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INTRAMOLECULAR MICHAEL REACTIONS OF VINYLNITROSO
COMPOUNDS AND STUDIES DIRECTED TOWARDS AN ASYMMETRIC
TOTAL SYNTHESIS OF THE STEMONA ALKALOID STEMOFOLINE

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Chemistry

by

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ABSTRACT

We have developed novel methodology that produced the first examples of intramolecular 1,4-conjugate additions of carbon and hetero nucleophiles to vinylnitroso compounds. Combining several new methods developed in these labs, we have been able to access the requisite precursors and optimize the reaction conditions for these transformations. Namely, we have shown that a vinylnitroso species generated from the corresponding $\alpha$-chlorosilyl-oximes using fluoride ion, interacts with a tethered nucleophile in a 1,4-manner producing a variety of carbocyclic and heterocyclic products. Recognizing that this methodology allows us facile entry into the stemofoline alkaloid skeleton, we have attempted to apply it to an asymmetric total synthesis of this metabolite. In the course of these studies new methodology for oxidation of $\alpha$-hydroxy-$\beta$-ketoesters to $\alpha$-diazo-$\beta$-ketoesters emerged, thus allowing us to generate some of the intermediates required to advance the synthesis.
TABLE OF CONTENTS

LIST OF FIGURES ..................................................................................................... vi

LIST OF TABLES ....................................................................................................... vii

ACKNOWLEDGEMENTS ......................................................................................... viii

Chapter 1  Background ......................................................................................... 1
  A. Stemofoline Alkaloids .............................................................................. 1
      Isolation and Structure Determination ................................................... 1
      Biological Activity ................................................................................. 3
      Proposed Biosynthesis ............................................................................ 4
  Previous Total Syntheses and Synthetic Approaches to the
    Stemofoline Alkaloids .............................................................................. 6
    Kende Synthesis of (+)-Isostemofoline (11) ................................... 6
    Overman’s Synthesis of (+)-Didehydrostefomoline
      (Asparagamine A) (6) and (−)-Isodidehydrostefomoline
      (12) ....................................................................................................... 9
    Thomas Approach to the Stemofoline Core .................................... 13
    Livinghouse Approach to the Stemofoline Core ............................. 16
    Gin Approach to the Stemofoline Core ........................................... 17
  B. Nitrosoalkenes .......................................................................................... 21
      Introduction ............................................................................................ 21
      Formation of nitrosoalkenes ............................................................... 22
      1,4-Elimination ............................................................................... 22
      Base promoted 1,4-elimination of α-heteroatom-substituted
        oximes ............................................................................................... 22
      1,4-Elimination of α-chloro-silylooximes with fluoride ion..... 23
      Synthesis of α-chlorooximes and α-chloro-silyloximes .......... 24
      1,3-N,C-Elimination of trialkylsilanols from silyl nitrotrates ..... 26
  Reactions of nitrosoalkenes ........................................................................... 28
      Cycloaddition reactions ................................................................ 28
      Introduction ...................................................................................... 28
      Nitrosoalkenes as 2π systems ............................................................ 29
      Nitrosoalkenes as 4π systems in cycloadditions with C=C
        bonds ................................................................................................. 29
      [3+2]-Cycloadditions of nitrosoalkenes with alkenes .......... 32
  1,4-Conjugate additions ............................................................................. 34
      Introduction ...................................................................................... 34
      Reactions with N, O, and S nucleophiles ........................................ 38
      Reactions with carbanions .............................................................. 41
  Aromatic substitution ................................................................................. 45

Chapter 2  Results and Discussion ........................................................................ 47
LIST OF FIGURES

Figure 1-1: Stemofoline Alkaloids.................................................................2

Figure 2-1: Catalysts for Olefin Metathesis..............................................48

Figure 2-2: ORTEP Plot of Bicyclo[2.2.2]octane 249 .............................74

Figure 2-2: ORTEP Plot of Azabicyclo[3.2.1]octane 433 .........................87
LIST OF TABLES

Table 1-1. Diastereoselective [4+2]-Cycloadditions of Nitrosoalkenes ...................... 30
Table 1-2. N-Alkylation of Azoles Using α-Bromooximes ........................................ 34
Table 1-3. N-, O-, and S-Nucleophilic Additions to Vinilnitroso Compounds .......... 46
Table 1-4. Carbon Nucleophiles ................................................................................. 49
Table 2-1 Optimization of Vinyl Chloride Metathesis ................................................. 51
Table 2-2. Vinyl Chloride Metathesis Examples ....................................................... 54
Table 2-3. Examples of α-Haloketone Formation ...................................................... 57
Table 2-4. α-Chloroketone Formation from Vinyl Chloride 329 ............................... 63
Table 2-5. α-Chloroketone Optimization Study ......................................................... 63
Table 2-6. Carbon Nucleophile Cyclization ............................................................... 65
Table 2-7. Bridged System Cyclization Optimization ............................................... 70
Table 2-8. Nitrogen Nucleophile Cyclization ............................................................ 83
Table 2-9. Optimization of N-H Insertion ................................................................. 96
Table 2-10. Preparation of Representative α-Diazo-β-Ketoesters ............................ 109
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Chapter 1

Background

A. Stemofoline Alkaloids

Isolation and Structure Determination

The *Stemona* family of plant alkaloids consists of over seventy natural products originally classified by Xu and coworkers into eight different groups. The alkaloids were recently reclassified by Pilli et al. into six groups according to their structural features: *Stenine*, *Stemoamide*, *Tuberostemospironine*, *Stemonamine*, *Parvistemoline* and a *Miscellaneous* group. Stemofoline (1), depicted in Figure 1-1, is the parent alkaloid of a small, unique subclass of seventeen compounds, categorized in the *Miscellaneous* group.

The first mention of stemofoline in the literature is in a 1970 article by Irie et al., who isolated 1 from the stems and leaves of *Stemona japonica* and elucidated its absolute stereochemistry via single crystal X-ray analysis of the hydrobromide salt by the heavy atom method. The assignment was recently confirmed by Seger et al. who used modern X-ray crystallographic methods combined with NMR NOE spectroscopy for the unequivocal assignment of the absolute configuration. According to this analysis stemofoline (1) possesses a caged 1-azatricyclo[5.3.0.0]decane core, showing these
alkaloids to be the most complex members of the *Stemona* family. The core of 1 incorporates a common furo[3,2-\(c\)]pyrrolo[1,2-\(a\)]-azepine motif. However, it is the two

Figure 1-1: Stemofoline Alkaloids
additional annelations over the usual *Stemona* alkaloids at C2-C8 and C3-C7 that give the molecule an unusual rigid skeleton, making its synthesis a formidable challenge.

Additional alkaloids in this family include: didehydrostemofoline, also known as asparagamine A (6), isolated from the roots of *Asparagus racemosus* –, isostemofoline (11) and isodidehydrostemofoline (12), from the roots of *Stemona burkii* – 11(S),12(R)-dihydrostemofoline (13) and 2’-hydroxystemofoline (2), from an unidentified *Stemona* sp. – (3’R)-stemofolenol (7), (3’S)-stemofolenol (8), methylstemofoline (10) and (2’S)-hydroxystemofoline (2). These alkaloids differ from stemofoline in the nature of the substituent at C-3 and the configuration of the double bond connecting the bridged core to the crotonolactone moiety. The optical antipodes of 1 and 4, known as parvistemoninine and parvistemolinol, respectively, have also been isolated from the roots of *Stemona parviflora* found on Hainan island, China. Recently a ring opened derivative, stemoburkilline (14), was isolated from *Stemona burkii*. An N-oxide analogue, 1’,2’-didehydrostemofoline-N-oxide (9), and a glycosidated alkaloid, stemofolinoside (15) were obtained from a *Stemona* sp. It should be noted, that interconversion of 6 into 12 has been observed via irradiation by visible light, and the possibility that 12 it is an artifact derived from 6 cannot be ruled out.

**Biological Activity**

The plants of *Stemonacea* have long been used in Chinese and Japanese folk medicine to treat upper respiratory diseases and as anthelmintics. Even today aqueous extracts from the roots of the plants are used as domestic insecticides against agricultural
insect pests in China. These compounds are also known to have antifeedant, insect repellent and antitussive activities. Murakoshi investigated the biological activity of stemofoline against silkworm larvae in 1978, and found it to have a high toxicity of >20~100 ppm. These insecticidal properties have been associated with acetylcholinesterase (AChE) inhibition. This activity was most recently investigated by Boonchalermkit and coworkers, who conducted a quantitative assay of the natural analogues \((11Z)-1’,2’\)-didehydrostemofoline, \((3’R)\)-stemofolenol, \((3’S)\)-stemofolenol, methyl stemofoline and \((3’S)\)-hydroxystemofoline, and the unnatural analogues \((11E)\)-methylstemofoline and \(3’R\)-hydroxystemofoline. As a result, it was found that \((11Z)-1’,2’\)-didehydrostemofoline is the most active with a minimum inhibitory concentration of \(1.3 \times 10^{-2}\) nmol.

**Proposed Biosynthesis**

Although the exact biosynthetic pathway for these alkaloids has not definitively been established, Seger et al. have proposed a possible biosynthetic route by drawing analogies to the known biosyntheses of related pyrrolizidine alkaloids (Scheme 1).

Thus, the first step of the proposed stemofoline biosynthesis involves oxidative deamination/cyclization of spermidine (16) to give aldehyde iminium ion 17. Addition of a \(C_{10}\) activated geranyl unit 18 to the iminium cation 17 would eventually lead to the pyrrolo[1,2-\(\alpha\)]azepine system 19. Attachment of an isoprene unit 20 at C5, followed by oxidative functionalization and ring formation would give protostemonine (23). Several ring closures followed by decarboxylation of the lactone moiety to form the hexyl
sidechain would provide stemofoline (1). No experimental studies on the biosynthesis of this group of alkaloids have been conducted, however.

Scheme 1.
Due to its unusual and complex caged structure, stemofoline has received considerable attention from the synthetic community. This and related alkaloids present a formidable synthetic challenge not only because of the nature of the core, but also potential difficulties associated with installing the crotonolactone moiety with the appropriate C11,12 double bond geometry. Almost 30 years after the discovery of stemofoline (1), Kende and coworkers reported the first successful total synthesis in this area in 1999, preparing racemic isostemofoline (11).15 The Overman group described total syntheses of racemic didehydrostemofoline (6) and isodidehydrostemofoline (12) in 2003.16 In addition, Thomas,17 Livinghouse18 and most recently Gin19 have reported methodological studies directed towards the skeleton of these natural products.

Kende Synthesis of (+)-Isostemofoline (11)

Kende’s synthesis features a [4+3]-cycloaddition between an alkoxy pyrrrole and a vinyl α-diazoester first developed by Davies20,21 to assemble a nortropinone intermediate, followed by sequential, stereocontrolled enolate chemistry to complete the synthesis as detailed in Schemes 2 through 4.12

Thus, synthesis of (±)-isostemofoline (11) commenced with Boc-protected alkoxy pyrrrole 25, available in five steps from 1,2-hexanediol (24) (Scheme 2). The formal [4+3]-cycloaddition of alkoxy pyrrrole 25 and vinyl α-diazoester 26 was catalyzed by rhodium octanoate dimer to cleanly afford bicyclic adduct 27. The silylenol ether moiety was then cleaved using TBAF, and the MOM enol ether was reduced using H2-
Pd/C, resulting exclusively in exo hydrogenation to give \( \beta \)-keto ester \( 28 \). Krapcho decarboxylation of this \( \beta \)-keto ester produced bicyclic ketone \( 29 \) in high yield. Sodium methoxide-catalyzed condensation of \( 29 \) with furfural then gave the \( \alpha,\beta \)-unsaturated ketone \( 30 \), and subsequent alkylation using allyl iodide produced a 2.1:1 mixture of enol ether \( 31 \) along with the allyl ketone \( 32 \) formed via a stereoselective Claisen rearrangement of \( 31 \). The mixture was then refluxed in toluene to complete the conversion of \( 31 \) to \( 32 \).

Scheme 2.

Next, the terminal alkene functionality of \( 32 \) was oxidatively cleaved using potassium osmate/NaIO\(_4\), and the resulting aldehyde was reduced to lactol \( 33 \) with Zn(BH\(_4\))\(_2\) (Scheme 3). This intermediate was converted to the TIPS-protected keto alcohol \( 34 \) by treatment with TIPSCl/imidazole. At this point the C10 methyl group was
stereoselectively installed by treating 34 with methyllithium/DMPU in ether to give the desired 1,4-adduct 35 as a single stereoisomer. Silyl group removal, followed by tosylation of the resulting alcohol gave furan 36, which was subjected to ozonolysis yielding acid 37. Conversion of acid 37 to aldehyde 38 was achieved by sodium borohydride reduction via the mixed anhydride followed by Dess-Martin oxidation.

Scheme 3.

Homologation of aldehyde 38 using the lithium enolate of 4-methoxy-3-methyl-2(5H)-furanone (39) resulted in a 2:1 mixture of diastereomeric alcohols 40, which was separated and each isomer individually oxidized using Dess-Martin periodinane giving the corresponding ketone diastereomers 41 (Scheme 4). Treatment of MOM ethers 41 with TFA effected a tandem double cyclization to give the desired hemiketals 42 as a
mixture containing all four possible diastereomers in approximately a 1:1:1:1 ratio. Finally, after much experimentation conditions for dehydration of 42 were found. Thus, treatment of 42 with Tf₂O gave (±)-isostemofoline (11) but only in low 12% yield, together with 14% of the undesired retro-aldol by-product 43.

Scheme 4.

Overman’s Synthesis of (±)-Didehydrostemofoline (Asparagamine A) (6) and (±)-Isodidehydrostemofoline (12)

Overman’s synthesis of (±)-didehydrostemofoline (asparagamine A) (6) and (±)-isodidehydrostemofoline (12) featured an aza-Cope-Mannich rearrangement of a formaldinium ion derivative 52 as the key step (Scheme 5). An important improvement
over Kende’s approach was the development of a route to circumvent the retro aldol and low yield issues encountered in installing the crotonolactone moiety.

The synthesis began with a Diels-Alder condensation of pyrrole 44 and ethyl (E)-3-nitroacrylate producing a mixture of regioisomeric adducts 45 and 46, which was unstable to chromatographic purification (Scheme 5). Hence, the crude mixture was hydrogenated to give 47 and 48 which could be separated by column chromatography. Scheme 5.
The desired isomer 47 was converted to alcohol 49 via standard chemistry. Conversion of this primary alcohol to the corresponding enolsilane by sequential Dess-Martin oxidation/TIPSOTf treatment, was followed by ozonolysis to give ketone 50. A stereoselective vinylation was then carried out using vinyl Grignard/CeCl₃ and the product was converted to its hydroiodide salt 51 using TMSI in methanol. At this point, the key aza-Cope-Mannich rearrangement was implemented. Thus, addition of paraformaldehyde to the amine salt 51 produced formaliminium ion 52 which underwent an aza-Cope rearrangement to give 53, followed by a subsequent Mannich step when the mixture was heated at 80 °C, producing the azatricyclo[5.3.0.0]decanone 54 product in high yield.

To continue the synthesis, the TIPS group of intermediate 54 was removed using TBAF and the resulting alcohol was oxidized to the corresponding aldehyde 55 in preparation for a Julia-Kocienski olefination, which resulted in isomerically pure E-alkene 56 (Scheme 6). The lithium enolate of ketone 56 was alkylated with ethyl iodoacetate to give axial product 57 with the undesired stereochemistry at C-9. However, substrate 57 was then epimerized to give the correct equatorial isomer 58 under the action of DBU. The methyl ether group of 58 was then cleaved with BBr₃ to give lactol 59. Silyl protection of 59, followed by alkylation of the lithium ester enolate with methyl iodide gave 60 with the incorrect configuration at C-10. The ester moiety was converted to the corresponding aldehyde 61 and a silica gel mediated epimerization of 61 was required to obtain the desired C10 isomer 62.
Finally, an elegant solution for installing the remaining furanone moiety was devised as demonstrated in Scheme 7. First, the lithium anion of 4-methoxy-3-methyl-2(5H)furanone (63) was coupled with aldehyde 62 to give adduct 64. Acidic cleavage of the silyl protecting group in 64, followed by IBX oxidation gave the desired stereoisomer 65. Condensation of this product with thiophosgene gave a separable mixture of thionocarbonate isomers 66 and 67. The ratio of 66/67 could be controlled by varying the reaction temperature between -50 and 0 °C, with product 66 being formed predominantly at -50 °C and 67 at 0 °C. In the final step, each of the thiocarbonate isomers 66 and 67 was heated at 120 °C with an excess of trimethyl phosphite to yield (±)-didehydrostemofoline (6) and (±)-isodidehydrostemofoline (12), respectively.
An initial approach by the Thomas group to stemofoline reported in 1992 focused on using an iminium ion cyclization to form tricyclic lactam 69, and relied on a regioselective Pb(OAc)$_4$ promoted remote oxidation to create the ether ring of tetracycle 72 (Scheme 8).

Thus, imine 69 was formed from readily available ketone 68 and cyclized upon treatment with methyl chloroformate and triethylamine to yield tropane 70.
Tropane 70 was elaborated to lactam 71 in several steps and the remote oxidation was implemented using Pb(OAc)$_4$ to give tetracyclic ether 72 corresponding to the tetracyclic core of stemofoline. In a later 2007 publication the authors showed that this substrate could not be used to install fragments corresponding to the C10, 11 side chain.$^{22}$

Scheme 8.

Revisiting the molecule in 2009, Thomas explored an alternative asymmetric synthesis of the tetracyclic core of stemofoline using a stereoselective intermolecular Mannich approach.$^{23}$ Employing Ellman’s$^{24-26}$ protocol for titanium(IV)-mediated addition of ester enolates to $N$-tert-butyl sulfinimides Thomas could generate a $\beta$-aminoester in enantiomerically pure form (Scheme 9). Thus, homochiral ester 74 and (S)-tert-butyl sulfinamide 73 were combined to form 75 which possessed the desired stereochemistry as confirmed by X-ray crystallography. The tert-butylsulfinyl auxiliary of 75 was then removed, and was replaced by a Boc protecting group, producing compound 76. The ester functionality of 76 was homologated to the corresponding $\beta$-ketoester and the alkene moiety was oxidatively cleaved to give diketoester 77 using standard chemistry. After some experimentation, conditions for converting the Boc protected amine 77 to keto diester 78 with the required, equatorial methyl ester
disposition were found using TFA in dichloromethane at 0 °C. Finally, in preparation for introducing the ring incorporating C5 and C6 of stemofoline, the β-keto ester 78 was allylated and the terminal alkene formed was oxidatively cleaved to form aldehyde 79. Unfortunately, all attempts to cleave the Boc group of 79 at this stage to form lactam 80 failed, resulting only in the undesired aldol product 81.

Scheme 9.
Livinghouse Approach to the Stemofoline Core

In 1996 Livinghouse et al. described a new protocol for stereocontrolled synthesis of pyrrolidines, isotropanes and bridged pyrrolizidines via TiCl₄-mediated intramolecular desilylative stepwise cyclizations of imines with 2-propylidene-1,3-bis(silanes). Recognizing that this methodology might be implemented in a stereoselective approach to the azatricyclic core of stemofoline, Livinghouse performed a model study on the system depicted in Scheme 10. Thus, readily available bis-allylsilane amine 82 was condensed with ethyl levulinate to give imine 83 which was treated with TiCl₄ (1 equiv) to effect a stereoselective allylsilane-imine cyclization-lactam formation to form pyrrolizidone 84 as a single diastereomer. This product was converted to thiolactam 85 using Lawesson’s reagent. Subsequent S-alkylation-intramolecular desilylative cyclization was accomplished by BF₃·etherate treatment, securing the bridged tricyclic pyrrolizidine 86 in 90% yield.

Scheme 10.
Gin Approach to the Stemofoline Core

In 2008 Gin and coworkers developed an intramolecular dipolar cycloaddition of an azomethine ylide as the key strategy in an enantioselective synthesis of the tricyclic core of the stemofoline alkaloids (Scheme 11). The synthesis began with commercially available (−)-2,3-O-isopropylidene-D-erythronolactone (87), which reacted with (trimethylsilyl)-methylamine to produce primary alcohol amide 88. Parikh-Doering oxidation of the alcohol 88 yielded hemiaminal 89, which was acetylated to give lactam 90. A Mannich reaction between lactam 90 and the silylketene acetal 91 derived from ethyl acetate proceeded cleanly to afford the ester product 92, which was hydrolyzed with LiOH to the corresponding carboxylic acid 93.

Scheme 11.
Lactam 93 was treated with Lawesson’s reagent to give thiolactam 94, followed by conversion of the C8-carboxyl group in 94 to the corresponding N-methoxy-N-methyl amide 95 (Scheme 12). Eschenmoser sulfide contraction was employed to install a vinylogous amide functionality giving 96. Treatment of 96 with ethynylmagnesium bromide gave alkynyl ketone 97, followed by addition of ethanethiol to generate substrate 98 ready for the key intramolecular [3+2] azomethine ylide cycloaddition step. This cycloaddition was then effected with triflic anhydride and TBAT, presumably proceeding via transition state 99, to afford the bridged pyrrolizidine substrate 100 containing the core of the stemofoline alkaloids.

Scheme 12.
Attempts to further advance cycloadduct 100 to stemofoline (1) consisted of hydrogenating the enol triflate moiety of 100 using Pd/C to give 101 and installation of the two-carbon functionality at C9 by enolate alkylolation of ketone 101 with ethyl iodoacetate, followed by DBU catalyzed equilibration producing 102 (Scheme 13). The ester group was hydrolyzed during the subsequent isopropylidene deprotection step producing carboxylic acid diol 103. It is unclear how the authors plan to differentiate between the hydroxyl groups of 103, or how the butenolide functionality of 1 would eventually be introduced.

Scheme 13.
Thus, several approaches to the stemofoline core have been described as well as the two total syntheses accomplished to date. An asymmetric total synthesis of stemofoline still remains to be achieved. The work detailed below outlines our efforts towards this end.
B. Nitrosoalkenes

Introduction

Nitrosoalkenes have long been known to organic chemists as highly reactive, versatile functional groups possessing structure 104. In fact, their existence as intermediates in the reaction of α-halooximes with nucleophilic bases was proposed by Mathaipoulos as early as 1898, but could not be confirmed due to the transient nature of these species. Since that time the scope and synthetic applications of nitrosoalkenes have been explored and several additional modes of reactivity have been uncovered. The most recent interest in nitrosoalkenes has been in connection with their potential as heterodiene components in [4+2]-cycloaddition reactions (see the Cycloaddition Reactions section). These investigations have resulted in the development of some new methods to generate nitrosoalkenes. Nitrosoalkenes are also highly activated for nucleophilic 1,4-conjugate addition reactions. The lifetimes of nitrosoalkenes are often very short and depend upon the substituents on the alkene. In general, bulky aryl, tert-alkyl, or halo substituents at the β-carbon atom are necessary to stabilize these highly reactive species if isolation is required and very few stable nitrosoalkenes have been

![Diagram](image_url)

104 105
prepared to date. It was not until 1960 that Griffin and Haszeldine isolated and characterized the first stable nitrosoalkene species – trifluoronitrosoethylene (106).29

Evidence for the intermediacy of nitrosoalkenes in reactions can be obtained by spectroscopy,30 or simple detection of a characteristic blue color due to the n→π* absorption band at λmax 675-795 nm. Nitrosoalkenes with lifetimes too short for detection by spectroscopic methods can be identified by trapping as Diels-Alder adducts.31-33 Some kinetic and stereochemical studies exploring the reactivity of nitrosoalkenes have been conducted.34

**Formation of nitrosoalkenes**

1,4-Elimination

*Base promoted 1,4-elimination of α-heteroatom-substituted oximes*

α-Heteroatom-substituted oximes are the most common precursors used to generate nitrosoalkenes, providing a simple and reliable route to these highly reactive intermediates from readily accessible precursors via base-promoted 1,4-elimination (Scheme 14). Chloride is most frequently the leaving group in this transformation but other halides are also suitable.35 In order to avoid nucleophilic addition of the solvent to
these reactive species, insoluble inorganic bases such as sodium carbonate or calcium hydroxide in non-nucleophilic organic solvents are commonly used. Insoluble inorganic bases also maintain a very low steady-state concentration of the highly reactive vinylnitroso intermediate, helping to avoid polymerization. In certain cases, the nucleophile itself can also be used as the base to promote formation of the nitrosoalkene \((\textit{vide infra})\).^{36}

Scheme 14

1,4-Elimination of \(\alpha\)-chloro-silyloximes with fluoride ion

A useful modification to the usual base promoted 1,4-elimination procedure using readily available \(\alpha\)-chloro-silyloximes to generate nitrosoalkenes has been developed by Denmark et al. (Scheme 15).^{37} In this methodology, fluoride sources such as tetrabutylammonium fluoride (TBAF), cesium fluoride, potassium fluoride or silver fluoride can be used to initiate the 1,4-elimination of \(\alpha\)-chloro-silyloximes, promoting efficient and controlled generation of nitrosoalkenes in acetonitrile.
Generally, $\alpha$-chloro-silyloximes are 2-3 times slower than simple $\alpha$-chlorooximes in production of nitrosoalkenes. Interestingly, the half-lives of vinyl nitroso compounds synthesized under these reaction conditions are 3-5 times shorter than the respective compounds derived from base-promoted 1,4-elimination of simple $\alpha$-chlorooximes. Therefore, a cycloaddition or addition of a nucleophile to the nitrosoalkene must be very fast in order for this methodology to be synthetically useful.

Synthesis of $\alpha$-chlorooximes and $\alpha$-chloro-silyloximes

As noted above, important precursors to nitrosoalkenes are $\alpha$-chlorooximes and $\alpha$-chloro-silyloximes, and several methods for their synthesis exist. Conversion of $\alpha$-chloroketones to $\alpha$-chlorooxime derivatives is usually a reliable method. Three permutations of this process have been studied in detail by Denmark et al. (Scheme 16):$^{37}$ Methods A and B lead to the simple oximes and use hydroxylamine. Method C has been developed specifically for conversion of acid labile compounds to silyloximes and uses milder conditions than methods A and B.

Method A employs hydroxylamine hydrochloride and sodium acetate in methanol under neutral conditions. Denmark found that $\alpha$-chlorohexanones oximes are much more
readily formed when the chlorine atom is located in the axial position of the starting \( \alpha \)-chloroketone (e.g. 112). In these cases the resulting \( \alpha \)-chlorooximes 113 were predominantly of \( Z \) configuration, whereas the equatorial isomer 110 produced the \( E \)-oxime 111 in low yield.

Scheme 16
Method B was found to be more general for oximation of $\alpha$-chloroketones 110 and 112 and uses potassium acetate in acetic acid. It was found that the rate of oxime formation from ketones using this method is highly dependent upon the reaction pH. The reaction rate is optimal at pH 5 and under these acidic conditions produces $E$-oxime 111 independent of the chlorine atom configuration, unlike method A.

Method C uses 2 equivalents of commercially available $O$-tert-butylidimethylsilylhydroxylamine and activated 4-Å molecular sieves in chloroform solution. Using this route, silyloximes can be formed from $\alpha$-chlorohexanones 110 and 112 in excellent yields without any dependence on the chlorine atom stereochemistry, also producing predominantly $E$-silyloximes 114 and 115.

Other known methods for the synthesis of $\alpha$-chlorooximes such as interaction of nitroalkenes with tin dichloride$^{38}$ or titanium tetrachloride,$^{30}$ and the addition of nitrosyl chloride to alkenes are, as yet, of limited utility and can only be applied to very specific substrates.

1,3-$N,C$-Elimination of trialkysilanols from silyl nitronates

An alternative method for generating nitrosoalkenes first reported by Seebach et al. in 1981 is the 1,3-$N,C$-elimination of trialkysilanols from silyl nitronates (Scheme 17).$^{39}$ Thus, nitrosoalkene 117 was proposed to form via alkyllithium-promoted elimination of tert-butylidimethylsilyl from tert-butylidimethylsilyl nitronate 116.
The intermediacy of β-substituted nitrosoalkenes was confirmed in a study by Ioffe et al. of trimethylsilylation of nitro compounds containing electron-withdrawing groups at the β-position such as 118 (Scheme 18). In this case trimethylsilyl nitronate 119 is formed via the silylation of nitro compound 118 with N,O-bis(trimethylsilyl) acetamide (BSA) and undergoes rapid elimination of trimethylsilanol to generate the reactive nitrosoalkene 120. This method provides an alternative way to generate nitrosoalkenes and may gain more popularity in the future, as nitro compounds containing electron-withdrawing groups at the β-position have recently become easily accessible.

Scheme 18
Reactions of nitrosoalkenes

Cycloaddition reactions

Introduction

The most studied mode of reactivity for nitrosoalkenes is in [4+2]-cycloadditions, and the various types are depicted in Scheme 19. Nitrosoalkenes 121 can participate as either $2\pi$ (pathway A) or $4\pi$ (pathways B, C and D) electron systems. No reports of reactions proceeding via pathway E where C=C bond serves as the $2\pi$ electron system forming adducts of type 127 exist to date.

Scheme 19
Nitrosoalkenes as 2π systems

The only compounds known to participate in [4+2]-cycloadditions as 2π systems are β-halo-β-alkyl- and β,β-dihalo-derivatives of nitrosoalkenes such as trichloronitrosoethylene (129) (Scheme 20). Viehe found the nitroso group to be a suitable heterodienophile in cycloadditions with electron rich dienes such as butadiene, 1-methoxybutadiene, cyclopentadiene (128), cyclohexadiene and benzene oxide.30 Cyclic diene adducts 130 tend to rearrange thermally, forming epoxy aziridines 131. However, transient formation of [4+2]-cycloaddition products 130 can be observed by low-temperature NMR.42

Scheme 20

Nitrosoalkenes as 4π systems in cycloadditions with C=C bonds

The most highly studied mode of reactivity for vinylnitroso compounds is in [4+2]-cycloadditions where the nitrosoalkenes act as 4π systems (Scheme 21). Here nitrosoalkenes can act as heterodienes in inverse electron demand Diels-Alder reactions with dienophiles to give various substituted oxazines. This concept was first proposed by Gilchrist, based on his calculations of the highest occupied molecular orbital (HOMO)
and the lowest unoccupied molecular orbital (LUMO) coefficients for nitrosoethylene using Hückel and CNDO methods.\textsuperscript{28} Thus, it was determined that the LUMO of the nitrosoalkene $121$ is closer in energy to and therefore interacts with the HOMO of the alkene $122$. The regioselectivity of the process is guided by the size of the coefficients on the interacting HOMO and LUMO orbitals. This transformation is commonly accepted to be a concerted process, although Zimmer and Reissig found from their PM3 calculations that despite the concerted nature of the reaction, in certain cases formation of the C-O bond can be slightly slower than the formation of the C-C bond, suggesting possibility an asynchronous process.\textsuperscript{43}

Scheme 21

Reissig et al. used cycloadditions of alkenes with 3,4-dihydro-1-nitrosonaphthalene ($133$) as a model to also investigate the diastereoselectivity of the cycloaddition process. Thus, the $\text{exo}$ mode of addition was found to be preferred for monosubstituted alkenes such as trimethylsilyloxyethylene (Table 1-1, Entry 1), where cycloadducts were formed in a $>$97:3 diastereomeric ratio.\textsuperscript{44} It was noted that the
presence of a methyl substituent on the double bond of the alkene caused the diastereoselectivity to decrease to 64:36. (Entry 2). A preference for endo–addition was observed in cyclic systems as with 1-trimethylsilyloxy cyclopentene (Entry 3). Interestingly, allyltrimethylsilane (Entry 4) does not follow the exo-addition trend observed for trimethylsilyloxyethylene, instead producing a 1:1 mixture of exo/-endo-adducts.

Table. 1-1. Diastereoselective [4+2]-Cycloadditions of Nitrosoalkenes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ratio</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>R&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt;97 : 3</td>
<td>H</td>
<td>H</td>
<td>OSiMe&lt;sub&gt;3&lt;/sub&gt;</td>
</tr>
<tr>
<td>2</td>
<td>64 : 36</td>
<td>Me</td>
<td>H</td>
<td>OSiMe&lt;sub&gt;3&lt;/sub&gt;</td>
</tr>
<tr>
<td>3</td>
<td>18 : 82</td>
<td>(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>OSiMe&lt;sub&gt;3&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1 : 1</td>
<td>H</td>
<td>H</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;OSiMe&lt;sub&gt;3&lt;/sub&gt;</td>
</tr>
</tbody>
</table>

Denmark et al. have studied the intramolecular variant of [4+2]-cycloadditions of nitrosoalkenes (Scheme 22).<sup>45</sup> When a 1:1 mixture of E- and Z-enol ether isomers of compound 137 was subjected to the cycloaddition reaction conditions nitrosoalkene 138 was formed, from which a 3.4 : 1 ratio of endo:exo cycloaddition products 139/140
resulted. This experiment suggests that the preferred orientation of the methoxy group is \textit{endo}-to the nitrosoalkene, which can be explained invoking secondary orbital interactions, an explanation common in intermolecular heterodiene Diels-Alder reactions.\textsuperscript{46}

Scheme 22

[3+2]-Cycloadditions of nitrosoalkenes with alkenes

Until very recently [3+2]-cycloadditions were observed only as side reactions along with the usual [4+2]-cycloadditions of nitrosoalkenes. One example is in the addition of 1-nitroso-1-phenylethylene (142), generated from α-chloroacetophenone oxime (141), to 2-methoxypropene where both [4+2]- and [3+2]-cycloaddition products were isolated (Scheme 23). The desired 1,2-oxazine 144 was the major product formed, but cyclic nitrone 145, corresponding to [3+2]-cycloaddition, was also observed as a minor product.

Scheme 23
However, in 2009 de los Santos et al. reported formation of a [3+2]-type cycloadduct alone, while attempting to effect a hetero-Diels–Alder process (Scheme 24). Thus, when 1,2-oxazabuta-1,3-diene 147, obtained from α-bromooxime 146, was reacted with enamines 149, formation of the hydroxypyrrole-3-phosphonates 150 was observed in high yield and regioselectivity. It was purported by the authors that in these transformations the initial conjugate addition of enamine 149 to nitrosoalkene 147 gives adduct 151 followed by cyclization resulting in formation of nitrone 152. In most cases this step is rapidly followed by elimination of the pyrrolidine residue leading to substituted N-hydroxypyrroles 150. When the reaction was extended to a variety of Scheme 24

![Scheme 24](image-url)
enamines three stable phosphorylated nitrone intermediates 152a-c were isolated, giving further support to the intermediate nitrone formation in the other reactions.

1,4-Conjugate additions

Introduction

Conjugate 1,4-nucleophilic additions permit nitrosoalkenes to act as enolonium ion equivalents 154b,47,48 producing α-nucleophile functionalized oximes such as 155 (Scheme 25). Therefore, these umpolung-type processes can serve as indirect routes to access α-functionalized ketones 157. It should be noted that direct SN2 displacements of halides α to ketones 156 are possible, but are often complicated by steric effects and competitive 1,2-nucleophilic addition into the carbonyl moiety.

Scheme 25

Two mechanistic routes are possible for the transformation of oxime 153 to 155:

1. 1,4-elimination-addition with intermediate formation of nitrosoalkenes 154 shown in
Scheme 25, and (2) direct substitution of the halogen of 153 by the nucleophile via a SN2 mechanism. To prove that 1,4-elimination-addition is indeed the usual mechanism involved in such transformations, Gilchrist et al. performed a semi-quantitative study on azole N-alkylation with α-bromooxime 159a (R = H), and the corresponding O-alkyl oxime 159b (R = CMe2OMe (Table 1-2).49

Table 1-2. N-Alkylation of Azoles Using α-Bromooxime Derivatives

<table>
<thead>
<tr>
<th>pKa</th>
<th>substrate</th>
<th>oxime</th>
<th>products</th>
<th>reaction time</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.10</td>
<td><img src="158" alt="Image" /></td>
<td><img src="159a,b" alt="Image" /></td>
<td><img src="160" alt="Image" /></td>
<td>0.2 h 24 h</td>
</tr>
<tr>
<td>4.12</td>
<td><img src="161" alt="Image" /></td>
<td><img src="159a,b" alt="Image" /></td>
<td><img src="160" alt="Image" /></td>
<td>0.5 h 48 h</td>
</tr>
<tr>
<td>3.32</td>
<td><img src="163" alt="Image" /></td>
<td><img src="159a,b" alt="Image" /></td>
<td><img src="164" alt="Image" /> + <img src="165" alt="Image" /></td>
<td>24 h -</td>
</tr>
<tr>
<td>2.52</td>
<td><img src="166" alt="Image" /></td>
<td><img src="159a,b" alt="Image" /></td>
<td><img src="167" alt="Image" /></td>
<td>72 -</td>
</tr>
<tr>
<td>2.27</td>
<td><img src="168" alt="Image" /></td>
<td><img src="159a,b" alt="Image" /></td>
<td><img src="169" alt="Image" /> + <img src="170" alt="Image" /></td>
<td>72 -</td>
</tr>
</tbody>
</table>

R=H (159a), R=CMe2OMe (159b)

It was theorized that a more basic nucleophile would serve to facilitate nitrosoalkene formation from 159a, leading to faster reaction times, whereas less basic nucleophiles would be slower to deprotonate the oxime. It can be seen from the data
presented in Table 1-2, that imidazole (158) and 3,5-dimethylpyrazole (161) react with the α-bromoxime 159a much faster then their less basic analogues 163, 166 and 168. Oxime ether 159b reacts only with the first two substrates 158 and 161, with rates comparable to those of the weakly basic azoles. Pyrazole (166) and 1,2,4-triazole (168) are not basic enough to deprotonate oxime 159a in order to form a nitrosoalkenes, and thus these substrates proceed via the slower S_N2 pathway. These experiments suggest that the reactions proceed via formation of the nitrosoalkene for the first two substrates. Further supporting the 1,4-elimination-addition mechanism with 159a, is a large increase in reaction rates for the last three substrates upon addition of sodium carbonate to promote formation of the nitrosoalkenes. In these cases the reaction is complete after just 10 minutes, and produces the corresponding N-alkylation products in high yield.

Formation of the ethyl α-nitrosoacrylate (171) from 159a was also confirmed by trapping it as the [4+2]-cycloadduct 173 with 2,5-dimethylfuran (172) (Scheme 26).

Scheme 26

Another study investigating the reactions of chloronitroso dimers with various nucleophiles by Ohno and Naruse also supports that these substitution reactions proceed through a vinylnitroso intermediate, rather than via direct S_N2 displacement (Scheme 27). Dimers 174 add methoxide to form α-methoxyoximes at a much faster rate than with piperidine to produce α-piperidinooximes. However, when 174 is treated simultaneously with both bases, piperidinooxime 176 is the major product. Since
formation of the nitrosoalkene 175 is the rate determining step in this reaction sequence, the observed ratio of the products must be the result of the softer nucleophile (piperidine) adding to the nitrosoalkene in the slow step.

Scheme 27

Finally, it was shown that only Z-morpholinoxime 181 results on addition of morpholine to both E/Z α-chloroacetophenone oximes 178 and 182 (Scheme 28). This experiment suggests that deprotonation of the bromooximes 178 and 182 leads to formation of nitrosostyrene rotamers s-trans 180 and s-cis 184, which preferentially add morpholine when in the s-trans conformation.

Scheme 28

As seen from these studies, good evidence exists for the intermediacy of nitrosoalkenes in nucleophilic displacement of α-halooximes. The basicity of the nucleophile can be an important factor in reactions of this type. Another important factor
is the acidity of the oxime, which can often be controlled by choice of the substituents on the oxime carbon.

Reactions with N, O, and S nucleophiles

Table 1-3. N, O, and S Nucleophilic Additions to Vinylnitroso Compounds

<table>
<thead>
<tr>
<th>Nitrosoalkenes</th>
<th>Types of nucleophiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₂=C(Me)NO</td>
<td>NH₃, R₂NH</td>
</tr>
<tr>
<td>CH₂=C(Ph)NO</td>
<td>SCN</td>
</tr>
<tr>
<td>CH₂=C(Ac)NO</td>
<td>(H₂N)₂CS, H₂NCH₂CN,</td>
</tr>
<tr>
<td></td>
<td>RCH(NH₂)CO₂Et,</td>
</tr>
<tr>
<td></td>
<td>Me(CH₂)₄OH</td>
</tr>
<tr>
<td>CH₂=C(COEt)NO</td>
<td>ArSH</td>
</tr>
<tr>
<td>R¹R²C=C(R³)NO</td>
<td>NH₂OH, NO₂⁻, N₃⁻</td>
</tr>
<tr>
<td>R¹=H, alk</td>
<td>ROH</td>
</tr>
<tr>
<td>R², R³ = alk, cyclo-alk</td>
<td></td>
</tr>
<tr>
<td>ClCH=CHNO</td>
<td>ArNH₂</td>
</tr>
<tr>
<td>Cl₂C=CHNO</td>
<td>ArNH₂</td>
</tr>
<tr>
<td>ArCH=C(R)NO</td>
<td>RNH₂, ROH, ArSH,</td>
</tr>
<tr>
<td></td>
<td>SCN⁻, EtOCS₂⁻</td>
</tr>
<tr>
<td>CH₂=C(CF₃)NO</td>
<td>Et₂NH, H₂O</td>
</tr>
</tbody>
</table>

Taken from the 1983 review by Gilchrist²⁸
A plethora of N, O and S nucleophiles participate in intermolecular additions to \textit{in situ}-generated nitrosoalkenes (Table 1-3). The most common examples involve amine additions to a variety of nitrosoalkene intermediates. Other nucleophiles include \textit{inter alia} alcohols, thiols, azide, hydroxylamine, NO\textsuperscript{–}, and water. These reactions work well for most N, O, and S nucleophiles. However, some of the adducts are prone to further rearrangements following the initial nucleophilic addition step.

For example, product 188 resulting from addition of chloroacetone oxime 186 with ammonia continues to react with another equivalent of nitrosoalkene 187 forming adduct 189, which can react with yet another equivalent of nitrosoalkene 187, finally affording tertiary amine 190 (Scheme 29).27

Similarly, in reactions of dichloroacetaldehyde oxime 191a (R=H) and chloral oxime 191b (R=Cl) with primary amines, the initially formed adducts 193a,b undergo elimination to imines 194a,b (Scheme 30).52
The lesser known 1,4-additions to phosphinyl- and phosphonyl-nitrosoalkenes such as compound 147 have been described by de los Santos et al. (Scheme 31). Their reactions with ammonia, amines and optically active amino esters yield α-amino phosphine oxides and α-amino phosphonates 196-204. Although these transformations lack stereoselectivity with optically active compounds, these products are potentially useful in organic and medicinal chemistry.53-55
Reactions with carbanions

Vinyl nitroso compounds are readily alkylated by carbon nucleophiles under mild conditions due to their high reactivity. Some examples of stabilized carbanions reacting with nitrosoalkenes via intermolecular 1,4-conjugate addition are shown in Table 1-4. A variety of 1,3-diketones, β-ketoesters, and malonate esters have been found to add to nitrosoalkenes possessing various alkyl and aromatic substituents.

Table 1-4. Carbon Nucleophiles

<table>
<thead>
<tr>
<th>Nitrosoalkenes</th>
<th>Types of carbon nucleophile</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₂=C(Me)NO</td>
<td>1,3-diketones, β-ketoesters, malonic esters</td>
</tr>
<tr>
<td>CH₂=C(t-Bu)NO</td>
<td>t-BuC(O)CH₂CO₂Et</td>
</tr>
<tr>
<td>CH₂=C(Ph)NO</td>
<td>β-ketoesters</td>
</tr>
<tr>
<td>R¹CH=C(R²)NO</td>
<td>CN⁻</td>
</tr>
<tr>
<td>CH₂=C(CO₂Et)NO</td>
<td>CH₂(CO₂Et)₂</td>
</tr>
<tr>
<td>CH₂=C(Ar)NO</td>
<td>MeNO₂</td>
</tr>
<tr>
<td>PhCH=C(Me)NO</td>
<td>AcCH₂CO₂Et, AcCH₂C(O)Ph</td>
</tr>
<tr>
<td>PhCH=C(R)NO</td>
<td>CH₂Ac₂, CH₂(CO₂Et)₂</td>
</tr>
<tr>
<td>CICH=CHNO</td>
<td>1,3-diketones, CH₂(CO₂Me)₂, EtO₂CCH₂CN</td>
</tr>
</tbody>
</table>

Although sodium ethoxide and ethanol most commonly serve as the base and solvent during additions of 1,3-dicarbonyl compounds to intermediate nitrosoalkenes generated from α-halooximes, in several cases sodium carbonate in dichloromethane,⁵⁶ or
in methyl tert-butyl ether, and piperidinium acetate in tetrahydrofuran\textsuperscript{57} have also been successfully employed.\textsuperscript{35} A few specific representative examples are shown below.

Sprio et al. reported early examples of various $\beta$-keto esters undergoing additions with $\alpha$-bromooximes \textsuperscript{205} and \textsuperscript{209} (Scheme 32).\textsuperscript{58-60} The sodium salts of these $\beta$-keto esters were generated under the action of sodium ethoxide in ethanol or sodium methoxide in methanol. The reaction products \textsuperscript{208} and \textsuperscript{211} were obtained in high yield.

\begin{scheme}

Several examples of vinylnitroso intermediates derived from 2-chlorocycloalkanone oximes undergoing 1,4-additions with the sodium salt of diethyl malonate were reported by Ohno et al.\textsuperscript{50,61} (Scheme 33). A large excess of the malonate sodium salt was combined with $\alpha$-chlorooximes \textsuperscript{212} and \textsuperscript{216} in order to facilitate the formation of the highly reactive vinylnitroso species \textsuperscript{214} and \textsuperscript{217}, respectively. Subsequent 1,4-conjugate addition of a second equivalent of the diethyl malonate sodium.
salt produced the adducts 215 and 218 in good yields. The authors suggest that stability of vinylnitroso compounds varies with ring size and is responsible for the lower yield observed with the cyclohexyl system.

Scheme 33

Zimmer et al. observed that the addition of the sodium salt of acetylacetone (220) to α-bromooxime 219 results in a mixture of tautomeric products 221-223 (Scheme 34).35

Scheme 34
Organolithiums\textsuperscript{61} and Grignard reagents\textsuperscript{62} are also known to participate in 1,4-additions to vinylnitroso compounds produced from \(\alpha\)-halooximes. Reactive carbanions such as EtC≡CLi (225) and EtMgBr (229) are usually used in two fold excess, where the first equivalent serves as the base to promote formation of the reactive nitrosoalkene intermediates 226 and 230 from the \(\alpha\)-halooximes (Scheme 35). The second equivalent serves as the nucleophile producing 1,4-adducts like 227 and 231 in good yields.\textsuperscript{63}

Scheme 35

Oppolzer et al. discovered that ketone lithium enolates like 233 can serve as good nucleophiles for 1,4-addition (Scheme 36).\textsuperscript{64} Alkylated cyclopentanone derivative 235 was obtained in good yield in this case.

Scheme 36
Aromatic substitution

Only highly electrophilic nitrosoalkenes such as 237 and electron-rich aromatic systems like 236 have been found to participate in aromatic substitutions. In this example a 1:4 mixture of regiosomeric products 238 and 239 was obtained (Scheme 37). Alkylations of 1,4-dimethoxybenzene, N,N-dimethylaniline and 2-naphthol with 237 proceeded with lower product yields. Furthermore, the less electrophilic ethyl α-nitrosoacrylate failed to alkylate 2-naphthol.35

![Scheme 37](image)

Reactions of nitrosoalkenes with electron rich heteroaromatic systems such as furans, benzofurans, pyrroles, and indoles are more general. It should be noted that it is possible that these transformations may not be direct 1,4-conjugate addition processes, but rather might involve initial [4+2]-cycloadditions.35 For example, in the reaction between pyrroles and nitrosoalkenes substitution occurs exclusively at the 2-position as shown in Scheme 38, producing mixtures of 1,4-conjugate addition products like 242 and formal Diels-Alder cycloadducts 244. The ratio observed depends on the presence and positions of the substituents on the pyrrole. At present, it is unclear whether adducts 242 are the result of a 1,4-conjugate addition, or if the initially formed Diels-Alder cycloadducts 244 rearrange to 242.66
Indoles are substituted exclusively at the C3-position with nitrosoalkenes (Scheme 39). Cyclic adducts 248 are only observed when a non-hydrogen substituent is present at the C3-position of the indole. These reactions are conducted at lower temperatures with highly electrophilic nitrosoalkenes like 246 (X = COMe, COOEt), since at elevated temperatures the reversibility of the process increases, resulting in low product yields.
Chapter 2

Results and Discussion

Introduction

As discussed in detail below, we have developed novel methodology that produced the first examples of intramolecular 1,4-conjugate additions of enolates and sulfonamides to vinylnitroso compounds. Combining several methods developed in these labs, we have been able to access the requisite cyclization precursors. Thus, we have shown that a vinylnitroso species generated from the corresponding $\alpha$-chlorosilyl-oximes using fluoride ion, interacts with a tethered nucleophile in a 1,4-manner producing a variety of carbocyclic and heterocyclic products. Recognizing that this methodology might allow facile entry into the stemofoline alkaloid skeleton, we have investigated an asymmetric total synthesis of stemofoline (1). In the course of these studies new methodology for oxidation of $\alpha$-hydroxy-$\beta$-ketoesters to $\alpha$-diazo-$\beta$-ketoesters has also emerged, thus helping to generate some of the intermediates required for the alkaloid synthesis.
I. Intramolecular conjugate additions of vinlylnitroso compounds

Background on key transformations used for the synthesis of cyclization precursors

A. Vinyl chloride ring closing metathesis methodology

Introduction

Olefin metathesis has developed into one of the most important reactions in synthetic organic chemistry since its discovery at Dupont in the 1950’s. With the advent of new ruthenium and molybdenum catalysts, the original limitations to its uses due to the absence of well characterized, air stable catalysts were assuaged allowing olefin metathesis to flourish. Of the five major variants of olefin metathesis: ring-opening metathesis polymerization (ROMP), ring-closing metathesis (RCM), acyclic diene metathesis polymerization (ADMET), ring-opening metathesis (ROM), and cross-metathesis (CM or XMET), RCM, in particular, has found great popularity. Large and medium rings, otherwise often difficult to form, are accessible via RCM and applications to syntheses of a number of complex molecules have been reported. It should be noted, that metathesis can also occur between an alkene and alkyne, known as enyne metathesis.

In 2003, the Weinreb group described the first examples of olefin metathesis involving vinyl chlorides, to form 5-, 6- and 7-membered carbocyclic and heterocyclic systems. Until that point, relatively few examples of RCM reactions involving heteroatom-substituted olefins were known. The methodology was subsequently applied
by the Weinreb group in an approach to a total synthesis of cylindricine B.\textsuperscript{81} Moreover, this reaction has played a pivotal role in our methodology, permitting facile access to a number of useful carbo- and heterocyclic vinyl chloride substrates (\textit{vide infra}).

\textit{Catalysts}

Diene metathesis has flourished since the discovery of the highly reactive, homogeneous, molybdenum and ruthenium catalysts shown in Figure 2-1. The first such catalyst was developed by Schrock in 1990.\textsuperscript{82} The Schrock molybdenum catalyst 249 allows formation of di-, tri-, and even some tetra-substituted double bonds by RCM. However, the catalyst suffers from high oxygen and moisture sensitivity, which makes handling on the bench-top difficult.

Grubbs developed the alternative more stable 1\textsuperscript{st} generation ruthenium catalysts 250 a and b, which were later modified, producing Grubbs 2\textsuperscript{nd} generation catalysts 251, and 252. Grubbs’ catalysts, although less reactive then Schrock’s due to the stabilizing effects of the ligands surrounding the metal, are much more oxygen and moisture stable. This stability, combined with their high tolerance towards an array of functional groups, makes them very useful in organic synthesis.

Figure 2-1. Catalysts for Olefin Metathesis
Hoveyda-Grubbs catalyst 253 is a phosphine-free compound that combines ease of product purification with high reactivity. There are fewer difficulties in removing catalyst decomposition byproducts with Hoveyda-Grubbs catalyst and it is also possible to recover this catalyst by silica gel column chromatography.

**Mechanism of RCM**

Extensive studies by Grubbs et al. support the catalytic cycle for RCM depicted in Scheme 40. In the initial stages of the process the active catalytic species, ethylidene 255, is generated. An alkene moiety of substrate 254 undergoes a [2+2]-cycloaddition.
with ethylidene 255 forming a metallocyclobutane 256. Subsequent cycloreversion, driven by the release of volatile ethylene, generates carbene 257. Metallocyclobutane 258 is the product of an intramolecular [2+2]-cycloaddition of intermediate 257. Following a second cycloreversion of 258, RCM product 259 is formed and the active catalytic species 255 is regenerated.

*Ring closing metathesis of vinyl chlorides*

An investigation towards the synthesis of the cylindricine alkaloids prompted an interest in RCM reactions with vinyl chlorides in the Weinreb group. In the course of that study Chao discovered that it is possible to effect RCM of diene 260 using Grubbs 2nd generation catalyst to form the tricyclic vinyl chloride 261 in high yield (Scheme 41).

Scheme 41

This discovery prompted an in depth investigation into the RCM reactions of vinyl chlorides. Initial optimization studies were carried out using diene sulfonamide 262. The results are depicted in Table 2-1.

Since catalysts 250 and 251 failed to effect the RCM in the initial experiments (entries 1 and 2), Grubbs 2nd generation catalyst 252 was used in these studies.
Temperature proved to be crucial to the reaction outcome. No reaction was observed at 25 °C (entry 3), and the reaction progress was very sluggish at 40-50 °C (entry 4), although some product was isolated. The best reaction temperature was found to be 65 °C. At 20 mol % catalyst loading, the RCM product 263 was formed in 94% yield (entry 6). Decreasing the catalyst loading to 10 mol % decreased the yield only slightly as seen in entry 6. However, using only 5 mol % of catalyst 252 caused the reaction to halt at 66% conversion, with 23% of starting material recovered (entry 5).

Table 2-1 Optimization of Vinyl Chloride Metathesis

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>conditions</th>
<th>isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>250</td>
<td>65 °C, 6 h</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>251</td>
<td>65 °C, 6 h</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>252</td>
<td>rt, 6 h</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>252 (5 mol %)</td>
<td>40-50 °C, &gt;10 h</td>
<td>66% + 23% SM</td>
</tr>
<tr>
<td>5</td>
<td>252 (10 mol %)</td>
<td>65 °C, 6 h</td>
<td>92%</td>
</tr>
<tr>
<td>6</td>
<td>252 (20 mol %)</td>
<td>65 °C, 2.5 h</td>
<td>94%</td>
</tr>
</tbody>
</table>

Substrates shown in Table 2-2 were used to further explore the scope of the vinyl chloride RCM reaction. It was found that the reaction proceeds with chloroalkenes 264,
265, and 266, producing five-, six- and seven-membered carbocyclic chloroalkenes 269, 270, and 271, respectively, in excellent yields. Terminal substituents on the olefin are tolerated, as seen in substrate 267. Heterocyclic chloroalkenes 272 and 273 could be prepared in high yields.

Table 2-2. Vinyl Chloride Metathesis Examples

<table>
<thead>
<tr>
<th>entry</th>
<th>vinyl chloride</th>
<th>cyclization product</th>
<th>isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtO₂C₂CO₂Et</td>
<td>EtO₂C₂CO₂Et</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>269</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>270</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>271</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>272</td>
<td></td>
</tr>
</tbody>
</table>

Some limitations to the process were uncovered upon further investigation (Scheme 42). For example, vinyl bromide 274 did not participate in the reaction, possibly due to steric factors. No tetrasubstituted products such as compound 277, nor
the larger 8- and 12- membered rings 279 and 281 could be formed using the standard conditions.

Scheme 42

An internal competition experiment with triene 282 conducted by Meketa demonstrated that the choloroalkene moiety is less reactive than mono- or disubstituted olefins in the methathesis cyclization process (Scheme 43).\textsuperscript{84} None of cyclization products 284 and 285 were observed.
Mechanistically, this experiment suggests that in the metathesis of vinyl chlorides, the metallocarbene is formed first with the less hindered terminal olefin and the reaction proceeds via intermediate 286. Although intermediate 287 could also undergo the RCM with formation of the observed product, and its formation cannot be ruled out based on this experiment. This supposition is further supported by recent findings from the Johnson group, who discovered that vinyl halides that fail to participate in RCM reactions form stable Ru complexes 291 and 292 (Scheme 44). It is presumed that vinyl halides 288 react with Grubbs catalyst 252 to form the unstable Fisher-carbene complex 289. Carbene 289 is unable to catalyze olefin metathesis and undergoes rearrangement to give stable phosphoniomethylidene complex 291 and terminal carbide complex 292 which can be isolated from these reactions.82
Since the initial report of vinyl chloride RCM, vinyl fluorides\textsuperscript{85} and fluoroacrylates\textsuperscript{86} have been found to successfully undergo RCM. According to \textit{ab initio} calculations conducted by Fomine et al., the size of the halogen substituent is of major importance in determining the activation energy of these reactions.\textsuperscript{84} Since vinyl halide metathesis is believed to be a kinetically controlled process, steric issues override any electronic factors. Thus, vinyl bromides are presumed to be too sterically hindered to participate in RCM, whereas fluorides and chlorides react.

B. Regioselective conversion of vinyl chlorides to $\alpha$-chloroketones

Conversion of vinyl halides into $\alpha$-haloketones has previously been effected using $N$-chlorosuccinimide, $N$-bromosuccinimide, or $N$-iodosuccinimide in aqueous acetonitrile with a catalytic amount of acid at room temperature.\textsuperscript{87-90} Our group has developed a new protocol for converting vinyl halides into $\alpha$-haloketones under very mild conditions using
10% sodium hypochlorite or hypobromite solution in a 2:5 mixture of glacial acetic acid : acetone at 0 °C (Scheme 45).91 We believe this transformation proceeds by the following mechanism: chloronium or bromonium cation 294 is initially generated under the reaction conditions from vinyl halide 293 and hypochlorous acid. Attack by water on ion 295 produces halohydrin 296, which eliminates hydrogen halide to generate the α-haloketone 297.

Scheme 45

The scope of this transformation was demonstrated by the reactions depicted in Table 2-3. Cyclic as well as acyclic chloro- and bromo-alkenes could be used in this process. Amides, esters and imines were found to be compatible with the mild reaction conditions, allowing for the formation of the respective α-chloroketones in high yield.
Table 2-3. Examples of α-Haloketone Formation\textsuperscript{92}

<table>
<thead>
<tr>
<th>entry</th>
<th>vinyl halide</th>
<th>haloketone</th>
<th>isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cl</td>
<td>O-Cl</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>O-Br</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>O-Br</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>O-Br</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>MeO₂C₂MeCl</td>
<td>MeO₂C₂MeO-Cl</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>Cl</td>
<td>O-Cl</td>
<td>66</td>
</tr>
<tr>
<td>7</td>
<td>CO₂Et</td>
<td>CO₂EtCl</td>
<td>81</td>
</tr>
<tr>
<td>8</td>
<td>MeO₂C₂NHAcCl</td>
<td>MeO₂C₂NHAcCl</td>
<td>99</td>
</tr>
<tr>
<td>9</td>
<td>Cl</td>
<td>O-Cl</td>
<td>52</td>
</tr>
</tbody>
</table>

Interestingly when α-bromostyrene (298) is exposed to sodium hypochlorite under the standard reaction conditions a 1:1 mixture of α-chloroacetophenone (303) and α-bromoacetophenone (304) results (Scheme 46). Since the α-chloroacetophenone did not
convert to the bromoacetophenone when treated with NaBr, the possibility of a Finkelstein halogen exchange can be ruled out. The following proposed mechanism could explain the scrambling of halogens observed in this experiment. The initially formed chloronium ion 299 is believed to partially rearrange to the bromonium ion 300 prior to hydrolysis to halohydrins 301 and 302. In contrast, when subjected to the same conditions, α-chlorostyrene (305) leads exclusively to the α-bromoacetophenone (304), which may indicate that the bromonium species 300 does not rearrange to the chloronium ion 299, or that this process is slower than the subsequent hydrolysis.91

Scheme 46

When vinyl chloride malonate 306 was subjected to 3 equivalents of sodium hypochlorite under the standard reaction conditions, dichlorination product 307 was isolated as the major product along with small amounts of trichloroacetate adduct 308 and α-chloroketone 309 (Scheme 47). However, when α-monosubstituted malonate 310
was subjected to these same conditions, the $\alpha$-chloroketone 311 was observed as the major product. Similar results were obtained with $\beta$-keto ester 313. This selectivity for conversion of vinyl chlorides into $\alpha$-chloroketones in the presence of a $\beta$-dicarbonyl functionality is of consequence in the new methodology described in this thesis (*vide infra*).

Scheme 47

It should also be noted, that Pace et al. have very recently reported on the use of calcium hypochlorite instead of NaOCl resulting in higher yields for conversion of vinyl chlorides to $\alpha$-chloroketones in select cases.93
Intramolecular Michael Reactions of VinylNitroso Compounds

Introduction

Prior to the work described in this thesis no examples had been reported of intramolecular Michael additions to vinylnitroso compounds. One possible reason for the absence of any such cases was the lack of efficient methods to synthesize suitable precursors for this process. Recognizing that by combining the two methods recently developed in our group (vide supra), we would be able to readily access the requisite precursors, and thereby explore this type of process we began this study. In the course of our investigation we established that a vinylnitroso species 317, generated from the corresponding α-chlorosilyl-oximes 316 using fluoride ion, interacts with a tethered nucleophile in a 1,4-manner producing a variety of carbocyclic and heterocyclic products 318 (Scheme 48).

Scheme 48

![Scheme 48](image)

Initial Feasibility Studies

The simple model system 319 depicted in Scheme 49 was first investigated to test the feasibility of the intramolecular Michael process leading to formation of piperidine 321 proceeding via vinylnitroso intermediate 320. A malonate anion was chosen as the
carbon nucleophile as such enolates are well documented as effective participants in many high yielding intermolecular conjugate additions to nitrosoalkenes (Cf. Scheme 32, Chapter 1).

Scheme 49

Our synthesis of the malonate substrate 319 began with ethyl phenylacetate (324), which was alkylated with 2-chloro-3-iodopropene (323), synthesized from commercially available 2,3-dichloropropene (322), to produce vinyl chloride 325 in high yield (Scheme 50). Reduction of ester 325 using lithium aluminum hydride produced the desired ene alcohol 326 in a moderate yield.

Scheme 50

Alcohol 326 was next converted to mesylate 327 by treatment with mesyl chloride (Scheme 51). Alkylation of sodio diethyl malonate with this mesylate proved to be a
poor reaction. Thus, 327 was converted to iodide 328 by Finkelstein exchange in high yield. Alkylation of diethyl malonate with this iodide using sodium hydride as base gave the desired malonate 329, which was isolated only in moderate yield due to difficulties in separating it from the corresponding dialkylation product 330, which exhibits similar chromatographic polarity.

Scheme 51

Subjection of chloroalkene 329 to our α-choroketone formation conditions (NaOCl, HOAc, acetone, 0 °C) resulted in formation of 331 but only in poor yield.91 Although we had previously found that monoalkyl malonates are not easily halogenated by this procedure at the α-position (Cf. Scheme 8), α-chlorinated by-product 332 was the major product observed under the various reaction conditions shown in Table 2-4. This result is reflective of the substrate specific nature of the α-chloroketone formation process. The highest yield of the desired α-chloroketone 329 was obtained using the originally reported conditions (entry 1).91 Increasing the temperature and the reaction time resulted in lower yields of α-chloroketone 331 (entries 2 and 3). Using N-chlorosuccinimide87-90 also failed to give 331 in acceptable yield (entries 4 and 5).
Table 2-4. \(\alpha\)-Chloroketone Formation from Vinyl Chloride \(\text{329}\)

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>reagent</th>
<th>solvent</th>
<th>isolated yield (331, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0.25-2</td>
<td>NaOCl/HOAc</td>
<td>Me(_2)CO</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>0-25</td>
<td>1</td>
<td>NaOCl/HOAc</td>
<td>Me(_2)CO</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>8</td>
<td>NaOCl/HOAc</td>
<td>Me(_2)CO</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>0-25</td>
<td>1-6</td>
<td>NCS</td>
<td>MeCN :water</td>
<td>&lt;10</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>0.5-6</td>
<td>NCS</td>
<td>MeCN :water</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

We anticipated that using a sufficiently sterically encumbered malonate ester might suppress the undesired \(\alpha\)-chlorination process. Thus, the bulkier diisopropyl, and

Table 2-5. \(\alpha\)-Chloroketone Optimization Study

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R = OEt</th>
<th>33% :</th>
<th>26% :</th>
<th>22% :</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R = i-Pr</td>
<td>28%</td>
<td>30%</td>
<td>27%</td>
</tr>
<tr>
<td>2</td>
<td>R = O-t-Bu</td>
<td>19%</td>
<td>57%</td>
<td>20%</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
di-tert-butyl substrates 2 and 3 were synthesized using the same route as for 329 (Table 2-5). In all cases, a mixture of $\alpha$-chloroketone 334 and $\alpha$-chlorinated product 335 was obtained. Attempts to separate the undesired product from the $\alpha$-chloroketone via silica gel chromatography proved to be difficult.

However, it was possible to convert a mixture of ethyl ester products 331 and 332 to the oxime 336, and $O$-TBS-protected oxime 319 in low to moderate overall yield based upon starting chloroalkene 329, thereby providing enough material to test the key cyclization step (Scheme 52). The oximes 319 and 336 appear to be about 1:1 mixtures of geometrical isomers, but separation was not done since Denmark has shown that oxime geometry has little or no effect on nitrosoalkene formation.37

Scheme 52

When oxime 336 was treated with CsCO$_3$ in acetonitrile at ambient temperature no cyclization product 321 was observed. Therefore, the pivotal cyclization was attempted with silyl-oxime 319 under the conditions shown in Table 2-6. We believed it
would be prudent to form the sodium salt of the malonate prior to generating the short lived nitrosoalkene species. Therefore, we initially used 1 equiv. of sodium hydride to deprotonate the malonate 319 (entry 1). However, subsequent addition of 1 equiv. of TBAF to generate the vinylnitroso species 320 did not result in the cyclization product 321. We envisioned that TBAF might serve a dual function, acting both as base to deprotonate the malonate and as a fluoride source. Thus 319 was treated with an excess of TBAF (entry 2), which successfully formed the desired cyclization product 321, albeit in a low yield. It was eventually found that optimal conditions for the cyclization were to treat compound 319 with 2.2 equiv. of TBAF in acetonitrile at 0 °C, producing the desired cyclohexanone oxime 321 in 75% yield as a single stereoisomer of unknown geometry. The oxime 321 was then converted to ketone 337 in moderate (unoptimized) yield with titanium trichloride for further characterization purposes.94

<table>
<thead>
<tr>
<th>entry</th>
<th>temp (°C)</th>
<th>time (min)</th>
<th>reagents</th>
<th>solvent</th>
<th>isolated yield (74, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>10</td>
<td>1) NaH,</td>
<td>THF</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2) TBAF (1eq)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>10</td>
<td>TBAF (excess)</td>
<td>MeCN</td>
<td>low</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>10</td>
<td>TBAF (2.2 eq)</td>
<td>MeCN</td>
<td>75</td>
</tr>
</tbody>
</table>
Synthesis of bicyclic systems

*Synthesis of a bicyclo[2.2.2]octane system*

With the viability of an intramolecular Michael cyclization of a nitrosoalkene established, we now turned our attention to efficient construction of more complex bridged and fused ring systems. The initial research focused on the preparation of bicyclo[2.2.2]octane system 340 from 338 via vinylnitroso species 339 (Scheme 53).

Scheme 53

For preparation of the necessary cyclization precursor 338, commercially available methyl 5-hexenoate (341) was alkylated with 2-chloro-3-iodopropene (323) to afford diene 342 in high yield (Scheme 54). RCM reaction of 342 catalyzed by the Grubbs 2nd generation catalyst produced the desired cyclic chloroalkene 343 in moderate yield, which did not improve with the more reactive Hoveyda-Grubbs catalyst. We believe that the volatility of this vinyl chloride 343 is partially responsible for the mediocre yield in the RCM reaction. Ester 343 was then converted to iodide 346 in high yield over three steps via alcohol 344 and mesylate 345. Substrates 344, 345, 346 are
also highly volatile and difficult to handle. Analogous to the simple iodide 328 (Cf. Scheme 51), dialkylation was a problem in coupling of the iodide 346 with diethyl malonate using sodium hydride in DMF. However, we were able to suppress dialkylation of 347 almost completely by employing the sterically bulky Verkade base\textsuperscript{92} for deprotonation of the malonate, thereby forming 347 in good yield.

Scheme 54

It was therefore deemed necessary to modify the route and to move the RCM step to a later stage in the sequence in light of the volatility concerns observed with substrates 343-346 (Scheme 55). Thus, ester 342 was first converted to the acyclic iodide 350 via alcohol 348 and mesylate 349, which could then be coupled with diethyl malonate using the Verkade base, to give RCM precursor 351. We found that treatment of diene 351 with the Grubbs 2\textsuperscript{nd} generation catalyst then produced cyclohexene 347 in good yield, without the volatility problems associated with the compounds in the initial route.
Treatment of vinyl chloride 347 with sodium hypochlorite under the standard conditions gave the desired α-chloroketone 353 in 47% yield (67% based on recovered starting material) accompanied by side product 352 (20%), presumably formed via intermediates 354 and 355 (Scheme 56). Both the chloroketone 353 and the byproduct 352 were formed as about 2:1 mixtures of diastereomers. Formation of the silyloxime 338 from 353 proceeded as anticipated, producing the desired product in high yield. Spectral data interpretation of 338 was further complicated by the complex mixture of the newly formed oxime isomers. However, as it has been shown by Denmark neither the chloride atom disposition nor the geometry of the oxime have any influence on the rate of nitrosoalkene formation. Thus, formation of an inseparable diastereomeric mixture in this case is inconsequential to the outcome of the pivotal cyclization step. Moreover this stereochemistry is destroyed in the process of nitrosoalkene formation.
With the cyclization precursor silyloxime 338 in hand, we proceeded to explore the key cyclization step. However, the cyclization conditions optimized for the monocyclic system (Cf. Table 2-6) (i.e. 2.2 equiv. of TBAF) failed to give the desired cyclization product 340. Thus, the various conditions shown in Table 2-7 were examined. It was found best to first deprotonate the malonate 338 with sodium hexamethyldisilazide in THF at low temperature prior to generating the transient nitrosoalkene species. This base avoided the problems encountered when using sodium hydride in the earlier study (Table 4-3, entry 1), namely poor solubility and difficulties associated with accurately measuring small amounts of the reagent. Subsequent addition
of tetrabutylammonium fluoride to the preformed sodium salt of malonate 338 at -78 °C produced the cyclization product 340, albeit in low yield in the first experiment (entry 1). It was eventually determined that temperature dramatically affects the reaction. Optimal conditions were found when the reaction was warmed from -78 °C to ambient temperature over three hours, affording the desired bicyclo[2.2.2]octane 340 in 74% yield (entry 3). Quenching the reaction with aqueous ammonium chloride at 0 °C resulted in low yields. Fluoride sources other than TBAF were also explored, but did not produce 340 in higher yields (entries 4-6). Product 340 appears to be a single oxime isomer as observed by NMR, but its configuration has not been unequivocally established.

Table 2-7. Bridged System Cyclization Optimization

<table>
<thead>
<tr>
<th>entry</th>
<th>reagent</th>
<th>temperature (°C)</th>
<th>time (h)</th>
<th>isolated yield (%, 340)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1) NaHMDS 2) TBAF</td>
<td>-78</td>
<td>4</td>
<td>&lt; 10%</td>
</tr>
<tr>
<td>2</td>
<td>1) NaHMDS 2) TBAF</td>
<td>-78</td>
<td>3.5</td>
<td>18%</td>
</tr>
<tr>
<td>3</td>
<td>1) NaHMDS 2) TBAF</td>
<td>-78</td>
<td>3</td>
<td>74%</td>
</tr>
<tr>
<td>4</td>
<td>1) NaHMDS 2) HF (2 equiv.)</td>
<td>-78 - rt</td>
<td>3</td>
<td>37%</td>
</tr>
<tr>
<td>5</td>
<td>1) NaHMDS 2) CsF (2 equiv.)</td>
<td>78 - rt</td>
<td>3</td>
<td>53%</td>
</tr>
<tr>
<td>6</td>
<td>1) KHMDS 2) CsF (2 equiv.)</td>
<td>-78 - rt</td>
<td>3</td>
<td>54%</td>
</tr>
</tbody>
</table>
Control experiments to rule out the possibility that 340 is formed by a direct S_{N2} process from α-chloro O-TBS oxime 338, were carried out on substrates 338 and 353 (Scheme 57). Treatment of silyloxime 338 with NaHMDS at -78 °C, followed by warming to room temperature in the absence of a fluoride source did not produce any cyclization product 356. In this experiment, only starting material 338 was recovered, thereby lending support to the intermediacy of a nitrosoalkene in the reaction in Table 4-4.

Scheme 57

We have also demonstrated that bicyclic system 357 can not be accessed directly from α-chloroketone 353 by simple S_{N2} displacement of the chloride. Thus, α-chloroketone 353 was treated with NaHMDS and allowed to warm to ambient temperature, but no cyclization product 357 was formed.
Encouraged by these results, we continued with the cyclization of an α-chlorosilyl-oxime system regioisomeric to 338, leading to a bicyclo[3.2.1]octane system 371 (Scheme 58). To prepare the required substrate, alcohol 358 was first synthesized in one step from 2,2-dichloropropene (322) and formaldehyde using Oda’s protocol. We believe that the high volatility of this compound is responsible for the low yield observed.

Alcohol 358 was next converted to tosylate 359, which did not undergo efficient alkylation with allyl malonate. Therefore, tosylate 359 was converted to the iodide 360 in good yield under Finkelstein conditions. Diethyl allyl malonate (361) was first deprotonated using sodium hydride and then reacted with iodide 360 to give malonate 362 in acceptable yield. Krapcho decarboxylation of malonate 362 then produced monoester 363. Ester 363 was converted to iodide 366 via alcohol 364 and mesylate 365. Alkylation of diethyl malonate using iodide 366 produced diene 367. Grubbs 2nd generation catalyst promoted RCM of diene 367 to give cyclohexene 368 in good yield.

α-Chloroketone 369 was obtained as a 2:1 mixture of diastereomers in moderate yield when vinyl chloride 368 was subjected to our standard α-chloroketone formation conditions (NaOCl, AcOH, acetone, 0 °C). Formation of the product 369 was accompanied by a series of unidentifiable side products. The nitrosoalkene precursor, silyl-oxime 370, was generated from α-chloroketone 369 using TBS-hydroxylamine producing a complex mixture of diastereomers and oxime geometric isomers. When subjected to cyclization conditions used for substrate 338, silyloxime 370 was converted to bicyclo[3.2.1]oxime diester 371 in nearly quantitative yield. This product is a single
stereoisomer with the \((E)\)-oxime configuration, as determined by X-ray analysis (Figure 2-2).

Scheme 58
Although the oxime functionality in compounds like 371 has potential use in a variety of reactions (eg. Beckmann rearrangement, reduction, etc), one useful Scheme 59
transformation is the conversion to the corresponding ketone (Scheme 59). An optimization study was performed using camphor oxime (372) as a model for deoximation. In this case the titanium trichloride procedure failed to produce any of the desired ketone 373. However, conversion of 372 to 373 could be effected using Dess-Martin periodinane. These conditions were successfully used for the bicyclo[3.2.1]octane system 371, and the desired ketone 374 was obtained in moderate yield.

*Synthesis of additional bridged systems*

Attempted formation of a heteroatom-substituted bicyclo[2.2.2]octane system

We next embarked on a synthesis of a bicyclo[2.2.2]octane derivative containing a ring oxygen, namely compound 378 (Scheme 60). Known aldehyde 375 was synthesized in two steps from diethyl malonate, and alkylation of 375 with 2,3-dichloropropene (322) using Oda’s protocol produced homoallylic alcohol 376.

Scheme 60
Next, a series of unsuccessful attempts at converting alcohol 376 to the ether substrate 379 was made (Scheme 61). Treatment of alcohol 376 with allyl bromide using two equivalents of sodium hydride resulted in the formation of lactone 381 instead of the desired ether 379. It was thought that using silver (I) oxide as the base might alleviate this lactonization problem. Unfortunately, lactone formation was again observed when alcohol 376 was treated with allyl bromide and silver (I) oxide in the dark. Also unsuccessful was an attempt to displace tosylate 380 with the sodium alkoxide of allyl alcohol to yield the desired ether 379. In view of these failures, this route was abandoned.

Scheme 61

Bicyclo[3.2.2]nonane and bicyclo[2.2.1]heptane systems

In order to extend the scope of this cyclization methodology, two more examples were explored by Kumar in our group, namely bicyclo[3.2.2]nonane 386 and
bicyclo[2.2.1]heptane 391. For the bicyclo[3.2.2]nonane 386, cyclization precursor O-silyl-oxime 385 was obtained in high overall yield from malonate 382 via chloroalkene 383 and α-chloroketone 384 using the methodology previously discussed (Scheme 62). Upon generation of the vinylnitroso species from 385 the desired cyclization gave bicyclo[3.2.2]nonane 386 in 53% yield. It should also be noted that product 386 was obtained as a 5:1 mixture of E/Z oxime geometric isomers.

Scheme 62

Bicyclo[2.2.1]heptane system 391 was also examined by Kumar (Scheme 63). Malonate 387 was efficiently converted to the silyloxime 390 in high overall yield via compounds 388 and 389 using the established methodology. This substrate cyclized to form the desired bicyclo[2.2.1]heptane 391 in 70% yield as a single oxime isomer.
Kumar also briefly explored the feasibility of employing carbon nucleophiles other than malonates in these cyclizations (Scheme 64). In order to obtain the monoester cyclization precursor 394, diester 388 was decarboxylated to produce monoester 392, which was converted to O-silyl-oxime 394 via chloroketone 393. The resulting silyl-
oxime 394 was first enolized with potassium hexamethyldisilazide, and then treated with TBAF, to give a mixture of three [2.2.1]bicyclic oxime esters 395, 396 and 397 (c.a. 10:7:8) in high total yield. Isomer 396 can be isolated in pure form by chromatography, but 395 and 397 were obtained as a mixture.

*Synthesis of a fused ring system*

Synthesis of the fused heterocyclic ring system 409 has also been explored (Scheme 65). Toward this end, known allyl alcohol ester 400 was synthesized via base promoted condensation of EtOAc and acrolein.99 Next, alkylation of the alcohol 400 using silver (I) oxide and 2-chloro-3-iodopropene (323) afforded the desired ether 401 in good yield.

Scheme 65

Ester 401 was further subjected to our standard methodology to produce the cyclization precursor 408 (Scheme 66). Thus, alcohol 402 was obtained from ester 401 in high yield by lithium aluminum hydride reduction. Mesylation of 402 to 403 followed by Finkelstein iodination afforded iodide 404. Alkylation of diethyl malonate using iodide 404 and Verkade’s base produced malonate 405, which underwent RCM catalyzed by Grubbs 2nd generation catalyst to afford 406. Elevated temperature was necessary to effect this RCM. Unlike the previous substrates, cyclization product 406 did not form
from 405 either at 65 °C in benzene, or at 95 °C in toluene. However, RCM product 406 could be isolated in moderate yield by refluxing the reaction in toluene for 3 days. Some cross metathesis by-product was also isolated from this reaction.

α-Chloroketone formation from chloroalkene 406 under our established reaction conditions (NaOCl, AcOH, acetone, 0 °C, 0.5 h) resulted in formation of the desired α-chloroketone as a mixture of diastereomers (~2:1 by 1H NMR), accompanied by several unidentifiable by-products. Conversion of the α-chloroketone 407 to corresponding O-silyl-oxime produced a complex mixture of stereoisomeric products 408. The fused bicyclo[5.5]oxime 409 was formed in 95% yield as a single oxime isomer using the Scheme 66.
optimized NaHMDS/TBAF procedure. It should be noted that although the stereochemistry of 409 has not been unequivocally established, one might reasonably assume that this compound has the cis-fused ring system shown due to strain factors.

*Use of nitrogen nucleophiles in intramolecular Michael cyclizations of nitrosoalkenes*

After our success with the carbon nucleophiles in intramolecular Michael cyclizations of nitrosoalkenes, we focused our attention on the possibility of employing nitrogen nucleophiles in these transformations. Initial studies were concentrated on the simple system depicted in Scheme 67. Namely, we were interested in exploring the formation of piperidine 412 from O-silyloxime 410 via vinylnitroso species 411.

Scheme 67

For preparation of the necessary precursor, mesylate 327 was treated with sodium azide to give azide 413 in good yield (Scheme 68). Staudinger reduction 100 of the azide generated the amine, which was converted immediately to sulfonamide 414 without purification. A range of conditions for converting chloroalkene 414 to the respective α-chloroketone 416 was surveyed. However, it was possible to isolate the desired α-chloroketone 416 in only 10% yield after careful purification by column chromatography.
N-Chlorination of the sulfonamide to afford 415 was the major side reaction under most conditions attempted. The α-chloroketone 416 was then converted to the O-silyl-oxime 410 using O-TBS hydroxylamine.

Scheme 68

Silyloxime 410 was used for the cyclization studies shown in Table 2-8. We initially believed that deprotonation of the sulfonamide prior to generating of the reactive nitrosoalkene species would be necessary. Thus, sodium hydride was first used to deprotonate sulfonamide 410, but subsequent addition of one equivalent of TBAF did not lead to formation of the desired product 412 (entry 1). It was anticipated that TBAF could simultaneously function as base and also provide the fluoride ion necessary for nitrosoalkene generation. However, treatment of oxime 410 with an excess of TBAF at 0 °C in dry acetonitrile produced only a small amount of cyclized piperidine 412 (entry 2). After some experimentation, 2.2 equiv. of TBAF was found to produce the desired piperidine 412 from 410 in 88% yield as a mixture of E/Z oxime isomers (c.a. 2:1 by 1H-NMR). For characterization purposes the product 412 was converted to ketone 417 using titanium trichloride and ammonium acetate in dioxane.
Table 2-8. Nitrogen Nucleophile Cyclization

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>reagent</th>
<th>temperature (°C)</th>
<th>time (min)</th>
<th>isolated yield (% 412)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>1) NaH, 2) TBAF(1eq)</td>
<td>0</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>MeCN</td>
<td>TBAF excess</td>
<td>0</td>
<td>10</td>
<td>low</td>
</tr>
<tr>
<td>3</td>
<td>MeCN</td>
<td>TBAF(3 eq.)</td>
<td>0</td>
<td>50</td>
<td>low</td>
</tr>
<tr>
<td>4</td>
<td>MeCN</td>
<td>TBAF(2.2 eq)</td>
<td>0</td>
<td>10</td>
<td>88</td>
</tr>
</tbody>
</table>

With the difficulties encountered in the α-chloroketone formation step with sulfonamide 414, a different amine protecting group was examined in an attempt to improve the yield. It was anticipated that a group such as N-benzoyl might be less susceptible to N-chlorination. Thus, vinyl chloride amide 418, prepared from azide 413, upon halogenation with sodium hypochlorite gave the desired α-chloroketone 418 in 50% yield along with some of the corresponding N-chloroamide (Scheme 69). Oximation of 419 proceeded to give O-silyl-oxime 420. However, the cyclization conditions optimized for cyclization of sulfonamide 420 to piperidine 421 failed to produce any of the desired oxime 421 from this substrate and only decomposition products were formed.
Having established the viability of sulfonamide nucleophiles in intramolecular Michael reactions of nitrosoalkenes we explored the possibility of forming bridged heterocyclic systems via this methodology (Scheme 70). For this purpose, previously synthesized mesylate 345 was treated with sodium azide to produce azide 422 in good yield. Staudinger reduction of 422 followed by tosylation produced sulfonamide 423 in moderate yield. Subjecting sulfonamide 423 to treatment with sodium hypochlorite and acetic acid in acetone at 0 °C produced the corresponding α-chloroketone as a mixture of diastereomers (2.5:1 by 1H NMR) in significantly higher yield than was observed for conversion of sulfonamide 414 to α-chloroketone 416. The increased reactivity of the more substituted, and therefore more electron rich, chloroalkene in 423 vs. the terminal vinyl chloride in 414 is probably responsible for the higher yield of the α-chloroketone product 424. Very little N-chlorination by-product (<10%) was observed in this case. α-
Chloroketone 424 was then treated with O-TBS hydroxylamine to obtain cyclization precursor 425 as a complex mixture of diastereomers and E/Z isomers. Exposing 425 to two equivalents of TBAF at 0 °C resulted in the desired azabicyclo[2.2.2]octane 426 as a mixture of oxime isomers (5.3:1 by 1H NMR) in unoptimized 34% yield.

Scheme 70

To further investigate nitrogen nucleophiles, a simplified method to access cyclization precursors to azabicyclo[3.2.1]octane system 433 was developed, and this procedure then was optimized by Wang in our group (Scheme 71). This route makes use of Diels-Alder chemistry to generate cyclic enol ethers such as 428 instead of the usual RCM, thereby allowing us to explore a different method of generating α-chloroketones. Lee et al. have previously described efficient formation of α-chloroketones from alkyl enol ethers under the action of NCS in the presence of sodium acetate at low temperatures.101 To this end, readily available dienol ether 427 was reacted with acrylonitrile to produce cyclic enol ether 428. The nitrile functionality in 428 was then reduced using lithium aluminum hydride and the resulting amine 429 was protected as
the corresponding sulfonamide 430. Difficulties associated with isolating the free amine are responsible for the low yield in this step. It should be noted that the free amine can be taken on to the next step without purification, thus increasing the overall yield. We were delighted to see that the subsequent formation of \( \alpha \)-chloroketone 431 from 430 proceeded in very high yield using NCS in the presence of sodium acetate at 0 °C. The desired cyclic \( \alpha \)-chloroketone 431 was obtained as an inseparable mixture of diastereomers and was next converted to the corresponding silyl oxime 432 using our established protocol in nearly quantitative yield. The pivotal cyclization was effected using 2.5 equivalents of TBAF in THF yielding the desired bridged bicyclic oxime 433 in excellent yield. The structure of 433 was confirmed to be a single stereoisomer by X-ray crystallography, and it was determined that similar to the other cyclization product (Cf. Figure 2-2) previously analyzed by X-ray, the oxime configuration is \( E \) as shown in Figure 2-3.

Scheme 71
The oxygen nucleophile cyclization precursor 435 was next prepared using chemistry similar to that described above (Scheme 72). Thus, previously synthesized alcohol vinyl chloride 344 was subjected to NaOCl/AcOH/acetone at 0 °C for 0.5 h, resulting in α-chloroketone 434 as a mixture of diastereomers (4.7:1 by 1H NMR). Treatment of 434 with O-TBS hydroxylamine produced the cyclization precursor 435 as a complex mixture of diastereomers and E/Z isomers. Treatment of 435 with NaHMDS followed by addition of TBAF at -78 °C resulted in the desired oxabicyclo[2.2.2]octane 436 in unoptimized 22% yield. Studies to extend the methodology to other nucleophiles and to improve the yields of products 426 and 436 are currently being investigated in the Weinreb group.
Conclusion

We have demonstrated that intramolecular conjugate additions of carbon and hetero nucleophiles to in situ-generated vinylnitroso compounds provide a novel approach to a wide array of highly functionalized bridged and fused ring systems. In the course of this study we have synthesized bicyclo [2.2.2]-octane 340, bicyclo[3.2.1]-octane 371, bicyclo[2.2.1]-heptane 391, and bicyclo[3.2.2]-nonane 386 ring systems. In addition, we have found that fused ring systems can be produced in good yield by this strategy, as exemplified by the [5.5]-compound 409. Aza- and oxabicyclo[2.2.2]octanes 426 and 436 have also been synthesized, as well as azabicyclo[3.2.1]octane 433. We are actively investigating the use of a broader range of carbanions, as well as hetero-nucleophiles, in these cyclizations, and have tried to apply this chemistry in the natural product synthesis described below.
II. Studies Directed Towards a Total Synthesis of Stemofoline

Retrosynthesis of Stemofoline (1)

Our interest in the stemofoline alkaloids was piqued by the recognition of the possibility of accessing the skeleton via an intramolecular Michael cyclization of a vinylnitroso compound (Scheme 73).\textsuperscript{102} Thus, it was our plan to utilize an intramolecular endocyclic Michael reaction of a vinylnitroso species with an $\beta$-ketoester enolate (as shown in intermediate 438) in a new approach to the caged tricyclic stemofoline skeleton. It was deemed prudent to conduct the initial studies on the racemic variant as shown although it should be possible to easily modify the route to effect an enantioselective synthesis (\textit{vide infra}). It should also be noted that conversion of 438 to 437 is formally the umpolung version of Overman’s construct of converting 53 to 54 (Cf. Scheme 5, Chapter 1).\textsuperscript{16} The precursor for this key transformation, TBS-oxime 439, could be Scheme 73.
obtained from diene \textbf{440} via our RCM/α-chloroketone formation/oximation sequence \textit{(vide supra)}. The chlorodiene \textbf{440} in turn would be formed from \textbf{441}, a product of a rhodium catalyzed N-H insertion reaction of the α-diazo-β-ketoester intermediate \textbf{442}. A procedure for preparation of related pyrrolidines via such rhodium carbene insertions was recently developed by Davis et al.\textsuperscript{103-105} Also, we have recently developed a protocol for the synthesis of α-diazo-β-ketoesters from aldehydes allowing us to easily access these compounds \textit{(vide infra)}.\textsuperscript{106}

\textbf{Approaches to the synthesis of intermediate 439}

Our synthetic work initially focused on the formation of carboxylic acid \textbf{447} with the intention of later converting the carboxyl group to a variety of carbamates via a Curtius rearrangement (Scheme 74). For the initial experiments, it was decided to form the racemic ester \textbf{446}, but the absolute stereochemistry could eventually be set by use of an Evans chiral auxiliary in the alkylation step ( Cf. \textbf{445-446}) permitting the possibility of an enantioselective synthesis. To this end, methyl 4,4-dimethoxybutanoate (\textbf{445}) was synthesized from methyl methacrylate (\textbf{443}) in two steps using a modified literature procedure.\textsuperscript{107} Thus, treatment of methyl methacrylate (\textbf{443}) with nitromethane in the presence of sodium hydroxide produced 4-nitrobutanoate (\textbf{444}) in fair yield, and this compound was then converted to methyl 4,4-dimethoxybutanoate (\textbf{445}) via a modified Nef reaction. Methyl 4,4-dimethoxybutanoate (\textbf{445}) was then alkylated with 2-chloro-3-iodopropene (\textbf{323}) to give ester \textbf{446} in good yield, and the ester functionality was saponified to the corresponding carboxylic acid \textbf{447} in nearly quantitative yield. This
acid served as the universal starting material for preparation of carbanates $449$, $474$ and $482$, amide $452$ and amine $451$ (*vide infra*). The synthesis of $447$ has been optimized on a multi-gram scale, allowing us to efficiently form large amounts of this key intermediate.

Scheme 74

It was decided that the Boc carbamate $448$ would be best for the proposed metal carbenoid N-H insertion step, since Davis et al. had previously described N-Boc protected substrates as participants in such transformations (Scheme 75).$^{104}$ Thus, carboxylic acid $447$ was subjected to Curtius rearrangement conditions with diphenylphosphoryl azide and triethylamine in benzene at reflux, followed by addition of *tert*-butanol to the intermediate isocyanate. Surprisingly, formation of the desired carbamate $448$ was not observed, rather only unidentified by-products were produced. The solvent was then replaced with toluene in hopes that elevated temperatures would promote formation of the desired carbamate product. Unfortunately, under these conditions, or when *tert*-butanol itself was used as solvent, no carbamate $448$ was formed. However it was possible to isolate isocyanate $449$ in nearly quantitative yield when the reaction was
worked up immediately following the Curtius rearrangement step. The compound 449 was characterized via NMR and mass spectrometry. However, treatment of isocyanate 449 with tert-butanol in toluene for prolonged periods of time did not produce the Boc-derivative, resulting only in recovery of the isocyanate.

Therefore, the route was revised to initially form free amine 450 by treating isocyanate 449 with aqueous LiOH. The desired amine 450 could be isolated but with some difficulty. Unfortunately, when amine 450 was treated with Boc anhydride at various temperatures, the desired Boc carbamate could not be detected, presumably due to the steric bulk of the amine slowing the acylation. Faced with this impasse, the Boc carbamate synthesis was abandoned and our attention shifted to other protecting groups.

Scheme 75

Although rhodium catalyzed N-H insertions are most common with amides and carbamates, insertions into amine N-H bonds have also been described.\textsuperscript{108,109} Therefore, efforts were directed towards the synthesis of N-H insertion precursor 462 (Scheme 76).
Thus, the previously formed free amine 450 was treated with trifluoroacetic anhydride and TEA in CH₂Cl₂ producing the desired amide 451 in good yield. Unfortunately N-alkylation of this substrate with bromoalkene 452 could not be accomplished.¹¹⁰ Mitsunobu conditions¹¹¹ also failed to produce the requisite diene 454, thereby causing us to reverse the order of steps.

Scheme 76

Thus, amine 450 was first N-alkylated with bromoalkene 452 using potassium carbonate in toluene at reflux over 4 days, giving the desired chloro diene 455 in fair yield (Scheme 77). We were happy to find that diene 455 successfully reacted with trifluoroacetic anhydride at low temperature, producing the desired TFA amide 456 in Scheme 77.
nearly quantitative yield. Continuing with the synthesis, we explored a RCM reaction of diene 451 using Grubbs 2nd generation catalyst, which produced the desired chloroalkene 457 in moderate yield. The acetal functionality of 457 was next converted in high yield to aldehyde 458 with p-TsOH and H2O in acetone.

The synthesis of the intramolecular N-H insertion precursor 462 was explored first by homologating aldehyde 458 to the corresponding β-ketoester 460 in good yield with ethyl diazoacetate in the presence of SnCl2 (Scheme 78).112 An attempt to convert β-ketoester 460 to the α-diazo-β-ketoester 461 under Regitz diazo transfer conditions gave the desired product 461, albeit in low 30% yield.113 It was discovered that when amide 461 was treated with BaOH to remove the TFA protecting group, the ethyl ester also hydrolyzed yielding carboxylic acid 463 instead of the desired ester 462.

Scheme 78

In light of these issues, homologation of the aldehyde 458 to the tert-butyl α-diazoester 466 was examined as shown in Scheme 79. Hence, aldehyde 460 was coupled with tert-butyl diazoacetate (464) using stannous chloride as catalyst to give 465, and the
$\beta$-ketoester was subjected to Regitz diazo-transfer conditions to form $\alpha$-diazo-$\beta$-ketoester 466, again in a low yield.\textsuperscript{112}

Scheme 79

The low yield in this sequence prompted the investigation of a new protocol for homologating aldehydes to $\alpha$-diazo-$\beta$-keto esters as described in detail in Part III. Applying this methodology, we were able to obtain the requisite substrate 466 in better overall yield by reacting aldehyde 458 with lithio \textit{tert}-butyl diazoacetate (464) to give $\alpha$-diazo-$\beta$-hydroxyester 467, which was then oxidized using DMP (Dess–Martin periodinane) to give $\alpha$-diazo-$\beta$-ketoester 466 (Scheme 80). Barium hydroxide treatment of amide 466 facilitated TFA removal producing free amine 468 without loss of the \textit{tert}-butyl ester functionality of 467.

Scheme 80

With the cyclization precursor 469 in hand, we now investigated conditions for the key N-H insertion. However, when $\alpha$-diazo-$\beta$-ketoester 469 was treated with with
Rh$_2$(OAc)$_4$ in MeCN at rt, a complex mixture of products resulted (Table 2-10 entry 1). These compounds were not separable by column chromatography, although an ion corresponding to the mass of 470 could be detected by mass spectrometry. Changing the reaction solvents to CH$_2$Cl$_2$, dichloroethane and increasing reaction time (entries 2-5) failed to improve the result. Next, CD$_2$Cl$_2$ was used as solvent and the reaction was Table 2-10. Optimization of N-H Insertion.

<table>
<thead>
<tr>
<th>entry</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>catalyst</th>
<th>solvent</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23</td>
<td>0.2</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>MeCN</td>
<td>470 observed by MS</td>
</tr>
<tr>
<td>2</td>
<td>23</td>
<td>2</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>CH$_2$Cl$_2$</td>
<td>none</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>2</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>MeCN</td>
<td>none</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>1.5</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>dichloroethane</td>
<td>none</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>48</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>dichloroethane</td>
<td>470 observed by MS</td>
</tr>
<tr>
<td>6</td>
<td>23</td>
<td>3</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>CD$_2$Cl$_2$</td>
<td>&lt;5% of 470</td>
</tr>
<tr>
<td>7</td>
<td>45</td>
<td>4</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>CH$_2$Cl$_2$</td>
<td>471 observed by MS</td>
</tr>
<tr>
<td>8</td>
<td>45</td>
<td>12</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>CH$_2$Cl$_2$</td>
<td>2 mg of 471 from 10</td>
</tr>
<tr>
<td>9</td>
<td>45</td>
<td>12</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>MeOH</td>
<td>none</td>
</tr>
<tr>
<td>10</td>
<td>45</td>
<td>12</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>MeCN</td>
<td>&lt;5% of 471</td>
</tr>
<tr>
<td>11</td>
<td>45</td>
<td>24</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>CDCl$_3$</td>
<td>12% of 471</td>
</tr>
<tr>
<td>12</td>
<td>45</td>
<td>12</td>
<td>[Ru$_2$(p-cymene)]$_2$</td>
<td>CH$_2$Cl$_2$</td>
<td>none</td>
</tr>
</tbody>
</table>
monitored by $^1$H NMR spectroscopy (entry 6). Complete consumption of the starting material was observed within the first 10 minutes, and a complex mixture of compounds began to form. After 90 minutes a very small amount of a compound with a molecular weight corresponding to that of compound 470 was isolated with difficulty. However, the identity of this compound could not be established with certainty as this intermediate quickly decomposed at room temperature. The same molecular weight compound was noted when the reaction temperature was increased to 45 °C, and the reaction mixture was purified by repeated preparative TLC purifications using 10% methanol:CH$_2$Cl$_2$ as eluent (entry 7).

Since it appeared that the synthesis of 470 could not be effected via this sequence, we investigated a new route to this type of substrate (vide infra). In the course of the later study we became aware of the general instability of α-amino-β-keto esters as was previously demonstrated by Van den Branden et al.$^{114,115}$ It has been suggested that such compounds decompose via enolization pathways to a variety of by-products. The original route in Table 2-10 was revisited at a later time, and we thus reduced the ketone functionality of 470 immediately following the carbenoid N-H insertion in order to form the presumably more stable β-hydroxy ester 471 (entries 8-10).$^{116}$ The highest yield of the reduction product 471 was obtained when 160 mg of the starting material 469 were heated with the catalyst in deuterated chloroform for 12 h, followed by addition of sodium borohydride. However, the reaction yielded only 10 mg of the desired borohydride reduction product 471, a 12% yield over the two steps (entry 11). Since Deng et al. have recently reported that [Ru$_2$(p-cymene)]$_2$ also promote these types of N-H
insertions, we tested this catalyst in our system. However, no desired product could be detected even by mass spectrometry (entry 12).

We were able to explore a few more steps of the projected route using the 10 mg of hydroxy ester 471 isolated in entry 11 (Scheme 81). Therefore, the alcohol functionality of 471 was protected as the acetate 472 and α-chloroketone formation was attempted. Unfortunately, the yield for this step was very low resulting in less than 10% of the desired α-chloro ketone 473. In light of a higher yielding route leading to this same intermediate having become available (vide infra), exploration of this route was terminated and synthesis was continued via the other pathway.

Scheme 81

In order to more closely investigate the problematic carbenoid N-H insertion step, synthesis of a more easily accessible substrate was investigated (Scheme 82). Towards this end, starting carboxylic acid 447 was subjected to a Curtius rearrangement, followed by addition of benzyl alcohol to the intermediate isocyanate, producing the desired Cbz-protected amino acetal 474 in good yield. The acetal in 474 was then cleaved using p-TsOH and water in acetone affording aldehyde 475. The α-diazo-β-ketoester functionality was installed employing our two step method to form the N-H insertion precursor α-diazo-β-ketoester 477. Thus, treatment of aldehyde 475 with lithio ethyl
diazoacetate gave $\alpha$-diazo-$\beta$-hydroxyester 476, which was then oxidized with DMP to produce $\alpha$-diazo-$\beta$-ketoester 477 in high yield.

Scheme 82

We were delighted to see that the N-H insertion of 477 proceeded cleanly. Thus, we were able to obtain the desired pyrrolidine as a 478 in good yield by treating $\alpha$-diazo-$\beta$-ketoester 477 with Rh$_2$(OAc)$_4$ at rt in CH$_2$Cl$_2$ (Scheme 83). This compound was obtained as an inseparable mixture of diastereomers and exhibited a complex $^1$H-NMR spectrum, making characterization difficult. Similar issues with related $N$-acyl pyrrolidines had been encountered by Moyer et al., attributed to carbamate rotamers.\textsuperscript{117} In our system, complete coalescence of the rotamers was not achieved at 65 °C but the spectrum simplified sufficiently to allow proton assignments to be made. The structure of 478 was confirmed using the proton decoupled $^{13}$C spectrum. It should be noted, that keto-enol tautomerization in 478 may also contribute to the complicated NMR spectrum.
Scheme 83

With pyrrolidine 478 in hand, we attempted to remove the Cbz group in order to form free amine 479. Due to the presence of the alkene functionality in 478 deprotection conditions involving hydrogenation could not be employed. However, a host of alternative deprotection conditions shown in Scheme 84 gave no amine product 479. Rather, a by-product formed in the reactions which was identified as hydroxy pyrrole 480, resulting from the oxidation of 479. Realizing that preventing this oxidation process would be difficult, it was decided to reduce the ketone functionality of 479 prior to deprotection.

Scheme 84

Towards that end, pyrrolidine 478 was treated with sodium borohydride in methanol at 0 °C, producing $\beta$-hydroxy ester 481 in good yield (Scheme 85). When
compound 481 was subjected to deprotection conditions using TMS iodide in acetonitrile the desired stable free amino alcohol 482 could be obtained in fair yield as a complex mixture of stereoisomers.

Scheme 85

While the above study on the Cbz carbamate was in progress, the Teoc carbamate variant 484 was also synthesized using the same route (Scheme 86). Thus, carboxylic acid 447 was subjected to Curtius rearrangement conditions and TMS-ethanol was added to the intermediate isocyanate producing carbamate 483 in high yield. Two routes were investigated for converting aldehyde 484 to the corresponding $\alpha$-diazo-$\beta$-keto ester 487. Homologation of aldehyde 484 to $\beta$-keto ester 485 could be accomplished with either SnCl$_2$ or BF$_3$-etherate as catalyst to give the desired product in fair yield.$^{112}$ The Regitz diazo-transfer protocol on 485 gave the desired $\alpha$-diaza-$\beta$-ketoester 487 only in moderate yield. However our newly developed two step methodology was successfully executed with this substrate furnishing $\alpha$-diaza-$\beta$-ketoester 487 following DMP oxidation of the intermediate $\beta$-ketoester 486 in significantly better overall yield.
Scheme 86

The carbenoid N-H insertion of 487 proceeded uneventfully forming the desired pyrrolidine 488 in good yield (Scheme 87). The ketone functionality of 488 was reduced using sodium borohydride and the resulting β-hydroxyester was acylated with acetic anhydride and DMAP in pyridine to give pyrrolidine 489 as a complex mixture of diastereomers inseparable by column chromatography. Treatment of 489 with TBAF in THF then gave the desired free amine 490 in good yield. N-Alkylation of amine 490 with bromoalkene 454 in the presence of potassium carbonate produced the desired chlorodiene 491 in 40% yield. Diene 491 was next subjected to Grubbs 2nd generation catalyzed RCM to give the desired bicyclic chloroalkene 492 in nearly quantitative yield.
Finally, the acetate protecting group of 492 was removed. Because potassium carbonate was found to hydrolyze the ester functionality of 492, potassium phthalimide in methanol was used instead, yielding compound 493 as shown in Scheme 88, which is the ethyl ester equivalent of our previously synthesized substrate 471 (Cf. Table 2-10). Furthermore, this sequence constitutes a new higher yielding route to the properly functionalized pyrrolo[1,2α]azepine system required for our synthesis.

We next attempted to oxidize the alcohol functionality in substrate 493 to the corresponding β-ketoester 494 by DMP treatment. This oxidation resulted only in decomposition products, as did all attempts to generate α-chloroketone 495 by subjecting chloroalkene 493 to our standard conditions (NaOCl, HOAc in acetone at 0 °C). Attempts to convert acetate 492 to the corresponding α-chloroketone 496 also did not produce any of the desired product 496. Pace at al. have recently reported that unprotected amines can be problematic in oxidative hydrolysis, thereby preventing interfering with conversion of vinyl chlorides to α-chloroketones.93 One might
reasonably assume that the nitrogen atom present in substrates 492 and 493 may negatively influence α-chloroketone formation and oxidation here as well. Thus, it became clear that modified conditions for the oxidation of these substrates need to be explored.

Scheme 88

Conclusions and future work

Synthetic efforts towards a total synthesis of stemofoline (1) have been described. Two viable routes to key intermediate pyrrolo[1,2α]azepine systems 471 and 493 have been developed, with the route to 493 proceeding via the Teoc protected carbamate being the higher yielding. Although initial efforts to convert vinyl chloride substrates 492 and 493 to the corresponding α-chloroketones have failed, this transformation requires further investigation. Future studies will focus on converting intermediate amine 492 to its triflate salt 497, presumably more stable to hypochlorite and oxidation conditions. It
should then be possible to oxidize the alcohol functionality in salt 497 to obtain β-ketoester ammonium salt 498 (Scheme 89). Treatment of substrate 498 with NaOCl and acetic acid in acetone should produce the corresponding α-chloroketone 499, which in turn will be converted to the α-chlorooxime 500 and subjected to our Michael cyclization conditions producing tricyclic intermediate 501, possessing the core of stemofoline (1). We can also employ an Evans chiral auxiliary\textsuperscript{122} to generate enantiopure acid 447, and complete an enantioselective total synthesis of stemofoline (1).

Scheme 89
III. A Mild, Efficient Method for the Oxidation of α-Diazo-β-hydroxyesters to α-Diazo-β-ketoesters

Introduction

In the course of our synthesis of stemofoline, conversion of aldehyde 458 into α-diazo-β-ketoester 466 was necessary (vide supra). The most common methodology for this transformation involves first homologating an aldehyde like 458 to the corresponding β-ketoester 456, followed by a Regitz diazo transfer step to produce 466 (Scheme 90). Since this route proved to be low yielding in the case of 458, we developed an alternative protocol to achieve the required transformation.

Scheme 90

An alternative and potentially more attractive route was to initially add a lithiodiazoacetate to aldehyde 458 to produce an α-diazo-β-hydroxyester 467, which would be oxidized to the desired diazo compound 466. Although the addition of metallated diazoacetates to aldehydes is well precedented, examples of the oxidation of adducts 467 to the corresponding ketones 466 are rare. Moreover, the only reagents which have been used for alcohol oxidation in these few examples are limited to manganese dioxide, IBX, or barium permanganate. We were particularly
interested in effecting this sequence starting with aliphatic aldehydes such as 458, and also required a mild oxidant for the second step that is compatible with sensitive functionality. Since there was good literature precedent that α-diazo-β-ketoesters are stable toward Dess–Martin periodinane (DMP),\textsuperscript{135,136} we chose to investigate this reagent for oxidation of substrates like 467.

**Optimization of the reaction sequence using simple model substrates**

The conditions for this two step protocol were optimized using aldehydes 502 and 503 as models before applying it to the actual system 467 (Scheme 91). Using the experimental procedure of Padwa et al.,\textsuperscript{124} aldehydes 502 and 503 and ethyl lithiodiazoacetate were coupled, resulting in α-hydroxy-β-ketoesters 504 and 505 respectively. It was found to be particularly important to generate the lithiodiazoacetate species in the presence of the aldehyde at low temperature to attain optimum yields. Exposure of compounds 504 and 505 to Dess–Martin periodinane in methylene chloride at room temperature indeed led to the formation of the corresponding α-diazo-β-ketoesters 506 and 507 in good yields.

Scheme 91
Synthesis of additional systems

As listed in Table 2-9, α-diazo-β-hydroxyesters 508, 511, 514, 517, and 520 were prepared by Majireck and Li in our group from a variety of aliphatic, aromatic, and unsaturated aldehydes using the optimized protocol. The corresponding α-diazo-β-ketoesters 510, 513, 516, 519, and 522 were formed in good to moderate yield. An interesting observation was that addition of excess pyridine (~12 equiv) to the oxidation reaction resulted in higher product yields in a few cases. This improvement may be due to the pyridine minimizing decomposition of the diazo compounds by adventitious acid. We were also able to extend this method to two other intermediates arising from our synthetic studies, namely α-diazo-β-ketoesters 477 and 487, generated from aldehydes 475 and 484, respectively, in fair yield. Finally, we applied this methodology to form α-diazo-β-ketoester 466, which had originally sparked our interest in this transformation. Thus, Dess–Martin periodinane appears to be a general, superior oxidant for conversion of all types of α-diazo-β-hydroxyesters to α-diazo-β-ketoesters and thereby expands the scope of this two-step procedure for synthesizing the latter class of compounds.
Table 2-10. Preparation of Representative $\alpha$-Diazo-$\beta$-Ketoesters

<table>
<thead>
<tr>
<th>entry</th>
<th>aldehyde substrate</th>
<th>$\alpha$-diazo-$\beta$-hydroxyester</th>
<th>$\alpha$-diazo-$\beta$-ketoester</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>(yield, %)</td>
<td>(yield, %)</td>
</tr>
<tr>
<td>1</td>
<td>$\text{H}$</td>
<td>$\text{508}$</td>
<td></td>
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<td></td>
<td>$\text{O}$</td>
<td>$\text{509}$ (85%)</td>
<td>$\text{510}$ (88%)</td>
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<tr>
<td>2</td>
<td>$\text{O}$</td>
<td>$\text{511}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\text{N}$</td>
<td>$\text{512}$ (60%)</td>
<td>$\text{513}$ (98%)</td>
</tr>
<tr>
<td>3</td>
<td>$\text{O}$</td>
<td>$\text{514}$</td>
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</tr>
<tr>
<td></td>
<td>$\text{Cl}$</td>
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<td>$\text{516}$ (78%)</td>
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</tr>
<tr>
<td></td>
<td>$\text{Cl}$</td>
<td>$\text{518}$ (97%)</td>
<td>$\text{519}$ (98%)</td>
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<tr>
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<td>$\text{520}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\text{O}$</td>
<td>$\text{521}$ (78%)</td>
<td>$\text{522}$ (78%)</td>
</tr>
<tr>
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<td>$\text{475}$</td>
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<tr>
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<td>$\text{477}$ (94%)</td>
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<tr>
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<td>$\text{TeocHN}$</td>
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<td>$\text{458}$</td>
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<tr>
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<td>$\text{Cl}$</td>
<td>$\text{467}$ (40%)</td>
<td>$\text{466}$ (90%)</td>
</tr>
</tbody>
</table>

* a 12 equiv pyridine added to reaction mixture.
Conclusion:

Thus, we have developed novel methodology that produced the first examples of intramolecular 1,4-conjugate additions of carbon and hetero nucleophiles to vinylnitroso compounds. Combining several new methods developed in these labs, we have been able to access the requisite precursors. We have shown that a vinylnitroso species generated from the corresponding $\alpha$-chlorosilyl-oximes using fluoride ion, interacts with a tethered nucleophile in a 1,4-manner producing a variety of carbocyclic and heterocyclic products. Recognizing that this methodology might allow facile entry into the stemofoline alkaloid skeleton, we have investigated an asymmetric total synthesis of stemofoline (1). Two viable routes to key intermediate pyrrolo[1,2$\alpha$]azepine systems 471 and 493 have been developed, with the route to 493 proceeding via the Teoc protected carbamate being the higher yielding. Finally, we have developed new methodology for oxidation of $\alpha$-hydroxy-$\beta$-ketoesters to $\alpha$-diazo-$\beta$-ketoesters, which emerged in the course of the stemofoline (1) study thus helping us to generate some of the intermediates required to advance the alkaloid synthesis.
Chapter 3

Experimental Procedures

**General Methods.** All non-aqueous reactions were carried out under an inert atmosphere of argon in flame-dried glassware. Air and moisture sensitive liquid reagents were added *via* a dry syringe or cannula. All solvents and reagents were used as obtained from commercial sources without further purification. Flash column chromatography was performed using EM Science silica gel 60 (230-400 mesh). Analytical and preparative thin layer chromatography (TLC) were performed on EM Science silica gel 60 PF<sub>254</sub> plates. <sup>1</sup>H and <sup>13</sup>C NMR spectral data were recorded on Bruker DPX-300, CDPX-300, AMX-360, or DRX 400 MHz spectrometers. Infrared spectral data were obtained using a Perkin-Elmer 1600 FTIR. Low resolution mass spectral data (MS) were obtained at 50-70 eV by electron impact (EI).

2-Chloro-3-iodopropene (323). To a solution of sodium iodide (14.7 g, 97.7 mmol) in acetone (50 mL) was added 2,3-dichloropropene (6.0 g, 54.6 mmol), and the mixture was stirred at rt for 12 h. The solvent was removed under reduced pressure, keeping the aluminum foil covered flask at 0 °C (compound is light sensitive and volatile). The residue was purified by flash column chromatography on silica gel (pentane) to afford the title compound 323 as a clear oil (10.0 g, 92%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 5.53 (d, J = 1.7 Hz, 1H), 5.25 (d, J = 1.7 Hz, 1H), 4.02 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 139.7, 115.7, 7.7.
**4-Chloro-2-phenylpent-4-enoic Acid Ethyl Ester (325).** To a stirred solution of LDA (2.0 M in THF, 5.5 mL, 11.0 mmol) and DMPU (1.4 mL) in THF (15 mL) was added dropwise ethyl phenylacetate (324) (1.64 g, 10.0 mmol) in THF (15 mL) at -78 °C. The resulting mixture was stirred for 45 min at -78 °C, 2-chloro-3-iodopropene (323) (2.42 g, 12.0 mmol) was then added and the reaction mixture was warmed to 0 °C. After 3 h the reaction mixture was diluted with saturated aqueous NH₄Cl (10 mL) and EtOAc (10 mL). The organic layer was dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford the title compound 325 as a yellow oil (2.32 g, 88%). ¹H NMR (300 MHz, CDCl₃) δ 7.17-7.09 (m, 5H), 5.08 (s, 1H), 4.92 (s, 1H), 4.02-3.94 (m, 2H), 3.82 (t, J = 7.5 Hz, 2H), 2.98 (d, J = 5.8 Hz, 1H), 2.58 (q, J = 5.6 Hz, 1H), 1.05 (t, J = 7.2 Hz, 3H).

**4-Chloro-2-phenylpent-4-en-1-ol (326).** To a suspension of LiAlH₄ (150 mg, 3.95 mmol) in THF (20 mL) at 0 °C was added dropwise ester 325 (523 mg, 2.20 mmol) in ether (20 mL) over 10 min. The mixture was stirred for 12 h at rt, and diluted with EtOAc (20 mL). The reaction mixture was then poured into 1 M HCl solution and saturated aqueous NH₄Cl (10 mL) and EtOAc (10 mL) were added. The organic layer was dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10-20% EtOAc/hexanes gradient) to afford the title compound 326 as a clear oil (300 mg, 70%). ¹H NMR (300 MHz, CDCl₃) δ 7.37-7.01 (m, 5H), 5.13 (s, 1H), 5.05 (s, 1H),
114

3.82 (d, J = 4.3 Hz, 1H), 3.26 (m, 1H), 2.83 (q, J = 5.3 Hz, 1H), 2.10 (q, J = 5.7 Hz, 1H);

^1^C NMR (75 MHz, CDCl\textsubscript{3}) \( \delta \) 141.2, 140.8, 129.1, 128.4, 127.5, 114.6, 66.6, 46.0, 42.1;

LRMS-ES\textsuperscript{+} \textit{m/z} (relative intensity) 195.0 (MH\textsuperscript{+}, 45).

4-Chloro-2-phenylpent-4-en-1-ol Methanesulfonate (327). To a solution of alcohol \( 326 \) (5.00 g, 25.5 mmol) in dichloromethane (30 mL) were added triethylamine (3.75 mL, 25.5 mmol) and mesyl chloride (1.88 mL, 25.5 mmol) at 0 °C. The mixture was stirred for 30 min, warmed to rt and stirred for an additional 30 min. The organic phase was washed consecutively with brine (10 mL), 1 M aqueous KHSO\textsubscript{4} (10 mL), brine (10 mL), 5\% aqueous NaHCO\textsubscript{3} (10 mL), brine (10 mL), and dried over Na\textsubscript{2}SO\textsubscript{4} overnight. Saturated aqueous NH\textsubscript{4}Cl (10 mL) and EtOAc (10 mL) were added. The organic layer was dried over MgSO\textsubscript{4}, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10%-20% EtOAc/hexanes gradient) affording the title compound \( 327 \) as a clear oil (6.98 g, 90\%). \(^1\)H NMR (300 MHz, CDCl\textsubscript{3}) \( \delta \) 7.28-7.16 (m, 5H), 5.05 (d, \( J = 1.4 \) Hz, 2H), 4.31 (m, 2H), 3.39 (m, 1H), 2.80 (dd, \( J = 6.5, 14.5 \) Hz, 1H), 2.73 (dd, \( J = 8.2, 14.5 \) Hz, 1H), 2.70 (s, 3H), 2.63(dd, \( J = 8.2, 14.5 \) Hz, 1H); LRMS-ES\textsuperscript{+} \textit{m/z} (relative intensity) 297.0 (M+Na\textsuperscript{+}, 100).

(3-Chloro-1-iodomethylbut-3-enyl)benzene (328). To a solution of mesylate \( 327 \) (1.4 g, 5.2 mmol) in acetone (10 mL) was added sodium iodide (3.0 g, 20.0 mmol) and the mixture was stirred at 60 °C for 12 h. The solvent was
removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (pentane) to afford the title compound 328 as a clear oil (1.4 g, 89%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.43-7.10 (m, 5H), 5.06 (d, $J = 23.1$ Hz, 2H), 3.39-3.31 (m, 2H), 3.20-3.17 (m, 1H), 2.83 (dd, $J = 6.8$, 14.3 Hz, 1H), 2.58 (dd, $J = 7.9$, 14.3 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 141.8, 140.0, 129.0, 128.0, 128.7, 115.3, 45.5, 45.1, 12.8; LRMS-ES$^+$ m/z (relative intensity) 307.0 (MH$^+$, 100).

2-(4-Chloro-2-phenylpent-4-enyl)malonic Acid Diethyl Ester (329). To a solution of iodide 328 (100 mg, 0.33 mmol) and diethyl malonate (44 mg, 0.27 mmol) in DMF (1 mL) was added sodium hydride (12 mg, 0.50 mmol) and the reaction mixture was heated at 100 °C for 24 h. The solvent was removed under reduced pressure, the residue was redissolved in THF and filtered through a silica gel pad, which was washed with THF. The filtrate was evaporated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to afford the title compound 329 as a clear oil (52 mg, 56%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.23-7.07 (m, 5H), 5.14 (s, 1H), 5.05 (s, 1H), 4.15 (dd, $J = 9.5$, 19.0 Hz, 2 H), 4.02-3.95 (m, 2H), 3.04 (dd, $J = 6.3$, 13.8 Hz, 1 H), 3.01-2.83 (m, 1H), 2.56-2.53 (m, 2H), 2.29-2.20 (m, 1H), 2.08-2.03 (m, 1H), 1.21 (t, $J = 9.0$ Hz, 3H), 1.11 (t, $J = 7.1$ Hz, 3H); LRMS-ES$^+$ m/z (relative intensity) 339.1 (MH$^+$, 100).

2-(5-Chloro-4-oxo-2-phenylpentyl)malonic Acid Diethyl Ester (331).
Method 1: To a solution of vinyl chloride 329 (186 mg, 0.5 mmol) in acetone (3.3 mL) and glacial acetic acid (1.3 mL) at 0 °C was added dropwise via syringe aqueous sodium hypochlorite (0.47 mL of 10% solution, 0.55 mmol). The reaction mixture was stirred at 0 °C for 1 h and quenched by addition of aqueous saturated Na₂CO₃ solution. The mixture was then extracted with dichloromethane (20 mL x 2). The organic layers were combined, washed with brine (10 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford the title compound 331 (50 mg, 26%). ¹H NMR (400 MHz, CDCl₃) δ 7.26-6.93 (m, 5H), 4.16 (dd, J = 7.1, 14.3 Hz, 2H), 4.00-3.96 (m, 2H), 3.81 (dd, =15.4, 29.0 Hz, 2H), 3.2-3.1 (m, 1H), 3.02 (q, J = 5.0 Hz, 1H), 2.93-2.82 (m, 2H), 2.22-2.09 (m, 2H), 1.23-1.18 (m, 1H), 1.13-1.09 (m, 1H); LRMS-ES⁺ m/z (relative intensity) 355.1 (MH⁺, 40), 377.1 (M+Na⁺, 90).

Method 2: To a solution of vinyl chloride 329 (40 mg, 0.11 mmol) in a 1:1 acetonitrile/water mixture (2.3 mL) was added concentrated HCl (6 drops) and N-chlorosuccinimide (10 mg, 0.1 mmol). After 1 h the reaction mixture was diluted with saturated aqueous NH₄Cl (10 mL) and EtOAc (10 mL). The organic layer was dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford the title compound 331 (7 mg, 20%).
2-(5-Chloro-4-tert-butyldimethylsilyloxyimino-2-phenylpentyl)malonic Acid Diethyl Ester (319). To a solution of α-chloroketone 331 as a 1:1 mixture with the chlorination byproduct 332 (196 mg, 1:1 mixture, 0.26 mmol of 331) in dry chloroform (7.0 mL) were added 4Å molecular sieves (crushed), a catalytic amount of PPTS and O-(tert-butyldimethylsilyl)-hydroxylamine (80 mg, 0.54 mmol). The mixture was stirred at rt for 12 h and then was filtered through a pad of Celite. The pad was washed with chloroform. The total filtrate was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford the title compound 319 as a clear oil (81 mg, 63%). ¹H NMR (400 MHz, CDCl₃) δ 7.21-7.00 (m, 5H), 4.17-4.09 (m, 2H), 4.01-3.96 (m, 3H), 3.10-3.05 (m, 1H), 3.05-3.03 (m, 1H), 2.65 (d, J = 10.0 Hz, 2H), 2.35-2.10 (m, 2H), 1.19 (t, J = 9.5 Hz, 3H), 1.11 (t, J = 9.5 Hz, 3H), 0.80 (s, 9H), 0.00 (6H); ¹³C NMR (75 MHz, CDCl₃) δ 169.6, 157.8, 142.6, 129.1, 129.0, 128.5, 128.3, 128.2, 127.9, 127.6, 127.3, 61.7, 50.4, 40.9, 40.6, 39.5, 39.3, 36.0, 35.3, 26.4, 26.3, 18.4, 14.5, 14.3; LRMS-ES⁺ m/z (relative intensity) 484.2 (MH⁺, 100).

2-(5-Chloro-4-hydroxyimino-2-phenylpentyl)malonic Acid Diethyl Ester (336). To a solution of α-chloroketone 331 (70 mg, 0.2 mmol) in methanol (0.2 mL) at 0 °C were added sodium acetate (18 mg, 0.21 mmol) and hydroxylamine hydrochloride (8 mg, 0.10 mmol). After 1 h, the reaction mixture was poured into water (4 mL) and extracted with Et₂O (1 mL x 3). The combined organic layers were washed with water (4 mL x 2), brine (4 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified
by flash column chromatography on silica gel (10% EtOAc/hexanes) to produce the title compound 336 as a clear oil (8 mg, 11%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.26-7.10 (m, 5H), 4.14-4.12 (m, 2H), 4.02-3.97 (m, 2H), 3.75 (d, $J$ = 11.8, 1H), 3.46 (d, $J$ = 11.8, 1H), 3.09-3.03 (m, 1H), 2.95-2.57 (m, 1H), 2.25-2.14 (m, 1H), 1.22-1.17 (m, 3H), 1.14-1.10 (m, 3H); LRMS-ES$^+$ m/z (relative intensity) 370.1 (MH$^+$, 100).

3-Hydroxyimino-5-phenylcyclohexane-1,1-dicarboxylic Acid Diethyl Ester (321). To a solution of silyl oxime 319 (50 mg, 0.1 mmol) in acetonitrile (0.6 mL) at 0 °C was added dropwise TBAF (1 M in THF, 0.1 mL, 0.1 mmol). After stirring the mixture for 10 min at 0 °C, saturated NH$_4$Cl solution was added and the mixture was extracted with EtOAc (10 mL x 2). The combined organic layers were dried over MgSO$_4$. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to afford the title compound 321 as a clear oil (25 mg, 75%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.28-7.02 (m, 5H), 4.19-4.09 (m, 4H), 3.00-2.90 (m, 1H), 2.55-2.53 (m, 2H), 2.18-1.97 (m, 2H), 1.25-1.14 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.5, 170.5, 156.0, 144.1, 129.0, 127.2, 127.1, 127.0, 62.3, 62.1, 56.2, 55.9, 40.1, 38.7, 38.6, 38.4, 29.0, 14.4, 14.3; LRMS-ES$^+$ m/z (relative intensity) 334.1 (MH$^+$, 100).

3-Oxo-5-phenylcyclohexane-1,1-dicarboxylic Acid Diethyl Ester (337). To a solution of oxime 321 (20 mg, 0.06 mmol) and ammonium acetate (60 mg, 0.78 mmol) in dioxane (1 mL) was added TiCl$_3$ (0.93 M in H$_2$O, 0.15 mL, 0.14 mmol) gradually at rt. After 1 h the reaction mixture was extracted with ether (20 mL). The organic extract was washed with saturated
NaCl (10 mL), NaHCO₃ (10 mL) and water (3 mL), and dried over MgSO₄. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford the title compound **337** as a clear oil (7 mg, 40%). ¹H NMR (300 MHz, CDCl₃) δ 7.30-6.83 (m, 5H), 4.19-4.10 (m, 4H), 3.06-3.01 (m, 2H), 2.61-2.54 (m, 3H), 2.49-2.39 (m, 1H), 2.26-2.22 (m, 1H), 1.23-1.11 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 206.3, 170.7, 143.2, 129.2, 127.5, 126.9, 62.4, 56.8, 47.9, 45.3, 39.7, 39.6, 14.4, 14.3; HRMS-ES⁺ (C₁₈H₂₂O₅) calcd 318.1467 (MH⁺), found 319.1542.

**2-(2-Chloroallyl)-hex-5-enoic Acid Methyl Ester (342).** To a solution of LDA (2 M in THF, 10 mL, 20.0 mmol) and DMPU (2.8 mL, 21.8 mmol) in THF (15 mL) was added 5-hexenoic acid methyl ester (**341**, 2.00 g, 15.6 mmol) in THF (15 mL) dropwise at -78 °C. The mixture was stirred for 45 min at -78 °C. 2-Chloro-3-iodopropene (4.0 g, 19.8 mmol) was added, and the reaction mixture was allowed to warm to 0 °C over 3 h. Saturated aqueous NH₄Cl (30 mL) and EtOAc (50 mL) were added. The organic layer was dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford the title compound **342** as a yellow oil (2.52 g, 80%). ¹H NMR (400 MHz, CDCl₃) δ 5.65 (m, 1H), 5.12 (dd, J = 1.1, 8.9 Hz, 2H), 4.99-4.93 (m, 0.5H), 4.95-4.93 (m, 1H), 4.91-4.90 (m, 0.5H), 3.61 (s, 3H), 2.63-2.60 (m, 1H), 2.64 (dd, J = 8.3, 22.6 Hz, 2H), 2.38 (dd, J = 6.2, 14.3 Hz, 1H), 2.01-1.98 (m, 2H), 1.63-1.72 (m 1H), 1.59-1.61 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 175.5, 140.2, 137.7, 115.7, 114.6, 51.9, 43.1, 41.9, 31.6, 31.1.
3-Chlorocyclohex-3-enecarboxylic Acid Methyl Ester (343).

**Method 1:** A 100-mL two neck flask equipped with a magnetic stirring bar and a condenser was flame dried *in vacuo*. The vinyl chloride substrate 342 (50 mg, 0.25 mmol) in benzene (60 mL) was added and the solution was deaerated by bubbling argon through the mixture for 2 h. Second-generation Grubbs catalyst (20 mg, 0.03 mmol) in 2 mL of benzene was added and the argon bubbling was continued for an additional 30 min. The mixture was heated and stirred at 65 °C for 2-3 days until TLC showed the reaction was complete. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10% Et₂O/pentane) to afford the title compound 343 as a yellow oil (24 mg, 56%).

**Method 2:** A 100-mL two neck flask equipped with a magnetic stirring bar and a condenser was flame dried *in vacuo*. The vinyl chloride substrate 342 (50 mg, 0.25 mmol) in benzene (60 mL) was added and the solution was deaerated by bubbling argon through the mixture for 2 h. Second-generation Hoveyda-Grubbs catalyst (25 mg, 0.03 mmol) in 2 mL of benzene was added and the argon bubbling was continued for an additional 30 min. The mixture was heated and stirred at 65 °C for 1-2 days until TLC showed the reaction was complete. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (10% Et₂O/pentane) to afford the title compound 343 as a yellow oil (26 mg, 60%).

\[ ^1H \text{ NMR (400 MHz, CDCl}_3\] \( \delta \) 5.76-5.74 (m, 1H), 3.65 (s, 3H), 2.66-2.59 (m, 1H), 2.53-2.44 (m, 2H), 1.95-1.89 (m, 1H), 1.66-1.50 (m, 1H); \[ ^13C \text{ NMR (75 MHz, CDCl}_3\] \( \delta \) 174.8, 130.0, 124.2, 52.1, 40.3, 34.6, 25.2, 24.2.
3-Chlorocyclohex-3-enyl)methanol (344). To a suspension of LiAlH₄ (100 mg, 2.61 mmol) in THF (10 mL) at 0 °C was added dropwise ester 343 (250 mg, 1.45 mmol) in ether (10 mL) over 5 min. The mixture was stirred for 4 h at rt, and diluted with EtOAc (20 mL). The mixture was then poured into 1 M HCl solution (10 mL). Saturated aqueous NH₄Cl (10 mL) and EtOAc (10 mL) were added. The organic layer was dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10-30% EtOAc/hexanes gradient) to afford the title compound 344 as a clear oil (117 mg, 96%). ¹H NMR (400 MHz, CDCl₃) δ 5.88-5.83 (m, 1H), 5.59 (d, J = 6.2 Hz, 2H), 2.42-2.37 (m, 2H), 2.17-2.09 (m, 3H), 2.00-1.96 (m, 1H), 1.83-1.78 (m, 1H), 1.47 (br s, 1H), 1.34-1.21 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 129.8, 123.4, 65.7, 36.6, 34.6, 24.3, 23.0.

Methanesulfonic Acid 3-Chlorocyclohex-3-enylmethyl Ester (345). To a solution of alcohol 344 (145 mg, 1.00 mmol) in dichloromethane (4 mL) at 0 °C were added portionwise triethylamine (0.22 mL, 1.50 mmol) and mesyl chloride (74 μL, 1.00 mmol). The mixture was stirred at 0 °C for 30 min, and then at rt for 30 min. The organic phase was washed consecutively with brine (10 mL), 1 M aqueous KHSO₄ (10 mL), brine (10 mL), 5% aqueous NaHCO₃ (10 mL), brine (10 mL), and dried over Na₂SO₄ overnight. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10%-20% EtOAc/hexanes gradient) to afford the title compound 345 as a clear oil (211 mg, 94%). ¹H NMR (400 MHz, CDCl₃) δ 5.78-5.75 (m, 1H), 4.17-4.01 (m, 2H), 2.95 (s, 3H), 2.37-
2.33 (m, 1H), 2.17-2.07 (m, 4H), 1.76-1.71 (m, 1H), 1.33-0.98 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 130.3, 124.7, 72.9, 37.7, 35.4, 35.1, 25.2, 24.0; HRMS-ES [M + Na]$^+$ calcd for C$_8$H$_{13}$O$_3$NaSCl, 247.0172; found, 247.0170.

1-Chloro-5-iodomethylcyclohexene (346). To a solution of mesylate 345 (221 mg, 0.94 mmol) in acetone (4 mL) was added sodium iodide (543 mg, 3.76 mmol) and the mixture was stirred at 70 °C for 12 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (pentane) to afford the title compound 346 as a clear oil (240 mg, 94%). $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 5.72-5.70 (m, 1H), 3.15 (d, $J =$ 13.0 Hz, 2H), 2.12-2.06 (m, 3H), 1.81-1.75 (m, 2H), 1.31-1.22 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 129.2, 123.1, 38.2, 36.1, 27.1, 24.3, 11.7; HRMS-EI [M]$^+$ calcd for C$_7$H$_{10}$ClI, 255.9516; found, 255.9516.

2-(3-Chlorocyclohex-3-enylmethyl)-malonic Acid Diethyl Ester (347). Method 1: To a solution of iodide 346 (240 mg, 0.94 mmol) and diethyl malonate (150 mg, 0.94 mmol) and DMF (4 mL) was added sodium hydride (60% dispersion in mineral oil, 40 mg, 0.94 mmol), and the reaction mixture was heated at 70 °C for 24 h. The solvent was removed under reduced pressure, the residue was redissolved in THF, and the mixture was filtered through a silica gel pad, which was washed with THF. The combined filtrate was evaporated under reduced pressure and the
residue was purified by flash column chromatography on silica gel (5-10% EtOAc/hexanes gradient) to afford the title compound 347 as a yellow oil (161 mg, 56%).

Method 2: To a solution of diethyl malonate (72 mg, 0.45 mmol) in acetonitrile (4 mL) was added Verkade’s base (98 mg, 0.45 mmol), and the mixture was stirred for 10 min at rt. Iodide 346 (112 mg, 0.43 mmol) was added and the mixture was stirred for 4 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (5-30% ether/pentane gradient) to afford the title compound 347 as a yellow oil (80 mg, 63%). \( ^1 \text{H NMR} \) (400 MHz, CDCl\(_3\) \( \delta \) 5.72-5.70 (m, 1H), 4.18-4.08 (m, 4H), 2.31-2.26 (m, 1H), 2.09-1.80 (m, 5.5 H), 1.67-5.58 (m, 2.5H), 1.20 (t, \( J = 8.0 \text{ Hz}, 6\)H); \( ^{13} \text{C NMR} \) (75 MHz, CDCl\(_3\) \( \delta \) 167.6, 128.7, 122.5, 59.7, 47.8, 36.9, 32.8, 31.1, 25.4, 23.7, 12.3; HRMS-AP [M + H]\(^+\) calcd for C\(_{14}\)H\(_{22}\)O\(_4\)Cl, 289.1214; found, 289.1207.

2-(2-Chloroallyl)-hex-5-en-1-ol (348). To a suspension of LiAlH\(_4\) (1.5 g, 39.8 mmol) in THF (50 mL) at 0 °C was added dropwise ester 342 (4.50 g, 22.3 mmol) in ether (50 mL) over 10 min. The mixture was stirred for 12 h at rt, and diluted with EtOAc (20 mL). The mixture was then poured into 1 M HCl solution (30 mL) and saturated aqueous NH\(_4\)Cl (10 mL) and EtOAc (10 mL) were added. The organic layer was dried over MgSO\(_4\). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (10-30% EtOAc/hexanes gradient) to afford the title compound 348 as a clear oil (3.09 g, 95%). \( ^1 \text{H NMR} \) (300 MHz, CDCl\(_3\) \( \delta \) 5.81-5.68 (m, 1H), 5.13 (dd, \( J =0.9, 11.7 \text{ Hz}, 2\)H), 5.01-4.88 (m, 2H), 3.55 (t, \( J \)
= 4.3 Hz, 2H), 2.40 (dd, J = 7.5, 14.3 Hz, 1H), 2.25 (dd, J = 6.7, 14.2 Hz, 1H), 2.12-1.99 (m, 2H), 1.93-1.80 (m, 1H), 1.49-1.30 (m, 2H); 13C NMR (75 MHz, CDCl3) δ 141.9, 138.9, 115.2, 114.3, 64.5, 41.5, 37.9, 31.4, 29.8; HRMS-EI [M]⁺ calcd for C₉H₁₅ClO, 174.0811; found, 175.0815.

**Methanesulfonic Acid 2-(2-Chloroallyl)-hex-5-enyl Ester (349).**

To a solution of alcohol 348 (152 mg, 0.87 mmol) in dichloromethane (3 mL) at 0 °C was added portionwise triethylamine (117 µL, 0.79 mmol) and mesyl chloride (40 µL, 0.54 mmol). The mixture was stirred at 0 °C for 30 min, and then at rt for 30 min. The organic phase was washed consecutively with brine (10 mL), 1 M aqueous KHSO₄ (10 mL), brine (10 mL), 5% aqueous NaHCO₃ (10 mL), brine (10 mL), and dried over Na₂SO₄ overnight. The solvent was removed under reduced pressure to afford the title compound 349 as a clear oil which was used for the next step without further purification (206 mg, 94%). ¹H NMR (75 MHz, CDCl₃) δ 5.81-5.72 (m, 1H), 5.20-5.09 (m, 4H), 4.21-4.19 (m, 2H), 3.03 (s, 3H), 2.45-2.40 (m, 2H), 2.21-2.17 (m, 2H), 1.92-1.86 (m, 1H), 1.73-1.70 (m, 2H); 13C NMR (300 MHz, CDCl₃) δ 142.4, 135.2, 118.2, 113.1, 71.6, 37.6, 36.9, 36.6, 35.2, 28.2; HRMS-ES [M + Na]⁺ calcd for C₁₀H₁₇O₃SClNa, 275.0485; found, 275.0487.

**2-Chloro-4-iodomethylocta-1,7-diene (350).** To a solution of mesylate 349 (3.09 g, 12.30 mmol) in acetone (30 mL) was added sodium iodide (5.51 g, 36.70 mmol), and the mixture was stirred at 60 °C for 5 h. The solvent was then removed under reduced pressure and the residue was purified by
flash column chromatography (pentane) to afford the title compound 350 as a clear oil (3.29 g, 94%). $^1$H NMR (400 MHz, CDCl$_3$) δ 5.87-5.78 (m, 1H), 5.29 (dd, $J = 0.7$, 7.6 Hz, 2H), 5.10-5.00 (m, 2H), 3.50 (ddd, $J = 0.9$, 7.0, 14.1 Hz, 1H), 3.32 (ddd, $J = 3.7$, 10.1, 21.6 Hz, 2H), 2.14 (dd, $J = 21.8$, 25.1, 1H), 2.04 (dd, $J = 21.8$, 25.1, 1H), 1.46-1.49 (m, 4H), 1.22-1.21 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 140.4, 138.1, 115.7, 115.3, 44.6, 34.7, 33.4, 31.0, 15.6; HRMS-EI [M]$^+$ calcd for C$_9$H$_{14}$ClI, 283.9822; found, 283.9829.

$^2$-[2-(2-Chloroallyl)-hex-5-enyl]-malonic Acid Diethyl Ester (351). To a solution of iodide 350 (816 mg, 2.90 mmol) and diethyl malonate (486 mg, 3.04 mmol) in acetonitrile (50 mL) was added Verkade’s base (656 mg, 3.04 mmol), and the reaction mixture was stirred at rt for 24 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (5-20% EtOAc/hexanes gradient) to afford the title compound 351 as a clear oil (653 mg, 74%). $^1$H NMR (300 MHz, CDCl$_3$) δ 5.87-5.73 (m, 1H), 5.22 (d, $J = 16.2$ Hz, 2H), 5.08-4.97 (m, 2H), 4.22 (dd, $J = 7.1$, 14.2 Hz, 4H), 3.54-3.45 (m, 1H), 2.39-2.26 (m, 2H), 2.14-2.04 (m, 2H), 1.96-1.91 (m, 2H), 1.84-1.76 (m, 1H), 1.60 (s, 1H), 1.49-1.32 (m, 1H), 1.30 (t, $J = 5.6$ Hz, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 138.6, 115.2, 114.5, 61.8, 50.2, 44.0, 33.1, 32.6, 32.0, 30.6, 14.4; HRMS-ES [M + Na]$^+$ calcd for C$_{16}$H$_{25}$ClNaO$_4$, 339.1339; found, 339.1349.
2-(3-Chlorocyclohex-3-enylmethyl)-malonic Acid Diethyl Ester (347). A flame dried 50 mL two necked flask equipped with a condenser and a magnetic stirring bar was charged with ester 351 (100 mg, 0.32 mmol) and benzene (40 mL). The mixture was deaerated with argon for 1 h. Grubbs 2\textsuperscript{nd} generation catalyst (20 mg, 0.03 mmol) in benzene (10 mL) was added via syringe. The mixture was deaerated with argon for another 20 min and then heated at 65 °C for three days. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (2 - 5% ether/pentane gradient) to afford the title compound 347 as a yellow oil (67 mg, 74%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 5.72-5.70 (m, 1H), 4.18-4.08 (m, 4H), 2.31-2.26 (m, 1H), 2.09-1.80 (m, 5.5H), 1.67-5.58 (m, 2.5H), 1.20 (t, \(J = 8.0\) Hz, 6H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 167.6, 128.7, 122.5, 59.7, 47.8, 36.9, 32.8, 31.1, 25.4, 23.7, 12.3; HRMS-AP [M + H]\textsuperscript{+} calcd for C\textsubscript{14}H\textsubscript{22}O\textsubscript{4}Cl, 289.1207; found, 289.1214.

2-(4-Chloro-3-Oxocyclohexylmethyl)-malonic Acid Diethyl Ester (353). To a solution of ester 347 (280 mg, 0.97 mmol), acetone (3.39 mL), glacial acetic acid (1.60 mL) at 0 °C was added dropwise aqueous sodium hypochlorite (638 µL of 10% solution, 0.97 mmol) via syringe. The reaction mixture was stirred at 0 °C for 30 min, and quenched by addition of aqueous saturated Na\textsubscript{2}CO\textsubscript{3} solution. The mixture was then extracted with dichloromethane (20 mL x 2). The combined organic layers were washed with brine (10 mL) and dried over Na\textsubscript{2}SO\textsubscript{4}. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (10% EtOAc/hexanes) to afford the title compound 353.
(yellow oil) as a 4:6 mixture of diastereomers (139 mg, 47%, 67% brsm). For characterization purposes the two diastereomers were separated by column chromatography. More polar major diastereomer: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.75-4.74 (m, 1H), 4.18-4.08 (m, 4H), 3.37-3.31 (m, 1H), 2.65-2.60 (m, 1H), 2.17-1.94 (m, 4H), 1.82-1.77 (m, 2H), 1.52-1.40 (m, 1H), 1.23-1.17 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 203.9, 169.6, 169.4, 62.2, 62.0, 61.9, 60.5, 49.6, 42.7, 37.1, 35.0, 34.8, 33.8, 32.7, 30.6, 25.9, 22.3, 14.4. Less polar minor diastereomer: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (m, 4.40-4.33, 1H), 4.16-4.09 (m, 4H), 3.30 (t, $J$ = 4.0 Hz, 1H), 2.68-2.63 (m, 1H), 2.48-2.44 (m, 1H), 2.06-1.79 (m, 6H), 1.50-1.49 (m, 1H), 1.23-1.17 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 202.5, 170.4, 64.9, 63.2, 50.9, 47.9, 38.7, 37.9, 36.1, 32.3, 15.5; HRMS-ES [M + Na]$^+$ calcd for C$_{14}$H$_{21}$ClNaO$_5$, 327.0975; found, 327.0984.

2-(4-Chloro-3-tert-butyldimethylsilyloxyimino-cyclohexylmethyl)-malonic Acid Diethyl Ester (338). To a solution of $\alpha$-chloroketone 353 (131 mg, 0.43 mmol) in dichloromethane (0.7 mL) were added O-(tert-butyldimethylsilyl)-hydroxylamine (127 mg, 0.86 mmol), 4Å molecular sieves (crushed), and a catalytic amount of PPTS. The mixture was stirred at rt for 12 h and then filtered through a pad of Celite. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (10% EtOAc/hexanes) to afford the title compound 338 as a clear oil which was an inseparable complex mixture of diastereomers (171 mg, 92%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.51 (br s, 0.3H), 4.95 (br s, 0.6H), 4.11-3.95 (m, 4H), 3.34-3.06 (m, 1H), 2.12-2.00 (m, 1H), 1.91-1.71 (m, 2H), 1.67-1.48 (m, 3H), 1.43-1.27 (m, 2H), 1.11 (t, $J$ = 7.1 Hz, 3H), 1.10
(t, J = 7.1 Hz, 3H), 0.74 (s, 9H), 0.00 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 169.7, 161.1, 160.2, 160.0, 61.9, 61.8, 59.4, 50.2, 49.8, 49.7, 47.4, 36.5, 35.9, 35.7, 35.4, 34.9, 33.5, 31.0, 26.4, 26.2, 25.1, 24.8, 18.5, 14.4; HRMS-ES [M + H]$^+$ calcd for C$_{20}$H$_{37}$NO$_5$SiCl, 434.2130; found, 434.2130.

6-Hydroxyiminobicyclo[2.2.2]octane-2,2-dicarboxylic Acid Diethyl Ester (340). To a solution of oxime 338 (20 mg, 0.046 mmol) in THF (0.5 mL) at -78 °C was added dropwise NaHMDS (2 M in THF, 31 µL, 0.062 mmol) via syringe, and the reaction mixture was stirred at -78 °C for 1 h. TBAF (1 M in THF, 62 µL, 0.062 mmol) was added dropwise via syringe, and the mixture was warmed to rt over 2 h. Saturated aqueous NH$_4$Cl (5 mL) was then added. The mixture was extracted with ether (10 mL x 3), and the combined extracts were dried over MgSO$_4$. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (50% ether/pentane) to afford the title compound 340 as a clear oil (10 mg, 74%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.55 (m, 1H), 4.25-4.11 (m, 4H), 3.07 (m, 1H), 2.41 (m, 2H), 2.25 (m, 2H), 2.21-1.97 (m, 1H), 1.96-1.90 (m, 1H), 1.65-1.47 (m, 3H), 1.28-1.19 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.5, 171.2, 161.0, 62.1, 62.0, 55.3, 37.6, 32.9, 30.4, 25.7, 24.3, 21.6, 14.4, 14.3; HRMS-ES [M + H]$^+$ calcd for C$_{14}$H$_{22}$NO$_5$, 284.1498; found, 284.1496.

3-Chloro-but-3-en-1-ol (358). To a solution of aqueous formaldehyde (3.3 g, 33 mmol) in benzene (12 mL) were added zinc powder (4.3 g, 66.0 mmol) and glacial acetic acid (0.6 mL). The reaction mixture was heated to
45 °C and 2,3-dichloropropene was added dropwise with vigorous stirring. After 2 h at 45 °C the suspension was cooled to rt and filtered through a pad of Celite which was washed with ether. The solvent was carefully removed under reduced pressure with ice cooling and the residue was purified by flash column chromatography on silica gel (10% Et$_2$O/pentane) to afford the title compound 358 as a clear oil (352 mg, 11%). $^1$H NMR (400 MHz, CDCl$_3$) δ 5.24-5.20 (m, 2H), 3.82-3.80 (m, 2H), 2.61-5.53 (m, 2H); HRMS-EI [M$^+$]$^+$ calcd for C$_4$H$_7$OCl, 106.0187; found, 106.0185.

Toluene-4-sulfonic Acid 3-Chlorobut-3-enyl Ester (359). To a solution of alcohol 358 (2.00 g, 20.0 mmol) in dichloromethane (30 mL) at 0 °C were added triethylamine (8.52 mL, 58.0 mmol) and tosyl chloride (4.38 g, 23.0 mmol). The mixture was stirred at rt overnight. The reaction mixture was then diluted with ether (50 mL) and washed with saturated aqueous NaHCO$_3$ (15 mL). The aqueous layer was extracted with ether (20 mL x 2). The combined organic extract was dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford the title compound 359 as a clear oil (3.45 g, 66%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.77 (d, $J$ = 8.0 Hz, 2H), 7.33 (d, $J$ = 8.0 Hz, 2H), 5.20 (dd, $J$ = 1.3, 11.3 Hz, 2H), 4.19 (t, $J$ = 6.0 Hz, 2H), 2.65 (t, $J$ = 6.0 Hz, 2H), 2.43 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 145.4, 137.1, 133.2, 130.3, 128.4, 116.0, 67.1, 39.1, 22.1; HRMS-AP [M + H]$^+$ calcd for C$_{11}$H$_{14}$OSCl, 261.0359; found, 261.0352.
2-Chloro-4-iodobut-1-ene (360). To a solution of tosylate 359 (3.45 g, 13.3 mmol) in acetone (50 mL) was added sodium iodide (7.0 g, 46.6 mmol) and the mixture was stirred at 60 °C for 12 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (pentane) to afford the title compound 360 as a clear oil (1.83 g, 63%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.25 (d, $J$ = 21.0 Hz, 2H), 3.32 (t, $J$ = 6.0 Hz, 2H), 2.83 (t, $J$ = 6.0 Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 140.8, 115.0, 43.3, 1.3; HRMS-EI [M]$^+$ calcd for C$_4$H$_6$ClI, 217.9168; found, 217.9173.

2-Allyl-2-(3-chlorobut-3-enyl)-malonic Acid Diethyl Ester (362). To a solution of iodide 360 (698 mg, 3.30 mmol) in THF (15 mL) was added diethyl allylmalonate (500 mg, 2.50 mmol) and sodium hydride (60% dispersion in mineral oil, 200 mg, 5.00 mmol), and the reaction mixture was heated at 70 °C for 24 h. The solvent was removed under reduced pressure. The residue was redissolved in THF and filtered through a silica gel pad, which was washed with THF. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (5-10% ether/pentane gradient) to afford the title compound 362 as a clear oil (300 mg, 50%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.64-5.54 (m, 1H), 5.16-4.79 (m, 4H), 4.12 (q, $J$ = 5.0 Hz, 4H), 2.59 (d, $J$ = 7.2 Hz, 2H), 2.23-2.19 (m, 2H), 2.09-1.99 (m, 2H), 1.21-1.78 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.2, 142.3, 132.5, 119.7, 112.8, 61.8, 57.2, 37.6, 34.5, 30.7, 14.5; HRMS-AP [M + H]$^+$ calcd for C$_{14}$H$_{22}$O$_4$Cl, 289.1196; found, 289.1207.
2-Allyl-5-chlorohex-5-enoic Acid Ethyl Ester (363). To a solution of ester 362 (710 mg, 2.46 mmol) in DMSO (10 mL) were added LiCl (228 mg, 5.42 mmol) and water (0.4 mL). The mixture was heated in an oil bath at 190 °C for 12 h, and cooled to rt. Aqueous NH₄OAc (10 mL) was added and the mixture was then extracted with ether (30 mL x 3). The organic layers were combined and dried over Na₂SO₄. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (5-10% ether/pentane gradient) to afford the title compound 363 as a clear oil (250 mg, 64%, 73% brsm). ¹H NMR (300 MHz, CDCl₃) δ 5.78-5.64 (m, 1H), 5.14-4.99 (m, 4H), 4.12 (dd, J = 7.1, 14.2 Hz, 2H), 3.45 (dd, J = 7.0, 14.0 Hz, 1H), 2.45-2.20 (m, 5H), 1.84-1.57 (m, 2H), 1.25-1.16 (m, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 175.3, 142.2, 135.4, 117.4, 113.1, 60.7, 44.4, 37.2, 36.8, 29.4, 14.7; HRMS-AP [M + H]⁺ calcd for C₁₁H₁₈O₂Cl, 217.1000; found, 217.0995.

2-Allyl-5-chlorohex-5-en-1-ol (364). To a suspension of LiAlH₄ (79 mg, 2.07 mmol) in THF (5 mL) at 0 °C was added dropwise ester 363 (250 mg, 1.15 mmol) in THF (5 mL). The mixture was stirred for 12 h at rt, and then diluted with EtOAc (20 mL). The mixture was poured into 1 M HCl solution (10 mL), and saturated aqueous NH₄Cl (10 mL) and EtOAc (10 mL) were added. The organic layer was dried over MgSO₄, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (10-20% ether/pentane gradient) to afford the title compound 364 as a clear oil (166 mg, 83%). ¹H NMR (400 MHz, CDCl₃) δ 5.82-5.73 (m, 1H), 5.18-5.06 (m, 4H), 4.18-3.96 (m, 2H), 3.50 (dd, J = 7.0, 14.0 Hz, 1H), 2.41 (t, J = 7.5 Hz, 2H), 2.17-2.07 (m, 2H), 1.88-1.76 (m, 1H), 1.67-1.59 (m, 2H);
$^{13}$C NMR  (75 MHz, CDCl$_3$) $\delta$ 135.9, 117.4, 112.7, 66.6, 36.8, 35.9, 28.8, 21.3, 14.4; HRMS-ES [M + Na]$^+$ calcd for C$_9$H$_{15}$ClO, 174.0811; found, 174.0815.

**Methanesulfonic Acid 2-Allyl-5-chlorohex-5-enyl Ester (365).** To a solution of alcohol 364 (166 g, 0.95 mmol) in dichloromethane (3.0 mL) at 0°C was added portionwise triethylamine (0.13 mL, 0.87 mmol) and mesyl chloride (0.042 mL, 0.57 mmol). The mixture was stirred at 0°C for 30 min, and then at rt for 30 min. The organic phase was diluted with dichloromethane (18 mL) and washed consecutively with brine (10 mL), 1 M aqueous KHSO$_4$ (10 mL), brine (10 mL), 5% aqueous NaHCO$_3$ (10 mL), brine (10 mL), and dried over Na$_2$SO$_4$ overnight. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (10-20% EtOAc/hexanes gradient) to afford the title compound 364 as a clear oil (159 mg, 66%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.81-5.73 (m, 1H), 5.20-5.10 (m, 4H), 4.21-4.15 (m, 2H), 3.03 (s, 3H), 2.43 (t, $J$ = 7.5 Hz, 2H), 2.19 (t, $J$ = 6.0 Hz, 2H), 1.94-1.86 (m, 1H), 1.73-1.63 (m, 2H); $^{13}$C NMR  (75 MHz, CDCl$_3$) $\delta$ 142.4, 135.2, 113.2, 113.1, 71.6, 36.9, 35.2, 30.1, 28.2; HRMS-ES [M+Na]$^+$ calcd for C$_{10}$H$_{17}$ClO$_3$SNa, 275.0485; found, 275.0480.

**2-Chloro-5-iodomethyl-octa-1,7-diene (366).** To a solution of mesylate 365 (155 mg, 0.62 mmol) in acetone (5 mL) was added sodium iodide (369 mg, 2.96 mmol) and the mixture was stirred at 60°C for 12 h. The solvent was then removed under reduced pressure and the residue was purified by flash column chromatography (pentane) to afford the title compound 366 as a clear oil (140 mg, 81%).
1H NMR (300 MHz, CDCl₃) δ 5.79-5.65 (m, 1H), 5.19-4.91 (m, 4H), 3.27 (d, J = 3.7 Hz, 2H), 2.41-2.34 (m, 2H), 2.19-2.06 (m, 2H), 1.68-1.61 (m, 1H), 1.35-1.22 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 142.6, 135.5, 117.9, 112.9, 38.7, 37.6, 36.6, 32.0, 15.0; HRMS-EI [M]+ calcd for C₉H₁₄ClI, 283.9829; found, 283.9841.

2-(2-Allyl-5-chlorohex-5-enyl)-malonic Acid Diethyl Ester (367). To a solution of iodide 366 (44 mg, 0.15 mmol) and diethyl malonate (26 mg, 0.16 mmol) in acetonitrile (5 mL) was added Verkade’s base (37 mg, 0.17 mmol), and the reaction mixture was stirred at rt for 24 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (5-20% ether/pentane gradient) to afford the title compound 367 as a clear oil (38 mg, 80%). ¹H NMR (400 MHz, CDCl₃) δ 5.81-5.68 (m, 1H), 5.14-5.04 (m, 4H), 4.20 (q, J =6.8 Hz, 4H), 3.46 (t, J = 7.5 Hz, 1H), 2.37 (t, J = 6.0 Hz, 2H), 2.10-2.08 (m 3H), 1.89 (t, J = 6.0 Hz, 2H), 1.63-1.39 (m, 3H), 1.27 (t, J = 7.5 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 169.9, 143.0, 135.9, 117.4, 112.5, 61.8, 50.2, 37.7, 36.5, 34.7, 32.7, 31.0, 14.5; HRMS-ES [M + H]⁺ calcd for C₁₆H₂₆ClO₄, 317.1520; found, 317.1512.

2-(4-Chlorocyclohex-3-enylmethyl)-malonic Acid Diethyl Ester (368). A flame dried 50 mL two necked flask equipped with a condenser and a magnetic stirring bar was charged with ester 367 (48 mg, 0.15 mmol) and benzene (20 mL). The mixture was deaerated with argon for 1 h. Grubbs 2nd generation catalyst (12 mg, 0.02 mmol) in benzene (2 mL) was added via syringe. The combined mixture was deaerated with argon for another 20 min, and then heated at 65 °C
for 12 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (2-5% ether/pentane gradient) to afford the title compound 368 as a yellow oil (42 mg, 95%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.83-5.66 (m, 1H), 4.20 (dd, $J = 7.0, 14.0$ Hz, 4H), 3.42 (t, $J = 7.5$ Hz, 1H), 2.56-2.26 (m, 4H), 1.97-1.84 (m, 4H), 1.51-1.50 (m, 2H), 1.49-1.39 (m, 1H), (t, $J = 6.0$ Hz, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 169.8, 132.1, 123.6, 61.8, 50.1, 34.7, 32.7, 32.3, 30.8, 29.8, 14.4; HRMS-ES [M + H]$^+$ calcd for C$_{14}$H$_{22}$ClO$_4$, 289.1207; found, 289.1202.

2-(3-Chloro-4-oxocyclohexylmethyl)-malonic Acid Diethyl Ester (369). To a solution of ester 368 (30 mg, 0.10 mmol), acetone (0.40 mL), and glacial acetic acid (0.17 mL) at 0 °C was added dropwise aqueous sodium hypochlorite (68 $\mu$L of 10% solution, 0.10 mmol) via syringe. The reaction mixture was stirred at 0 °C for 30 min and quenched by addition of aqueous saturated Na$_2$CO$_3$ solution. The mixture was then extracted with dichloromethane (20 mL x 2). The organic layers were combined, washed with brine (10 mL) and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (10% ether/pentane) to afford the title compound 369 as a yellow oil containing a 1:1 mixture of diastereomers (16 mg, 50%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.78 (0.2 H), 4.33-4.06 (m, 4.8H), 3.47-3.7 (m, 1H), 3.03-2.94 (m, 0.6H), 2.99-2.96 (m, 1H), 2.35-2.22 (m, 2H), 2.13-2.07 (m, 2H), 1.97-1.86 (m, 3H), 1.81-1.79 (m, 1H), 1.32-1.27 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 204.6, 169.7, 169.6, 169.5, 168.0, 62.1, 62.0, 59.8, 50.2, 50.0, 41.0, 37.2, 35.8, 34.2, 33.9, 32.6, 30.1, 29.1, 28.9, 22.4, 14.5; HRMS-ES [M + Na]$^+$ calcd for C$_{14}$H$_{21}$ClO$_5$Na, 327.0975; found, 327.0984.
2-(3-Chloro-4-\textit{tert}-butyldimethylsilyloxyimino-cyclohexylmethyl)-malonic Acid Diethyl Ester (370). To a solution of \(\alpha\)-chloroketone 369 (11 mg, 0.037 mmol) in dichloromethane (0.5 mL) were added \(O-(\textit{tert}-\text{butyldimethylsilyl})\)-hydroxylamine (11 mg, 0.075 mmol), 4Å molecular sieves (crushed), and a catalytic amount of PPTS. The mixture was stirred at rt for 12 h, and then filtered through a pad of Celite. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (10-20% ether/pentane gradient) to afford the title compound 370 as a clear oil containing an inseparable mixture of diastereomers (12 mg, 75%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.68 (br s, 0.4H), 5.14 (br s, 0.6H), 4.24 (q, \(J = 7.0\) Hz, 4H), 3.45 (t, \(J = 7.7\) Hz, 1H), 3.36-3.23 (m, 0.6H), 2.60-2.58 (m, 0.4H), 2.41-1.85 (m, 6H), 1.66-1.53 (m, 1H), 1.31 (t, \(J = 7.0\), 6H), 0.91 (s, 9H), 0.18 (s, 6H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 169.8, 161.6, 169.7, 160.2, 61.9, 59.3, 57.8, 52.6, 50.0, 47.2, 41.4, 40.2, 34.9, 32.5, 31.5, 30.1, 29.7, 29.6, 27.1, 26.6, 26.4, 20.0, 18.6, 14.4, -4.9, -5.3; HRMS-ES [M + H]\(^+\) calcd for C\(_{20}\)H\(_{37}\)NClO\(_5\)Si, 434.2130; found, 434.2132.

4-Hydroxyiminobicyclo[3.2.1]octane-6,6-dicarboxylic Acid Diethyl Ester (371). To a solution of oxime 370 (8 mg, 0.018 mmol) in THF (0.5 mL) at -78 °C was added dropwise NaHMDS (2 M in THF, 12 \(\mu\)L, 0.025 mmol). After stirring the mixture for 1 h at -78 °C, TBAF (1 M in THF, 24 \(\mu\)L, 0.024 mmol) was added and the reaction mixture was warmed to rt over 2 h. Saturated \(\text{NH}_4\text{Cl}\) was added and the mixture was extracted with EtOAc (10 mL x 2). The combined organic layers were dried over MgSO\(_4\), and the solvent was removed under
reduced pressure. The residue was purified by flash column chromatography (20% EtOAc/hexanes) to afford the title compound 371 as a white crystalline solid (5 mg, 99%) which was recrystallized from chloroform to afford colorless crystals suitable for X-ray analysis.  

\[ \text{1H NMR (400 MHz, CDCl}_3\text{) } \delta 7.58 \text{ (br s, 1H), 4.23-4.14 (m, 4H), 3.49 (d, } J \text{ = 4.4 Hz, 1H), 3.03 (q, } J = 8.0 \text{ Hz, 1H), 2.6 (d, } J = 14.5 \text{ Hz, 1H), 2.44 (br s, 1H), 2.27 (q, } J = 7.4 \text{ Hz, 1H), 2.15-2.03 (m, 2H), 1.75-1.85 (m, 1H), 1.66-1.61 (m, 2H), 1.27-1.20 (m, 6H); } \]

\[ \text{13C NMR (75 MHz, CDCl}_3\text{) } \delta 171.9, 170.2, 160.0, 63.4, 62.0, 61.9, 49.3, 38.3, 36.3, 34.3, 30.4, 18.3, 14.4, 14.3; \text{ HRMS-ES [M + H]}^+ \text{ calcd for C}_{14}H_{22}NO_5, 284.1498; \text{ found, 284.1504.} \]

**4-Oxobicyclo[3.2.1]octane-6,6-dicarboxylic Acid Diethyl Ester (374).** To a solution of oxime 371 (23 mg, 0.084 mmol) in dichloromethane (0.5 mL) at rt was added DMP (20 mg, 0.088 mmol). After stirring the mixture for 10 min at rt, dichloromethane (10 mL) and aqueous NaHSO\(_4\) (10 mL) were added. The mixture was shaken for 5 min and extracted with dichloromethane (10 mL x 2). The combined organic layers were dried over MgSO\(_4\) and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/hexanes) to afford the title compound 374 as a clear oil (15 mg, 65%).  

\[ \text{1H NMR (400 MHz, CDCl}_3\text{) } \delta 4.25-4.41 \text{ (m, 4H), 3.31 (d, } J = 4.6 \text{ Hz, 1H), 2.75-2.67 (m, 1H), 2.65-2.55 (m, 1H), 2.49-2.44 (m, 1H), 2.43-2.34 (m, 2H), 2.28-2.23 (m, 1H), 1.92-1.89 (m, 1H), 1.80-1.76 (m, 1H), 1.29-1.22 (m, 6H); } \]

\[ \text{13C NMR (75 MHz, CDCl}_3\text{) } \delta 209.5, 171.3, 170.5, 77.6, 62.8, 62.49, 62.45, 58.8, 38.3, 36.6, 35.9, 34.3, 32.0, 30.1, 14.39, 14.31. \]
2-(2-Chlorallyloxy)-but-3-en-1-ol (402). To a suspension of LiAlH₄ (0.18 g, 4.73 mmol) in THF (20 mL) at 0 °C was added dropwise ester 401 (1.00 g, 4.73 mmol) in ether (20 mL) over 5 min. The mixture was stirred for 2 h at rt, and diluted with EtOAc (10 mL). The mixture was then poured into saturated aqueous NH₄Cl (10 mL) and extracted with EtOAc (10 mL). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (10-30% EtOAc/hexanes gradient) to afford the title compound 402 as a clear oil (0.75 g, 90%). ¹H NMR (300 MHz, CDCl₃) δ 6.18-5.45 (m, 1H), 5.49 (d, J = 1.2Hz, 1H), 5.39 (d, J = 0.6 Hz, 1H), 5.29 (dd, J = 0.6, 0.7 Hz, 1H), 5.26 (dd, J = 3.8, 0.8 Hz, 1H), 4.16-4.01 (m, 3H), 3.96-3.79 (m, 2H), 2.35 (m, 1H), 1.90-1.82 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 138.7, 137.8, 118.5, 114.4, 80.2, 70.9, 60.7, 38.2; HRMS-ES [M + Na]⁺ calcd for C₈H₁₃ClO₂Na, 199.0502; found 199.0500.

Methanesulfonic Acid 2-(2-Chlorallyloxy)-but-3-enyl Ester (403). To a solution of alcohol 402 (150 mg, 0.85 mmol) in dichloromethane (21 mL) at 0 °C was added triethylamine (928 µL, 6.27 mmol) and mesyl chloride (562 µL, 7.59 mmol) portionwise. The mixture was stirred at 0 °C for 30 min, and then at rt for 30 min. The organic phase was washed consecutively with brine (10 mL), 1 M aqueous KHSO₄ (10 mL), brine (10 mL), 5% aqueous NaHCO₃ (10 mL), brine (10 mL), and dried over Na₂SO₄ overnight. The solvent was removed under reduced pressure to afford the title compound 403 as a clear oil used for the next step without further purification (206 mg, 94%). ¹H NMR (300 MHz, CDCl₃) δ 5.70-
5.67 (m, 1H), 5.45 (s, 1H), 5.44 (s, 1H), 5.37-5.27 (m, 2H), 4.43-4.33 (m, 2H), 4.13-4.08 (m, 1H), 3.97-3.93 (m, 2H), 3.02 (s, 3H), 2.06-1.97 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 138.6, 137.2, 119.4, 114.4, 77.4, 71.0, 67.1, 37.6, 35.4; HRMS-ES [M + H]$^+$ calcd for C$_9$H$_{16}$ClO$_4$S, 254.0458; found 255.0463.

3-(2-Chloroallyloxy)-5-iodopent-1-ene (404). To a solution of mesylate 403 (400 mg, 1.60 mmol) in acetone (10 mL) was added sodium iodide (964 mg, 6.40 mmol), and the mixture was stirred at 60 °C for 5 h. The solvent was then removed under reduced pressure and the residue was purified by flash column chromatography (pentane) to afford the title compound 404 as a clear oil (399 mg, 88%). $^1$H NMR (300 MHz, CDCl$_3$) δ 5.77-5.65 (m, 1H), 5.47 (dd, $J = 1.3, 2.6$ Hz, 1H), 5.39-5.29 (m, 3H), 4.15-3.80 (m, 3H), 3.76-3.22 (m, 2H), 2.23-1.94 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 138.6, 137.2, 119.0, 114.0, 80.8, 71.1, 39.5, 2.3; HRMS-AP [M+H]$^+$ calcd for C$_8$H$_{13}$ClO, 286.9700; found, 286.9706.

2-[3-(2-Chloroallyloxy)-pent-4-enyl]-malonic Acid Diethyl Ester (405). To a solution of iodide 404 (881 mg, 3.09 mmol) and diethyl malonate (520 mg, 3.24 mmol) in acetonitrile (40 mL) was added Verkade’s base (700 mg, 3.24 mmol), and the reaction mixture was stirred at rt for 24 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (5-20% EtOAc/hexanes gradient) to afford the title compound 405 as a clear oil (827 mg, 86%). $^1$H NMR (300 MHz, CDCl$_3$) δ 5.73-5.61 (m, 1H), 5.45-5.20 (m, 4H), 4.25-4.17 (m, 4H), 4.00 (dd, $J = 13.8, 44.4$ Hz, 2H), 3.77 (q, $J = 7.1$ Hz, 2H), 3.42 (d, $J = 13.8$ Hz, 4H), 2.28-2.12 (m, 4H), 1.24-1.14 (t, $J = 7.1$ Hz, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 147.1, 138.6, 137.2, 119.0, 114.0, 77.4, 71.0, 70.0, 37.6, 35.4; HRMS-AP [M+H]$^+$ calcd for C$_9$H$_{16}$ClO$_4$S, 254.0458; found 255.0463.
Hz, 1H), 3.37 (m, 1H), 2.09-1.89 (m, 2H), 1.80-1.46 (m, 2H), 1.27 (t, J=6.9 Hz, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 169.7, 138.8, 138.0, 118.5, 113.5, 80.6, 70.7, 61.6, 52.0, 33.1, 25.0, 14.4; HRMS-ES [M+H]$^+$ calcd for C$_{15}$H$_{24}$ClO$_5$, 319.1312; found, 319.1310.

2-[2-(4-Chloro-2,5-dihydrofuran-2-yl)-ethyl]-malonic Acid Diethyl Ester (406). A flame dried 50 mL two necked flask equipped with a condenser and a magnetic stirring bar was charged with ester 405 (100 mg, 0.35 mmol) and toluene (60 mL). The mixture was deaerated with argon for 1 h. Grubbs 2$^{nd}$ generation catalyst (30 mg, 0.03 mmol) in toluene (10 mL) was added via syringe. The combined mixture was deaerated with argon for another 20 min and then heated at 120 °C for 24 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (2-5% ether/pentane gradient) to afford the title compound 406 as a yellow oil (63 mg, 62%). $^1$H NMR (400 MHz, CDCl$_3$) δ 5.78-5.74 (m, 1H), 4.92-4.87 (m, 1H), 4.55-4.50 (m, 2H), 4.23-4.17 (m, 4H), 3.36 (t, J = 6.0 Hz, 1H), 1.98-1.93 (m, 2H), 1.65-1.60 (m, 2H), 1.27 (t, J = 9.5 Hz, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 169.7, 129.0, 124.9, 85.9, 76.1, 61.8, 52.1, 33.6, 24.5, 14.4; HRMS-ES [M+H]$^+$ calcd for C$_{13}$H$_{20}$ClO$_5$, 291.0999; found, 291.0995.

2-[2-(3-Chloro-4-oxotetrahydrofuran-2-yl)-ethyl]-malonic Acid Diethyl Ester (407). To a solution of ester 406 (125 mg, 0.43 mmol), in acetone (1.86 mL), and glacial acetic acid (0.75 mL) at 0 °C was added dropwise aqueous sodium hypochlorite (300 µL of 10% solution, 0.47 mmol) via syringe. The reaction mixture was stirred for 20 min at 0 °C and quenched by addition of aqueous
saturated Na₂CO₃ solution. The mixture was then extracted with dichloromethane (20 mL x 2). The combined organic layers were washed with brine (10 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (10% EtOAc/hexanes) to afford the title compound 407 (yellow oil) as an inseparable 1:1 mixture of diastereomers (73 mg, 56%). ¹H NMR (400 MHz, CDCl₃) δ 4.38-3.92 (m, 6H), 3.91-3.82 (m, 1H), 3.42-3.35 (m, 1H), 2.31-1.67 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 207.3, 169.7, 169.4, 124.9, 85.9, 80.6, 77.8, 77.4, 69.6, 61.9, 61.8, 57.7, 52.1, 52.0, 51.9, 51.0, 42.9, 41.7, 38.3, 33.6, 28.1, 24.8, 24.5, 22.8, 17.0, 14.4, 14.3; HRMS-ES [M+H]⁺ calcd for C₁₃H₂₀ClO₆, 307.0948; found, 307.0943.

2-[2-(3-Chloro-4-tert-butylmethyisilyloxyimino-tetrahydrofuran-2-yl)-ethyl]-malonic Acid Diethyl Ester (408). To a solution of α-chloroketone 407 (10 mg, 0.03 mmol) in dichloromethane (0.5 mL) were added O-(tert-butylmethyisilyl)-hydroxylamine (10 mg, 0.07 mmol), 4Å molecular sieves (crushed) and a catalytic amount of PPTS. The mixture was stirred at rt for 24 h and then filtered through a pad of Celite. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (10% EtOAc/hexanes) to afford the title compound 408 (clear oil) as an inseparable mixture of diastereomers (6 mg, 43%). ¹H NMR (400 MHz, CDCl₃) δ 4.76-4.36 (m, 3H), 4.30-4.18 (m, 4H), 4.21-4.01 (m, 1H), 4.47-4.36 (m, 3H), 4.30-4.19 (m, 4H), 3.43-3.37 (m, 6H), 1.33-1.24 (m, 6H), 0.94 (s, 9H), 0.16 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 169.5, 126.1, 115.2, 77.6, 73.4, 66.5, 61.7, 54.9, 36.4, 26.5, 26.3, 20.0 14.4; HRMS-ES [M+H]⁺ calcd for C₁₉H₃₅ClNO₆Si, 436.1922; found, 436.1928.
3-Hydroxyiminohexahydrocyclopenta[b]furan-4,4-dicarboxylic Acid Diethyl Ester (409). To a solution of oxime 408 (8 mg, 0.018 mmol) in THF (0.5 mL) at -78 °C was added dropwise NaHMDS (2 M in THF, 24 µL, 0.024 mmol) via syringe, and the reaction mixture was stirred at -78 °C for 1 h. TBAF (1 M in THF, 48 µL, 0.048 mmol) was then added dropwise via syringe, and the mixture was warmed to 0 °C over 2 h. Saturated aqueous NH₄Cl (5 mL) was then added. The mixture was extracted with ether (10 mL x 3), and the combined extracts were dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (50% ether/pentane) to afford the title compound 409 as a clear oil (6 mg, 95%). ¹H NMR (400 MHz, CDCl₃) δ 4.77 (t, J = 5.2 Hz, 1H), 4.52 (dd, J = 15.2, 41.1 Hz, 2H), 4.45-4.02 (m, 5H), 2.64 (td, J = 6.7, 13.3 Hz, 2H), 2.26 (q, J = 6.8 Hz, 1H), 2.04 (q, J = 7.2 Hz, 1H), 1.72-1.62 (m, 1H), 1.29 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 171.5, 169.4, 164.2, 85.5, 77.6, 67.7, 65.5, 62.4, 62.0, 50.9, 33.0, 32.2, 30.1, 14.3; HRMS-ES [M+H]⁺ calcd for C₁₃H₂₀NO₆, 286.1291; found, 286.1290.

(1-Azidomethyl-3-chlorobut-3-enyl)benzene (413). To a solution of sodium azide (1.68 g, 25.9 mmol) in DMF (20 mL) was added mesylate 327 (2.14 g, 9.0 mmol) and the mixture was heated at 50 °C for 48 h (care must be taken not to exceed 50 °C, as higher temperature leads to decomposition of the product). The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (10% EtOAc/hexanes) to afford the title compound 413 as a clear oil (1.21 g, 61%). ¹H NMR (300 MHz, CDCl₃) δ 7.95-7.14 (m, 5H), 5.06
(s, 1H), 4.97 (s, 1H), 3.53-3.41 (m, 2H), 3.22-3.20 (m, 1H), 2.73 (dd, $J = 6.9$, 14.4 Hz, 2H), 2.57 (dd, $J = 8.0$, 14.4 Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 140.9, 140.1, 129.2, 128.9, 128.2, 127.8, 115.2, 56.1, 43.4, 43.2; LRMS-ES$^+$ m/z (relative intensity) 194.1 (MH$^+$-N$_2$, 100)

$N$-(4-Chloro-2-phenylpent-4-enyl)-4-methylbenzenesulfonamide (414). To a solution of azide 413 (146 mg, 0.66 mmol) in THF (3.0 mL) were added triphenylphosphine (430 mg, 1.63 mmol) and water (145 $\mu$L). The reaction mixture was stirred vigorously at rt for 24 h and the mixture was partitioned between ether and brine. The ether layer was washed with brine (10 mL x 2) and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (10 mL). To the solution were added triethylamine (catalytic amount) and tosyl chloride (515 mg, 2.71 mmol) at 0 °C and the mixture was stirred for 2 h at rt. The reaction mixture was then partitioned between ether (10 mL) and saturated aqueous NaHCO$_3$ (10 mL). The aqueous layer was extracted with ether (10 mL x 2). The combined organics were dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford the title compound 414 as a clear oil (220 mg, 95%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.59 (d, $J = 8.3$ Hz, 2H), 7.23-7.17 (m, 5H), 6.96 (dd, $J = 3.0$, 4.3 Hz, 2H), 5.01 (s, 1H), 4.90 (s, 1H), 4.12-4.10 (m, 1H), 3.26-3.22 (m, 1H), 3.02-2.98 (m, 2H), 2.58-2.56 (m, 1H), 2.47-2.36 (m, 1H), 2.20 (s, 3H); LRMS-ES$^+$ m/z (relative intensity) 350.1 (MH$^+$, 100).
**N-(5-Chloro-4-oxo-2-phenylpentyl)-4-methylbenzenesulfonamide (416).** To a solution of sulfonamide 414 (25 mg, 0.07 mmol) in acetone (0.3 mL) and glacial acetic acid (0.12 mL) at 0 °C was added dropwise aqueous sodium hypochlorite (0.06 mL of 10% solution, 0.07 mmol) via syringe. The reaction mixture was stirred at 0 °C for 1 h, and quenched by addition of saturated Na₂CO₃ solution. The mixture was then extracted with dichloromethane (20 mL x 2). The organic layers were combined, washed with brine (10 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford the title compound 416 as a clear oil (3 mg, 10%). $^{13}$C NMR (75 MHz, CDCl₃) δ 156.0, 142.6, 139.5, 136.1, 128.9, 128.2, 128.1, 126.8, 126.5, 126.2, 47.2, 41.2, 35.0, 35.0, 34.9, 25.2, 25.0, 20.8, 17.1; LRMS-ES⁺ m/z (relative intensity) 388 (M+Na⁺, 60), 388 (M+Na⁺, 50).

**N-(5-Chloro-4-tert-butyldimethylsilyloxyimino-2-phenylpentyl)-4-methylbenzenesulfonamide (410).** To a solution of α-chloroketone 416 (25 mg, 0.07 mmol) in chloroform (1 mL) were added O-(tert-butyldimethylsilyl)-hydroxylamine (10 mg, 0.07 mmol), 4Å molecular sieves (crushed), and a catalytic amount of PPTS. The mixture was stirred at rt for 12 h, and then filtered through a pad of Celite, and the pad was washed with chloroform. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford the title compound 410 as a clear oil containing an inseparable mixture of E/Z isomers (11 mg, 42%). $^1$H NMR (300 MHz, CDCl₃) δ 7.62 (d, $J = 11.0$ Hz, 2H), 7.25-7.16 (m, 5H), 7.02-6.98 (m, 2H), 4.05 (m, 1H), 3.30-3.20 (m,
1H), 3.09-2.99 (m, 2H), 2.64-2.60 (m, 2H), 2.37 (s, 3H), 0.79 (s, 9H), 0.00 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 156.0, 142.6, 139.5, 136.1, 128.9, 128.3, 128.1, 126.8, 126.5, 126.2, 47.2, 41.2, 35.0, 34.9, 25.2, 25.1, 20.7, 17.17; LRMS-ES$^+$ m/z (relative intensity) 495 (MH$^+$, 60), 517.2 (M+Na$^+$, 100).

5-Phenyl-1-(toluene-4-sulfonyl)piperidin-3-one Oxime (412). To a solution of oxime 410 (33 mg, 0.07 mmol) in acetonitrile (0.67 mL) at 0 °C was added dropwise TBAF (1 M in THF, 0.07 mL, 0.07 mmol). After stirring the mixture for 10 min at 0 °C saturated NH$_4$Cl solution was added and the mixture was extracted with EtOAc (10 mL x 2). The combined organic layers were dried over MgSO$_4$. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to afford the title compound 412 as a white solid (20 mg, 88%). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.90-7.57 (m, 2H), 7.27-7.09 (m, 7H), 5.02 (d, $J = 15.0$ Hz, 0.5 H), 4.10 (d, $J = 13.4$ Hz, 0.5H), 4.06-3.80 (m, 1 H), 3.12-3.05 (m, 1H), 3.00-2.91 (m, 1H), 2.66-2.49 (m, 1.5H), 2.37-2.01 (m, 3.5H), 2.00-1.91 (m, 1.5H), 1.21-1.16 (m, 2.5H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 153.0, 152.8, 144.4, 141.2, 140.9, 133.6, 130.2, 129.2, 128.2, 128.1, 127.8, 127.4, 127.3, 52.6, 52.1, 49.4, 42.3, 41.2, 40.6, 35.7, 30.1, 22.0; LRMS-ES$^+$ m/z (relative intensity) 345.1(MH$^+$, 20), 367 (M+Na$^+$, 100).

5-Phenyl-1-(toluene-4-sulfonyl)piperidin-3-one (417). To a solution of oxime 412 (10 mg, 0.03 mmol) and ammonium acetate (30 mg, 0.38 mmol) in dioxane (0.6 mL) was gradually added TiCl$_3$ (0.93 M in H$_2$O, 10 mL, 0.07
mmol). After 1 h at rt, the reaction mixture was extracted with ether (10 mL). The extract was washed with saturated NaCl (5 mL), NaHCO₃ (5 mL), water (5 mL) and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to afford the title compound 417 as a clear oil (4 mg, 40%). IR (film) 2920, 1727, 1597, 1454, 1348, 1164, 983 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.58 (d, J = 8.6 Hz, 2H), 7.28-7.09 (m, 7H), 4.01 (d, J = 15.8 Hz, 1H), 3.89-3.86 (m, 1H), 3.26-3.20 (m, 2H), 2.77 (dd, J = 10.6, 12.0 Hz, 1H), 2.46 (dd, J = 11.9, 15.9 Hz, 1H), 2.46 (dd, J = 11.9, 15.9 Hz, 1H), 2.37 (s, 3H), ¹³C NMR (75 MHz, CDCl₃) δ 202.4, 144.7, 140.3, 133.0, 130.4, 129.4, 128.1, 128.0, 127.2, 55.6, 51.4, 45.4, 40.8, 32.3, 30.1, 29.7, 23.1, 21.9, 14.5; LRMS-ES⁺ m/z (relative intensity) 330.1 (MH⁺, 70).

**N-(4-Chloro-2-phenylpent-4-enyl)benzamide (418).** To a solution of azide 413 (239 mg, 1.08 mmol) in THF (3.5 mL) were added triphenylphosphine (701 mg, 2.66 mmol) and water (237 μL). The reaction mixture was stirred vigorously at rt for 24 h and the mixture was partitioned between ether and brine. The ether layer was washed with brine (10 mL x 2), and dried over Na₂SO₄. The solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane (1 mL). To this solution were added DMAP (catalytic amount) and TEA (catalytic amount), and the reaction mixture was cooled to 0 °C. Benzoyl chloride (0.04 mL, 0.47 mmol) was then added dropwise via syringe. The reaction mixture was warmed to rt and stirred overnight. Saturated aqueous NH₄Cl (10 mL) and EtOAc (10 mL) were added and the organic layer was dried over MgSO₄. The solvent was removed under reduced
pressure and the residue was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to afford the title compound **418** as a yellow oil (299 mg, 92%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.12-7.48 (m, 9H), 6.20 (m, 1H), 5.34 (d, $J = 13.9$ Hz, 2H), 4.22-4.17 (m, 1H), 3.76-3.62 (m, 2H), 3.01-2.95 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 166.2, 139.7, 138.6, 133.2, 130.2, 127.6, 127.3, 126.5, 126.0, 125.5, 113.2, 43.1, 42.3, 41.9; LRMS-ES$^+$ $m/z$ (relative intensity) 300.1 (MH$^+$, 100).

**N-(5-Chloro-4-oxo-2-phenylpentyl)benzamide (419).** To a solution of benzamide **418** (25 mg, 0.08 mmol) in a 5:2 mixture of acetone: glacial acetic acid (0.73 mL) at 0 °C was added dropwise via syringe aqueous sodium hypochlorite (0.06 mL of 10% solution, 0.08 mmol). The reaction mixture was stirred at 0 °C for 1 h and quenched by addition of saturated Na$_2$CO$_3$ solution. The mixture was then extracted with dichloromethane (10 mL x 2). The organic layers were combined, washed with brine (10 mL) and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford the title compound **419** as a clear oil (13 mg, 50%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.59-7.56 (m, 2H), 7.41-7.17 (m, 8H), 6.10 (m, 1H), 3.97 (d, $J = 15.6$, 1H), 3.91 (dd, $J = 15.6$, 1H), 3.71-3.68 (m, 1H), 3.54-3.51 (m, 2H), 2.97 (dd, $J = 6.0$, 2.0 Hz, 1H), 2.89 (dd, $J = 6.0$, 6.8 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 201.7, 168.1, 141.6, 132.0, 129.4, 129.0, 127.9, 127.8, 127.2, 48.9, 45.2, 43.9, 41.2; LRMS-ES$^+$ $m/z$ (relative intensity) 316.1(MH$^+$, 100).
**5-Azidomethyl-1-chlorocyclohexene (422).** A 5 mL round bottomed flask equipped with a magnetic stirring bar and a reflux condenser was charged with sodium azide (106 mg, 1.63 mmol), iodide 345 (131 mg, 0.51 mmol) and DMF (1.5 mL). The mixture was stirred at rt for 12 h and diluted with ether (60 mL). The organic phase was washed with H2O (6 mL x 3) and dried over Na2SO4. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (5% EtOAc/hexanes) to afford the title compound 422 as a clear oil (70 mg, 78%). 1H NMR (400 MHz, CDCl3) δ 5.85-5.84 (m, 1H), 3.29 (d, J = 6.4 Hz, 2H), 2.43-2.37 (m, 1H), 2.19-1.99 (m, 4H), 1.82-1.61 (m, 1H), 1.37-1.13 (m, 1H); 13C NMR (75 MHz, CDCl3) δ 130.6, 124.7, 56.5, 36.7, 35.6, 25.5, 25.3.

**N-(3-Chlorocyclohex-3-enylmethyl)-4-methyl-benzenesulfonamide (423).** To a solution of azide 422 (70 mg, 0.41 mmol) in THF (1.5 mL) were added triphenylphosphine (262 mg, 1.0 mmol) and H2O (88 µL), and the reaction mixture was stirred at rt for 24 h. The mixture was partitioned between ether (10 mL) and brine (10 mL). The organic layer was washed with brine (10 mL x 2) and dried over Na2SO4. The solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (1 mL) and the solution was cooled to 0 °C. Triethylamine (catalytic amount) and tosyl chloride (233 mg, 1.22 mmol) were added and the mixture stirred for 2 h at rt. The reaction mixture was diluted with ether (10 mL) and saturated aqueous NaHCO3 (10 mL). The aqueous layer was extracted with ether (10 mL x 2) and the combined organic extracts were dried over Na2SO4. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica
gel (5-100% Et$_2$O/pentane gradient) to afford the title compound 423 as a clear oil (70 mg, 58%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.77 (d, $J = 8.1$ Hz, 2H), 7.33 (d, $J = 8.0$ Hz, 2H), 5.77 (br s, 1H), 5.23 (t, $J = 6.0$ Hz, 1H), 2.87 (t, $J = 7.5$ Hz, 2H), 2.44 (s, 3H), 2.34-2.23 (m, 1H), 1.95-1.70 (m, 4H), 1.69-1.61 (m, 1H), 1.27-1.11 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 143.9, 137.2, 130.6, 130.2, 127.4, 124.7, 48.0, 36.8, 35.5, 25.4, 25.1, 21.9.

$N$-(4-Chloro-3-oxocyclohexylmethyl)-4-methyl-benzenesulfonamide (424). To a solution of sulfonamide 423 (25 mg, 0.08 mmol) in acetone (0.12 mL) and glacial acetic acid (0.30 mL) at 0 °C was added dropwise via syringe aqueous sodium hypochlorite (52 $\mu$L of 10% solution, 0.08 mmol). The reaction mixture was stirred at 0 °C and quenched by addition of aqueous Na$_2$CO$_3$ (10 mL). The mixture was then extracted with dichloromethane (20 mL x 2). The organic layers were combined, washed with brine (10 mL) and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10% Et$_2$O/pentane) to afford the title compound 424 as a yellow oil containing a 1 : 4 mixture of diastereomers (9 mg, 34%, 60% brsm). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.75 (d, $J = 8.1$ Hz, 2H), 7.34 (d, $J = 8.0$, 2H), 4.89-4.80 (m, 0.2H), 4.67-4.62 (m, 0.8H), 4.59-4.51 (m, 0.2H), 4.43 (q, $J = 6.1$ Hz, 0.2H), 4.25 (m, 0.8H), 2.96-2.91 (m, 2H), 2.68 (t, $J = 11.9$ Hz, 1H), 2.46 (s, 3H), 2.36-2.23 (m, 1H), 2.15-2.00 (m, 3H), 1.85-1.78 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 203.4, 144.1, 137.1, 130.2, 127.4, 60.4, 48.4, 40.5, 39.5, 33.5, 30.1, 23.6, 22.2, 21.9.
**N-(4-Chloro-3-hydroxyiminocyclohexylmethyl)-4-methyl-benzenesulfonamide (425).** To a solution of α-chloroketone 424 (8.0 mg, 0.025 mmol) in dichloromethane (0.5 mL) were added O-(tert-butyldimethylsilyl)-hydroxylamine (6.7 mg, 0.025 mmol), 4Å molecular sieves (crushed), and a catalytic amount of PPTS. The mixture was stirred at rt for 12 h and filtered through a pad of Celite. The pad was washed with chloroform. The filtrate was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford the title compound 425 as a clear oil containing an inseparable mixture of diastereomers (10 mg, 89%). ¹H NMR (300 MHz, CDCl₃) δ 7.79-7.72 (m, 2H), 7.36-7.29 (m, 2H), 5.65 (s, 0.4H), 4.76 (s, 0.4H), 4.67-4.63 (m, 0.4H), 4.50-4.46 (m, 0.8H), 3.35 (d, J = 16.4 Hz, 0.4H), 2.99-2.90 (m, 2H), 2.46 (s, 3H), 2.25-2.10 (m, 2H), 1.90-1.59 (m, 5H), 0.95 (s, 9H), 0.18 (s, 6H); HRMS-ES [M + H]⁺ calcd for C₂₀H₃₄N₂ClO₃S₁₁Si, 445.1746; found, 445.1748.

**2-(Toluene-4-sulfonyl)-2-azabicyclo[2.2.2]octan-6-one Oxime (426).** To a solution of silyl oxime 425 (9 mg, 0.02 mmol) in acetonitrile (0.5 mL) at 0 °C was added dropwise TBAF (1 M in THF, 0.05 mL, 0.05 mmol) at 0 °C. Saturated NH₄Cl solution was added after 30 min, and the mixture was extracted with EtOAc (10 mL x 2). The combined organic layers were dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (30-50% Et₂O/pentane gradient) to afford the title compound 426 as a clear oil containing an inseparable 1 : 5.3 mixture of E/Z isomers (2 mg, 34%). ¹H NMR (400 MHz, CDCl₃) δ 7.76 (d, J = 6.2 Hz, 0.4H), 7.71 (d, J = 6.2 Hz,
2H), 7.34 (d, J = 6.0 Hz, 0.4H), 7.28 (d, J = 6.0 Hz, 2H), 4.46 (t, J = 4.7 Hz, 0.2H), 4.42 (t, J = 2.3 Hz, 1H), 3.54-3.49 (m, 1H), 3.16-3.12 (m, 1H), 3.02-2.93 (m, 0.6H), 2.45-2.43 (m, 4H), 2.18-2.16 (m, 2H), 1.98-1.92 (m, 1H), 1.82-1.70 (m, 3H). HRMS-ES [M + H]⁺ calcd for C₁₄H₁₉N₂O₃S, 295.1124; found, 295.1116.

**2-Chloro-5-hydroxymethylcyclohexanone (434).** To a solution of alcohol 344 (25 mg, 0.17 mmol) in acetone (0.6 mL) and glacial acetic acid (0.24 mL) at 0 °C was added dropwise via syringe aqueous sodium hypochlorite (106 μL of 10% solution, 0.17 mmol). The reaction mixture was stirred at 0 °C for 30 min and quenched by addition of aqueous saturated Na₂CO₃ (10 mL). The mixture was then extracted with dichloromethane (20 mL x 2). The organic layers were combined, washed with brine (10 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10% Et₂O/pentane) to afford the title compound 434 as a mixture of diastereomers (16 mg, 58%). ¹H NMR (400 MHz, CDCl₃) δ 4.89-4.89 (m, 1H), 4.46 (q, J = 1.0 Hz, 0.6H), 4.18-4.21 (m, 1.8H), 3.36-3.62 (m, 2.4H), 3.55-3.47 (m, 5.5H), 2.77-2.73 (m, 7.2H), 2.31-2.10 (m, 2.1H), 2.09-2.06 (m, 4.1H), 1.66-1.60 (m, 3.1H); ¹³C NMR (75 MHz, CDCl₃) δ 204.5, 168.0, 103.5, 100.9, 73.2, 67.2, 66.8, 66.2, 62.4, 60.9, 41.7, 41.2, 39.9, 37.5, 36.1, 34.0, 31.9, 30.5, 23.0, 22.7, 22.4, 21.2, 15.6, 14.5, 14.4.

**2-Chloro-5-hydroxymethylcyclohexanone Oxime (435).** To a solution of α-chloroketone 434 (16 mg, 0.1 mmol) in dichloromethane
(0.5 mL) were added O-(tert-butyldimethylsilyl)-hydroxylamine (30 mg, 0.2 mmol), 4Å molecular sieves (crushed), and a catalytic amount of PPTS. The mixture was stirred at rt for 12 h, and filtered through a pad of Celite. The pad was rinsed with chloroform. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford the title compound 435 as an inseparable mixture of isomers as a clear oil (14 mg, 48%). HRMS-ES [M + H]+ calcd for C_{13}H_{27}NO_{2}ClSi, 292.1508; found, 292.1500.

**2-Oxabicyclo[2.2.2]octan-6-one Oxime (436).** To a solution of oxime 435 (14 mg, 0.05 mmol) in dry acetonitrile (0.5 mL) at -78 °C was added dropwise NaHMDS (2 M solution in THF, 32 μL, 0.06 mmol). After 1 h at -78 °C TBAF (1 M solution in THF, 64 μL, 0.06 mmol) was added and the reaction mixture was warmed to rt over 2 h. Saturated aqueous NH₄Cl solution was added and the mixture was extracted with EtOAc (10 mL x 2). The combined organic layers were dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (50% EtOAc/hexanes) to afford the title compound 436 as a white solid (2 mg, 23%). ¹H NMR (400 MHz, CDCl₃) δ 6.3-6.1 (m, 2H), 3.72-3.64 (m, 2H), 3.09 (d, J = 15.0 Hz, 1H), 2.39-2.35 (m, 1H), 2.16-2.03 (m, 4H); HRMS-ES [AP]+ calcd for C₇H₁₂NO₂, 142.0863; found, 142.0868.

**2-Methoxy-1,3-butadiene (427)** To a two-necked 25 mL round bottom
flask equipped with a distillation head, thermometer, and a Vigreux column were added 1,3,3-trimethoxybutane (12 g, 81.1 mmol) and dried NaHSO₄ (0.04 g, 0.33 mmol). The mixture was heated to 150 °C with trimethoxybutane being continuously added at such a rate as to keep about 9 mL of liquid in the flask at all times. The products were collected over an aqueous 5% Na₂CO₃ solution (10 mL). The organic layer was separated, washed with water and dried over calcium chloride. Distillation through an efficient column yielded the title compound 427 as a clear oil (3.05 g, 45 % yield), bp 80 °C at atmospheric pressure. ¹H NMR (400 MHz, CDCl₃) δ 6.23-6.16 (m, 1H), 5.52 (d, J = 24 Hz, 1H), 5.21 (d, J = 28 Hz, 1H), 4.18 (d, J = 6 Hz, 2H), 3.65 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 159.2, 139.2, 133.1, 116.6, 99.7, 86.6, 77.0, 54.1, 48.8, 23.3.

4-Methoxycyclohex-3-enecarbonitrile (436) To a thick walled pressure flask were added diene 435 (5.86 g, 31.8 mmol), toluene (10 mL) and acrylonitrile (2.00 g, 33.3 mmol). The flask was sealed tightly and the mixture was stirred for 16 h at 145 °C to afford the title compound 436 as a viscous yellow oil (2.66 g, 61 %). ¹H NMR (400 MHz, CDCl₃) δ 4.57 (s, 1H), 3.57 (s, 4.6H), 2.91-2.78 (m, 1.13H), 2.45- 2.41 (m, 3.4H), 2.41-2.37 (m, 1.6H), 2.27-2.19 (m, 1.6H), 2.19-2.02 (m, 2.7H), 1.99 (s, 1.36H); ¹³C NMR (75 MHz, CDCl₃) δ 129.5, 128.6, 125.7, 90.2, 54.5, 27.3, 26.0, 25.4, 25.2, 21.8.

C-(4-Methoxycyclohex-3-enyl)-methylamine (429). To a suspension of LiAlH₄ (1.47 g, 38.6 mmol) in THF (60 mL) was added nitrile 428 (2.66 g, 19.3 mmol) dropwise with stirring. The mixture was stirred for 2 h and cooled in an ice bath. A mixture of THF/H₂O (5/1 mL) was then added, followed by
addition of 15% aqueous NaOH (10 mL) with stirring and cooling. The aqueous layer was extracted with EtOAc (20 mL x 2), and the combined organics were dried over Na₂SO₄. The solvent was removed under reduced pressure to afford the title compound 429 as a yellow oil (0.96 g, 61%). The resulting compound was used for the next step without purification. \(^1\)H NMR (400 MHz, CDCl₃) δ 4.59 (s, 1H), 3.50 (s, 3H), 2.42 (d, J = 100 Hz, 2H), 2.25-2.03 (m, 5.5H), 1.86-1.76 (m, 2.1H), 1.76-1.62 (m, 0.9H), 1.58-1.12 (m, 1.2H);

\(^{13}\)C NMR (75 MHz, CDCl₃) δ 155.6, 93.4, 92.3, 54.3, 47.7, 37.5, 28.1, 27.6, 26.9, 23.2.

**N-(4-Methoxycyclohex-3-enylmethyl)-4-methylbenzenesulfonamide (430).** To a solution of amine 429 (0.95 g, 6.76 mmol) in dichloromethane (30 mL) was added triethylamine (1.0 mL, 6.8 mmol), tosyl chloride (3.88 g, 20.4 mmol), and a catalytic amount of 4-dimethylaminopyridine. The mixture was stirred at rt overnight, and diluted with dichloromethane (20 mL). The extract was washed with aqueous NaHCO₃ (15 mL). The aqueous layer was extracted with dichloromethane (20 mL x 2), and the combined organic extracts were dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (25% EtOAc/hexanes) to afford the title compound 430 as a yellow oil (0.79 g, 40% yield). \(^1\)H NMR (400 MHz, CDCl₃) δ 7.77 (d, J = 4.0 Hz, 2H), 7.32 (d, J = 4.0 Hz, 2H), 4.78 (s, 1H), 4.41 (s, 1H), 3.49 (s, 3H), 2.87 (t, J = 8.0 Hz, 2H), 2.45 (s, 3H), 2.16-2.05 (m, 3H), 2.13-1.89 (m, 3.4 H), 1.76-1.71 (m, 3.8 H), 1.33-1.16 (m, 1.6 H); \(^{13}\)C NMR (75 MHz, CDCl₃) δ 155.4, 143.8, 137.4, 130.1, 127.5, 91.77, 54.4, 48.5, 34.4, 27.8, 27.2, 26.6, 22.0.
\textbf{N-(3-Chloro-4-oxocyclohexylmethyl)-4-methyl-benzenesulfonamide (431).} To a solution of \textit{N}-chlorosuccinimide (15.5 mg, 1.15 mmol) and NaOAc (10.6 mg, 0.11 mmol) in 1:1 THF/H\textsubscript{2}O (30 mL) at 0 °C was added dropwise tosylate 430 (277 mg, 0.939 mmol) in THF (15 mL). The reaction mixture was stirred at 0 °C for 7 h and was extracted with dichloromethane (10 mL x 2). The combined organic extracts were dried over Na\textsubscript{2}SO\textsubscript{4}. The solvent was removed under reduced pressure and the residue purified by flash column chromatography on silica gel (50\% EtOAc/hexanes) to afford the title compound 431 as a yellow oil containing an inseparable mixture of diastereomers (299 mg, 94\%). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 7.74 (\(J = 4\) Hz d, 2H) 7.31 (\(J = 4\) Hz, d, 2H), 5.56 (s, 0.8H), 4.19 (s, 0.8H), 4.13-4.08 (m, 2.4H), 2.87 (s, 2.8H), 2.47-2.32 (m, 3.2H), 2.28-2.19 (m, 2.9H), 2.16-2.11 (m, 5.1H), 2.10-1.98 (m, 1.2H), 1.86-1.37 (m, 1.1H), 1.29-1.24 (m, 3.8H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 204.1, 171.2, 143.6, 136.9, 129.9, 129.5, 217.0, 60.5, 59.2, 47.1, 38.2, 35.0, 31.0, 29.7, 21.5, 21.0, 14.1.

\textbf{N-(3-Chloro-4-tert-butyldimethylsilyloxyimino-cyclohexylmethyl)-4-methylbenzenesulfonamide (432).} To a solution of \textit{\(\alpha\)-chloroketone 439 (24 mg, 0.076 mmol) in dichloromethane (2 mL) were added O-(\textit{\(\alpha\)}-tert-butyldimethylsilyl)-hydroxylamine (20 mg, 0.75 mmol), 4Å molecular sieves 50 mg (crushed), and a catalytic amount of PPTS. The mixture was stirred at rt for 12 h, filtered through a pad of Celite, and washed with dichloromethane. The total filtrate was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (25\% EtOAc/hexanes) to afford the title compound 432 as a
yellow oil (40 mg, 99% yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.75 (d, $J = 4$ Hz, 2H) 7.31 (d, $J = 4$ Hz, 2H), 2.78-2.66 (m, 2H) 2.41-2.13 (m, 4H), 1.66-1.50 (m, 2H), 1.25-1.11 (m, 1.1H), 1.00-1.04 (m, 1.1H), 0.79-0.62 (m, 13.3H), 0.03-0.05 (m, 8.5H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.6, 161.2, 159.3, 130.2, 130.2, 127.5, 60.9, 59.0, 53.8, 48.4, 47.0, 39.3, 32.0, 29.2, 26.4, 23.1, 22.0, 19.7, 18.6.

6-(Toluene-4-sulfonyl)-6-azabicyclo[3.2.1]octan-4-one Oxime (433). To a solution of oxime 430 (24 mg, 0.054 mmol) in acetonitrile (1.5 mL) was added dropwise TBAF (1 M in THF, 0.135 mL, 0.135 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min. Saturated NH$_4$Cl was added and the mixture was extracted with EtOAc (10 mL x 2). The combined organic layers were dried over MgSO$_4$ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc/hexanes) to afford the title compound 433 as a white crystalline solid (17 mg, 99%) which was recrystallized from chloroform to afford colorless crystals suitable for X-ray analysis.$^{138}$ $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.75 (d, $J = 4.5$ Hz, 2H) 7.31 (t, $J = 9$ Hz, 2H), 4.54 (d, $J = 3$ Hz, 0.9H), 4.18-4.09 (m, 0.44H), 3.54-3.49 (m, 1H), 3.24 (d, $J = 6.0$ Hz, 0.9H), 2.96 (dd, $J = 3$, 7.5 Hz, 0.9H), 2.58 (s, 0.9H), 2.45 (s, 3.1H), 2.2 (s, 0.5H), 2.1 (s, 0.7H), 1.87-1.51 (m, 6.2H), 1.48-1.39 (m, 1.2H), 1.31-1.27 (m, 1.7H), 0.99-0.09 (m, 0.6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 158.4, 143.8, 136.1, 130.1, 127.7, 60.9, 51.7, 37.6, 34.7, 30.1, 29.1, 22.0, 19.2; HRMS-EI [M]+$^+$ calcd for C$_{14}$H$_{18}$N$_2$O$_3$S, 295.1116; found, 295.1107.
Methyl γ-Nitrobutyrate (444). To a stirred solution of methyl acrylate (42.8 g, 0.4 mmol) and nitromethane (30.4 g, 0.4 mmol) in CH₂Cl₂ (100 mL) was added a solution of NaOH (2.4 g) in water (25 mL) at rt. The mixture, was stirred at rt for 24 h. The organic layer was separated, washed with brine, and dried (MgSO₄). The solvent was removed under reduced pressure and the residue was distilled under vacuum (90-100 °C/0.4 mmHg) to afford the title compound 444 as a clear oil (35.0 g, 60%). ¹H NMR (300 MHz, CDCl₃) δ 1.93 (td, J = 7.5, 5.5 Hz, 2H), 2.39 (t, J = 7.5 Hz, 2H), 3.33 (s, 6H), 3.68 (s, 3H), 4.40 (t, J = 5.5 Hz, 1H); LRMS-ES⁺ m/z (relative intensity) 148.1 (MH⁺, 100).

4,4-Dimethoxybutyric Acid Methyl Ester (445). To a stirred solution of methyl γ-nitrobutyrate (444) (9.97 g, 67.7 mmol) was added a 0.5 N solution of methanolic sodium methoxide (52.0 mL) and the mixture was stirred at rt for 20 min. Separately, in a 500 mL round-bottomed flask, sulfuric acid (18 mL) was added dropwise to methanol (40 mL) while maintaining the temperature at -10 °C. The temperature was then lowered to -20 °C at which point the mixture of nitro ester/NaOMe was added dropwise at a rate of about 1 drop per second while maintaining the temperature at -20 to -30 °C. After the addition was complete, the reaction mixture was stirred at rt overnight and poured into CH₂Cl₂ (300 mL). The organic layer was separated, washed with ice-water, aqueous NaOH, and dried over K₂CO₃. The solvent was removed under reduced pressure and the residue was distilled (100-115 °C/8 mm Hg) to afford the title compound 445 as a yellow oil (12.00 g, 80%) ¹H NMR (300 MHz, CDCl₃) δ 4.37 (t, J = 4.2 Hz, 1H), 3.64 (s, 1H), 3.29 (s, 1H), 2.35 (t, J = 5.6, 2H), 1.91
(dt, $J = 1.93$ Hz, $J = 5.7$ Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 174.1, 104.0, 53.6, 53.0, 29.5, 28.2; LRMS-ES$^+$ m/z (relative intensity) 163.0 (MH$^+$, 100).

4-Chloro-2-(2,2-dimethoxy-ethyl)-pent-4-enoic Acid Methyl Ester (446). To a freshly prepared solution of LDA (1.0 M in THF, 25.0 mL, 50 mmol) and DMPU (2.5 mL, 19.0 mmol) in THF (100 mL) was added dropwise 4,4-dimethoxy-butyric acid methyl ester (445, 7.48 g, 45.0 mmol) in THF (100 mL) at -78 °C. The resulting mixture was stirred for 45 min at -78 °C, 2-chloro-3-iodopropene (323, 10.0 g, 50.0 mmol) was then added and the reaction mixture was warmed to 0 °C. After 3 h the reaction mixture was diluted with saturated aqueous NH$_4$Cl (100 mL), EtOAc (100 mL) and the organic layer was dried over MgSO$_4$. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford the title compound 446 as a yellow oil (10.0 g, 94%). $^1$H NMR (400 MHz, CDCl$_3$) δ 5.23 (dd, $J = 1.0$, 11.7 Hz, 2H), 4.43-4.40 (m, 1H), 3.71 (s, 3H), 3.34 (s, 3H), 3.33 (s, 3H), 2.96-2.86 (m, 1H), 2.71 (ddd, $J = 9.7$, 19, 94 Hz, 2H), 2.03-1.93 (m, 1H), 1.83-1.75 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 175.3, 139.8, 115.1, 103.2, 53.9, 53.5, 52.2, 42.3, 39.8, 34.7; LRMS-ES$^+$ m/z (relative intensity) 327.0 (MH$^+$, 100).

4-Chloro-2-(2,2-dimethoxyethyl)-pent-4-enoic Acid (447). To a stirred solution of ester 446 (3.0 g, 13.0 mmol) in THF (50 mL) was added methanol (50 mL) and 1M aqueous LiOH (50 mL). The resulting mixture was stirred at rt for 3 h, and the solvents were partially removed under vacuum. The residue
was acidified to pH 5 using 2 M aqueous HCl and was extracted with ether (100 mL x 3). The extract was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (10% methanol/CH₂Cl₂) to afford the title compound **447** as a clear oil (2.9 g, 99%). ¹H NMR (300 MHz, CDCl₃) δ 5.27 (dd, J = 1.1, 5.9 Hz, 2H), 4.50 (t, J = 5.55 Hz, 1H), 3.37 (s, 1H), 3.36 (s, 1H), 2.96-2.95 (m, 1H), 2.78 (ddd, J = 7.3, 14.4, 77.2 Hz, 2H), 2.06-1.96 (m, 1H), 1.89-1.81 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 139.6, 115.5, 103.2, 54.1, 53.4, 42.0, 39.5, 34.3, 30.1; LRMS-ES⁺ m/z (relative intensity) 223.0 (MH⁺, 100).

**2-Chloro-4-isocyanato-6,6-dimethoxyhex-1-ene (449).**

To a solution of acid **447** (90 mg, 0.4 mmol) in benzene (200 mL) were added diphenylphosphoryl azide (4.7 mL, 0.5 mmol) and triethylamine (81 mg, 0.5 mmol). The reaction mixture was stirred at rt for 1 h and then heated at 80 °C for 7 h. The solvent was removed under reduced pressure and the residue was dissolved in ether (100 mL). The organic solution was washed with water (50 mL), brine (50 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford the title compound **449** as a clear oil (86 mg, 99%). ¹H NMR (300 MHz, CDCl₃) δ 5.56-5.54 (m, 0.8 H), 5.27 (d, J = 19.6 Hz, 2H), 4.50 (dd, J = 4.7, 6.3 Hz, 1H), 4.18-4.12 (m, 1H), 3.37 (s, 3H), 3.35 (s, 3H), 2.7 (ddd, J = 6.8, 14.4, 49.7 Hz, 2H), 1.95-1.82 (m, 2H); LRMS-ES⁺ m/z (relative intensity) 220.0 (MH⁺, 100).
**[3-Chloro-1-(2,2-dimethoxyethyl)-but-3-enyl] Carbamic Acid Benzyl Ester (474).** To a solution of acid 447 (227 mg, 1.02 mmol) in benzene (7 mL) were added diphenylphosphoryl azide (280 mg, 1.02 mmol) and triethylamine (132 mg, 1.3 mmol). The reaction mixture was stirred at rt for 1 h, heated at 80 °C for 1 h, and benzyl alcohol (123 mg, 1.10 mmol) was added. The resulting mixture was stirred at 80 °C for 18 h and partitioned between ether (10 mL) and aqueous citric acid (5 mL of 5% solution). The organic layer was washed with water (5 mL), saturated aqueous NaHCO₃ (5 mL), water (5 mL), brine (5 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10-30% EtOAc/hexanes) to afford the title compound 474 as a clear oil (301 mg, 93%). ¹H NMR (300 MHz, CDCl₃) δ 7.42-2.29 (m, 5H), 5.23 (d, J = 18.0 Hz, 2H), 5.12 (s, 2H), 5.51 (dd, J = 4.7, 64.4 Hz, 1H), 4.11-4.05 (m, 1H), 3.36 (s, 3H), 3.33 (s, 3H), 2.62 (ddd, J = 7.1, 15.0, 51.9 Hz, 2H), 1.95-1.84 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 156.1, 139.2, 136.9, 128.9, 128.5, 128.5, 115.6, 102.9, 67.0, 53.8, 53.5, 46.9, 44.5, 36.7, 30.2; LRMS-ES⁺ m/z (relative intensity) 328.1 (MH⁺, 100).

**[3-Chloro-1-(2,2-dimethoxyethyl)-but-3-enyl]-carbamic Acid 2-Trimethylsilanylethyl Ester (483).** To a solution of acid 447 (20 mg, 0.09 mmol) in benzene (0.6 mL) were added diphenylphosphoryl azide (30 μL, 0.09 mmol), and triethylamine (15 μL, 0.09 mmol). The reaction mixture was stirred at rt for 1 h, heated at 80 °C for 1 h, and 2-trimethylsilanylethanol (12 μL, 0.09 mmol) was added. The resulting mixture was stirred at 80 °C for 18 h and partitioned between ether
(10 mL) and aqueous citric acid (5 mL of 5%). The organic layer was washed with water (5 mL), saturated aqueous NaHCO₃ (5 mL), water (5 mL), brine (5 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10-30% EtOAc/hexanes) to afford the title compound 483 as a clear oil (28 mg, 93%). ¹H NMR (400 MHz, CDCl₃) δ 5.23 (d, J = 21.6 Hz, 2H), 5.06-5.05 (m, 0.8H), 4.45-4.42 (m, 1H), 4.09-4.02 (m, 2H), 3.97-3.92 (m, 1H), 2.59-5.57 (m, 1H), 2.45-2.40 (m, 1H), 1.85-1.76 (m, 2H), 0.93-0.88 (m, 2H), 0 (s, 9H); LRMS-ES⁺ m/z (relative intensity) 338.1 (MH⁺, 100).

3-Chloro-1-(2,2-dimethoxyethyl)-but-3-enylamine (450). To a solution of acid 447 (20 mg, 0.09 mmol) in benzene (0.6 mL) were added diphenylphosphoryl azide (30 μL, 0.09 mmol) and triethylamine (15 μL, 0.09 mmol). The reaction mixture was stirred at rt for 1 h, heated at 80 °C for 4 h, and the solvent was removed under reduced pressure. The residue was dissolved in THF (1 mL) and 1 M aqueous LiOH (1 mL) was added. The reaction mixture was stirred at rt for 30 min and partitioned between ethyl acetate (10 mL) and water (10 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 2) and the combined organics were dried over Na₂SO₄. The solvent was removed under reduced pressure to afford the title compound 450 as a clear oil (19 mg, 99%). ¹H NMR (300 MHz, CDCl₃) δ 5.24 (d, J = 8.8 Hz, 2H), 4.87-4.85 (m, 1H), 4.54-4.51 (m, 1H), 4.1-3.9 (m, 1H), 3.36 (s, 3H), 3.35 (s, 3H), 2.68-2.94 (m, 1H), 2.55-2.52 (m, 1H), 1.95-1.8 (m, 1H), 1.82-1.77 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 164.2, 152.0, 151.9, 139.4, 130.1, 124.9, 120.5, 119.2, 115.4, 114.9, 103.7, 54.4, 53.7, 46.2, 54.0, 37.7; LRMS-ES⁺ m/z (relative intensity) 193.1 (MH⁺, 10).
**N-[3-Chloro-1-(2,2-dimethoxyethyl)-but-3-enyl]-2,2,2-trifluoroacetamide (451).** To a solution of amine 450 (50 mg, 0.3 mmol) in CH₂Cl₂ (0.6 mL) were added trifluoroacetic anhydride (38.0 μL, 0.3 mmol) and triethylamine (0.1 mL, 0.7 mmol) dropwise at 0 °C. The reaction mixture was warmed to rt and stirred for 1 h, at which point the mixture was diluted with saturated aqueous NH₄Cl (10 mL) and EtOAc (10 mL). The organic layer was dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1% MeOH/CH₂Cl₂) to afford the title compound 451 as a yellow oil (74 mg, 99%). ¹H NMR (300 MHz, CDCl₃) δ 7.15-7.09 (m, 1H), 5.30 (d, J = 22.4 Hz, 2H), 4.53 (t, J = 5.2 Hz, 1H), 4.40-4.31 (m, 1H), 3.41 (s, 3H), 3.38 (s, 3H), 2.81 (ddd, J = 6.8, 14.4, 62.9 Hz, 2H), 2.05-1.92 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 157.8, 157.3, 118.0, 116.2, 114.2, 103.1, 54.1, 46.2, 43.2, 35.6, 35.2; LRMS-ES⁺ m/z (relative intensity) 312.0 (M+Na⁺, 100).

**[3-Chloro-1-(2-oxoethyl)-but-3-enyl]-carbamic Acid 2-Trimethylsilanyylethyl Ester (484).** To a solution of acetal 483 (4.0 g, 13.7 mmol) in acetone (400 mL) was added p-toluenesulfonic acid (0.3 g, 1.4 mmol) and H₂O (0.5 mL, 0.3 mmol). The mixture was stirred at rt overnight. The solvent was removed under reduced pressure and the residue was dissolved in ether (50 mL). The organic phase was washed with saturated aqueous NaHCO₃ (10 mL), brine (10 mL), and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10% MeOH/CH₂Cl₂) to afford the
title compound 484 as a clear oil (1.8 g, 99%). ¹H NMR (300 MHz, CDCl₃) δ 9.77 (s, 1H), 5.29 (d, J = 18.8 Hz, 2H), 5.07-5.04 (m, 1H), 4.39-4.32 (m, 1H), 4.15 (t, J = 9 Hz, 2H), 2.8-2.7 (m, 2H), 2.65-2.58 (m, 2H), 1.01-0.95 (m, 2H), 0.05 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 201.1, 156.4, 139.3, 138.8, 116.0, 115.5, 102.8, 63.6, 63.3, 53.7, 53.4, 51.0, 47.3, 46.7, 45.3, 44.5, 43.7, 41.5, 36.8, 18.0, -1.0; LRMS-ES⁺ m/z (relative intensity) 132.0 (MH⁺, 100).

7-Chloro-2-diazo-3-hydroxy-5-(2-trimethylsilanyl-ethoxycarbonylamino)-oct-7-enioic Acid Ethyl Ester (486). To a mixture of aldehyde 484 (119 mg, 0.45 mmol), and ethyl diazoacetate (103 mg, 0.9 mmol), in THF (10 mL) at -78 °C was added a freshly prepared solution of LDA (2.0 M in THF, 0.45 mL, 0.9 mmol) dropwise via syringe. The resulting mixture was allowed to warm to -20 °C over 3 h and then quenched by addition of saturated aqueous NH₄Cl (100 mL). The aqueous layer was extracted with ether (30 mL x 3). The combined organic layers were washed with saturated aqueous NaHCO₃ (10 mL), brine (10 mL), and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford the title compound 486 as a yellow oil containing an inseparable mixture of diastereomers (114 mg, 65%). ¹H NMR (400 MHz, CDCl₃) δ 5.26 (d, J = 23.4 Hz, 2H), 5.86-4.79 (m, 1H), 4.29-4.23 (m, 2H), 4.18-4.14 (m, 2H), 4.04-4.02 (m, 1H), 3.20-3.10 (m, 1H), 2.80-2.60 (m, 2H), 2.00-1.96 (m, 2H), 1.6 (s, 1H), 1.32-1.21 (m, 3H), 1.01-0.97 (m, 2H), 0.05 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 166.6, 156.7, 151.1, 138.9, 116.0, 65.4, 61.4, 47.5, 46.0, 38.9, 26.0, 18.0, 14.8, -1.0; LRMS-ES⁺ m/z (relative intensity) 246.0 (MH⁺, 100).
7-Chloro-3-oxo-5-(2-trimethylsilanyl-ethoxycarbonylamino)-oct-7-enoic Acid Ethyl Ester (485).

**Method 1:** To a solution of aldehyde 484 (58 mg, 0.2 mmol) in CH₂Cl₂ (5 mL) was added ethyl diazoacetate (63 mg, 0.4 mmol) and SnCl₂ (10 mg, 0.04 mmol). The reaction mixture was stirred at rt in the dark for 12 h, diluted with brine (10 mL), and extracted with CH₂Cl₂ (10 mL x 3). The extract was and dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10% ethyl acetate/hexanes) to afford the title compound 485 as yellow oil (15 mg, 20%).

**Method 2:** To a solution of aldehyde 484 (727 mg, 2.95 mmol) and activated 4 Å molecular sieves (360 mg) in CH₂Cl₂ (5 mL) was added ethyl diazoacetate (310 mg, 3.54 mmol), and the reaction mixture was stirred in the dark at rt for 15 min. The temperature was then lowered to 0 °C and BF₃·OEt₂ (152 mg, 1.40 mmol) was added. The reaction mixture was stirred at rt in the dark for 30 min and then quenched by addition of 5% aqueous NaHCO₃ (10 mL). The mixture was filtered through Celite and extracted with CH₂Cl₂ (50 mL). The extract was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (25% ethyl acetate/hexanes) to afford the title compound 485 as yellow oil (250 mg, 36%).

¹H NMR (300 MHz, CDCl₃) δ 5.30-5.21 (m, 1H), 5.17 (d, J = 12.2 Hz, 2H), 4.40-4.05 (m, 5H), 3.41 (s, 2H), 2.95-2.05 (m, 4H), 1.24 (t, J = 7.14 Hz, 3H), 0.95-0.90 (m, 2H), 0.00 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 202.0, 172.7, 167.1, 156.3, 139.2, 115.8,
7-Chloro-2-diazo-3-oxo-5-(2-trimethylsilanyl-ethoxycarbonylamino)-oct-7-enoic Acid Ethyl Ester (487).

Method 1: To a solution of α-diazo-β-hydroxyester 486 (81 mg, 0.33 mmol) in CH₂Cl₂ (3.0 mL) was added DMP (208 mg, 0.49 mmol). The heterogeneous mixture was stirred at rt until the complete consumption of the starting material was observed by TLC (1–3 h). The reaction mixture was diluted with a 1:1 mixture of saturated aqueous NaHCO₃ (10 mL) and saturated aqueous Na₂S₂O₃ (10 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried with Na₂SO₄ and the solvent was removed under reduced pressure. The resulting crude residue was purified by flash column chromatography on silica gel (25% ethyl acetate/hexanes) to afford the title compound 487 as yellow oil (88 mg, 66%).

Method 2: To a solution of β-ketoester 485 (250 mg, 0.9 mmol) in acetonitrile (6.4 mL) was added p-acetamidobenzenesulfonyl azide (273 mg, 1.17 mmol) and triethylamine (264 mg, 3.15 mmol) at 0 °C. The mixture was stirred in the dark at rt for 48 h, solvents were removed under reduced pressure and the resulting crude residue was purified by flash column chromatography on silica gel (25% ethyl acetate/hexanes) to afford the title compound 487 as yellow oil (280 mg, 43%). ¹H NMR (300 MHz, CDCl₃) δ 5.24-5.16 (m, 2H), 4.30-4.23 (m, 2H), 4.14-4.06 (m, 2H), 3.30 (d, J = 7.47 Hz, 1H), 3.31-3.10 (m, 1H), 2.74-2.54 (m, 2H), 1.36-1.22 (m, 3H), 0.94-0.92 (m, 2H), 0.02-0.01 (m, 9H), LRMS-ES⁺ m/z (relative intensity) 404.0 (MH⁺, 100).
5-(2-Chloroallyl)-3-oxopyrrolidine-1,2-dicarboxylic Acid 2-Ethyl Ester 1-(2-Trimethylsilanylethyl) Ester (488). To a solution of α-diazo-β-ketoester 487 (1.25 g, 3.10 mmol) in CH₂Cl₂ was added Rh₂(OAc)₄ (141 mg, 0.32 mmol) and the reaction mixture was stirred at for 3 h at rt. The mixture was diluted with CH₂Cl₂ and filtered through Celite. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:1 pentane/ether) to afford the title compound 488 as a yellow oil (0.91 g, 78%). ¹H NMR (300 MHz, CDCl₃) δ 5.95-5.21 (m, 2H), 4.83-4.65 (m, 1H), 4.39-4.17 (m, 4H), 3.25-2.87 (m, 2H), 2.68-2.47 (m, 2H), 1.75-1.70 (m, 1H), 1.5-1.27 (m, 3H), 1.11-0.90 (m, 2H), 0.07-0.05 (m, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 204.1, 203.8, 203.4, 166.7, 166.2, 165.9, 154.9, 154.8, 154.7, 154.6, 142.0, 138.9, 138.8, 138.2, 138.1, 133.7, 132.0, 130.6, 128.4, 116.8, 116.0, 115.8, 66.8, 65.9, 64.9, 64.7, 62.8, 62.7, 52.8, 52.6, 52.4, 52.2, 45.2, 44.5, 44.1, 43.1, 42.5, 42.2, 41.7, 41.3, 30.0, 18.1, 14.5, -1.1; LRMS-ES⁺ m/z (relative intensity) 376.0 (MH⁺, 100).

5-(2-Chloroallyl)-3-hydroxypyrrolidine-1,2-dicarboxylic Acid 2-Ethyl Ester 1-(2-Trimethylsilanylethyl) Ester (489a). To a solution of pyrrolidine 488 (139 mg, 0.37 mmol) in methanol (3 mL) was added NaBH₄ (10 mg, 0.26 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min and diluted with H₂O. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate (10 mL) and water (10 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 2). The combined organics were washed with brine (10 mL) and...
dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford the title compound **489a** as a clear oil (122 mg, 88%). ¹H NMR (400 MHz, CDCl₃) δ 5.12 (d, J = 23.7 Hz, 2H), 4.55-4.3 (m, 2H), 4.23-3.99 (m, 4H), 3.79-3.60 (m, 1H), 3.20-2.30 (m, 1H), 2.15-1.70 (m, 3H), 1.20-1.13 (m, 3H), 0.84-0.83 (m, 2H), -0.07 (m, 9H); LRMS-ES⁺ m/z (relative intensity) 378.0 (MH⁺, 100)

**3-Acetoxy-5-(2-chloroallyl)-pyrrolidine-2-carboxylic Acid Ethyl Ester (498).** To a mixture of β-hydroxy ester **488** (122 mg, 0.32 mmol) in pyridine (7 mL) was added acetic anhydride (101 mg, 0.98 mmol) and DMAP (8 mg, 0.52 mmol). The reaction mixture was stirred at rt for 12 h and quenched by addition of methanol. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to afford the title compound **489** as a clear oil (100 mg, 99%). ¹H NMR (300 MHz, CDCl₃) δ 5.43-5.23 (m, 1H), 5.18 (d, J = 2.8 Hz, 2H), 4.66-4.50 (m, 1H), 5.49-4.07 (m, 5H), 3.50-2.70 (m, 1H), 2.69-2.50 (m, 1H), 2.49-2.10 (m, 2H), 2.04-1.95 (m, 3H), 1.27-1.19 (m, 3H), 1.04-0.81 (m, 2H), 0.0 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 170.3, 170.2, 169.7, 169.2, 168.8, 155.2, 154.7, 154.6, 139.9, 139.4, 115.5, 115.1, 114.9, 72.7, 72.4, 64.4, 64.3, 64.2, 63.4, 62.6, 61.6, 61.5, 61.0, 55.8, 55.4, 54.7, 44.5, 43.6, 35.5, 34.4, 21.2, 21.0, 18.0, 14.6, -1.2; LRMS-ES⁺ m/z (relative intensity) 392.1 (MH⁺, 100), 442 (M+Na⁺, 60).

**3-Acetoxy-5-(2-chloroallyl)-pyrrolidine-1,2-dicarboxylic Acid 2-Ethyl**
**Ester 1-(2-Trimethylsilanylethyl) Ester (490).** To a mixture of pyrrolidine 489 (386 mg, 0.95 mmol) in tetrahydrofuran (2 mL) was added TBAF (1 M in THF, 10 mL, 0.10 mmol) and the mixture was stirred at rt for 1 h. The reaction mixture was partitioned between ethyl acetate (10 mL) and water (10 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 2) and the combined organics were washed with brine (10 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (50% EtOAc/hexanes) to afford the title compound 489 as a clear oil (243 mg, 99%). ¹H NMR (400 MHz, CDCl₃) δ 5.40-5.60 (m, 1H), 5.26-5.20 (m, 2H), 4.19-4.15 (m, 2H), 3.90-3.88 (m, 1H), 3.49-3.47 (m, 1H), 2.65-2.38 (m, 4H), 1.99 (s, 3H), 1.26-1.23 (m, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 170.9, 170.3, 170.2, 170.1, 140.3, 140.0, 115.1, 114.8, 114.4, 75.8, 75.4, 64.7, 64.6, 64.1, 61.5, 54.9, 46.7, 46.0, 38.4, 21.3, 14.6, 14.5; LRMS-ES⁺ m/z (relative intensity) 260.1 (MH⁺, 100).

**3-Acetoxy-1-but-3-enyl-5-(2-chloroallyl)-pyrrolidine-2-carboxylic Acid Ethyl Ester (491).**

To a solution of amine 490 (100 mg, 0.52 mmol) in toluene (1.1 mL) was added 4-bromo-1-butene (77 mg, 0.57 mmol), and K₂CO₃ (100 mg, 72 mmol). The reaction mixture was heated at 110 °C for 12 h, and the solvent removed under reduced pressure. The residue was used for the next step without purification. Alternatively, to a solution of amine 490 (250 mg, 0.96 mmol) in toluene (20 mL) was added 4-iodo-1-butene (496 mg, 2.74 mmol), and K₂CO₃ (250 mg, 0.72 mmol). The reaction mixture was heated at 110 °C for 12 h, and partitioned between ethyl acetate (100 mL) and water (50 mL). The
aqueous layer was extracted with ethyl acetate (100 mL x 2). The combined organics were washed with brine (10 mL) and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (50% EtOAc/hexanes) to afford the title compound 491 as a clear oil (123 mg, 40%).

\[ \text{^1H NMR (400 MHz, CDCl}_3\text{)} \delta 5.79-5.68 \text{ (m, 1H), 5.36-6.31 (m, 1H), 5.16-5.15 (m, 2H), 5.03-4.94 (m, 2H), 4.17-4.12 (m, 2H), 3.65 (d, J = 6.9 Hz, 1H), 3.14-3.11 (m, 1H), 2.80-2.67 (m, 3H), 2.47-2.41 (m, 1H), 2.37-2.30 (m, 1H), 2.19-2.00 (m, 2H), 1.97 (s, 3H), 1.97-1.72 (s, 1H), 1.10 (t, J = 7.3 Hz, 3H); } \text{^13C NMR (75 MHz, CDCl}_3\text{)} \delta 171.0, 170.5, 140.5, 136.4, 116.4, 114.6, 73.3, 69.2, 61.2, 59.8, 53.1, 45.9, 36.4, 32.2, 21.3, 14.7; LRMS-ES\textsuperscript{+} m/z (relative intensity) 330.0 (MH\textsuperscript{+}, 100).

### 2-Acetoxy-8-chloro-2,3,5,6,9,9a-hexahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylic Acid Ethyl Ester (492).

A flame dried 50 mL two-necked flask equipped with a condenser and a magnetic stirring bar was charged with ester 491 (130 mg, 0.39 mmol) and toluene (55 mL). The mixture was deaerated with argon for 1 h. Grubbs 2\textsuperscript{nd} generation catalyst (30 mg, 0.05 mmol) in toluene (10 mL) was added via syringe. The mixture was deaerated with argon for 20 min, and then heated at 110 °C for 12 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (2-5% ether/pentane gradient) to afford the title compound 492 as a yellow oil (73 mg, 60%).

\[ \text{^1H NMR (300 MHz, CDCl}_3\text{)} \delta 6.01-5.98 \text{ (m, 1H), 3.37-5.32 (m, 1H), 4.27-4.09 (m, 2H), 3.30-3.28 (m, 1H), 3.13-3.12 (m, 1H), 3.13-3.09 (m, 1H), 2.60-2.17 (m, 3H), 2.04-1.96 (m, 5H), 1.26-1.21 (m, 5H); } \text{^13C NMR} \]
(75 MHz, CDCl₃) δ 170.7, 133.8, 128.8, 77.0, 72.8, 72.3, 62.2, 61.5, 53.3, 43.8, 39.7, 35.6, 30.1, 28.3, 21.4, 14.7; LRMS-ES⁺ m/z (relative intensity) 302.3 (MH⁺, 60).

8-Chloro-2-hydroxy-2,3,5,6,9,9a-hexahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylic Acid Ethyl Ester (493). To a solution of azepine 492 (10 mg, 0.03 mmol) in methanol 0.5 mL was added potassium phthalimide (30 mg, 0.16 mmol), and the reaction mixture was stirred at rt for 12 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (25% ether/hexanes) to afford the title compound 493 as a yellow oil (7 mg, 90%). ¹H NMR (300 MHz, CDCl₃) δ 6.13-6.03 (m, 1H), 4.46-4.39 (m, 1H), 4.31-4.24 (m, 2H), 3.24 (d, J = 5.7 Hz, 1H), 3.15-3.14 (m, 1H), 3.14-2.95 (1H), 2.57-2.41 (m, 5H), 2.40-2.05 (m, 2H), 2.04-1.65 (m, 1H), 1.35-1.28 (m, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 170.2, 134.0, 128.7, 75.2, 71.1, 61.9, 61.4, 53.1, 44.8, 42.3, 28.6, 14.6; LRMS-ES⁺ m/z (relative intensity) 260.1 (MH⁺, 60).

N-But-3-enyl-N-[3-chloro-1-(2,2-dimethoxyethyl)-but-3-enyl]-2,2,2-trifluoroacetamide (455). To a solution of amine 451 (2.68 g, 13.8 mmol) in toluene (40 mL) was added 4-bromo-1-butene (5.58 g, 41.4 mmol), and K₂CO₃ (3.8 g, 27.6 mmol). The reaction mixture was heated at 110 °C for 12 h, and the solvent was removed under reduced pressure. The residue was dissolved in CH₂Cl₂ (37 mL), cooled to 0 °C and TFAA (1.1 mL, 15.2 mmol) was added followed by addition of triethylamine (3.9 mL, 13.8 mmol). The reaction mixture was stirred at rt overnight and then quenched with water (10 mL). The aqueous layer was extracted with ethyl acetate (30 mL x 3), the organic layers were combined and dried over MgSO₄. The
solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1% MeOH/hexanes) to afford the title compound **455** as a clear oil (3.32 g, 70%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.78-5.69 (m, 1H), 5.32-5.10 (m, 4H), 4.37-4.34 (m, 1H), 3.80-3.60 (m, 1H), 3.69-3.67 (m, 2H), 3.34 (s, 3H), 3.32 (s, 3H), 3.07 (q, $J = 10.6$ Hz, 1H), 2.78 (q, $J = 8.5$ Hz, 1H), 2.50-2.30 (m, 3H), 2.09-2.03 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 157.5, 157.0, 156.5, 139.1, 138.0, 143.8, 133.9, 122.3, 118.4, 118.2, 117.7, 116.5, 116.2, 114.6, 102.7, 102.0, 57.3, 54.1, 53.5, 53.4, 53.0, 52.8, 50.4, 44.3, 43.5, 41.9, 34.8, 34.0, 33.5, 32.4, 30.0; LRMS-ES$^+$ $m/z$ (relative intensity) 344.0 (MH$^+$, 100).

1-[4-Chloro-2-(2,2-dimethoxyethyl)-2,3,6,7-tetrahydroazepin-1-yl]-2,2,2-trifluoroacetamide (458). A flame dried 500 mL two necked flask equipped with a condenser and a magnetic stirring bar was charged with chlorodiene **457** (1.0 g, 3.4 mmol) and toluene (332 mL). The mixture was deaerated with argon for 1 h. Grubbs 2$^{nd}$ generation catalyst (289 mg, 0.34 mmol) in toluene (10 mL) was added via syringe. The combined mixture was deaerated with argon for another 20 min, and then heated at 85 °C for 24 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (2-5% ether/pentane gradient) to afford the title compound **458** as a yellow oil (0.64 g, 60%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.96 (t, $J = 8.0$ Hz, 0.3 H), 5.89 (t, $J = 5.6$ Hz, 0.7 H), 4.80-4.77 (m, 1H), 4.42-4.09 (m, 2H), 3.76-3.71 (m, 1H), 3.32-3.29 (m, 6H), 2.84-2.82 (m, 2H), 2.38-2.34 (m, 2H), 2.03-1.84 (m, 2H); LRMS-ES$^+$ $m/z$ (relative intensity) 316.0 (MH$^+$, 100)
[4-Chloro-1-(2,2,2-trifluoroacetyl)-2,3,6,7-tetrahydro-1H-azepin-2-yl]-acetaldehyde (459). To a solution of acetal 458 (160 mg, 0.47 mmol) in acetone (12 mL) was added a catalytic amount of p-toluenesulfonic acid and 8 drops of H2O. The mixture was stirred at rt overnight. The solvent was removed under reduced pressure and the residue was dissolved in ether (50 mL). The organic solution was washed with saturated aqueous NaHCO3 (10 mL), brine (10 mL), and dried over Na2SO4. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10% MeOH/CH2Cl2) to afford the title compound 459 as a clear oil (137 mg, 99%). 1H NMR (300 MHz, CDCl3) δ 9.7 (s, 0.3 H), 9.73 (s, 0.7 H), 5.99 (t, J = 8.0 Hz, 0.3H), 5.90 (t, J = 6.0 Hz, 0.7H), 5.05-4.99 (m, 0.7H), 4.90-4.70 (m, 0.3H), 4.25-4.11 (m, 0.6H), 3.86-3.71 (m, 1.4H), 3.12-2.81 (m, 4H), 2.52-2.37 (m, 2H); 13C NMR (75 MHz, CDCl3) δ 198.7, 197.6, 157.5, 157.1, 129.9, 129.6, 127.7, 126.2, 118.6, 114.8, 51.0, 49.4, 46.5, 45.9, 41.9, 41.8, 41.7, 39.6, 39.5, 30.2, 27.5, 14.5; LRMS-ES+ m/z (relative intensity) 270.0 (MH+, 100).

4-[4-Chloro-1-(2,2,2-trifluoroacetyl)-2,3,6,7-tetrahydro-1H-azepin-2-yl]-3-oxobutyric Acid tert-Butyl Ester (465). To a solution of aldehyde 458 (80 mg, 0.297 mmol) in CH2Cl2 (5 mL) was added tert-butyl diazoacetate (63 mg, 0.445 mmol) and SnCl2 (10 mg, 0.039 mmol). The reaction mixture was stirred at rt, in the dark for 12 h, diluted with brine (10 mL) and extracted with CH2Cl2 (10 mL x 3). The extract was dried over MgSO4, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on
silica gel (10% ethyl acetate/hexanes) to afford the title compound 465 as yellow oil (110 mg, 96%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.95-5.85 (m, 1H), 4.93-4.83 (m, 1H), 3.96-3.75 (m, 2H), 3.37-3.30 (m, 2H), 3.09-2.78 (m, 4H), 2.43-2.03 (m, 2H), 1.49-1.25 (m, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 200.5, 199.4, 172.7, 166.4, 157.4, 156.9, 130.3, 130.0, 129.7, 127.5, 127.1, 126.0, 118.6, 114.8, 93.7, 83.0, 82.7, 81.7, 53.7, 52.1, 51.1, 51.0, 50.5, 45.6, 44.4, 42.1, 42.1, 41.4, 39.8, 39.2, 39.1, 36.9, 30.3, 30.0, 28.6, 28.3, 27.4; LRMS-ES$^+$ $m/z$ (relative intensity) 401.1 (M$+\text{NH}_4^+$, 100), 406 (M$+\text{Na}^+$, 80).

4-(4-Chloro-2,3,6,7-tetrahydro-1H-azepin-2-yl)-3-oxobutyric Acid tert-Butyl Ester (465). To a solution of $\beta$-ketoester 458 (25 mg, 0.07 mmol) in THF (1 mL) was added a solution of saturated Ba(OH)$_2$ in H$_2$O (1 mL). The reaction mixture was stirred at rt overnight. The mixture was poured into a separatory funnel containing brine and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO$_4$ and concentrated under reduced pressure to give diazoketone 465 as a pale yellow oil that was used in subsequent steps without further purification (20 mg, 99%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.03-5.90 (m, 1H), 4.16-4.02 (m, 1H), 3.39-3.37 (m, 2H), 3.10-3.06 (m, 1H), 2.98-2.96 (m, 2H), 2.81-2.78 (m, 2H), 2.56-2.52 (m, 1H), 2.24-2.21 (m, 2H), 1.57-1.51 (m, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 200.5, 199.4, 172.7, 166.4, 157.4, 156.9, 130.3, 130.0, 129.7, 127.5, 127.1, 126.0, 118.6, 114.8, 93.7, 83.0, 82.7, 81.7, 53.7, 52.1, 51.1, 51.0, 50.5, 45.6, 44.4, 42.1, 42.1, 41.4, 39.8, 39.2, 39.1, 36.9, 30.3, 30.0, 28.6, 28.3, 27.4; LRMS-ES$^+$ $m/z$ (relative intensity) 288.2 (MH$^+$, 100).
4-(4-Chloro-2,3,6,7-tetrahydro-1H-azepin-2-yl)-2-diazo-3-oxobutyric Acid tert-Butyl Ester (466). To a solution of β-ketoester 465 (28 mg, 0.10 mmol) in acetonitrile (1 mL) was added p-acetamidobenzenesulfonyl azide (32 mg, 0.13 mmol) and triethylamine (38 mg, 0.28 mmol) at 0 °C. The reaction mixture was stirred at rt in the dark for 12 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1-10% methanol/CH$_2$Cl$_2$) to afford the title compound 466 as yellow oil (38 mg, 91%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.02 (br t, $J$ = 6.0 Hz, 1H), 3.50-3.30 (m, 1H), 3.10-3.01 (m, 1H), 2.58 (s, 1H), 2.52 (s, 1H), 2.27-2.10 (m, 3H), 1.58-1.50 (m, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 192.06, 160.7, 144.2, 133.7, 129.4, 128.9, 119.8, 83.8, 53.2, 47.0, 46.7, 46.4, 30.9, 28.6, 25.1; LRMS-ES$^+$ $m/z$ (relative intensity) 314.3 (MH$^+$, 100).

8-Chloro-2-oxo-2,3,5,6,9,9a-hexahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylic Acid tert-Butyl Ester (469). To a solution of β-ketoester 468 (160 mg, 0.54 mmol) in CH$_2$Cl$_2$ (1 mL) was added a catalytic amount of Rh$_2$(OAc)$_4$ and the reaction mixture was stirred at for 3 h at rt. The mixture was diluted with CH$_2$Cl$_2$ and filtered through Celite. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:1 pentane/ether) to afford the title compound 469 as a yellow oil (17 mg, 12%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.28-4.19 (m, 1H), 3.75-3.61 (m, 1H), 1.72-1.50 (m, 4H), 1.49-1.46 (m, 3H), 1.43-1.27 (7H), 0.96-0.90 (m, 4H); $^{13}$C NMR (75 MHz,
CDCl₃) δ 168.2, 132.8, 131.3, 129.2, 127.9, 68.5, 39.1, 30.7, 30.1, 29.3, 29.1, 28.5, 24.1, 23.4, 14.4, 11.3, 1.4; LRMS-ES⁺ m/z (relative intensity) 286.3 (MH⁺, 100).

8-Chloro-2-hydroxy-2,3,5,6,9,9a-hexahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylic Acid tert-butyl Ester (470). To a solution of pyrroloazepine 468 (4 mg, 0.01 mmol) in methanol (1 mL) at 0 °C was added NaBH₄ (0.3 mg, 0.01 mmol). The reaction mixture was stirred at 0 °C for 15 min and quenched with H₂O. The solvent was removed under reduced pressure and the residue remaining was partitioned between ethyl acetate (10 mL) and water (10 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 2) and the combined organics were washed with brine (10 mL) and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford the title compound 470 as a clear oil (3 mg, 95%). ¹H NMR (400 MHz, CDCl₃) δ 6.05-5.99 (m, 1H), 4.33-4.24 (m, 1H), 3.13-3.09 (m, 2H), 2.92-2.87 (m, 1H), 2.55-2.46 (m, 5H), 2.43-2.03 (m, 2H), 1.61-1.50 (m, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 169.2, 134.0, 128.7, 82.2, 75.3, 71.1, 64.6, 62.0, 53.1, 44.8, 42.1, 40.8, 30.1, 28.6, 28.5; LRMS-ES⁺ m/z (relative intensity) 288.2 (MH⁺, 20), 310.3 (M+Na⁺, 80).

2-Acetoxy-8-chloro-2,3,5,6,9,9a-hexahydro-1H-pyrrolo[1,2-a]azepine-3-carboxylic Acid tert-Butyl Ester (471). To a mixture of β-hydroxy ester 470 (20 mg, 0.069 mmol) in pyridine (1 mL) was added acetic anhydride (21 mg, 0.209 mmol) and DMAP (1 mg, 0.066 mmol). The reaction
mixture was stirred at rt for 12 h and quenched by addition of methanol. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to afford the title compound \( \text{471} \) as a clear oil (10 mg, 44%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 6.03-6.01 (m, 1H), 4.17-4.09 (m, 1H), 3.50-3.41 (m, 2H), 3.36-3.01 (m, 2H), 2.99-2.24 (m, 9H), 2.03-2.00 (m, 3H), 1.58-1.49 (m, 2H), 1.24-1.16 (m, 2H); LRMS-ES\(^+\) m/z (relative intensity) 330.1 (MH\(^+\), 100).

2-Acetoxy-7-chloro-8-oxooctahydropyrrolo[1,2-a]azepine-3-carboxylic Acid tert-Butyl Ester (473). To a solution of ester \( \text{471} \) (10 mg, 0.03), acetone (0.13 mL), and glacial acetic acid (0.06 mL) at 0 °C was added dropwise aqueous sodium hypochlorite (22 μL of 10% solution, 0.03 mmol) via syringe. The reaction mixture was stirred at 0 °C for 30 min and quenched by with aqueous saturated Na\(_2\)CO\(_3\) solution. The mixture was then extracted with CH\(_2\)Cl\(_2\) (20 mL x 2). The organic layers were combined, washed with brine (10 mL) and dried over Na\(_2\)SO\(_4\). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (10% ether/pentane) to afford the title compound 473 as a yellow oil containing a 1:1 mixture of diastereomers (2 mg, 50%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 4.78 (0.2 H), 4.33-4.06 (m, 4.8H), 3.47-3.7 (m, 1H), 3.03-2.94 (m, 0.6H), 2.99-2.96 (m, 1H), 2.35-2.22 (m, 2H), 2.13-2.07 (m, 2H), 1.97-1.86 (m, 3H), 1.81-1.79 (m, 1H), 1.32-1.27 (m, 6H); \(^1\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 204.6, 169.7, 169.6, 169.5, 168.0, 62.1, 62.0, 59.8, 50.2, 50.0, 41.0, 37.2, 35.8, 34.2, 33.9, 32.6, 30.1, 29.1, 28.9, 22.4, 14.5; LRMS-ES\(^+\) m/z (relative intensity) 132.0 (MH\(^+\), 100)
4-[4-Chloro-1-(2,2,2-trifluoroacetyl)-2,3,6,7-tetrahydro-1H-azepin-2-yl]-3-oxobutyric Acid Ethyl Ester (461). To a solution of aldehyde 459 (30 mg, 0.11 mmol) in CH₂Cl₂ (2 mL) was added ethyl diazoacetate (19 mg, 0.17 mmol) and SnCl₂ (10 mg, 0.06 mmol). The reaction mixture was stirred at rt in the dark for 12 h, diluted with brine (10 mL) and extracted with CH₂Cl₂ (10 mL x 3). The extract was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10% ethyl acetate/hexanes) to afford the title compound 461 as yellow oil (25 mg, 64%). ¹H NMR (300 MHz, CDCl₃) δ 5.99-5.88 (m, 1H), 4.92-4.88 (m, 1H), 4.23-4.20 (m, 2H), 3.80-3.77 (m, 2H), 3.15-3.10 (m, 2H), 3.08-2.85 (m, 2H), 2.60-2.21 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 200.1, 167.2, 130.3, 129.8, 127.6, 126.0, 113.3, 62.1, 62.0, 53.6, 52.2, 49.7, 49.6, 45.6, 44.4, 42.1, 41.4, 39.8, 39.1, 30.2, 30.0, 27.5, 14.5, 14.4; LRMS-ES⁺ m/z (relative intensity) 356.1 (MH⁺, 100).

4-(4-Chloro-2,3,6,7-tetrahydro-1H-azepin-2-yl)-3-oxobutyric Acid tert-Butyl Ester (464). To a solution of diazoketone 461 (25 mg, 0.07 mmol) in THF (1 mL) was added a solution of saturated Ba(OH)₂ in H₂O (1 mL). The reaction was stirred at rt overnight. The crude mixture was poured into a separatory funnel containing brine and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄ and concentrated under reduced
pressure to give carboxylic acid 464 as a pale yellow oil (8 mg, 50%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.01-5.98 (m, 1H), 4.94 (br s, 1H), 4.34-4.30 (m, 1H), 4.21-4.19 (1H), 3.47-3.33 (m, 3H), 2.93-2.61 (m, 2H), 2.42-2.06 (2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 202.6, 166.7, 129.6, 127.9, 53.9, 47.9, 45.1, 43.3, 43.0, 28.9; LRMS-ES$^+$ m/z (relative intensity) 232.2 (MH$^+$, 100).

[3-Chloro-1-(2-oxoethyl)-but-3-enyl]-carbamic Acid Benzyl Ester (474). To a solution of acetal 473 (160 mg, 0.47 mmol) in acetone (12 mL) was added a catalytic amount of p-toluenesulfonic acid and 8 drops of H$_2$O. The mixture was stirred at rt overnight. The solvent was removed under reduced pressure. The residue was dissolved in ether (50 mL), washed with saturated aqueous NaHCO$_3$ (10 mL), brine (10 mL), and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10% MeOH/CH$_2$Cl$_2$) to afford the title compound 474 as a clear oil (118 mg, 85%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.78 (s, 1H), 7.49-7.20 (m, 5H), 4.53-4.31 (m, 1H), 2.96-2.73 (m, 3H), 2.65-2.56 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 200.9, 155.9, 138.7, 136.6, 128.9, 128.6, 128.5, 116.2, 67.2, 47.0, 45.4, 43.6; LRMS-ES$^+$ m/z (relative intensity) 282.0 (MH$^+$, 60).

5-Benzzyloxy carbonylamino-7-chloro-2-diazo-3-hydroxy-oct-7-enoic Acid Ethyl Ester (476). To a mixture of aldehyde 474 (119 mg, 0.45 mmol), and ethyl diazoacetate (103 mg, 0.9 mmol) in THF (10 mL) at -78 °C was added a freshly made solution of LDA (2.0 M in THF, 0.45 mL, 0.9 mmol)
dropwise via syringe. The resulting mixture was allowed to warm to -20 °C over 3 h and then quenched by with saturated aqueous NH₄Cl (100 mL). The aqueous layer was extracted with ether (30 mL x 3). The organic layers were combined and washed with saturated aqueous NaHCO₃ (10 mL), brine (10 mL), and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford the title compound 476 as a yellow oil (44 mg, 25%). ¹H NMR (300 MHz, CDCl₃) δ 7.37-7.29 (m, 5H), 5.28-5.11 (m, 4H), 4.83-4.77 (m, 1H), 4.36-4.22 (m, 2H), 4.10-4.04 (m, 1H), 2.76-2.57 (2H), 1.39-1.28 (m, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 166.7, 156.4, 138.8, 136.7, 128.9, 128.6, 128.5, 116.0, 67.3, 65.3, 61.5, 47.7, 44.6, 38.7, 30.1, 14.8, LRMS-ES⁺ m/z (relative intensity) 418.0 (M+Na⁺, 100).

5-Benzylxycarbonylamino-7-chloro-2-diazo-3-oxooct-7-enoic Acid Ethyl Ester (477). To a solution of alcohol 476 (0.51 mmol) in CH₂Cl₂ (7.5 mL) was added DMP (0.76 mmol). The heterogeneous mixture was stirred at rt until the complete consumption of the starting material was observed by TLC (1–3 h). The reaction mixture was diluted with a 1:1 mixture of NaHCO₃ (aq) and Na₂S₂O₃ (aq). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried with Na₂SO₄ and the solvent was removed under reduced pressure. The resulting crude residue was purified by flash column chromatography on silica gel (25% ethyl acetate/hexanes) to afford the title compound 477 as a yellow oil (xx mg, xx%). ¹H NMR (300 MHz, CDCl₃) δ 7.39-7.8 (m, 5H), 5.40 (d, J = 3.0 Hz, 1H), 5.22 (d, J = 9.0 Hz, 2H), 5.09 (s, 2H), 4.44-4.39 (m, 1H),
4.37-4.27 (dd, $J = 7.1, 14.3$ Hz, 2H), 3.18(ddd, $J = 5.1, 17.9, 52.3$ Hz, 2H), 2.27-2.61 (m, 2H), 1.29 (m, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 191.2, 161.5, 156.0, 139.1, 136.8, 128.8, 128.4, 128.4, 115.8, 67.0, 63.0, 46.7, 43.9, 43.2, 30.1, 14.7; LRMS-ES$^+$ m/z (relative intensity) 394.1 (MH$^+$, 100)

5-(2-Chloroallyl)-3-oxopyrrolidine-1,2-dicarboxylic Acid 1-Benzyl Ester 2-Ethyl Ester (477). To a solution of $\beta$-ketoester 478 (40 mg, 0.1 mmol) in CH$_2$Cl$_2$ (10 mL) was added a catalytic amount of Rh$_2$(OAc)$_4$. The reaction mixture was stirred at rt for 3 h, diluted with CH$_2$Cl$_2$ and filtered through Celite. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (1:1 pentane/ether) to afford the title compound 477 as a yellow oil (25 mg, 68%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.63-7.27 (m, 5H), 5.39-5.25 (m, 4H), 4.61-4.57 (m, 2H), 4.15-4.01 (m, 2H), 3.40-3.35 (m, 2H), 1.76-1.62 (m, 2H), 1.51-1.28 (m, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 202.6, 166.4, 156.0, 139.1, 136.8, 128.9, 128.5, 128.4, 115.9, 82.7, 67.1, 51.3, 46.1, 45.4, 43.2, 28.7, 28.3; LRMS-ES$^+$ m/z (relative intensity) 366.1 (MH$^+$, 100)

5-(2-Chloroallyl)-3-hydroxypyrrolidine-2-carboxylic Acid Ethyl Ester (479). To a solution of pyrrolidine 478 (4 mg, 0.01 mmol) in methanol (1 mL) at 0 °C was added NaBH$_4$ (0.3 mg, 0.01 mmol). The reaction mixture was stirred at 0 °C for 15 min and quenched with H$_2$O. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate (10 mL) and water (10 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 2) and the
combined organics were washed with brine (10 mL) and dried over MgSO$_4$. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford the title compound 479 as a clear oil (3 mg, 95%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.59 (d, $J = 8.3$ Hz, 2H), 7.23-7.17 (m, 5H), 6.96 (dd, $J = 3.0, 4.3$ Hz, 2H), 5.01 (s, 1H), 4.90 (s, 1H), 4.12-4.10 (m, 1H), 3.26-3.22 (m, 1H), 3.02-2.98 (m, 2H), 2.58-2.56 (m, 1H), 2.47-2.36 (m, 1H), 2.20 (s, 3H); LRMS-ES$^+$ m/z (relative intensity) 350.1 (MH$^+$, 100).

2-Diazo-3-hydroxyhexanoic Acid Ethyl Ester (504). To a mixture of aldehyde 502 (68 mg, 0.95 mmol) and ethyl diazoacetate (103 mg, 0.9 mmol), in THF (10 mL) at -78 °C was added a freshly made solution of LDA (2.0 M in THF, 0.45 mL, 0.9 mmol) dropwise via syringe. The resulting mixture was allowed to warm to -20 °C over 3 h and then quenched with of saturated aqueous NH$_4$Cl (100 mL). The aqueous layer was extracted with ether (30 mL x 3). The organic layers were combined and washed with saturated aqueous NaHCO$_3$ (10 mL), brine (10 mL), and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford the title compound 504 as a yellow oil (51 mg, 62%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.71 (t, $J = 4.9$ Hz, 1H), 4.28 (q, $J = 7.1$ Hz, 2H), 2.54 (br s, 1H), 1.88-1.43 (m, 4H), 1.31 (t, $J = 7.1$ Hz, 2H), 0.98 (t, $J = 5.1$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 167.1, 66.8, 61.4, 36.3, 19.2, 14.9, 14.1; LRMS-ES$^+$ m/z (relative intensity) 187.0 (MH$^+$, 20), 209.1 (M+Na$^+$, 100).
2-Diazo-3-hydroxyhexanoic Acid Ethyl Ester (506). To a solution of alcohol 504 (94 mg, 0.51 mmol) in CH₂Cl₂ (7.5 mL) was added DMP (185 mg, 0.76 mmol). The heterogeneous mixture was stirred at rt until the complete consumption of the starting material was observed by TLC (1–3 h). The reaction mixture was diluted with a 1:1 mixture of NaHCO₃ (aq) and Na₂S₂O₃ (aq). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried with Na₂SO₄ and the solvent was removed under reduced pressure. The resulting crude residue was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to afford the title compound 506 as a yellow oil (60 mg, 64%). ¹H NMR (300 MHz, CDCl₃) δ 7.17-7.09 (m, 5H), 5.08 (s, 1H), 4.92 (s, 1H), 4.02-3.94 (m, 2H), 3.82 (t, J = 7.5 Hz, 2H), 2.98 (d, J = 5.8 Hz, 1H), 2.58 (q, J = 5.6 Hz, 1H), 1.05 (t, J = 7.2 Hz, 3H); LRMS-ES⁺ m/z (relative intensity) 185.0 (MH⁺, 100)

2-Diazo-3-hydroxy-3-phenylpropionic Acid Ethyl Ester (505). To a mixture of aldehyde 503 (150 mg, 1.41 mmol), and ethyl diazoacetate (321 mg, 2.82 mmol), in THF (10 mL) at -78 °C was added a freshly made solution of LDA (2.0 M in THF, 1.38 mL, 2.78 mmol) dropwise via syringe. The resulting mixture was allowed to warm to -20 °C over 3 h and then quenched with saturated aqueous NH₄Cl (100 mL). The aqueous layer was extracted with ether (30 mL x 3), the organic layers were combined and washed with saturated aqueous NaHCO₃ (10 mL), brine (10 mL), and dried over Na₂SO₄. The solvent was removed under reduced
pressure and the residue was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford the title compound 505 as a yellow oil (320 mg, 99%). ¹H NMR (300 MHz, CDCl₃) δ 7.46-7.30 (m, 5H), 5.91 (s, 1H), 4.24 (q, J = 7.1 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 167.0, 139.7, 129.1, 128.5, 126.1, 68.7, 57.7, 14.8; LRMS-ES⁺ m/z (relative intensity) 221.0 (MH⁺, 100).

2-Diazo-3-oxo-3-phenylpropionic Acid Ethyl Ester (507).

To a solution of β-hydroxyester 505 (31 mg, 0.14 mmol) in CH₂Cl₂ (2.0 mL) was added DMP (56 mg, 0.23 mmol). The heterogeneous mixture was stirred at rt until the complete consumption of the starting material was observed by TLC (1–3 h). The reaction mixture was diluted with a 1:1 mixture of NaHCO₃(aq) and Na₂S₂O₃(aq). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried with Na₂SO₄ and the solvent was removed under reduced pressure. The resulting crude residue was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to afford the title compound 507 as a yellow oil (23 mg, 75%). ¹H NMR (300 MHz, CDCl₃) δ 7.66-7.41 (m, 5H), 4.25 (q, J = 2.0 Hz, 2H), 1.25 (t, J = 2.0, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 187.3, 161.4, 137.5, 132.6, 128.7, 128.2, 62.0, 14.616; LRMS-ES⁺ m/z (relative intensity) 219.0 (MH⁺, 100).
References and Notes:


191


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VITA

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Ilia Korboukh was born and raised in Moscow, Russia, immigrated to Germany in 1990, and later to the United States. He attended the University of California, Irvine and received his bachelor’s degree in chemistry in 2000. He did his undergraduate research under the tutelage of Professor Patric J. Farmer in the area of bioinorganic chemistry. In May of 2000 he joined a lead optimization team in the drug discovery department of ICN Pharmaceuticals headed by Dr. Zhi Hong, where he worked as a synthetic chemist developing anti-cancer and anti-viral therapeutics. In September of 2003 he returned to school and began graduate education at the Pennsylvania State University under the mentorship of Professor Steven M. Weinreb in the area of synthetic organic chemistry.