NR</td>
</tr>
<tr>
<td>3</td>
<td>KH (1.5)</td>
<td></td>
<td>THF</td>
<td>80</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>NaH (2)</td>
<td>DMSO</td>
<td>80</td>
<td></td>
<td>Decomposition</td>
</tr>
<tr>
<td>5</td>
<td>NaH (2)</td>
<td></td>
<td>DMF</td>
<td>80</td>
<td>Decomposition</td>
</tr>
<tr>
<td>6</td>
<td>NaH (2)</td>
<td></td>
<td>DMF</td>
<td>rt</td>
<td>39</td>
</tr>
<tr>
<td>7</td>
<td>NaH (2)</td>
<td></td>
<td>DMF</td>
<td>50</td>
<td>27</td>
</tr>
</tbody>
</table>

**aNR = no reaction, bbrsm = based on recovered starting material**

The synthesis of nitrogen-tethered tert-butyl enecarbamate 11.0i was attempted, as shown in Scheme 28, but was not completely successful. Azidination of alcohol 16.4 followed by Staudinger reduction and trapping with di-tert-butyl-dicarbonate successfully afforded carbamate 28.2. However, further attempts to alkylate carbamate 28.2 were

Scheme 28: Attempted Synthesis of tert-Butyl carbamate Cyclization Precursor
problematic. Conditions for the alkylation reaction, shown in Table 5, that produced at least a little product for carbamates 26.1 and 27.2 gave no either no reaction or decomposition. Although this reaction was not further investigated, there are still a variety of other reactions conditions that can be attempted.

Table 5: Reaction Conditions attempted for Alkylation of Carbamate 28.2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv NaH</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Yield (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>DMF</td>
<td>rt</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>DMF</td>
<td>50</td>
<td>Decomposition</td>
</tr>
</tbody>
</table>

*NR = no reaction.

B. Cycloisomerization Reactions

With substrates 11.0a-h in hand, treatment with silver(I) trifluoromethanesulfonate gave cycloisomerization products 11.1a-h, as anticipated (Table 6). While both enesulfonamides 11.0a and 11.0b showed fairly good reactivity, phenyl-substituted enesulfonamide 11.0b reacted faster than its non-substituted counterpart 11.0a (entries 1 and 2). It is possible that the bulky phenyl ring forces the alkyne tether away from one side of the 6-membered ring, and closer to the side where it can react with the enesulfonamide moiety. Oxygen-tethered enecarbamates 11.0c and 11.0d were more reactive than enesulfonamides 11.0a and 11.0b, and they did not require
Table 6: AgOTf-Catalyzed Cycloisomerizations of 11.0a-h

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>X</th>
<th>Y</th>
<th>P</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11.0a</td>
<td>O</td>
<td>H</td>
<td>Ts</td>
<td>80</td>
<td>16</td>
<td>11.1a</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>trans-11.0b</td>
<td>O</td>
<td>Ph</td>
<td>Ts</td>
<td>80</td>
<td>6</td>
<td>trans-11.1b</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>11.0c</td>
<td>O</td>
<td>H</td>
<td>CO₂Me</td>
<td>rt → 60</td>
<td>1.25</td>
<td>11.1c</td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td>11.0d</td>
<td>O</td>
<td>H</td>
<td>CO₂'Bu</td>
<td>rt</td>
<td>0.3</td>
<td>11.1d</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>11.0e</td>
<td>N-Boc</td>
<td>H</td>
<td>Ts</td>
<td>80</td>
<td>3</td>
<td>11.1e</td>
<td>81</td>
</tr>
<tr>
<td>6</td>
<td>trans-11.0f</td>
<td>N-Boc</td>
<td>Ph</td>
<td>Ts</td>
<td>80</td>
<td>3.5°</td>
<td>trans-11.1f</td>
<td>20</td>
</tr>
<tr>
<td>7</td>
<td>cis-11.0g</td>
<td>N-Boc</td>
<td>Ph</td>
<td>Ts</td>
<td>80</td>
<td>3.5</td>
<td>cis-11.1g</td>
<td>63</td>
</tr>
<tr>
<td>8</td>
<td>11.0h</td>
<td>N-Boc</td>
<td>H</td>
<td>CO₂Me</td>
<td>rt</td>
<td>24</td>
<td>11.1h</td>
<td>52</td>
</tr>
</tbody>
</table>

*5 mol% AgOTf was used.

heating to promote product formation (entries 3 and 4). Nitrogen-tethered enesulfonamides 11.0e-g were overall more reactive than the oxygen-tethered enesulfonamides, based on reaction time. Cycloisomerization of nitrogen-tethered 11.0e was complete in 3 hours with good yield (entry 5). Diastereomer 11.0g cyclized similarly, but with a poorer yield (entry 7). Diastereomer 11.0f showed only 30% conversion after 23 h when 2 mol% AgOTf was used. Using 5 mol% AgOTf decreased reaction time, but the yield was poor. The cycloisomerization product was very difficult to separate from another byproduct formed. Surprisingly, the cis diastereomer 11.0g cyclizes more readily than trans diastereomer 11.0f. With the phenyl ring and the nitrogen tether on the same side of the ring in 11.0g, perhaps the steric bulk of the phenyl ring is more pronounced and keeps the alkyne tether locked in the correct position to react with the enesulfonamide moiety. That is, steric bulk from the phenyl ring minimizes rotation
about the C-X bond, so that the alkyne is more likely to be in the correct position to cyclize with the enesulfonamide. Similar to the oxygen-tethered substrates, nitrogen-tethered enecarbamate 11.0h cyclized successfully at room temperature, although the yield was poor (entry 8).

The NMR data for all cyclization products 11.1a-h can be found in the Appendix. Formation of the diene products 11.1 can be confirmed by NMR spectroscopy. Structural assignments of substrates 11.1b, 11.1d, and 11.1e were established by $^1$H-$^1$H COSY 2D NMR spectroscopy, as well as HMQC spectroscopy (see Appendix). In the $^{13}$C NMR spectra, the two signals between 75-95 ppm due to the alkynyl carbons in the cyclization substrates 11.0 are replaced with two new signals between 100-130 ppm, due to the newly formed carbon-carbon double bond. In the $^1$H NMR spectra of the oxygen-tethered substrates, the cyclization products can be recognized by the formation of two doublet of doublets between 4.5-5.1 ppm, that are characteristic of the two diastereotopic protons formed after cyclization (H-5 and H-5' in Figure 5). In the nitrogen-tethered substrate, the signals from the two diastereotopic protons overlap, to form a broad singlet. The cis configuration of the diene is confirmed by the NOE correlation between the alkenyl protons, as shown in Figure 5.

![Figure 5: $^1$H Selective NOE Correlation between alkenyl protons in 11.1](image)

A mechanism for the cycloisomerization is proposed in Scheme 29, based on literature precedent of other metal-catalyzed cycloisomerizations.²⁰ Silver (I) can coordinate to the alkyne of substrate 11.0 and activate it for nucleophilic attack from the enesulfonamide moiety, to give iminium ion 29.1. Elimination would give...
enesulfonamide or enecarbamate 29.2. Protodemetalation followed by isomerization would give the experimentally observed product 11.1.

As previously mentioned, the enecarbamate substrates were more reactive than the enesulfonamide substrates, and they underwent cycloisomerization at room temperature. Enecarbamate 11.1d was heated in a mixture of methanol/dichloromethane in a test tube about 5 cm above a hotplate. Upon heating, diene 11.1d had formed dimer 11.1D through a [2+2] cycloaddition of the enecarbamate moiety. Such [2+2] cycloadditions of enecarbamates have been previously reported in the literature.\textsuperscript{61,62} Solid state molecular structure 11.1DS in Scheme 30 confirms the formation of diene 11.1d and also confirms the Z orientation of the ester on the alkene.
C. Further Results

Further reactivity of diene 11.1 to the Diels Alder reaction was tested. Scheme 31 shows that treatment of diene 11.1a with acrolein and boron trifluoride diethyl etherate at 
\(-78 \, ^\circ C\) affords cycloadduct 11.21a. Solid state molecular structure 11.21aS verifies the stereochemistry of product 11.20a. However, the transition state depiction of this reaction, shown in 32.0 of Scheme 32, predicts formation of cycloadduct 11.21a. However, the expected product 11.21a is different than the obtained product 11.20a, with respect to the stereochemistry at the center alpha to the ester group. There are three possible explanations for this discrepancy. One explanation is that the stereochemistry of

Scheme 31: Diels Alder Reaction of Diene 11.1a with Acrolein

Scheme 32: Transition State Depiction for Diels Alder Reaction of Diene 11.1a with Acrolein
starting material is not that shown in 11.0a, but is actually that shown in 11.11a in Scheme 33. The transition state depiction of the Diels Alder reaction starting with 11.11a predicts a product with the same stereochemistry as the obtained product. Another possible explanation is epimerization at the center alpha to the ester group, since that proton is slightly acidic. Finally, if the reaction proceeds through a stepwise mechanism, rather than a concerted mechanism, this can also explain the stereochemistry of the obtained product. In order to fully understand what occurring, it would be necessary to conduct further investigations.

Diene 11.1a also undergoes reaction with methacrolein in the presence of boron trifluoride diethyl etherate at -78 °C to afford cycloaduct 11.22a and an inseparable mixture of diastereomers 11.23a and 11.24a (Scheme 34).
III. Conclusion and Future Research

Eight substrates of the general structure 11.0 in Scheme 35 were synthesized. The substrates differed with respect to the heteroatom tether, nitrogen protecting group, and substitution on the ring. The key silver(I)-catalyzed cycloisomerizations of each substrate successfully gave products 11.1a-h. The enecarbamate substrates were generally more reactive than the enesulfonamide substrates, and they underwent cycloisomerization at room temperature. The product yields were generally good (63-81%), except for the poor yields of the methyl carbamate products (36-52%). While these product yields are generally reasonable, they are not as good as the 99% yields obtained from the cycloisomerizations of the all-carbon substrates.26 The routes to synthesize cyclization precursors 11.0a-h could also be optimized either to minimize the number steps or to improve the yields of individual steps.

![Scheme 35: Key silver (I)-catalyzed cycloisomerization](image)

On the other hand, one advantage of the methodology is the success of the cycloisomerizations using different nitrogen protecting groups. The reaction times are also fairly reasonable (0.3 – 24 h). Furthermore, the cyclization products 11.1a-h are useful for other reactions such as the Diels Alder reaction, where more complex carbon frameworks can be synthesized in one step. Further research can also be conducted using dienes 11.1a-h as precursors to furans and pyrroles through migration of the two alkenes.
into the five-membered ring, as shown in Scheme 36. This sort of alkene migration is precedent in the literature.^63,^64

Scheme 36: Alkene Migration for Formation of Furans and Pyrroles

Overall, the silver(I)-catalyzed cyclizations were successful in producing the desired diene products in fair yields, reasonable reaction times, and functional group variability.
IV. Experimental

A. General

All reactions were performed under a nitrogen atmosphere in flame-dried glassware. Tetrahydrofuran (THF) and diethyl ether (EtO) were distilled from sodium benzophenone ketyl under an atmosphere of dry argon. Dichloromethane, triethylamine and toluene were distilled from calcium hydride under an atmosphere of dry argon. Reagents were purchased from Aldrich and purified by standard distillation. Solutions of n-BuLi were purchased from commercial sources and standardized by titration with a solution of N-benzylbenzamide in tetrahydrofuran. Methanesulfonyl chloride and methyl chloroformate were distilled from phosphorus pentoxide. Methanol, pentane, and pyridine were distilled from calcium hydride under an atmosphere of nitrogen. N,N-dimethylformamide was distilled from magnesium chloride under an atmosphere of nitrogen, then sequentially stored over flame dried 4 Å molecular sieves. Propargyl alcohol and benzaldehyde were vacuum distilled over potassium carbonate and anhydrous magnesium sulfate, respectively. Benzene and diisopropylamine were distilled over sodium under an atmosphere of nitrogen. Acrolein and methacrolein were distilled over quinoline under an atmosphere of nitrogen.

Thin layer chromatography (TLC) was performed on DC-Fertigplatten SIL G-25 UV 254 pre-coated TLC plates. Column chromatography was performed on Silicycle ultrapure silica gel (40-63μm, 230-400 mesh). Triethylamine washed silica gel was stirred with triethylamine before packing, then sequentially flushed with polar solvent component and solvent system of choice.

Proton nuclear magnetic resonance spectra and carbon nuclear magnetic resonance spectra were both recorded in deuterochloroform using either a Bruker AV-300, a Bruker WH-400 or a Bruker AV-400 spectrometer. Chemical shifts are recorded in parts per million and are referenced to the centerline of deuterochloroform (7.24 ppm \(^1\)H NMR; 77.0 ppm \(^{13}\)C NMR). Coupling constants (J values) are given in Hertz (Hz).
Infrared (IR) spectra were obtained using a Perkin-Elmer 1710 FT-IR spectrometer. Melting points were performed using a Mel-Temp II apparatus (Lab devices USA) and are uncorrected. Low resolution mass spectra were recorded by the Microanalytical Laboratory at the University of British Columbia on a Waters/Micromass LCT spectrometer for electrospray ionization (ESI) or on a Kratos MS-50 spectrometer for electron ionization (EI). Microanalyses were performed by the Microanalytical Laboratory at the University of British Columbia on a Carlo Erba Elemental Analyzer EA 1008.

B. Synthesis of Substrates

![](image)

1-(Toluene-4-sulfonyl)-piperidin-2-one (12.1)

A solution of n-butyllithium (80.0 mL, 0.128 mol, 1.60 M in hexanes) was added dropwise to a solution of 12.1 g of 5-valerolactam (0.122 mol, 1.00 equiv) in 300 mL of THF at −78 °C. The reaction mixture was stirred for 3 h at −78 °C before a solution of 25.6 g of toluenesulfonyl chloride (0.134 mol, 1.10 equiv) in 100 mL THF was added dropwise. The reaction mixture was warmed to rt and stirred overnight. The white reaction mixture was diluted with dichloromethane and washed sequentially with water and a saturated aqueous brine solution. The combined aqueous washes were extracted with dichloromethane. The combined organic fractions were dried over anhydrous sodium sulfate and concentrated by rotary evaporation in vacuo to afford a pale yellow powder. Trituration with diethyl ether afforded 29.9 g (97%) of a white powder (mp 139-141 °C).

IR (film): 2954, 1687, 1349 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ ppm 7.87 (d, J=8.2 Hz, 2 H), 7.28 (d, J=8.2 Hz, 2 H), 3.87 (t, J=5.9 Hz, 2 H), 2.41 - 2.31 (m, 5 H), 1.93 - 1.80 (m, 2 H), 1.80 - 1.67 (m, 2 H).
1-(Toluene-4-sulfonyl)-piperidin-2-ol (12.2)\textsuperscript{28,30}

A solution of diisobutylaluminum hydride (129 mL, 0.129 mol, 1.00 M in hexanes) was added dropwise to a solution of 12.1 in 350 mL dichloromethane at \(-78 °C\). The reaction mixture was stirred for 1 h at \(-78 °C\) before it was quenched by slow addition of 40 mL of a solution of saturated aqueous ammonium chloride. The white reaction mixture was stirred and warmed to rt over 45 min. Anhydrous magnesium sulfate was added, and the reaction mixture was stirred for 30 min before it was filtered through a pad of Celite. Concentration by rotary evaporation \textit{in vacuo} afforded 16.4 g (80\%) of a white powder (mp 102-104 °C).

\[
\text{IR (film): 3487, 2957, 1327, 1158 cm}^{-1}. \quad ^1\text{H NMR (300 MHz, CDCl}_3\text{): } \delta 7.70 (d, J=8.7 \text{ Hz, 2 H}), 7.27 (d, J=8.2 \text{ Hz, 2 H}), 5.47 - 5.56 (m, 1 H), 3.57 - 3.46 (m, 1 H), 3.07 (td, J=12.2, 2.5 Hz, 1 H), 2.56 (d, J=3.2 Hz, 1 H), 2.38 (s, 3 H), 1.84 - 1.42 (m, 6 H).
\]

1-(Toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridine (12.3)\textsuperscript{28,30}

To a solution of 16.4 g of alcohol 12.2 (64.3 mmol, 1.00 equiv) in 300 mL of dichloromethane was added 0.391 g of 4-(dimethyl)-aminopyridine (3.20 mmol, 0.05 equiv). The reaction was cooled to 0 °C before the dropwise addition of 10.0 mL of methanesulfonyl chloride (0.129 mol, 2.00 equiv) to give a pale yellow reaction mixture. After the reaction mixture was stirred at 0 °C for 15 min, it was allowed to warm to rt over 15 min. To the orange reaction mixture was added 300 mL of a saturated solution of aqueous ammonium chloride and allowed to stir for 20 minutes. The resulting reaction mixture was diluted with water and the separated aqueous layer was extracted with dichloromethane. The combined organic phases were washed sequentially with a saturated solution of aqueous ammonium chloride and brine, dried over anhydrous
sodium sulfate, and concentrated by rotary evaporation *in vacuo* to afford bright orange solid. Purification by column chromatography on triethylamine washed silica gel (7:1 hexanes/ethyl acetate to 5:1 hexanes/ethyl acetate) afforded 11.6 g (76%) of a white solid (mp 48-50 °C).

IR (film): 3060, 2936, 1650, 1340, 1166 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.64 (d, \( J=8.2 \) Hz, 2 H), 7.28 (d, \( J=7.8 \) Hz, 2 H), 6.61 (ddd, \( J=8.3, 2.1, 1.9 \) Hz, 1 H), 4.98 - 4.91 (m, 1 H), 3.37 - 3.31 (m, 2 H), 2.41 (s, 3 H), 1.92 - 1.85 (m, 2 H), 1.68 - 1.59 (m, 1 H).

3-Bromo-2-methoxy-1-(toluene-4-sulfonyl)-piperidine (12.4)

A solution of 11.6 g of 12.3 (48.9 mmol, 1.00 equiv) in 50 mL of methanol was transferred dropwise by cannula into a solution of 1.24 g of sodium (0.154 mol, 1.10 equiv) in 200 mL of methanol at 0 °C. To this reaction mixture was added dropwise 2.76 mL of bromine (53.8 mmol, 1.10 equiv). The resulting orange reaction mixture was warmed to rt and stirred for 3 h, before being concentrated to one half volume by rotary evaporation *in vacuo*. The reaction mixture was diluted with diethyl ether, then washed with water. The separated aqueous layer was extracted with diethyl ether. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, and concentrated by rotary evaporation *in vacuo* to afford a white powder. Purification by column chromatography on triethylamine washed silica gel afforded (5:2 hexanes/ethyl acetate) afforded 38.1 g (93%) of a white solid, 102-104 °C.

IR (film): 2952, 1598, 1335, 1163 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.85 (d, \( J=8.3 \) Hz, 2 H), 7.28 (d, \( J=7.9 \) Hz, 2 H), 5.28 (d, \( J=1.7 \) Hz, 1 H), 4.33 (q, \( J=2.8 \) Hz, 1 H), 3.40 (s, 3 H), 3.37 - 3.30 (m, 1 H), 3.12 - 3.02 (m, 1 H), 2.41 (s, 3 H), 2.28 - 2.18 (m, 1 H), 1.88 - 1.73 (m, 2 H), 1.44 - 1.35 (m, 1 H).
6-Methoxy-1-(toluene-4-sulfonyl)-1, 2, 3, 6-tetrahydro-pyridine (12.5)\textsuperscript{29,30}

To a solution of 38.1 g of 12.4 (0.109 mol, 1.00 equiv) in 500 mL of N,N-dimethylformamide was added 19.6 mL of 1,8-diazabicyclo[5,4,0]undec-7-ene (0.131 mol, 1.20 equiv). The reaction mixture was stirred overnight at 90 °C. The yellow solution was diluted with diethyl ether then washed with water. The separated aqueous layer was washed with diethyl ether. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, and concentrated by rotary evaporation \textit{in vacuo} to afford a pale yellow oil. Purification by column chromatography on triethylamine washed silica gel (9:1 hexanes/ethyl acetate to 5:1 hexanes/ethyl acetate to 3:1 hexanes/ethyl acetate) afforded 11.6 g (74% brsm) of a white powder and 17.5 g of starting material.

When the above procedure was performed using the following quantities of reagents and solvents: 1.97 g of 12.4 (5.66 mmol, 1.0 equiv) in 250 mL of N,N-dimethylformamide, 1.02 mL of 1,8-diazabicyclo[5,4,0]undec-7-ene (6.79 mmol, 1.20 equiv), workup and purification afforded 1.41 g (94%) of a white powder (mp 53-55 °C).

IR (film): 3042, 2933, 1656, 1598, 1338, 1162 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \(\delta\) 7.68 (d, \(J=8.2\) Hz, 2 H), 7.24 (d, \(J=7.8\) Hz, 2 H), 5.85 - 5.71 (m, 2 H), 5.29 - 5.24 (m, 1 H), 3.76 - 3.66 (m, 1 H), 3.39 (s, 3 H), 3.31 - 3.19 (m, 1 H), 2.39 (s, 3 H), 1.76 - 1.68 (m, 2 H).

4-Prop-2-ynyloxy-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridine (12.6)\textsuperscript{30}

To a solution of 41.1 mg of ytterbium (III) trifluoromethanesulfonate (0.0748 mmol, 0.0200 equiv) in 2.61 mL of propargyl alcohol (44.9 mmol, 12.0 equiv) was added a
solution of 1.00 g of 12.5 (3.74 mmol, 1.00 equiv) in 10 mL THF. The reaction mixture was stirred for 5 h before it was diluted with diethyl ether. The separated organic layer was washed sequentially with a solution of saturated sodium bicarbonate and brine, dried over anhydrous sodium sulfate, and concentrated by rotary evaporation in vacuo to afford a colourless oil. Purification by column chromatography on triethylamine washed silica gel (3:1 petroleum ether/ether) afforded 0.336 g (31% brsm) of a colourless oil.

Ytterbium (III) trifluoromethanesulfonate (5.0 mg, 0.0093 mmol) was dried under vacuum for 2 h before being dissolved in 0.26 mL of propargyl alcohol. To the resulting solution was added a solution of 0.10 g of 12.5 (0.37 mmol, 1.0 equiv) in 1 mL of THF. The reaction mixture was stirred for 22 h before the addition of 5.0 mg of ytterbium (III) trifluoromethanesulfonate. After 1 h, the reaction mixture was diluted with diethyl ether. The separated organic layer was washed sequentially with a solution of saturated sodium bicarbonate and brine, dried over anhydrous sodium sulfate, and concentrated by rotary evaporation in vacuo to afford a colourless oil. Purification by column chromatography on triethylamine washed silica gel (3:1 petroleum ether/ether) afforded 0.093 g (85%) of a colourless oil.

IR (film): 3284, 2932, 2116, 1641, 1354, 1169, 1067 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.63 (d, J=8.3 Hz, 2 H), 7.28 (d, J=8.3 Hz, 2 H), 6.81 (d, J=8.7 Hz, 1 H), 5.10 (ddd, J=8.3, 4.8, 1.3 Hz, 1 H), 4.08 (d, J=2.2 Hz, 2 H), 3.94 (q, J=4.2 Hz, 1 H), 3.64 (dt, J=11.8, 4.4 Hz, 1 H), 3.07 (td, J=12.2, 3.1 Hz, 1 H), 2.41 (s, 4 H), 1.95 - 1.87 (m, 1 H), 1.69 - 1.58 (m, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ 143.8, 134.8, 129.7, 128.4, 126.8, 105.5, 79.8, 74.2, 65.7, 54.7, 39.4, 26.8, 21.4. HRMS (ESI): Calcd for C₁₅H₁₇NO₃NaS (M + Na⁺) 314.0827, found 314.0834.
4-[1-(Toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridin-4-yloxy]-but-2-ynoic acid methyl ester (11.0a)\textsuperscript{30}

A solution of \textit{n}-butyllithium (0.732 mL, 1.17 mmol, 1.60 M in hexanes) was added dropwise to a solution of 0.310 g of \textbf{12.6} (1.06 mmol, 1.00 equiv) in 11 mL of diethyl ether at \textdegree{}78 °C. After the reaction mixture was stirred at \textdegree{}78 °C for 1 h, 0.428 mL of methyl chloroformate (5.53 mmol, 5.20 equiv) was added. The reaction mixture was stirred at \textdegree{}78 °C for 20 min, then warmed to rt over 45 min. After 4 mL of THF were added, the reaction mixture was stirred overnight. The reaction mixture was diluted with diethyl ether, then washed sequentially with water and brine. The aqueous washes were back-extracted with diethyl ether. The combined organic phases were dried over anhydrous sodium sulfate and concentrated \textit{in vacuo} to afford an orange oil. Purification by column chromatography on triethylamine washed silica gel (6:1 hexanes/ethyl acetate to 4:1 hexanes ethyl acetate) afforded 0.310 g (84\%) of a pale yellow oil.

\begin{align*}
\text{IR (film): } & 2954, 2238, 1718, 1641, 1354, 1262, 1169 \text{ cm}^{-1}.
\text{\textsuperscript{1}H NMR (400 MHz, } \text{CDCl}_3): \delta 7.72 - 7.60 (m, 2 H), 7.28 (d, J=7.0 \text{ Hz}, 2 H), 6.83 (dd, J=8.3, 3.1 \text{ Hz}, 1 H), 5.13 - 5.04 (m, 1 H), 4.20 (s, 2 H), 3.97 - 3.90 (m, 1 H), 3.75 (s, 3 H), 3.70 - 3.62 (m, 1 H), 3.10 - 2.99 (m, 1 H), 2.40 (s, 3 H), 1.90 (d, J=14.0 \text{ Hz}, 1 H), 1.70 - 1.58 (m, 1 H).
\text{\textsuperscript{13}C NMR (100 MHz, } \text{CDCl}_3): \delta 153.4, 144.0, 134.9, 129.9, 129.0, 126.9, 104.8, 83.7, 77.5, 66.4, 54.5, 52.8, 39.3, 26.9, 21.5.
\text{HRMS (ESI): Calcd for } \text{C}_{17}\text{H}_{19}\text{NO}_{5}\text{NaS (M + Na})^+ 372.0882, \text{found } 372.0885.
\end{align*}
Zinc chloride was dried by being heated at 150 °C overnight under vacuum, then stored under a nitrogen atmosphere in a boxglove. A suspension of 81.8 mg of anhydrous zinc chloride (0.600 mmol, 0.0120 equiv) in 15.9 mL of triethylamine (0.114 mol, 2.28 equiv) was stirred for 1 h. A solution of 5.60 mL of 4-methoxy-3-buten-2-one (50.0 mmol, 1.00 equiv) in 15 mL of benzene was added to the reaction mixture in one portion. After the yellow reaction mixture was stirred for 5 min, it was cooled to 0 °C and 13.0 mL of trimethylchlorosilane (0.100 mol, 2.00 equiv) were added in one portion. The pinkish-orange reaction was stirred at 0 °C for 45 min before the resulting brown reaction mixture was warmed to rt and stirred overnight at 45 °C. The thick dark brown reaction mixture was poured into 50 mL of anhydrous diethyl ether and was stirred for 5 min, until white smoke no longer evolved from the reaction mixture. The reaction mixture was filtered over a pad of Celite, dissolved in 50 mL of anhydrous ether, and re-filtered over a pad of Celite. Concentration by rotary evaporation in vacuo afforded 7.51 g (87%) of a dark brown oil.

IR (film): 2960, 1654, 1322, 1023, 849 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 6.81 (d, J=12.3 Hz, 1 H), 5.33 (d, J=12.3 Hz, 1 H), 4.07 (d, J=12.3 Hz, 2 H), 3.56 (s, 3 H), 0.26 - 0.16 (s, 9 H).

**N-Benzylidene-4-methyl-benzenesulfonamide (13.3)**

To a solution of 55.1 g of p-toluenesulfonamide (0.316 mol, 1.00 equiv) in 500 mL of toluene was added 33.8 mL of benzaldehyde (0.316 mol, 1.00 equiv), 48.0 g of 5 Å molecular sieves, and 0.640 g of Amberlyst 15 ion-exchange resin. The reaction mixture was heated to reflux overnight with a Dean Starks apparatus before it was filtered through
a glass frit and washed with toluene. Concentration by rotary evaporation in vacuo afforded a yellow oil, which solidified after 3 h of storage in the refrigerator. The pale yellow solid was washed with pentane then recrystallized in ethyl acetate/pentane to afford 18.9 g (23%) of white crystals.

To a solution of 17.1 g of p-toluenesulfonamide (0.101 mol, 1.00 equiv) in 165 mL toluene was added 10.3 mL of benzaldehyde (0.101 mol, 1.00 equiv), 15.0 g of 5 Å molecular sieves, and 0.200 g of Amberlyst 15 ion-exchange resin. The reaction mixture was heated to reflux overnight with a Dean Starks apparatus before it was filtered through a glass frit and washed with toluene. Concentration by rotary evaporation in vacuo afforded a pale yellow solid, which was washed with pentane then recrystallized in ethyl acetate/pentane and filtered to afford 3.71 g of white crystals. The filtrate was concentrated again by rotary evaporation in vacuo and recrystallized to afford 4.72 g of white crystals. Recrystallization of the filtrate a third time afforded 0.552 g of white crystals, which gave a total of 8.98 g (35%) of white crystals (mp 89-92 °C).

IR (film): 3259, 1597, 1446, 1301, 1223, 1156 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 9.01 (s, 1 H), 8.02 - 7.79 (m, 4 H), 7.59 (t, J=7.3 Hz, 1 H), 7.46 (t, J=7.5 Hz, 2 H), 7.32 (d, J=8.2 Hz, 2 H), 2.41 (s, 3 H).

2-Phenyl-1-(toluene-4-sulfonyl)-2,3-dihydro-1H-pyridin-4-one (13.4)

A solution of 2.59 g of copper (I) trifluoromethanesulfonate toluene complex (5.00 mmol, 0.100 equiv) and 2.62 g of triphenylphosphine (10.0 mmol, 0.200 equiv) in 280 mL of dichloromethane was stirred for 2 h. To the resulting olive green solution was cannulated a solution of 12.9 g of N-Benzylidene-4-methyl-benzenesulfonamide 13.3 (50.0 mmol, 1.00 equiv) in 350 mL of dichloromethane. After the reaction mixture was stirred for 10 min, to the reaction mixture was added 11.7 g of (3-methoxy-1-methylene-
allyloxy)-dimethyl-silane 13.1 (68.0 mmol, 1.36 equiv). The resulting brown solution was stirred for 4 h before 90 mL of trifluoroacetic acid were added. After the reaction mixture was stirred for 1 h, it was neutralized by the addition of a solution of saturated sodium bicarbonate. The reaction mixture was extracted with dichloromethane, dried over anhydrous potassium carbonate, and concentrated by rotary evaporation in vacuo to afford a thick brown sludge. Purification by column chromatography on triethylamine washed silica gel (2:1 hexanes/ethyl acetate to 1:1 hexanes/ethyl acetate) afforded 10.3 g (63%) of a bright orange solid (mp 102-104.5 °C).

IR (film): 3063, 1674, 1597, 1367, 1170 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.81 (d, \(J=8.3\) Hz, 1 H), 7.61 (d, \(J=8.3\) Hz, 2 H), 7.35 - 7.14 (m, 7 H), 5.53 (d, \(J=6.5\) Hz, 1 H), 5.42 (d, \(J=8.3\) Hz, 1 H), 2.85 (dd, \(J=16.6, 7.0\) Hz, 1 H), 2.75 - 2.62 (m, 1 H), 2.41 (s, 3 H).

2-Phenyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridin-4-ol (13.5)\(^{35,37}\)

To a solution of 10.3 g of 13.4 (31.4 mmol, 1.00 equiv) in 80 mL of methanol and 6 mL of THF was added 11.7 g of cerium trichloride heptahydrate (31.4 mmol, 1.00 equiv). The reaction mixture was cooled to 0 °C and 1.19 g of sodium borohydride (31.4 mmol, 1.00 equiv) was added in portions, over 30 min. After the reaction mixture was stirred for 5 min, 30 mL of water was added and the reaction mixture was concentrated to one half volume by rotary evaporation in vacuo. The reaction mixture was extracted with diethyl ether, dried over potassium carbonate, and concentrated by rotary evaporation in vacuo to afford a thick yellow paste. Purification by column chromatography on triethylamine washed silica gel (2:1 hexanes/ethyl acetate) afforded 8.49 g (82%) of a white solid.
When the above procedure was performed using the following quantities of reagents and solvents: 3.0 g of 13.4 (9.16 mmol, 1.0 equiv) in 22 mL methanol and 6 mL THF; 3.41 g of cerium trichloride heptahydrate (9.16 mmol, 1.0 equiv); and 0.35 g of sodium borohydride (9.16 mmol, 1.0 equiv), purification by column chromatography on triethylamine washed silica gel (3:2 hexanes/ethyl acetate) afforded 2.77 g (92%) of a white solid (mp 80-82 °C).

IR (film): 3529, 3031, 1646, 1342, 1168 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.57 (d, J=7.9 Hz, 2 H), 7.27 - 7.09 (m, 8 H), 6.80 (d, J=8.3 Hz, 1 H), 5.06 (br. s., 1 H), 4.90 (d, J=8.3 Hz, 1 H), 3.77 (br. s., 1 H), 2.62 (br. s., 1 H), 2.35 (s, 3 H), 2.12 (d, J=10.0 Hz, 1 H), 1.50 - 1.36 (m, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ 143.6, 139.3, 135.5, 129.5, 128.1, 127.0, 126.5, 125.2, 124.7, 111.8, 60.0, 55.8, 35.1, 21.2. MS (ESI): 352.2 (M + Na⁺). Anal. Calcd for C₁₈H₁₉NO₃S: C, 65.63; H, 5.81; N, 4.25. Found: C, 65.84; H, 5.80; N, 4.24.

2-Phenyl-4-prop-2ynyloxy-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridine (13.6)⁴⁰

A solution of 0.372 g of 13.5 (1.13 mmol, 1.00 equiv) and 0.0429 g of sodium hydride (1.70 mmol, 1.50 equiv) in 12.0 mL of THF was stirred for 1 h. To the pale yellow solution was added 0.630 mL of propargyl bromide (5.66 mmol, 5.00 equiv). The resulting light brown solution was stirred overnight. The reaction mixture was diluted with ethyl ether and washed with water. The combined aqueous phases were back-extracted with diethyl ether, dried over anhydrous sodium sulfate, and concentrated by rotary evaporation in vacuo to afford a light brown liquid. Purification by column chromatography on triethylamine washed silica gel (5:1 hexanes/ethyl acetate) afforded 0.140 g (54%) of a pale yellow solid (mp 116.5 - 118 °C).
IR (film): 3283, 2929, 1649, 1169, 1086 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.64 (d, \(J=8.3\) Hz, 2 H), 7.33 - 7.20 (m, 8 H), 6.94 (d, \(J=8.3\) Hz, 1 H), 5.17 - 5.08 (m, 2 H), 4.02 (d, \(J=2.2\) Hz, 2 H), 3.80 - 3.73 (m, 1 H), 2.41 (s, 3 H), 2.37 - 2.30 (m, 2 H), 1.56 (dd, \(J=12.6, 10.5, 4.8\) Hz, 1 H). \(^1^3\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 143.7, 139.3, 135.7, 130.0, 128.4, 127.2, 126.7, 126.0, 125.5, 108.7, 79.5, 74.3, 67.6, 55.8, 55.7, 32.3, 21.4. MS (ESI): 390.2 (M + Na\(^+\)). Anal. Calcd for C\(_{21}\)H\(_{21}\)NO\(_3\)S: C, 68.83; H, 5.78; N, 3.82. Found: C, 68.41; H, 5.76; N, 3.84.

4-[[2-Phenyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridin-4-yloxy]-but-2-ynoic acid methyl ester (11.0b)\(^3\)0

A solution of n-butyllithium (0.49 mL, 0.61 mmol, 1.2 M in hexanes) was added dropwise to a solution of 0.20 g of 13.6 in 5.5 mL of diethyl ether and 1 mL THF at -78 °C. After the reaction mixture was stirred at -78 °C for 1 h, 0.22 mL of methyl chloroformate (2.9 mmol, 5.2 equiv) were added. The reaction mixture was stirred at -78 °C for 20 min, then warmed to rt and stirred overnight. The reaction mixture was diluted with diethyl ether, then washed sequentially with water and brine. The aqueous washes were back-extracted with diethyl ether. The combined organic phases were dried over anhydrous sodium sulfate and concentrated by rotary evaporation in vacuo to afford an orange oil. Purification by column chromatography on triethylamine washed silica gel (6:1 hexanes/ethyl acetate to 4:1 hexanes ethyl acetate) afforded 0.17 g (72%) of a pale yellow oil.

IR (film): 2955, 2240, 1718, 1347, 1261, 1167 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.63 (d, \(J=8.3\) Hz, 2 H), 7.33 - 7.20 (m, 7 H), 6.95 (d, \(J=7.9\) Hz, 1 H), 5.16 - 5.06 (m, 2 H), 4.14 (s, 2 H), 3.75 (s, 4 H), 2.42 (s, 3 H), 2.39 - 2.29 (m, 1 H), 1.64 - 1.53 (m, 1 H). \(^1^3\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 153.3, 143.9, 139.2, 135.8, 130.0, 128.5, 127.4, 126.8,
126.5, 125.6, 108.2, 83.5, 77.5, 68.6, 55.8, 55.7, 52.7, 32.4, 21.5. HRMS (ESI): Calcd for C_{23}H_{22}NO_3NaS (M + Na^+) 448.1195, found 448.1192.

4-Oxo-piperidine-1-carboxylic acid methyl ester (14.1)\textsuperscript{37}

A solution of 13.0 g of sodium hydroxide (0.326 mol, 1.00 equiv) in 75 mL of deionized water was added dropwise to a solution of 50.0 g of 4-piperidone monohydrate hydrochloride (0.326 mol) in 75 mL of deionized water at 0 °C. The reaction mixture was diluted with 250 mL of diethyl ether then 12.6 mL of methyl chloroformate (0.163 mol, 0.500 equiv) were added dropwise over 15 min at 0 °C. The reaction mixture was stirred for 5 min before 12.6 mL of methyl chloroformate (0.163 mol, 0.500 equiv) and a solution of 13.0 g of sodium hydroxide (0.326 mol, 1.00 equiv) in 75 mL of deionized water were added dropwise simultaneously over 15 min. After the reaction mixture was stirred for 1.5 h, the separated aqueous layer was extracted with diethyl ether. The combined organics were dried over anhydrous sodium sulfate and concentrated \textit{in vacuo} to afford 43.3 g (85%) of a colourless viscous oil.

IR (film): 2959, 1702, 1451, 1236, 1125 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \delta 3.68 - 3.46 (m, 7 H), 2.29 (t, \textit{J}=6.2 Hz, 4 H).

6-Bromo-1,4-dioxo-8-aza-spiro[4.5]decane-8-carboxylic acid methyl ester (14.2)\textsuperscript{37}

To a solution of 53.3 g of 14.1 (0.341 mol, 1.00 equiv) in 450 mL of ethylene glycol at 50 °C was added 31.2 mL of bromine (0.606 mol, 1.78 equiv) in small portions over 3 h.
The orange-red reaction mixture was stirred for 3 h at 50 °C before 47.1 g of anhydrous potassium carbonate (0.341 mol, 1.00 equiv) were added in portions over 30 min. The reaction mixture was extracted with diethyl ether, dried over anhydrous sodium sulfate, and concentrated by rotary evaporation in vacuo to afford an orange solid. Purification by column chromatography on silica gel (5:1 hexanes/ethyl acetate to 3:1 hexanes/ethyl acetate) afforded 74.1 g (78%) of a pale orange solid (mp 61-63 °C).

IR (film): 2958, 1718, 1447, 1239, 1136 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 3.98 - 3.75 (m, 6 H), 3.59 - 3.51 (m, 1 H), 3.49 (s, 3 H), 3.35 (br. s., 1 H), 3.23 - 3.11 (m, 1 H), 1.82 (d, J=13.1 Hz, 1 H), 1.46 (ddd, J=13.6, 9.5, 4.4 Hz, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ 154.9, 105.7, 65.3, 52.3, 51.6, 48.5, 41.2, 33.6. MS (ESI): 302.1 (M + Na⁺).

Anal. Calcd for C₉₀₄H₄₄BrN: C, 38.59; H, 5.04; N, 5.00. Found: C, 38.64; H, 5.00; N, 4.97.

4-Oxo-3,4-dihydro-2H-pyridine-1-carboxylic acid methyl ester (14.4)³⁷

To a solution of 68.4 g of 14.2 (0.244 mol, 1.00 equiv) in 500 mL of dimethyl sulfoxide was added 43.8 mL of 1,8-diazobicyclo[5,4,0]undec-7-ene (0.293 mol, 1.20 equiv). The reaction mixture was stirred overnight at 80 °C before it was diluted with water and extracted with diethyl ether. The combined organic phases were washed with water, dried over anhydrous potassium carbonate, and concentrated by rotary evaporation in vacuo to afford 35.0 g of a crude brown oil. The crude product was dissolved in 430 mL of methanol and 28.5 mL of a 3 N aqueous solution of hydrochloric acid were added. After the reaction mixture was stirred for 30 min, the reaction mixture was concentrated to one half volume by rotary evaporation in vacuo. The reaction mixture was diluted with water and extracted with diethyl ether. The combined organic phases were dried over anhydrous potassium carbonate and concentrated by rotary evaporation in vacuo to afford an orange oil. Purification by column chromatography on triethylamine washed
silica gel (3:1 hexanes/ethyl acetate to 1:1 hexanes/ethyl acetate) afforded 7.87 g (21% over two steps) of a white solid.

To a solution of 2.13 g of 14.3 (10.7 mmol, 1.00 equiv.) in 43 mL of dimethyl sulfoxide was added 3.11 mL of 1,8-diazobicyclo[5,4,0]undec-7-ene (20.4 mmol, 2.00 equiv.). The reaction mixture was stirred overnight at 80 °C before it was diluted with water and extracted with diethyl ether. The combined organic phases were washed with water, dried over anhydrous potassium carbonate, and concentrated by rotary evaporation in vacuo to afford 2.13 g of a crude brown oil. The crude product was dissolved in 20 mL of methanol and 1.3 mL of a 3 N aqueous solution of hydrochloric acid were added. After the reaction mixture was stirred for 15 min, the reaction mixture was concentrated to by rotary evaporation in vacuo to afford a biphasic oil. Purification by column chromatography on triethylamine washed silica gel (5:1 hexanes/ethyl acetate to 3:1 hexanes/ethyl acetate to 1:1 hexanes/ethyl acetate) afforded 1.55 g (98% over two steps) of a white solid (mp 50-58 °C).

IR (film): 3086, 2956, 1738, 1663, 1600, 1450, 1223, 1185, 765 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.60 (d, J=7.0 Hz, 1 H), 5.06 (d, J=8.3 Hz, 1 H), 3.79 (t, J=7.2 Hz, 2 H), 3.62 (s, 3 H), 2.30 (t, J=7.4 Hz, 2 H).

4-Hydroxy-3,4-dihydro-2H-pyridine-1-carboxylic acid methyl ester (14.5)³⁵,³⁷
To a solution of 3.95 g of 14.4 (25.5 mmol, 1.00 equiv) in 65 mL of methanol was added 9.49 g of cerium trichloride heptahydrate (25.5 mmol, 1.00 equiv). The reaction mixture was cooled to 0 °C and 0.965 g of sodium borohydride (25.5 mmol, 1.00 equiv) were added in portions, over 1 h. After the reaction mixture was stirred for 5 min, 30 mL of water were added and the reaction mixture was concentrated to one half volume by rotary evaporation in vacuo. The reaction mixture was extracted with diethyl ether, dried over
potassium carbonate, and concentrated by rotary evaporation in vacuo to afford a thick yellow paste. Purification by column chromatography on silica gel (1:2 hexanes/ethyl acetate) afforded 3.76 g (94%) of a white solid (mp 29-31 °C).

IR (film): 3411, 2957, 1718, 1651, 1449, 1364, 1236, 1121, 1061, 768 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 6.61 - 6.29 (m, 1 H), 4.71 - 4.52 (m, 1 H), 3.93 (br. s., 1 H), 3.74 (br. s., 1 H), 3.44 - 3.25 (m, 4 H), 3.01 (br. s., 1 H), 1.40 (br. s., 2 H). ¹³C NMR (100 MHz, CDCl₃): δ 152.7, 125.5, 107.5, 59.2, 52.0, 37.1, 29.4. MS (ESI): 180.2 (M + Na⁺). Anal. Calcd for C₇H₁₁NO₃: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.43; H 7.13; N, 8.76.

4-Prop-2-ynyloxy-3,4-dihydro-2H-pyridine-1-carboxylic acid methyl ester (14.6)

A solution of 0.51 g of 14.5 (3.3 mmol, 1.0 equiv) and 0.12 g of sodium hydride (4.9 mmol, 1.5 equiv) in 50 mL of THF was stirred for 15 min. To the pale yellow solution was added 1.8 mL of propargyl bromide (16 mmol, 5.0 equiv) in one portion. The resulting light brown solution was stirred overnight. The reaction mixture was diluted with ethyl ether and washed with water. The combined aqueous phases were back-extracted with diethyl ether, dried over anhydrous sodium sulfate, and concentrated by rotary evaporation in vacuo to afford a light brown liquid. Purification by column chromatography on triethylamine washed silica gel (5:1 hexanes/ethyl acetate) afforded 0.36 g (83% brsm) of a yellow oil.

IR (film): 3279, 2957, 2238, 1718, 1646, 1446, 1361, 1256, 1059 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 6.99 - 6.68 (m, 1 H), 5.01 - 4.80 (m, 1 H), 4.01 (s, 2 H), 3.91 (q, J=3.9 Hz, 1 H), 3.79 - 3.62 (m, 1 H), 3.58 (s, 3 H), 3.19 (t, J=12.2 Hz, 1 H), 2.33 (t, J=2.4 Hz, 1 H), 1.81 (br. s., 1 H), 1.69 - 1.54 (m, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ 153.2, 128.0,
4-(3-Methoxycarbonyl-prop-2-ynyloxy)-3,4-dihydro-2H-pyridine-1-carboxylic acid methyl ester (11.0c)\textsuperscript{30}

Following the procedure for the synthesis of methyl ester 11.0a, methyl ester 11.0c was synthesized using the following quantities of reagents and solvents: 1.5 mL of n-butyllithium (1.9 mmol, 1.2 M in hexanes); 0.33 g of 11.0 (1.7 mmol, 1.0 equiv) in 17 mL of diethyl ether; 0.68 mL of methyl chloroformate (8.8 mmol, 5.2 equiv). Workup and purification by column chromatography on triethylamine washed silica gel (5:1 hexanes/ethyl acetate) afforded 0.21 g (56%) of a pale yellow oil.

IR (film): 2957, 2238, 1718, 1445, 1361, 1255, 1058 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 7.19 - 6.86 (m, 1 H), 5.19 - 4.93 (m, 1 H), 4.29 (s, 2 H), 4.12 - 4.01 (m, 1 H), 3.88 - 3.72 (m, 7 H), 3.33 (t, J=12.2 Hz, 1 H), 1.97 (d, J=12.2 Hz, 1 H), 1.88 - 1.70 (m, 1 H).

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ 154.1, 153.5, 129.0, 104.1, 84.1, 77.2, 67.2, 54.5, 53.2, 52.8, 37.8, 27.2. HRMS (ESI): Calcd for C\textsubscript{12}H\textsubscript{17}NO\textsubscript{3}Na (M + Na\textsuperscript{+}) 276.0848, found 276.0844.

3,6-Dihydro-2H-pyridine-1-carboxylic acid \textit{tert}-butyl ester (16.2)\textsuperscript{32}

To a solution of 30.2 g of \textit{di}-\textit{tert}-butyl-dicarbonate (13.8 mmol, 1.20 equiv) in 230 mL of methanol at 0 °C was added 9.29 mL of pyridine (11.5 mmol, 1.00 equiv). The reaction mixture was stirred for 30 min before 13.1 g of sodium borohydride (34.6 mmol, 3.00
equiv) were added over 40 min. After the reaction mixture was stirred at 0 °C for 9 h, it was poured into 200 mL of crushed ice. The separated aqueous layer was extracted with diethyl ether and the combined organic phases were concentrated by rotary evaporation in vacuo. The resulting biphasic oil was diluted with diethyl ether and the aqueous layer was extracted with diethyl ether. The combined organic phases were dried over anhydrous sodium sulfate and concentrated by rotary evaporation in vacuo to afford 10.5 g of a crude yellow oil 16.1, which was used without further purification.

To a solution of 13.1 g of 16.1 (0.0724 mol, 1.00 equiv) in 330 mL of benzene at 0 °C was sequentially added 5.48 g of sodium borohydride (0.145 mol, 2.00 equiv) and 18.6 g of 10-camphorsulfonic acid (0.0797 mol, 1.10 equiv). The reaction mixture was stirred at 0 °C for 4 h before it was poured into a saturated aqueous solution of sodium bicarbonate in crushed ice. The separated aqueous layer was extracted with diethyl ether. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, and concentrated by rotary evaporation in vacuo to afford a pale yellow oil. Purification by column chromatography on triethylamine washed silica gel (15:1 hexanes/ethyl acetate) afforded 6.56 g (49% over two steps) of a colourless oil.

IR (film): 2976, 1698, 1655, 1366, 1248, 1173 cm⁻¹. ¹H NMR (300 MHz, CDCl₃):
δ 5.80 - 5.48 (m, 2 H), 3.85 - 3.73 (m, 2 H), 3.42 (t, J=5.7 Hz, 2 H), 2.06 (br. s., 2 H), 1.40 (s, 9 H).

7-Oxa-3-aza-bicyclo[4.1.0]heptane-3-carboxylic acid tert-butyl ester (16.3)

To a solution of 6.35 g of 16.2 (34.7 mmol, 1.00 equiv) in 130 mL of dichloromethane at 0 °C was added 11.7 g (52.0 mmol, 1.50 equiv) of m-chloroperbenzoic acid. The reaction mixture was stirred at 0 °C for 15 min before it was warmed to rt and stirred for 11 h. The white mixture was diluted with dichloromethane and washed with water. The
separated aqueous layer was extracted with dichloromethane washed with a 1N aqueous solution of sodium hydroxide. The combined organic phases were dried over sodium sulfate and concentrated by rotary evaporation in vacuo to afford a colourless oil. Purification by column chromatography on triethylamine washed silica gel (hexanes to 3:1 hexanes/ethyl acetate to 2:1 hexanes/ethyl acetate) afforded 5.02 g (73%) of a pale yellow oil.

IR (film): 2976, 1693, 1249, 1174 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 3.98 - 3.73 (m, 1 H), 3.73 - 3.56 (m, 1 H), 3.48 - 3.34 (m, 1 H), 3.23 (br. s., 1 H), 3.16 (br. s., 1 H), 3.07 (ddd, J=13.3, 9.1, 4.1 Hz, 1 H), 2.07 - 1.93 (m, 1 H), 1.93 - 1.79 (m, 1 H), 1.41 (s, 9 H).

**4-Hydroxy-3,4-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (16.4)**

To a solution of 7.08 mL of diisopropylamine (50.6 mmol, 2.00 equiv) in 110 mL of THF at -78 °C was added 36.0 mL of a solution of n-butyllithium (46.8 mmol, 1.85 equiv). The reaction mixture was stirred at -78 °C for 30 min before a solution of 5.04 g of 16.3 (25.3 mmol, 1.0 equiv) in 150 mL of THF was added. The reaction mixture was stirred for 2.5 h at -78 °C before 100 mL of a 1:1 solution of water-saturated aqueous solution of sodium bicarbonate was added. The reaction mixture was warmed to rt and the separated aqueous layer was extracted with diethyl ether. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, and concentrated by rotary evaporation to afford a light brown oil. Purification by column chromatography on triethylamine washed silica gel afforded 4.81 g (96%) of a yellow oil.

IR (film): 3423, 2977, 1708, 1646, 1370, 1169, 1060 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 6.99 - 6.70 (m, 1 H), 5.08 - 4.79 (m, 1 H), 4.19 - 4.06 (m, 1 H), 3.75 (br. s., 1 H), 3.41 - 3.17 (m, 1 H), 2.48 (br. s., 1 H), 1.87 - 1.66 (m, 2 H), 1.40 (s, 9 H).
Following the procedure for the synthesis of ether 13.6, ether 16.5 was synthesized using the following quantities of reagents and solvents: 1.27 g of 16.4 (6.39 mmol, 1.00 equiv); 0.242 g of sodium hydride (9.58 mmol, 1.50 equiv) in 100 mL of THF; 3.56 mL of propargyl bromide (31.9 mmol, 5.00 equiv). Workup and purification by column chromatography on triethylamine washed silica gel (hexanes to 5:1 hexanes/ethyl acetate to ethyl acetate) afforded 0.518 g of starting material and 0.649 g (90% brsm) of a yellow oil.

IR (film): 3294, 2976, 1708, 1642, 1367, 1241, 1169, 1072 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 6.98 - 6.64 (m, 1 H), 4.96 - 4.73 (m, 1 H), 4.02 (s, 2 H), 3.91 (q, J=3.9 Hz, 1 H), 3.80 - 3.57 (m, 1 H), 3.14 (d, J=10.0 Hz, 1 H), 2.31 (t, J=2.4 Hz, 1 H), 1.82 (d, J=13.5 Hz, 1 H), 1.59 (dddd, J=14.0, 12.3, 4.1, 4.0 Hz, 1 H), 1.32 (s, 9 H). ¹³C NMR (100 MHz, CDCl₃): δ 151.7, 128.5, 102.8, 80.6, 79.8, 73.9, 66.3, 54.3, 37.4, 27.8, 26.9. HRMS (ESI): Calcd for C₁₃H₁₉NO₃Na (M + Na⁺) 260.1263, found 260.1259.

Following the procedure for the synthesis of methyl ester 11.0a, methyl ester 11.0d was synthesized using the following quantities of reagents and solvents: 3.08 mL of n-butyllithium (3.97 mmol, 1.29 M in hexanes); 0.857 g of 16.5 (3.61 mmol, 1.00 equiv) in 36 mL of diethyl ether; 1.54 mL of methyl chloroformate (19.9 mmol, 5.50 equiv). Workup and purification by column chromatography on triethylamine washed silica gel
(hexanes to 9:1 hexanes/ethyl acetate) afforded 0.347 g of starting material and 0.598 g (94% brsm) of a yellow oil.

IR (film): 2979, 2241, 1718, 1641, 1368, 1256, 1168, 1057 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.01 - 6.74 (m, 1 H), 4.99 - 4.75 (m, 1 H), 4.19 (s, 2 H), 3.93 (q, \(J=3.9\) Hz, 1 H), 3.76 (br. s., 1 H), 3.64 (s, 3 H), 3.16 (d, \(J=10.0\) Hz, 1 H), 1.85 (d, \(J=11.3\) Hz, 1 H), 1.68 - 1.57 (m, 1 H), 1.35 (s, 9 H). \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 153.2, 151.8, 129.0, 102.0, 83.9, 80.8, 77.1, 67.1, 54.1, 52.4, 37.3, 27.9, 26.9. MS (ESI): 318.3 (M + Na\(^+\)).

Acetic acid 1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridin-4-yl ester (17.2)\(^30\)

6-Methoxy-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydro-pyridine 12.5 (8.19 g, 30.6 mmol) was dissolved in a 5 mL of glacial acetic acid. After the solution was stirred for 5 min, it was neutralized by the slow addition of a saturated solution of sodium bicarbonate. The separated aqueous layer was then extracted with diethyl ether. The combined organic phases were dried anhydrous sodium sulfate and concentrated by rotary evaporation \textit{in vacuo} to afford a yellow oil. Purification by triethylamine washed silica gel (5:1 hexanes/ethyl acetate) afforded 3.28 g (83%) of a yellow oil.

IR (film): 3095, 2936, 1734, 1645, 1358 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.63 (d, \(J=8.3\) Hz, 2 H), 7.29 (d, \(J=7.9\) Hz, 2 H), 6.84 (d, \(J=7.9\) Hz, 1 H), 5.12 - 5.01 (m, 2 H), 3.67 (dt, \(J=12.2, 4.4\) Hz, 1 H), 3.09 (td, \(J=12.0, 3.1\) Hz, 1 H), 2.40 (s, 3 H), 1.93 (s, 3 H), 1.90 - 1.81 (m, 1 H), 1.77 - 1.67 (m, 1 H). \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 170.0, 144.1, 134.9, 129.9, 129.2, 126.9, 104.7, 62.8, 39.5, 27.1, 21.5, 21.1. MS (ESI): 318.3
1-(Toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridin-4-ol (18.1)

To a solution of 6.4 g of 16.2 (22 mmol, 2.0 equiv) in 150 mL of methanol was added 0.43 g of sodium hydroxide (11 mmol, 1.0 equiv). The reaction mixture was stirred for 5 h before it was neutralized by a 1 M solution of hydrochloric acid. A saturated solution of sodium bicarbonate was added, and the separated aqueous layer was extracted with dichloromethane. The combined organic phases were washed with water, dried over anhydrous sodium sulfate, and concentrated in vacuo to afford a yellow oil. Purification by column chromatography on triethylamine washed silica gel (5:1 ethyl/acetate to 3:1 hexanes/ethyl acetate to 1:1 hexanes/ethyl acetate to ethyl acetate) afforded 1.6 g (29%) of a white solid (mp 59-61 °C).

IR (film): 3387, 3066, 2927, 1645, 1353, 1168 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.53 (d, J=8.3 Hz, 2 H), 7.20 (d, J=8.3 Hz, 2 H), 6.59 (d, J=8.3 Hz, 1 H), 4.93 (dd, J=7.9, 4.4 Hz, 1 H), 3.87 (br. s., 1 H), 3.51 - 3.40 (m, 1 H), 3.11 - 2.96 (m, 2 H), 2.28 (s, 3 H), 1.67 - 1.55 (m, 1 H), 1.55 - 1.43 (m, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ 143.9, 134.5, 129.7, 126.8, 126.7, 129.3, 59.3, 39.3, 29.8, 21.3. MS (ESI): 276.2 (M + Na⁺). Anal. Calcd for C₁₂H₁₅N₂O₃S: C, 56.9; H, 5.97; N 5.53. Found: C, 57.19; H, 5.89, N, 5.49.

4-Azido-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridine (20.1)⁵⁶

To a solution of 1.0 g of 17.1 (4.1 mmol, 1.0 equiv) in 16 mL of toluene was added 0.63 mL of 1,8-diazabicyclo[5,4,0]undec-7-ene (4.1 mmol, 1.0 equiv). The reaction mixture was cooled to 0 °C, and 0.92 mL of diphenylphosphoryl azide (4.1 mmol, 1.0 equiv) were added. The reaction mixture was warmed to rt and stirred overnight. After the reaction mixture was diluted with water, the separated aqueous layer was extracted with...
dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate and concentrated by rotary evaporation \textit{in vacuo} to afford a light brown oil. Purification by column chromatography on triethylamine washed silica gel (9:1 hexanes/ethyl acetate to 3:1 hexanes/ethyl acetate to ethyl acetate) afforded 0.30 g of starting material and 0.79 g (69%) of a light brown oil.

IR (film): 2929, 2095, 1640, 1358, 1169 cm\(^{-1}\). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta 7.63\) (d, \(J=8.2\) Hz, 2 H), 7.30 (d, \(J=7.8\) Hz, 2 H), 6.93 (d, \(J=8.2\) Hz, 1 H), 5.07 – 4.95 (m, 1 H), 3.83 (q, \(J=4.4\) Hz, 1 H), 3.62 - 3.71 (m, 1 H), 3.04 (ddd, \(J=12.3, 10.3, 4.3\) Hz, 1 H), 2.41 (s, 3 H), 1.89 - 1.71 (m, 2 H). \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 144.2, 134.4, 129.9, 129.4, 127.0, 102.9, 51.02, 39.6, 27.5, 21.5\). HRMS (EI): Calcd for C\(_{17}H_{19}NO_3NaS (M^+)\) 278.0838, found 278.0839.

\[ \text{N} \quad \text{a) PPh}_3 \quad \text{THF:H}_2\text{O, 80°C} \quad \text{Boc} \quad \text{b) Boc}_2\text{O} \quad \text{THF} \]

\[ \text{[1-(Toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridin-4-yl]-carbamic acid tert-butyl ester (24.1)\textsuperscript{58}} \]

A solution 0.51 g of 23.0 (1.8 mmol, 1.0 equiv) and 0.96 g of triphenylphosphine (3.7 mmol, 2.0 equiv) in 18 mL of THF and 0.7 mL of water was heated to reflux for 2 h. The reaction mixture was concentrated by rotary evaporation \textit{in vacuo}. To the pale yellow solid was added 0.80 g of di-\textit{tert}-butyl-dicarbonate (3.7 mmol, 2.0 equiv) and 18 mL of THF. The reaction mixture was heated to reflux for 1.5 h. Concentration by rotary evaporation \textit{in vacuo} afforded a pale yellow oil. Purification by column chromatography on triethylamine washed silica gel (10:1 hexanes/ethyl acetate to 3:1 hexanes/ethyl acetate) afforded 0.59 g (91%) of a white solid (mp 133-135 °C).

IR (film): 3377, 2977, 1702, 1646, 1510, 1366, 1169 cm\(^{-1}\). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta 7.63\) (d, \(J=8.2\) Hz, 2 H), 7.30 (d, \(J=7.9\) Hz, 2 H), 6.74 (d, \(J=8.7\) Hz, 1 H), 4.89 (dd, \(J=8.3, 4.4\) Hz, 1 H), 4.35 (br. s., 1 H), 4.04 (br. s., 1 H), 3.57 - 3.44 (m, 1 H), 3.24 - 3.08
(m, 1 H), 2.42 (s, 3 H), 1.82 - 1.68 (m, 2 H), 1.39 (s, 9 H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 154.6, 144.0, 134.8, 129.9, 127.8, 127.0, 107.1, 79.7, 41.7, 40.4, 30.3, 28.3, 21.6.

HRMS (ESI): Calcld for C$_{17}$H$_{24}$N$_2$O$_4$NaS (M + Na$^+$) 375.1354, found 375.1355.

Prop-2-ynyl-[1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridin-4-yl]-carbamic acid tert-butyl ester (24.2)$^{59}$

A suspension of 0.67 g of 23.1 (1.91 mmol, 1.00 equiv) and 0.097 g of sodium hydride (3.8 mmol, 2.0 equiv) in 20 mL of N,N-dimethyl formamide was stirred for 1 h. The reaction mixture was stirred at 0°C before 1.0 mL of propargyl bromide (12 mmol, 6.0 equiv) were added dropwise. The reaction mixture was warmed to rt and stirred overnight. After the reaction mixture was diluted with water, it was extracted with dichloromethane. The separated organic layer was washed sequentially with water and brine. The combined organic phases were dried over anhydrous sodium sulfate and concentrated in vacuo to afford a yellow oil. Purification by column chromatography on triethylamine washed silica gel (3:1 petroleum ether/diethyl ether) afforded 0.59 g (79%) of a colourless oil.

IR (film): 3288, 2976, 1696, 1365, 1267, 1167 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.62 (d, $J$=8.3 Hz, 2 H), 7.28 (d, $J$=8.3 Hz, 2 H), 6.78 (dd, $J$=8.5, 2.0 Hz, 1 H), 4.80 (d, $J$=6.5 Hz, 1 H), 3.78 - 3.66 (m, 1 H), 3.65 - 3.51 (m, 2 H), 3.26 - 3.07 (m, 1 H), 2.38 (s, 3 H), 2.03 (t, $J$=2.4 Hz, 1 H), 1.87 - 1.74 (m, 2 H), 1.40 (s, 9 H), 1.36 (s, 1 H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 154.5, 143.9, 134.4, 129.7, 128.8, 126.8, 107.6, 81.1, 80.4, 70.0, 47.7, 42.1, 32.4, 28.1, 25.9, 21.4. HRMS (ESI): Calcld for C$_{20}$H$_{26}$N$_2$O$_4$NaS (M + Na$^+$) 413.1511, found 413.1513.
4-\{\text{tert}-\text{Butoxycarbonyl}-\left[\text{1-}\left(\text{toluene}-4\text{-sulfonyl}\right)\text{-1,2,3,4-tetrahydro-pyridin-4-yl}\right]\text{-amino}\}\text{-but-2-ynoic acid methyl ester (11.0e)}^{30}

Following the synthesis of methyl ester 11.0a, methyl 11.0e was synthesized using the following quantities of reagents and solvents: 0.96 mL of \text{n-butyllithium} (1.2 mmol, 1.2 M in hexanes); 0.39 g of 23.2 (0.99 mmol, 1.0 equiv) in 10 mL of diethyl ether; 0.40 mL of methyl chloroformate (5.1 mmol, 5.2 equiv). Workup and purification by column chromatography on triethylamine washed silica gel (5:1 hexanes/ethyl acetate) afforded 0.40 g (91%) of a yellow oil.

IR (film): 2978, 2241, 1698, 1366, 1256, 1167 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.62 (d, \(J=8.3\) Hz, 2 H), 7.28 (d, \(J=8.3\) Hz, 2 H), 6.80 (dd, \(J=8.3,\) 1.7 Hz, 1 H), 4.76 (d, \(J=6.5\) Hz, 1 H), 4.62 (br. s., 1 H), 3.86 - 3.67 (m, 2 H), 3.72 (s, 3 H), 3.60 - 3.51 (m, 1 H), 3.20 (t, \(J=10.0\) Hz, 1 H), 2.38 (s, 3 H), 1.91 - 1.79 (m, 1 H), 1.71 (br. s., 1 H), 1.40 (s, 9 H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 154.3, 153.5, 144.2, 134.4, 129.8, 129.5, 126.9, 107.1, 85.2, 81.1, 71.8, 52.6, 47.8, 42.1, 32.6, 28.2, 26.1, 21.4. HRMS (ESI): Calcd for C\(_{22}\)H\(_{28}\)N\(_2\)O\(_6\)NaS (M + Na\(^{+}\)) 471.1566, found 471.1575.

Trans-4-Azido-2-phenyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridine (24.3f) and Cis-4-Azido-2-phenyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridine (25.3g)\(^{56}\)

To a solution of 1.2 g of 13.5 (3.6 mmol, 1.0 equiv) in 15 mL of toluene was added 2.4 mL of diphenylphosphoryl azide (11 mmol, 3.0 equiv). The yellow reaction mixture was cooled to 0 °C and 1.6 mL of 1,8-diazabicyclo[5,4,0]undec-7-ene (11 mmol, 3.0 equiv) were added. The light brown reaction mixture was stirred at 0 °C for 1 h and the
resulting dark brown reaction mixture was warmed to rt and stirred overnight. The reaction mixture was diluted with water and filtered through a pad of Celite. The separated aqueous layer was extracted with dichloromethane. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, and concentrated by rotary evaporation in vacuo to afford a thick dark brown oil. The above procedure was performed using the following quantities of reagents and solvents: 0.57 g of 13.5 (1.7 mmol, 1.0 equiv) in 7 mL of toluene, 1.2 mL of diphenylphosphoryl azide (5.2 mmol, 3.0 equiv) and 11 mL of 1,8-diazabicyclo[5, 4, 0]undec-7-ene (5.2 mL, 3.0 equiv). The combined crude materials from both experiments were purified by column chromatography on triethylamine washed silica gel (12:1 hexanes/ethyl acetate, 5% benzene) to afford 0.67 g (35%) of a yellow oil 25.3f and 0.43 g (23%) of a yellow solid 25.3g.

To a solution of 0.72 g of 13.5 (2.2 mmol, 1.0 equiv) in 8.8 mL of toluene was added 1.4 mL of diphenylphosphoryl azide (6.6 mmol, 3.0 equiv). The yellow reaction mixture was cooled to 0 °C and 0.99 mL of 1,8-diazabicyclo[5, 4, 0]undec-7-ene (6.6 mmol, 3.00 equiv) were added. The light brown reaction mixture was warmed to rt and stirred for 2 days. The reaction mixture was diluted with water and filtered over a pad of Celite. The separated aqueous layer was extracted with dichloromethane. The combined organic phases were washed with brine, dried over anhydrous magnesium sulfate, and concentrated by rotary evaporation in vacuo to afford a thick dark brown oil. Purification by column chromatography on triethylamine washed silica gel (10:1 hexanes/ethyl acetate) afforded 0.19 g (24%) of a yellow oil 25.3f and 0.36 (47%) of a yellow solid 25.3g (mp 36-38 °C).

25.3f - IR (film): 2928, 2101, 1646, 1364, 1169 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.63 (d, J=8.3 Hz, 2 H), 7.31 - 7.24 (m, 5 H), 7.20 - 7.15 (m, 2 H), 7.08 - 7.03 (m, 1 H), 5.16 (t, J=3.7 Hz, 1 H), 5.03 - 4.98 (m, 1 H), 3.57 - 3.50 (m, 1 H), 2.42 (s, 3 H), 2.27 - 2.20 (m, 1 H), 1.59 - 1.49 (m, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ 144.1, 138.7, 135.6, 130.0, 128.7, 127.6, 127.5, 126.9, 125.5, 106.4, 55.6, 50.6, 32.2, 21.6. HRMS (EI): Calcd for C₁₈H₁₈N₄O₂S (M⁺) 354.1151, found 354.1153.
25.3g - IR (film): 3063, 2101, 1646, 1364, 1170 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.64 (d, \(J=8.3\) Hz, 2 H), 7.39 - 7.32 (m, 2 H), 7.29 - 7.17 (m, 6 H), 5.29 (dd, \(J=4.8, 2.6\) Hz, 1 H), 5.17 - 5.11 (m, 1 H), 3.86 (t, \(J=5.0\) Hz, 1 H), 2.40 (s, 3 H), 2.39 - 2.32 (m, 1 H), 1.80 (dt, \(J=14.4, 5.2\) Hz, 1 H). \(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 144.1, 138.1, 136.0, 129.8, 128.8, 128.3, 127.0, 125.8, 120.2, 103.6, 53.9, 49.6, 33.6, 21.6. HRMS (EI): Calcd for C\(_{18}\)H\(_{18}\)N\(_4\)O\(_2\)S (M\(^+\)) 354.1151, found 354.1151.

\[
\begin{align*}
\text{N}_3 & \xrightarrow{\text{a) PPh}_3} \quad \text{THF-H}_2\text{O, 80 °C} \quad \text{Boc-} \quad \text{N}^+ \\
\text{Ts} & \quad \text{Ts}
\end{align*}
\]

**Trans-[2-Phenyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridin-4-yl]-carbamic acid tert-butyl ester (26.1f)**

Following the procedure for the synthesis of carbamate 24.1, carbamate 26.1f was synthesized using the following quantities of reagents and solvents: 0.84 g of 25.3f (2.4 mmol, 1.0 equiv); 1.2 g of triphenylphosphine (4.7 mmol, 2.0 equiv) in 24 mL of THF and 1 mL of water; 1.0 g of di-tert-butyl-dicarbonate (4.7 mmol, 2.0 equiv) in 24 mL of THF. Purification by column chromatography on triethylamine washed silica gel (5:1 hexanes/ethyl acetate to 3:1 hexanes/ethyl acetate) afforded 0.72 g (70%) of a white solid (mp 118-120 °C).

IR (film): 3392, 2976, 1703, 1651, 1496, 1365, 1168 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): 7.59 (d, \(J=7.0\) Hz, 2 H), 7.33 - 7.12 (m, 7 H), 6.93 (d, \(J=8.3\) Hz, 1 H), 5.16 (br. s., 1 H), 4.89 (d, \(J=7.9\) Hz, 1 H), 4.40 - 4.25 (m, 1 H), 3.89 (br. s., 1 H), 2.41 (s, 3 H), 2.33 (d, \(J=10.5\) Hz, 1 H), 1.37 (br. s., 10 H). \(\delta\) \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 155.0, 143.7, 138.9, 136.0, 129.7, 128.5, 127.4, 126.9, 126.1, 125.7, 109.7, 79.6, 56.1, 40.8, 33.4, 28.3, 21.5. HRMS (ESI): Calcd for C\(_{23}\)H\(_{28}\)N\(_2\)O\(_4\)NaS (M + Na\(^+\)) 451.1667, found 451.1653.
Trans-[2-Phenyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridin-4-yl]-prop-2-ynyl-carbamic acid tert-butyl ester (26.2f)

A suspension of 0.19 g of 26.1f (0.43 mmol, 1.0 equiv) and 0.016 g of sodium hydride (0.65 mmol, 1.5 equiv) in 1.5 mL of N, N-dimethyl formamide was stirred for 1.5 h. The reaction mixture was cooled to 0 °C before 0.14 mL of propargyl bromide (1.3 mmol, 3.0 equiv) were added dropwise. The reaction mixture was warmed to rt and stirred for 6 h before 0.013 g of sodium hydride (0.32 mmol, 0.75 equiv) and 0.14 mL of propargyl bromide (1.3 mmol, 3.0 equiv) were added. The reaction mixture was stirred overnight. After the reaction mixture was diluted with water, it was extracted with dichloromethane. The separated organic layer was washed sequentially with water and brine. The combined organic phases were dried over anhydrous sodium sulfate and concentrated in vacuo to afford a brown oil. Purification by column chromatography on triethylamine washed silica gel (3:1 petroleum ether/diethyl ether) afforded 0.097 g (68% brsm) of a colourless oil.

IR (film): 3305, 2975, 1696, 1393, 1365, 1167 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.67 (br. s., 2 H), 7.34 - 7.20 (m, 7 H), 7.02 (d, J=8.3 Hz, 1 H), 5.23 (br. s., 1 H), 4.99 (br. s., 1 H), 4.65 - 4.11 (m, 1 H), 3.86 - 3.44 (m, 2 H), 2.43 (s, 3 H), 2.12 (br. s., 1 H), 2.06 (s, 1 H), 1.68 (td, J=12.2, 4.8 Hz, 2 H), 1.52 - 1.20 (m, 9 H). ¹³C NMR (100 MHz, CDCl₃): δ 154.5, 143.9, 138.7, 135.8, 129.7, 128.5, 128.0, 127.3, 126.9, 125.6, 109.5, 81.4, 80.5, 70.1, 56.2, 46.4, 32.4, 29.7, 28.2, 21.5. HRMS (ESI): Calcd for C₂₈H₃₂N₂O₆NaS (M + Na⁺) 547.1879, found 547.1870.
Trans-[2-Phenyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridin-4-yl]-prop-2-ynyl-carbamic acid tert-butyl ester (11.0f)

Following the procedure for the synthesis of methyl ester 11.0a, methyl ester 11.0f was synthesized using the following quantities of reagents and solvents: 0.33 mL of n-butyllithium (0.41 mmol, 1.2 M in hexanes); 0.12 g of 26.2f in 2.6 mL of diethyl ether; 0.11 mL of methyl chloroformate (1.4 mmol, 5.5 equiv). Workup and purification by column chromatography on triethylamine washed silica gel (3:1 petroleum ether/diethyl ether to 3:2 petroleum ether/diethyl ether) afforded 0.066 g (49%) of a yellow oil.

IR (film): 2976, 2240, 1714, 1366, 1256, 1167 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.60 (br. s., 2 H), 7.33 - 7.08 (m, 7 H), 6.99 (d, J=7.4 Hz, 1 H), 5.20 (br. s., 1 H), 4.97 - 4.75 (m, 1 H), 4.54 - 4.07 (m, 1 H), 3.88 - 3.70 (m, 1 H), 3.75 (s, 3 H), 3.70 - 3.51 (m, 1 H), 2.38 (s, 3 H), 2.19 - 1.99 (m, 1 H), 1.54 (td, J=12.2, 4.8 Hz, 1 H), 1.45 - 1.18 (m, 9 H). ¹³C NMR (100 MHz, CDCl₃): δ 154.2, 153.6, 144.1, 138.5, 135.7, 129.7, 128.5, 127.4, 126.9, 125.6, 125.5, 109.1, 85.3, 81.1, 73.9, 56.2, 52.6, 46.4, 32.4, 30.3, 28.1, 21.5. MS (ESI): 547.1 (M + Na⁺).

Cis-[2-Phenyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridin-4-yl]-carbamic acid tert-butyl ester (26.1g)

Following the experimental procedure for the preparation of carbamate 24.1, carbamate 26.1g was prepared using the following quantities of reagents and solvents: 0.92 g of 25.3g (2.6 mmol, 1.0 equiv), 1.4 g of triphenylphosphine (5.2 mmol, 2.0 equiv) in 26 mL of THF and 1 mL of water, 1.1 g of di-tert-butyl-dicarbonate (5.2 mmol, 2.0 equiv) and
26 mL of THF. Purification by column chromatography on triethylamine washed silica gel (5:1 hexanes/ethyl acetate) afforded 0.91 g (92%) of a white solid (mp 159-160 °C).

IR (film): 3437, 2977, 1708, 1649, 1366, 1168 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)):
\[\delta 7.65 (d, J=8.3 \text{ Hz}, 2 \text{ H}), 7.30 - 7.18 (m, 7 \text{ H}), 7.03 (d, J=8.3 \text{ Hz}, 1 \text{ H}), 5.25 (\text{br. s.}, 1 \text{ H}), 5.10 - 5.02 (m, 1 \text{ H}), 3.95 - 3.87 (m, 1 \text{ H}), 3.41 (d, J=9.2 \text{ Hz}, 1 \text{ H}), 2.45 - 2.35 (m, 1 \text{ H}), 2.40 (s, 3 \text{ H}), 1.61 (dd, J=14.2, 5.0, 4.8 \text{ Hz}, 1 \text{ H}), 1.22 (\text{s}, 9 \text{ H}). \]
\(^1^3\)C NMR (100 MHz, CDCl\(_3\)):
\[\delta 154.4, 144.0, 139.0, 136.0, 129.8, 128.7, 127.0, 126.8, 126.7, 125.5, 108.2, 78.9, 54.1, 40.3, 34.0, 28.1, 21.5. \] MS (ESI): 451.3 (M + Na\(^+\)). Anal. Calcd for C\(_{23}\)H\(_{28}\)N\(_2\)O\(_4\)S: C, 64.46; H, 6.58; N, 6.54. Found: C, 64.28; H 6.57; N, 6.38.

\[\text{Cis-}[2\text{-Phenyl-1-}(\text{toluene-4-sulfonyl})\text{-1,2,3,4-tetrahydro-pyridin-4-yl]-prop-2-ynyl-carbamic acid tert-butyl ester (26.2g) }^{59}\]
A suspension of 0.19 g of 26.1g (0.45 mmol, 1.0 equiv) and 0.017 g of sodium hydride (0.68 mmol, 1.5 equiv) in 1.5 mL of N,N-dimethyl formamide was stirred for 1 h before 0.15 mL of propargyl bromide (1.4 mmol, 3.0 equiv) were added dropwise. The reaction mixture was stirred for 5 h before the addition of 0.014 g of sodium hydride (0.34 mmol, 1.3 equiv) and 0.15 mL of propargyl bromide (1.4 mmol, 3.0 equiv). The reaction mixture was stirred overnight before it was diluted with water and extracted with dichloromethane. The combined organic phases were washed sequentially with water and brine, dried over anhydrous sodium sulfate and concentrated \textit{in vacuo} to afford a brown oil. Purification by column chromatography on triethylamine washed silica gel (2:1 petroleum ether/diethyl ether) afforded 66.4 mg of starting material and 0.060 g (46% brsm) of a white solid (50-52 °C).

IR (film): 3307, 2977, 1690, 1366, 1169 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)):
\[\delta 7.64 (d, J=8.7 \text{ Hz}, 2 \text{ H}), 7.33 - 7.19 (m, 7 \text{ H}), 7.10 (dd, J=8.3, 1.7 \text{ Hz}, 1 \text{ H}), 5.20 (\text{br. s.}, 1 \text{ H}), 4.95\]
(br. s., 1 H), 4.32 (br. s., 1 H), 2.92 (br. s., 2 H), 2.69 – 2.57 (m, 1 H), 2.44 (s, 3 H), 2.02 (s, 1 H), 1.65 (br. s., 1 H), 1.51 - 1.37 (m, 9 H). 13C NMR (100 MHz, CDCl3): δ 154.5, 144.1, 139.6, 135.4, 129.8, 128.9, 128.3, 127.1, 127.0, 126.1, 107.6, 81.6, 80.2, 69.7, 55.2, 46.8, 34.3, 32.7, 28.3, 21.5. HRMS (ESI): Calcd for C26H30N2O4NaS (M + Na+) 489.1824, found 489.1815.

Cis-[2-phenyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridin-4-yl]-prop-2-ynylcarbamic acid tert-butyl ester (11.0g) 30

Following the procedure for the synthesis of methyl ester 11.0a, methyl ester 11.0g was synthesized using the following quantities of reagents and solvents: 0.53 mL of n-butyllithium (0.65 mmol, 1.2 M in hexanes); 0.20 g of 26.2g in 4.3 mL of diethyl ether; 0.18 mL of methyl chloroformate (2.4 mmol, 5.5 equiv). Workup and purification by column chromatography on triethylamine washed silica gel (7:1 hexanes/ethyl acetate) afforded 0.047 g of starting material and 0.11 g (61% brsm) of a yellow oil.

IR (film): 2975, 2239, 1718, 1367, 1251, 1170 cm⁻¹. 1H NMR (400 MHz, CDCl3): δ 7.66 (d, J=8.3 Hz, 2 H), 7.33 - 7.18 (m, 7 H), 7.13 (d, J=8.7 Hz, 1 H), 5.18- 5.03 (m, 2 H), 4.28 (br. s., 1 H), 3.71 (s, 3 H), 3.03 - 2.77 (m, 2 H), 2.71 – 2.61 (m, 1 H), 2.43 (s, 3 H), 1.64 - 1.53 (m, 1 H), 1.39 (br. s., 9 H). 13C NMR (100 MHz, CDCl3): δ 154.0, 153.7, 144.1, 139.1, 135.5, 129.9, 129.3, 128.4, 127.2, 126.9, 126.0, 106.6, 85.8, 80.7, 73.5, 54.5, 52.5, 46.4, 33.7, 32.8, 28.2, 21.5. HRMS (ESI): Calcd for C28H32N2O6NaS (M + Na+) 547.1879, found 547.1880.
4-tert-Butoxycarbonylamino-3,4-dihydro-2H-pyridine-1-carboxylic acid methyl ester (27.2)\textsuperscript{56,58}

To a solution of 2.11 g of 14.5 (13.4 mmol, 1.00 equiv) in 38 mL of toluene was added 1.02 mL of 1,8-diazabicyclo[5,4,0]undec-7-ene (26.9 mmol, 2.00 equiv). The reaction mixture was cooled to 0 °C, and 6.00 mL of diphenylphosphoryl azide (26.9 mmol, 2.00 equiv) were added. The reaction mixture was warmed to rt and stirred for 1 h before it was diluted with water. The separated aqueous layer was extracted with dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate and concentrated by rotary evaporation \textit{in vacuo} to afford a light brown oil. Purification by column chromatography on triethylamine washed silica gel (9:1 hexanes/ethyl acetate) afforded 2.45 g of a mixture of 27.1 and diphenylphosphoryl azide.

A solution 2.45 g of 27.1 (13.4 mmol, 1.00 equiv) and 7.00 g of triphenylphosphine (26.8 mmol, 2.00 equiv) in 13 mL of THF and 4.8 mL of water was heated at 50 °C for 40 min. The reaction mixture was concentrated by rotary evaporation \textit{in vacuo}. To the pale yellow solid was added 5.83 g of di-tert-butyl-dicarbonate (26.8 mmol, 2.00 equiv) and 13 mL of THF. The reaction mixture was heated at 50 °C for 2 h then at 60 °C for 1 h. Concentration by rotary evaporation \textit{in vacuo} to afforded a pale yellow oil. Purification by column chromatography on triethylamine washed silica gel (7:1 hexanes/ethyl acetate to 5:1 hexanes/ethyl acetate) afforded 1.51 g (44% over two steps) of a white solid (mp 133-135 °C).

\textbf{27.1} - IR (film): 2957, 2095, 1718, 1647, 1445, 1358, 1235, 1191, 768 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 7.19 - 6.96 (m, 1 H), 5.10 - 4.86 (m, 1 H), 3.94 (q, \(J=4.4\) Hz, 1 H), 3.91 - 3.79 (m, 1 H), 3.75 (s, 3 H), 3.43 - 3.32 (m, 1 H), 1.97 - 1.82 (m, 2 H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 129.3, 120.2, 101.6, 53.2, 51.9, 38.2, 27.8. HRMS (EI): Calcd for C\textsubscript{7}H\textsubscript{16}N\textsubscript{4}O\textsubscript{2} (M\textsuperscript{+}) 182.0804, found 182.0803.
27.2 - IR (film): 3344, 2977, 1712, 1652, 1447, 1366, 1238, 1170 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.04 - 6.76\) (m, 1 H), 4.93 - 4.74 (m, 1 H), 4.55 (d, \(J=4.8\) Hz, 1 H), 4.15 (br. s., 1 H), 3.82 - 3.66 (m, 4 H), 3.38 (ddd, \(J=13.1, 9.6, 3.5\) Hz, 1 H), 1.97 - 1.74 (m, 2 H), 1.40 (s, 9 H). \(^1^3\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 155.1, 153.9, 127.5, 106.1, 79.7, 53.3, 42.5, 39.2, 28.8, 28.6\). HRMS (ESI): Calcd for C\(_{12}\)H\(_{20}\)N\(_2\)O\(_4\)Na (M + Na\(^+\)) 279.1321, found 279.1316.

\[
\begin{align*}
\text{Boc} & \quad \text{Br} & \quad \text{NaH} & \quad \text{DMF} \\
\text{N} & \quad \text{Br} & \quad \text{C} & \quad \text{O} & \quad \text{O}
\end{align*}
\]

4-( tert-Butoxycarbonyl-prop-2-ynyl-amino)-3,4-dihydro-2H-pyridine-1-carboxylic acid methyl ester (27.3)

A suspension of 1.1 g of 26.2 (4.1 mmol, 1.0 equiv) and 0.052 g of sodium hydride (21 mmol, 5.0 equiv) in 25 mL of N, N-dimethyl formamide and 1 mL of THF was stirred for 15 min before 2.3 mL of propargyl bromide (21 mmol, 5.0 equiv) were added dropwise. The reaction mixture was stirred overnight before it was diluted with water and extracted with dichloromethane. The combined organic phases were washed sequentially with water and brine, dried over anhydrous sodium sulfate and concentrated \textit{in vacuo} to afford a brown oil. Purification by column chromatography on triethylamine washed silica gel (13:1 hexanes/ethyl acetate) afforded 0.32 g of starting material and 0.48 g (57% brsm) of a white solid (mp 97-99.5 °C).

IR (film): 3307, 2977, 2252, 1695, 1652, 1446, 1397, 1167, 734 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.04 - 6.77\) (m, 1 H), 4.71 (br. s., 1 H), 4.65 (br. s., 1 H), 4.03 - 3.77 (m, 2 H), 3.73 (br. s., 1 H), 3.67 (s, 3 H), 3.47 - 3.33 (m, 1 H), 2.07 (t, \(J=2.4\) Hz, 1 H), 1.89 (br. s., 2 H), 1.39 (s, 9 H). \(^1^3\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 154.9, 153.0, 128.9, 105.9,\)
81.6, 80.6, 70.2, 53.2, 48.6, 40.8, 32.9, 28.4, 26.9. HRMS (ESI): Calcd for 
C\textsubscript{15}H\textsubscript{22}N\textsubscript{2}O\textsubscript{4}Na (M + Na\textsuperscript{+}) 317.1477, found 317.1473.

4-[tert-Butoxycarbonyl-(3-methoxycarbonyl-prop-2-ynyl)-amino]-3,4-dihydro-2H-
pyridine-1-carboxylic acid methyl ester (11.0h)

A solution of n-butyllithium (1.9 mL, 2.5 mmol, 1.4 M in hexanes) was added dropwise 
to a solution of 0.46 g of 27.3 in 16 mL of diethyl ether at \(-78\) \(^\circ\)C. After the reaction 
mixture was stirred at \(-78\) \(^\circ\)C for 1 h, 0.66 mL of methyl chloroformate (8.6 mmol, 5.5 
equiv) were added. The reaction mixture was stirred at \(-78\) \(^\circ\)C for 30 min, then warmed 
to rt and stirred for 1 h. After 1.7 mL of THF were added, the reaction mixture was 
stirred overnight. The above procedure was repeated using the following quantities of 
reagents and solvents: 0.21 mL of n-butyllithium (0.29 mmol, 1.4 M in hexanes); 0.053 g 
of 27.3 in 16 mL of diethyl ether; and 7.7 \(\mu\)L of methyl chloroformate (0.99 mmol, 5.5 
equiv). After both of the above reaction mixtures were diluted with diethyl ether, they 
were combined and washed sequentially with water and brine. The aqueous washes were 
back-extracted with diethyl ether. The combined organic phases were dried over 
anhydrous sodium sulfate and concentrated by rotary evaporation \textit{in vacuo} to afford a 
yellow oil. Purification by column chromatography on triethylamine washed silica gel 
(9:1 hexanes/ethyl acetate to 7:1 hexanes/ethyl acetate 3:1 hexanes/ethyl acetate) afforded 
0.080 g of starting material and 0.430 g (83% brsm) of a yellow oil.

IR (film): 2956, 2239, 1718, 1652, 1445, 1255, 1164 cm\(^{-1}\). \(^1\)H NMR (300 MHz, C\textsubscript{6}D\textsubscript{6}): 
\(\delta\ 7.14\mbox{ -}6.84 \mbox{ (m, 1 H)}, 5.03\mbox{ -}4.58 \mbox{ (m, 2 H)}, 3.98 \mbox{ (br. s., 2 H)}, 3.95 \mbox{ -}3.76 \mbox{ (m, 1 H)}, 3.73 
(d, \(J=3.1\) Hz, 6 H), 3.53 \mbox{ -}3.41 \mbox{ (m, 1 H)}, 2.09 \mbox{ -}1.78 \mbox{ (m, 2 H)}, 1.45 \mbox{ (s, 9 H)}. \(^{13}\)C NMR 
(100 MHz, C\textsubscript{6}D\textsubscript{6}): \(\delta\ 154.5, 154.0, 153.7, 129.7, 105.0, 85.6, 81.1, 73.9, 53.1, 52.6, \)
48.5, 40.6, 32.8, 28.3, 26.8. HRMS (ESI): Calcd for C\textsubscript{17}H\textsubscript{24}N\textsubscript{2}O\textsubscript{6}Na (M + Na\textsuperscript{+}) \(375.1532\), found 375.1539.

\[
\text{N} \quad \text{OH} \quad \text{a) DBU, toluene} \quad \text{N}_3 \quad \text{OH} \\
\text{Boc} \quad \text{b) DPPA} \quad \text{Boc} \\
\]

4-Azido-3,4-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (28.1)

Following the procedure for the synthesis of azide 27.1, azide 28.1 was synthesized using the following quantities of reagents and solvents: 2.1 g of alcohol 16.4 (11 mmol, 1.0 equiv) in 30 mL of toluene; 3.2 mL of 1,8-diazabicyclo[5, 4, 0]undec-7-ene (21 mmol, 2.0 equiv); 4.7 mL of diphenylphosphoryl azide (21 mmol, 2.0 equiv). Workup and purification by column chromatography on triethylamine washed silica gel (hexanes to 15:1 hexanes/ethyl acetate) afforded 1.7 g (73%) of a colourless oil.

IR (film): 2978,2093, 1713, 1645, 1359,1237, 1167 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 7.15 - 6.85 (m, 1 H), 5.00 - 4.72 (m, 1 H), 3.96 - 3.68 (m, 2 H), 3.33 - 3.17 (m, 1 H), 1.91 - 1.75 (m, 2 H), 1.41 (s, 9 H). \(^1\)\text{C} NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 151.7, 129.6, 100.4, 81.3, 51.8, 37.8, 28.0, 27.7. MS (ESI): 228 (M). Anal. Calcd for C\textsubscript{10}H\textsubscript{16}N\textsubscript{4}O\textsubscript{2}: C, 52.61; H, 7.06; N, 24.54. Found: C, 56.24; H, 7.48; N, 23.12.

\[
\text{N} \quad \text{OH} \quad \text{a) PPh\textsubscript{3}} \quad \text{THF/H\textsubscript{2}O, 80 °C} \quad \text{N}_3 \quad \text{OH} \\
\text{Boc} \quad \text{b) Boc}_\text{2}O \quad \text{THF} \\
\]

4-tert-Butoxycarbonylamino-3,4-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (28.2)

A solution 0.76 g of 28.1 (3.34 mmol, 1.00 equiv) and 1.8 g of triphenylphosphine (6.7 mmol, 2.0 equiv) in 33 mL of THF and 1.2 mL of water was heated to reflux for 1 h. The reaction mixture was concentrated by rotary evaporation in vacuo. To the pale yellow solid was added 1.5 g of di-tert-butyl-dicarbonate (6.7 mmol, 2.0 equiv) and 33 mL of
THF. The reaction mixture was heated to reflux for 4 h. Concentration by rotary evaporation *in vacuo* to afforded a pale yellow oil. Purification by column chromatography on triethylamine washed silica gel (hexanes/ethyl acetate to 5:1 hexanes/ethyl acetate) afforded 0.94 g (94%) of a white solid (mp 112-114 °C).

IR (film): 3341, 2979, 1696, 1651, 1515, 1367, 1239, 1170 cm⁻¹. \(^1\)H NMR (400 MHz, CDCl₃): δ 6.92 - 6.58 (m, 1 H), 4.77 (d, \(J=6.1\) Hz, 1 H), 4.72 - 4.55 (m, 1 H), 4.02 (br. s., 1 H), 3.58 (br. s., 1 H), 3.29 - 3.16 (m, 1 H), 1.75 (br. s., 1 H), 1.68 (br. s., 1 H), 1.24 - 1.40 (m, 18 H). \(^1^3\)C NMR (100 MHz, CDCl₃): δ 154.7, 151.8, 127.6, 104.7, 99.8, 80.7, 78.9, 42.1, 38.4, 28.4, 28.1, 27.9. MS (ESI): 321.3 (M + Na⁺). Anal. Calcd for C₁₅H₂₆N₂O₄: C, 60.38; H, 8.78; N, 9.39. Found: C, 60.12; H, 8.53; N, 9.28.

C. Cycloisomerization reactions

\[
\begin{array}{c}
\text{O} \\
\text{Ts} \\
\text{THF/CH₂Cl₂} \\
\text{80 °C} \\
\end{array}
\text{2 mol% AgOTf} \\
\rightarrow \\
\begin{array}{c}
\text{O} \\
\text{Ts} \\
\text{CO₂CH₃} \\
\end{array}
\]

[5-(Toluene-4-sulfonyl)-5,6,7,7a-tetrahydro-furo[3,2-c]pyridin-3-ylidene]-acetic acid methyl ester (11.1a)

A solution of 0.22 g of 11.0 (0.63 mmol, 1.0 equiv) and 3.2 mg of silver trifluoromethanesulfonate (0.013 mmol, 0.02 equiv) in 10 mL of THF and 40 μL of dichloromethane was heated to reflux for 16 h. Concentration of the reaction mixture by rotary evaporation *in vacuo* afforded a yellow oil. Purification by column chromatography on triethylamine washed silica gel (6:1 hexanes/ethyl acetate) afforded 0.16 g (73%) of a pale yellow oil.

IR (film): 2950, 1703, 1621, 1354, 1280, 1163 cm⁻¹. \(^1\)H NMR (400 MHz, CDCl₃): δ 7.65 (d, \(J=8.3\) Hz, 2 H), 7.37 - 7.28 (m, 3 H), 5.93 (t, \(J=2.4\) Hz, 1 H), 5.09 (dd, \(J=16.1, 2.2\) Hz,
1H), 4.63 (dd, J = 16.6, 2.6 Hz, 1H), 4.22 (ddd, J = 10.4, 5.6, 1.5 Hz, 1H), 3.90 (dt,
J = 13.1, 3.5 Hz, 1H), 3.69 (s, 3H), 3.03 (td, J = 13.4, 2.8 Hz, 1H), 2.41 (s, 3H), 2.29 -
2.21 (m, 1H), 1.42 - 1.38 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 167.1, 155.4, 144.6,
134.4, 130.1, 127.0, 122.3, 120.0, 103.7, 74.0, 73.3, 51.3, 41.4, 26.2, 21.6. HRMS (ESI): Calcd for
C$_{17}$H$_{15}$NO$_3$NaS (M + Na$^+$) 372.0882, found 372.0875.

[6-Phenyl-5-(toluene-4-sulfonyl)-5,6,7a-tetrahydro-furo[3,2-c]pyridin-3-ylidene]-
acetic acid methyl ester (11.1b)

A solution of 0.057 g of 11.0b (0.13 mmol, 1.0 equiv) and 0.7 mg of silver
trifluoromethanesulfonate (0.0027 mmol, 0.02 equiv) in 2.2 mL of THF and 10 $\mu$L of
dichloromethane was heated to reflux for 6 h. Concentration of the reaction mixture by
rotary evaporation in vacuo afforded an off white solid. Purification by column
chromatography on triethylamine washed silica gel (6:1 hexanes/ethyl acetate) afforded
0.040 g (70%) of a white solid.

IR (film): 2918, 1704, 1622, 1357, 1164 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.65 -
7.54 (m, 3H), 7.29 - 7.17 (m, 5H), 7.09 - 7.01 (m, 2H), 6.00 (t, J = 2.5 Hz, 1H), 5.24
(dd, J = 4.6, 2.3 Hz, 1H), 5.07 (dd, J = 16.7, 2.1 Hz, 1H), 4.55 (dd, J = 16.5, 2.7 Hz, 1H),
3.90 (ddd, J = 10.5, 5.5, 1.4 Hz, 1H), 3.70 (s, 3H), 2.48 - 2.35 (m, 4H), 1.37 (ddd,
J = 12.1, 10.7, 4.6 Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 167.1, 155.6, 144.6, 139.0,
135.3, 130.0, 128.6, 127.6, 127.0, 125.4, 122.7, 119.6, 103.6, 73.2, 71.4, 56.3, 51.3, 32.1,
21.6. HRMS (ESI): Calcd for C$_{23}$H$_{23}$NO$_3$NaS (M + Na$^+$) 448.1195, found 448.1195.
3-Methoxycarbonylmethylene-2,3,7,7a-tetrahydro-6H-furo[3,2-c]pyridine-5-carboxylic acid methyl ester (11.1c)

A solution of 0.078 g of 11.0c (0.31 mmol, 1.0 equiv) and 1.6 mg of silver trifluoromethanesulfonate (0.0062 mmol, 0.02 equiv) in 5.0 mL of THF and 20 μL of dichloromethane was stirred at rt for 1 h 15 min. The reaction mixture was then heated to 60 °C and stirred for 35 min. Concentration of the reaction mixture by rotary evaporation in vacuo afforded a brown residue. Purification by column chromatography on triethylamine washed silica gel (5:1 hexanes/ethyl acetate) afforded 0.028 g (36%) of a white solid.

IR (film): 2955, 1712, 1617, 1441, 1197 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.60 - 7.36 (m, 1 H), 5.92 (br. s., 1 H), 5.14 (dd, J=16.6, 2.2 Hz, 1 H), 4.70 (dd, J=16.6, 2.6 Hz, 1 H), 4.44 - 4.35 (m, 1 H), 4.12 (br. s., 1 H), 3.82 (s, 3 H), 3.72 (s, 3 H), 3.20 (br. s., 1 H), 2.38 (br. s., 1 H), 1.31 - 1.21 (m, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ 167.3, 156.0, 153.7, 122.5, 119.1, 103.1, 74.7, 73.4, 53.7, 51.2, 40.4, 22.4. MS (ESI): 254.2 (M + Na⁺).

3-Methoxycarbonylmethylene-2,3,7,7a-tetrahydro-6H-furo[3,2-c]pyridine-5-carboxylic acid tert-butyl ester (11.1d)

A solution of 0.054 g of 11.0d (0.18 mmol, 1.0 equiv) and 0.9 mg of silver trifluoromethanesulfonate (0.0036 mmol, 0.02 equiv) in 1.8 mL of THF and 0.50 mL of dichloromethane was stirred at rt for 20 min. The reaction mixture was cooled to −78 °C and concentrated by rotary evaporation in vacuo afforded a brown solid. Purification by
column chromatography on triethylamine washed silica gel (7:1 hexanes/ethyl acetate) afforded 0.041 g (75%) of a white solid.

IR (film): 2976, 1705, 1620, 1367, 1152 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.67 - 7.29 (m, 1 H), 5.88 (s, 1 H), 5.14 (dd, J=16.1, 2.2 Hz, 1 H), 4.70 (dd, J=16.4, 2.4 Hz, 1 H), 4.38 (ddd, J=10.3, 5.5, 1.3 Hz, 1 H), 4.27 - 3.99 (m, 1 H), 3.70 (s, 3 H), 3.17 (br. s., 1 H), 2.35 (br. s., 1 H), 1.55 - 1.48 (m, 10 H). ¹³C NMR (100 MHz, CDCl₃): δ 167.3, 156.3, 152.9, 123.1, 113.6, 103.2, 82.5, 74.8, 73.5, 51.2, 40.2, 28.3, 28.2. HRMS (ESI): Calcd for C₁₅H₂₁NO₅Na (M + Na⁺) 318.1317, found 318.1316.

3-Methoxycarbonylmethylene-5-(toluene-4-sulfonyl)-2,3,5,6,7,7a-hexahydro-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (11.1e)

A solution of 0.074 g of 11.0e (0.16 mmol, 1.0 equiv) and 0.8 mg of silver trifluoromethanesulfonate (0.0033 mmol, 0.02 equiv) in 2.7 mL of THF and 10 µL of dichloromethane was heated to reflux for 3 h. Concentration by rotary evaporation in vacuo afforded a golden-brown oil. Purification by column chromatography on triethylamine washed silica gel (3:1 petroleum ether/diethyl ether) afforded 0.060 g (81%) of a colourless oil.

IR (film): 2932, 1702, 1616, 1358, 1164 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.65 (d, J=8.3 Hz, 2 H), 7.35 - 7.29 (m, 3 H), 5.94 (t, J=2.4 Hz, 1 H), 4.50 (br. s., 2 H), 4.00 - 3.91 (m, 1 H), 3.86 (dt, J=13.1, 3.3 Hz, 1 H), 3.69 (s, 3 H), 3.06 (td, J=13.1, 3.1 Hz, 1 H), 2.41 (s, 3 H), 1.48 - 1.35 (m, 10 H), 1.27 - 1.13 (m, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ 166.9, 155.1, 152.5, 144.6, 134.3, 130.1, 127.0, 123.3, 118.2, 104.1, 80.3, 54.7, 53.4, 51.2, 42.2, 28.4, 27.8, 21.6. MS (ESI): 471.1 (M + Na⁺).
Trans-3-Methoxycarbonylmethylene-6-phenyl-5-(toluene-4-sulfonyl)-2,3,5,6,7,7a-hexahydro-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (11.1f)

A solution of 0.025 g of 11.0f (0.048 mmol, 1.0 equiv) and 0.6 mg of silver trifluoromethanesulfonate (0.0024 mmol, 0.05 equiv) in 0.80 mL of THF and 10 μL of dichloromethane was heated to reflux for 3.5 h. Concentration by rotary evaporation in vacuo afforded a golden-brown oil. Purification by column chromatography on triethylamine washed silica gel (5:1 petroleum ether/diethyl ether) afforded 0.0052 g (20%) of a colourless oil.

IR (film): 2027, 1702, 1617, 1358, 1193 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.64 - 7.54 (m, 4 H), 7.23 - 7.15 (m, 4 H), 7.09 - 7.03 (m, 2 H), 6.00 (t, J=2.6 Hz, 1 H), 5.23 - 5.19 (m, 1 H), 4.57- 4.43 (m, 2 H), 3.71 (s, 3 H), 3.09 (br. s., 1 H), 2.40 (s, 3 H), 1.41 (s, 3 H), 1.36 (br. s., 9 H). ¹³C NMR (100 MHz, CDCl₃): δ 166.9, 154.6, 144.2, 135.9, 135.2, 132.4, 130.0, 129.7, 128.6, 128.4, 127.5, 127.3, 125.8, 106.7, 80.2, 56.3, 55.0, 53.0, 51.3, 51.2, 28.3, 21.5. HRMS (ESI): Calcd for C₂₈H₃₂N₂O₆NaS (M + Na⁺) 547.1879, found 547.1874.

Cis-3-Methoxycarbonylmethylene-6-phenyl-5-(toluene-4-sulfonyl)-2,3,5,6,7,7a-hexahydro-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (11.1g)

A solution of 0.051 g of 11.0g (0.098 mmol, 1.0 equiv) and 0.5 mg of silver trifluoromethanesulfonate (0.0020 mmol, 0.02 equiv) in 0.80 mL of THF and 10 μL of dichloromethane was heated to reflux for 3.5 h. Concentration by rotary evaporation in vacuo afforded a golden-brown oil. Purification by column chromatography on
triethylamine washed silica gel (7:1 hexanes/ethyl acetate to 5:1 hexanes/ethyl acetate) afforded 0.032 g (63%) of a yellow solid.

IR (film): 2976, 1701, 1616, 1358, 1169 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.47 - 7.32\) (m, 3 H), 7.20 - 7.09 (m, 8 H), 6.09 (t, \(J=2.5\) Hz, 1 H), 4.54 (br. s., 3 H), 3.97 (ddd, \(J=10.7, 3.2, 3.0\) Hz, 1 H), 3.73 (s, 3 H), 3.07 (br. s., 1 H), 2.38 (s, 3 H), 1.76 - 1.56 (m, 1 H), 1.43 - 1.32 (m, 9 H). \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 166.9, 154.8, 151.6, 144.1, 140.0, 134.9, 129.6, 128.3, 127.6, 127.0, 126.8, 124.8, 123.1, 105.6, 80.4, 59.5, 54.6, 53.2, 51.4, 29.4, 28.3, 21.5\). HRMS (ESI): Calcd for C\(_{28}\)H\(_{32}\)N\(_2\)O\(_6\)Na (M + Na\(^+\)) 547.1879, found 547.1866.

3-Methoxycarbonylmethylene-2,3,7,7a-tetrahydro-6H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylic acid 1-tert-butyl ester 5-methyl ester (11.1h)

A solution of 0.044 g of 11.0h (0.12 mmol, 1.0 equiv) and 0.6 mg of silver trifluoromethanesulfonate (0.0025 mmol, 0.02 equiv) in 1.3 mL of THF and 30 \(\mu\)L of dichloromethane was stirred at room temperature for 24 h. Concentration by rotary evaporation in vacuo afforded a yellow solid. Purification by column chromatography on triethylamine washed silica gel (3:1 petroleum ether/diethyl ether) afforded 0.023 g (52%) of a yellow solid.

IR (film): 2954, 1708, 1614, 1365, 1166 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.65 - 7.34\) (m, 1 H), 5.94 (br. s., 1 H), 4.56 (br. s., 2 H), 4.12 (br. s., 2 H), 3.81 (s, 3 H), 3.69 (s, 3 H), 3.25 (br. s., 1 H), 2.93 (br. s., 1 H), 1.64 - 1.39 (m, 10 H). \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 167.1, 155.3, 154.0, 153.2, 123.6, 117.9, 103.7, 80.2, 55.2, 53.7, 51.2, 41.4, 30.0, 28.5, 27.3\). HRMS (ESI): Calcd for C\(_{17}\)H\(_{24}\)N\(_2\)O\(_6\)Na (M + Na\(^+\)) 375.1532, found 375.1521.
D. Diels Alder reactions

![Diels Alder Reaction Diagram]

8-Hydroxymethyl-1-(toluene-4-sulfonyl)-2,3,3a,5,6,7,8,8a-octahydro-1H-furo[2,3,de]quinoline-6-carboxylic acid methyl ester (11.20a)

To a solution of 0.062 g of diene 11.1a (0.18 mmol, 1.0 equiv.) in 2.5 mL of dichloromethane was added 94 µL of acrolein (1.4 mmol, 7.8 equiv.). The reaction mixture was cooled to −78 °C and 4.0 µL of boron trifluoride diethyl etherate (0.029 mmol, 0.16 equiv.) were added. The reaction mixture was stirred at −78 °C for 1 h before 4.0 µL of boron trifluoride diethyl etherate (0.011 mmol, 0.16 equiv.) were added. The reaction mixture was stirred at −78 °C for another hour before it was warmed to rt. After the reaction was stirred at rt for another hour, 2.0 µL of boron trifluoride diethyl etherate (0.0054 mmol, 0.080 equiv.) were added. A 1:1 mixture of methanol/water was added to the reaction mixture, and the reaction mixture was then diluted with dichloromethane. The separated aqueous layer was extracted with dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate and concentrated by rotary evaporation in vacuo to afford a yellow solid. Purification by column chromatography on silica gel (3:1 hexanes/ethyl acetate) afforded 0.035 g of 11.20a (49%).

**11.21a:** IR (film): 2956, 1738, 1347, 1165 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 10.03 (s, 1 H), 7.68 (d, J=8.3 Hz, 1 H), 7.35 (d, J=7.9 Hz, 1 H), 4.62 - 4.55 (m, 1 H), 4.49 - 4.36 (m, 1 H), 4.16 - 4.11 (m, 1 H), 3.76 - 3.68 (m, 1 H), 3.66 (s, 2 H), 3.42 - 3.34 (m, 1 H), 2.80 (ddd, J=12.75, 9.92, 3.05 Hz, 1 H), 2.58 (ddd, J=14.06, 5.78, 3.71 Hz, 1 H), 2.44 (s, 3 H), 2.07 (ddd, J=12.92, 6.38, 6.21, 2.83 Hz, 1 H), 1.87 (dddd, J=14.28, 10.79, 3.49, 1.53 Hz, 1 H), 1.63 - 1.53 (m, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ 203.2, 172.1, 144.6, 133.7, 132.8, 132.1, 130.0, 127.8, 80.8, 75.8, 54.0, 52.2, 48.0, 44.4, 37.0, 31.7, 25.7, 21.6. HRMS (ESI): Calcd for C₂₀H₂₃NO₆NaS (M + Na⁺) 428.1144, found 428.1138.
8-Formyl-8-methyl-1-(toluene-4-sulfonyl)-2,3,3a,5,6,7,8,8a-octahydro-1H-furo[2,3,4-de]quinoline-6-carboxylic acid methyl ester (11.22a)

To a solution of 0.023 g of diene 11.1a (0.067 mmol, 1.0 equiv.) in 1 mL of dichloromethane was added 43 μL of methacrolein (0.52 mmol, 7.8 equiv.). The reaction mixture was cooled to -78 °C and 1.0 μL of boron trifluoride diethyl etherate (0.011 mmol, 0.16 equiv.) was added. The reaction mixture was stirred at -78 °C for 1 h before 1 μL of boron trifluoride diethyl etherate (0.011 mmol, 0.16 equiv.) was added. Over a period of 3 h, 1 μL of boron trifluoride diethyl etherate (0.011 mmol, 0.16 equiv.) was added every hour. The reaction mixture was then warmed to rt over 2 h and a 1:1 mixture of methanol/water was added. The reaction mixture was diluted with dichloromethane. The separated aqueous layer was extracted with dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate and concentrated by
rotary evaporation in vacuo to afford a cloudy oil. Purification by column chromatography on silica gel (3:1 hexanes/ethyl acetate) afforded 0.015 g of **11.22a** (53%) and 0.012 g of a mixture of **11.23a** and **11.24a** (42%).

**11.22a**: IR (film): 2954, 1734, 1348, 1162 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 9.65 (d, J=1.74 Hz, 1 H), 7.73 (d, J=8.28 Hz, 2 H), 7.32 (d, J=7.85 Hz, 2 H), 4.70 (br. s., 1 H), 4.61 - 4.52 (m, 1 H), 4.48 - 4.40 (m, 1 H), 4.19 - 4.10 (m, 1 H), 3.76 - 3.64 (m, 5 H), 2.87 (dd, J=15.48, 12.42, 5.67 Hz, 1 H), 2.43 (s, 3 H), 2.29 (dd, J=14.17, 5.89 Hz, 1 H), 1.94 - 1.78 (m, 2 H), 1.43 (s, 3 H), 1.34 (dd, J=14.55, 5.94, 3.27, 1.09 Hz, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ 203.8, 171.6, 144.0, 137.3, 133.4, 132.1, 130.1, 127.5, 78.4, 75.4, 59.1, 52.2, 50.7, 42.4, 38.2, 33.6, 30.7, 21.6, 21.5. HRMS (ESI): Calcd for C₂₁H₂₅NO₆NaS (M + Na⁺) 442.1300, found 442.1292.

**11.23a and 11.24a**: IR (film): 2926, 1724, 1698, 1325, 1161 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 9.70 - 9.67 (m, 1 H), 7.75 - 7.66 (m, 2 H), 7.30 (d, J=7.8 Hz, 2 H), 4.86 - 4.80 (m, 1 H), 4.61 (br. s., 1 H), 4.54 - 4.45 (m, 1 H), 4.34 - 4.25 (m, 1 H), 3.72 (s, 3 H), 3.54 (dd, J=15.3, 7.0 Hz, 1 H), 3.18 - 3.12 (m, 1 H), 3.09 - 2.98 (m, 1 H), 2.49 (dd, J=14.6, 3.3 Hz, 1 H), 2.42 (s, 3 H), 2.05 - 1.97 (m, 1 H), 1.92 (dd, J=14.4, 7.4 Hz, 1 H), 1.58 (br. s., 1 H), 1.39 - 1.34 (m, 3H).

Signals attributable to **11.23a**:

¹³C NMR (100 MHz, CDCl₃): δ 203.8, 171.9, 144.3, 136.9, 132.7, 132.3, 130.0, 127.6, 79.0, 75.8, 58.2, 52.4, 49.5, 42.6, 37.2, 33.3, 31.6, 21.6, 21.6.

Signals attributable to **11.24a**:

¹³C NMR (100 MHz, CDCl₃): δ 202.9, 171.9, 144.3, 136.9, 132.3, 132.3, 130.0, 127.6, 78.7, 75.0, 53.9, 52.4, 51.3, 42.0, 37.2, 31.9, 31.3, 29.4, 12.4.
V. References

Boc

24.2
Table 7: NMR data for 11.0a

<table>
<thead>
<tr>
<th>Carbon No.</th>
<th>(^{13})C (ppm)*</th>
<th>Mult.</th>
<th>(^{1}H) (ppm) (mult., J (Hz))(^{b,c,d})</th>
</tr>
</thead>
</table>
| 2          | 41.4            | CH\(_2\) | H-2: 3.90 (dt, 13.1, 3.5)  
H-2': 3.03 (td, 13.4, 2.8) |
| 3          | 26.2            | CH\(_2\) | H-3: 2.25 (dddd, 9.1, 6.1, 2.9, 2.8)  
H-3': 1.42-1.38 (m) |
| 3a         | 74.0            | CH      | H-3a: 4.22 (ddd, 10.4, 5.6, 1.5) |
| 5          | 73.3            | CH\(_2\) | H-5: 5.09 (dd, 16.1, 2.2)  
H-5': 4.63 (dd, 16.6, 2.6) |
| 6, 6a      | 155.4, 120.0    | Q       |                                             |
| 7          | 122.3           | CH      | H-7: 7.37-7.28 (m) |
| 8          | 103.7           | CH      | H-8: 5.93 (t, 2.4) |
| 9          | 167.1           | Q       |                                             |
| 10         | 51.3            | CH\(_3\) | H-10: 3.69 (s) |
| 11, 14     | 134.4, 144.6    | Q       |                                             |
| 12, 17     | 127.0           | CH      | H-12, H-17: 7.65 (d, 8.3) |
| 13, 16     | 130.1           | CH      | H-13, H-16: 7.37-7.28 (m) |
| 15         | 21.6            | CH\(_3\) | H-15: 2.41 (s) |

\(^{a}\)Recorded at 100 MHz. \(^{b}\)Recorded at 400 MHz. \(^{c}\)Methylene protons are arbitrarily designated H-X and H-X'. \(^{d}\)The signals for H-7 and H-13/H-16 overlap.
Table 8: NMR data for 11.0b

<table>
<thead>
<tr>
<th>Carbon No.</th>
<th>$^{13}$C (ppm)$^a$</th>
<th>Mult.</th>
<th>$^1$H (ppm) (mult., J (Hz))$^{b,c,d}$</th>
<th>COSY Correlations$^e$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>56.3</td>
<td>CH$_2$</td>
<td>H-2: 5.24 (dd, 4.6, 2.3)</td>
<td>H-3, H-3'</td>
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<tr>
<td>3</td>
<td>32.1</td>
<td>CH$_2$</td>
<td>H-3: 2.48-2.35 (m)</td>
<td>H-2, H-3', H-3a</td>
</tr>
<tr>
<td>3a</td>
<td>71.4</td>
<td>CH</td>
<td>H-3a: 3.90 (ddd, 10.5, 5.5, 1.4)</td>
<td>H-3, H-3'</td>
</tr>
<tr>
<td>5</td>
<td>73.2</td>
<td>CH$_2$</td>
<td>H-5: 4.55 (dd, 16.5, 2.7)</td>
<td>H-5', H-8</td>
</tr>
<tr>
<td>6, 6a</td>
<td>155.6, 119.6</td>
<td>Q</td>
<td>H-5': 5.07 (dd, 16.7, 2.1)</td>
<td>H-5, H-8</td>
</tr>
<tr>
<td>7</td>
<td>103.6</td>
<td>CH</td>
<td>H-7: 7.65-7.54 (m)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>122.7</td>
<td>CH</td>
<td>H-8: 6.00 (t, 2.5)</td>
<td>H-5, H-5'</td>
</tr>
<tr>
<td>9</td>
<td>167.1</td>
<td>Q</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>51.3</td>
<td>CH$_3$</td>
<td>H-10: 3.70 (s)</td>
<td></td>
</tr>
<tr>
<td>11, 14</td>
<td>134.4, 144.6</td>
<td>Q</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12, 17</td>
<td>127.0</td>
<td>CH</td>
<td>H-12, H-17: 7.65-7.54 (m)</td>
<td></td>
</tr>
<tr>
<td>13, 16</td>
<td>130.0</td>
<td>CH</td>
<td>H-13, H-16: 7.29-7.17 (m)</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>21.6</td>
<td>CH$_3$</td>
<td>H-15: 2.41 (s)</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>129.0</td>
<td>Q</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>125.4</td>
<td>CH</td>
<td>H-21: 7.29-7.17 (m)</td>
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<tr>
<td>19, 23</td>
<td>127.6</td>
<td>CH</td>
<td>H-19, H-23: 7.09-7.01 (m)</td>
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<tr>
<td>20, 22</td>
<td>128.6</td>
<td>CH</td>
<td>H-20, H-22: 7.29-7.17 (m)</td>
<td></td>
</tr>
</tbody>
</table>

$^a$Recorded at 100 MHz. $^b$Recorded at 400 MHz. $^c$Methylene protons are arbitrarily designated H-X and H-X'. $^d$The signals for H-3 and H-15 overlap. The signals for H-7 and H-12, H-17 overlap. $^e$Only those correlations which could be unambiguously assigned are recorded.
Table 9: $^1$H Selective NOE Data for 11.0b

<table>
<thead>
<tr>
<th>Proton No.</th>
<th>$^1$H</th>
<th>$^1$H Selective NOE Correlation$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irradiated</td>
<td>$\delta$ (ppm) (mult., J (Hz))$^a$</td>
<td></td>
</tr>
<tr>
<td>H-8</td>
<td>6.00 (t, 2.5)</td>
<td>H-7</td>
</tr>
<tr>
<td>H-2</td>
<td>5.24 (dd, 4.6, 2.3)</td>
<td>H-3, H-3', H-19, H-23</td>
</tr>
</tbody>
</table>

$^a$Recorded at 400 MHz. $^b$Only those correlations which could be unambiguously assigned are recorded.
Table 10: NMR data for 11.0c

<table>
<thead>
<tr>
<th>Carbon No.</th>
<th>$^{13}$C (ppm)$^a$</th>
<th>Mult.</th>
<th>$^1$H (ppm) (mult., J (Hz))$^{b,c}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>40.4</td>
<td>CH$_2$</td>
<td>H-2: 3.20 (br. s.)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>H-2': 4.12 (br. s.)</td>
</tr>
<tr>
<td>3</td>
<td>22.4</td>
<td>CH$_2$</td>
<td>H-3: 2.38 (br. s.)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>H-3': 1.31-1.21 (m)</td>
</tr>
<tr>
<td>3a</td>
<td>74.7</td>
<td>CH</td>
<td>H-3a: 4.44-4.35 (m)</td>
</tr>
<tr>
<td>5</td>
<td>73.4</td>
<td>CH$_2$</td>
<td>H-5: 5.14 (dd, 16.6, 2.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>H-5': 4.70 (dd, 16.6, 2.6)</td>
</tr>
<tr>
<td>6, 6a</td>
<td>153.7, 119.1</td>
<td>Q</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>122.5</td>
<td>CH</td>
<td>H-7: 5.92 (br. s.)</td>
</tr>
<tr>
<td>8</td>
<td>103.1</td>
<td>CH</td>
<td>H-8: 7.60-7.36 (m)</td>
</tr>
<tr>
<td>9</td>
<td>167.3</td>
<td>Q</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>53.7</td>
<td>CH$_3$</td>
<td>H-10: 3.82 (s)</td>
</tr>
<tr>
<td>11</td>
<td>156.0</td>
<td>Q</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>51.2</td>
<td>CH$_3$</td>
<td>H-12: 3.72 (s)</td>
</tr>
</tbody>
</table>

$^a$Recorded at 100 MHz.  $^b$Recorded at 400 MHz.  $^c$Methylene protons are arbitrarily designated H-X and H-X'. 
Table 11: NMR data for 11.0d

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Carbon No.</th>
<th>$^{13}$C (ppm)$^a$</th>
<th>Mult.</th>
<th>$^1$H (ppm) (mult., J (Hz))$^{b,c,d}$</th>
<th>COSY Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>40.2</td>
<td>CH$_2$</td>
<td>H-2: 4.24-3.99 (m) H-2': 3.17 (br. s.)</td>
<td>H-2'</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>H-2: 2.35 (br. s.) H-2': 1.55-1.48 (m)</td>
<td>H-2</td>
</tr>
<tr>
<td>3</td>
<td>28.2</td>
<td>CH$_2$</td>
<td>H-3: 2.17 (br. s.) H-3': 2.17-2.35 (m)</td>
<td>H-3', H-3a</td>
</tr>
<tr>
<td>3a</td>
<td>74.8</td>
<td>CH</td>
<td>H-3a: 4.38 (dd, 10.3, 5.5, 1.3) H-3, H-3a</td>
<td>H-3, H-3'</td>
</tr>
<tr>
<td>5</td>
<td>73.5</td>
<td>CH$_2$</td>
<td>H-5: 5.14 (dd, 16.1, 2.2) H-5': 4.70 (dd, 16.4, 2.4)</td>
<td>H-5', H-8 H-5, H-8</td>
</tr>
<tr>
<td>6, 6a</td>
<td>152.9, 113.6</td>
<td>Q</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>123.1</td>
<td>CH</td>
<td>H-7: 7.67-7.29 (m)</td>
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<tr>
<td>8</td>
<td>102.3</td>
<td>CH</td>
<td>H-8: 5.88 (t, 2.4)</td>
<td>H-5, H-5'</td>
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<tr>
<td>9</td>
<td>167.3</td>
<td>Q</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>51.2</td>
<td>CH$_3$</td>
<td>H-10: 3.70 (s)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>156.3</td>
<td>Q</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>82.5</td>
<td>Q</td>
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<tr>
<td>13</td>
<td>28.3</td>
<td>CH$_3$</td>
<td>H-13: 1.55-1.48 (m)</td>
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</tbody>
</table>

$^a$Recorded at 100 MHz. $^b$Recorded at 400 MHz. $^c$Methylene protons are arbitrarily designated H-X and H-X'. $^d$The signals for H-3' and H-13 overlap.
Table 12: $^1$H Selective NOE Data for 11.0d

| Proton No. | $^1$H $\delta$ (ppm) (mult., J (Hz)) | $^1$H Selective NOE Correlation

| H-8         | 5.88 (s)                             | H-7               |

*Recorded at 400 MHz. *Only those correlations which could be unambiguously assigned are recorded.
Table 13: NMR data for 11.0e

<table>
<thead>
<tr>
<th>Carbon No.</th>
<th>$^{13}$C (ppm)*</th>
<th>Mult.</th>
<th>$^1$H (ppm) (mult., J (Hz))$^{b,c,d}$</th>
<th>COSY Correlations$^e$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>42.2</td>
<td>CH$_2$</td>
<td>H-2: 3.86 (dt, 13.1, 3.3)</td>
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<td></td>
<td></td>
<td></td>
<td>H-2': 3.06 (td, 13.1, 3.1)</td>
<td>H-2, H-3, H-3a</td>
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<tr>
<td>3</td>
<td>27.8</td>
<td>CH$_2$</td>
<td>H-3: 1.48-1.35 (m)</td>
<td>H-2, H-3a</td>
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<td></td>
<td></td>
<td></td>
<td>H-3': 1.27-1.13 (m)</td>
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</tr>
<tr>
<td>3a</td>
<td>54.7</td>
<td>CH</td>
<td>H-3a: 4.00-3.90 (m)</td>
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<td>7</td>
<td>123.3</td>
<td>CH</td>
<td>H-7: 7.35-7.29 (m)</td>
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<td>H-8: 5.94 (t, 2.4)</td>
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<td>51.2</td>
<td>CH$_3$</td>
<td>H-10: 3.69 (s)</td>
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<td>11, 14</td>
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<td>Q</td>
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<td>CH</td>
<td>H-12, H-17: 7.35-7.29 (m)</td>
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<td>H-13, H-16: 7.65 (d, 8.3)</td>
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<tr>
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<td>21.6</td>
<td>CH$_3$</td>
<td>H-15: 2.41 (s)</td>
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<td>18</td>
<td>155.1</td>
<td>Q</td>
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<td>80.3</td>
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</tr>
<tr>
<td>20</td>
<td>28.4</td>
<td>CH$_3$</td>
<td>H-20: 1.48-1.35 (m)</td>
<td></td>
</tr>
</tbody>
</table>

*Recorded at 100 MHz. $^a$Recorded at 400 MHz. $^b$Methylene protons are arbitrarily designated H-X and H-X'. $^c$The signals for H-3 and H-20 overlap. The signals for H-7 and H-12/H-17 overlap. $^d$Only those correlations which could be unambiguously assigned are recorded.
Table 14: $^1$H Selective NOE Data for **11.0e**

<table>
<thead>
<tr>
<th>Proton No.</th>
<th>$^1$H</th>
<th>$^1$H Selective NOE Correlation$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irradiated</td>
<td>$\delta$ (ppm) (mult., J (Hz))$^a$</td>
<td></td>
</tr>
<tr>
<td>H-8</td>
<td>5.94 (s)</td>
<td>H-7</td>
</tr>
</tbody>
</table>

$^a$Recorded at 400 MHz. $^b$Only those correlations which could be unambiguously assigned are recorded.
Table 15: NMR data for 11.0g

<table>
<thead>
<tr>
<th>Carbon No.</th>
<th>$^{13}$C (ppm)$^a$</th>
<th>Mult.</th>
<th>$^1$H (ppm) (mult., J (Hz))$^{b,c,d}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>54.6</td>
<td>CH$_2$</td>
<td>H-2: 4.54 (br. s.)</td>
</tr>
<tr>
<td>3</td>
<td>28.3</td>
<td>CH$_2$</td>
<td>H-3: 3.07 (br. s.) H-3': 1.76-1.56 (m)</td>
</tr>
<tr>
<td>3a</td>
<td>59.5</td>
<td>CH</td>
<td>H-3a: 3.97 (dd, 10.5)</td>
</tr>
<tr>
<td>5</td>
<td>53.2</td>
<td>CH$_2$</td>
<td>H-5: 4.54 (br. s.)</td>
</tr>
<tr>
<td>6, 6a</td>
<td>151.6, 123.1</td>
<td>Q</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>124.8</td>
<td>CH$_1$</td>
<td>H-7: 7.20-7.09 (m)</td>
</tr>
<tr>
<td>8</td>
<td>105.6</td>
<td>CH</td>
<td>H-8: 6.09 (t, 2.5)</td>
</tr>
<tr>
<td>9</td>
<td>166.9</td>
<td>Q</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>51.4</td>
<td>CH$_3$</td>
<td>H-10: 3.73 (s)</td>
</tr>
<tr>
<td>11, 14</td>
<td>134.9, 144.1</td>
<td>Q</td>
<td></td>
</tr>
<tr>
<td>12, 17</td>
<td>126.8</td>
<td>CH</td>
<td>H-12, H-17: 7.47-7.32 (m)</td>
</tr>
<tr>
<td>13, 16</td>
<td>129.6</td>
<td>CH</td>
<td>H-13, H-16: 7.20-7.09 (m)</td>
</tr>
<tr>
<td>15</td>
<td>21.5</td>
<td>CH$_3$</td>
<td>H-15: 2.38 (s)</td>
</tr>
</tbody>
</table>

$^a$Recorded at 100 MHz. $^b$Recorded at 400 MHz. $^c$Methylene protons are arbitrarily designated H-X and H-X'. $^d$The signals for H-3 and H-15 overlap. $^e$Only those correlations which could be unambiguously assigned are recorded.
Table 15: NMR data for 11.0g (cont.)

![Chemical Structure Image]

<table>
<thead>
<tr>
<th>Carbon No.</th>
<th>$^{13}$C (ppm)$^a$</th>
<th>Mult.</th>
<th>$^1$H (ppm) (mult., J (Hz))$^{b,c,d}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>140.0</td>
<td>Q</td>
<td></td>
</tr>
<tr>
<td>19, 23</td>
<td>127.6</td>
<td>CH</td>
<td>H-19, H-23: 7.20-7.09 (m)</td>
</tr>
<tr>
<td>20, 22</td>
<td>128.3</td>
<td>CH</td>
<td>H-20, H-22: 7.20-7.09 (m)</td>
</tr>
<tr>
<td>21</td>
<td>125.4</td>
<td>CH</td>
<td>H-21: 7.47-7.32 (m)</td>
</tr>
<tr>
<td>24, 25</td>
<td>154.8, 80.4</td>
<td>Q</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>29.4</td>
<td>CH$_3$</td>
<td>H-26: 1.43-1.32 (m)</td>
</tr>
</tbody>
</table>

$^a$Recorded at 100 MHz. $^b$Recorded at 400 MHz. $^c$Methylene protons are arbitrarily designated H-X and H-X'. $^d$The signals for H-3 and H-15 overlap. $^e$Only those correlations which could be unambiguously assigned are recorded.
Table 16: NMR data for 11.0h

*Recorded at 100 MHz. *Recorded at 400 MHz. *Methylene protons are arbitrarily designated H-X and H-X'. *The signals for H-7 and H-13/H-16 overlap.

<table>
<thead>
<tr>
<th>Carbon No.</th>
<th>$^{13}$C (ppm)$^*^a$</th>
<th>Mult.</th>
<th>$^1$H (ppm) (mult., J (Hz))$^b,c,d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>30.0</td>
<td>CH$_2$</td>
<td>H-2: 4.12 (br. s.)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>H-2': 3.25 (br. s.)</td>
</tr>
<tr>
<td>3</td>
<td>27.3</td>
<td>CH$_2$</td>
<td>H-3: 2.93 (br. s.)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>H-3': 1.64-1.39 (m)</td>
</tr>
<tr>
<td>3a</td>
<td>51.2</td>
<td>CH</td>
<td>H-3a: 4.12 (br. s.)</td>
</tr>
<tr>
<td>5</td>
<td>41.4</td>
<td>CH$_2$</td>
<td>H-5: 4.56 (br. s.)</td>
</tr>
<tr>
<td>6, 6a</td>
<td>153.2, 117.9</td>
<td>Q</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>123.6</td>
<td>CH</td>
<td>H-7: 7.65-7.34 (m)</td>
</tr>
<tr>
<td>8</td>
<td>103.7</td>
<td>CH</td>
<td>H-8: 5.94 (br. s.)</td>
</tr>
<tr>
<td>9</td>
<td>167.1</td>
<td>Q</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>55.2</td>
<td>CH$_3$</td>
<td>H-10: 3.81 (s)</td>
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<tr>
<td>11</td>
<td>154.0</td>
<td>Q</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>53.7</td>
<td>CH$_3$</td>
<td>H-12: 3.69 (s)</td>
</tr>
<tr>
<td>13</td>
<td>155.3</td>
<td>Q</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>80.2</td>
<td>Q</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>28.5</td>
<td>CH$_3$</td>
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</table>
Table 17: X-Ray Crystallographic Experimental Data

<table>
<thead>
<tr>
<th>Compound</th>
<th>11.1DS</th>
<th>11.21aS</th>
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<tbody>
<tr>
<td>Empirical Formula</td>
<td>C₃₀H₄₂N₂O₁₀</td>
<td>C₂₀H₂₃NO₆S</td>
</tr>
<tr>
<td>Formula Weight</td>
<td>590.66</td>
<td>405.45</td>
</tr>
<tr>
<td>Crystal Color, Habit</td>
<td>colourless, tablet</td>
<td>colourless, plate</td>
</tr>
<tr>
<td>Crystal Dimensions</td>
<td>0.05 X 0.15 X 0.25 mm</td>
<td>0.05 X 0.30 X 0.35 mm</td>
</tr>
<tr>
<td>Crystal System</td>
<td>triclinic</td>
<td>monoclinic</td>
</tr>
<tr>
<td>Lattice Type</td>
<td>primitive</td>
<td>primitive</td>
</tr>
<tr>
<td>Lattice Parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>6.6103(5) Å</td>
<td>21.244(2) Å</td>
</tr>
<tr>
<td>b</td>
<td>9.5311(8) Å</td>
<td>6.1472(5) Å</td>
</tr>
<tr>
<td>c</td>
<td>12.8219(11) Å</td>
<td>14.4329(13) Å</td>
</tr>
<tr>
<td>α</td>
<td>99.752(4) °</td>
<td>90.0 °</td>
</tr>
<tr>
<td>β</td>
<td>97.082(4) °</td>
<td>95.699(5) °</td>
</tr>
<tr>
<td>γ</td>
<td>107.239(4) °</td>
<td>90.0 °</td>
</tr>
<tr>
<td>V</td>
<td>747.36(11) Å³</td>
<td>6848.2(2) Å³</td>
</tr>
<tr>
<td>Space Group</td>
<td>P -1 (#2)</td>
<td>P 2₁/c (#14)</td>
</tr>
<tr>
<td>Z value</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Dcalc</td>
<td>1.312 g/cm³</td>
<td>1.436 g/cm³</td>
</tr>
<tr>
<td>F000</td>
<td>316.00</td>
<td>856.00</td>
</tr>
<tr>
<td>μ(MoKα)</td>
<td>0.98 cm⁻¹</td>
<td>2.11 cm⁻¹</td>
</tr>
</tbody>
</table>