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The Synthesis and Biological Activity of 2'-Fluoro-N-methanocarbathymidine Epimers and An Approach Towards the Synthesis of Morphine

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The Synthesis and Biological Activity of 2'-Fluoro-N-methanocarbathymidine Epimers

And

An Approach Towards the Synthesis of Morphine

A dissertation submitted in partial satisfaction of the

requirements for the Doctor of Philosophy

in Chemistry

By

Timothy Andersen Dwight

2014

ABSTRACT OF THE DISSERTATION

The Synthesis and Biological Activity of 2'-Fluoro-N-methanocarbathymidine Epimers

And

An Approach Towards the Synthesis of Morphine

by

Timothy Andersen Dwight

Doctor of Philosophy in Chemistry

University of California, Los Angeles, 2014

Professor Michael E. Jung, Chair

In Chapter 1, the syntheses of 2'-fluoro-N-methanocarbathymidine (2'F-NMC) and arabino 2'-fluoro-N-methanocarbathymidine (ara-2'F-NMC) are detailed. The syntheses of both molecules begin with the simple precursor cyclopenten-1-one. Asymmetry is introduced into the

molecule by means of a Corey-Bakshi-Shibata asymmetric reduction. The cyclopropane was installed using a directed Simmons-Smith cyclopropanation reaction. The Michael addition of dibenzylamine with the fluoroenone was observed with good diastereoselectivity. The biological activity of the monomer incorporated oligonucleotides will also be discussed.

In Chapter 2, multiple approaches towards a synthesis of morphine were attempted. A palladium-catalyzed Tsuji-Trost reaction will be featured as an attempt to form the C-ring of morphine's carbon framework. A new palladium-catalyzed cyclopropanation reaction to form vinylcyclopropyl ketones was discovered during this pursuit. Another approach towards synthesizing morphine will feature an attempt to form the C-ring by means of a Diels-Alder reaction. The last approach discussed, will be an attempted oxy-Cope rearrangement reaction to potentially install the quaternary center of morphine.

The dissertation of Timothy Andersen Dwight is approved.

Jorge R. Barrio

Craig A. Merlic

Michael E. Jung, Committee Chair

University of California, Los Angeles

2014

In memory of my loving grandparents, who

always supported me. They were truly

inspirational people.

Frederick Waldemar Andersen

(September 9, 1915 – August 17, 2014)

And

Ruth Trebing Andersen

(November 20, 1918 – April 25, 2007)

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PUBLICATIONS AND PRESENTATIONS

Ostergaard, M. E.; Dwight, T.; Berdeja, A.; Swayze, E. E.; Jung, M. E., Seth, P. P. "Comparison of Duplex Stabilizing Properties of 2'-Fluorinated Nucleic Acid Analogues with Furanose and Non-Furanose Sugar Rings" *J. Org. Chem.* DOI: 10.1021/jo501381q.

Dwight, T. A.; Vigant, F.; Ostergaard, M. E.; Swayze, E. E.; Seth, P. P.; Jung, M. E. "Synthesis and Duplex-Stabilizing Properties of Fluorinated N-Methanocarbothymidine Analogues Locked in the C3'-*endo* Conformation" *Angew. Chem. Int. Edit.* DOI: 10.1002/anie.201405283

Dwight, T. A.; Vigant, F.; Jung, M. E. "Synthesis and Biological Activity of Fluorinated N-Methanocarbathymidine Analogs," American Chemical Society Conference, Santa Clara, CA, October 2013

Potavathri, S.; Dumas, A. S.; Dwight, T. A.; Naumiec, G. R.; Hammann, J. M.; Deboef, B. "Oxidant-Controlled Regioselectivity in the Oxidative Arylation of *N*-Acetylindoles" *Tetrahedron Lett.*, **2008**, *49*, 4050-4053.

Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. "C-C Bond Formation via Double C-H Functionalization: Aerobic Oxidative Coupling as a Method for Synthesizing Heterocoupled Biaryls," *Org. Lett.*, **2007**, *9*, 3137-3139.

Dwight, T. A.; Deboef, B. "Palladium Catalyzed Oxidative Coupling – Formation of Biaryl Compounds," American Chemical Society Conference, Boston, MA, August 2007

Chapter 1: The Synthesis and Biological Activity of 2'-Fluoro-N-methanocarbathymidine Epimers

Introduction

Antisense oligonucleotide and RNA interference therapies have emerged over the years as very promising treatments of a wide-range of diseases and infections. After identification of a specific sequence of RNA that codes for a particular protein that is implicated in these problems, a short natural or synthetic sequence of nucleosides can potentially be developed to complementary base-pair with this sequence. In doing so, the binding effectively modulates gene expression from DNA to protein or in the case of viral infections prevents replication by blocking the translation of viral mRNA into protein in a similar fashion. In addition, this technology is also used as a tool for studying biological processes. The oligonucleotides are short sequences of about 13-25 base pairs. This is important to give selectivity of binding one sequence of RNA over another.[1–3]

There are currently three synthetic oligonucleotide drugs approved for use by the FDA, which include Fomivirsen (currently discontinued, brand name Vitravene) which treats cytomegalovirus retinitis, Mipomersen (Kynamro) which treats familial cholesterolemia, and Pegaptanib (Macugen) which treats age-related macular degeneration.[4,5]

Many structural modifications have been studied for nucleosides. The improvements that have been sought after when making such alterations include the increase in Watson-Crick base-pairing, increase in RNase H-dependent degradation, better drug delivery, and increased nuclease stability.

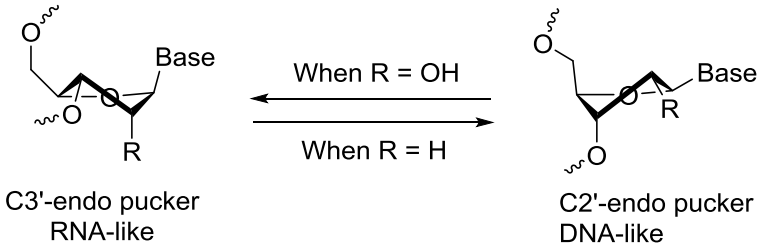
Alterations to the backbone of synthetic nucleosides have been extensively studied. These changes are made mainly because natural nucleotides bearing a phosphodiester linkage are

prone to rapid degradation by endogenous nucleases. The most prominent change has been to change the phosphodiester linkage to a phosphorothioate linkage (P=O to P=S). This modification is utilized in most of the pre-clinical antisense drugs. It's known to increase RNase-H activity, which is an enzyme that cleaves one of the P-O bonds (7-10 nucleotides from 5'-end of the RNA) from the resulting RNA/antisense duplex. This increase in degradation increases the potency of the drug. In addition, the phosphorothioate modification allows for better drug delivery as it has increased plasma protein binding.

Other less prominent but significant changes to the backbone would include those of phosphorodiamidate morpholino oligomers (deoxyribose ring changed to a morpholine ring and phosphodiester linkage to that of a phosphorodiamidate), peptide nucleic acids (uncharged polyamide backbone directly linked to nucleobases), phosphoramidate oligomers (3'N to 5'P linkage, 3'O changed to 3'N), and methylphosphonate oligomers (one non-bridging P-O bond changed to methyl and the group is uncharged). Most of these changes have very good if not excellent binding properties but are not cleavable by RNase-H enzymes and are generally utilized in siRNA modified oligonucleotides which are different in that they are degraded by an RNA-induced silencing complex (RISC) as well as administered as a duplex.[2,3]

Since it has been shown RNA binds tighter with itself, structural modifications of the sugar moiety have sought to mimic that of RNA. The conformations of the sugar ring in RNA and DNA are in an equilibrium between a C3'-endo conformation and a C2'-endo conformation (Scheme 1). The 2'-OH substituent of RNA influences its conformation and shifts this equilibrium towards the C3'-endo conformation. DNA, which is devoid of the 2'-OH substituent, is favored in the C2'-endo conformation. It is beneficial to incorporate a C2'-

electronegative substituent, such as an oxygen or fluorine atom, to favor the C2'-endo pucker (RNA-like) of the nucleoside sugar ring.[6,7]



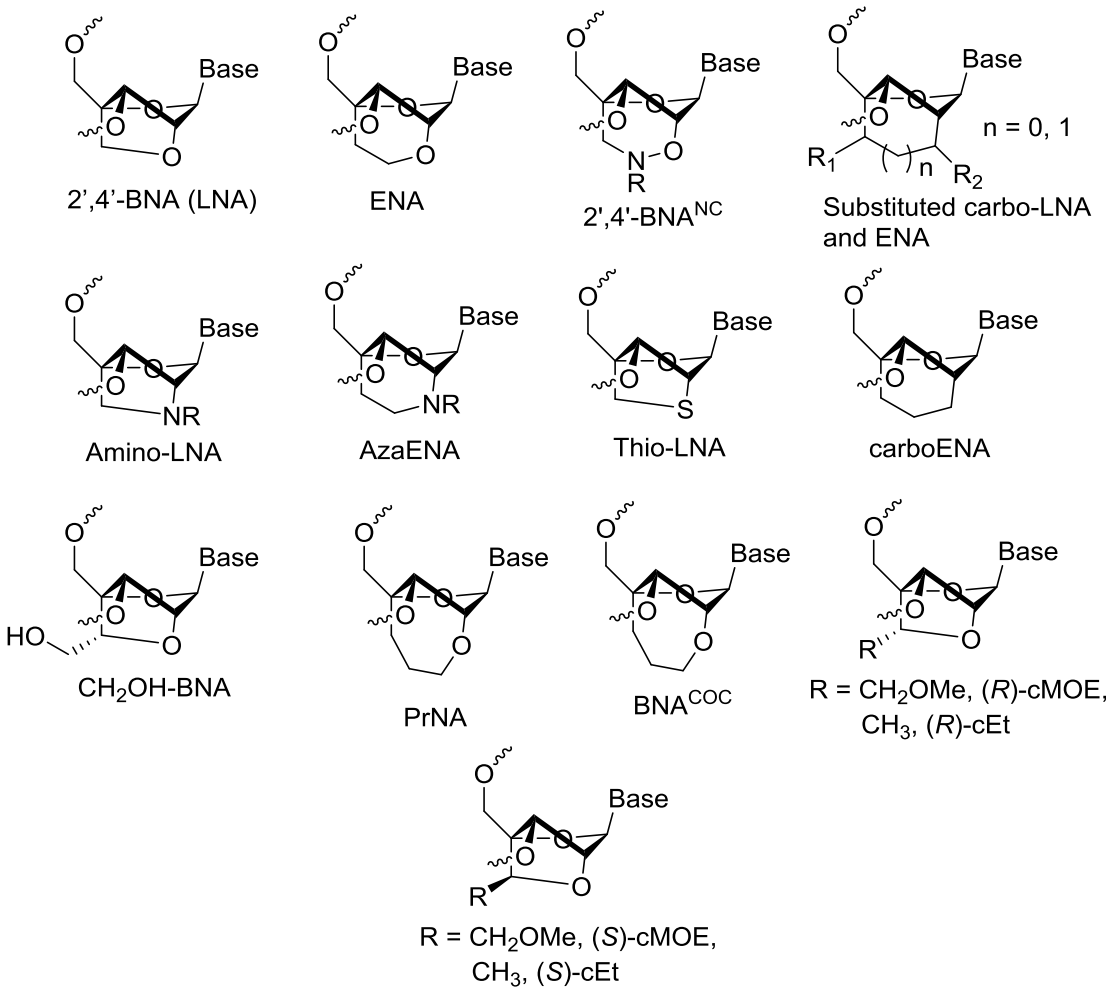
Scheme 1. Favored conformations of RNA (C3'-endo) and DNA (C2'-endo) nucleic acids.

Although many modifications of nucleoside sugar rings have been experimented with, the focus of the remaining part of this discussion shall be on locked nucleic acids and those that have fluorine incorporated into their structure. These pursuits have been a part of an ongoing effort to limit the conformation of the sugar ring to that of a C3'-endo-like pucker in order to mimic RNA. The modifications are evaluated for their effectiveness by measuring the melting temperature (T_m values) of a duplex formed from the synthetic strand and a natural strand with a complementary sequence. This melting temperature is compared to an unmodified duplex with the same sequence.

Locked nucleic acids (LNAs) feature a bridge between the 2'- and 4'-carbon atoms of the sugar ring. This locks the ring structure into the preferred C3'-endo conformation. This modification has allowed increases in thermal duplex stability from 1 ^{o}C to 8 ^{o}C against DNA and 2 ^{o}C to 10 ^{o}C against RNA.[8] In addition, a single inclusion of a locked nucleic acid into a

sequence has been shown to increase the C3'-endo conformation character of an adjacent nucleotide up to 94%.[9,10]

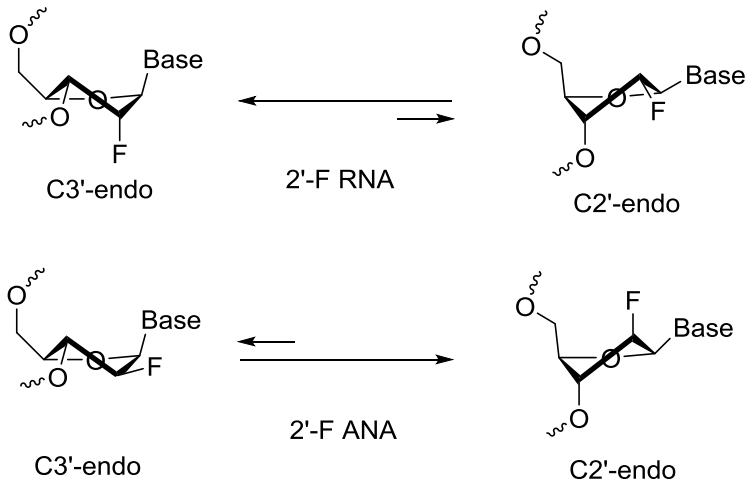
The first synthesis of LNA was carried out by Imanishi and coworkers. It features a bicyclo[2.2.1] heptane ring system with the 2'-oxygen incorporated as a methylene-oxo bridge. The synthesis utilizes uridine as a starting material. The conformation of the sugar ring is locked



Scheme 2. Examples of synthesized locked nucleic acids.[11]

into the C3'-endo conformation.[12] This type of structure was later incorporated into oligomers of nine base-pairs (9-mer) and found to impart increases in melting temperatures of +3 to +5 ^{o}C towards DNA and +4 to +8 ^{o}C towards RNA for a single inclusion.[13] A significant number of derivatives of locked nucleic acids have been synthesized since the first synthesis of LNA (Scheme 2). Most of these locked nucleic acids did not perform as well as LNA itself with regard to thermal stability experiments. The exceptions are thio-LNA, BNA^{NC}, and *S*-cEt, which show similar or modest increases in thermal stability experiments relative to LNA incorporated oligonucleotides.[11,14,15]

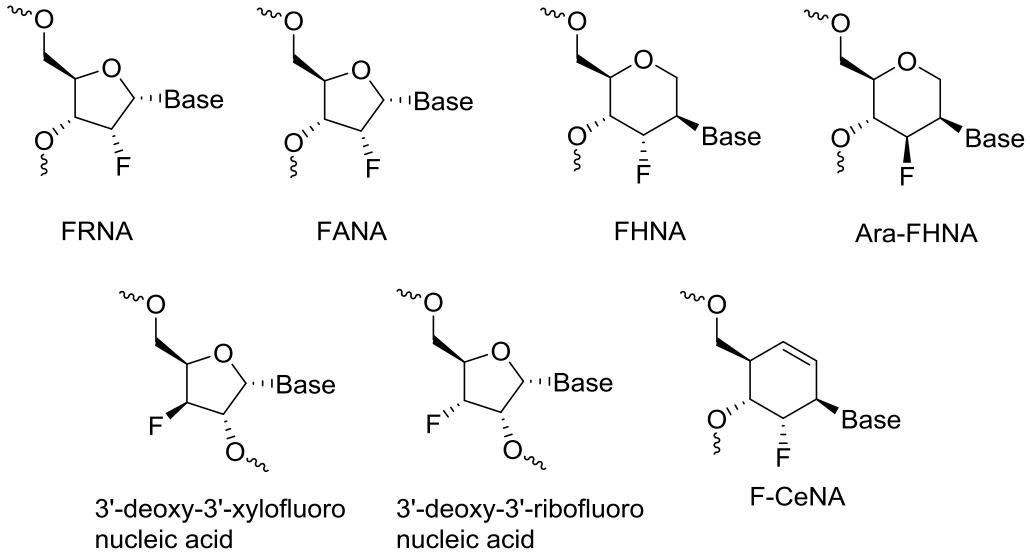
Fluorine has been incorporated into nucleosides for electronic reasons and because it serves as a good bioisostere for oxygen. It has been examined both as a substituent on the sugar ring and on the nucleobase itself. Due to its strong electronegativity, fluorine effects both the electronics and conformation of nucleoside sugars.[16] In the case of 2'-deoxy-2'-fluoro-nucleosides (2'-F RNA), the effect is large enough that the distribution between 3'-endo and 2'-endo conformations exceeds that of ribonucleosides.[17] As a result this enhances binding when incorporated into oligonucleotides that bind to RNA. If the configuration of the 2' C-F bond is switched to the arabino 2'-deoxy-2'-fluoronucleoside (2'F-ANA) the effect remains but the C2'-endo (DNA-like) conformation predominates (Scheme 3). This nucleoside, 2'F-ANA, also improves the duplex thermostability. This is thought to be due to hydrogen bonding that occurs between a hydrogen atom of the purine bases and the fluorine atom.[18,19] 3'-Deoxy-3'ribofluoro/xylofluoro nucleosides also have been synthesized and show similar conformational effects with fluorine incorporation as 2'F-ANA and 2'F-RNA.[16]



Scheme 3. Equilibria of 2'-F RNA and 2'-F ANA.[16]

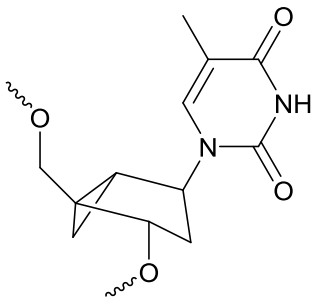
Fluoro-cyclohexenyl nucleic acids (F-CeNA) have also been prepared but showed only modest improvement in thermal experiments when compared to their non-fluorinated counterpart and were less effective than 2'F-ANA.[19] 3'-Fluoro hexitol derivatives (FHNA and Ara-FHNA) have been synthesized (Scheme 4). FHNA showed modest improvements over hexitol nucleic acid (HNA) and Ara-FHNA was destabilizing. However when incorporated into oligonucleotides, both were found to have substantial resilience towards exonuclease digestion relative to LNA, 2'-*O*-(2-methoxyethyl) nucleic acids (MOE), and DNA.[20]

Another example of forming a rigid scaffold to mimic that of a RNA-like sugar pucker has been demonstrated with a bicyclo[3.1.0]hexane scaffold (Scheme 5). This structure has been shown by Marquez and Altmann to adopt a rigid pseudoboat conformation that mimics the 3'-



Scheme 4. Examples of fluorinated nucleoside derivatives.

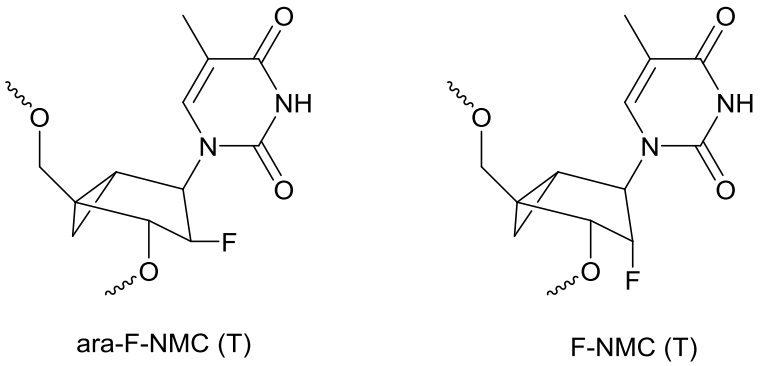
endo-like pucker of RNA sugars. When they were incorporated into oligonucleotides, these compounds enhanced RNA binding. They have also proved to be more resilient to nuclease degradation.[21–23]



N-methanocarbathymidine (N-MCT)

Scheme 5. N-methanocarbathymidine (N-MCT) – featuring a bicyclo[3.1.0]hexane framework.

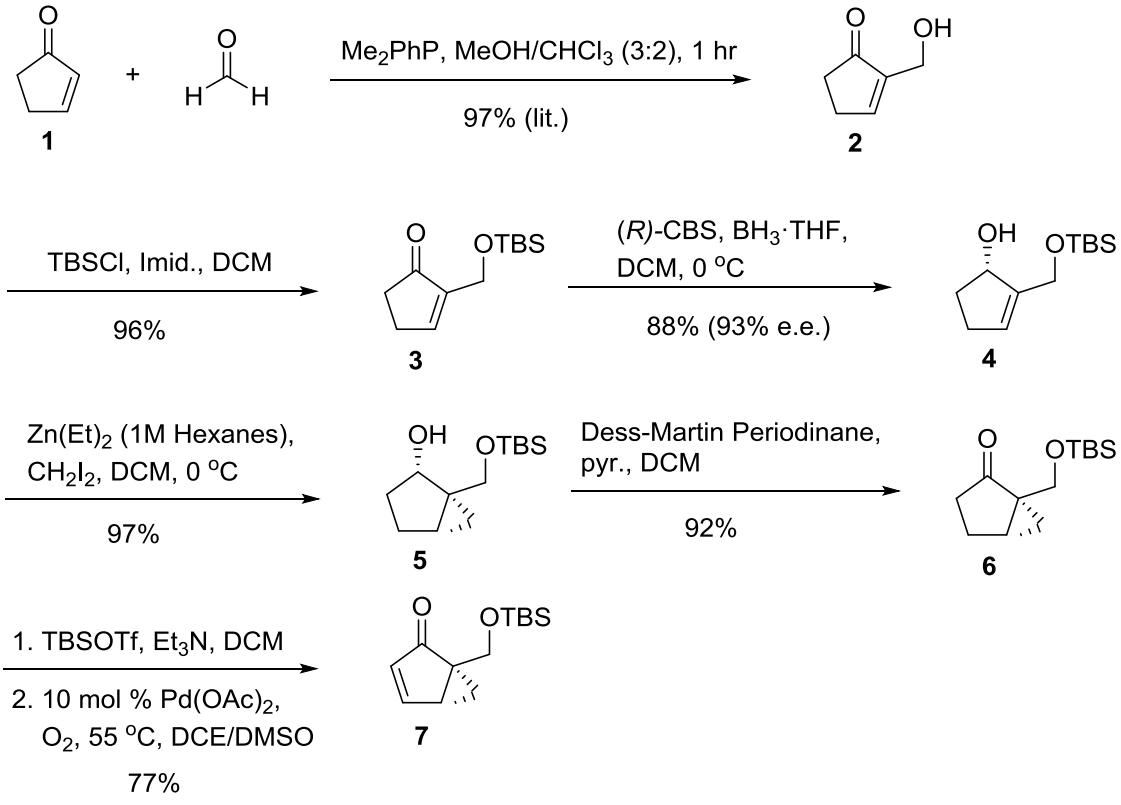
The focus of this research was on studying the combination of using a bicyclo[3.1.0]hexane framework and the incorporation of a 2'-fluorine atom into a synthetic nucleic acid. It was hoped that the fluorine atom would accentuate the 3'-endo-like pucker of this structure as well as increase the Watson-Crick base pairing of the nucleobase through electronic effects. The syntheses of both 2'-fluoro-N-methanocarbathymidine (F-NMC) and its epimer, arabino 2'-fluoro-N-methanocarbathymidine (ara-F-NMC), will be described (Scheme 6). These monomers were used as single point incorporations into 12-mer oligonucleotides at different positions. The binding of these oligonucleotides were measured against a known sequence of both RNA and DNA. The results of those experiments will also be described.



Scheme 6. The structures of ara-F-NMC (T) and F-NMC (T).

Results and Discussion

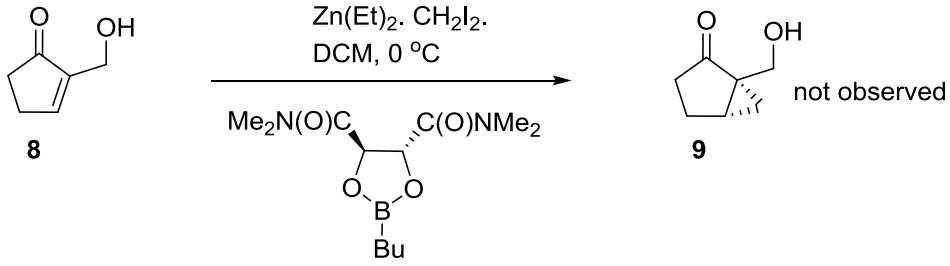
Initial synthetic efforts focused on preparing the cyclopentenone derivative **7** (Scheme 7), which might function as a Michael acceptor for a 1,4-addition from a nitrogenous base. Starting from cyclopentenone **1**, a Baylis-Hilman reaction was performed using a known procedure outlined in the literature to give enone **2**.[24] Additional conditions using additives such as tributylphosphine and DABCO were also employed but were not as efficient as dimethylphenylphosphine for this transformation. It was thought that this product might be



Scheme 7. Optimized conditions for the formation of enone **7**.

further elaborated directly to ketone **9**, using a Charette-modified Simmons-Smith reaction (Scheme 8).[25] However, under all conditions tested, the desired product was not observed. In general, lower yields would be expected when an electron withdrawing group is in conjugation with the olefin.[26]

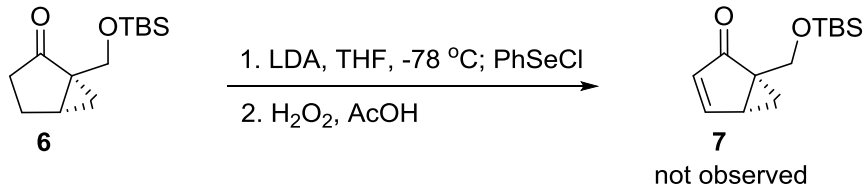
An alternative longer approach was selected for installing the cyclopropane. The primary alcohol **2** was protected using *tert*-butyldimethylsilyl chloride and imidazole in dichloromethane, which afforded the silyl ether **3** in excellent yield. The enone **3** was reduced under Corey-Bakshi-Shibata conditions to provide the corresponding allylic alcohol **4** in high enantiomeric excess (93%).[27–29] The (*R*)-CBS reagent was used to direct the approach of the borane hydride to the β-face of enone **3**.



Scheme 8. Charette-modified Simmons-Smith Reaction using (*L*)-dioxaboralane.

Subjection of compound **4** to Simmons-Smith cyclopropanation conditions using diethylzinc and diiodomethane gave cyclopropane **5** in 97% yield as a single diastereomer. The allylic alcohol directs the cyclopropantion reaction to the same face of the molecule, thus transferring chirality in the process.[30] Oxidation of the alcohol with Dess-Martin periodinane in

the presence of pyridine afforded ketone **6** in excellent yield. Swern, PCC, and IBX oxidation conditions were not as high-yielding, affording 71%, 50%, and 0% yields of **6**, respectively. Using a Saegusa-oxidation protocol, ketone **6** was transformed into the corresponding silyl enol ether using *tert*-butyldimethylsilyl triflate and triethylamine followed by oxidation using catalytic palladium(II) acetate (10 mol %) under an oxygen atmosphere at 55 ^{o}C to give the enone **7** in 77% yield. These are optimized conditions over the original procedure which utilized higher catalyst loading (30 mol %) and higher dilution of the substrate due to its immiscibility in dimethyl sulfoxide or acetonitrile solvents alone. This was later remedied by introducing dichloroethane with dimethyl sulfoxide as a solvent mixture. An attempt at oxidizing the ketone to the enone via a phenylselenoxide 2,3-elimination protocol did not yield the desired product (Scheme 9).[31]



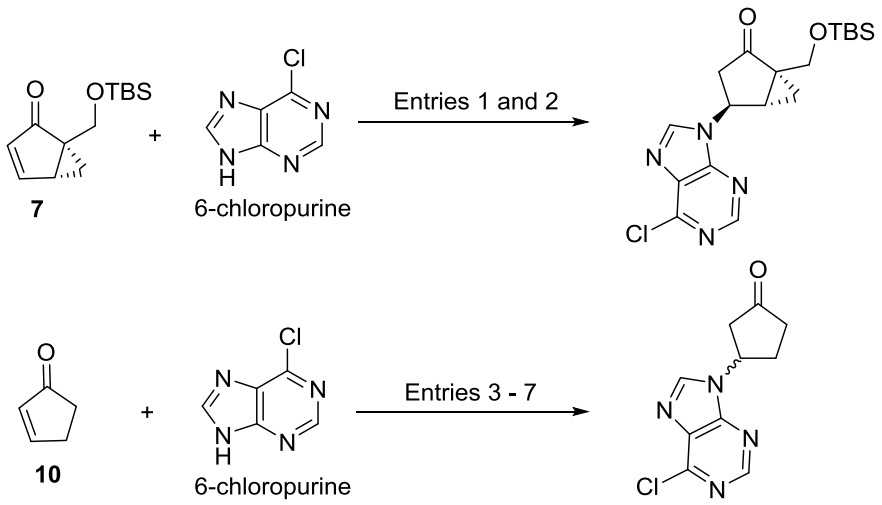
6 **7** not observed

Scheme 9. Phenylselenoxide elimination protocol.

Purine Base Addition and Subsequent Fluorination

With enone **7** in hand, a number of attempts were made to install the 6-chloropurine unit through 1,4-addition to either the enone **7** or to cylopentenone **10** itself (Scheme 10). Deprotonation of 6-chloropurine using sodium hydride in THF followed by addition to the enone **7** produced a complex mixture of products (entry 1). Additionally, these same conditions were

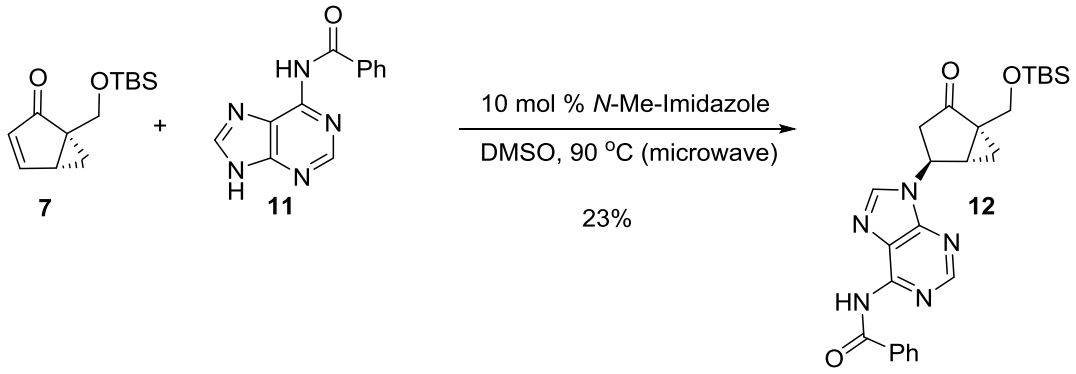
performed followed by addition of TBSCl in an attempt to trap the enolate, but this gave a complex mixture as well. A combination of triethylamine and acetic acid was used to assist the reaction but a complex mixture forms (entry 2). Attempts at adding 6-chloropurine to cyclopentenone using DBU or sodium hydride in DMF, high temperature microwave in water, or under Lewis acid conditions all gave no conversion of the starting materials (entries 3 – 7).



Entry	Conditions	Result
1	NaH, 0 ^{o}C, THF	No Product - Complex Mixture
2	5 equiv. AcOH, 0.2 equiv Et_3N, DCM	No Product - Complex Mixture
3	2 equiv. DBU, CH_3CN	No Conversion
4	NaH, DMF	No Conversion
5	H_2O, 100 ^{o}C (microwave)	No Conversion
6	0.2 equiv. $ZnCl_2$, Toluene/THF (1:1)	No Conversion
7	1.2 equiv. NaI, 1.4 equiv. $CeCl_3$, Alumina, CH_3CN	No Conversion

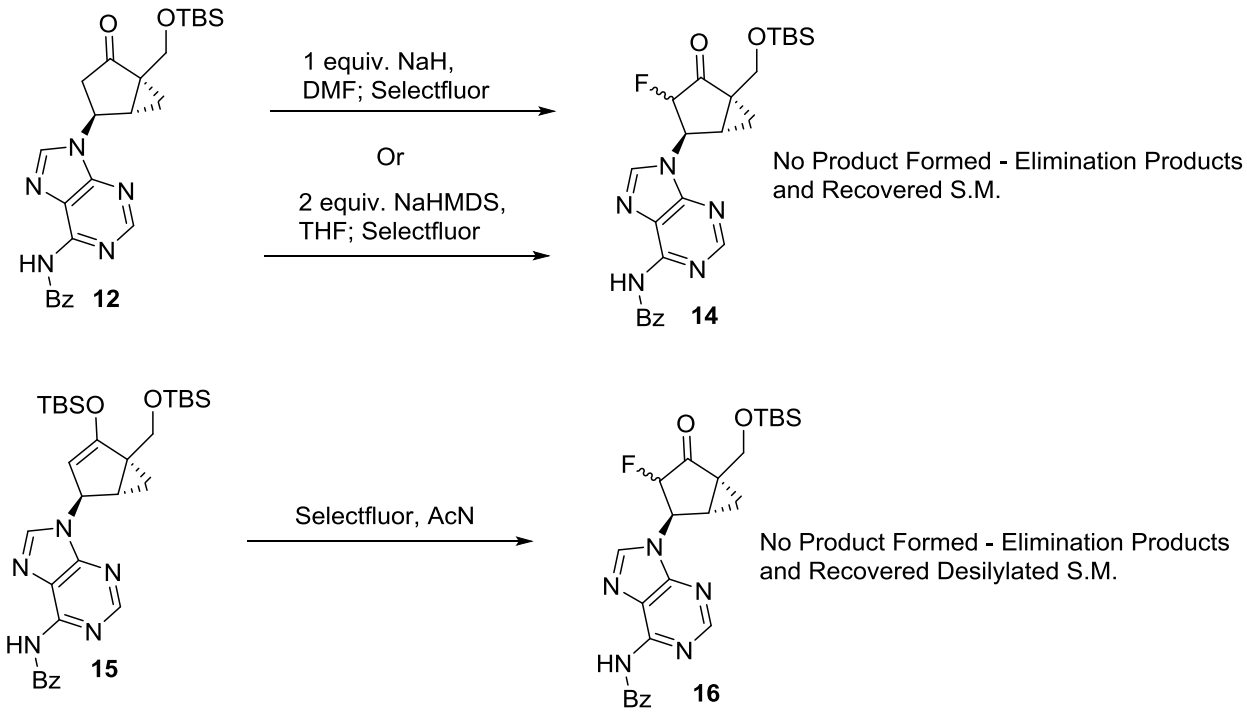
Scheme 10. Attempted reaction conditions for conjugate addition of 6-chloropurine to the enones **7** and **10**.

Since two of the attempts gave partial conversion to a number of different compounds, it was hypothesized that the 6-chloropurine addition may have given rise to different regioisomers among other side reactions. To circumvent this possible problem, *N*-benzoyl adenine **11** was synthesized[32] because it might provide sufficient steric bulk to block the addition of N7 to enone **7**. The conditions for the addition of *N*-benzoyl adenine **11** to enone **7** were *N*-methyl-imidazole in DMSO at 90 ^{o}C (thermally or μwave) to give the ketone **12** as a single diastereomer in 23% yield. Although this reaction was low yielding, it gave only one product which is assumed to have added from the less sterically hindered β-face of enone **7**, as required for the synthesis of the desired target (Scheme 11).



Scheme 11. Conjugate addition of *N*-benzoyl adenine **11** to the enone **7**.

Treatment of the ketone **12** with sodium hydride at 0 ^{o}C in DMF followed by addition of Selectfluor resulted in the recovery of starting material as well as enone **7** as the β-eliminated product (Scheme 12). This same result occurred when the ketone **12** was treated with sodium bis(trimethylsilyl)amide at -78 ^{o}C in THF followed by addition of Selectfluor. It is reasonable



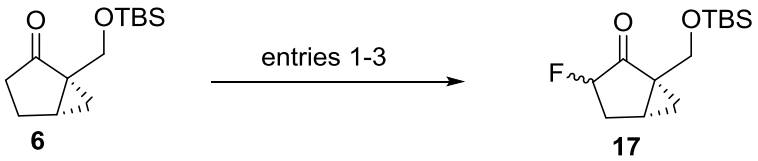
Scheme 12. Attempts at fluorinating ketone **12**.

to speculate that the β-elimination process is favorable due to the weak basicity of the anion of *N*-benzoyl adenine, which makes it a good leaving group. The silyl enol ether **15** can be formed through treatment of the ketone **12** with *tert*-butyldimethylsilyl triflate and triethylamine in dichloromethane (34% yield). Subsequent treatment of the enol ether **15** with Selectfluor in acetonitrile results in β-elimination of the nitrogenous base as well as recovery of starting material.

Synthesis Via Initial C-F Bond Formation

As a result of the problem of elimination of the purine base in the Michael adducts under basic conditions, we sought to install the C-F bond prior to the 1,4-addition reaction. The ketone **6** was subjected initially to sodium hydride followed by the addition of Selectfluor, but resulted

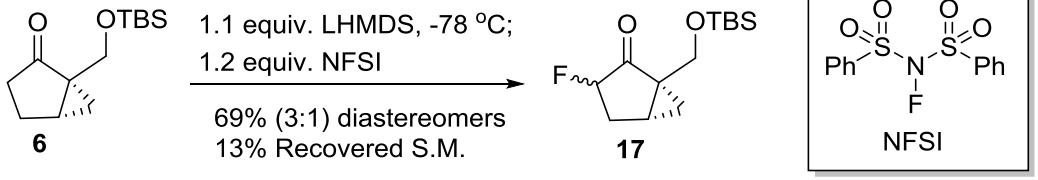
in almost complete recovery of the starting material (Scheme 13, entry 1). Alternative conditions of forming the silyl enol ether prior to treatment with Selectfluor resulted initially in almost complete recovery of starting material. Additional drying of the solvent prior to the reaction showed partial conversion to the α-fluoro ketone **17** (entries 2 and 3). These results were discouraging. As a result, the same conditions of prior formation of the silyl enol ether followed by fluorination were conducted on the simpler cylcopentanone **18.** This resulted in 30% yield of the corresponding α-fluoro ketone **19**, which meant that ketone **6** was more resistant to fluorination by Selectfluor. It was later discovered that treatment of the ketone **6** with LHMDS



6 **17**

Entry	Conditions	Result
1	2.2 equiv. NaH, THF; Selectfluor in CH_3CN, -40 ^oC to rt	94% Recovered S.M.
2	i. TMSOTf, pyr, DCM ii. Selectfluor, CH_3CN	92% Recovered S.M.
3	i. TMSOTf, pyr, DCM ii. Selectfluor, CH_3CN, mol. sieves.	Partial Conversion to Cmpd. **17**.

18 **19**



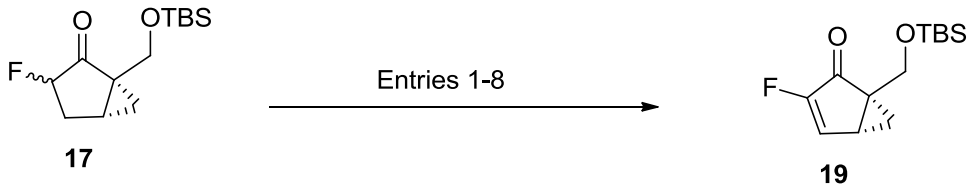
6 **17**

Scheme 13. α-Fluorination of the ketone **6**.

(or NaHMDS) followed by addition of an alternate fluorination agent, *N*-fluorobenzene-sulfonimide (NFSI), affords the product **17** in good yield as a 3:1 mixture of diastereomers.

Oxidation of α-fluoroketone **17** to the corresponding enone **19** proved to be problematic. Applying the same conditions that were used for the oxidation of the des-fluoro ketone **6** for the oxidation of the α-fluoroketone **17** afforded a complex mixture of products (Scheme 14, entry 1). Using a bromination-dehydrobromination sequence resulted in a similar outcome (entry 2). It was hoped that the oxidation would occur well using a 2,3-elimination process. Attempted installation of a phenylsulfoxide moiety using strong base and the methylbenzene sulfinate prior to a thermal rearrangement gave a complex mixture (entry 3).

Formation of the α-phenylselenide from ketone **17** using NaHMDS followed by the addition of phenylselenyl chloride resulted in complete conversion. The subsequent oxidation of the selenide prior to the 2,3-rearrangement required optimization (entries 4-8). Treatment of the crude mixture after the selenide formation with sodium metaperiodate in THF and water afforded the desired product in 20% yield (entry 4). Attempts at oxidizing with hydrogen peroxide (30% aq) in ethyl acetate/THF in the presence of sodium bicarbonate, gave the product with a slightly better yield of 31% (entry 5). Changing the base to *N*,*N*-diethylamine and oxidizing with hydrogen peroxide in THF gave products that were highly polar by thin layer chromatography (entry 6). It is possible that the amine may have added to the desired product. Oxidation with sodium metaperiodate and sodium bicarbonate in a methanol and water mixture resulted in poor conversion as well as the unexpected formation of a heavy precipitate (entry 7). The conditions of pyridine and hydrogen peroxide (30% aq) in dichloromethane at ^{o}C were found to give the enone **19** in good yield (82%) (entry 8).



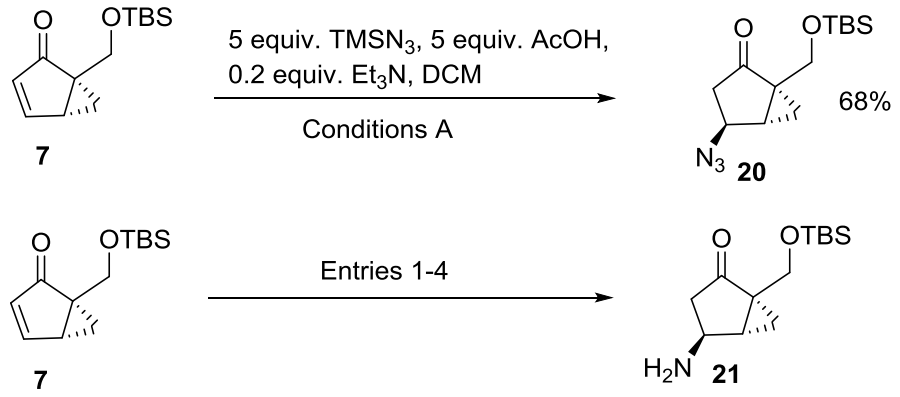
17 **19**

Entry	Conditions	Result
1	i. TBSOTf, Et_3N, DCM ii. 10 mol % $Pd(OAc)_2$, O_2, 45 ^oC, DMSO/DME	Complex Mixture
2	i. NaHMDS, THF, -78 ^oC; Br_2 ii. KOH	Complex Mixture
3	i. LDA, THF, -78 ^oC; PhS(O)OMe ii. Toluene, reflux	Complex Mixture
4	i. NaHMDS, THF, -78 ^oC; PhSeCl ii. 10 equiv. $NaIO_4$, THF/H_2O (1:1)	20% Yield
5	i. NaHMDS, THF, -78 ^oC; PhSeCl ii. $NaHCO_3$, H_2O_2, EtOAc/THF (2:1)	31% Yield
6	i. NaHMDS, THF, -78 ^oC; PhSeCl ii. Et_2NH, H_2O_2, THF	Undesired Polar Products
7	i. NaHMDS, THF, -78 ^oC; PhSeCl ii. $NaHCO_3$, $NaIO_4$, MeOH/H_2O (6:1)	Poor Conversion - w/Heavy ppt.
8	i. NaHMDS, THF, -78 ^oC; PhSeCl ii. Pyr., H_2O_2, DCM, 0 ^oC	82% (avg. of two runs)

Scheme 14. Oxidation of the α-fluoroketone **17** to the enone **19**.

Synthesis of the β-Amino Ketone (21)

During the course of investigating the oxidation of ketone **17** to enone **19**, we also looked into the formation of β-amino ketone **21** from des-fluoro enone **7**. Addition of trimethylsilyl azide and acetic acid followed by the addition of triethylamine and the starting material were found to give azide **20** in good yield as a single diastereomer (Scheme 15). It is assumed that the addition occurred to the less sterically hindered β-face of enone **7** to give the azide **20**. A few



Entry	Conditions	Result
1	i. Conditions A ii. TMSCl, NaI, CH_3CN	Complex Mixture
2	i. Conditions A ii. PPh_3, THF/H_2O	Complete Conversion
3	i. Conditions A ii. 5% Pd/C, H_2, EtOAc/MeOH	Isolation of Ketone **6** in 37% Yield
4	i. NH_4OH, MeOH	Not Isolated - Complete Conversion to Desired Product by NMR

Scheme 15. Conversion of the enone **7** to the β-amino ketone **21**.

different methods were attempted to reduce the corresponding azide **20** to the primary amine **21**. Treatment of the azide with trimethylsilyl chloride and sodium iodide in acetonitrile gave a complex mixture of products (entry 1).[33] Hydrogenation conditions, palladium on carbon under a hydrogen atmosphere, resulted in isolation of the completely reduced ketone **6** in 37% yield (entry 3). This process was assumed to occur via elimination of an azide anion followed by reduction of the enone. Staudinger reduction conditions were found to be sufficient for the reduction of the azide **20** to give the amine **21** (entry 2). However, we elected to use a more direct means of forming this product through the addition of ammonia by adding the substrate to

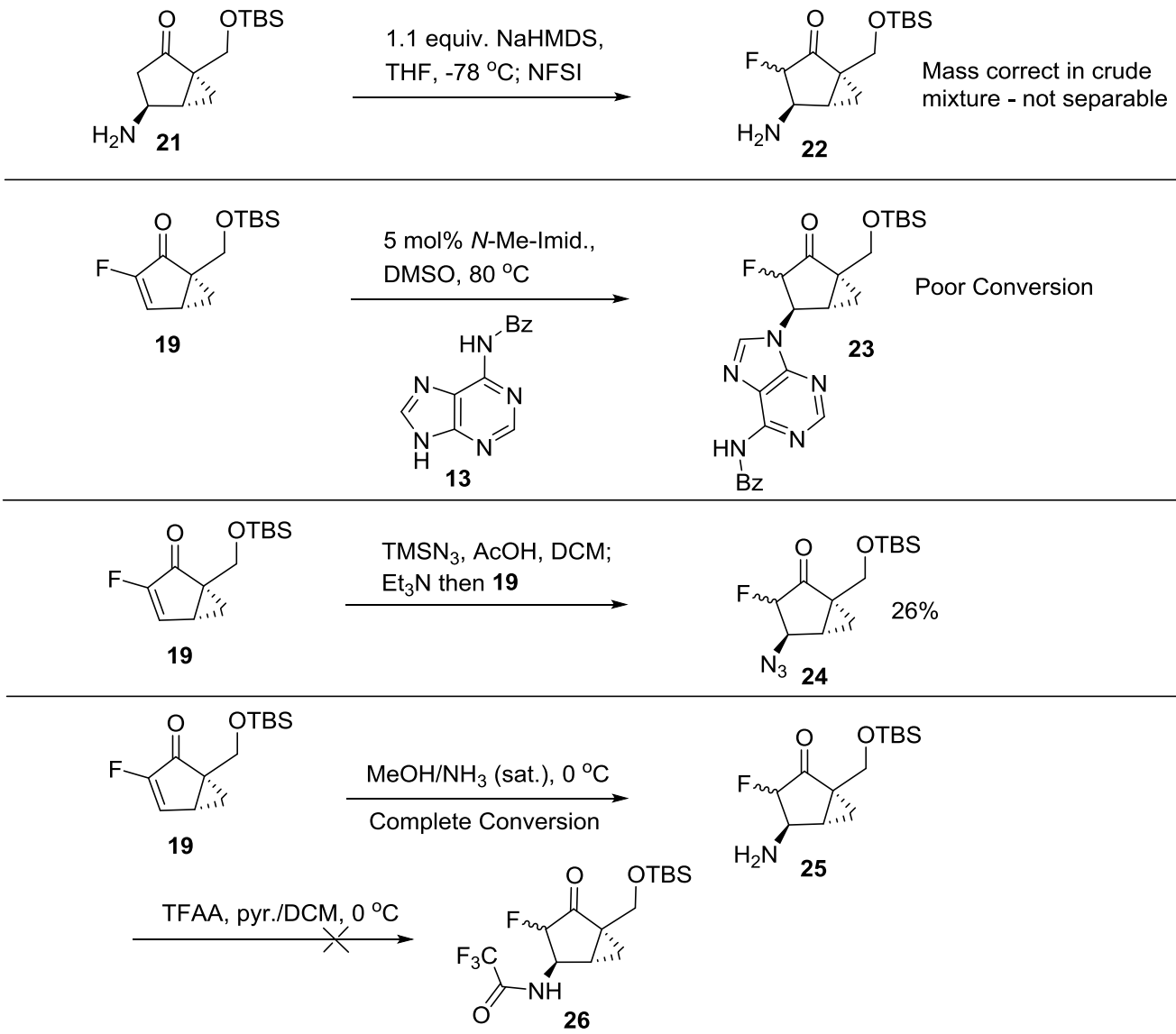
ammonium hydroxide in methanol (entry 4). This compound was never isolated but rather detected by crude NMR.

Combining Methods for Forming C-F and C-N Stereocenters

Up to this point, we had attempted to find conditions for both the nucleophilic addition of a nitrogen nucleophile (addition of a purine base, azide, or ammonia) and the installation of fluorine were resolved independently of each other. Thus combining these methods by adding a nucleophile to an already fluorinated substrate was the logical next step.

In an attempt to form the fluorinated ketone **22**, the β-amino ketone **21** was treated with NaHMDS followed by NFSI. The resulting crude mixture was found to have the correct mass by LCMS, but proved to be inseparable by flash column chromatography on silica gel (Scheme 16). Next, the 1,4-addition of the nucleophiles, *N*-benzoyl adenine **13**, azide, and ammonia, to the α-fluoro enone **19** was studied (Scheme 16). Treatment of the enone **19** with 5 mol% of *N*-methylimidazole and the purine **13** in dimethyl sulfoxide at 80 ^{o}C resulted in little or no conversion of the starting material. These were the same conditions previously used to add *N*-benzoyl adenine to the simple enone **7** in 23% yield. Combining trimethylsilyl azide, acetic acid, triethylamine and the enone **19** afforded the desired azide **24** in 26% yield. We had anticipated that the fluoro enone **17** would be more electrophilic, which would result from the electronegativity of fluorine stabilizing the developing charge alpha to the carbonyl during the addition process. What was puzzling was that the yield of the addition of azide to the fluoro enone **19** (26% yield) was much less than what resulted from adding it to the des-fluoro enone **7** (68% yield). Treatment of the enone **19** with saturated ammonia in methanol resulted in

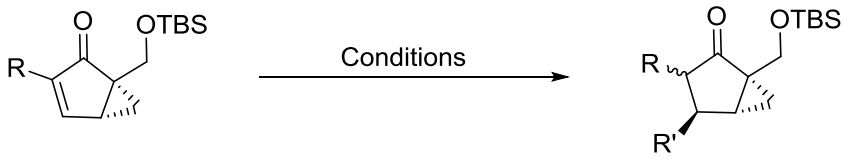
complete conversion, presumably to the Mannich base **25**. Attempts to isolate this molecule as the trifluoroacetamide **26** failed.



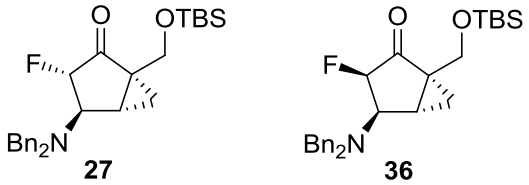
Scheme 16. Fluorine addition to the β-amino ketone **21** and addition of nitrogen nucleophiles to the α-fluoro-enone **19**.

Disappointed by the difference in reactivity between the des-fluoro enone **7** and the fluoro enone **19**, we then turned our attention to additional nucleophiles. Attempts at conjugate addition of benzyl carbamate to either the des-fluoro enone **7** or the fluoro enone **19** under Lewis acid conditions were not fruitful and resulted in complex mixtures, desilylation, no conversion, or conversion to an undesired product (Scheme 17, entries 1-5). No conversion was observed when the ketone **19** was treated with acetic acid and sodium nitrite in tetrahydrofuran, which would have given the β-nitro ketone (entry 6).[34,35] Switching to benzylamine as a nucleophile was thought to remedy the difficulties that were seen with the addition of ammonia. The idea was that it may have better facial selectivity, improve the mobilization on silica during purification, as well as limit any formation of the Schiff base that may have formed with a less bulky nucleophile. The addition, which was performed in methanol and with DBU as a catalyst, resulted in moderate conversion to a complex mixture. The thought was that a single benzyl group may not have offered enough steric bulk to prevent some of the addition occurring on the α-face of enone **19** (entry 7). Addition of the larger reagent, dibenzylamine, to the enone **19** in the presence of DBU in a THF/H_2O mixture resulted in 15 % of the trans isomer **27** and 9% of the cis isomer **36**. These compounds were removed from the reaction mixture and the crude mixture could then be concentrated and resubjected to the same reaction conditions. The recycling of the material allowed for an additional 6% of the trans isomer to be isolated (entry 8). The catalyst was then switched to *N*,*N*-dimethylaminopyridine (DMAP), the reaction was performed in acetonitrile, and the concentration of dibenzylamine was lowered. This resulted in the isolation of the trans isomer in 24% yield. Due to the poor conversion and the similarity in yield, it was hypothesized that the products were in equilibrium with the starting material. In an effort to push the equilibrium towards the products, the concentration of dibenzylamine was

increased and found to have little or no impact on the distribution of products by thin layer chromatography. When a small quantity of lithium chloride was added to the fluoro enone, DMAP, and dibenzylamine in dimethyl sulfoxide, a preferential dissolution of the products was observed. Adding lithium chloride in three portions over the course of six hours increased the yield of the reaction to 59% of the trans and 15% of the cis addition products.

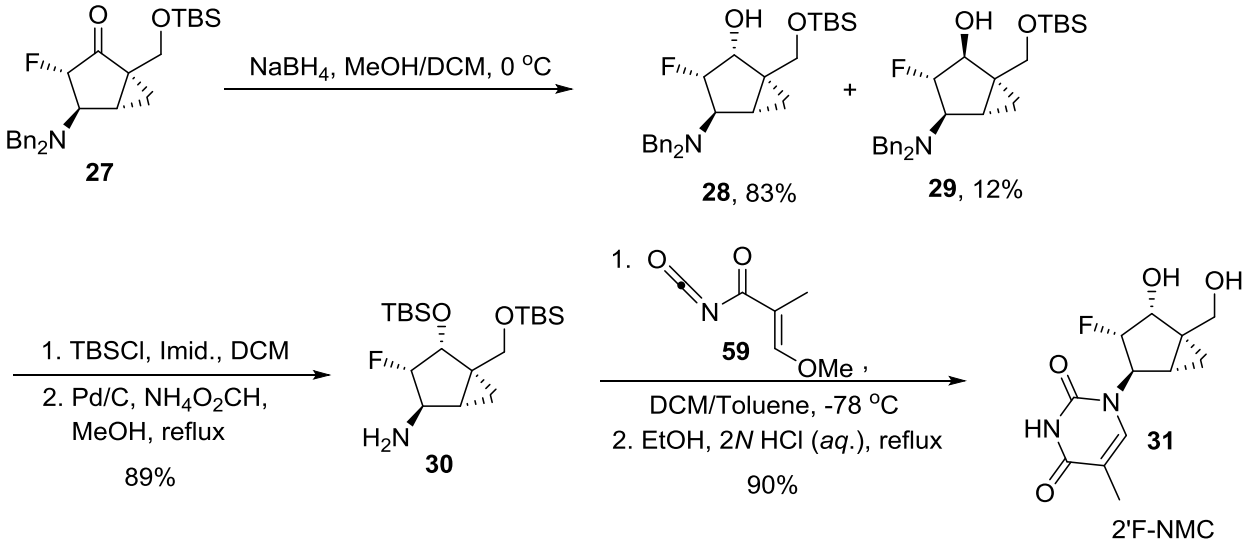


Entry	Additive	Nucleophile (R')	R	Solvent	Result
1	$Bi(NO)_3$	$NH_2C(O)OCH_2Ph$	H	DCM	Slow Conversion to Complex Mixture
2	$Cu(OTf)_2$	$NH_2C(O)OCH_2Ph$	H	DCM	Conversion to Unknown Product
3	$Cu(OTf)_2$	$NH_2C(O)OCH_2Ph$	F	DCM	Desilylation Occurred
4	$ZnCl_2$	$NH_2C(O)OCH_2Ph$	F	DCM	No Conversion
5	$BF_3{\cdot}OEt_2$	$NH_2C(O)OCH_2Ph$	F	DCM	Desilylation Occurred
6	AcOH	$NaNO_2$	F	THF	No Conversion
7	DBU	NH_2Bn	F	MeOH	Moderate Conversion to Complex Mixture
8	DBU	10 eq. $NHBn_2$	F	THF/H_2O	15% trans Addition Product **27** 9% cis Addition Product **36** Additional 6% trans Addition Product **27** (Recycled Crude)
9	DMAP	1.7 eq. $NHBn_2$	F	CH_3CN	24% trans Addition Product **27**
10	DMAP, LiCl	$NHBn_2$	F	DMSO	59% trans Addition Product **27** 15% cis Addition Product **36**



Scheme 17. Addition of benzyl carbamate, sodium nitrite, benzylamine, and dibenzylamine to the fluoro enone **19** and the enone **7**.

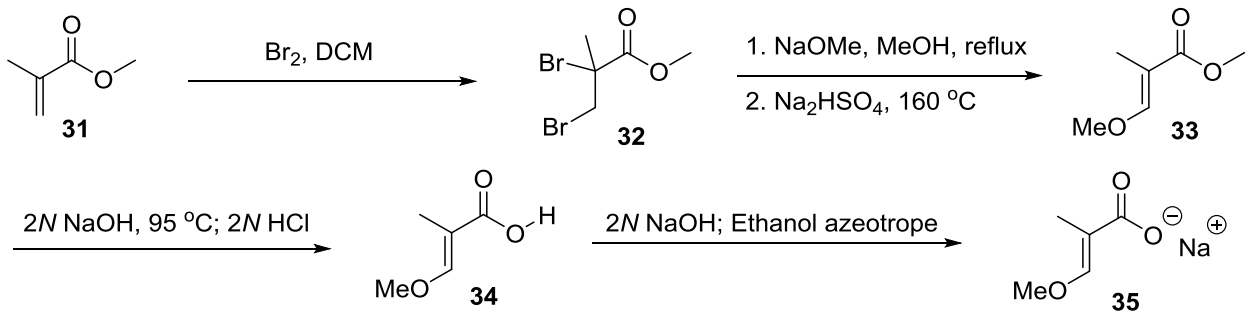
With both the trans and cis 1,4-conjugate addition products **27** and **36** in hand, we then turned towards the reduction of the ketone. Addition of sodium borohydride to the ketone **27** in a methanol/dichloromethane solvent mixture afforded the desired reduction product **28** in 83% yield and the corresponding epimer **29** in 12% yield (Scheme 18). Investigations into the reduction of 2-fluoro-4-*t*-butylcyclohexanones have shown that when a C-F bond α to a ketone is in an axial orientation, a strong electronic bias favors the antiperiplanar axial attack by hydride reducing agents. If the C-F bond is equatorial, less electrostatic effects are observed, and thus equatorial attack predominates.[36,37] In this case, this strong electronic bias of reduction was enough to overcome the strong steric hindrance that would be encountered from the dibenzylamine substituent obstructing attack from the Dunitz-angle on the β-face of the ketone **27**.



Scheme 18. Synthesis of 2'F-NMC **31** from the ketone **27**.

The newly formed alcohol **28**, was silylated with *t*-butyldimethylsilyl chloride (TBSCl) in the presence of imidazole in DCM to give the silyl ether **28b** (not shown) in excellent yield. This was installed to prevent the addition of the alcohol to electrophile in subsequent steps. Both benzyl groups were removed in high yield through a hydrogenolysis reaction with palladium on carbon and ammonium formate to give the primary amine **30** in 89% yield.

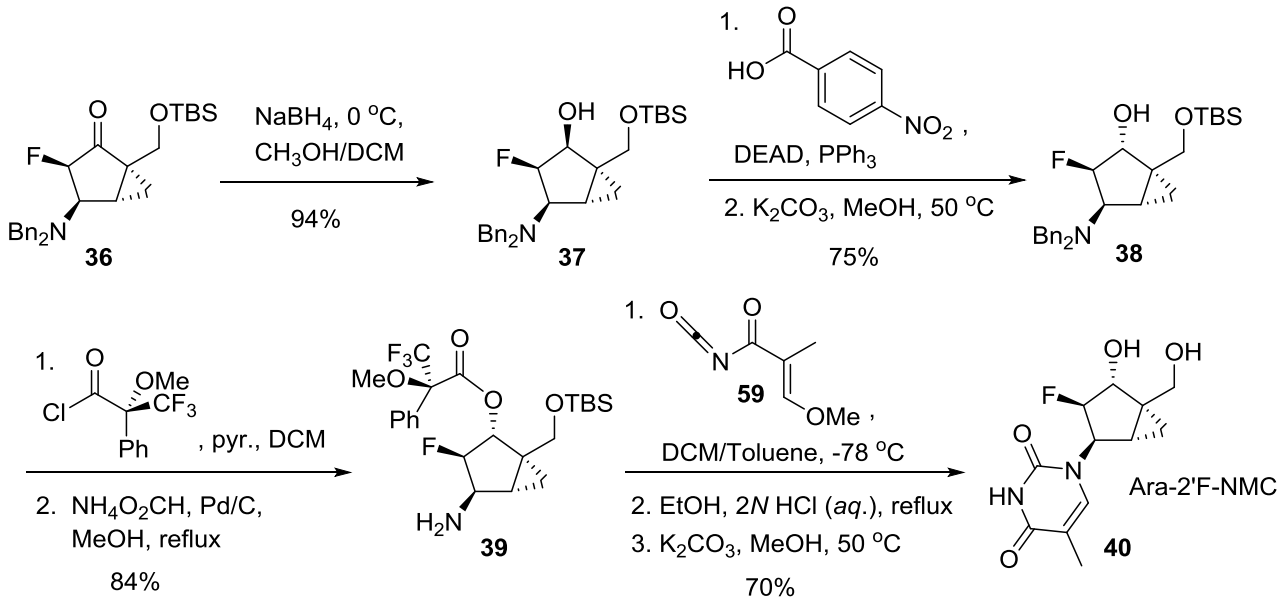
The thymine portion of the molecule was assembled via addition of (*E*)-3-methoxy-2-methyl-2-propenoyl isocyanate **59** to the amine **30**. The requisite carboxylate salt **35** was synthesized using a combination of procedures already known in the literature.[38,39] Methyl methacrylate was brominated using bromine to give the vicinal dibromo ester **32** (Scheme 19). Exposing this compound to sodium methoxide in methanol at reflux resulted in the nucleophilic addition of methoxide. The crude mixture was treated with a catalytic amount of sodium hydrogen sulfate at 160 ^{o}C to eliminate one equivalent of methanol, which gave the β-methoxy ester **33**. Saponification using 2*N* sodium hydroxide (aqueous), followed by acidification of the salt afforded the carboxylic acid **34**. After recrystallization, the sodium carboxylate salt **35** was easily prepared through deprotonation and subsequent azeotropic removal of residual water.



Scheme 19. Synthesis of the carboxylate salt **35**.

In order to form the heterocycle, the acyl isocyanate of **35** was formed *in situ* by treating the carboxylate salt **35** with oxalyl chloride. The acid chloride was refluxed with silver cyanate in toluene to give the isocyanate **59**. This reagent was then added to the primary amine **30** to afford the mono-addition product. The intermediate was refluxed with acidic ethanol to both remove the silyl protecting groups as well as catalyze the cyclization process. This ultimately produced the 2'-fluoro-*N*-methanocarbothymidine (2'F-NMC) **31** in high yield.

The synthesis of arabino 2'-fluoro-*N*-methanocarbathymidine, ara 2'F-NMC, **40**, was carried out by starting with the minor product **36** obtained from the addition of *N*,*N*-dibenzylamine to the fluoro enone **19.** Reduction of this compound with sodium borohydride in a methanol/dichloromethane solvent mixture at 0 ^{o}C afforded the undesired alcohol in 94% yield (Scheme 20). This reduction had occurred from the α-face of the molecule, which should be much less sterically hindered. The other isomer was not observed in this process. In contrast to the reduction of the ketone **27**, the C-F bond in this case is in a pseudo-equatorial orientation, thus it has less interaction with the anti-bonding orbital of the neighboring ketone. The electronic bias for reducing from a given face over another was less prominent vs what was observed before (*vide supra).* Instead, sterics seem to be the predominating factor, which would account for the lack of detection of the other isomer. The configuration of the C3 alcohol was inverted via a Mitsunobu reaction. The alcohol **37** was treated with *p*-nitrobenzoic acid, diethyl azodicarboxylate, and triphenylphosphine, which afforded the inverted benzoate in good yield. The benzoate was subsequently cleaved using potassium carbonate in warm methanol, affording

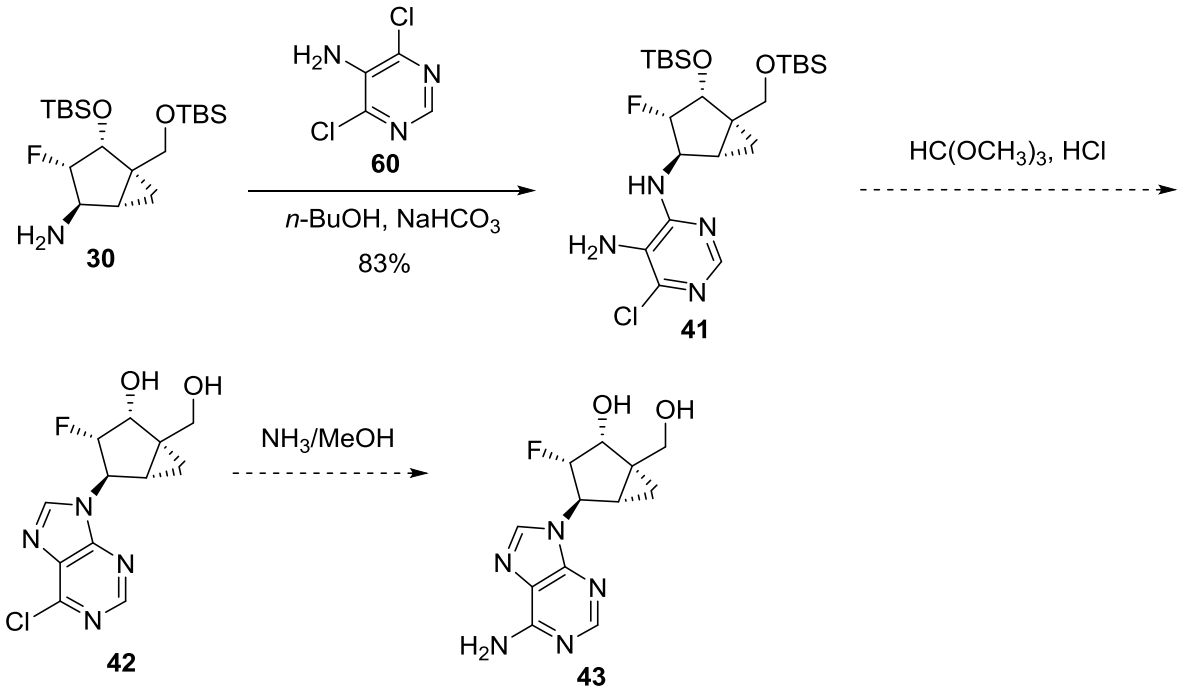


Scheme 20. The synthesis of the ara 2'F-NMC **40** from the fluoro ketone **36**.

the desired configuration of the alcohol **38**. The alcohol **38** was converted to the Mosher's ester in excellent yield using pyridine and the acid chloride derived from (*R*)-(+)-2-methoxy-2-(trifluoromethyl)phenylacetic acid. The installation of this ester was performed to ensure the optical purity of this late-stage intermediate. The primary amine **39** was obtained in an overall yield of 84% after a hydrogenolysis reaction using palladium on carbon and ammonium formate in refluxing methanol. The cyclization of the thymine portion of this molecule was done as before using the acyl isocyanate **59**, except that in this case the ester did not cleave in refluxing acidic ethanol. The cleavage of the ester was accomplished using potassium carbonate in warm methanol, as was done with the benzoate, to ultimately give the ara 2'F-NMC **40** in good yield.

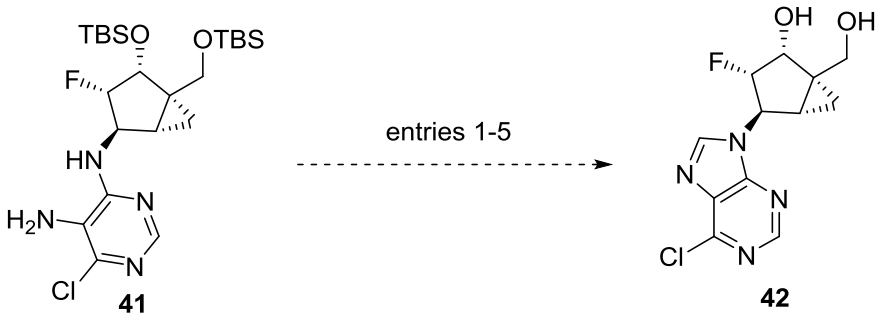
Attempted Synthesis of Adenine Variant of N-Methanocarbathymidine

During these studies, attempts were made to synthesize an adenosine mimetic from the primary amine **30**. We elected to use a synthetic sequence outlined by Wiemer and coworkers in which they form a adenine heterocycle from the primary amine bearing (*R*)-2-amino-1-propanol.[40] The sequence started with an S_NAr addition reaction on 5-amino-4,6-dichloropyrimidine **60** in the presence of a mild base. The addition of the primary amine **30** to **60** proceeded smoothly to give the pyrimidine addition product **41** in high yield (Scheme 21). The idea was to perform the ring closure in the presence of trimethyl orthoformate and acid catalyst according to the published protocol, and then subsequently add ammonia to the 6-chloropurine bearing compound **42** to furnish the completed adenosine-like analog **43**.



Scheme 21. Proposed synthetic sequence for making the adenosine mimetic **43** from the primary amine **30.**

Attempts to perform the ring closure on the bis-amino pyrimidine compound **41** failed (Scheme 22). Reacting this substrate with an abundance of either hydrochloric acid or trimethylsilyl triflate in trimethyl orthoformate resulted in a large number of products (Scheme 22, entries 1 and 3). The addition of a catalytic amount of tosic acid resulted in the addition of trimethyl orthoformate without ring closure (entry 2). The same result occurred when an abundance of acetic anhydride was used to catalyze the reaction (entry 4). Considering that partial addition was occurring, a fifth attempt was made to perform the addition in the presence of triethyl orthoformate, pyridine hydrochloride, and DMF at 120 ^{o}C. In this case, no conversion was observed (entry 5).

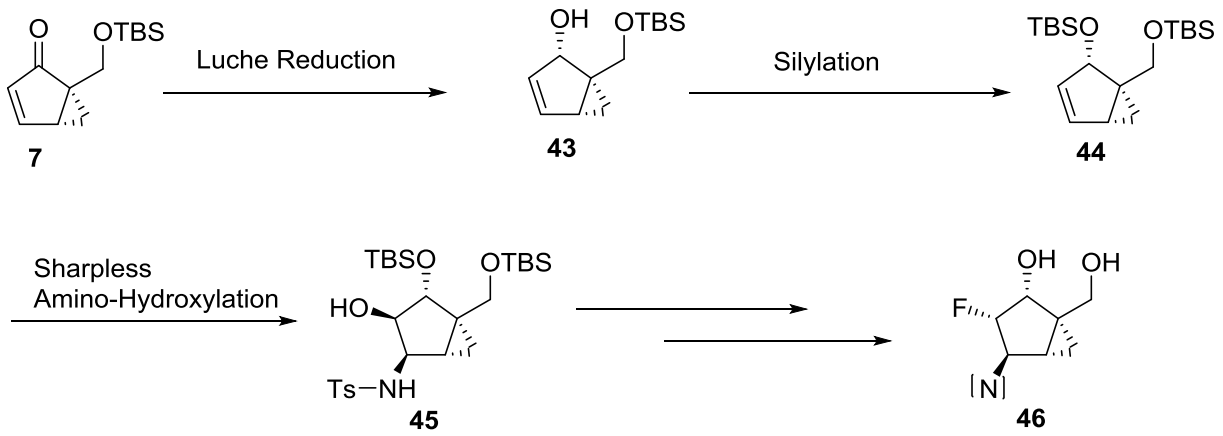


Entry	Conditions	Result
1	0.25M $CH(OMe)_3$, 2 equiv. TMSOTf	Complex Mixture
2	0.25M $CH(OMe)_3$, 0.1 equiv. TsOH	Stalls - Addition w/o ring closure
3	0.25M $CH(OMe)_3$, 5 equiv. 12M HCl (aq.)	Complex Mixture
4	0.25M $CH(OMe)_3/Ac_2O$ (1:1)	Stalls - Addition w/o ring closure
5	$CH(OEt)_3$, pyridine hydrochloride, DMF, 120 ^{o}C	No Conversion

Scheme 22. The various attempts of performing the 6-chloropurine ring closure.

Synthetic Route Utilizing Sharpless Asymmetric Amino-Hydroxylation

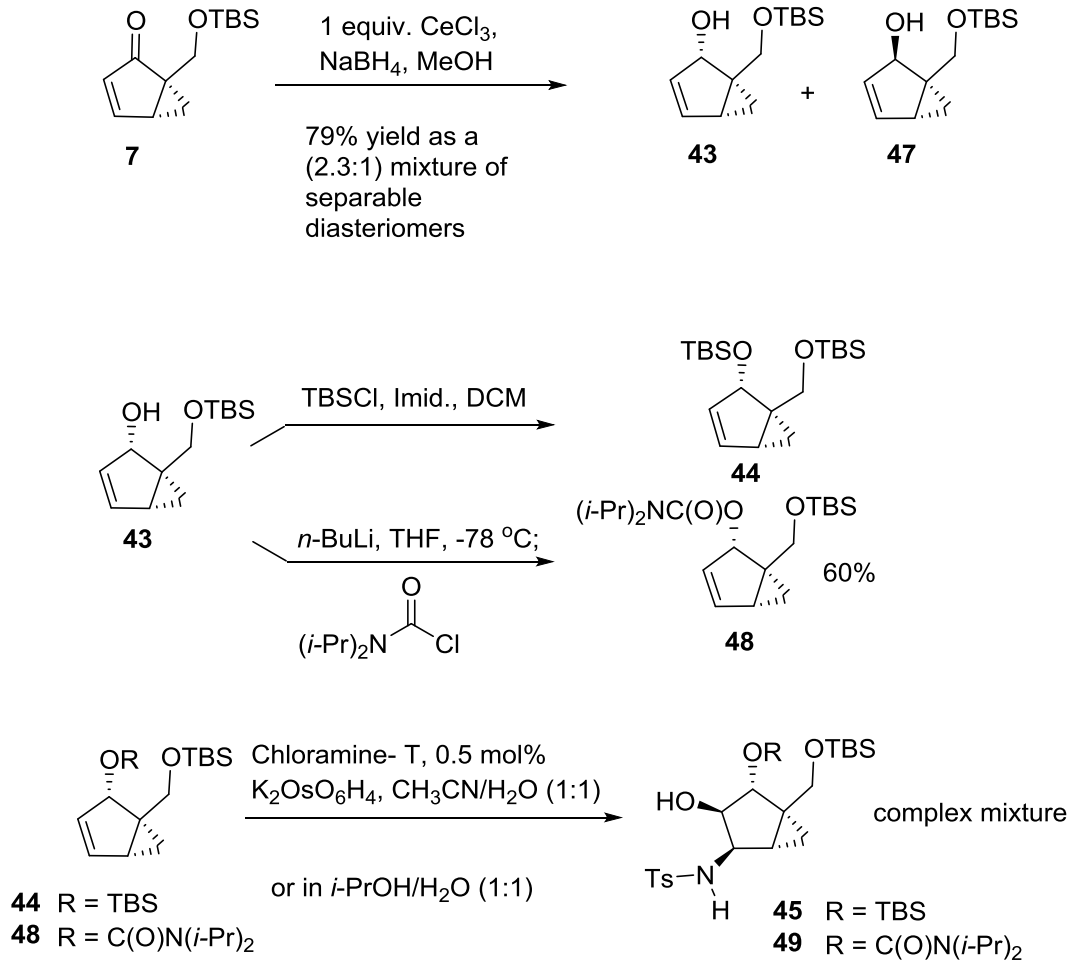
During the course of these studies, another route involving a Sharpless amino-hydroxylation reaction was proposed. It was envisioned that enone **7** could be reduced under Luche conditions to give allylic alcohol **43**. It was hoped that after protection of the alcohol with a sterically bulky group, an amino-hydroxylation reaction might form the aminoalcohol **45** (Scheme 23). The alcohol in this case would serve as a precursor for the installation of fluorine with inversion, for example via treatment with diethylaminosulfur trifluoride (DAST).



Scheme 23. Original proposed forward synthesis using Sharpless asymmetric amino-hydroxylation.

Treatment of enone **7** with sodium borohydride in the presence of cerium (III) chloride heptahydrate in methanol afforded the allylic alcohols, **43** and **47**, in 79% as a 2.3:1 mixture of diastereomers (Scheme 24). The exact stereochemical assignment could not be made; however, it was assumed that the major product would involve addition of hydride from the face opposite

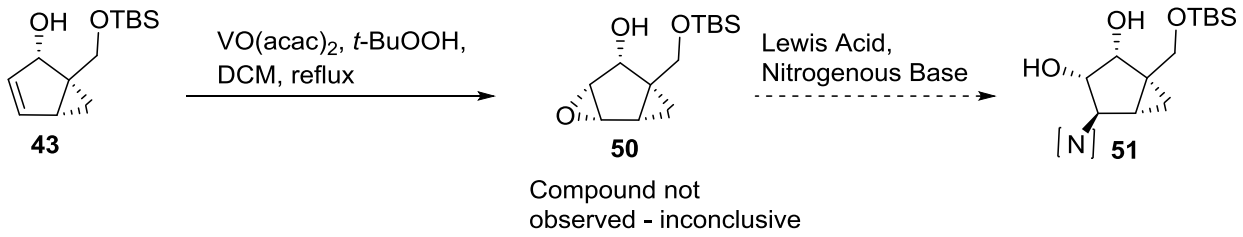
of the cyclopropane for steric reasons. The major product **43** was carried on to the silyl ether **44** through treatment with TBSCl and imidazole. The allylic alcohol **43** was also elaborated to the bulky carbamate **48** in moderate yield through treatment with *n*-butyllithium followed by *N*,*N*-diisopropylcarbamoyl chloride. Both the silyl ether **44** and the carbamate **48** were treated under Sharpless asymmetric amino-hydroxylation conditions in either an acetonitrile/water or



Scheme 24. Attempted elaboration of enone **7** to amino-alcohols **45** and **49** using a Sharpless amino-hydroxylation protocol.

isopropanol/water solvent mixtures. All of these reactions gave good conversion but resulted in a large mixture of products. Therefore this amino-hydroxylation approach was abandoned.

One future goal would be to utilize the alcohol of **43** for the directed epoxidation of the olefin of this compound (Scheme 25). Attempts were made to carry out this transformation using vanadyl acetylacetonate and *tert*-butylhydroperoxide at reflux. The corresponding epoxide **50** was not observed. This approach was therefore abandoned.



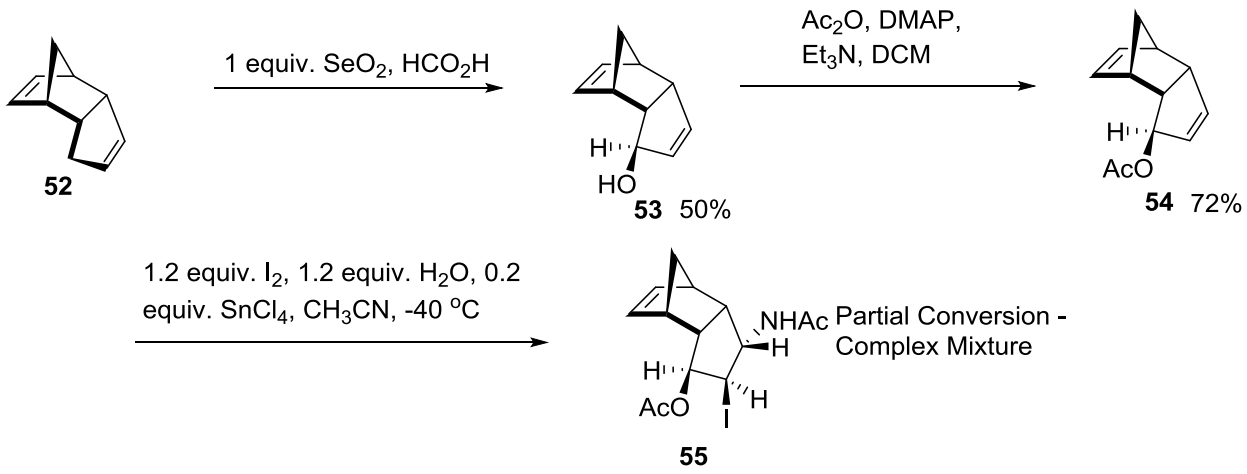
Scheme 25. Vanadyl acetylacetonate directed epoxidation of allylic alchol **43**.

Other Synthetic Approaches

Another proposed route towards 2'F-NMC and ara-2'F-NMC was briefly investigated. This involved starting with dicyclopentadiene **52**, which was envisioned to protect the requisite olefin necessary for cyclopropanation. We thought that the C-F and C-N functionalized stereocenters might be installed prior to cyclopropanation. The dicyclopentadiene adduct could then undergo a retro-Diels-Alder reaction to release the olefin necessary for cyclopropanation.

Using an existing protocol, dicyclopentadiene **52** was treated with selenium dioxide in the presence of formic acid, which gave the allylic alcohol **53** in 50% yield (Scheme 26).[41] Subsequent acetylation using acetic anhydride, dimethylaminopyridine, and triethylamine

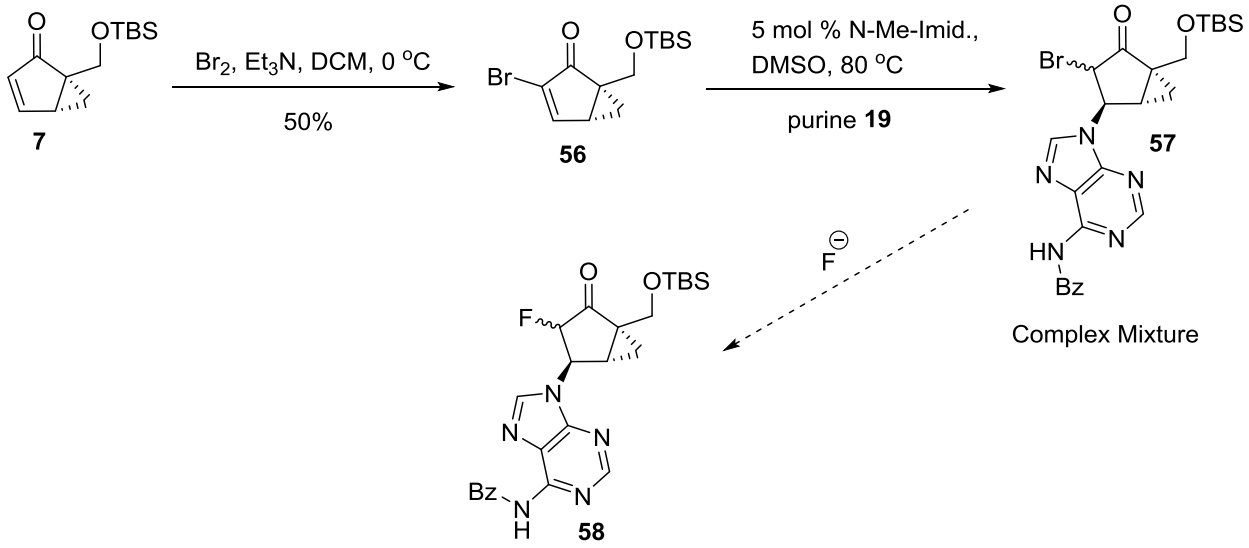
afforded the allylic acetate **54** in good yield. The next attempted transformation utilized a methodology developed by Corey in his synthetic approach to Tamiflu.[42,43]



Scheme 26. Attempted utilization of cyclopentadiene as a protection group – installation of C-F and C-N functionalized stereocenters prior to cyclopropanation.

The allylic acetate **54** was treated with iodine in the presence of water and a Lewis acid in acetonitrile. This reaction resulted in only partial conversion to a large number of products. We originally thought that a three-centered two-electron iodonium intermediate would form from the olefin nearest to the acetate group and on the less hindered face of the molecule. Subsequent S_N2 type nucleophilic opening of this iodonium intermediate by acetonitrile, followed by hydration to the acetamide might give rise to **55**. Unfortunately this was not the case for this system. The other olefin may have reacted preferentially.

Finally, enone **7** was transformed into the α-bromo enone **56** using bromine and triethylamine in dichloromethane (Scheme 27). It was thought that substitution of bromine by an anionic fluorine source, such as silver(I) fluoride, under conditions that did not foster carbanion would prevent elimination of the purine base and thus give the α-fluoro ketone **58**. Unfortunately, reaction of the purine base **19** under the usual conditions resulted in many products.



Scheme 27. Conversion of the enone **7** into the α-bromo enone **56** and attempted conjugate addition of purine **19** to the α-bromo enone **56**.

Biological Data

Both synthetic nucleosides F-NMC **31** and ara-F-NMC **40** were incorporated into 12-mer oligonucleotides at various positions in the sequence. Their melting temperatures were assessed with a known sequence of DNA and RNA (Table 1). It was found that the average melting

temperature change for a single inclusion of F-NMC **31** in the sequence effectively increased by +2.2 ^{o}C against RNA and decreased by -1.9 ^{o}C against DNA. The increase in melting temperature against RNA was on average +1.4 ^{o}C higher than that of F-RNA (U) per single inclusion in the sequence. In contrast, incorporation of ara-F-NMC **40** was destabilizing vs RNA for any modification made. The average destabilization against RNA was -2.8 ^{o}C and against DNA was -6.2 ^{o}C. In addition, this molecule was more destabilizing when included in the sequence vs F-RNA (U).

T_m/mod. (^{o}C) Against RNA

5' to 3' Sequence	31	40	F-RNA (U)
GGA**T**GTTCTCGA	+2.2	-2.6	+1.1
GGATG**T**TCTCGA	+2.7	-2.2	-0.3
GGATGT**T**CTCGA	+2.0	-4.3	+1.3
GGATGTTC**T**CGA	+2.6	-2.1	+1.2
Avg. Chg. in T_m/mod.	+2.2	-2.8	+0.8

T_m/mod. (^{o}C) Against DNA

5' to 3' Sequence	31	40	F-RNA (U)
GGA**T**GTTCTCGA	-2.7	-7.3	-0.5
GGATG**T**TCTCGA	-0.9	-4.6	-1.3
GGATGT**T**CTCGA	-3.0	-8.1	-1.9
GGATGTTC**T**CGA	-1.1	-4.9	-1.0
Avg. Chg. in T_m/mod.	-1.9	-6.2	-1.2

Melting temperatures recorded in a medium consisting of sodium phosphate buffer (7.2 pH, 10 mM) and sodium chloride (10 mM) and EDTA (0.1 mM) by using the RNA complementary strand 5'-r(UCGAGAACAUCC)-3'. The bold letters in the sequence represent the position of synthetic monomer incorporation. The synthesis of the oligomers and the melting temperature experiments were performed by Isis Pharmaceuticals, Inc.

Table 1. Melting temperatures of modified oligonucleotide duplexes that incorporate synthetic monomers F-NMC **31**, ara-F-NMC **40**, or F-RNA (U).[44]

Conclusion

In conclusion, the synthetic nucleosides F-NMC **31** and ara-F-NMC **40** were synthesized in 13 and 16 steps "respectively" from cyclopentenone. The key features of the syntheses are the facile desymmetrization using the CBS-reagent, fluorine installation using NFSI, and a diastereoselective 1,4-addition using dibenzylamine. When incorporated into oligonucleotides, the synthetic nucleoside F-NMC **31** proved to be beneficial towards increasing binding with RNA.

Chapter 2: An Approach Towards the Synthesis of Morphine

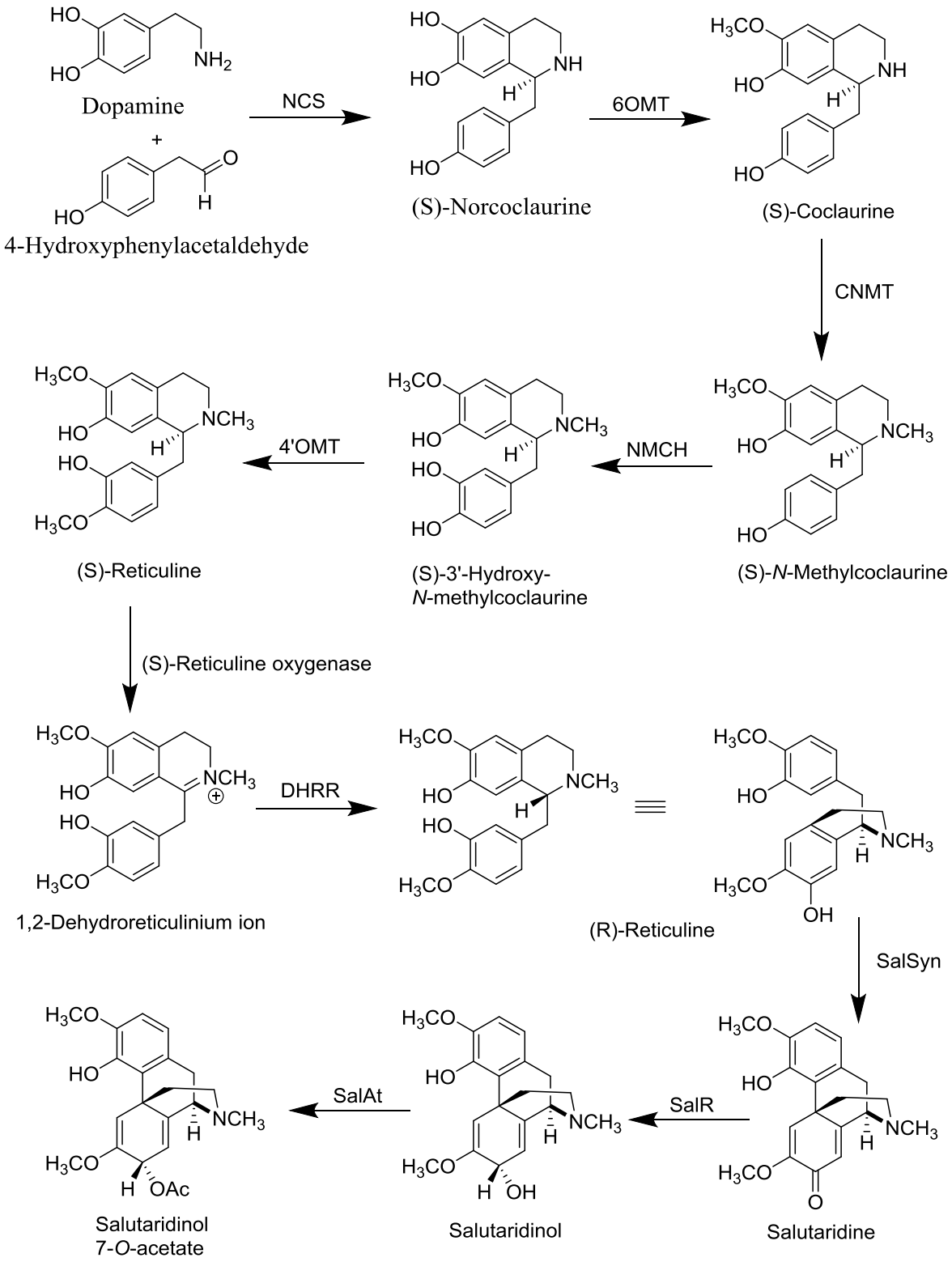
Introduction

Morphine Production

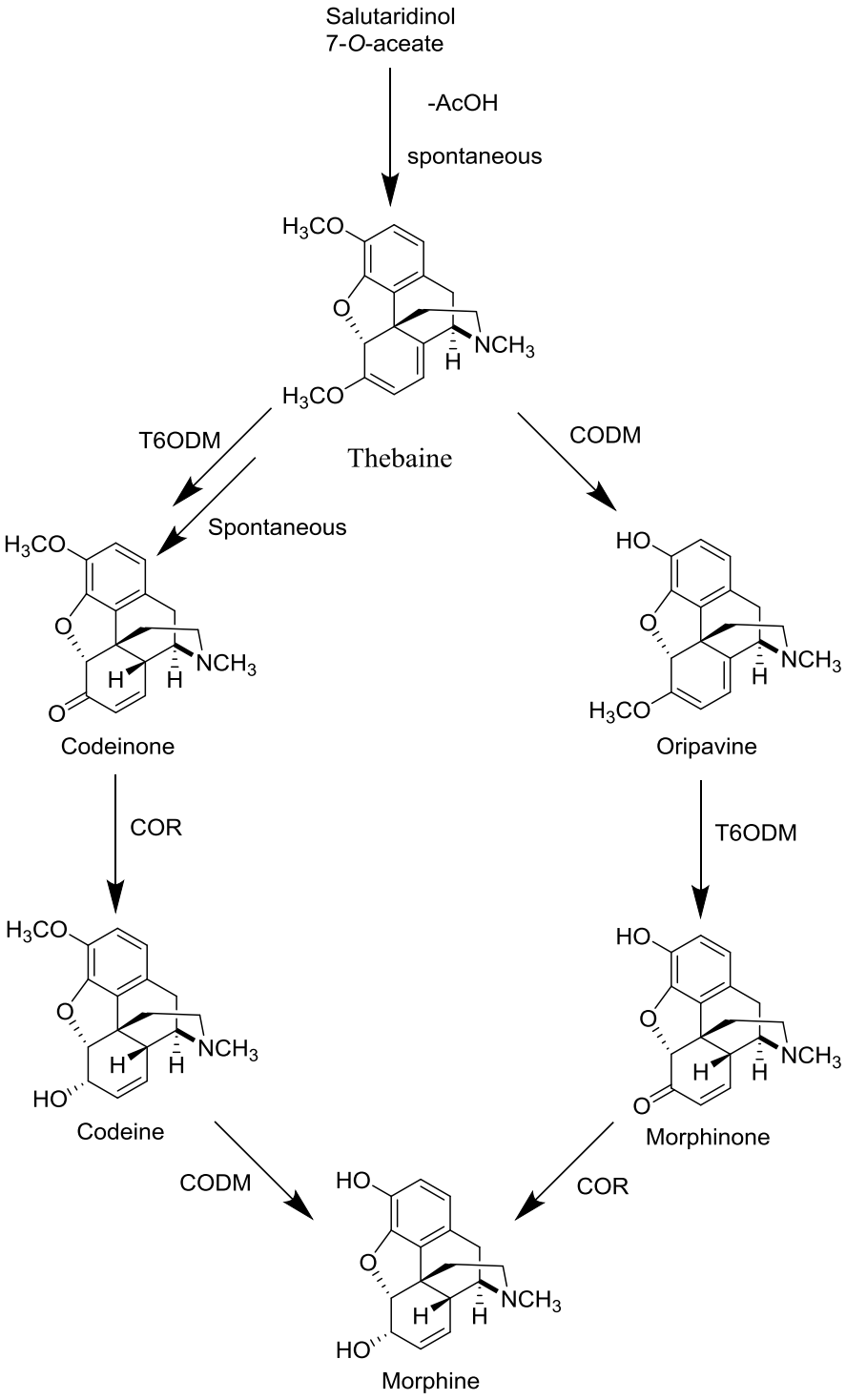
The principle components isolated from opium poppy (*Papaver somniferum*) for medicinal purposes are morphine, codeine, and thebaine. These compounds can be isolated from either opium straw (95% of global production) or from opium (5% of global production). The global farm production of morphine-rich raw materials in 2014 is expected to be 709 tons and the demand for medicinal purposes is expected to be 445 tons (87% of demand). Opium raw materials contain approximately 9.5-12.0% morphine, 2.5% codeine, and 1.0-1.5% thebaine by weight.[45,46] There has been a rise in the production of thebaine due to a *top1* variety of poppy plant produced in Australia. This is thought to arise from a defect in the 6-*O*-demethylation of thebaine and oripavine, preventing further conversion to morphine and codeine.[47]

Morphine Biosynthesis

All of the enzymes involved in the biosynthesis of codeine and morphine from dopamine and 4-hydroxyphenylacetaldehyde are known (Schemes 28 & 29).[47–49] Many of these processes require oxygen or the co-catalysts, NADPH and NADP. From dopamine and 4-hydroxyphenylacetaldehyde, both of which are derived from L-tyrosine, (*S*)-reticuline can be intercepted via intermediates (*S*)-norcoclaurine, (*S*)-coclaurine, (*S*)-*N*-methylcoclaurine, and (*S*)-3'-hydroxy-*N*-methylcoclaurine. The enzymes involved in these processes are norcoclaurine synthase (NCS), norcoclaurine 6-*O*-methyltransferase (6OMT), (*S*)-coclaurine *N*-methyltransferase (CNMT), *N*-methylcoclaurine 3'-hydroxylase (NMCH), and 3'-hydroxy *N*-



Scheme 28. Morphine and codeine biosynthesis: dopamine to salutaridinol-7-*O*-acetate.



Scheme 29. Morphine and codeine biosynthesis: salutaridinol-7-*O*-acetate to morphine and codeine.

methylcoclaurine 4'-*O*-methyltransferase (4'-OMT). These processes effectively perform the intial condensation and aromatic addition reaction of dopamine and 4-hydroxyphenyl-acetaldehyde, the 6'-*O*-methylation, *N*-methylation, 3'-oxidative aromatic hydroxylation, and 4'-*O*-methylation reactions to give (*S*)-reticuline. (*S*)-Reticuline is converted to (*R*)-Reticuline by the intial oxidation by (*S*)-reticuline-oxygenase to give an intermediate iminium ion which is stereospecifically reduced by 1,2-dehydroreticuline reductase (DHRR). The reduction is not reversible by the same enzyme. The ring closure to give the quaternary carbon has long been assumed to proceed through a radical coupling process to give salutaridine.[50] This process is mediated by a cytochrome p450 enzyme called salutaridine synthase (SalSyn).[51] Salutaridine is then reduced by salutaridine reductase (SalR) and acetylated by 7-*O*-acetyltransferase (SalAt), which spontaneously loses acetic acid and closes the furyl ring through an S_N2' reaction, producing thebaine. Thebaine is *O*-demethylated by 6-*O*-demethylase (T6ODM) to neopinone which equilibrates with codeinone. Codeinone reductase (COR) catalyzes the reduction of codeinone by NADPH to give codeine. A similar reduction occurs by the same enzyme to reduce morphinone to morphine. Codeine can be transformed into morphine by the enzyme codeine-*O*-demethylase (CODM). This enzyme can also demethylate thebaine at the same position in an alternative route to morphine and yields oripavine. Oripavine is demethylated by T6ODM to morphinone before it is converted to morphine by means of a COR catalyzed reduction with NADPH.

Drug Derivatives

There are a number of important morphinans relevant for the treatment of pain. This is a restricted discussion to morphine-like drugs that lie in the top 60 best-selling drugs of 2013.[52]

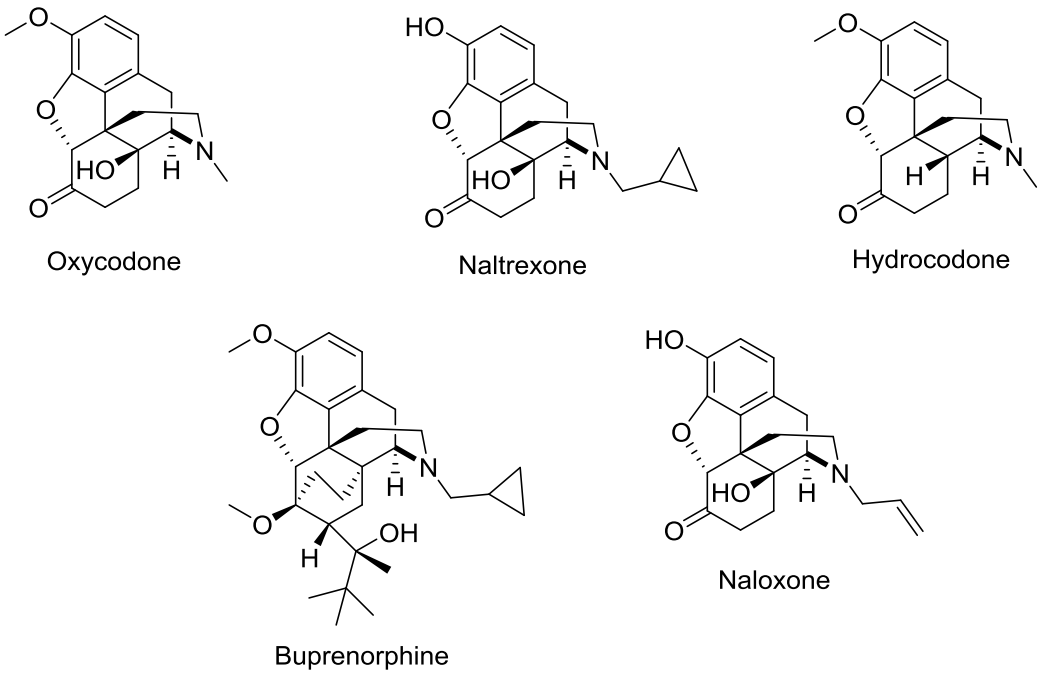
Oxycodone is a mu-agonist with stronger *in vivo* potency vs morphine. However, its affinity for the mu-opioid receptor is >20 times less than morphine. Its oral availability is higher than morphine (60% vs 20-40%). Its primary use is for visceral pain relief. The blood-brain-barrier concentration of oxycodone vs its concentration in the blood is 6 times higher than morphine. The greater efficacy of oxycodone vs morphine is attributed to this effect.[53]

Buprenorphine is about 25 to 100 times more potent than morphine. It's a semi-synthetic opioid derived from thebaine. Unlike most of the morphinans administered, it has a "ceiling effect" with regard to respiratory depression, a common side effect that can result in accidental death. Due to its lipophilicity, it has a long half-life (37 hours). Its a partial mu-opioid receptor agonist, but at clinical doses it behaves like a full agonist. Compared to other opioid agonists, buprenorphine has a marked antihyperalgesic effect. Hyperalgesia is an event that causes increased pain associated with use. This antihyperalgesic effect is thought to arise from buprenorphine's kappa-opioid receptor antagonism.[54]

Naltrexone is a mu- and kappa-opioid receptor antagonist and is used primarily to treat alcohol dependence.[55] It is a derivative of oxymorphone, where the *N*-methyl substituent is replaced by a methylene cyclopropane.

Naloxone, like naltrexone, is a opioid receptor antagonist, but its used primarily to treat symptoms of opioid withdrawal. It has a higher affinity for the mu-opioid receptor and slight affinity for the kappa- and delta-opioid receptors. The structure of this compound resembles oxymorphone except that the *N*-methyl group is replaced by an *N*-allyl group.

As of 2011, hydrocodone was the most prescribed morphinan for the treatment of pain in the United States. It has a high affinity for the mu-opioid receptor and a slight affinity for the kappa- and delta-opioid receptors. Hydrocodone, like codeine, retains the 3'-*O*-methyl group and thus requires metabolism to hydromorphone to increase its activity after absorption. It is commonly prescribed in conjunction with acetaminophen, ibuprofen, and aspirin.[56]



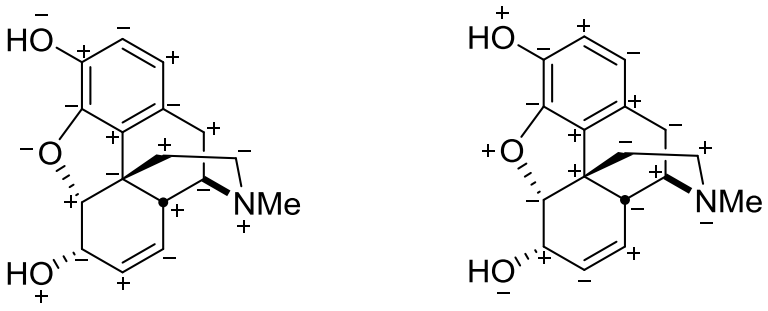
Scheme 30. Prominent morphine-like drugs.

Synthesis of Morphine

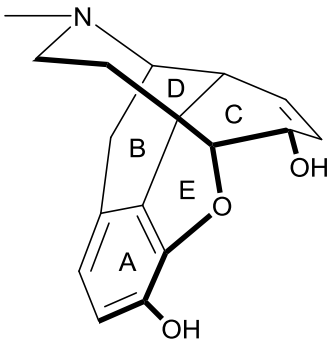
Morphine has intrigued organic chemists as a synthetic target for many years. It has been synthesized over 26 times, and it is unquestionable that many more attempts have been made as

well. The highest yielding synthesis to date was by Rice and coworkers and the highest enantioselective synthesis was by Magnus and coworkers.[57,58]

It has been argued by Hudlicky and Reed that morphine's attractiveness to chemists is not due to its complexity but because of its "total dissonance" and that any polarization assignment would amount to an incorrect assignment of charge on at least one of the electronegative atoms (Scheme 31).[59] It is my opinion that this is not the only reason that it is intriguing to chemists. The molecule possesses a great deal of strain and steric congestion centering on the five contiguous stereocenters. The all-carbon quaternary center, which lies at the heart of this molecule, is highly obstructed and is a part of four out of five of the rings. The molecule has three faces, two of which are "cupped" (Scheme 32). For all of these reasons this molecule has proven to be quite challenging to synthesize. It is also coupled with a very rich cultural and scientific history. Most of the syntheses and partial syntheses of this molecule will not be discussed in this thesis; however, the total syntheses have been reviewed many times.[48,59–63]



Scheme 31. "Dissonant relationships in morphine connectivity. A = phenol priority assignment; B = amine priority assignment." [59]



Scheme 32. 3-Dimensional representation of morphine.

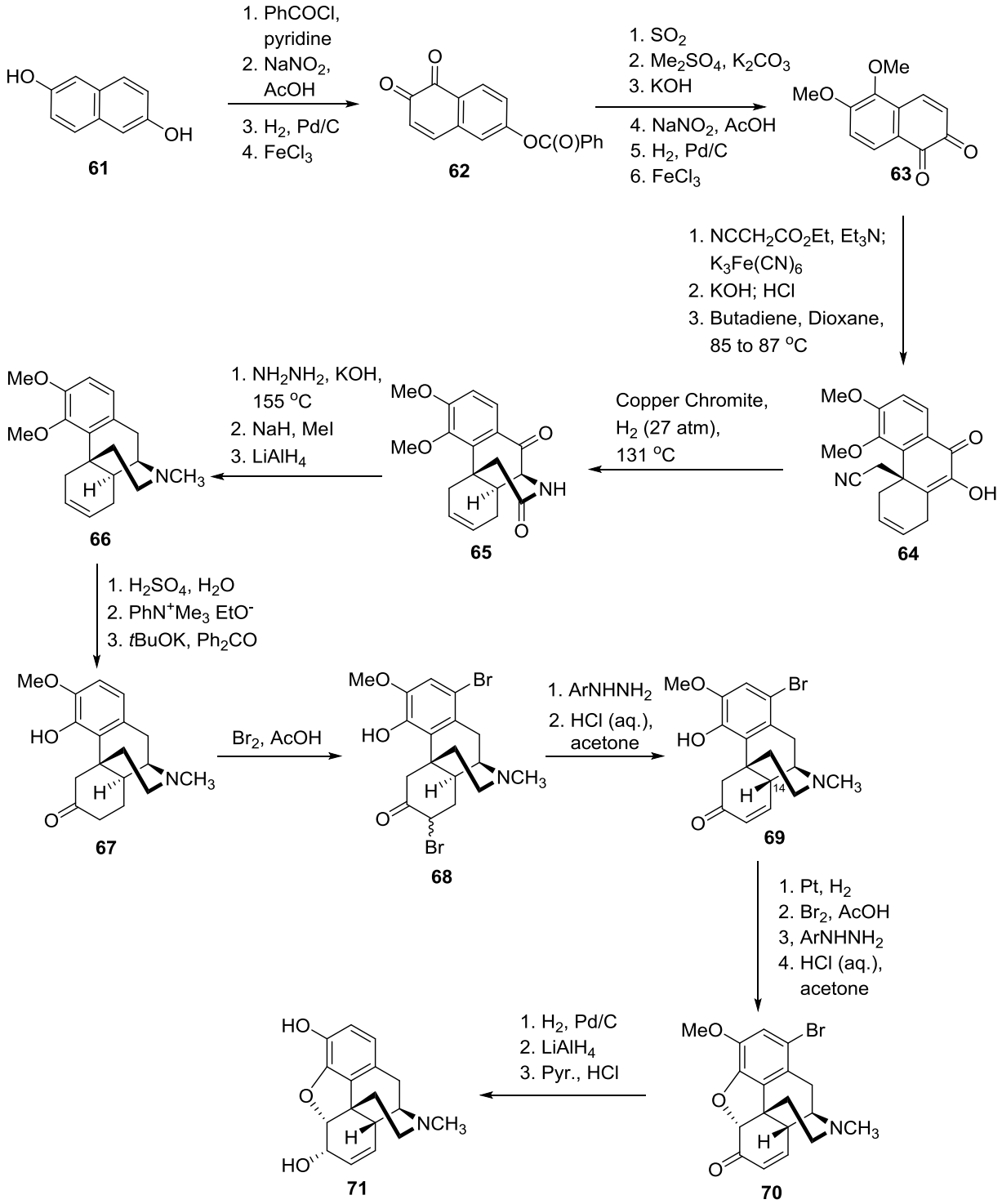
Since it has been demonstrated that codeine can be 3'-*O*-demethylated quite easily[64], many of the approaches towards the synthesis of morphine are formal syntheses that target codeine. This is especially true considering that morphine itself oxidizes when exposed to air, thus making handling of any late-stage phenolic intermediates difficult.

Notable Syntheses of Morphine

Gates Synthesis

The first total synthesis of morphine was reported by Gates in 1955.[65,66] Although the over-all yield of the synthesis is low, it was an important confirmation of morphine's structure, which had been reported almost 30 years prior. The synthesis starts with the A- and B-rings intact by utilizing 2,6-dihydroxynaphthalene **61** as a starting material (Scheme 33).[61] This substrate is mono-protected as the benzoate and oxidized to a nitroso intermediate. This in turn is reduced to the amine and subsequently oxidized by iron(III) chloride to the *o*-naphthoquinone

62. This material was treated with sulfur dioxide to give the sulfate from the quinone, which is methylated using dimethyl sulfate, and the benzoate cleaved to give the phenol. An identical sequence of steps of nitrosation, reduction, and oxidation gave the quinone on the opposing ring. The synthetic equivalent of the ethyl amine portion of the molecule was introduced as a cyanomethyl unit by treating the naphthoquinone **63** with ethyl cyanoacetate. The conjugate addition product was reoxidized to the quinone with $K_3Fe(CN)_6$. The acetate was removed by saponification of the ester and subsequent acidification with the release of CO_2. Formation of the C-ring and the quaternary stereocenter of morphine was accomplished through a Diels-Alder reaction with butadiene to give the enone **64**. High pressure reductive coupling of the enol and nitrile using copper chromite and hydrogen gas created the D-ring as the lactam **65**. Wolff-Kishner reduction of the ketone, methylation of the amide using sodium hydride and methyl iodide, and reduction with lithium aluminum hydride gave the amine **66**. Resolution of the enantiomers was accomplished using dibenzoyl tartaric acid. Acid catalyzed hydration of the olefin, mono-demethylation of the dimethyl catechol portion of the molecule using base, and oxidation of the alcohol under Oppenauer-like conditions yielded the intermediate ketone **67**. This product was brominated using bromine and acetic acid, which brominates both para to the phenolic hydroxyl group as well as alpha to the ketone with good regioselectivity at the less sterically hindered carbon. Condensation of the α-bromoketone **68** with 2,4-dinitrophenylhydrazine facilitated the dehydrobromination of the C-ring as well as the equilibration and thus epimerization of the C-14 C-H bond. Removal of the hydrazone using aqueous HCl and acetone afforded the enone **69**. Platinum catalyzed hydrogenation of the olefin and a repeat of the procedures of bromination, dehydrobromination using 2,4-DNPH, and removal of the hydrazone gave 1-bromocodeinone **70**. This time the bromination sequence



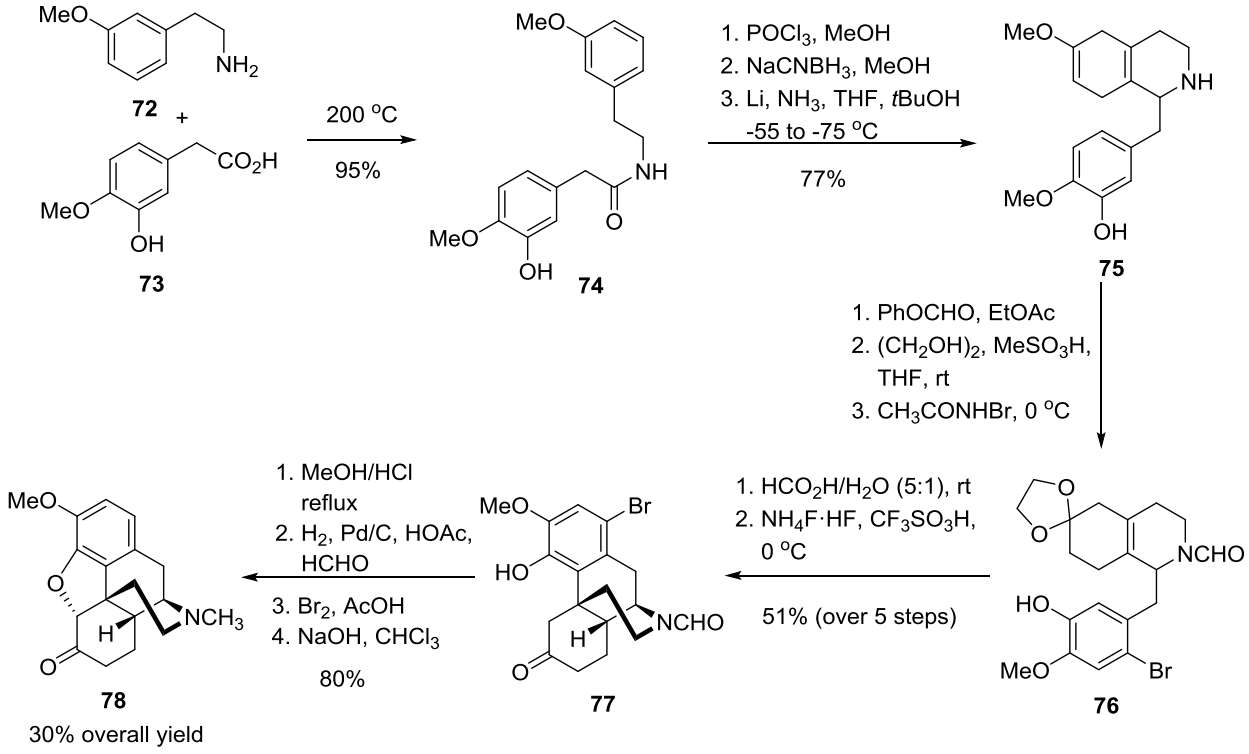
Scheme 33. Gates synthesis of morphine.[59,65,66]

allowed for the α-bromination of the ketone at C-5, resulting in the furan ring closure. Stereospecific reduction of the carbonyl using lithium aluminum hydride also resulted in the loss of the aryl bromide in 65% yield to give codeine. The synthesis ended with the verification that codeine could be demethylated under the conditions of Rapoport and coworkers[67] with HCl and pyridine to give morphine **71** in 22% yield**.**

Rice Synthesis

The Rice formal synthesis of morphine is the highest yielding to date (racemic product).[57] The synthesis commences with a condensation reaction between the amine **72** and the carboxylic acid **73** to give the amide **74** (Scheme 34). Utilizing a Bischler-Napieralski process, the cyclization of the amide with the aromatic ring could be carried out. The resulting amide is reduced under slightly acidic conditions using sodium cyanoborohydride and the crude material is subjected to Birch reduction conditions to give the methyl enol ether **75**. The crude material of the preceding reaction is converted to the formamide as a mixture of rotamers. The enol ether was converted to the ketal under acidic conditions in ethylene glycol/THF and the aromatic ring was brominated using *N*-bromoacetamide to give the para-brominated product **76**. This appears to have been a method to prevent poor regioselectivity in the Grewe cyclization step. The ketal was removed using a mixture of formic acid and water. The Grewe cyclization was carried out using strong acidic conditions and yielded both the cyclization product **77** as well as some of the enone stemming from isomerization of the olefin and deketalization of the starting material. The product was *N*-deformylated using HCl in methanol and the aryl bromide was hydrogenated under acidic conditions in the presence of formaldehyde and palladium on carbon, which also resulted in the hydrogenation of the *in situ* formed iminium salt. The furyl E-ring was closed by

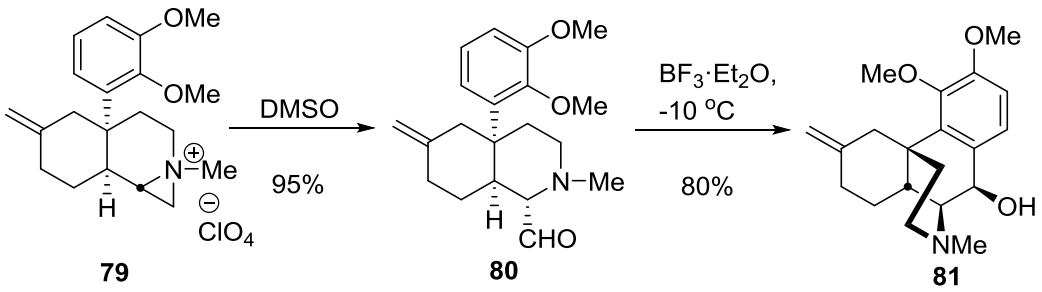
first brominating alpha to the ketone and subsequently treating the product with base to yield dihydrocodeinone **78**. The overall yield of this synthesis was 30%.



Scheme 34. Rice - formal synthesis of morphine.[57]

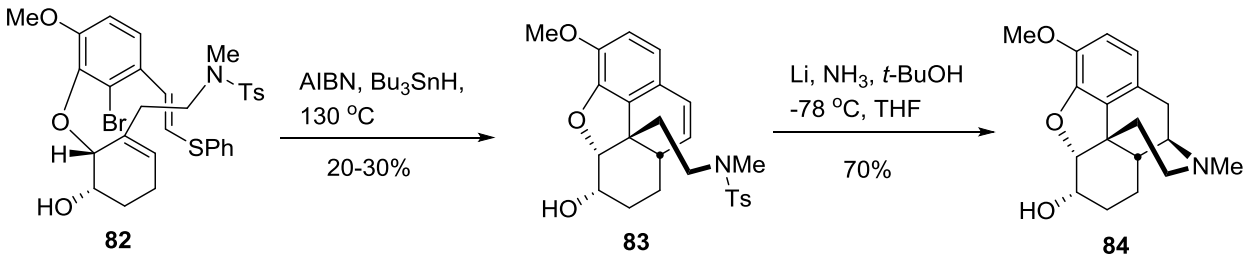
Considering that the ideas of how to assemble morphine in this thesis surround the early synthesis of the A-, C-, and E-rings from a benzofuran-based intermediate, as well as a late simultaneous fashioning of the B- and D-rings, the remaining focus shall be on aspects of total syntheses that share this similarity.

Evans and Mitch performed an interesting closure of the B- and D-rings of morphine by treating the aziridinium salt **79** with dimethyl sulfoxide (Scheme 35).[68] This resulted in the addition and elimination of dimethyl sulfide, which would be the expected by-product of a Kornblum-like oxidation. The pendant aldehyde and aromatic ring of the amine **80** were then brought together using boron trifluoride. The newly formed alcohol **81** was later removed reductively.



Scheme 35. Evans' ring closure of B- and D-rings of morphine.[68]

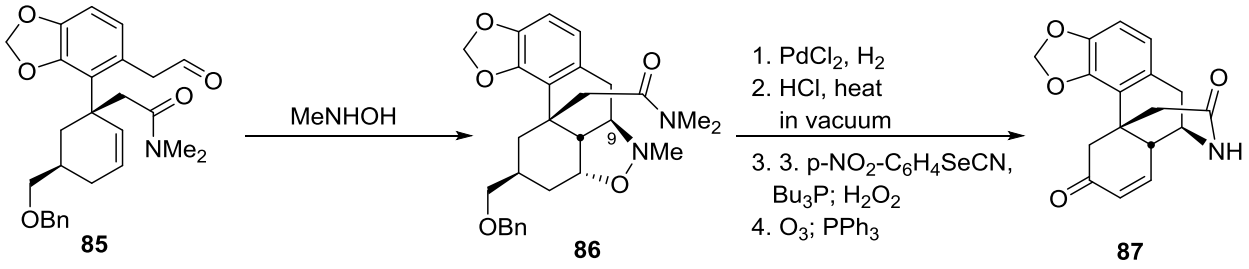
Parker and Fokas took a radical cyclization approach for the construction of the B-, D-, and E-rings (Scheme 36).[69] Treatment of the aryl bromide **82** with AIBN and a catalytic amount of tributyl stannane at 130 °C in benzene, promoted their tandem cyclization/elimination sequence. The newly formed styrenyl compound **83** was treated with lithium and ammonia in



Scheme 36. Parker's cyclization of the B-, D-, and E-rings.[69]

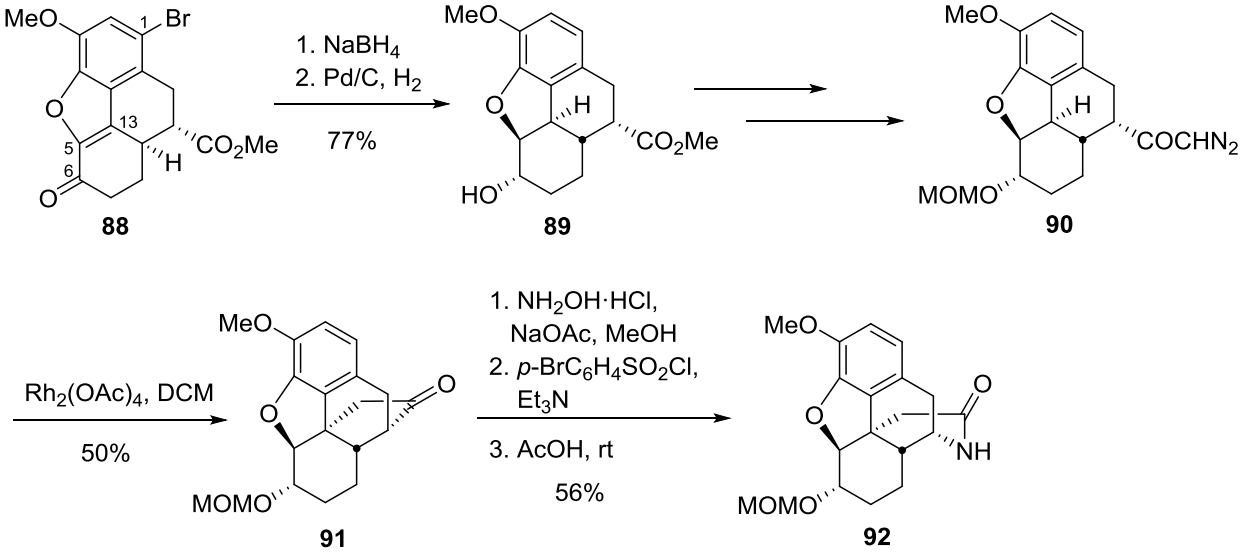
tetrahydrofuran which underwent a reductive de-tosylation to give an electrophilic aminyl radical and reacted with the electron-rich olefin to give dihydrocodeine **84**.

Parsons and coworkers elected to close the B-ring and set the C-9 C-N bond through a nitrone-olefin 2,3-dipolar cycloaddition (Scheme 37).[70] The D-ring closure was then simply accomplished by first hydrogenating the isoxazolidine and benzyl ether (compound **86**), and then using an acid promoted cyclization to form the lactam **87**.



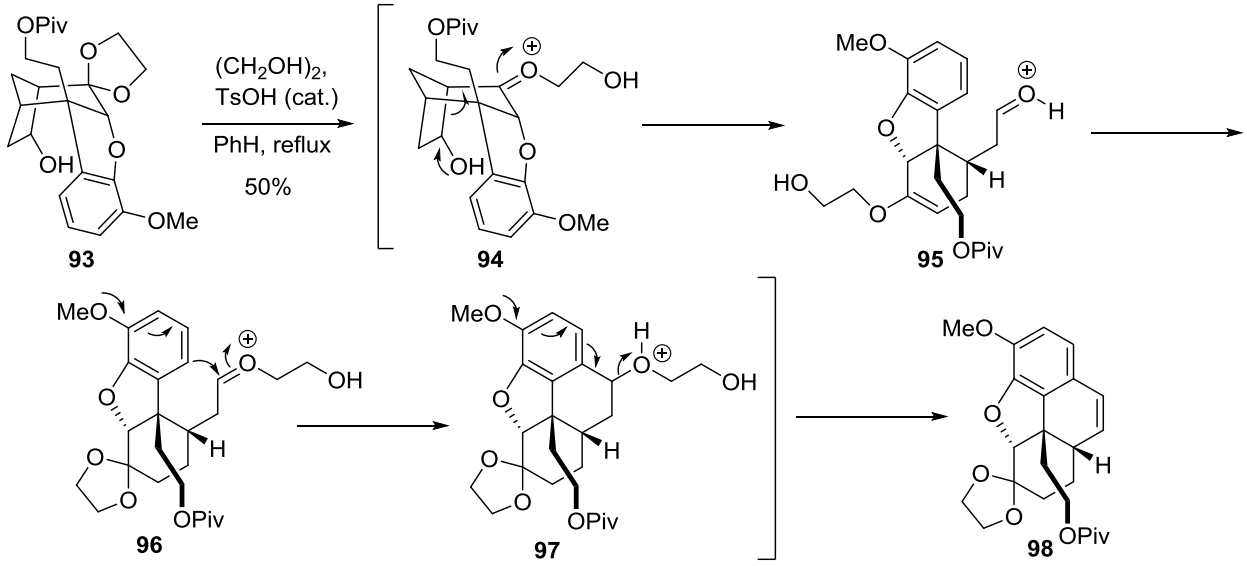
Scheme 37. Parsons and coworkers' closure of the B- and D-rings.[70]

The White, Hrnciar, and Stappenbeck synthesis of morphine is one of only a few that features a benzofuran intermediate (Scheme 38).[71] Since it is known that morphine itself can decompose into a phenanthrene-like skeleton, they sought to investigate a synthesis beginning with a dihydrophenanthrene substrate. Intermediate **88** was initially hydrogenated using palladium on carbon in an attempt to simply remove the C-1 bromine as well as hydrogenate the C-5 to C-13 olefin. This resulted, but not before the complete deoxygenation of the C-6 ketone. This was remedied by reducing the ketone with sodium borohydride prior to hydrogenation. It is interesting that the olefin could be reduced under very mild conditions. This olefin is not only highly substituted but also exhibits aromatic character. The intermediate alcohol **89** was elaborated to the α-diazoketone **90**, which was utilized in a dirhodium tetraacetate catalyzed C-H insertion reaction to form the quaternary stereocenter. The lactam **92** was formed through a Beckman rearrangement from the sulfonyl oxime.



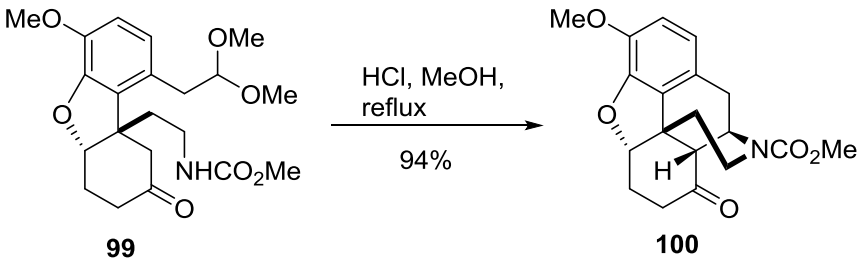
Scheme 38. White's synthesis of (+)-morphine.[71]

Ogasawara took a unique approach towards forming the B-ring of (-)-morphine, by using a retro-aldol condensation reaction. This also served as an oxocarbenium intermediate allowing a condensation reaction to ensue with the aryl ring (Scheme 39).[72] The formation of the D-ring used an approach similar to that of Parker and coworkers (*vide supra*).



Scheme 39. Retro-Aldol reaction performed by Ogasawara and coworkers.[72]

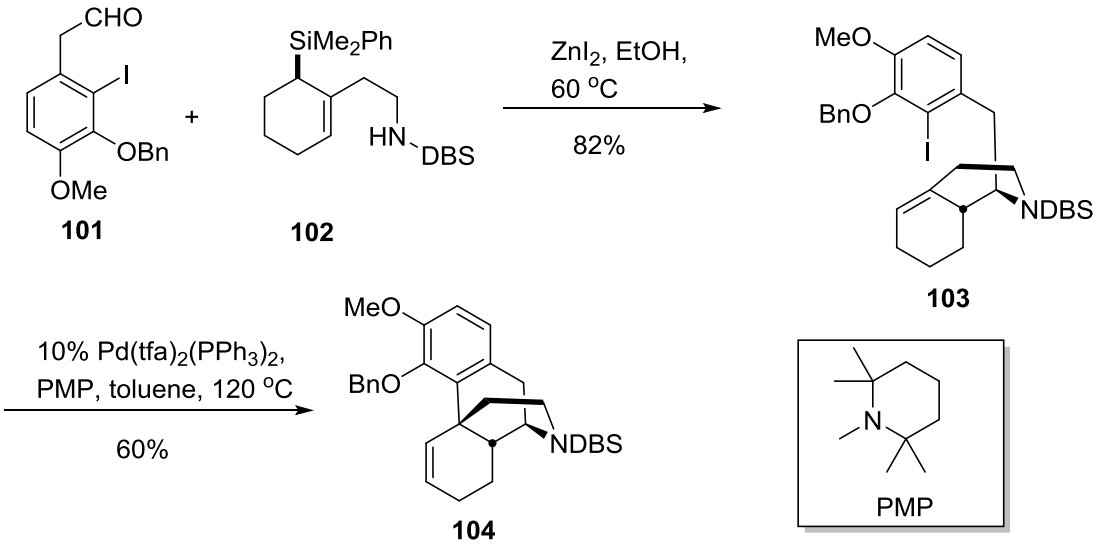
Fukuyama synthesized racemic morphine using a Heck reaction to assemble the quaternary center and an aldol condensation/1,4-conjugate addition or a Mannich-type addition to make the B- and D-rings (Scheme 40).[73] Many of the steps of this synthesis are very efficient, but overall, the synthesis suffers from lack of efficiency in the step count (25 steps).



99 100

Scheme 40. Fukuyama and coworkers: addition sequence to form B- and D-rings of morphine.[73]

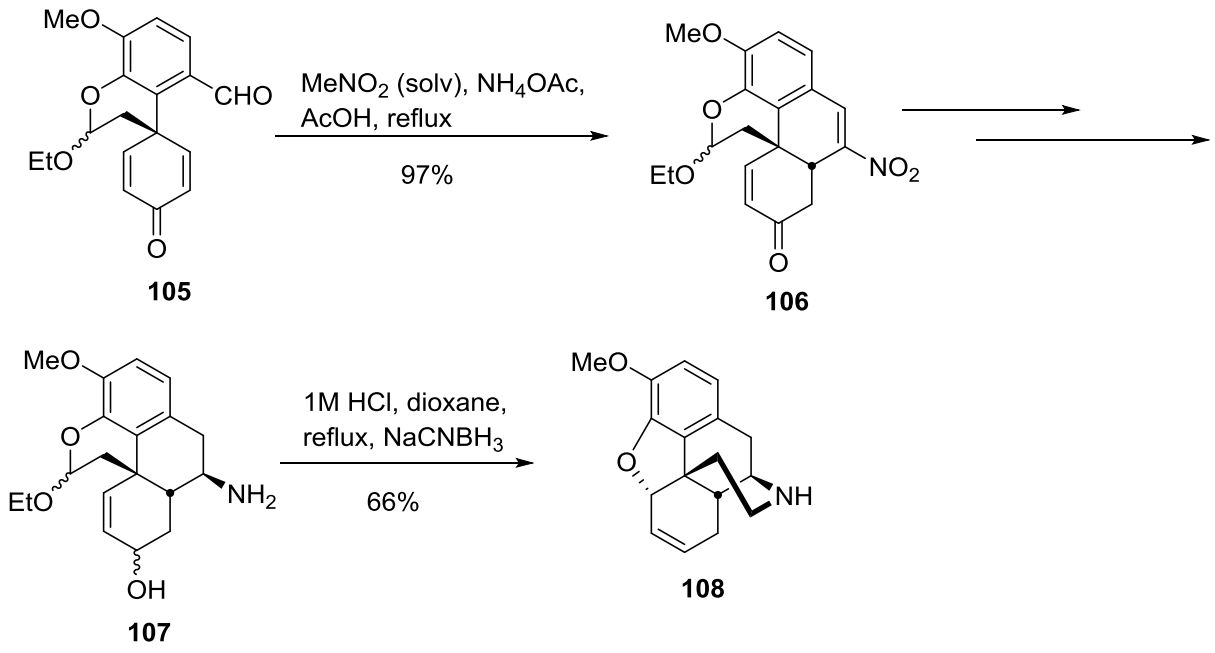
Overman and coworkers utilized a iminium cyclization and Heck reaction to form the B- and D-ring as well as the quaternary center of morphine (Scheme 41).[74] A zinc iodide catalyzed condensation reaction of silane **102** with the aldehyde **101** led to an intermediate iminium ion, to which the allyl silane added, affording the tricyclic compound **103** in high enantiomeric excess. Under conditions of $Pd(tfa)_2(PPh_3)_2$ and base, the Heck cyclization formed the quaternary center giving the tetracyclic compound **104**.



101 102 103 104

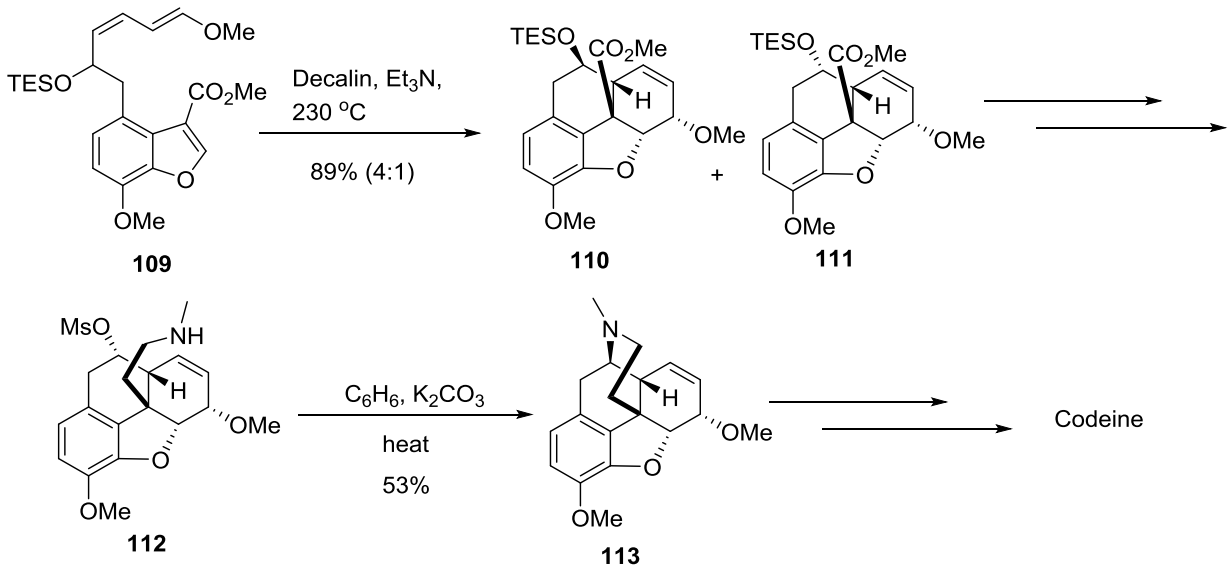
Scheme 41. Overman synthesis of morphine – allyl silane addition and Heck cyclization steps.[74]

The synthesis of codeine performed by Magnus and coworkers represents the most efficient asymmetric synthesis to date (20.1% overall yield, Scheme 42).[58] Their method of closing the B-ring involves a Henry/aldol reaction which was performed with ammonium acetate, nitromethane, and acetic acid. After a series of reduction steps on the nitrostyrenyl compound **106,** the amine **107** was formed. This compound, which features a masked aldehyde, was condensed in an intramolecular fashion with the amine to give an intermediate iminium species, which was reduced with sodium cyanoborohydride to the secondary amine **108** giving the D-ring.



Scheme 42. Magnus synthesis of codeine – Henry/aldol condensation and reductive amination steps.[58]

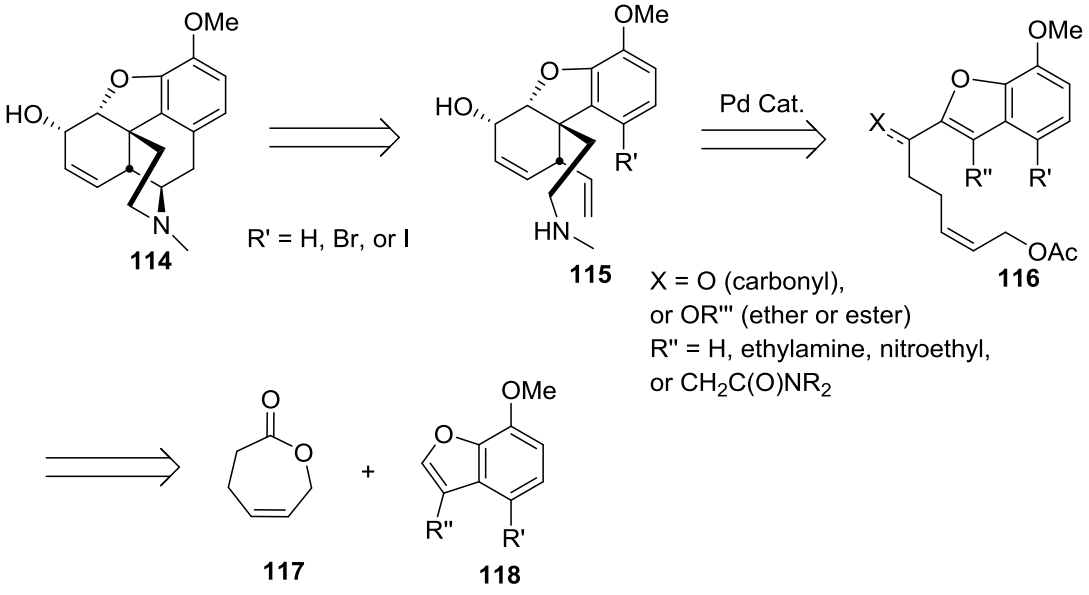
The Stork synthesis of morphine utilizes an Intramolecular Diels-Alder reaction (IMDA) to form the B- and C-rings (Scheme 43).[75] It should be noted that there have been other investigations into IMDA reactions with benzofuran as a dienophile to possibly form morphine.[76,77] In this case, the Stork group heated the methoxydiene **109** in decalin to 230 ^{o}C and obtained a 4:1 mixture of two adducts (**110** and **111**) in excellent yield. After a series of manipulations, the pendant ester was transformed into the secondary amine **112**, which in turn added in an S_N2 fashion to the mesylate to form the D-ring. After a few manipulations, this intermediate was transformed into codeine.



Scheme 43. Stork synthesis of morphine – IMDA and amine addition steps.[75]

Results and Discussion

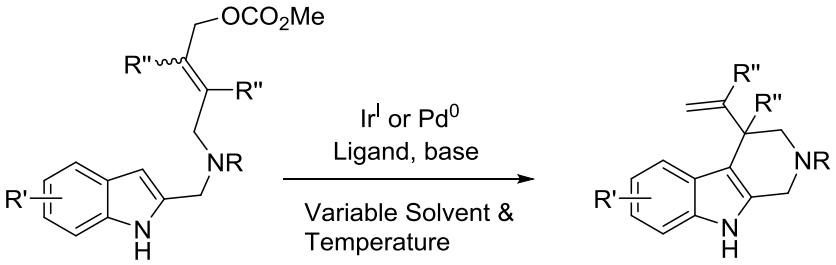
Like many of the known syntheses, a total synthesis of codeine represents a formal synthesis of morphine because the methoxy group can be easily cleaved. Our original analysis of codeine looked at disconnecting the B- and D-rings (Scheme 44). The thought was that these two rings could possibly be assembled simultaneously by either using a transition metal catalyzed cross-coupling/carboamination sequence or oxidatively using an oxidant such as iodine or phenylselenyl chloride (PhSeCl). In the event that neither of these approaches worked, the olefin would serve as a suitable functional group for derivitization. It was thought the intermediate **115** could possibly arise from a palladium-catalyzed allylation process, in which the benzofuran might act as a nucleophile in a reaction with a π-allyl palladium complex. The pendant allylic



Scheme 44. Initial retrosynthetic analysis of codeine **114**.

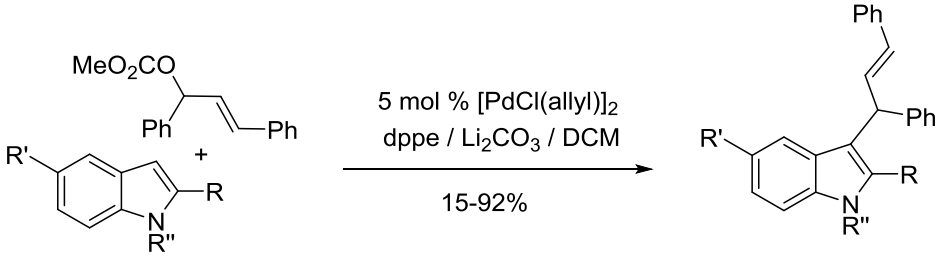
acetate **116** would come from the direct addition of the lithiate of a C-3 substituted (or unsubstituted) 7-methoxybenzofuran to the lactone **117** or its equivalent.

Iridium and Palladium Catalyzed Intramolecular Tsuji-Trost/Friedel-Crafts Allylation



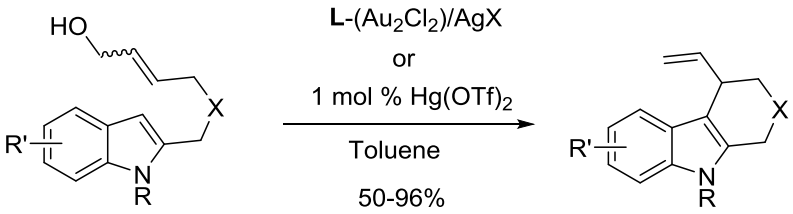
R = Bn, Me, allyl R' = H, OMe, Br, Cl, F, Me, pyrrole R'' = H, Me

Palladium Catalyzed Intermolecular Tsuji-Trost/Friedel-Crafts Allylation



R = H, Me, Ph R' = H, OBn, Br, CN R'' = H, Me R'' = SO_2Ph (0% yield)

Lewis Acid Catalyzed Intramolecular Friedel-Crafts Allylation



R = H, Ts, Me, Bn, or allyl R' = H, MeO, Me, Cl X = NTs, $C(CO_2Et)_2$,

*note: not all substitutions given are necessarily compatible with all the conditions shown, but are compatible with at least one of them.

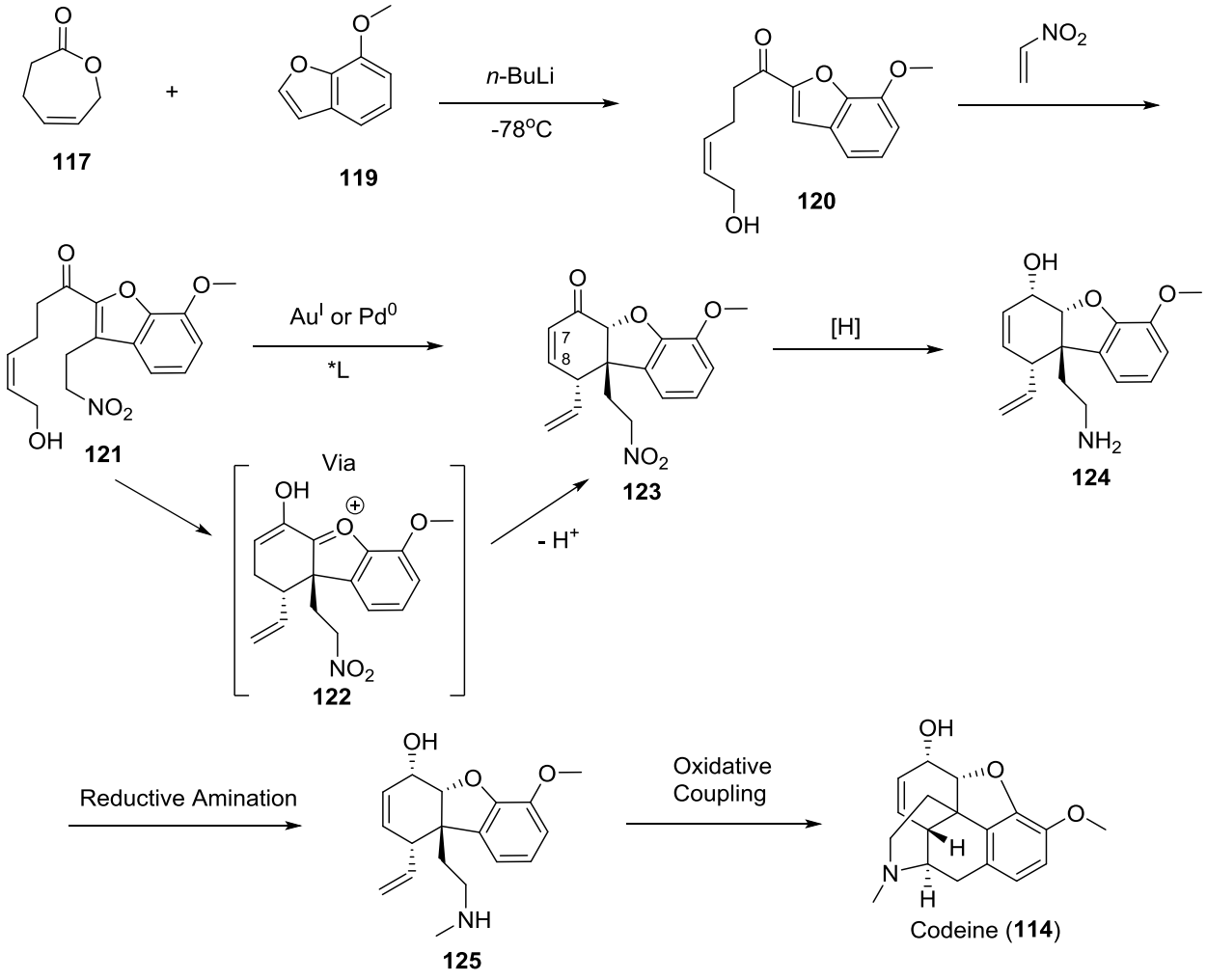
Scheme 45. C-3 allylation of Indoles.

As it pertains to the allylation process, these types of Tsuji-Trost/Friedel-Crafts reactions are known for indoles and are catalyzed by either iridium(I) or palladium(0) complexes.[78–80] The reactions have been demonstrated in both an inter- and intramolecular sense (Scheme 45). Most of these reactions are done with an unsubstituted aryl N-H, but in the case of the intermolecular palladium-catalyzed reaction it has also been shown to work with an *N*-methyl substituent but in low yield. This is important since we hoped these reactions could be extended to benzofurans and not just indoles. It seems that the reactivity of a benzofuran-based nucleophile may have been better correlated with the purely Friedel-Crafts reactions. These reactions have been demonstrated with cationic gold(I) complexes as well as mercury(II) triflate.[81,82] In these cases, the substitution of the aryl nitrogen was well tolerated. Mercury(II) triflate was also able to cyclize with the aryl nitrogen substituent being a sulfonamide. The electron withdrawing nature of the sulfonyl group on the nitrogen of the indole in this example may be a better indication that one might possibly extend this reaction to benzofuran cationic cyclizations. These lewis acid conditions were not attempted in our pursuit of a synthesis of morphine, but would be a logical next step for exploration.

Forward Synthesis

The proposed forward synthesis involves the addition of the corresponding C-2 lithiate of 7-methoxybenzofuran **119** to the lactone **117** to give the allylic alcohol **120** (Scheme 46). We thought that nitroethylene could be used at this juncture to alkylate at C-3 of this benzofuran **120** or perhaps that could be done prior to the addition of the lactone **117**. Nitroethylene has been shown in the literature to react at C-3 of *N*-methylindoles and the thought was that this method could be possibly extended to benzofuran-based substrates.[83] In our case, the carbonyl compound

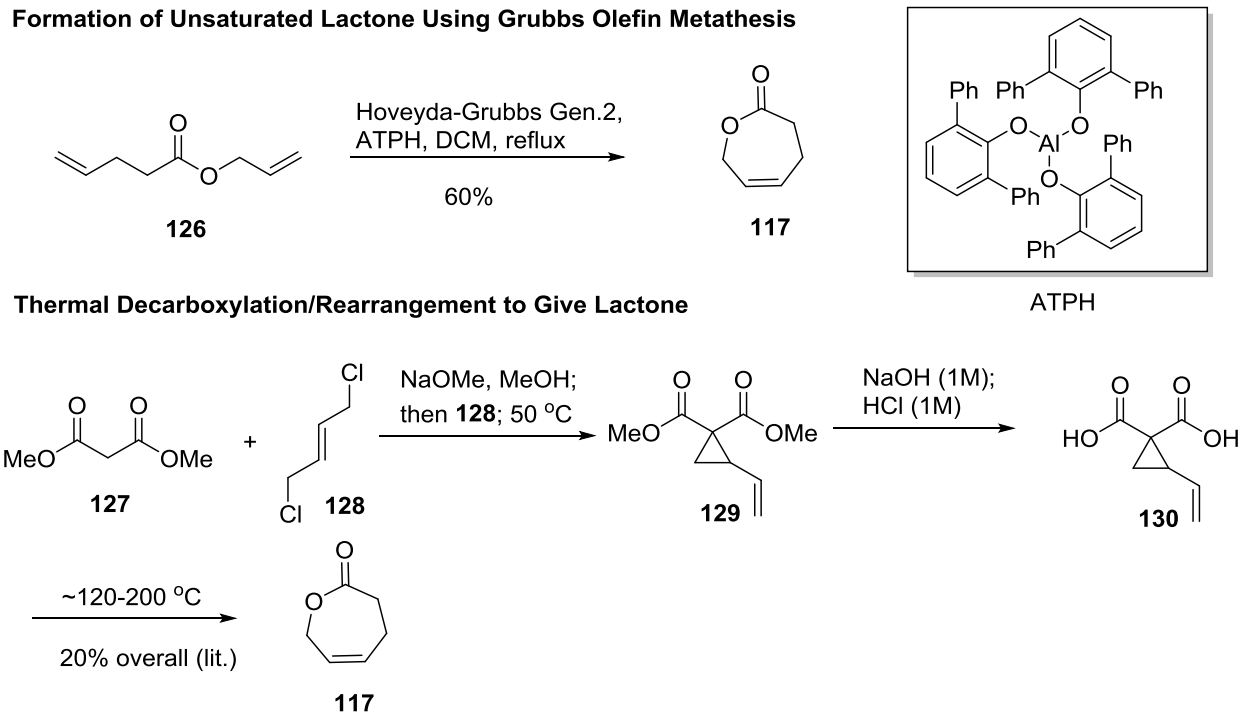
120 may need to be reduced prior to this type of reaction in order to make C-3 more electron-rich. If the C-3 alkylated substrate **121** could be assembled, it was proposed that it might undergo a Friedel-Crafts type reaction in the presence of a gold(I) cationic complex or undergo a Tsuji-Trost/Friedel-Crafts allylation with a palladium(0) complex (*vide supra*). The reaction was envisioned to proceed through oxocarbenium intermediate **121** which could lose a proton to



Scheme 46. Proposed forward synthesis.

quench the charge and form the product **123**. This reaction would produce three new stereocenters and the requisite oxidation state of codeine at C-7 and C-8. In hindsight, retaining the nitroalkane and carbonyl functionalities at this step would most likely present themselves as liabilities that would need to be addressed. The cyclized nitro compound **123** would then be reduced to give the amine **124**. Reductive amination of this primary amine with possibly formaldehyde and sodium cyanoborohydride would give the secondary amine **125**. At this point, the proposed oxidative coupling could ensue to give the B- and D-rings of codeine.

The lactone **117** has been prepared before.[84–87] The first method involves a ring closing metathesis in the presence of a bulky aluminum-based Lewis acid to form the olefinic oxepinone



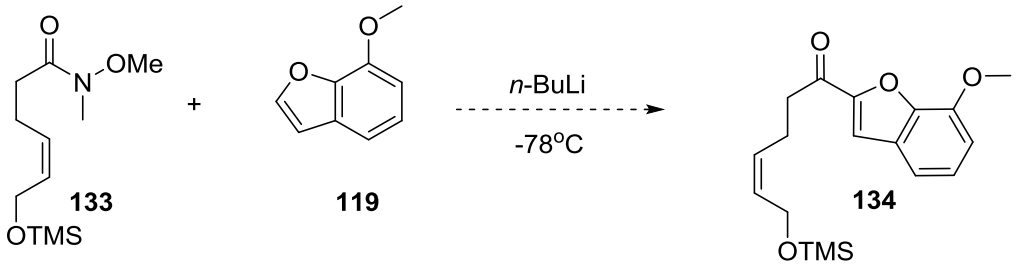
Scheme 47. Known procedures for synthesizing oxepinone **117**.[84–87]

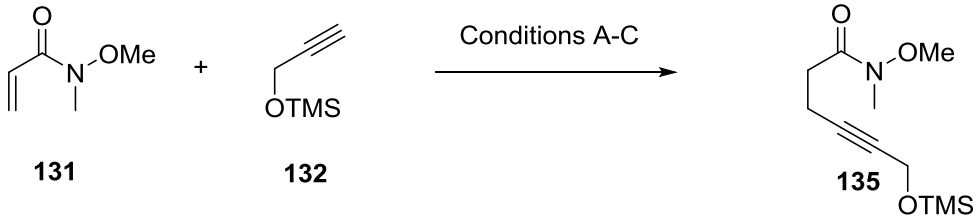
117 (Scheme 47). The second method required the preformation of the diacid of 1,1-bis(methoxycarbonyl)-2-vinylcyclopropane followed by the distillation and decarboxylation of this compound to form lactone **117**. This procedure required brief flash chromatography on silica gel, which is also known to slowly catalyze the lactone's decomposition. Due to the volatility of this compound, the ambiguity in the procedures outlined to prepare them, and the tendancy for the compound to rearrange on silica gel, we were not able to reproduce these conditions.

Attention was turned toward synthesizing an open chain equivalent of **117**, namely the Weinreb amide **133**. In an analogous fashion as the lactone **117**, amide **133** would serve as an electrophile for the addition of the lithiate of 7-methoxybenzofuran **119** (Scheme 48).

The acrylamide **131** was synthesized by adding *N*,*O*-dimethylhydroxylamine hydrochloride to a solution of acryloyl chloride and triethylamine in dichloromethane. The silyl ether **132** was synthesized according to a known procedure in which propargyl alcohol and hexamethyldisilazane are heated together at reflux for 12 hours.[88]

There are a number of methods to add acetylides to α,β-unsaturated ketones and esters, but little information can be found regarding the conjugate addition of acetylides to α,β-unsaturated amides. Tetrakis(acetonitrile)copper(I) hexafluorophosphate has been shown to catalyze the addition of alkynes to α,β-unsaturated thioamides.[89,90] The reaction typically requires a catalytic amount of base to form the initial copper(I) acetylide species. A variation of this method was attempted for adding the propargyl ether **132** to the α,β-unsaturated amide **131**, but there was no conversion (Scheme 48, entry C). This type of reaction was also attempted





Conditions	Reagents	Result
A	$[Cu(CH_3CN)_4]PF_6$, dppe, Et_3N, THF, 50 °C	No Conversion
B	$Pd(OAc)_2$, PMe_3, THF, 60 °C	No Conversion
C	$[Cu(CH_3CN)_4]PF_6$, dppe, LiHMDS, THF, 80 °C	No Conversion

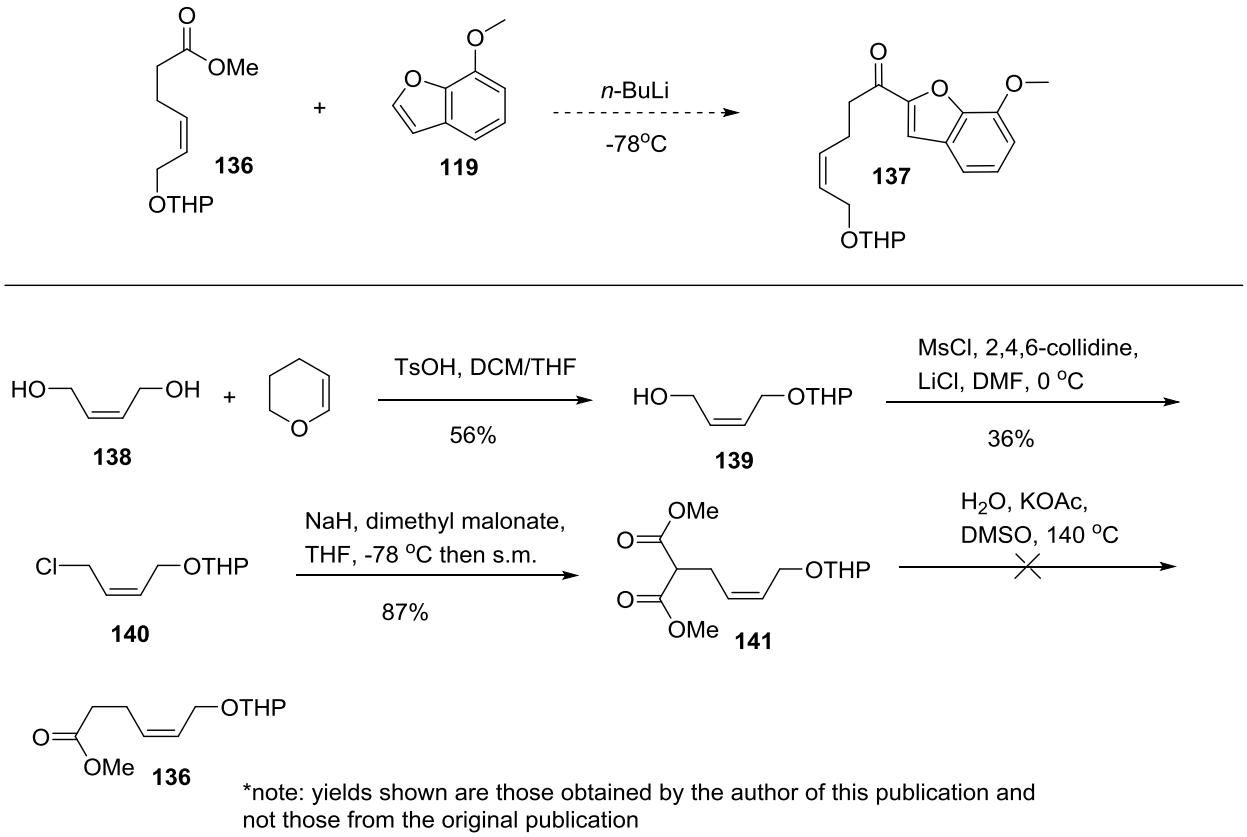
Scheme 48. Attempted assembly of the Weinreb amide **133** through acetylide 1,4-addition.

using a more mild base (Scheme 48, entry A). Palladium acetate has been shown to facilitate acetylide 1,4-additions to vinylketones.[91] Employing this method resulted in no conversion of the reactants (**131** and **132**) to products (Scheme 48, entry B).

After the failed attempts at assembling the amide **133**, our focus was turned towards a known procedure for making a similar ester-bearing structure.[92,93] Like the lactone **117** and the

amide **133**, the ester **136** could potentially serve as an electrophile to make the desired ketone **137** (Scheme 49).

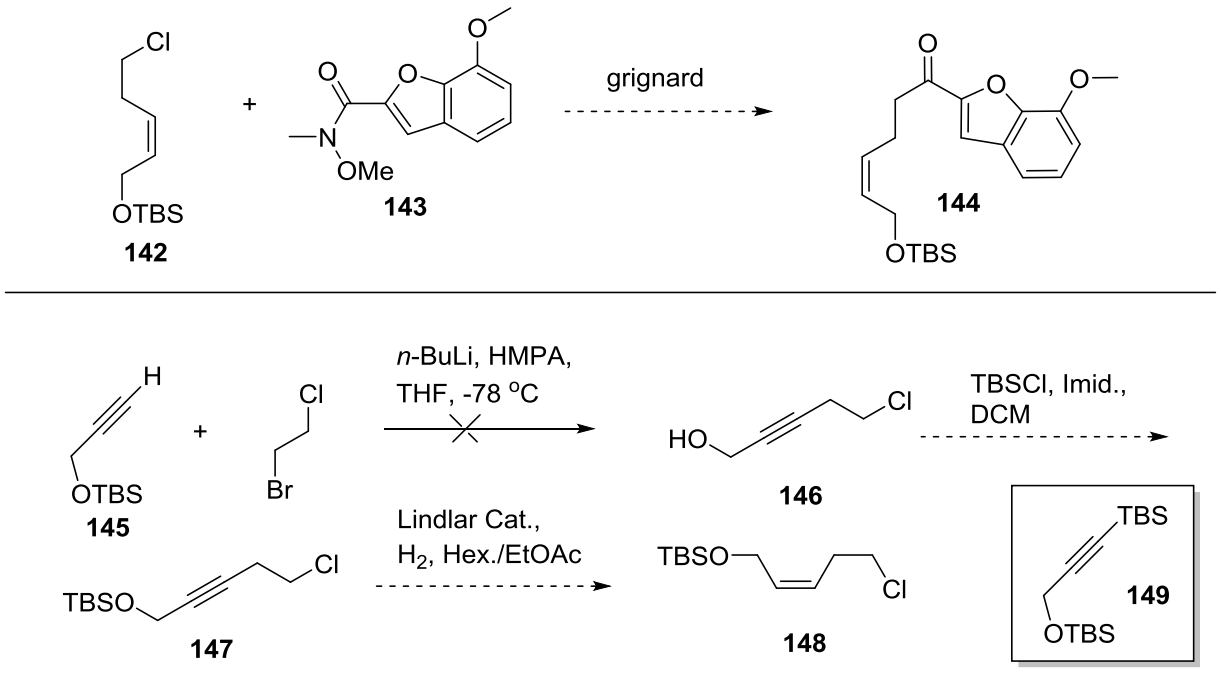
The linear sequence for making the ester **136** started with mono-protection of cis-1,4-dihydroxy-2-butene with dihydropyran to give the THP ether alcohol **139** in 56% yield. Mesylation of the primary alcohol with mesyl chloride in the presence of collidine and displacement by chloride anion (Finkelstein reaction) which afforded the allylic chloride **140** in 36% yield. This compound was used to alkylate dimethylmalonate anion to give the diester **141**



Scheme 49. The synthesis of ester **136**.

in 87% yield. Unfortunately, the Krapcho-decarboxylation step didn't work intially. Although this procedure might have worked on further experimentation, alternative approaches were simultaneously being looked into and we decided to forego this route.

A third method for synthesizing the linear chain precursor prior to the Tsuji-Trost/Friedel-Crafts-type cyclization involved a Grignard addition to a Weinreb-amide functionalized benzofuran **143** (scheme 50). This concept was not without flaws, since forming a nucleophile from the primary chloride **142** could potentially cause a reaction with another molecule of itself in an intermolecular fashion, or it could act as a base and cause elimination. Nevertheless, this reaction was pursued.

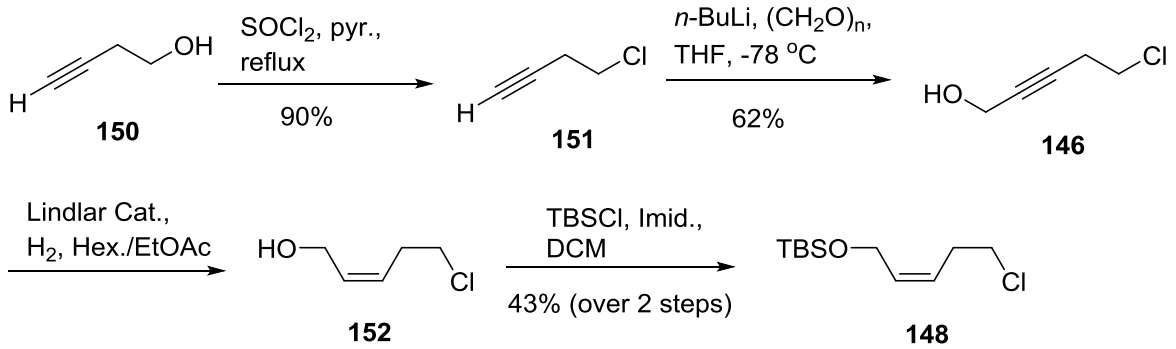


Scheme 50. Grignard addition approach towards the assembly of the ketone **144** and the theoretical synthesis of the homoallylic chloride **148**.

A short three-step sequence was envisioned to make the homo-allylic chloride **148** (Scheme 50). These steps involved the initial S_N2 addition of an acetylide anion to 1-bromo-2-chloroethane, protection of the alcohol as the silyl ether **146**, and cis-reduction of the alkyne to the olefin using Lindlar's catalyst and hydrogen gas.

Upon addition of the corresponding acetylide anion of the propargylic silyl ether **145** to 1-bromo-2-chloroethane in the presence of hexamethylphosphoramide (HMPA), the undesired bis-silylated compound **149** formed. This desired mode of addition is known to occur when lithium amide is used.[94] Attempts to procure the product using this procedure failed also. As such, a revised approach towards synthesizing the homoallylic chloride **148** was undertaken.

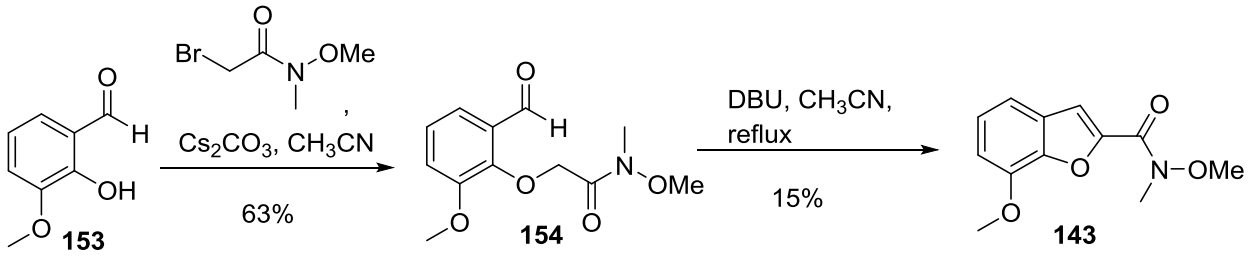
Homopropargylic chloride can be prepared in 90% yield from 3-butyn-1-ol using thionyl chloride and pyridine (Scheme 51).[95] Treatment of the acetylide anion of alkyne **151** with a stream of formaldehyde from cracked paraformaldehyde at -78 ^oC afforded the alcohol **146** in 62% yield. Surprisingly, this reaction proceeded without any elimination of the chloride. The cis-reduction of this compound was attempted using palladium on calcium carbonate, hydrogen



Scheme 51. The synthesis of the homoallylic chloride **148**.

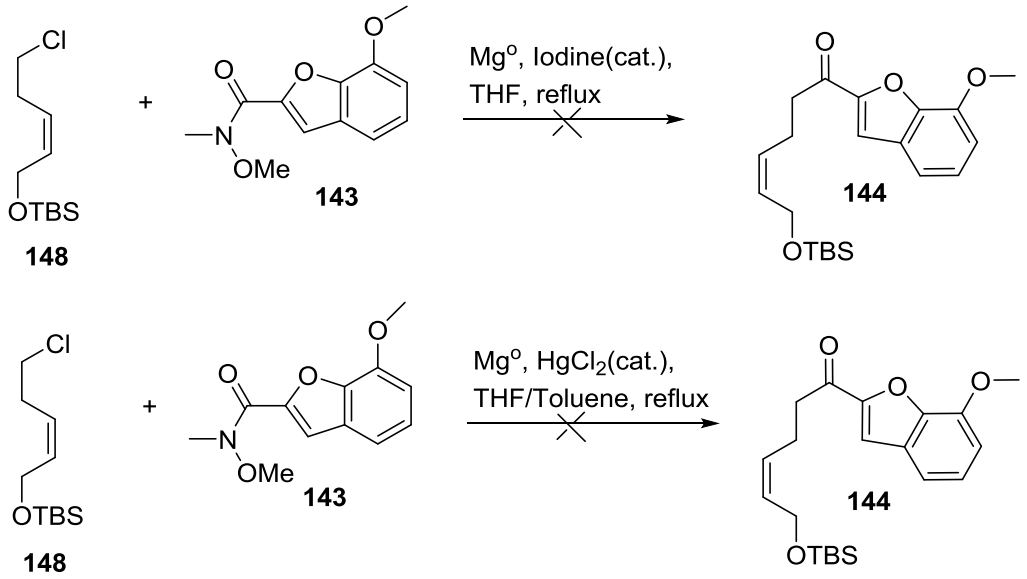
gas, and quinoline but afforded a mixture of alkene isomers (60:40 cis/trans by nmr). Not surprisingly, Lindlar's catalyst worked well to give the cis-alkene **152** selectively. The crude product was silylated to afford the allylic silyl ether **148** in 43% yield (over 2 steps).

The synthesis of the amide **143** was accomplished using a common sequence for making 2-substituted benzofurans (Scheme 52). 2-Bromo-*N*-methoxy-*N*-methylacetamide was synthesized by treating bromoacetyl bromide with *N*,*O*-dimethylhydroxylamine hydrochloride and potassium carbonate in acetonitrile.[96] This reagent was added to the phenoxide of *o*-vanillin **153** to obtain the aryl ether **154** in 63% yield. The addition and condensation reaction was expected to occur in a single reaction step based on what is known for a similar set of substrates; however, this did not occur.[97] In order to induce the condensation reaction, amide **154** was exposed to a stronger base with greater solubility in refluxing acetonitrile, to give the substituted benzofuran **143** in 15% yield.



Scheme 52. The synthesis of the Weinreb amide substituted benzofuran **143**.

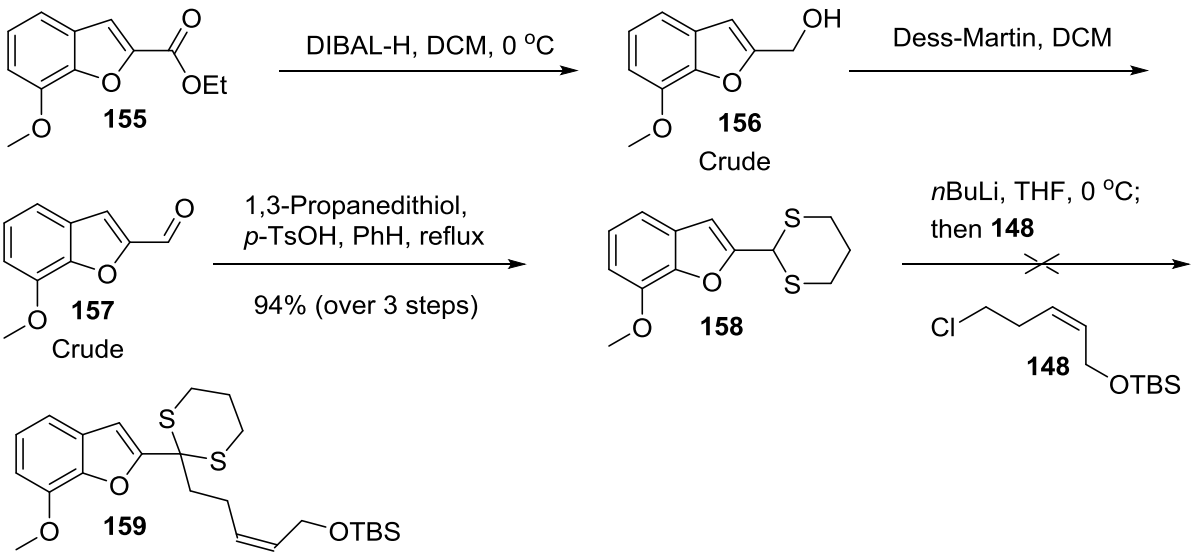
With the alkyl chloride **148** and the Weinreb amide **143** in hand, the Grignard addition was attempted (Scheme 53). Adding the alkyl chloride **148** to magnesium turnings in tetrahydrofuran at 0 ^{o}C followed by refluxing, did not initiate the formation of the Grignard reagent. Attempts to further activate the magnesium with iodine also did not promote the addition process. Restarting the reaction in a refluxing tetrahydrofuran/toluene solvent mixture, followed by the addition of a small quantity of mercury chloride to form a magnesium/mercury amalgam, did nothing to advance the reaction. Performing a Finkelstein-type reaction on the alkyl chloride **148** with sodium iodide in refluxing acetone led to decomposition, thus ruling out switching to a more reactive substrate for the Grignard formation.



Scheme 53. Attempted synthesis of the ketone **144** using a Grignard addition process.

Considering that we had the homoallylic chloride **148** prepared, it seemed reasonable that this might serve as a good electrophile for additions. A benzofuran bearing a dithiane substituent could serve as a nucleophile, thereby providing the additional carbon necessary for the linear chain, as well as the necessary oxidation state of the carbon directly attached to the aryl ring.

Preparation of the dithiane **158** was accomplished by starting with ethyl 7-methoxybenzofuran-2-carboxylate **155**, which can be easily prepared in one step from *o*-vanillin **153**.[98] The ester was reduced using diisobutylaluminum hydride (DIBAL-H) in dichloromethane to afford the alcohol **156** (Scheme 54). The crude reaction mixture was oxidized to the aldehyde **157** using Dess-Martin periodinane in dichloromethane. Using the crude reaction mixture again, the aldehyde **157** was converted to the dithiane **158** using 1,3-propanedithiol in the presence of a



Scheme 54. The synthesis of the dithiane **158** from the aryl ester **155** and the attempted alkylation of the dithiane **158**.

catalytic amount of tosic acid. The yield of the dithiane **158** was 94% over 3 steps. Unfortunately, the attempted alkylation of the anion of the dithiane with the alkyl chloride **148** was met with the appearance of many additional side-products. The quantity of these products rendered the separation from the desired compound impractical.

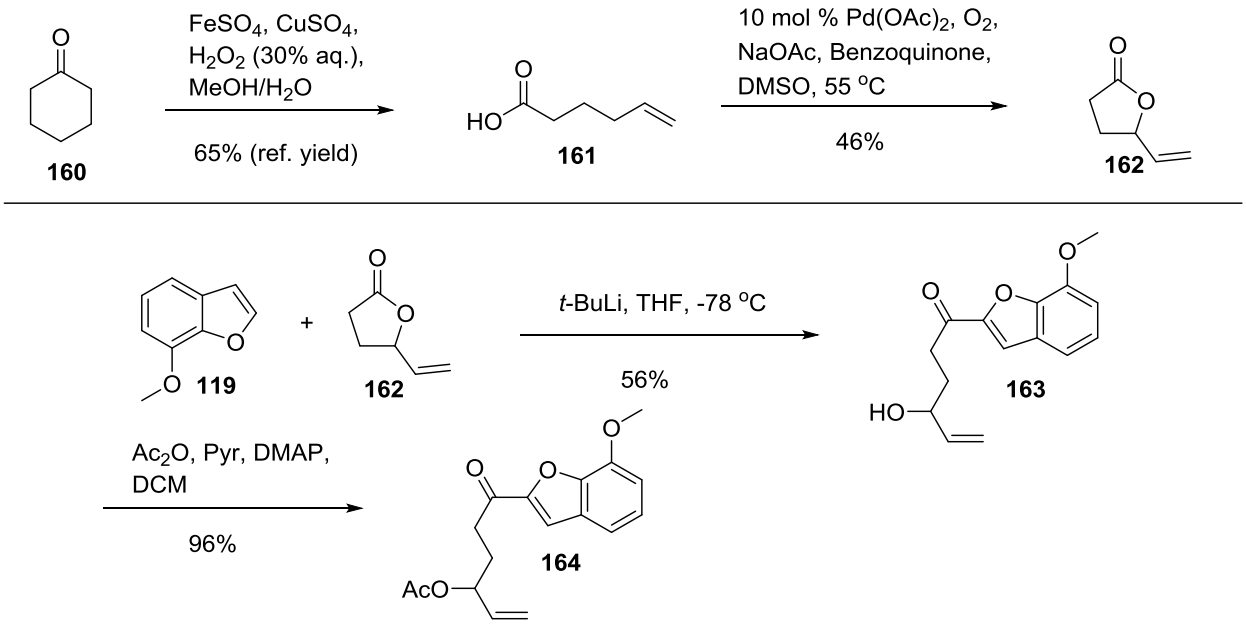
As a result of these problems of assembling the acyclic precursor for potential cyclization of the C-ring of codeine, a simpler lactone was made instead. The synthesis of the 7-membered lactone **117** was pursued because it would have potentially assembled the requisite allylic alcohol or acetate with the more substituted olefin (see compound **121**). This would have better matched the other substrates that have undergone these types of cyclizations. However, it is known that after π-allyl palladium complexes form, the complex can isomerize and transpose the olefin. Thus the starting material for the cyclization could be either the secondary or the primary allylic acetate (or alcohol). Thus we decided to use the vinyl lactone **162**.

The precursor for **162** was 5-hexenoic acid **161**, which was easily prepared from cyclohexanone **160** (Scheme 55).[99] The vinyl lactone **162** was prepared using a combination of procedures outlined by Larock, Pietruszka, and coworkers.[100,101] The original procedure by Larock and Hightower involved the palladium catalyzed intramolecular lactonization of a carboxylic acid directly onto an olefin, but it was later discovered that similar reaction conditions could perform an allylic oxidation to afford lactones. Thus we were able to prepare the vinyl lactone **162** in 46% yield from **161**.

7-Methoxybenzofuran **119** can be prepared by the decarboxylation of commercially available 7-methoxy-2-benzofuran-2-carboxylic acid.[102] Treatment of compound **119** with *t*-butyllithium at -78 ^{o}C followed by the rapid addition of the lactone **162** afforded the allylic

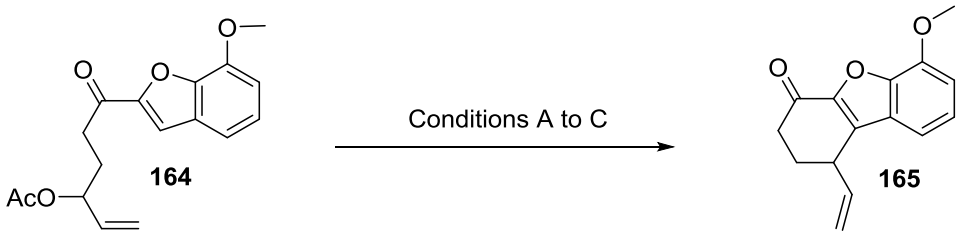
alcohol **163** in 56% yield. The allylic alcohol was easily transformed into the allylic acetate **164** using acetic anhydride, 4-dimethylaminopyridine (DMAP), and pyridine, in 96% yield.

The palladium catalyzed intramolecular cyclization reaction was first explored on the allylic acetate **164**. The cyclization was attempted with the low valent metal complex tris(dibenzylideneacetone)dipalladium(0), Xantphos, and cesium carbonate (Scheme 56, entry A). No cyclization was observed based on the retention of the benzofuran C-3 aromatic proton. However, the starting material was converted to a new product to which we have assigned the structure **197**. These conditions were further investigated (*vide infra*).

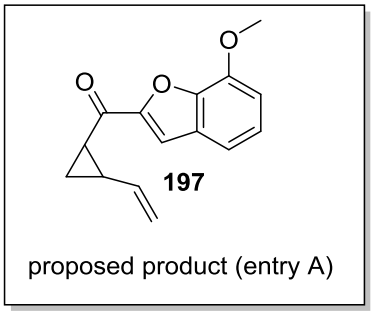


Scheme 55. The preparation of the lactone **162** from cyclohexanone and the assembly of the allylic acetate **164** from 7-methoxybenzofuran **119** and the lactone **162**.

The cyclization was again performed using the same catalyst, but the ligand was switched to 1,2-bis(diphenylphosphino)ethane (dppe) and the base was removed. The absence of added base occurs in these types of reactions when the leaving group of the π-allyl complex is a strong enough base to deprotonate an acidic intermediate or starting material. Normally this occurs with allylic carbonates in the case of malonates being used as a coupling partner. In our case the intermediate that forms is one that mimics that of an electrophilic aromatic substitution, and the acetate leaving group would be strong enough to deprotonate a charged intermediate that forms in this process.

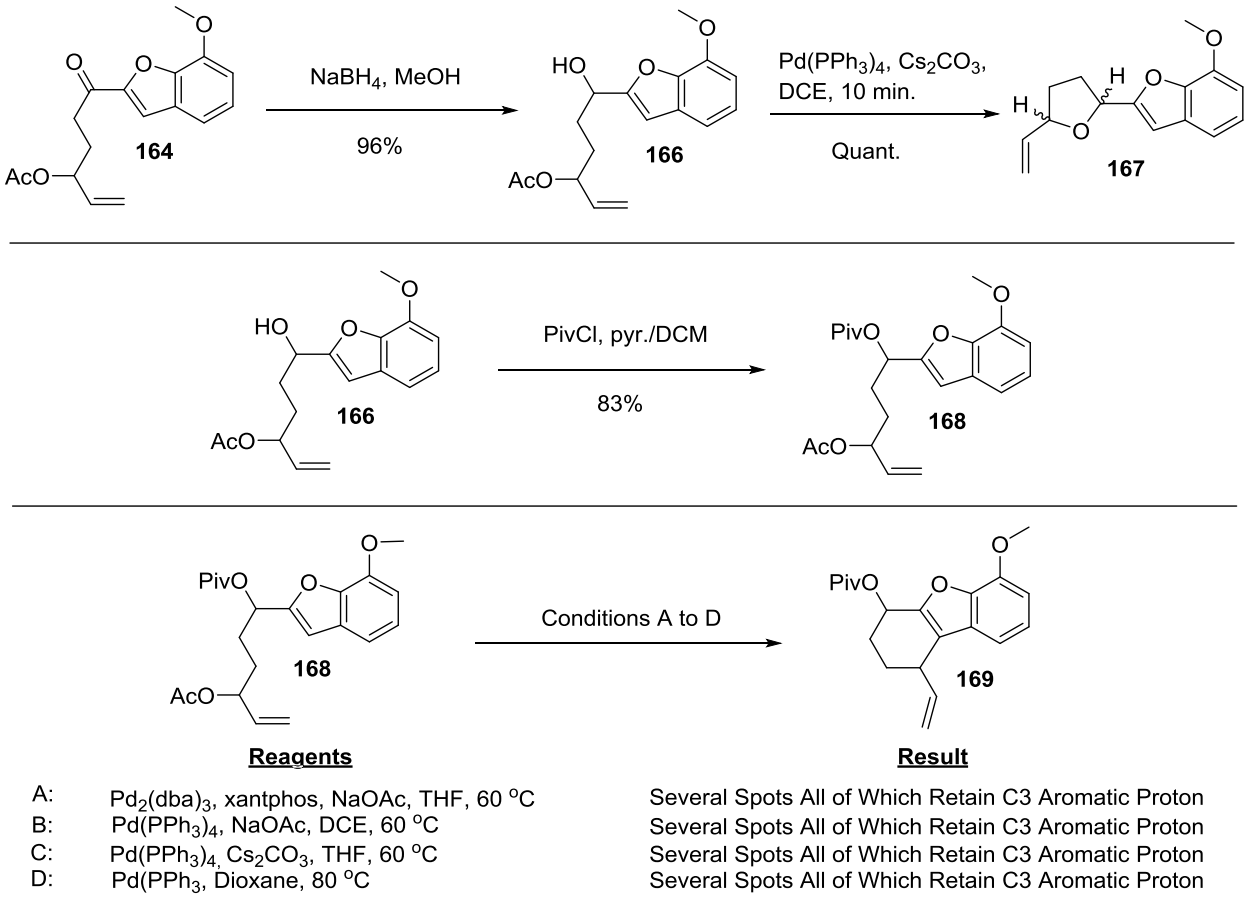


	Reagents	Result
A:	$Pd_2(dba)_3$, Cs_2CO_3, Xantphos, DCM	Product **197**
B:	$Pd_2(dba)_3$, dppe, DCE	Small Conversion to Transposed Allylic Acetate
C:	$Pd_2(dba)_3$, dppe, CH_3CN	Small Conversion to Transposed Allylic Acetate



Scheme 56. The attempted palladium catalyzed cyclization of the allylic acetate **164**.

These reaction conditions were attempted in both a polar aprotic solvent, which would stabilize the formation of a charged intermediate, as well as dichloromethane (entries B and C). In both cases, there was only a small amount of conversion to what was tentatively assigned by NMR as the transposed allylic acetate. The results are not very surprising given that there is a carbonyl in conjugation with the π-system, which reduces the nucleophilicity of the carbon of interest, C-3 of the benzofuran.

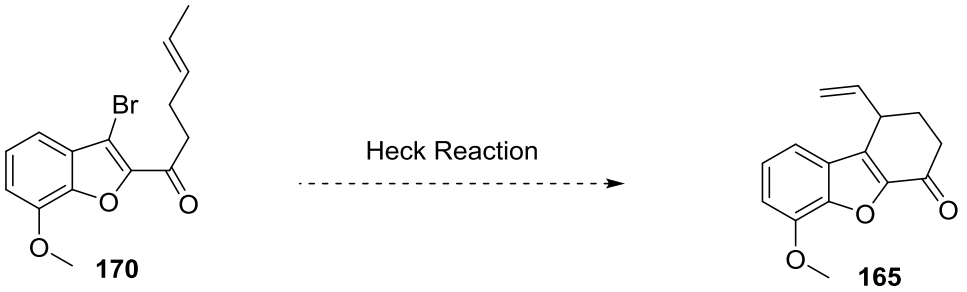


Scheme 57. Attempted palladium catalyzed cyclizations of the unprotected alcohol **166** and the pivalate ester **168**.

The logical solution to the ketone reducing the nucleophilicity of C-3 was the reduction of the ketone **164**, to give the potentially more nucleophilic alcohol. The reduction was carried out using sodium borohydride to give the alcohol **166** in excellent yield (96%) (Scheme 57). The cyclization was attempted on the unprotected alcohol using the more typical catalyst of tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$). The result was unsurprising, the secondary alcohol **166** simply cyclized rapidly to give the tetrahydrofuran **167**. To try to prevent this, the alcohol was protected as the pivalate ester **168** in 83% yield as a mixture of trans and cis diastereomers.

Four different reaction conditions were examined for the cyclization of the allylic acetate **168** bearing the newly formed pivalate ester. $Pd_2(dba)_3$, Xantphos (ligand), and sodium acetate in tetrahydrofuran was first examined (entry A) and found to give conversion to various products that retained the C-3 aromatic proton of the benzofuran. Using $Pd(PPh)_4$ as the catalyst, with or without base in dichloromethane, tetrehydrofuran, or dioxane, also afforded a similar reaction profile with products that retained the C-3 aromatic proton (entries B-D).

Considering the cyclization efforts using palladium catalysis did not yield the desired product, attention was turned towards an alternate route of cyclization of the C-ring. A Heck-type reaction involving the prefunctionalization of the benzofuran was deemed as a good way of promoting the cyclization as well as leaving the unsaturation of the pendant vinyl group (Scheme 58).



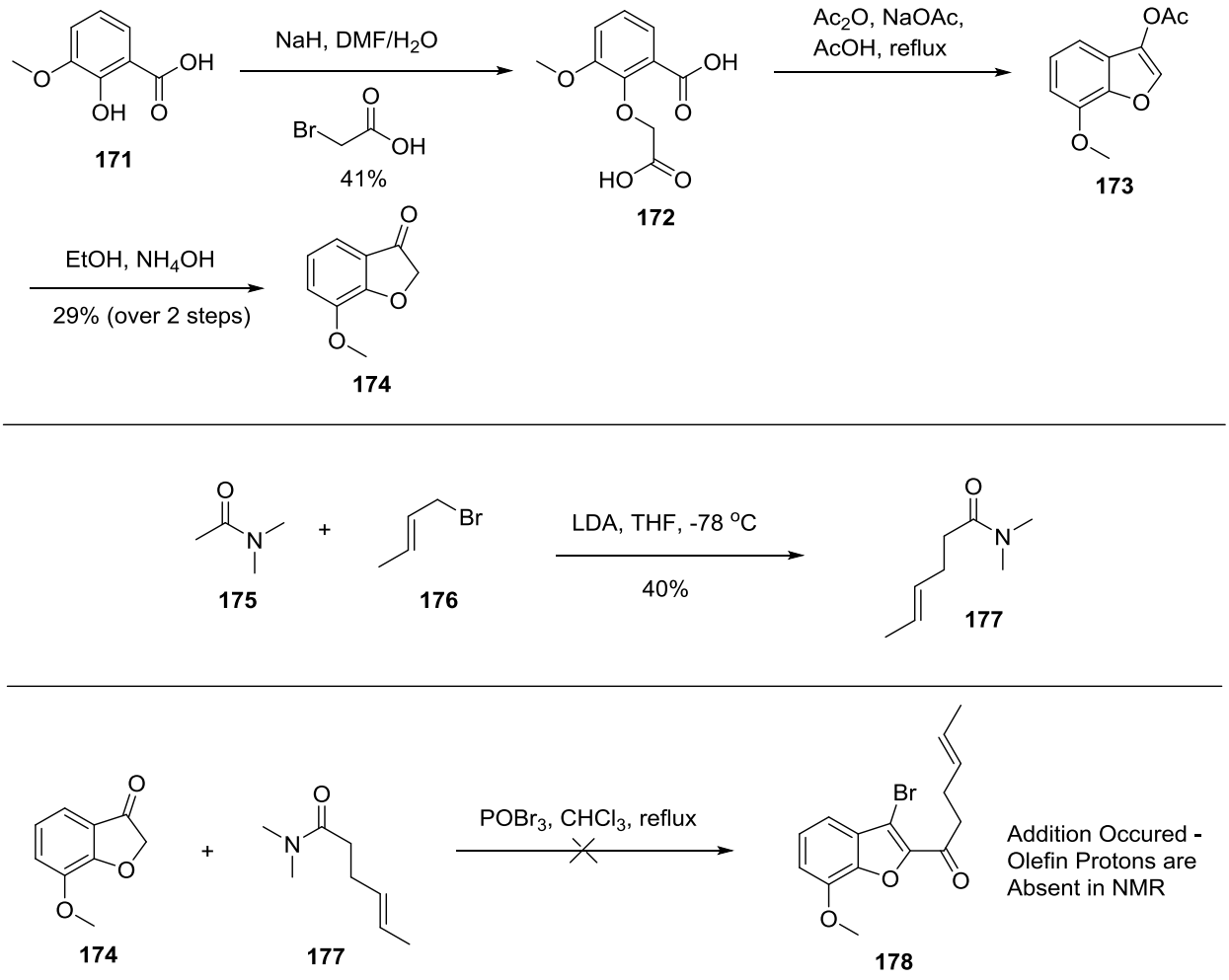
Scheme 58. Proposed Heck-type cyclization of the brominated compound **170**.

As a means of producing the brominated substrate **178**, direct bromination of 7-methoxybenzofuran **119** was performed and found to brominate both *ortho* and *para* to the methoxy group. This was an unusual result as normally the C-3 position of benzofuran is the most electron-rich carbon of the bicyclic ring system and thus it should be the most reactive in electrophilic aromatic substitution reactions.

To circumvent the poor regioselectivity seen in the bromination reaction, a new method which was used to transform a benzofuranone into the corresponding 3-bromobenzofuran-2-carbaldehyde was attempted (Scheme 59).[103] The process works through a Vilsmeier-Haack process with additional dehydration and bromination. We postulated that the amide **177** could be used in lieu of dimethylformamide.

The benzofuranone **174** was synthesized using a three step process. The dianion of 2-hydroxy-3-methoxybenzoic acid **171** was alkylated in modest yield (46%) with 2-bromoacetic acid. The decarboxylative cyclization of the dicarboxylic acid **172** was accomplished using sodium acetate in a refluxing acetic anhydride/acetic acid mixture. The intermediate acetate **173**

was particularly labile, as exposure to strong acid or base led to rapid decomposition. It took many attempts to find a suitable medium for the desired deacetylation to occur preferentially. The mild conditions of ammonium hydroxide in ethanol was eventually used to cleave the acetate to the corresponding benzofuranone **174**. Thus it was produced in 29% yield over two



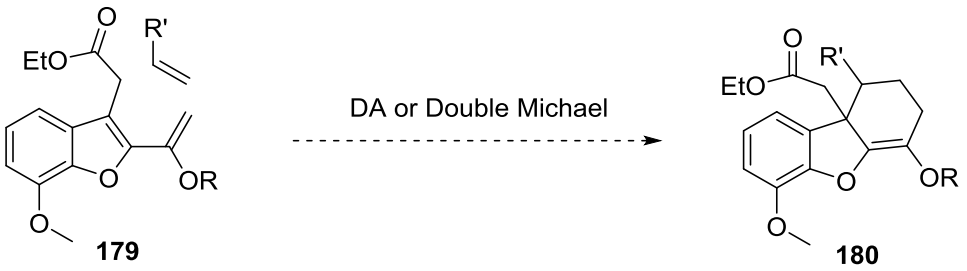
Scheme 59. The synthesis of the benzofuranone **174**, the amide precursor **177** and the Vilsmeier-Haack/dehydration/bromination reaction.

steps from **172**. The amide **177** was synthesized in 40% yield by alkylation of the enolate of *N*,*N*-dimethyl acetamide **175** with (*E*)-1-bromobut-2-ene **176**.

After treating the benzofuranone **174** and the amide **177** with phosphorus oxybromide ($POBr_3$), it was found that a reaction had occurred but the desired product was not formed.

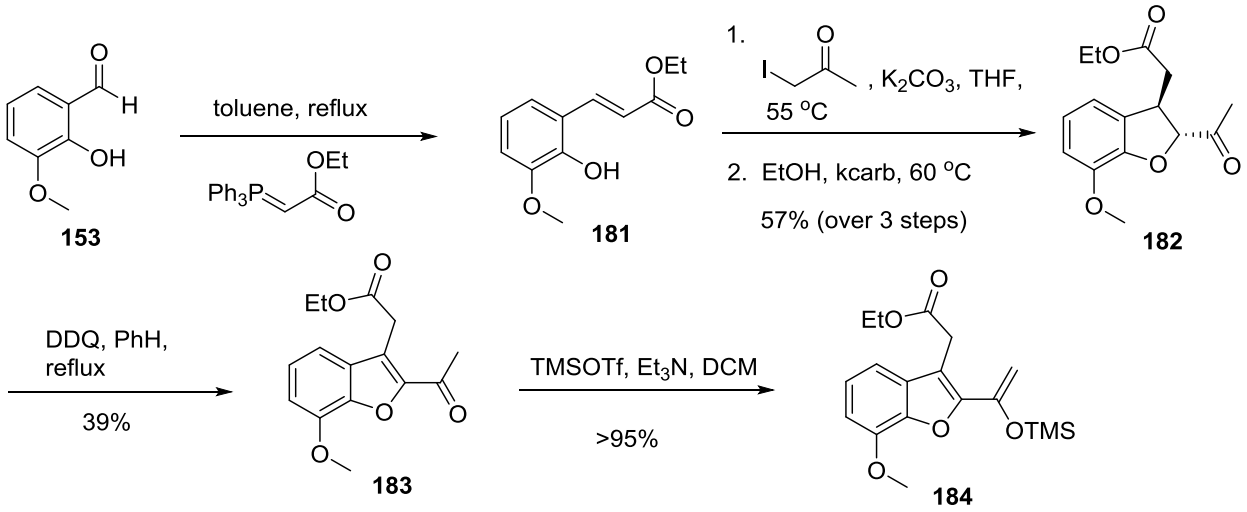
Diels-Alder Approach Towards Synthesizing Morphine

A Diels-Alder reaction, or double Michael addition, was also envisioned for synthesizing the C-ring of morphine (Scheme 60). We believed that the diene **179** could be prepared quite readily, and we hoped that various strong dienophiles, with or without Lewis acid assistance, could react with this substance to give the cyclized product **180**. The idealized electrophile for this transformation was acrolein because it would provide a functional group which would allow a single transformation for making the vinyl substituent at R'.



Scheme 60. The Diels-Alder reaction as a means of assembling the c-ring of morphine.

The synthesis of the trimethylsilyloxy diene **184** commenced with the addition of the ylide, (carbethoxymethylene)triphenylphosphorane, to the aldehyde of *o*-vanillin **153**, giving the Horner-Wadsworth-Emmons product **181** (Scheme 61). This crude material was subjected to the next step because the product overlapped with the starting material on silica gel thin-layer-chromatography and attempts to remove the phosphine oxide by filtration through a short pad of silica gel was not effective. The phosphine oxide was assumed to be inert towards the reaction conditions of the following step. Deprotonation of the phenol **181** with potassium carbonate and subsequent alkylation with 1-iodoacetone produced the desired addition product. The expectation was that the alkylation and Michael addition would occur in one step, which may have occurred if the solvent had been more polar. The solvent was removed and replaced with ethanol and additional base. The reaction was gently heated to afford the cyclized product **182** in moderate yield (57%) over three steps. NMR analysis indicated that this is one diastereomer; we



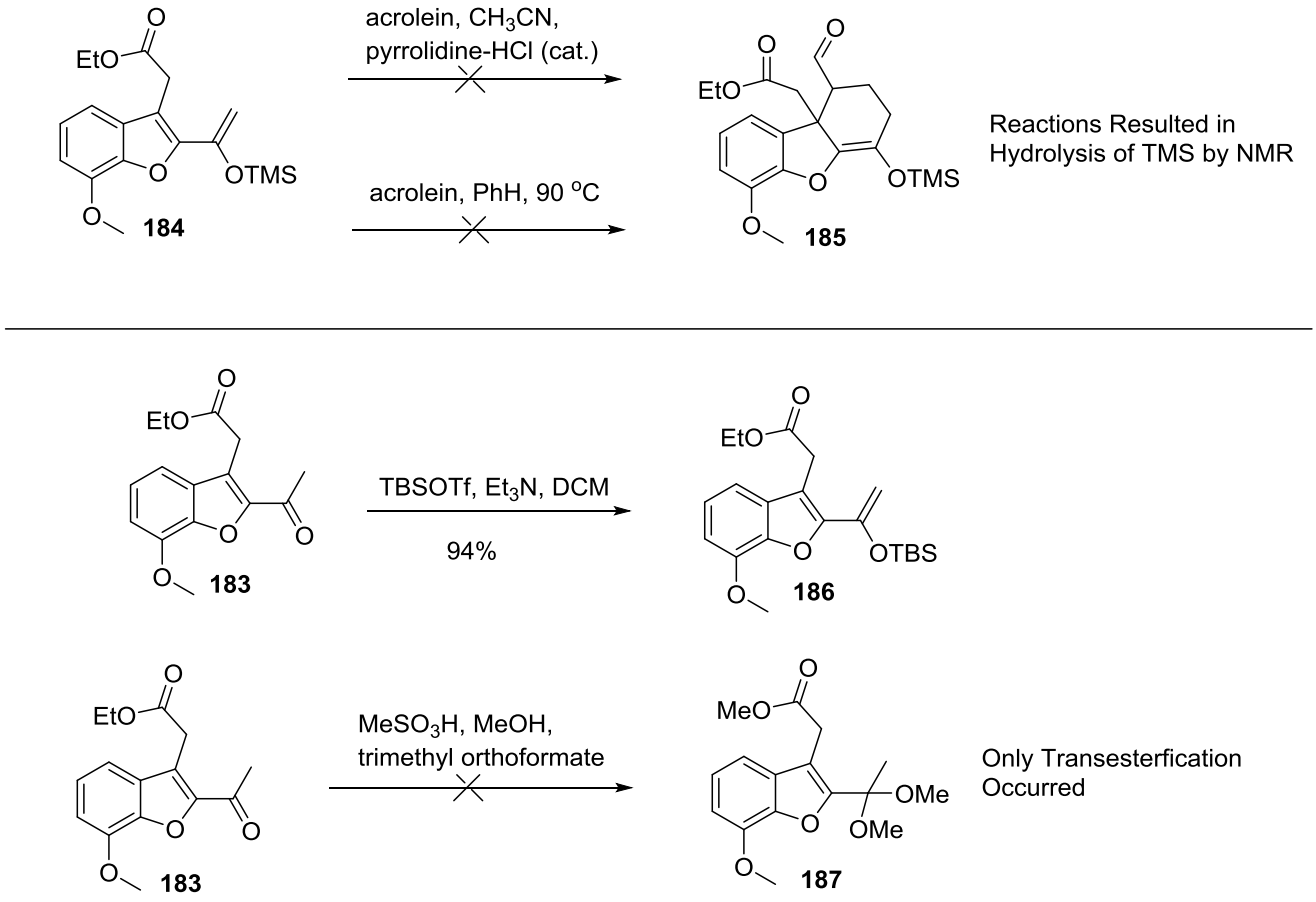
Scheme 61. The synthesis of the diene **184** from *o*-vanillin **153**.

assume it is the trans isomer. Treatment of the dihydrobenzofuran **182** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing benzene provided the desired oxidized product **183** in 39% yield. In the presence of triethylamine, the dicarbonyl compound **183** was treated with an excess of trimethylsilyl triflate (TMSOTf) in dichloromethane. An excess is used because presumably the reagent reacts first with the more electron-rich ester to form the silyl ketene acetal and then the desired silyl enol ether forms. The silyl ketene acetal is easily hydrolyzed during work-up of the reaction to afford the mono-silylated product **184** in excellent yield without the need for chromatography.

Initial studies on the addition of acrolein as a dienophile failed because of the labile nature of the trimethylsilyl enol ether functional group (Scheme 62). Using pyrrolidine hydrochloride as a catalyst to form a more reactive vinyl iminium ion species *in situ*, resulted in hydrolysis of the trimethylsilyl (TMS) functional group. The acidic nature of the medium is most likely the cause of this result. However, the same result was observed with an attempted addition of acrolein thermally without any additives, which was curious. A number of other attempts were tried with Lewis acids as additives (not shown), but each resulted in hydrolysis or no conversion.

To remedy the issue of the rapid hydrolysis of the trimethylsilyl group, the *t*-butyldimethylsilyl enol ether was prepared instead (Scheme 62). Thus treatment of the ketone **183** with TBSOTf and triethylamine gave **186** in 94% yield. We also tried to prepare the methoxy diene, but the dimethyl ketal precursor **187** did not form when **183** was treated with acidic methanol and trimethyl orthoformate. For steric reasons, the methoxy diene may have

been a more suitable choice for the Diels-Alder reaction because it would have maintained better coplanarity of the diene vs. the silyloxy dienes, which are more sterically bulky.



Scheme 62. Attempted cycloaddition of acrolein, thermally or with pyrrolidine hydrochloride and the synthesis of the siloxy diene **186**.

A number of conditions were tried to effect the Diels-Alder reaction with acrolein (Scheme 63). These reactions were performed in dichloromethane as a solvent and typically

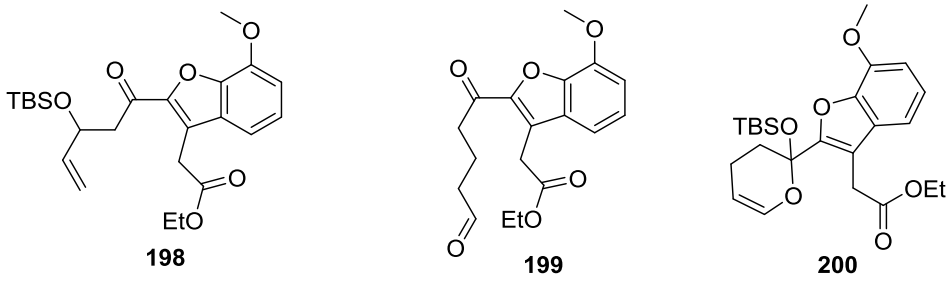
included molecular sieves to prevent the hydrolysis of the silyl group by water. An interesting result was discovered when indium(III) chloride was utilized as a Lewis acid catalyst. Both 1,4- and 1,2-addition of acrolein to the terminal carbon of the vinyl ether with concomitant silyl transfer was observed. The 1,4-addition product was hydrolyzed in ethanol and hydrochloric acid to confirm the structure (Scheme 63, entry A, Compounds **198** and **199**). The desired regioselectivity, as it relates to a possible double Michael addition reaction, was quite good and gave hope for the second ring closure step to occur.

When the Lewis acid was switched to either a Corey-Bakshi-Shibata reagent or titanium(IV) isopropoxide, no reaction was observed (entries B and D). When the substrates were subjected to an (*S*)-Binol-based aluminum Lewis-acid catalyst prepared *in situ*, a hetero Diels-Alder reaction between acrolein and the pendant vinyl group was seen giving the dihydropyran **200** in modest yield (entry F). The Bronsted acid, triflimide was also tried (entry C), but this reaction resulted in hydrolysis of the silyl group, perhaps due to the small unavoidable quantity of water that may have been present.

In addition to acrolein, acrylonitrile was heated with the diene **186** at 110 ^{o}C in xylenes (entry L). The higher boiling point of this electrophile vs. acrolein allowed this type of study. However, no reaction was observed.

Other different strong dienophiles were also attempted for the cycloaddition reaction. No reaction was observed when *N*-benzylmaleimide was heated with the diene **186** to 140 ^{o}C in xylenes (entry G). These same substrates were dissolved in dichloromethane and treated with indium(III) chloride which resulted in no reaction. When this was observed, a small quantity of

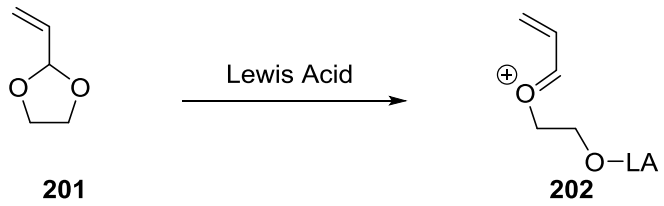
Conditions		Result
A:	$InCl_3$, Acrolein, DCM, mol. sieves	Rapid 1,4 and 1,2 Addition to Acrolein w/ Silyl Transfer
B:	R-CBS, Acrolein, DCM, mol. sieves	No Reaction
C:	10 mol% Triflimide, Acrolein, DCM, mol. sieves	hydrolysis of TBS
D:	Ti(*i*-PrO)$_4$, Acrolein, DCM, mol. sieves	No Reaction
E:	$InCl_3$, Acrolein, -42 ^oC, DCM, mol. sieves	Rxn Stalls and is Sluggish
F:	(S)-BINOL, $AlMe_3$, Acrolein, DCM	39% Hetero Diels-Alder Product
G:	*N*-Benzyl Maleimide, Xylenes, 140 ^oC	No Reaction
H:	*N*-Benzyl Maleimide, DCM, $InCl_3$, mol. Sieves; $MgBr_2$	Partial Hydrolysis of Silyl Group
I:	Acrolein Ethyleneacetal, $TiCl_4$, DCM	Partial Conv. - Crude Shows HOTBS - Inconclusive
J:	Acrolein Ethyleneacetal, $InCl_3$, DCM	No Reaction
K:	Maleic Anhydride, neat, 140 ^oC	Many Products
L:	Acrylonitrile, Xylenes, 110 ^oC	No Reaction



Scheme 63. Various attempted conditions and substrates for the cycloaddition with the siloxy diene **186**.

anhydrous magnesium bromide was added to the same reaction mixture which partially hydrolyzed the silyl group (entry H). Maleic anhydride was heated with the diene **186** neat at 140 ^oC and resulted in a very large quantity of products (entry K) and thus this reaction was abandoned.

The final attempts at the Diels-Alder study with the diene **186** was with 2-vinyl-1,3-dioxolane **201**, which forms an allyl cation **202** and has been examined in the literature as a highly reactive electrophile for these types of reactions (Scheme 64).[104] In our case, both the Lewis acids, indium(III) chloride and titanium(IV) chloride, were used to catalyze the formation of the allyl cation intermediate. It was not surprising that the indium(III) chloride reaction

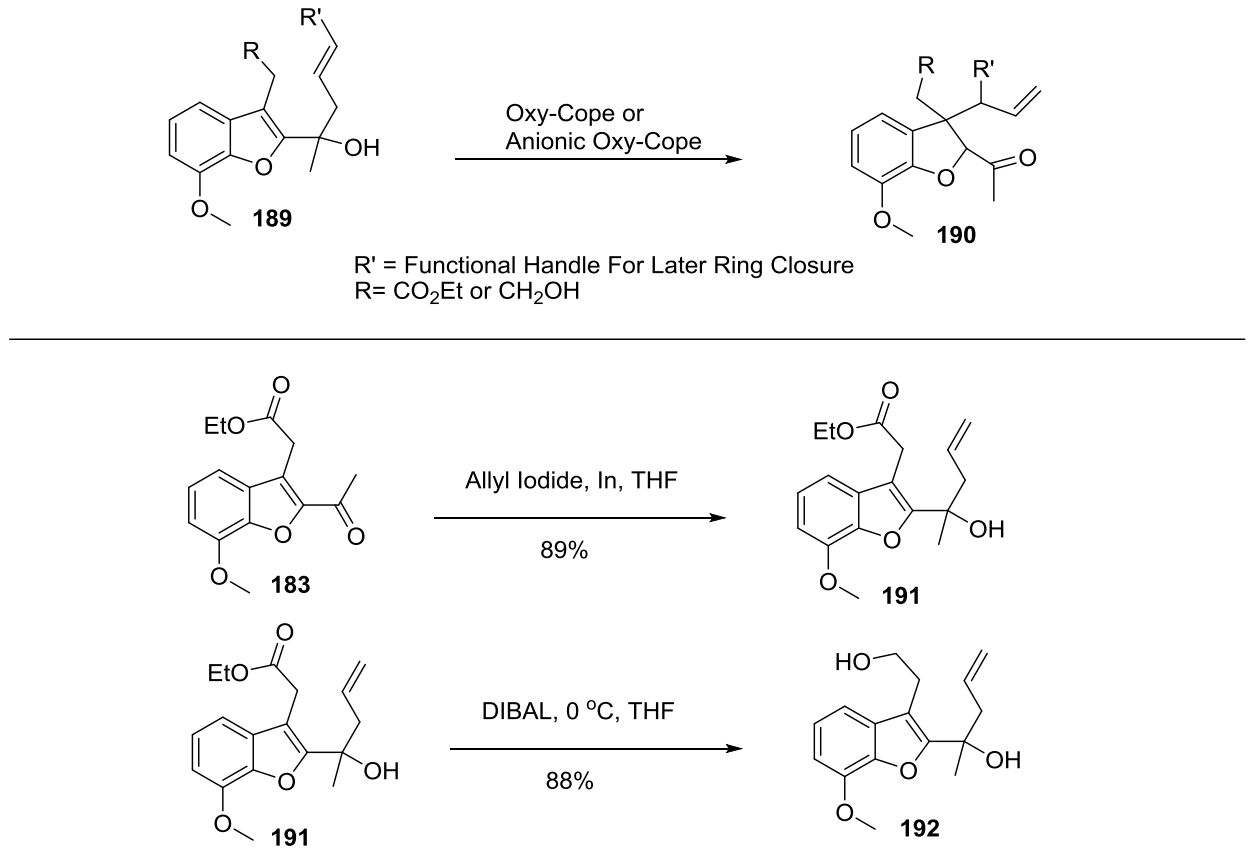


201 **202**

Scheme 64. Formation of the allyl cation **202** after treatment of 2-vinyl-1,3-dioxolane **201** with a Lewis Acid.

resulted in no conversion of the starting material. It may not have generated the allyl cation due to its weak Lewis acidity (entry J). The titanium Lewis acid, however, resulted in a small amount of conversion to an unknown compound. The crude nmr showed the presence of *t*-butyldimethylsilanol which indicated that the desired compound most likely didn't form (entry I). We were unable to conclusively assign the structure for this product.

The last idea of performing the cyclization of the C-ring as well as forming the quaternary center of morphine involved an oxy-Cope or an anionic oxy-Cope sigmatropic rearrangement (Scheme 65). The thought was that if the rearrangement worked on the simpler

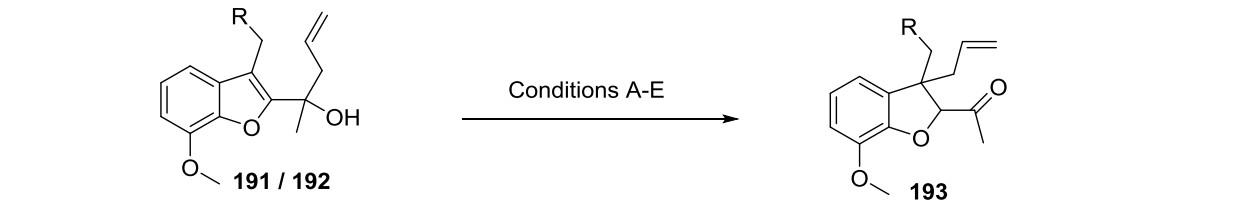


Scheme 65. Oxy-Cope and anionic oxy-Cope concept and synthesis of rearrangement precursors.

substrate, the homoallylic alcohol **191**, then the more substituted substrate **190** might be able to be prepared which would feature a functional group that could be used to close the C-ring of morphine. This functionality would most likely have been the masked aldehyde as the acetal and could fashion the ring together through an aldol-condensation reaction with the methyl ketone. In addition, both the quaternary center and the adjacent chiral center of the product **190** could be controlled with excellent stereospecificity considering the Cope rearrangement is known to transfer chirality from the starting material to the product in the transition state.

The ester bearing homoallylic alcohol **191** was synthesized as a simplified model system using a Barbier-type reaction of the ketone **183** with indium metal and allyl iodide to give **191** in 89% yield. The ester of this product was also reduced to the alcohol **192** using diisobutylaluminum hydride (DIBAL) in 88% yield. This reduced product was synthesized after the initial studies of the oxy-Cope reaction on the ester-bearing compound **191** had failed.

The studies of the oxy-Cope reaction began with the attempted thermal rearrangement of the homoallylic alcohol **191** in xylenes at 150 ^{o}C. The result was conversion to a number of different compounds that were demethylated or had none of the expected peaks in the NMR spectrum (Scheme 66, entry A). This substrate was then subjected to the anionic oxy-Cope conditions of potassium hydride at room temperature. When no reaction was observed, the reaction was heated followed by the addition of the crown ether, 18-crown-6. Again, no reaction was observed (Scheme 66, entry B). Both the alkoxide and the enolate may have formed due to the abundance of potassium hydride and may not have been conducive for the reaction to occur. In addition, the formation of the alkoxide exclusively should have cyclized to give the lactone. Since palladium(II) chloride complexes are known to catalyze [3,3]-sigmatropic rearrangements of 1,5-dienes, this was also explored and found to give one predominant product (Scheme 66, entry C).[105,106] Unfortunately, this product was not the desired one, and at the moment its structure remains unknown. The last attempt was using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to catalyze the reaction. Unfortunately, the lactone was observed during this study, which should have been expected (Scheme 66, entry D). The reduced compound **192** was next studied under the conditions of the anionic oxy-Cope and again a new unidentified product was formed. This result should be further studied (Scheme 66, entry E).



R = C(O)OEt

A: 150 °C, xylenes — Many products - nothing in 2-3 ppm region by NMR
B: KH, THF, RT then 80 °C, then to 120 °C, then 18-crown-6 — No reaction
C: $PdCl_2(AcN)_2$, DCM — Isolated major product - unknown structure
D: DBU, DCM — Partial conversion to lactone

R = CH_2OH

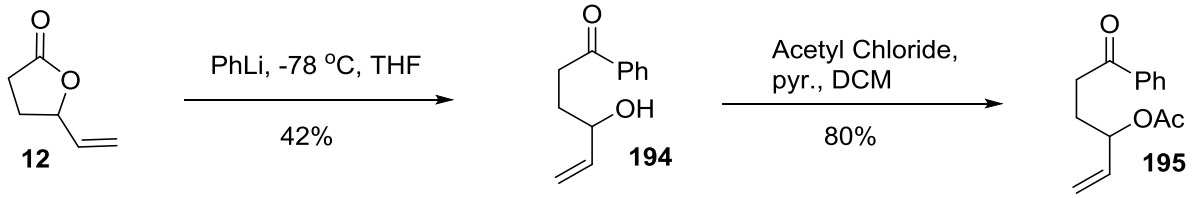
E: KH, 18-crown-6, THF — ~Half conversion to another compound - For future research.

Scheme 66. Oxy-Cope and anionic oxy-Cope rearrangement studies of the ester **191** and the alcohol **192**.

Investigation of Palladium Catalyzed Intramolecular Cyclopropanation of π-Allyl Complexes

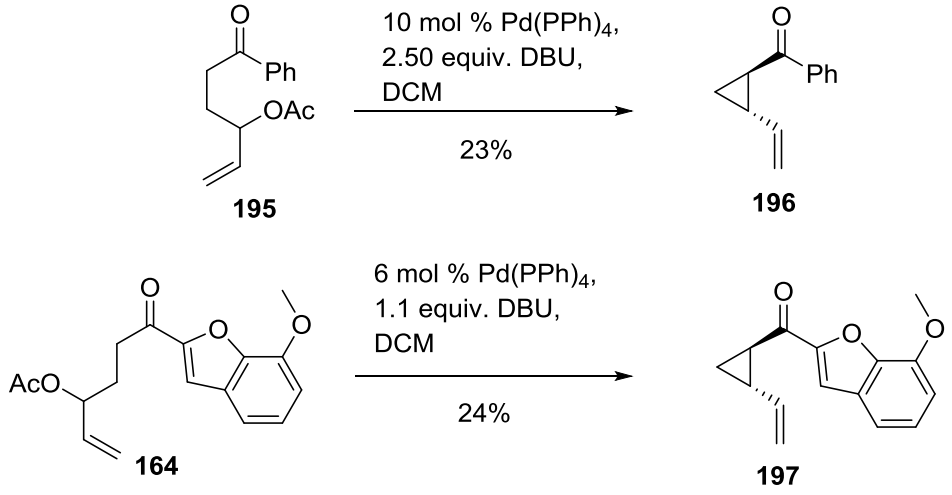
As stated before, during the attempted cyclization of the benzofuran on to a pendant π-allyl palladium complex (substrate **164**), a vinyl cylcopropyl ketone was formed instead. To further study this reaction, the phenyl derivative **195** was synthesized because the corresponding vinylcyclopropyl ketone **196** was known and there was analytical data available (schemes 67 and 68). This addition of phenyllithium to the vinyl lactone **162** gave, in 42% yield, the phenyl ketone **194**, the alcohol of which was acetylated to give **195** in 80% yield.

The initial attempt at forming the cyclopropane from **195** using palladium catalysis involved the original conditions used with the benzofuran-substituted substrate **164** (*vide supra*). These conditions did not work for the phenyl ketone **195** and the reason remains unclear. A



Scheme 67. The synthesis of the phenyl precursor for the palladium catalyzed cyclopropanation reaction.

hypothesis was that maybe a stronger base was needed. Moving from the inorganic and insoluble base of cesium carbonate to the stronger and soluble base of DBU, as well as switching the catalyst to tetrakis(triphenylphosphine)palladium(0), allowed for complete conversion of the starting material (Scheme 68). The complete conversion of the starting material **195** to two new spots by thin layer chromatography seemed to indicate that the reaction was high yielding. The



Scheme 68. The palladium catalyzed synthesis of the vinylcyclopropyl ketones, **196** and **197**.

highest yield for the phenyl substituted vinylcyclopropyl ketone **196** was 23% and for the benzofuran substituted vinylcyclopropyl ketone **197** it was 24%. Both of these products were almost exclusively the trans isomers. The assignment of the stereochemistry of **196** was made by comparison of the proton NMR with that reported in the literature.[107,108] The low yields may be due to the substrate being unstable during the purification process on silica gel.

Future Work

In future work, the synthesis of morphine using modifications of the routes reported herein, should be focused on the Diels-Alder and oxy-Cope approaches, as they seem to be the most promising. As for the former, perhaps an intramolecular-type Diels alder addition should be studied. For the latter, it still remains to be seen as to whether the reduced compound **192** can undergo the anionic oxy-Cope cyclization with added base and heat.

The palladium-catalyzed reaction to form vinylcyclopropyl ketones is promising. The low yields might be overcome by studying other catalyst structures that could be used in the reaction and should not be limited to palladium(0) complexes. In addition, the byproducts and their mechanism of formation should be elucidated. A study should also be performed using an internal standard to assess the relative yield of the product before and after any work-up/separation is performed to see if hydrolysis or some other type of transformation is occurring. Finally, perhaps a more reactive substrate such as switching from a ketone to a β-ketoester or a silyl enol ether could be used. In addition, a substrate bearing an allylic carbonate should be investigated.

Experimental Section

Materials and Methods

All NMR spectra were recorded on Bruker spectrometers at 400 or 500 MHz for ^{1}H, 100 or 125 MHz for ^{13}C, and 375 MHz for ^{19}F. High resolution mass spectra were obtained from the UCLA Molecular Instrumentation Center. Optical rotation measurements were carried out using a Rudolph Research Autopol IV automatic polarimeter. Reagents were purchased through Fischer Scientific or Sigma-Aldrich. ACS grade solvents were purchased from Fischer Scientific. Toluene, benzene, THF, and diethyl ether solvents were dried prior to use by distilling over sodium metal and benzoquinone. Dichloromethane was distilled over calcium hydride. Methanol was distilled over magnesium turnings. Ethanol (200 proof) was purchased from Fischer Scientific and was used without further drying. Silica gel P60 was purchased from Silicycle. All oxygen or moisture sensitive reactions were performed under an inert Argon atmosphere unless otherwise noted. X-ray crystallography was performed at the J.D. McCullough Crystallography Laboratory.

Experimental Procedures

2-[((1,1-Dimethylethyl)dimethylsilyloxy)methyl]cyclopent-2-en-1-one, 3.

To a solution of **2** (8.72 g, 77.8 mmol) in 220 mL of dichloromethane was added *tert*-butyldimethylsilyl chloride (TBSCl) (14.07 g, 93.3 mmol) and imidazole (11.65 g, 171.1 mmol). The solution was stirred at 22 °C for 12 h. The reaction mixture was partitioned with brine and extracted with dichloromethane (4x). The combined extracts were dried with magnesium sulfate,

filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes, $R_f = 0.35$). The silyl ether **3** was obtained as a colorless oil (16.88 g, 74.6 mmol) in 96% yield.

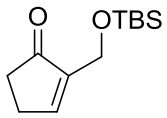
^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.54-7.51 (m, 1H)

4.38-4.33 (m, 2H)

2.63-2.57 (m, 2H)

2.46-2.40 (m, 2H)



3

0.91 (s, 9H)

0.07 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 208.5, 157.9, 146.4, 58.3, 35.4, 26.7, 25.9, 18.3, -5.44.

HRMS-ESI (*m/z)* $[M+Na]^+$ calcd for $C_{12}H_{22}O_2NaSi$ 249.1287; found 249.1314.

_(S)_-2-[((1,1-Dimethylethyl)dimethylsilyloxy)methyl]cyclopent-2-en-1-ol, 4.

To a solution of (*R*)-CBS[28] (1M in toluene, 8.24 mL, 8.24 mmol) in 80 mL of dichloromethane was added borane (1M in tetrahydrofuran, 24.7 mL, 24.7 mmol) at 0 °C. After 5 min., the enone **3** (9.33 g, 41.2 mmol) in 20 mL of dichloromethane was added with rapid stirring over 4 min via

a syringe pump. The reaction was stirred for a further 4 min before adding 40 mL of methanol. The solution was concentrated *in vacuo* and the crude residue purified by flash column chromatography on silica gel (gradient: 5% to 15% ethyl acetate in hexanes). The alcohol **4** was obtained as a colorless oil (8.29 g, 36.29 mmol) in 88% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

5.72 (m, 1H)

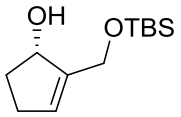
4.83-4.77 (m, 1H)

4.39-4.29 (m, 2H)

2.68-2.37 (m, 2H)

2.31-2.14 (m, 2H)

1.82-1.69 (m, 1H)



4

0.90 (s, 9H)

0.079 (s, 3H)

0.075 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3, 129.3, 77.8, 61.5, 33.5, 30.0, 25.9, 18.3, -5.44, -5.46.

HRMS-ESI (*m/z)* $[M+Na]^+$ calcd for $C_{12}H_{24}O_2NaSi$ 251.1443; found 251.1485.

$[\alpha]_D^{22}$ -44.1° (c = 0.79, $CHCl_3$).

Enantiopurity: The optical rotation of the allylic alcohol **4** was measured and compared with the same compound prepared from the enantio-enriched ester **202**, to verify the absolute configuration. The ester **202** was prepared using conditions outlined in the literature (Candish, L.; Lupton, D.W. *Org. Lett.* **2010**, *12*, 4836).

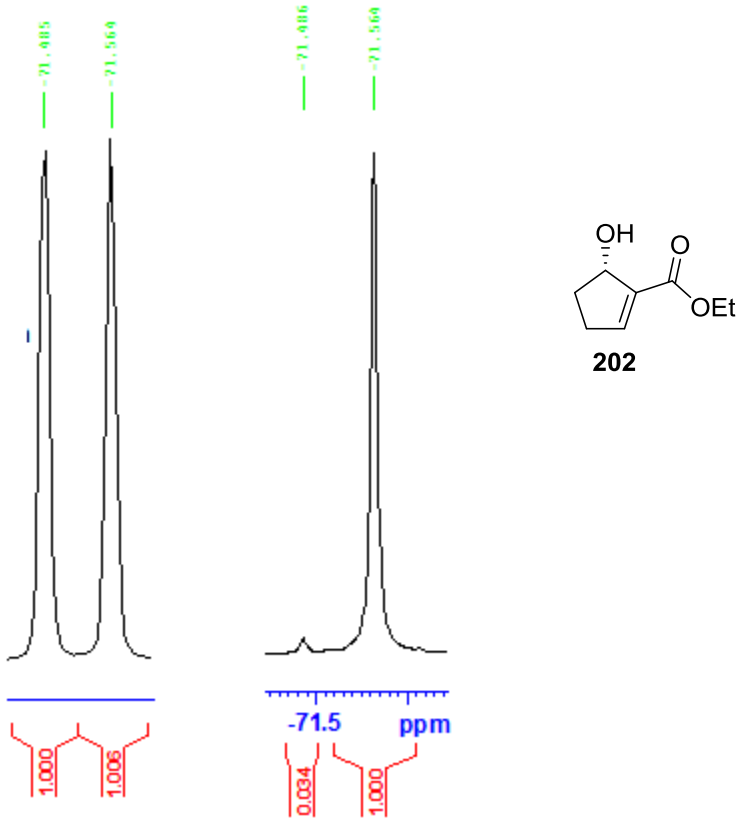


Figure 1. ^{19}F NMR of Mosher's esters derived from racemic (left) and enriched (right) mixtures of allylic alcohols.

The ester was reduced using DIBAL and the alcohol-bearing product was selectively silylated using TBSCl to give the allylic alcohol **4** with excellent enantiopurity. The corresponding Mosher's esters were prepared and the enantiopurities assessed by means of ^{19}F NMR. The CBS reduction was found to give the desired enantiomer in 93.4% e.e. (29.4:1 e.r.)

(1*R*,2*S*,5*S*)-1-[((1,1-Dimethylethyl)dimethylsilyloxy)methyl]bicyclo[3.1.0]hexan-2-ol, 5.

Solution A: To a solution of the allylic alcohol **4** (11.37 g, 49.8 mmol) in dichloromethane (125 mL) at 0 °C was added diethylzinc (1M in hexanes, 54.7 mL, 54.7 mmol) over 2 min. Solution B: To dichloromethane (125 mL) cooled to 0 °C was added diethylzinc (1M in hexanes, 49.8 mL, 49.8 mmol) followed by diiodomethane (8.42 mL, 104.5 mmol). After 10 min, solution A was transferred via cannula to solution B. The reaction mixture was allowed to warm to 22 °C over 16 h, whereupon a solution of saturated aqueous sodium bicarbonate was added followed by a small quantity of water. A precipitate developed and the biphasic mixture was filtered. The precipitate was washed with dichloromethane. The biphasic mixture was separated and the aqueous layer further extracted with dichloromethane (5x). The combined filtrate and dichloromethane extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was separated by flash column chromatography on silica gel (10% ethyl acetate in hexanes). Compound **5** was isolated as a colorless oil (11.67 g, 48.14 mmol) in 97% yield.

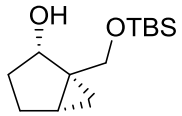
^{1}H NMR (400 MHz, $CDCl_3$) δ:

4.49 (dd, *J* = 8.1, 8.1 Hz, 1H)

3.92 (d, *J* = 10.3 Hz, 1H)

3.52 (d, *J* = 10.4 Hz, 1H)

2.49 (br s, 1H)



5

1.95-1.85 (m, 1H)

1.77-1.61 (m, 2H)

1.26-1.10 (m, 2H)

0.88 (s, 9H)

0.84 (dd, *J* = 4.5, 4.5 Hz, 1H)

0.37 (dd, *J* = 8.0, 5.1 Hz, 1H)

0.04 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 76.6, 67.9, 34.2, 29.2, 25.9, 24.7, 21.1, 18.2, 9.9, -5.35, -5.43.

HRMS-ESI (*m/z)* $[M+Na]^+$ calcd for $C_{13}H_{26}NaO_2Si$ 265.1600; found 265.1636.

(1*R*,5*S*)-1-[((1,1-Dimethylethyl)dimethylsilyloxy)methyl]bicycle[3.1.0]hexan-2-one, 6.

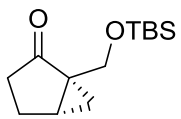
To a solution of the alcohol **5** (11.66 g, 48.10 mmol) and pyridine (15.50 mL, 192.39 mmol) in dichloromethane (240 mL) was added Dess-Martin periodinane (24.48 g, 57.71 mmol). The reaction mixture was stirred for 1.5 h before quenching with a 1:1 saturated solution of sodium

bicarbonate (aq) and sodium thiosulfate (aq). The biphasic mixture was stirred rapidly for several hours. The organic layer was removed and the aqueous layer was further extracted with dichloromethane (4x). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The crude residue was separated by flash column chromatography on silica gel (10% ethyl acetate in hexanes, $R_f = 0.30$). The ketone **6** was isolated as a colorless oil (10.72 g, 44.59 mmol) in 92% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

4.04 (d, *J* = 10.9 Hz, 1H)

3.77 (d, *J* = 10.9 Hz, 1H)



6

2.24-2.02 (m, 4H)

2.00-1.91 (m, 1H)

1.36-1.29 (m, 1H)

0.94 (dd, *J* = 4.3, 4.3 Hz, 1H)

0.86 (s, 9H)

0.040 (s, 3H)

0.036 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 214.6, 59.2, 39.0, 33.0, 25.8, 25.7, 21.6, 18.3, 16.4, -5.42, -5.46.

HRMS-ESI (*m/z)* $[M+Na]^+$ calcd for $C_{13}H_{26}NaO_2Si$ 263.1443; found 263.1465.

(1*R*,3*S*,5*R*)-1-[((1,1-Dimethylethyl)dimethylsilyloxy)methyl]-3-fluorobicyclo[3.1.0]hexan-2-one, 17a and (1*R*,3*R*,5*R*)-1-[((1,1-dimethylethyl)dimethylsilyloxy)methyl]-3-fluorobicyclo[3.1.0]hexan-2-one, 17b.

To a solution of lithium bis(trimethylsilyl)amide (1M in tetrahydrofuran, 18.86 mL, 18.86 mmol) in tetrahydrofuran (171.5 mL) cooled to -78 °C was added dropwise a solution of the ketone **6** (4.12 g, 17.13 mmol) in tetrahydrofuran (4 mL). The solution was stirred for 30 min before rapidly adding a solution of *N*-fluorobenzenesulfonimide (NFSI) (6.48g, 20.56 mmol) in tetrahydrofuran (30 mL). The solution was further stirred for 1 h before warming to 22 °C. The reaction was quenched with a saturated ammonium chloride solution (aq). Hexanes (60 mL) were added and the organic layer separated from the aqueous layer. The aqueous layer was further extracted with dichloromethane (5x). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated *in vacuo*. To the residue was added hexanes and subsequently sonicated. The solid that resulted was filtered and washed with hexanes. The combined washes were concentrated. The crude residue was purified by flash column chromatography on silica gel (40% hexanes in dichloromethane). The fluorinated compounds **17a** and **17b** were isolated together as a colorless oil (3.23 g, 12.50 mmol) in a combined yield of 73% and .

17a: ^{1}H NMR (400 MHz, $CDCl_3$) δ:

4.54 (dd, *J* = 51.2, 8.1 Hz, 1H)

4.08 (d, *J* = 11.1 Hz, 1H)

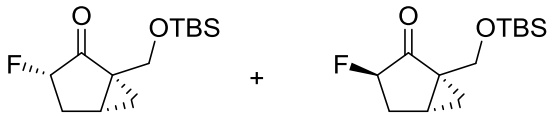
3.66 (d, *J* = 11.1 Hz, 1H)

2.39 (ddddd, *J* = 31.6, 15.3, 7.9, 5.1, 2.3 Hz, 1H)

2.12-1.96 (m, 2H)

1.44-1.37 (m, 1H)

1.30 (ddd, *J* = 4.7, 4.7, 1.7 Hz, 1H)



17a **17b**

0.83 (s, 9H)

0.011 (s, 3H)

0.003 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 206.7 (d, *J* = 12.6 Hz), 90.4 (d, *J* = 183.2 Hz), 59.4, 38.7,

30.1 (d, *J* = 20.5 Hz), 25.8, 23.2, 18.2, 18.0 (d, *J* = 1.7 Hz), -5.50, -5.53.

^{19}F NMR (376 MHz, $CDCl_3$) δ 159.5 (proton decoupled).

HRMS-ESI (*m/z)* $[2M+H]^+$ calcd for $C_{13}H_{24}FO_2Si$ 517.2981; found 517.3038 (acquired as a

mixture of both **17a** and **17b**).

17b: ^{1}H NMR (500 MHz, $CDCl_3$) δ

4.93 (ddd, *J* = 51.1, 9.0, 7.9 Hz, 1H)

4.00 (d, *J* = 10.9 Hz, 1H)

3.93 (d, *J* = 10.9 Hz, 1H)

2.63-2.55 (m, 1H)

2.27-2.08 (m, 2H)

1.48-1.40 (m, 1H)

1.06 (dd, *J* = 4.8, 4.8 Hz, 1H)

0.86 (s, 9H)

0.041 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 207.0 (d, *J* = 15.5 Hz), 89.9 (d, *J* = 191.1 Hz), 58.4 (d, *J* = 1.2 Hz), 36.1, 29.2 (d, *J* = 20.0 Hz), 25.8, 24.2 (d, *J* = 8.3 Hz), 18.2, 18.0, -5.26, -5.49.

^{19}F NMR (376 MHz, $CDCl_3$): δ 128.7 (proton decoupled).

HRMS-ESI (*m/z)* $[2M+H]^+$ calcd for $C_{13}H_{24}FO_2Si$ 517.2981; found 517.3038 (acquired as a mixture of both **17a** and **17b**).

(1*R*,5*R*)-1-[((1,1-Dimethylethyl)dimethylsilyloxy)methyl]-3-fluorobicyclo[3.1.0]hex-3-en-2-one, 19.

To a solution of **17ab** (480 mg, 1.86 mmol) in tetrahydrofuran (14.88 mL) cooled to -78 °C was added lithium bis(trimethylsilyl)amide (1M in tetrahydrofuran, 2.04 mL, 2.04 mmol). After stirring for 10 min, a solution of phenylselenyl chloride (427 mg, 2.23 mmol) in tetrahydrofuran (3.72 mL) was added dropwise. After the addition was complete, the reaction was allowed to warm to 22 °C. A saturated solution of 1:1 sodium bicarbonate (aq) and brine (aq) were added and the mixture subsequently partitioned with dichloromethane. The aqueous layer was further extracted with dichloromethane (5x). The combined extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was dissolved in dichloromethane (7.44 mL) and pyridine (0.45 mL) was added. The solution was cooled to 0 °C and aqueous hydrogen peroxide (30%, 2.37 mL) was added. The resulting biphasic mixture was rapidly stirred for 2 h and the organic layer was separated from the aqueous layer. The aqueous layer was further extracted with dichloromethane (4x). The combined extracts were dried over sodium sulfate, filtered, and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (40% hexanes in dichloromethane). The fluoroenone **19** was isolated as a colorless oil (350 mg, 1.37 mmol) in 73% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

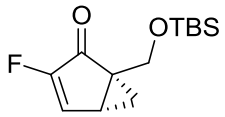
6.94 (dd, *J* = 2.9, 0.8 Hz, 1H)

4.22 (d, *J* = 10.8 Hz, 1H)

3.85 (d, *J* = 10.8 Hz, 1H)

2.39-2.30 (m, 1H)

1.62 (ddd, *J* = 6.4, 4.0, 4.0 Hz, 1H)



19

1.55-1.52 (m, 1H)

0.86 (s, 9H)

0.055 (s, 3H)

0.049 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 196.2 (d, *J* = 20.0 Hz), 155.8 (d, *J* = 285.0 Hz), 134.8 (d, *J* =8.8 Hz), 59.0 (d, *J* = 1.2 Hz), 39.5 (d, *J* = 5.0 Hz), 33.2 (d, *J* = 5.0 Hz), 25.8, 18.4 (d, *J* =7.5 Hz), 18.2, -5.46, -5.49.

^{19}F NMR (376 MHz, $CDCl_3$) δ -140.87 (dd, *J* = 2.9, 2.9 Hz, 1F).

HRMS-ESI (*m/z)* $[M+Na]^+$ calcd for $C_{13}H_{21}FNaO_2Si$ 279.1193; found 279.1099.

(1*R*,3*S*,4*R*,5*S*)-1-[((1,1-Dimethylethyl)dimethylsilyloxy)methyl]-4-[bis(phenylmethy)amino]-3-fluorobicyclo[3.1.0]hexan-2-one, 27a and (1*R*,3*R*,4*R*,5*S*)-1-[((1,1-dimethylethyl)dimethylsilyloxy)methyl]-4-[bis(phenylmethyl)amino]-3-fluorobicyclo[3.1.0]hexan-2-one, 36b.

To a solution of the enone **19** (3.66g, 14.26 mmol) and 4-dimethylaminopyridine (1.74 g, 21.40 mmol) in dimethyl sulfoxide (11 mL) was added dibenzylamine (3.03 mL, 17.10 mmol) and the mixture was stirred at 22 °C for 3 d. Following this, lithium chloride (1.81 g, 42.78 mmol) was added in 3 portions every 6 h. A white solid precipitated slowly from the solution with each incremental addition. Water (100 mL) was then added and the heterogeneous mixture was filtered and washed with a small quantity of water. The solid was dissolved in dichloromethane and then dried over sodium sulfate. The solution was concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes). The adducts **27** (3.82 g, 8.42 mmol) and **36** (1.00 g, 2.20 mmol) were isolated as white solids in 59% and 15% yield, respectively.

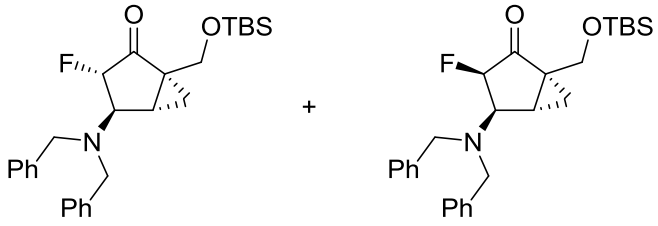
27: ^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.40-7.21 (m, 10H)

4.66 (d, *J* = 49.7 Hz, 1H)

4.34 (d, *J* = 9.6 Hz, 1H)

3.94 (d, *J* = 14.4 Hz, 2H)



27 **36**

3.50-3.31 (m, 4H)

2.17 (m, 1H)

1.35 (m, 1H)

1.10 (ddd, *J* = 5.1, 5.1, 2.25, 1H)

0.76 (s, 9H)

-0.02 (s, 3H)

-0.04 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 205.4, 138.7, 128.7, 128.4, 127.3, 91.9 (d, *J* = 189.2 Hz),

60.7 (d, *J* = 19.9 Hz), 60.4, 54.3, 39.9, 25.9, 25.7, 18.2, 15.5, -5.61, -5.64.

^{19}F NMR (376 MHz, $CDCl_3$): δ -178.4 (dddd, *J* = 48.8, 22.1, 2.8, 2.8 Hz, 1F).

HRMS-ESI (*m/z)* $[M+H]^+$ calcd for $C_{27}H_{37}FNO_2Si$ 454.2578; found 454.2550.

36: ^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.37 (d, *J* = 6.2 Hz, 4H)

7.30 (t, *J* = 7.3 Hz, 4H)

7.22 (t, *J* = 7.3 Hz, 2H)

5.03 (ddd, *J* = 48.4, 6.9, 2.2 Hz, 1H)

4.18 (d, *J* = 10.7 Hz, 1H)

3.91 (d, *J* = 13.5 Hz, 2H)

3.8-3.65 (m, 4H)

2.29 (m, 1H)

1.36 (m, 1H)

0.94 (br dd, *J* = 6.1, 5.0 Hz, 1H)

0.79 (s, 9H)

-0.02 (s, 3H)

-0.03 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 204.7 (d, *J* = 15.0 Hz), 140.0, 128.8, 128.2, 127.0, 92.8 (d, *J* = 203.0 Hz), 60.1, 54.1 (d, *J* = 3.1 Hz), 53.9 (d, *J* = 14.1 Hz), 35.5, 28.5 (d, *J* = 3.9 Hz), 25.6, 18.1, 16.1, -5.81, -5.93.

^{19}F NMR (376 MHz, $CDCl_3$) δ -219.7 (dd, *J* = 48.5, 2.9 Hz, 1F).

HRMS-ESI (*m/z)* $[M+H]^+$ calcd for $C_{27}H_{37}FNO_2Si$ 454.2578; found 454.2554.

(1*R*,2*R*,3*S*,4*R*,5*S*)-1-[((1,1-Dimethylethyl)dimethylsilyloxy)methyl]-4-[bis(phenylmethyl)amino]-3-fluorobicyclo[3.1.0]hexan-2-ol, 28 and (1*R*,2*S*,3*S*,4*R*,5*S*)-1-[((1,1-dimethylethyl)dimethylsilyloxy)methyl]-4-[bis(phenylmethyl)amino]-3-fluorobicyclo[3.1.0]hexan-2-ol, 29.

To a solution of **27** (139.8 mg, 0.308 mmol) in 1:1 methanol/dichloromethane (1.66 mL) was added sodium borohydride (11.7 mg, 0.308 mmol) at 0 °C. After 30 min, the reaction mixture was concentrated. The residue was dissolved in dichloromethane and partitioned with water. The organic layer was separated and the water layer further extracted with dichloromethane (5x). The combined organic layers were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was separated by flash column chromatography on silica gel (gradient: 5% to 15% ethyl acetate in hexanes). The alcohols **28** (116.0 mg, 0.255 mmol) and **29** (16.2 mg, 0.036 mmol) were isolated as white solids in 83% and 12% yield respectively.

28: ^{1}H NMR (400 MHz, C_6D_6) δ:

7.36 (d, *J* = 7.3 Hz, 4H)

7.19 (t, *J* = 7.9 Hz, 4H)

7.08 (t, *J* = 7.4 Hz, 2H)

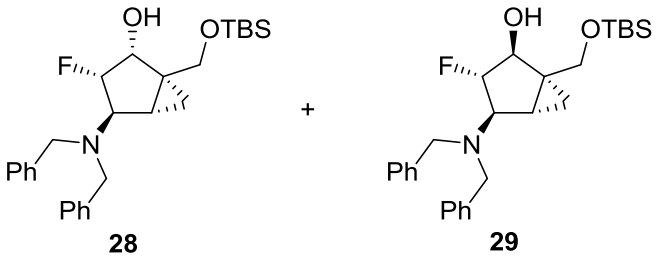
4.78 (ddd, *J* = 51.4, 6.3, 1.0 Hz, 1H)

4.71-4.59 (m, 1H)

4.13 (d, *J* = 10.7 Hz, 1H)

3.97 (d, *J* = 13.6 Hz, 2H)

3.54 (d, *J* = 22.7 Hz, 1H)



3.11 (d, *J* = 13.6 Hz, 2H)

3.95 (d, *J* = 10.8 Hz, 1H)

1.78 (dd, *J* = 10.6, 4.2 Hz, 1H)

1.30-1.19 (m, 1H)

0.80 (s, 9H)

0.62-0.56 (m, 1H)

0.23-0.15 (m, 1H)

-0.02 (s, 3H)

-0.11 (s, 3H).

^{13}C-NMR (100 MHz, C_6D_6): δ 139.9, 129.1, 128.6, 127.4, 93.1 (d, *J* = 230.0 Hz), 73.1 (d, *J* = 20.7 Hz), 66.0 (d, *J* = 25.6 Hz), 64.7, 54.7, 36.5, 26.0, 23.7, 18.4, 10.4 (d, *J* = 6.2 Hz), -5.4, -5.5.

^{19}F NMR (376 MHz, C_6D_6): δ 140.1 (proton decoupled).

HRMS-ESI (*m/z)* $[M+H]^+$ calcd for $C_{27}H_{39}FNO_2Si$ 456.2734; found 456.2742.

29: ^{1}H NMR (400 MHz, C_6D_6) δ:

7.51 (d, *J* = 7.2 Hz, 4H)

7.27 (t, *J* = 7.3 Hz, 4H)

7.16 (t, *J* = 7.4 Hz, 2H)

5.29 (d, *J* = 48.7 Hz, 1H)

4.51 (dd, *J* = 17.7, 3.6 Hz, 1H)

4.20 (dd, *J* = 3.6, 2.6 Hz, 1H)

4.09 (d, *J* = 13.9 Hz, 2H)

3.95 (d, *J* = 11.1 Hz, 1H)

3.63 (t, *J* = 11.2 Hz, 2H)

3.60 (s, 1H)

3.15 (d, *J* = 11.1 Hz, 1H)

1.48-1.41 (m, 1H)

0.82 (s, 9H)

0.43-0.37 (m, 1H)

0.37-0.29 (m, 1H)

-0.06 (s, 3H)

-0.12 (s, 3H).

^{19}F NMR (376 MHz, C_6D_6): δ = 162.9 (proton decoupled).

HRMS-ESI (*m/z)* $[M+H]^+$ calcd for $C_{27}H_{39}FNO_2Si$ 456.2734; found 456.2717.

(1*S*,2*R*,3*S*,4*R*,5*S*)-*N*,*N*-bis(phenylmethyl)-4-[(1,1-dimethylethyl)dimethylsilyloxy)]-5-[((1,1-dimethylethyl)dimethylsilyloxy)methyl]-3-fluorobicyclo[3.1.0]hexan-2-amine, 28b.

To a solution of the alcohol **28** (116.0 mg, 0.255 mmol) and imidazole (38.1 mg, 0.560 mmol) in dichloromethane (2.55 mL) was added *tert*-butyldimethylsilyl chloride (46.0 mg, 0.305 mmol) at 22 °C. The reaction was stirred for 16 h before adding brine. The organic layer was removed and the aqueous layer further extracted with dichloromethane (3x). The combined organic layers were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes). The silyl ether **28b** was isolated as a white solid (132.8 mg, 0.233 mmol) in 91% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.40 (d, *J* = 7.3 Hz, 4H)

7.33 (t, *J* = 7.2 Hz, 4H)

7.25 (t, *J* = 7.2 Hz, 2H)

4.79 (dd, *J* = 43.4, 6.2 Hz, 1H)

4.71-4.66 (m, 1H)

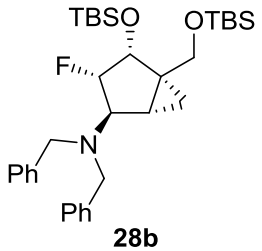
4.19 (d, *J* = 10.7 Hz, 1H)

4.02 (d, *J* = 13.7 Hz, 2H)

3.39 (d, *J* = 13.7 Hz, 2H)

3.36 (m, 1H)

3.10 (d, *J* = 10.8 Hz, 1H)



28b

1.31-1.23 (m, 1H)

0.97 (s, 9H)

0.92-0.86 (m, 1H)

0.78 (s, 9H)

0.55-0.48 (m, 1H)

0.17 (s, 3H)

0.16 (s, 3H)

0.01 (s, 3H)

-0.06 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 128.8, 128.2, 126.9, 92.5 (d, *J* = 192.6 Hz),

72.7 (d, *J* = 16.2), 66.3 (d, *J* = 21.2 Hz), 64.5, 54.6, 36.2, 25.9, 25.8, 22.2 (d, *J* = 2.3 Hz), 18.3 (d, *J* = 24.2 Hz), 11.1 (d, *J* = 4.8 Hz), -4.62, -4.83, -5.58, -5.61.

^{19}F NMR (376 MHz, $CDCl_3$): δ 142.9 (proton decoupled).

HRMS-ESI (*m/z)* $[M+H]^+$ calcd for $C_{33}H_{53}FNO_2Si_2$ 470.3599; found 470.3563.

(1*S*,2*R*,3*S*,4*R*,5*S*)-4-[(1,1-Dimethylethyl)dimethylsilyloxy)]-5-[((1,1-dimethylethyl)dimethylsilyloxy)methyl]-3-fluorobicyclo[3.1.0]hexan-2-amine, 30.

To a solution of bis(benzyl)amine **28b** (3.37 g, 5.91 mmol) in a small quantity of ethyl acetate was added 10 wt % palladium on carbon (337 mg). Methanol (60 mL) was added, followed by ammonium formate (1.86 g, 29.6 mmol). The heterogeneous mixture was heated to reflux for 3 h. The solution was allowed to cool to 22 °C and then filtered through a pad of Celite. The Celite was further rinsed with a small quantity of methanol. The methanol was removed under reduced pressure and the crude residue was further purified using flash column chromatography with a small quantity of silica gel (3% saturated ammonia/methanol in dichloromethane). The primary amine **30** was isolated as a colorless oil (2.26 g, 5.79 mmol) in 98% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

4.68 (dd, *J* = 18.4, 5.4 Hz, 1H)

4.25 (dd, *J* = 52.2, 5.4 Hz, 1H)

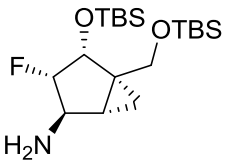
4.09 (d, *J* = 10.6 Hz, 1H)

3.33 (d, *J* = 15.3 Hz, 1H)

3.05 (d, *J* = 10.6 Hz, 1H)

1.34 (bs, 2H)

1.16-1.11 (m, 1H)



30

1.10-1.03 (m, 1H)

0.91 (s, 9H)

0.89 (s, 9H)

0.56-0.48 (m, 1H)

0.10 (s, 3H)

0.09 (s, 3H)

0.04 (s, 3H)

0.03 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 98.3 (d, *J* = 241.7 Hz), 71.6 (d, *J* = 20.0 Hz), 63.9,

56.8 (d, *J* =47.2 Hz), 34.5, 26.4, 25.9, 25.8, 18.3, 18.2, 11.5 (d, *J* = 10.0 Hz), -4.75, -4.86, -5.36,

-5.40.

^{19}F NMR (376 MHz, $CDCl_3$) δ 144.0 (proton decoupled).

HRMS-ESI (*m/z)* $[M+H]^+$ calcd for $C_{19}H_{41}FNO_2Si_2$ 390.2660; found 390.2637.

1-((1*S*,2*R*,3*S*,4*R*,5*S*)-3-Fluoro-4-hydroxy-5-(hydroxymethyl)bicyclo[3.1.0]hexan-2-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione, 31.

To the sodium salt of 3-methoxy-2-methylpropenoic acid (2.33 g, 16.92 mmol) in 1:1 dichloromethane/pentane was added dropwise oxalyl chloride (7.26 mL, 84.6 mmol) at 0 °C. The reaction mixture was allowed to warm to 22 °C and further stirred for 4 h. The heterogeneous mixture was quickly filtered through a course porosity sintered glass funnel and the funnel was washed once with pentane. The filtrate was concentrated slowly under reduced pressure and the flask was briefly exposed to a separate vacuum (20 mmHg). The acid chloride was dissolved in toluene (50 mL) and silver cyanate (3.04 g, 20.30 mmol) was added. The heterogeneous mixture was refluxed under an argon atmosphere for 1.5 h before allowing to cool to 22 °C. The precipitate was allowed to settle and the supernatant was transferred via cannula to a flask fitted with a rubber septum. The precipitate was further washed with a small quantity of dry dichloromethane and also transferred to the same flask. The solution was cooled to -78 °C and the amine **30** (2.20 g, 5.64 mmol) in dichloromethane (10 mL) was added dropwise over 3 min. The solution was allowed to warm to 22 °C and stirred for 16 h. Ethanol (5 mL) was added

and the reaction mixture was concentrated *in vacuo*. The intermediate has an R_f value of 0.30 by thin layer chromatography (2% ethyl acetate in dichloromethane).

To the crude residue was added ethanol (37 mL) and 2M HCl (12 mL). The reaction mixture was refluxed for 20 h. The reaction was cooled to 22 °C and the solution was concentrated. The residual water was azeotroped four times with ethanol (100 mL). The crude residue was dissolved in ethanol and concentrated *in vacuo* onto a small quantity of silica gel before purifying by flash column chromatography (gradient: 5% to 10% methanol in dichloromethane). Compound **31** was isolated as a white solid (1.37 g, 5.06 mmol) in 90% yield.

^{1}H NMR (500 MHz, DMSO-d_6) δ:

11.29 (s, 1H)

7.86 (s, 1H)

5.14 (dd, *J* = 4.9, 4.9 Hz, 1H)

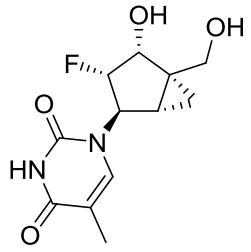
4.97 (d, *J* = 7.5 Hz, 1H)

4.75 (d, *J* = 17.8 Hz, 1H)

4.58-4.40 (m, 2H)

4.05 (dd, *J* = 11.4, 5.1 Hz, 1H)

3.06 (dd, *J* = 11.5, 4.7 Hz, 1H)



31

1.71 (s, 3H)

1.38-1.27 (m, 1H)

1.03-0.91 (m, 1H)

0.73-0.60 (m, 1H).

^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 164.2, 151.2, 137.7, 109.4, 95.9 (d, *J* = 190.0 Hz),

70.3 (d, *J* =38.2 Hz), 61.9, 60.0 (d, *J* = 26.2 Hz), 36.6, 21.4, 12.7, 11.4 (d, *J* =6.2 Hz).

^{19}F-NMR (376 MHz, $(CD_3)_2SO$) δ -186.5 (app. dtd, *J* = 45.0, 18.8, 3.8 Hz, 1F).

HRMS-ESI (*m/z)* $[M+H]^+$ calcd for $C_{12}H_{16}FN_2O_4$ 271.1094; found 271.1115.

(1*R*,2*S*,3*R*,4*R*,5*S*)-1-[((1,1-Dimethylethyl)dimethylsilyloxy)methyl]-4-(dibenzylamino)-3-fluorobicyclo[3.1.0]hexan-2-ol, 37.

To a solution of the ketone **36** (72.2 mg, 0.159 mmol) in 1:1 methanol/dichloromethane (1.59 mL) was added sodium borohydride (12.1 mg, 0.320 mmol) at 22 °C. The reaction mixture was stirred for 2 h before removing the solvent by reduced pressure evaporation. The residue was partitioned between a saturated solution of sodium bicarbonate (aq) and dichloromethane. The organic layer was removed and the aqueous layer was further extracted with dichloromethane (4x). The combined organic layers were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (10% ethyl

acetate in hexanes, R_f = 0.30). The alcohol **37** was isolated as a white solid (68.0 mg, 0.149 mmol) in 94% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.39 (d, *J* = 7.2 Hz, 4H)

7.31 (t, *J* = 7.7 Hz, 4H)

7.22 (t, *J* = 7.2 Hz, 2H)

4.76 (ddd, *J* = 49.2, 5.8, 5.8 Hz, 1H)

4.27-4.18 (m, 1H)

4.00 (d, *J* = 14.1 Hz, 2H)

3.86 (d, *J* = 14.2 Hz, 2H)

3.73 (d, *J* = 10.8 Hz, 1H)

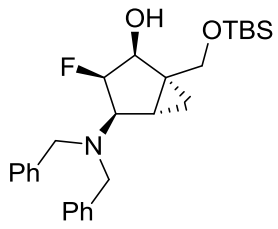
3.71 (d, *J* = 10.8 Hz, 1H)

3.51 (dd, *J* = 5.1, 2.0 Hz, 1H)

3.43 (dd, *J* = 5.7, 5.7 Hz, 1H)

1.54 (dt, *J* = 9.0, 3.7 Hz, 1H)

0.84 (s, 9H)



37

0.69 (dd, *J* = 8.6, 5.9 Hz, 1H)

0.06 (dd, *J* = 5.7, 4.1 Hz, 1H)

0.03 (s, 3H)

0.003 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 128.7, 128.2, 126.7, 97.5 (d, *J* = 197.3 Hz),

72.3 (d, *J* = 15.9 Hz), 64.4, 60.6 (d, *J* = 14.9 Hz), 55.7 (d, *J* = 3.2 Hz), 32.9 (d, *J* = 2.3 Hz), 25.8,

24.3 (d, *J* = 2.7 Hz), 18.2, 13.5, -5.48, -5.52.

^{19}F NMR (376 MHz, $CDCl_3$): δ 113.8 (d, *J* = 49 Hz, 1F).

HRMS-ESI (*m/z)* $[M+H]^+$ calcd for $C_{27}H_{39}FNO_2Si$ 456.2734; found 456.2712.

(1*R*,2*R*,3*R*,4*R*,5*S*)-1-[((1,1-Dimethylethyl)dimethylsilyloxy)methyl]-4-[bis(phenylmethyl)amino]-3-fluorobicyclo[3.1.0]hexan-2-yl-4-nitrobenzoate, 38b.

To a solution of **37** (53.0 mg, 0.116 mmol), triphenylphosphine (81.0 mg, 0.465 mmol), and 4-nitrobenzoic acid (77.8 mg, 0.465 mmol) in tetrahydrofuran (0.89 mL) cooled to 0 °C was slowly added diethyl azodicarboxylate (40% wt. in toluene, 81.0 mg, 0.465 mmol). The reaction mixture was allowed to warm to 22 °C and stir for 2 d. The solution was diluted with diethyl ether and saturated sodium bicarbonate (aq) was added. The organic layer was separated and the aqueous layer further extracted with diethyl ether (4x). The combined organic extracts were washed with brine, dried with magnesium sulfate, filtered, and concentrated *in vacuo*. The crude

residue was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes, R_f = 0.25). The *p*-nitrobenzoate **38b** was isolated as a colorless oil (56.7 mg, 0.094 mmol) in 81% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

8.31 (d, *J* = 9.0 Hz, 2H)

8.24 (d, *J* = 9.0 Hz, 2H)

7.42 (d, *J* = 7.1 Hz, 4H)

7.32 (t, *J* = 7.6 Hz, 4H)

7.24 (t, *J* = 7.3 Hz, 2H)

6.30 (dd, *J* = 21.7, 5.4 Hz, 1H)

5.97 (ddd, *J* = 50.4, 6.4, 6.4 Hz, 1H)

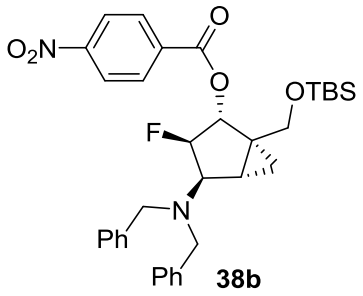
4.15 (d, *J* = 13.7 Hz, 2H)

4.00 (d, *J* = 10.8 Hz, 1H)

3.88 (d, *J* = 13.6 Hz, 2H)

3.57 (d, *J* = 6.8 Hz, 1H)

3.36 (d, *J* = 10.4 Hz, 1H)



38b

1.64 (ddd, *J* = 8.7, 4.0, 4.0 Hz, 1H)

0.76 (s, 9H)

0.75-0.68 (m, 1H)

0.59 (dd, *J* = 4.6, 4.6 Hz, 1H)

-0.04 (s, 3H)

-0.09 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 150.6, 140.3, 135.6, 130.9, 128.8, 128.2, 126.8, 123.5, 101.3 (d, *J* = 196.1 Hz), 81.2 (d, *J* = 25.6 Hz), 64.2, 57.4 (d, *J* = 15.6 Hz), 54.5 (d, *J* = 3.6 Hz), 31.9 (d, *J* = 8.6 Hz), 25.7, 25.4 (d, *J* = 2.8 Hz), 18.2, 11.4, -5.70, -5.71.

^{19}F NMR (376 MHz, $CDCl_3$) δ 125.62 (dd, *J* = 50.6, 23.4 Hz, 1F).

HRMS-ESI (*m/z)* $[M+H]^+$ calcd for $C_{34}H_{42}FN_2O_5Si$ 605.2847; found 605.2821.

(1*R*,2*R*,3*R*,4*R*,5*S*)-1-[((1,1-dimethylethyl)Dimethylsilyloxy)methyl]-4-[bis(phenylmethyl)amino]-3-fluorobicyclo[3.1.0]hexan-2-ol, 38.

To a solution of **38b** (54.4 mg, 0.090 mmol) in dry methanol (3.0 mL) was added potassium carbonate (130.0 mg, 0.941 mmol). The heterogeneous solution was stirred at 22 °C for 2 days. The solvent was removed and the crude residue was partitioned between water and dichloromethane. The organic layer was removed and the aqueous layer was further extracted

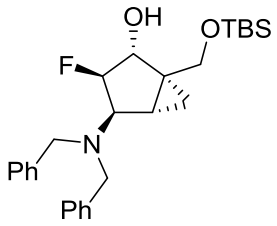
with dichloromethane (5x). The combined organic layers were dried with magnesium sulfate, filtered, and then concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (40% ethyl acetate in hexanes). The alcohol **38** was isolated as a colorless solid (38.0 mg, 0.083 mmol) in 93% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.41 (d, *J* = 7.3 Hz, 4H)

7.32 (t, *J* = 7.2 Hz, 4H)

7.23 (t, *J* = 7.2 Hz, 2H)



38

4.89 (bdd, *J* = 24.0, 5.6 Hz, 1H)

4.67 (ddd, *J* = 50.7, 6.5, 6.5 Hz, 1H)

4.01 (d, *J* = 13.8 Hz, 2H)

3.88-3.77 (m, 3H)

3.59 (d, *J* = 10.6 Hz, 1H)

3.49 (d, *J* = 6.8 Hz, 1H)

2.50 (bs, 1H)

1.64 (ddd, *J* = 8.4, 4.1, 4.1 Hz, 1H)

0.84 (s, 9H)

0.56-0.41 (m, 2H)

0.04 (s, 3H)

-0.002 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 128.7, 128.2, 126.8, 103.7 (d, *J* = 192.3 Hz),

78.7 (d, *J* = 23.4 Hz), 66.2, 57.7 (d, *J* = 15.8 Hz), 54.6 (d, *J* = 3.6 Hz), 32.8 (d, *J* = 10.3 Hz),

25.8, 23.8 (d, *J* = 3.1 Hz), 18.2, 11.5, -5.52, -5.55.

^{19}F NMR (376 MHz, $CDCl_3$): δ 124.6 (ddd, *J* = 53.8, 25.4, 2.6 Hz, 1F).

HRMS-ESI (*m/z)* $[M+H]^+$ calcd for $C_{27}H_{39}FNO_2Si$ 456.2734; found 605.2703.

(1*R*,2*R*,3*R*,4*R*,5*S*)-1-[((1,1-Dimethylethyl)dimethylsilyloxy)methyl]-4-[bis(phenylmethyl)amino]-3-fluorobicyclo[3.1.0]hexan-2-yl-(*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate, 39b.

To a solution of (*R*)-(+)-α-methoxy-α-trifluoromethylacetic acid (26.2 mg, 0.112 mmol) and dimethylformamide (1 μL) in dichloromethane (0.75 mL) was added dropwise oxalyl chloride (32 μL, 0.373 mmol). The solution was stirred at 22 °C for 30 min and then concentrated *in vacuo*. The acid chloride was left under high vacuum (1.0 mm Hg) for a short period of time. The acid chloride was dissolved in dichloromethane (0.15 mL) and subsequently added dropwise to a solution of the alcohol **38** (34.0 mg, 0.075 mmol) in pyridine (0.15 mL). After solidification

of the reaction mixture, dichloromethane (0.45 mL) was added and the resulting solution was stirred for 1 h at 22 °C. The solution was purified directly by flash column chromatography on silica gel (gradient: 30% to 100% dichloromethane in hexanes). The Mosher's ester **39b** was isolated as a colorless oil (45.1 mg, 0.067 mmol) in 90% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.65-7.55 (m, 2H)

7.47-7.39 (m, 7H)

7.33 (t, *J* = 7.2 Hz, 4H)

7.28-7.21 (m, 2H)

6.34 (dd, *J* = 21.5, 5.8 Hz, 1H)

4.90 (ddd, *J* = 50.5, 6.4, 6.4 Hz, 1H)

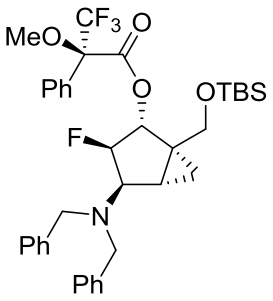
4.19 (d, *J* = 13.7 Hz, 2H)

4.05 (d, *J* = 10.8 Hz, 1H)

3.88 (d, *J* = 13.6 Hz, 2H)

3.60 (s, 3H)

3.53 (d, *J* = 6.8 Hz, 1H)



39b

3.16 (d, *J* = 10.9 Hz, 1H)

1.62 (ddd, *J* = 8.8, 4.1, 4.1 Hz, 1H)

0.80 (s, 9H)

0.59 (dd, *J* = 6.9, 6.9 Hz, 1H)

0.42 (dd, *J* = 6.2, 4.6 Hz, 1H)

0.03 (s, 3H)

-0.05 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 140.3, 132.3, 129.7, 128.8, 128.5, 128.2, 127.4, 126.8,

123.5 (d, *J* = 290 Hz), 101.0 (d, *J* = 195.3 Hz), 81.3 (d, *J* = 25.2 Hz), 63.7, 57.1 (d, *J* = 15.5 Hz),

55.3, 54.4 (d, *J* = 3.3 Hz), 31.6 (d, *J* = 8.7 Hz), 25.7, 25.63, 25.60, 18.2, 10.9, -5.67, -5.79.

^{19}F NMR (376 MHz, $CDCl_3$) δ 124.8 (bdd, *J* = 50.4, 21.3 Hz, 1F), -72.1 (s, 3F).

HRMS-ESI (*m/z)* $[M+H]^+$ calcd for $C_{37}H_{46}F_4NO_4Si$ 672.3132; found 672.3115.

(1*R*,2*R*,3*R*,4*R*,5*S*)-4-Amino-1-[((1,1-dimethylethyl)dimethylsilyloxy)methyl]-3-fluorobicyclo[3.1.0]hexan-2-yl-(*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate, 39.

The Mosher's ester **39b** (210.0 mg, 0.313 mmol) in methanol (3.0 mL) was added to palladium on carbon (10% wt., 21.0 mg) prewetted with a small quantity of tetrahydrofuran. Ammonium

formate (100.0 mg, 1.586 mmol) was added and the resulting solution was refluxed for 6 h. The heterogeneous solution was filtered through a pad of Celite. The filtrate was concentrated *in vacuo* and the crude residue purified by flash column chromatography on silica gel (2% ammonia/methanol (saturated) in dichloromethane). The amine **39** was isolated as a colorless oil (141.7 mg, 0.288 mmol) in 93% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.56-7.48 (m, 2H)

7.43-7.35 (m, 3H)

6.02 (dd, *J* = 19.2, 6.3 Hz, 1H)

4.65-4.42 (ddd, *J* = 52.5, 5.8, 5.8, 1H)

3.97 (d, *J* = 10.7 Hz, 1H)

3.55 (s, 3H)

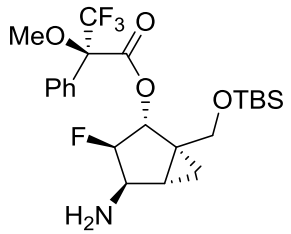
3.44 (d, *J* = 5.4 Hz, 1H)

3.07 (dd, *J* = 10.7, 1.6 Hz, 1H)

1.46 (ddd, *J* = 8.6, 4.6, 4.3, Hz, 1H)

1.46-1.21 (brs, 2H)

0.91 (s, 9H)



39

0.77-0.62 (m, 2H)

0.08 (s, 3H)

0.04 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 132.2, 129.7, 128.4, 127.4, 123.4 (d, *J* = 288 Hz),

96.7 (d, *J* = 189.0 Hz), 84.8 (d, *J* = 27.3 Hz), 79.2 (d, *J* = 24.7 Hz), 63.2, 55.3,

51.4 (d, *J* = 18.1 Hz), 30.9 (d, *J* = 7.7 Hz), 26.7 (d, *J* = 2.3 Hz), 25.9, 18.2, 11.1, -5.53, -5.55.

^{19}F NMR (376 MHz, $CDCl_3$): δ 119.8 (ddd, *J* = 52.5, 19.1, 4.1 Hz, 1F), -72.2 (s, 3F).

HRMS-ESI (*m/z)* $[M+H]^+$ calcd for $C_{23}H_{34}F_4NO_4Si$ 492.2193; found 492.2190.

1-((1*S*,2*R*,3*R*,4*R*,5*R*)-3-Fluoro-4-hydroxy-5-(hydroxymethyl)bicyclo[3.1.0]hexan-2-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione, 40.

To the sodium salt of 3-methoxy-2-methylpropenoic acid (114.4 mg, 0.828 mmol) in 1:1 dichloromethane/pentane (1.10 mL) was added oxalyl chloride (0.36 mL, 4.14 mmol) dropwise at 0 °C. The solution was stirred for 1 h before rapidly filtering through a course sintered glass funnel. The filtrate was slowly concentrated *in vacuo* and the residue left briefly on a vacuum pump (20 mmHg). The acid chloride was dissolved in toluene (2.76 mL) and silver cyanate (149.0 mg, 0.994 mmol) was added. The heterogeneous mixture was refluxed under an argon atmosphere for 1.5 h before allowing to cool to 22 °C. The precipitate was allowed to settle and the supernatant was transferred via syringe to a flask fitted with a rubber septum. The precipitate

was further washed with a small quantity of dry dichloromethane and also transferred to the same flask. The solution was cooled to -78 °C and **39** (135.7 mg, 0.276 mmol) in dichloromethane (1 mL) was added dropwise over 3 min. The solution was allowed to warm to 22 °C and stirred for 16 h. Ethanol (1 mL) was added and the reaction mixture was concentrated *in vacuo*.

To the crude residue was added ethanol (1.8 mL) and 2M HCl (0.6 mL). The reaction mixture was refluxed for 20 h. The reaction was cooled to 22 °C and the solution was concentrated. The residual water was azeotroped four times with ethanol (100 mL). The crude residue was dissolved in dry methanol (4 mL) and an abundance of potassium carbonate was added. The heterogeneous solution was heated to 55 °C for 8 h. The solution was slowly acidified to pH 1 with concentrated hydrochloric acid and then concentrated *in vacuo*. Residual water was removed from the crude residue by azeotroping once with a small quantity of ethanol. The solid was dissolved in hot ethanol and concentrated onto a small quantity of silica gel, which was subsequently applied to a silica gel column and separated using 10% methanol in ethyl acetate. Compound **40** was isolated as a white solid (37.0 mg, 0.137 mmol) in 50% yield.

^{1}H NMR (500 MHz, C_6D_6/MeOD 3.5:1) δ:

8.11 (s, 1H)

5.08 (d, J = 6.7 Hz, 1H)

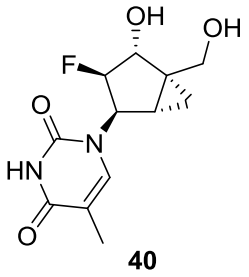
4.72 (dd, J = 23.4, 6.4 Hz, 1H)

4.56 (ddd, *J* = 50.5, 6.5, 6.5 Hz, 1H)

4.28 (d, *J* = 11.7 Hz, 1H)

2.99 (dd, *J* = 11.7, 1.9 Hz, 1H)

1.84 (d, *J* = 1.1 Hz, 3H)



40

1.13 (ddd, *J* = 8.8, 3.8, 3.8 Hz, 1H)

0.64 (dd, *J* = 6.4, 4.0, 1H)

0.45 (dd, *J* = 7.7, 7.7 Hz, 1H).

^{1}H NMR (400 MHz, $CDCl_3$, alcohol protons) δ:

3.05-2.80 (brs, 1H)

1.80-1.60 (brs, 1H).

^{13}C NMR (100 MHz, MeOD) δ 166.3, 153.4, 139.9, 111.3, 99.0 (d, *J* = 192.9 Hz),

75.4 (d, *J* = 23.6 Hz), 63.6, 55.3 (d, *J* = 16.2 Hz), 34.5 (d, *J* = 9.9 Hz), 22.6, 12.3, 11.6.

^{19}F NMR (376 MHz, MeOD): δ 122.7 (dd, *J* = 51.7, 25.4 Hz, 1F).

HRMS-ESI (*m/z)* $[M+H]^+$ calcd for $C_{12}H_{16}FN_2O_4$ 271.1094; found 271.1085.

(1*R*,5*R*)-1-[(((1,1-Dimethylethyl)dimethylsilyloxy)methyl)]bicyclo[3.1.0]hex-3-en-2-one, 7.

To a solution of the ketone **6** (0.647 g, 2.69 mmol) in dichloromethane (13.5 mL) was added *tert*-butyldimethylsilyl triflate (TBSOTf, 0.742 mL, 3.23 mmol). Triethylamine (1.12 mL, 8.07 mmol) was added dropwise and the reaction was subsequently stirred at 22 ^{o}C for 1 h. The reaction mixture was then partitioned over a saturated aq solution of sodium bicarbonate. The organic layer was removed and the aqueous layer was further extracted with dichloromethane (4x). The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was submitted to a short column of silica pretreated with 3% triethylamine in hexanes. The residue was eluted with 1% triethylamine in hexanes. The fractions were concentrated *in vacuo* to give a colorless liquid that was dissolved in dimethyl sulfoxide (26.9 mL). To the solution was added palladium(II) acetate (60.4 mg, 0.269 mmol) and the flask head-space was purged with molecular oxygen before fixing the top with a balloon filled with oxygen. The flask was heated in an oil bath to 55 ^{o}C for 2 d. After cooling to 22 ^{o}C, the reaction mixture was extracted directly with hexanes (5x). The combined hexanes fractions were dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (gradient: 3% to 8% ethyl acetate in hexanes, R_f = 0.3). The enone **7** was isolated as a colorless oil (0.495 g, 2.08 mmol) in 77% yield over two steps.

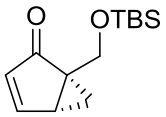
^{1}H NMR (400 MHz, C_6D_6) δ:

6.90 (dd, *J* = 5.7, 2.8 Hz, 1H)

5.42 (d, *J* = 5.7 Hz, 1H)

4.22 (d, *J* = 10.5 Hz, 1H)

3.68 (d, *J* = 10.5 Hz, 1H)



7

2.02 (ddd, *J* = 6.8, 2.9, 2.9, 1H)

1.11 (dd, *J* = 6.9, 3.3 Hz, 1H)

0.93-0.82 (m, 10H)

0.022 (s, 6H).

^{13}C NMR (100 MHz, C_6D_6) δ 204.5, 162.0, 128.8, 60.0, 37.6, 36.1, 26.3, 26.1, 18.5, -5.27, -5.34.

HRMS-ESI (*m/z)* $[M+Na]^+$ calcd for $C_{13}H_{23}O_2Si$ 261.1287; found 261.1300.

_N_-(9-((1_S_,2_S_,5_R_)-5-[((1,1-Dimethylethyl)dimethylsilyloxy)methyl]-4-oxobicyclo[3.1.0]hexan-2-yl)-9_H_-purin-6-yl)benzamide, 12.

The enone **7** (100 mg, 0.42 mmol), *N*-methylimidazole (3.35 µL, 0.042 mmol), and *N*-(9*H*-purin-6-yl)benzamide (120 mg, 0.50 mmol) were dissolved in dimethyl sulfoxide (0.42 mL) in a sealed pressure vessel. The reaction mixture was heated to 90 ^{o}C in a µWave reactor (120W, 50 psi) for 12 h. The reaction mixture was allowed to cool to 22 ^{o}C before adding 5 mL of water. The heterogeneous mixture was briefly sonicated and then allowed to stand for 5 min before filtering. The precipitate was washed with a small quantity of water and then dissolved in dichloromethane. The solution was dried over anhydrous sodium sulfate, filtered, and

concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (gradient: 1% to 6% methanol in dichloromethane). The desired compound co-elutes with another isomer. A small quantity of diethyl ether was added after these fractions were concentrated and the desired adduct **12** crystallized out of solution slowly as colorless crystals (47 mg, 98.5 µmol) in 23% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

9.23 (s, 1H)

8.78 (s, 1H)

8.41 (s, 1H)

8.01 (d, *J* = 7.5 Hz, 2H)

7.59 (t, *J* = 7.5 Hz, 1H)

7.50 (t, *J* = 6.9 Hz, 2H)

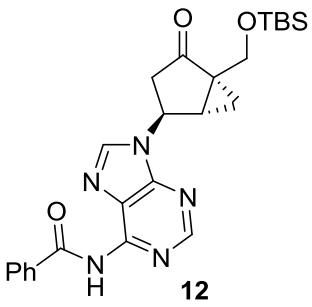
4.52 (d, *J* = 11.1 Hz, 1H)

3.61 (d, *J* = 11.0 Hz, 1H)

2.87 (ddd, *J* = 18.9, 7.2, 1.8 Hz, 1H)

2.42 (dd, *J* = 8.1, 4.3 Hz, 1H)

2.29 (d, *J* = 18.9 Hz, 1H)



12

1.53 (ddd, J = 8.6, 6.2, 1.4 Hz, 1H)

1.21 (m, 2H)

0.88 (s, 9H)

0.10 (s, 3H)

0.07 (s, 3H).

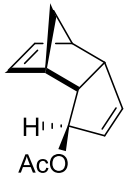
^{13}C NMR (100 MHz, $CDCl_3$) δ 208.2, 164.7, 152.7, 151.3, 149.7, 140.8, 133.8, 132.7, 128.8,

127.9, 122.9, 59.8, 50.5, 41.7, 39.7, 29.7, 25.9, 18.4, 16.1, -5.40, -5.53.

HRMS-ESI (*m/z)* $[M+H]^+$ calcd for $C_{25}H_{32}N_5O_3Si$ 478.2274; found 478.2251.

(±)-exo-3-Acetoxydicyclopentadiene, 54.

To a solution of the alcohol **53** (1.38g, 9.32 mmol), triethyl amine (1.43 mL, 10.26 mmol), and 4-dimethylaminopyridine (114 mg, 0.93 mmol) in 37 mL of dichloromethane was added acetic anhydride (1.75 mL, 18.65 mmol). The reaction was stirred for 12 h before partitioning with 1N HCl (aq). The organic layer was removed and was washed with a saturated solution of sodium bicarbonate (aq). The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (R_f = 0.40, 10% ethyl acetate in hexanes). The acetate **54** was isolated as a colorless oil (1.27 g, 6.68 mmol) in 72% yield.



54

The ^{1}H NMR matches that reported by Moriya, M.; Tanaka, K.; Ogasawara, K.; Takano, S. *Synthesis,***1994**, *7*, 687-688.

_N_-(9-((1_S_,2_R_,5_R_)-4-(((1,1-Dimethylethyl)dimethylsilyl)oxy)-5-((((1,1-dimethylethyl)dimethylsilyl)oxy)methyl)bicyclo[3.1.0]hex-3-en-2-yl)-9_H_-purin-6-yl)benzamide, 15.

To a solution of ketone **12** (38.8 mg, 0.082 mmol) in 0.41 mL of benzene was added triethylamine (56.8 μL, 0.409 mmol) and *t*-butyldimethylsilyl triflate (47.0 μL, 0.204 mmol). The resulting solution was heated to reflux for 16 h before adding a saturated solution of sodium bicarbonate (aq). The organic layers was removed and the aqueous layer was further extracted with dichloromethane (5x). The combined extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel pretreated with 3% triethylamine in hexanes (R_f = 0.40 with triethylamine pretreated tlc plate and eluent of 40% ethyl acetate in hexanes, gradients of column: 1-10% ethyl acetate in 3% triethylamine and hexanes; then 50%-100% ethyl acetate in 3% triethylamine and hexanes). The silyl enol ether **15** (16.4 mg, 0.0277 mmol) was isolated in 34% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

9.21 (s, 1H)

9.11 (s, 1H)

8.58 (s, 1H)

7.83 (d, *J* = 7.1 Hz, 2H)

7.11 (t, *J* = 7.4 Hz, 1H)

7.04-6.97 (m, 2H)

5.60 (d, *J* = 2.5 Hz, 1H)

4.41 (d, *J* = 11.0 Hz, 1H)

4.25-4.22 (m, 1H)

2.98 (d, *J* = 10.9 Hz, 1H)

1.52-1.46 (m, 1H)

1.02 (s, 18H)

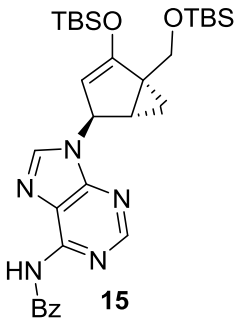
0.75 (dd, *J* = 8.2, 4.4 Hz, 1H)

0.50 (dd, *J* = 4.3, 4.3 Hz, 1H)

0.17 (s, 3H)

0.11 (s, 3H)

0.099 (s, 3H)



15

0.096 (s, 3H).

(1*R*,4*S*,5*S*)-4-Azido-1-((((1,1-dimethylethyl)dimethylsilyl)oxy)methyl)bicyclo[3.1.0]hexan-2-one, 20.

To a solution of trimethylsilyl azide (0.55 mL, 4.19 mmol) in 3.36 mL of dichloromethane was added acetic acid (0.24 mL, 4.19 mmol) and stirred for 20 min. Triethylamine (23.3 μL, 0.168 mmol) was added and followed by the enone **7** (200.0 mg, 0.839 mmol). The resulting mixture was stirred for 20 h. The volume of the reaction mixture was reduced to 1/3 through evaporation *in vacuo*, and the remaining solution was separated directly by flash column chromatography on silica gel (100% dichloromethane). The azide **20** (161.0 mg, 0.572 mmol) was isolated in 68% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

4.11 (d, *J* = 6.2 Hz, 1H)

4.01 (d, *J* = 10.9 Hz, 1H)

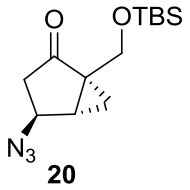
3.84 (d, *J* = 10.9 Hz, 1H)

2.46 (ddd, *J* = 18.2, 6.2, 2.0 Hz, 1H)

2.28 (dd, *J* = 8.2, 4.4 Hz, 1H)

2.13 (ddd, *J* = 18.7, 0.6, 0.6 Hz, 1H)

1.43 (ddd, *J* = 8.2, 5.2, 2.1 Hz, 1H)



20

0.91 (dd, J = 5.1, 4.4 Hz, 1H)

0.85 (s, 9H)

0.027 (s, 3H)

0.023 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 209.6, 58.2, 57.1, 40.2, 38.4, 29.7, 25.8, 18.2, 15.0, -5.52.

((1*R*,2*S*,5*R*)-1-(((1,1-Dimethylethyl)dimethylsilyloxy)methyl)bicyclo[3.1.0]hex-3-en-2-yl diisopropylcarbamate, 48.

To a solution of the alcohol **43** (64.8 mg, 0.270 mmol) in 1.35 mL of tetrahydrofuran at -78 ^{o}C was added dropwise *n*-butyl lithium (1.6M in hexanes, 0.169 mL, 0.270 mmol). The solution was stirred for 5 min before adding dropwise a solution of *N*,*N*-diisopropylcarbamoyl chloride (44.1 mg, 0.270 mmol) in 1.35 mL tetrahydrofuran. The reaction mixture was warmed to 22 ^{o}C before adding a saturated solution of ammonium chloride (aq), followed by further dilution with dichloromethane. The organic layer was separated and the aqueous layer was further extracted with dichloromethane (5x). The combined organic layers were dried with anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (R_f = 0.25, 5% ethyl acetate in hexanes). The carbamate **48** was isolated as a colorless oil (59.6 mg, 0.162 mmol) in 60% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

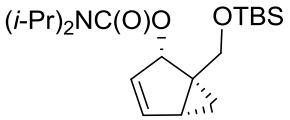
6.26-6.21 (m, 1H)

5.56-5.51 (m, 2H)

4.21 (d, *J* = 10.3 Hz, 1H)

4.10-3.75 (m, 2H)

3.67 (d, *J* = 10.3 Hz, 1H)



48

1.91-1.84 (m, 1H)

1.25 (dd, *J* = 7.2, 3.6 Hz, 1H)

1.23-1.17 (m, 12H)

0.86 (s, 9H)

0.17 (dd, *J* = 3.3, 3.2 Hz, 1H)

0.011 (s, 3H)

0.009 (s, 3H).

(1*R*,2*S*,5*R*)-1-(((1,1-Dimethylethyl)dimethylsilyloxy)methyl)bicyclo[3.1.0]hex-3-en-2-ol, 43 and (1*R*,2*R*,5*R*)-1-(((1,1-Dimethylethyl)dimethylsilyloxy)methyl)bicyclo[3.1.0]hex-3-en-2-ol, 47.

A solution of the ketone **7** (850 mg, 3.57 mmol) in 3.0 mL of methanol was added to a solution of cerium(III) chloride heptahydrate (1.33 g, 3.57 mmol) in 9.0 mL of methanol at -15 ^{o}C. This was followed by the portionwise addition of sodium borohydride (135 mg, 3.57 mmol). The reaction was further stirred for 2 h before quenching with 12 mL of water. The reaction mixture was partitioned with a 1:1 mixture of diethyl ether and hexanes. The organic layer was removed and the aqueous layer was further extracted with the same solvent mixture (2x). The aqueous layer was further extracted with dichloromethane (3x). The combined organic layers were dried with magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (R_f = 0.40 (cmpd **47**) & 0.60 (cmpd **43**) using 20% diethyl ether in pentanes, column: 5 to 10% diethyl ether in pentanes). The minor alcohol product **47** (205.4, 0.854 mmol) and the major alcohol product (468.4 mg, 1.965 mmol) were isolated as colorless oils in 24% and 55% yield respectively (yield of cmpd **43** was calculated by NMR and was corrected based on the presence of TBSOH impurity).

Alcohol **43**: ^{1}H NMR (400 MHz, $CDCl_3$) δ:

6.17-6.13 (m, 1H)

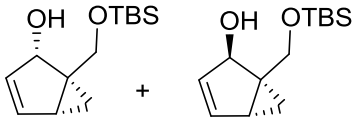
5.55 (dd, *J* = 5.6, 2.0 Hz, 1H)

4.57-4.52 (m, 1H)

4.06 (d, *J* = 10.8 Hz, 1H)

3.84 (d, *J* = 10.8 Hz, 1H)

2.93 (d, *J* = 7.3 Hz, 1H)



43 **47**

1.81-1.75 (m, 1H)

1.05 (dd, *J* = 7.3, 4.0 Hz, 1H)

0.88 (s, 9H)

0.18 (dd, *J* = 3.6, 3.5 Hz, 1H)

0.058 (s, 3H)

0.050 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.5, 131.3, 78.2, 64.4, 36.0, 27.02, 26.99, 25.85, 18.2,

-5.39, -5.44.

Alcohol **47**: ^{1}H NMR (400 MHz, $CDCl_3$) δ:

5.95 (bd, *J* = 5.6 Hz, 1H)

5.29 (dd, *J* = 5.5, 1.2 Hz, 1H)

5.13 (m, 1H)

3.73-3.71 (app. m, 2H)

1.75-1.70 (app. m, 1H)

0.85 (s, 9H)

0.68 (dd, *J* = 7.4, 3.9 Hz, 1H)

0.58 (dd, *J* = 3.7, 3.6 Hz, 1H)

0.015 (br s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.3, 131.4, 79.5, 65.9, 31.2, 27.6, 25.9, 21.3, 18.2, -5.36.

(1*R*,5*R*)-3-Bromo-1-(((1,1-dimethylethyl)dimethylsilyloxy)methyl)bicyclo[3.1.0]hex-3-en-2-one, 56.

To a solution of the enone **7** (100.0 mg, 0.419 mmol) in 1 mL of dichloromethane cooled to 0 ^{o}C was added dropwise a solution of bromine (21.6 μL, 0.419 mmol) over 10 min. The mixture was stirred at this temperature for an additional 1 h before adding triethylamine (87.7 μL, 0.629 mmol) dropwise. The reaction was stirred for an additional 6 h before adding a saturated solution of sodium thiosulfate (aq). The organic layer was removed and the aqueous layer was further extracted with dichloromethane (5x). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was separated by flash column chromatography on silica gel (5% ethyl acetate in hexanes). The bromoenone **56** was isolated as a white solid (67.0 mg, 0.211 mmol) in 50% yield.

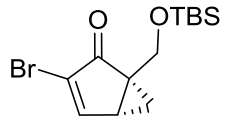
^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.72 (d, *J* = 2.8 Hz, 1H)

4.22 (d, *J* = 10.8 Hz, 1H)

3.92 (d, *J* = 10.8 Hz, 1H)

2.55 (ddd, *J* = 6.7, 3.3, 3.2 Hz, 1H)



56

1.63 (dd, *J* = 6.7, 3.8 Hz, 1H)

1.51 (dd, *J* = 3.6, 3.6 Hz, 1H)

0.85 (s, 9H)

0.050 (s, 3H)

0.040 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.4, 159.9, 120.8, 59.1, 38.4, 34.9, 25.8, 25.7, 18.2, -5.45, -5.47.

N^4-((1*S*,2*R*,3*S*,4*R*,5*R*)-4-((1,1-Dimethylethyl)dimethylsilyloxy)-5-(((1,1-dimethylethyl)dimethylsilyloxy)methyl)-3-fluorobicyclo[3.1.0]hexan-2-yl)-6-chloropyrimidine-4,5-diamine, 41.

Amine **30** (150.0 mg, 0.385 mmol), 5-amino-4,6-dichloropyrimidine (66.3 mg, 0.404 mmol), sodium bicarbonate (37.2 mg, 0.443 mmol), and 0.86 mL of *n*-butanol were combined and heated in a sealed vial for 3 d at 120 ^{o}C. An additional quantity of 5-amino-4,6-dichloropyrimidine (66.3 mg, 0.404 mmol) was added and the reaction continued the same way for 1 d. The solvent was removed and the crude residue was separated by flash column chromatography on silica gel (0 to 30% ethyl acetate in dichloromethane). The pyrimidine compound **41** was isolated as a pink solid (167.0 mg, 0.323 mmol) in 83% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

8.07 (s, 1H)

5.10 (d, *J* = 6.5 Hz, 1H)

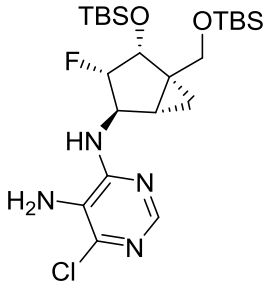
4.63 (dd, *J* = 19.8, 5.4 Hz, 1H)

4.54 (dd, *J* = 13.7, 6.6 Hz, 1H)

4.42 (dd, *J* = 51.0, 5.4 Hz, 1H)

4.17 (d, *J* = 10.8 Hz, 1H)

3.48 (br s, 2H)



41

3.07 (d, *J* = 10.8 Hz, 1H)

1.33-1.28 (m, 1H)

1.25-1.19 (m, 1H)

0.91 (s, 9H)

0.89 (s, 9H)

0.64-0.56 (m, 1H)

0.08-0.05 (s, 9H)

0.046 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.5, 149.5, 143.1, 122.0, 94.1 (d, *J* = 195.9 Hz), 71.7 (d, *J* = 16.1 Hz), 64.0, 62.6, 56.6 (d, *J* = 25.4 Hz), 35.8, 26.0, 25.8, 23.5, 18.3 (d, *J* = 11.7 Hz),11.4 (d, *J* = 8.5 Hz), -4.59, -4.85, -5.27, -5.34.

tert-Butyl((1R,2S,5R)-2-((1,1-dimethylethyl)silyloxy)bicyclo[3.1.0]hex-3-en-1-yl)methoxy)dimethylsilane, 44.

To a solution of the alcohol **43** (73.0 mg, 0.304 mmol) and imidazole (45.5 mg, 0.668 mmol) in 3.0 mL of dichloromethane was added *tert*-butyldimethylsilyl chloride (54.9 mg, 0.364 mmol). The reaction mixture was stirred for 16 h before partitioning with a saturated solution of sodium bicarbonate (aq). The organic layer was removed and the aqueous layer was further extracted

with dichloromethane (5x). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was separated by flash column chromatography on silica gel (3% ethyl acetate in hexanes). The silyl ether **44** was obtained as a colorless oil (96.7 mg, 0.273 mmol) in 90% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

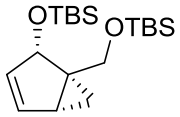
6.14 (ddd, *J* = 5.6, 1.9, 0.8 Hz, 1H)

5.42 (dd, *J* = 5.5, 2.0 Hz, 1H)

4.55 (br s, 1H)

4.33 (d, *J* = 10.3 Hz, 1H)

3.51 (d, *J* = 10.3 Hz, 1H)



44

1.82-1.78 (m, 1H)

1.52-1.48 (m, 1H)

1.16 (dd, *J* = 7.2, 3.5 Hz, 1H)

0.91 (s, 9H)

0.88 (s, 9H)

0.12 (s, 3H)

0.11 (s, 3H)

0.031 (br s, 6H).

5-Chloropent-2-yn-1-ol, 146.

To a solution of the alkyne **151** (4.05 g, 45.7 mmol) in 183 mL of tetrahydrofuran cooled to -78 °C was added *n*-butyllithium (1.6 M in hexanes, 30.0 mL, 48.0 mmol) and the mixture was stirred for 30 min. A stream of formaldehyde was bubbled into the solution via a rubber tube fitted with a pipet at both ends which was inserted into a rubber septum atop a separate flask containing paraformaldehyde (2.65 g, 88.2 mmol), which was heated above 120 °C. This process was assisted by the flow of argon into the paraformaldehyde containing flask. When the addition was complete, the reaction mixture was stirred for an additional 2 h and then quenched with a saturated ammonium chloride solution (aq) and partitioned with diethyl ether. The aqueous solution was further extracted with diethyl ether (4x) and the combined extracts were dried with brine. The brine was back extracted once with diethyl ether. The combined ether extracts were further dried over magnesium sulfate and filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel. The propargylic alcohol **146** was obtained as a colorless liquid (3.37 g, 28.4 mmol) in 62% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

4.07 (t, J = 2.0 Hz, 2H)

4.00-3.85 (bs, 1H)

3.44 (t, *J* = 7.2 Hz, 2H)

146

2.53 (tt, *J* = 7.2, 2.0 Hz, 2H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 81.7, 80.4, 50.4, 42.3, 23.0.

(*Z*)-1-((1,1-Dimethylethyl)dimethylsilyloxy)-5-chloro-2-pentene, 148.

To a solution of propargyl alcohol **146** (3.37 g, 28.4 mmol) in 30 mL of hexanes/ethyl acetate/methanol (1:1:1) was added quinoline (0.188 mL, 1.59 mmol) and Lindlar's catalyst (412 mg, 2 mmol). The reaction head space was purged with hydrogen gas and the flask was affixed with a hydrogen balloon. The reaction mixture was stirred for 2 d. The reaction mixture was filtered through Celite and further washed with methanol. The filtrate was concentrated *in vacuo* and a short column on silica gel was performed (30% ethyl acetate in hexanes). The purified material contained an abundance of quinoline and was taken on crude to the next step.

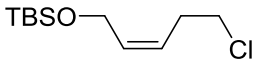
To the crude mixture dissolved in 36 ml of dichloromethane was added imidazole (1.93 g, 28.4 mmol) and *t*-butyldimethylsilyl chloride (4.28 g, 28.4 mmol). The mixture was stirred for 2 h before partitioning with a saturated sodium bicarbonate solution (aq) and extracting with dichloromethane. The combined dichloromethane extracts were dried with magnesium sulfate and filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel. The allylic silyl ether **148** was obtained as a colorless liquid (2.9 g, 12.3 mmol) in 43% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

5.67 (dtt, *J* = 11.0, 6.1, 1.6 Hz, 1H)

5.46 (dtt, *J* = 11.1, 7.4, 1.7 Hz, 1H)

4.23 (ddt, *J* = 6.2, 1.7, 0.8 Hz, 2H)



148

3.51 (t, *J* = 7.0 Hz, 2H)

2.53 (dtdt, *J* = 7.3, 7.0, 1.6, 0.8 Hz, 2H)

0.90 (s, 9H)

0.07 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 132.7, 126.0, 59.4, 43.9, 31.0, 25.9, 18.3, -5.16.

2-(2-formyl-6-methoxyphenoxy)-*N*-methoxy-*N*-methylacetamide, 154.

To a solution of *o*-vanillin (5.04 g, 27.7 mmol) in 270 mL of acetonitrile was added cesium carbonate (9.02 g, 27.7 mmol). The mixture was stirred for 10 min before adding 2-bromo-*N*-methoxy-*N*-methylacetamide (3.83 g, 25.2 mmol). The mixture was stirred for 12 h and then concentrated *in vacuo*. Water was added to the crude solid and it was partitioned with dichloromethane. The organic layer was removed and the water layer was further extracted with dichloromethane (4x). The combined dichloromethane layers were concentrated *in vacuo*. The

crude residue was purified by flash column chromatography on silica gel (30% ethyl acetate in hexanes). The aryl ether **154** was obtained as a white solid (4.44 g, 17.5 mmol) in 63% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

10.64 (s, 1H)

7.43 (m, 1H)

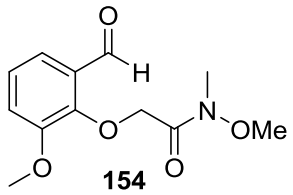
7.14-7.09 (m, 2H)

5.02 (s, 2H)

3.88 (s, 3H)

3.68 (s, 3H)

3.17 (s, 3H).



154

^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.9, 152.0, 150.6, 130.1, 129.1, 124.2, 119.3, 118.0, 69.7, 61.4, 56.2, 32.3.

***N*,7-Dimethoxy-*N*-methylbenzofuran-2-carboxamide, 143.**

A solution of the aldehyde **154** (4.44 g, 17.5 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.52 mL, 3.5 mmol) in 35 mL of acetonitrile was heated to reflux for 24 h. The mixture was

cooled and the solvent was removed. The crude residue was purified by flash column chromatography on silica gel (R_f = 0.40, 40% ethyl acetate in hexanes). The benzofuran **143** was obtained as a white solid (0.65 g, 2.74 mmol) in 15% yield.

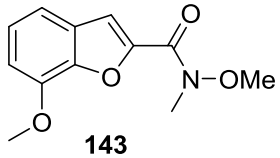
^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.34 (s, 1H)

7.09 (dd, *J* = 7.9, 1.1 Hz, 1H)

7.04 (t, *J* = 7.8 Hz, 1H)

6.73 (dd, *J* = 7.7, 1.0 Hz, 1H)



143

3.84 (s, 3H)

3.69 (s, 3H)

3.26 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.4, 146.9, 145.8, 144.4, 128.9, 124.1, 114.4, 113.2, 108.5, 61.5, 55.9, 33.3.

2-(1,3-Dithian-2-yl)-7-methoxybenzofuran, 158.

To a solution of ethyl 7-methoxybenzofuran-2-carboxylate **155** (2.68 g, 12.17 mmol) in 61 mL of dichloromethane cooled to 0 °C was added diisobutylaluminum hydride (1M in hexanes, 30.4

mL, 30.42 mmol). After the mixture stirred for 45 min, 12 mL of methanol was added and the reaction mixture was allowed to warm to 22 °C and further stirred for 30 min. Sodium tartrate (12 g) dissolved in 100 mL of water was added to the reaction mixture and it was stirred rapidly until the complete dissolution of any solids. The organic layer was removed and the water layer was further extracted with dichloromethane (5x). The combined extracts were dried over magnesium sulfate, filtered and then concentrated *in vacuo*. The crude residue was dissolved in 61 mL of dichloromethane and Dess-Martin periodinane (7.74 g, 18.26 mmol) was added. The resulting homogeneous mixture was stirred for 1 h before adding 50 mL of a solution of sodium hydroxide (1M) and copious amounts of sodium thiosulfate. The biphasic mixture was rapidly stirred for ~1 h and then separated from the organic layer. The aqueous layer was further extracted with dichloromethane (5x). The combined extracts were dried over magnesium sulfate, filtered and then concentrated *in vacuo*. (R_f of compound of interest = 0.60, 30% ethyl acetate in hexanes). The crude material, 1,3-propanedithiol (1.47 mL, 14.60 mmol), and a catalytic amount of *p*-TsOH was dissolved in 24 mL of benzene. The reaction flask was fitted with a Dean-Stark trap and the reaction was refluxed for 4 h. After cooling to 23 ^{o}C, the reaction mixture was partitioned with a solution of sodium hydroxide (1M, aq) and the organic layer separated. The aqueous layer was further extracted with dichloromethane (5x). The combined extracts were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (R_f = 0.30, 15% ethyl acetate in hexanes). The dithiane **158** was obtained as a light yellow crystalline solid (3.07 g, 11.51 mmol) in 94% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

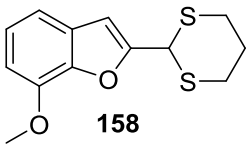
7.13 (d, *J* = 5.6 Hz, 1H)

7.12 (d, *J* = 3.6 Hz, 1H)

6.80 (d, *J* = 0.88 Hz, 1H)

6.78 (dd, *J* = 5.4, 3.5 Hz, 1H)

5.27 (s, 1H)



158

3.98 (s, 3H)

3.02 (ddd, *J* = 14.0, 6.8, 3.2 Hz, 2H)

2.92 (ddd, *J* = 14.0, 9.6, 3.2 Hz, 2H)

2.19-2.09 (m, 1H)

2.08-1.97 (m, 1H).

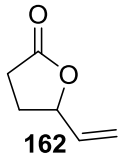
^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.1, 145.3, 143.9, 129.8, 123.7, 113.3, 106.8, 105.1, 56.0,

41.7, 29.9, 25.3.

5-Ethenyldihydrofuran-2(3*H*)-one, 162.

5-Hexenoic acid **161** (4.25 g, 37.23 mmol), palladium acetate (0.83 g, 3.69 mmol), sodium acetate (6.1 g, 74.47 mmol), and *p*-benzoquinone (0.50 g, 4.63 mmol) were dissolved in 372 mL

of dimethyl sulfoxide. The reaction flask was fitted with a septum and the head space was purged with oxygen gas. The flask was affixed with an oxygen containing balloon and the reaction mixture was gently heated to 55 ^{o}C for 4 d. The reaction mixture was added to ice and then partitioned with ether/pentane (1:1). The organic layer was separated and the DMSO/water layer was further extracted twice with ether/pentane (1:1). The combined extracts were dried using brine, layered over magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (R_f = 0.50, 100% dichloromethane). The vinyl lactone **162** was obtained as a colorless liquid (1.91 g, 17.03 mmol) in 46% yield.



162

The ^{1}H and ^{13}C NMR spectra match those reported by Grover, H. K.; Emmett, M. R.; Kerr, M. A. *Org. Lett.* **2013**, *15*, 4838-4841.

4-hydroxy-1-(7-methoxybenzofuran-2-yl)hex-5-en-1-one, 163.

To a solution of 7-methoxybenzofuran **119** (329 mg, 2.22 mmol) in 10 mL of diethyl ether at -78 ^{o}C was slowly added *tert*-butyllithium (1.7 M in pentane, 1.31 mL, 2.22 mmol). The reaction mixture was stirred for 1 h before adding dropwise a solution of the vinyl lactone **47** (274 mg, 2.44 mmol) in 2 mL of diethyl ether dropwise. The reaction mixture was stirred for 20 min before warming to 22 ^{o}C. The reaction mixture was partitioned with a saturated solution of sodium bicarbonate (aq) and the organic layer was removed. The aqueous layer was further

extracted with dichloromethane (5x). The combined extracts were dried with sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (gradient: 5 to 25% ethyl acetate in dichloromethane). The allylic alcohol **163** was obtained as a colorless oil (322 mg, 1.24 mmol) in 56% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.48 (s, 1H)

7.24 (dd, *J* = 7.9, 1.2 Hz, 1H)

7.19 (t, *J* =7.9 Hz, 1H)

6.91 (dd, *J* =7.7, 1.2 Hz, 1H)

5.89 (ddd, *J* =17.2, 10.4, 5.8 Hz, 1H)

5.26 (ddd, *J* = 17.2, 1.5, 1.5 Hz, 1H)

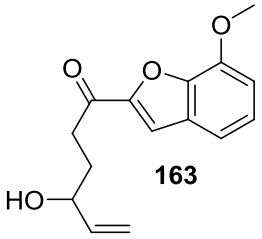
5.12 (ddd, *J* = 10.5, 1.4, 1.4 Hz, 1H)

4.24 (m, 1H)

4.00 (s, 3H)

3.13 (t, *J* = 7.2 Hz, 2H)

2.29 (d, *J* = 4.6 Hz, 1H)



163

2.00 (m, 2H).

6-(7-Methoxybenzofuran-2-yl)-6-oxohex-1-en-3-yl acetate, 164.

To a solution of the allylic alcohol **163** (226 mg, 0.868 mmol) in 3.5 mL of dichloromethane was added pyridine (0.18 mL, 2.17 mmol), acetic anhydride (0.16 mL, 1.74 mmol), and a crystal of 4-dimethylaminopyridine (DMAP). The resulting mixture was stirred for 16 h. The solvent was removed and the crude residue was directly purified by flash column chromatography on silica gel (gradient: 20 to 30% ethyl acetate in hexanes). The allylic acetate **164** was obtained as a colorless oil (252 mg, 0.833 mmol) in 96% yield.

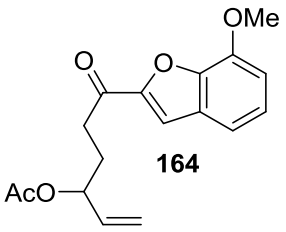
^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.46 (s, 1H)

7.24 (dd, *J* = 8.0, 1.2 Hz, 1H)

7.19 (t, *J* =7.7 Hz, 1H)

6.91 (dd, *J* = 7.7, 1.1 Hz, 1H)



164

5.80 (ddd, *J* = 17.3, 10.6, 6.2 Hz, 1H)

5.34 (btd, *J* = 6.2, 6.2 Hz, 1H)

5.26 (ddd, *J* = 17.2, 1.3, 1.3 Hz, 1H)

5.19 (ddd, *J* = 10.6, 1.2, 1.2 Hz, 1H)

3.99 (s, 3H)

3.03 (dt, *J* = 7.8, 1.9 Hz, 2H)

2.15-2.05 (m, 2H)

2.03 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.2, 170.2, 152.8, 146.0, 145.2, 135.9, 128.7, 124.6, 117.2,

115.0, 112.5, 109.4, 73.8, 56.1, 34.3, 28.0, 21.1.

6-Hydroxy-6-(7-methoxybenzofuran-2-yl)hex-1-en-3-yl acetate, 166.

To a solution of the allylic acetate **164** (53.6 mg, 0.177 mmol) in 0.7 mL of methanol at 0 ^{o}C was added sodium borohydride (6.7 mg, 0.177 mmol). After 10 min, to the reaction was added a saturated solution of sodium bicarbonate (aq) and dichloromethane. The organic layer was removed and the aqueous layer was further extracted with dichloromethane (5x). The combined extracts were dried over magnesium sulfate, filtered and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (R_f = 0.15, 20% ethyl acetate in hexanes). The alcohol **166** was obtained as a 1:1 mixture of diastereomers and as a colorless oil (51.6 mg, 0.170 mmol) in 96% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.12 (d, *J* = 6.0 Hz, 1H)

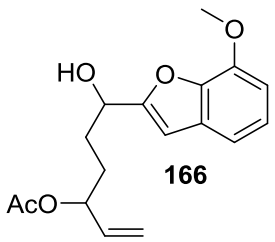
7.12 (d, *J* = 3.0 Hz, 1H)

6.78 (dd, *J* = 5.9, 3.0 Hz, 1H)

6.61 (s, 1H)

5.76 (ddd, *J* = 17.3, 10.6, 6.3 Hz, 1H)

5.29 (app. pent., *J* = 7.0 Hz, 1H)



166

5.23 (bd, *J* = 17.3 Hz, 1H)

5.16 (bd, *J* = 10.6 Hz, 1H)

4.84 (bt, *J* = 6.3 Hz, 1H)

3.99 (s, 3H)

2.50 (bs, 1H)

2.05 (s, 3H)

2.02-1.90 (m, 2H)

1.89 (m, 1H)

1.79-1.66 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ:

170.4, 170.3, 159.29, 159.26, 145.1, 143.8, 136.0, 129.6, 123.4, 116.91, 116.87, 113.3,

106.2, 102.8, 102.7, 74.4, 74.2, 67.8, 67.7, 55.8, 31.0, 30.8, 30.0, 29.9, 21.11, 21.10.

7-Methoxy-2-(5-ethenyltetrahydrofuran-2-yl)benzofuran, 167.

To a solution of the alcohol **166** (15.0 mg, 0.049 mmol) in 0.2 mL of dichloroethane was added cesium carbonate (32.1 mg, 0.099 mmol) and tetrakis(triphenylphosphine)palladium(0) (5.7 mg, 0.0049 mmol). After the mixture stirred for 10 min, the solvent was removed. The crude residue was purified by flash column chromatography on silica gel (R_f = 0.25, 10% ethyl acetate in hexanes). The dihydrofurans **167** were isolated as an oily 3:2 mixture of isomers A and B (12.0 mg, 0.049 mmol) in quantitative yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ:

7.14-7.11 (app. m, 2H)

6.78 (d, *J* = 4.3 Hz, 1H)

6.77 (d, *J* = 4.3 Hz, 1H)

6.65 (isomer A, s, 1H)

6.64 (isomer B, s, 1H)

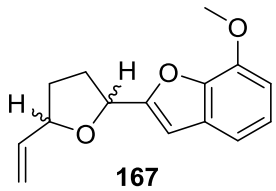
5.98 (isomer A, ddd, *J* = 17.1, 10.4, 6.7 Hz, 1H)

5.90 (isomer B, ddd, *J* = 17.1, 10.4, 6.3 Hz, 1H)

5.34 (isomer A, ddd, *J* = 12.1, 1.2, 1.2 Hz, 1H)

5.31 (isomer B, ddd, *J* = 12.1, 1.3, 1.2 Hz, 1H)

5.28-5.12 (app. m, 2H)



167

4.67 (isomer B, ddd, *J* = 6.3, 6.3, 6.3 Hz, 1H)

4.49 (isomer A, ddd, *J* = 6.7, 6.7, 6.7 Hz, 1H)

4.00 (s, 3H)

2.45-2.10 (m, 3H)

1.90-1.76 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 158.8, 158.5, 145.2, 145.1, 144.1, 144.0, 138.7, 138.5, 129.9, 129.8, 123.2, 116.0, 115.5, 113.2, 106.11, 106.09, 103.1, 81.3, 80.3, 74.8, 74.4, 55.94, 55.89, 32.0, 31.5, 31.2, 30.8.

4-Acetoxy-1-(7-methoxybenzofuran-2-yl)hex-5-en-1-yl-2,2,2-trimethylacetate, 168.

To a solution of the alcohol **166** (51.0 mg, 0.168 mmol) and pyridine (68 μL, 0.838 mmol) in 0.67 mL of dichloromethane at 22 ^{o}C was added pivaloyl chloride (41 μL, 0.335 mmol). After

the reaction stirred for 16 h, a saturated solution of sodium bicarbonate (aq) was added. The organic layer was removed and the aqueous layer was further extracted with dichloromethane (5x). The combined extracts were dried over magnesium sulfate, filtered and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (R_f = 0.20, 10% ethyl acetate in hexanes). The pivalate ester **168** was obtained as a colorless oil (54.0 mg, 0.139 mmol) in 83% yield.

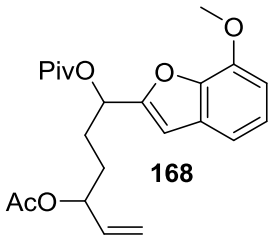
^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.13 (d, *J* = 5.6 Hz, 1H)

7.12 (d, *J* = 4.0 Hz, 1H)

6.79 (dd, *J* = 5.2, 3.7 Hz, 1H)

6.63 (s, 1H)



168

5.96 (td, *J* = 6.6, 6.6 Hz, 1H),

5.74 (dddd, *J* = 17.2, 10.5, 6.4, 0.7 Hz, 1H)

5.30-5.20 (m, 2H)

5.16 (ddd, *J* = 10.5, 1.2, 1.2 Hz, 1H)

4.00 (s, 3H)

2.15-2.03 (m, 2H)

2.05 (s, 3H)

1.80-1.60 (m, 2H)

1.22 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.3, 170.12, 170.11, 145.3, 144.0, 135.83, 135.80, 129.5, 123.5, 117.08, 117.07, 113.4, 106.6, 104.67, 104.65, 74.00, 73.95, 68.6, 68.5, 56.0, 38.8, 29.7, 29.6, 28.5, 28.4, 27.0, 26.9, 21.1.

2-(Carboxymethoxy)-3-methoxybenzoic acid, 172.

To a solution of 2-hydroxy-3-methoxybenzoic acid **171** (12.5 g, 74.33 mmol) in 300 mL of dimethyl formamide at 0 ^{o}C was added portion-wise sodium hydride (60% dispersion in mineral oil, 8.92 g, 223 mmol). After gas evolution ceased, bromoacetic acid (10.33 g, 74.33 mmol) was added slowly. The reaction was stirred for 2 h before adding 150 mL of water (or until complete dissolution of the salts). The mixture was stirred for an additional 16 h before it was concentrated *in vacuo*. The crude white solid was dissolved in water and washed twice with dichloromethane. The aqueous layer was acidified to pH 1 using concentrated hydrochloric acid. The aqueous layer was extracted with ethyl acetate (3x). The combined extracts were dried with brine, layered over magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was recrystallized from ethyl acetate. The bis(carboxylic acid) **172** was obtained as a white solid (6.82 g, 30.15 mmol) in 41% yield.

^{1}H NMR (500 MHz, DMSO-d_6) δ:

14.00-11.50 (brs, 1H)

7.20 (bd, J = 8.1 Hz, 1H)

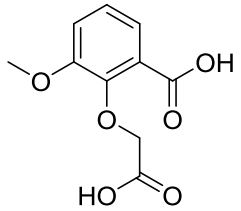
7.17 (bd, J = 7.6 Hz, 1H)

7.11 (dd, J = 7.9, 7.9 Hz, 1H)

4.50 (s, 2H)

4.50-2.00 (brs, 1H)

3.78 (s, 3H).



172

^{13}C NMR (126 MHz, DMSO-d_6) δ: 170.5, 167.5, 152.8, 145.8, 127.2, 124.6, 121.8, 116.4, 69.6, 56.4.

7-Methoxybenzofuran-3(2*H*)-one, 174.

A mixture of the bis(carboxylic acid) **172** (6.82 g, 30.15 mmol), acetic anhydride (28.3 mL, 0.302 mol), acetic acid (10.37 mL, 0.181 mol), and sodium acetate (4.95 g, 60.3 mmol) was heated to reflux for 12h. The hot mixture was poured over ice and stirred in the presence of dichloromethane for 30 min. The organic layer was removed and the aqueous layer was further extracted with dichloromethane (4x). The combined extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was dissolved in 240 mL of ethanol and 20

mL of ammonium hydroxide (14.8 M) was slowly added. The resulting solution was stirred for 1.5 h. The solvent was removed and then the residual water and ammonium hydroxide were azeotroped a few times with small quantities of ethanol. The crude residue was subjected to a short column of silica gel (R_f = 0.30, 20% ethyl acetate in hexanes). The fractions were concentrated to give a red crystalline solid that contained an impurity that was washed away with small quanitities of diethyl ether. The benzofuranone **174** was obtained as a red solid (1.42 g, 8.65 mmol) in 29% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ:

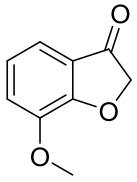
7.20 (dd, *J* = 7.7, 1.0 Hz, 1H)

7.07 (bd, *J* = 7.3 Hz, 1H)

6.98 (t, *J* = 7.8 Hz, 1H)

4.64 (s, 2H)

3.92 (s, 3H).



174

^{13}C NMR (126 MHz, $CDCl_3$) δ: 199.7, 163.9, 146.7, 122.4, 122.2, 118.1, 115.0, 75.0, 56.1.

(*E*)-*N*,*N*-dimethylhex-4-enamide, 177.

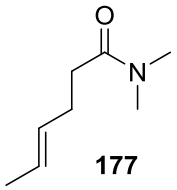
To a solution of diisopropyamine (22.2 mL, 0.158 mol) in 500 mL of tetrahydrofuran cooled to -78 ^{o}C was slowly added *n*-butyllithium (1.6 M in hexanes, 99 mL, 0.158 mol). After the solution stirred for 1 h, dimethylacetamide (14.0 mL, 0.150 mol) was slowly added. After an additional 1 h of stirring, crotyl bromide (16.0 mL, 0.158 mol) was added dropwise and the resulting mixture was allowed to warm to 22 ^{o}C over 16 h. The reaction was quenched by the addition of a 6 mL solution of saturated ammonium chloride (aq). The solvent was concentrated *in vacuo* and the crude mixture was partitioned between water and dichloromethane. The organic layer was removed and the aqueous layer was further extracted with dichloromethane (3x). The combined organic layers were dried with brine, which was back-extracted once with dichloromethane, then dried with magnesium sulfate, filtered and then concentrated *in vacuo*. The crude oil was distilled (92 ^{o}C, 1 torr) and the amide **177** was obtained as a yellow oil (8.90 g, 63.0 mmol) in 40% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

5.45-5.41 (m, 2H)

2.95 (s, 3H)

2.90 (s, 3H)



177

2.35-2.21 (m, 4H)

1.61-1.58 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.4, 130.0, 125.5, 37.1, 35.2, 33.2, 28.0, 17.7.

***trans*-Ethyl 2-(2-acetyl-7-methoxy-2,3-dihydrobenzofuran-3-yl)acetate, 182.**

To a solution of *o*-vanillin (8 g, 52.58 mmol) in 315 mL of toluene was added a solution of (carbethoxymethylene)triphenylphosphorane (19.23 g, 55.20 mmol) in 210 mL of toluene. The resulting mixture was heated to refluxed for 24 h. After cooling, the solvent was removed and the crude residue was carried on to the next step. The R_f of the product overlaps with *o*-vanillin when a ethyl acetate/hexanes solvent mixture is used as the eluent.

Prior to the next step, in a separatory funnel chloroacetone (4.19 mL, 52.58 mmol) dissolved in 53 mL of acetone was periodically shaken in the presence of sodium iodide (11.82 g, 78.87 mmol) over 16 h. The heterogeneous mixture was filtered and washed with a small quantity of acetone.

The crude material from the first step was dissolved in 210 mL of tetrahydrofuran and potassium carbonate (7.27 g, 52.58 mmol) was added. The heterogeneous mixture was heated to 55 ^{o}C for 4 h and cooled back to 22 ^{o}C. The preformed iodoacetone dissolved in acetone was added to the solution and it was stirred for 24 h, at which time an additional quantity of chloroacetone (4.19 mL, 52.58 mmol) was added. The mixture was heated to 50 ^{o}C for 5 h and another equivalent of chloroacetone (4.19 mL, 52.58 mmol) was added. The mixture was stirred at the same temperature for 1 h before cooling to 22 ^{o}C. The solvent was reduced to half volume through reduced pressure evaporation and an equivalent volume of hexanes was added. The heterogenous mixture was filtered and the precipitate was washed with a small quantity of

hexanes. The filtrate was concentrated *in vacuo*. The crude residue was dissolved in 500 mL of anhydrous ethanol and potassium carbonate (7.27 g, 52.58 mmol) was added. The mixture was stirred at 22 ^{o}C for 9 h then heated to 60 ^{o}C for 1 h. Another equivalent of potassium carbonate (7.27 g, 52.58 mmol) was added and the reaction mixture was heated for a further 16 h. The solvent was evaporated and the crude mixture was partioned between water and dichloromethane. The organic layer was removed and the aqueous layer was further extracted with dichloromethane (5x). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was separated by flash column chromatography on silica gel (eluent: ethyl acetate/hexanes). The dihydrobenzofuran **182** was obtained as a colorless oil (8.39 g, 30.14 mmol) in 57% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

6.86 (dd, *J* = 8.4, 7.2 Hz, 1H)

6.80 (d, *J* = 8.0 Hz, 1H)

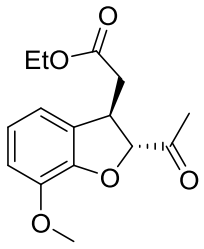
6.77 (bd, *J* = 7.2 Hz, 1H)

4.82 (d, *J* = 5.8 Hz, 1H)

4.17 (q, *J* = 7.1 Hz, 2H)

3.97 (ddd, *J* = 7.5, 6.7, 5.8 Hz, 1H)

3.89 (s, 3H)



182

2.72 (dd, *J* = 16.0, 6.7 Hz, 1H)

2.71 (dd, *J* = 16.0, 7.5 Hz, 1H)

2.31 (s, 3H)

1.25 (t, *J* = 6.9 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ: 207.0, 170.9, 146.8, 144.5, 129.2, 122.2, 116.4, 112.1, 90.8,

60.8, 56.0, 42.1, 39.6, 26.1, 14.0.

Ethyl 2-(2-acetyl-7-methoxybenzofuran-3-yl)acetate, 183.

To a solution of the dihydrofuran **182** (8.4 g, 30.18 mmol) in 135 mL of benzene was added DDQ (8.45 g, 37.21 mmol) and the resulting mixture was heated to reflux for 24 h. After cooling to 22 ^{o}C, the reaction mixture was filtered. The filtrate was concentrated *in vacuo* and the crude residue was separated by flash column chromatography on silica gel (20% ethyl acetate in hexanes). The fractions containing the product also included an impurity. The solid from these fractions was recrystallized using hexanes. The substituted benzofuran **183** was obtained as a white solid (3.21 g, 11.62 mmol) in 39% yield.

^{1}H NMR (400 MHz, C_6D_6) δ:

7.06 (dd, *J* = 8.0, 0.9 Hz, 1H)

6.93 (dd, *J* = 7.9, 7.9 Hz, 1H)

6.47 (dd, *J* = 7.9, 0.8 Hz, 1H)

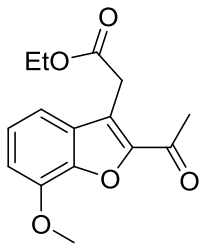
4.12 (s, 2H)

3.90 (q, *J* = 7.0 Hz, 2H)

3.35 (s, 3H)

2.18 (s, 3H)

0.87 (t, *J* = 7.1 Hz, 3H).



183

^{13}C NMR (100 MHz, C_6D_6) δ: 190.1, 169.0, 148.8, 146.0, 143.6, 130.3, 123.9, 120.1, 113.2, 109.1, 60.4, 55.0, 29.9, 26.7, 13.7.

Ethyl 2-(7-methoxy-2-(1-((trimethylsilyl)oxy)ethenyl)benzofuran-3-yl)acetate, 184.

To a solution of the benzofuran **183** (200 mg, 0.724 mmol) and triethylamine (0.50 mL, 3.62 mmol) in 2.50 mL dichloromethane was added dropwise trimethylsilyl triflate (0.33 mL, 1.81 mmol). After 10 min, water was added and the resulting biphasic mixture was separated. The aqueous layer was further extracted with dichloromethane (3x). The combined organic layers were dried with magnesium sulfate, filtered and concentrate *in vacuo*. Residual triethylamine and silanol was removed by azeotroping with benzene. The siloxy diene **184** was obtained as a colorless oil in >95% yield.

^{1}H NMR (500 MHz, C_6D_6) δ:

7.16-7.10 (m, 1H)

6.99 (dd, *J* = 7.9, 7.9 Hz, 1H)

6.48 (dd, *J* = 7.8, 0.5 Hz, 1H)

5.37 (d, *J* = 1.9 Hz, 1H)

4.45 (d, *J* = 1.9 Hz, 1H)

3.93 (s, 2H)

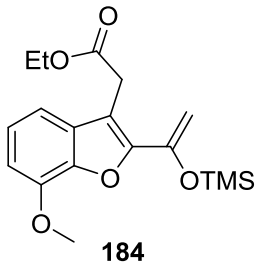
3.89 (d, *J* = 7.2 Hz, 1H)

3.86 (d, *J* = 7.2 Hz, 1H)

3.40 (s, 3H)

0.70 (t, *J* = 7.3 Hz, 3H)

0.16 (s, 9H).



184

Ethyl 2-(2-(1-(((1,1-dimethylethyl)dimethylsilyl)oxy)ethenyl)-7-methoxybenzofuran-3-yl)acetate, 186.

To a solution of the benzofuran **183** (150 mg, 0.543 mmol) and pyridine (0.11 mL, 1.36 mmol) in 2.17 mL dichloromethane was added TBSOTf (275 μL, 1.19 mmol) dropwise. After

had stirred for 20 h, a saturated solution of sodium bicarbonate (aq) was added and the resulting biphasic mixture was separated. The aqueous layer was further extracted with dichloromethane (3x). The combined organic layers were dried with magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified flash column chromatography on silica gel (10% ethyl acetate and 1% triethylamine in hexanes). The silyloxy diene **186** was obtained as a colorless oil (200 mg, 0.512 mmol) in 94% yield.

^{1}H NMR (400 MHz, C_6D_6) δ:

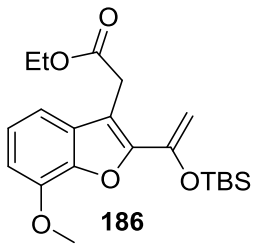
7.20 (dd, *J* = 7.9, 0.9 Hz, 1H)

7.03 (dd, *J* = 7.9, 7.9 Hz, 1H)

6.52 (dd, *J* = 7.9, 0.9 Hz, 1H)

5.37 (d, *J* = 1.8 Hz, 1H)

4.58 (d, *J* = 1.8 Hz, 1H)



186

3.99 (s, 2H)

3.89 (q, *J* = 7.1 Hz, 2H)

3.45 (s, 3H)

0.98 (s, 9H)

0.89 (t, *J* = 6.9 Hz, 3H)

0.17 (s, 6H).

^{13}C NMR (100 MHz, C_6D_6) δ: 169.7, 149.3, 148.8, 145.5, 143.3, 131.6, 123.2, 112.3, 110.9, 107.6, 94.8, 60.2, 55.2, 30.2, 25.6, 18.2, 13.7, -4.85.

Ethyl 2-(2-(2-(((1,1-dimethylethyl)dimethylsilyl)oxy)-3,4-dihydro-2*H*-pyran-2-yl)-7-methoxybenzofuran-3-yl)acetate, 200.

A solution of the silyloxy diene **186** (50.0 mg, 0.128 mmol) and acrolein (10.37 μL, 0.153 mmol) in 0.5 mL dichloromethane was prestirred in the presence of 4 Å molecular sieves. In a separate flask, trimethylaluminum (2M in hexanes, 12.8 μL, 0.0256 mmol) was added to a solution of (*S*)-BINOL (8.06 mg, 0.028 mmol) in 0.14 ml of dichloromethane at 0 ^{o}C. After 10 min, the silyloxy diene/acrolein solution was added to the Lewis acid-containing solution and the resulting mixture was stirred for 24 h at 22 ^{o}C. A saturated solution of sodium tartrate (aq) was added and the biphasic mixture was stirred for 30 min. The organic layer was removed and the aqueous layer was further extracted with dichloromethane (5x). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified flash column chromatography on silica gel (R_f = same as starting material, eluent: ethyl acetate/hexanes). The hetero-Diels-Alder product **200** was obtained as a colorless oil (22.5 mg, 0.0504 mmol) in 39% yield.

^{1}H NMR (400 MHz, C_6D_6) δ:

7.13-7.09 (d, *J* = 8.0, 1.0 Hz, 1H)

6.99 (dd, *J* = 7.9, 7.9 Hz, 1H)

6.46 (dd, *J* = 7.9, 0.9 Hz, 1H)

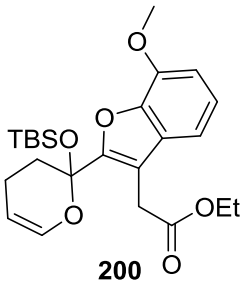
6.16 (ddd, *J* = 6.0, 2.4, 1.2 Hz, 1H)

4.65 (dddd, *J* = 6.0, 6.0, 2.0, 1.6 Hz, 1H)

3.95 (d, *J* = 16.4 Hz, 1H)

3.94-3.82 (m, 2H)

3.79 (d, *J* = 16.4 Hz, 1H)



200

3.41 (s, 3H)

2.36-2.28 (dddd, *J* = 13.2, 5.6, 2.1, 1.9 Hz, 1H)

2.26-2.14 (m, 1H)

1.88-1.76 (ddd, *J* = 17.6, 12.0, 5.6 Hz, 1H)

1.66-1.56 (m, 1H)

0.99 (s, 9H)

0.87 (t, *J* = 7.1 Hz, 3H)

0.07 (s, 3H)

-0.007 (s, 3H).

^{13}C NMR (100 MHz, C_6D_6) δ: 170.0, 153.3, 145.7, 142.9, 139.7, 131.4, 123.2, 112.0, 109.5, 107.1, 102.1, 96.1, 60.1, 55.2, 33.3, 29.8, 25.6, 18.0, 16.2, 13.8, -4.24, -4.81.

Ethyl 2-(2-(3-(((1,1-dimethylethyl)dimethylsilyl)oxy)pent-4-enoyl)-7-methoxybenzofuran-3-yl)acetate, 198 and ethyl 2-(7-methoxy-2-(5-oxopentanoyl)benzofuran-3-yl)acetate, 199.

To a solution of the silyloxy diene **186** (38 mg, 0.097 mmol) and acrolein (7.8 μL, 0.117 mmol) in dichloromethane was added powdered 4 Å molecular sieves and the mixture was stirred for 15 min. Indium(III) chloride (2.15 mg, 0.0097 mmol) was added and the reaction was allowed to stir for 2 h. The solvent was then removed and the crude residue was separated by flash column chromatography on silica gel (eluent: ethyl acetate in hexanes). Two compounds were isolated. The silyl ether **198** was isolated as a slightly impure colorless oil (2.4 mg, 0.0067 mmol) in 7% yield. The second compound contained a mixture of isomers containing both an aldehyde and silyl ether functionality (8.4 mg). This mixture of compounds was dissolved in ethanol and 1N HCl was added. The solvent was evaporated and subsequently azeotroped with ethanol. The crude residue was dissolved in dichloromethane and a saturated solution of sodium bicarbonate (aq) was added. The organic layer was removed and the aqueous layer was further extracted with dichloromethane. The combined extracts were dried, filtered and concentrated. This yielded the desilylated product **199** (slightly impure), for which a tentative structure has been assigned.

Silyl ether **198**: ^{1}H NMR (400 MHz, C_6D_6) δ:

7.22 (d, *J* = 6.8 Hz, 1H)

7.21 (d, *J* = 2.0 Hz, 1H)

6.95 (dd, *J* = 6.8, 2.0 Hz, 1H)

5.93 (ddd, *J* = 17.1, 10.3, 5.9 Hz, 1H)

5.25 (ddd, *J* = 17.2, 1.4, 1.4 Hz, 1H)

5.06 (ddd, *J* = 10.4, 1.4, 1.3 Hz, 1H)

4.85 (ddd, *J* = 6.0, 6.0, 6.0 Hz, 1H)

4.16 (q, *J* = 7.2 Hz, 2H)

4.03 (s, 3H)

3.39 (dd, *J* = 15.4, 7.3 Hz, 1H)

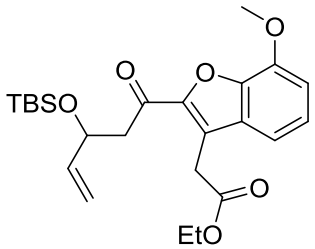
3.09 (dd, *J* = 15.4, 5.8 Hz, 1H)

2.17 (s, 2H)

1.24 (t, *J* = 7.1, 3H)

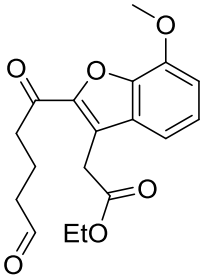
0.81 (s, 9H)

0.043 (s, 3H)



198

+



199

0.009 (s, 3H).

Compound **199**: ^{1}H NMR (500 MHz, $CDCl_3$) δ:

9.81 (s, 1H)

7.26-7.19 (app. m, 2H)

6.95 (dd, *J* = 6.3, 1.2 Hz, 1H)

4.17 (q, *J* = 7.0 Hz, 2H)

4.03 (s, 3H)

3.15 (t, *J* = 7.1 Hz, 2H)

2.58 (dt, *J* = 7.3, 1.2 Hz, 2H)

2.08 (t, *J* = 7.3 Hz, 2H)

1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 201.7, 192.7, 169.7, 148.4, 145.9, 143.5, 129.9, 124.3, 120.6,

113.3, 109.4, 61.0, 56.0, 42.9, 38.3, 30.0, 15.6, 14.1.

Ethyl 2-(2-(2-hydroxypent-4-en-2-yl)-7-methoxybenzofuran-3-yl)acetate, 191.

Allyl iodide (23.4 μL, 0.255 mmol) was added dropwise to a mixture of the ketone **183** (60.0 mg, 0.217 mmol) and indium powder (27.4 mg, 0.239 mmol) in 0.7 mL THF/H_2O (10:1). After stirring for 1 h, the reaction was diluted with dichloromethane and a saturated solution of sodium bicarbonate (aq) was added. The organic layer was removed and the aqueous layer was further extracted with dichloromethane (5x). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude residue (67.1 mg), containing both starting material and product **191** (90% purity, 89% yield by nmr), was used in later steps without further purification due to the same R_f of both compounds on silica gel.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.15 (dd, *J* = 8.0, 8.0 Hz, 1H)

7.09 (dd, *J* = 8.0, 1.2 Hz, 1H)

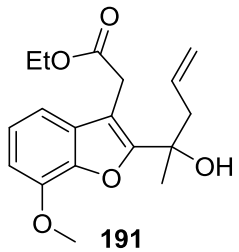
6.78 (dd, *J* = 7.8, 1.1 Hz, 1H)

5.83-5.70 (m, 1H)

5.18-5.07 (m, 2H)

4.15 (q, *J* = 7.3 Hz, 2H)

3.99 (s, 3H)



191

3.95 (d, *J* = 15.2 Hz, 1H)

3.89 (d, *J* = 15.2 Hz, 1H)

3.75 (s, 1H)

2.90 (dd, *J* = 13.8, 6.4 Hz, 1H)

2.60 (dd, *J* = 13.8, 8.1 Hz, 1H)

1.65 (s, 3H)

1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.8, 158.5, 145.1, 142.5, 133.2, 131.2, 123.2, 119.0, 111.1,

108.2, 106.6, 73.4, 61.3, 56.0, 46.4, 29.6, 28.3, 14.0.

2-(3-(2-Hydroxyethyl)-7-methoxybenzofuran-2-yl)pent-4-en-2-ol, 192.

To a solution of the tertiary alcohol ester **191** (18.9 mg, 0.059 mmol) in 0.24 mL of tetrahydrofuran at 0 ^{o}C was added diisobutylaluminum hydride (1M in hexanes, 148 μL, 0.148 mmol). After the reaction stirred for 2 h, a saturated solution of sodium tartrate (aq) was added and the biphasic mixture was stirred for 2 h. The organic layer was removed and the aqueous layer was further extracted with diethyl ether (5x). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified flash

column chromatography on silica gel (R_f = 0.25, 40% ethyl acetate in hexanes). The reduction product **192** was obtained as a colorless oil (14.5 mg, 0.0524 mmol) in 88% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

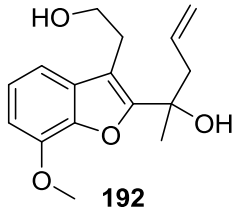
7.14 (dd, *J* = 7.9, 7.9 Hz, 1H)

7.03 (dd, *J* = 8.0, 0.8 Hz, 1H)

6.78 (d, *J* = 8.0 Hz, 1H)

5.82-5.69 (m, 1H)

5.14-5.04 (m, 2H)



192

4.00 (s, 3H)

3.83 (t, *J* = 6.0 Hz, 2H)

3.20-2.90 (m, 4H)

2.84 (dd, *J* = 13.7, 7.3 Hz, 1H)

2.57 (dd, *J* = 13.8, 8.1 Hz, 1H)

1.63 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.3, 145.1, 142.6, 133.5, 131.4, 122.9, 118.8, 111.4, 111.0, 106.5, 73.4, 61.2, 56.1, 46.6, 28.7, 25.7.

4-Hydroxy-1-phenylhex-5-en-1-one, 194.

To a solution of the vinyl lactone **162** (500 mg, 4.46 mmol) in 18 mL of THF cooled to -78 ^{o}C was added dropwise phenyllithium (1.8M in di-*n*-butyl ether, 2.48 mL, 4.46 mmol). The solution was stirred for 30 min before being allowed to warm to 22 ^{o}C. A saturated solution of sodium bicarbonate (aq) was added as well as an abundance of dichloromethane. The organic layer was removed and the aqueous layer was further extracted with dichloromethane (5x). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified flash column chromatography on silica gel (10% ethyl acetate in hexanes). The allylic alcohol **194** was obtained as a colorless oil (355 mg, 1.87 mmol) in 42% yield.

^{1}H NMR (400 MHz, C_6D_6) δ:

7.81-7.76 (m, 2H)

7.09-7.04 (m, 1H)

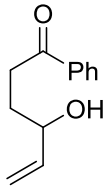
7.02-6.97 (m, 2H)

5.68 (ddd, *J* = 17.2, 10.5, 5.3 Hz, 1H)

5.12 (ddd, *J* = 17.2, 1.6, 1.6 Hz, 1H)

4.90 (ddd, *J* = 10.5, 1.8, 1.4 Hz, 1H)

4.00-3.94 (m, 1H)



194

2.74 (bt, J = 7.1 Hz, 2H)

1.98-1.72 (m, 2H).

^{13}C NMR (400 MHz, C_6D_6) δ: 199.2, 141.2, 137.1, 132.3, 128.1, 127.9, 113.6, 71.5, 33.9, 30.9.

6-Oxo-6-phenylhex-1-en-3-yl acetate, 195.

To a solution of the allylic alcohol **194** (316 mg, 1.66 mmol) and pyridine (0.40 mL, 4.97 mmol) in 6 mL of dichloromethane was added acetyl chloride (0.17 mL, 2.32 mmol) dropwise. The solution was stirred for 1 h before quenching with a saturated solution of sodium bicarbonate (aq). The organic layer was removed and the aqueous layer was further extracted with dichloromethane (5x). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes). The allylic acetate **195** was obtained as a colorless oil (309 mg, 1.33 mmol) in 80% yield.

^{1}H NMR (400 MHz, C_6D_6) δ:

7.77 (m, 2H)

7.12-7.07 (m, 1H)

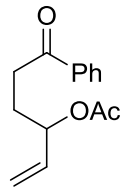
7.05-6.99 (m, 2H)

5.57 (ddd, *J* = 17.2, 10.6, 6.3 Hz, 1H)

5.35 (dddd, *J* = 6.3, 6.3, 6.3, 1.2 Hz, 1H)

5.10 (ddd, *J* = 17.2, 1.4, 1.4 Hz, 1H)

4.92 (ddd, *J* = 10.5, 1.4, 1.2 Hz, 1H)



195

2.62-2.56 (m, 2H)

2.00-1.93 (m, 2H)

1.61 (s, 3H).

^{13}C NMR (100 MHz, C_6D_6) δ: 197.5, 168.9, 137.0, 136.3, 132.3, 128.2, 127.7, 116.3, 73.5, 33.6, 28.2, 20.2.

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***trans* Phenyl(2-vinylcyclopropyl)methanone, 196.**

To a solution of the allylic acetate **195** (23.2 mg, 0.10 mmol) in 0.5 mL of dichloromethane was added DBU (37.7 μL, 0.25 mmol) and then tetrakis(triphenylphosphine)palladium(0) (11.6 mg, 0.01 mmol). The solution was stirred for ~1 h and then was applied directly to a column of silica gel prewetted with 5% diethyl ether in pentane. The compound of interest was further eluted using this solvent ratio. The vinylcyclopropyl ketone **196** was obtained as a colorless oil (3.9 mg, 0.0226 mmol) in 23% yield.

^{1}H NMR (300 MHz, C_6D_6) δ:

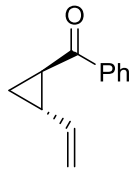
7.88-7.82 (m, 2H)

7.14-7.00 (m, 3H)

5.23 (ddd, *J* = 17.1, 10.1, 1.7 Hz, 1H)

4.94 (dd, *J* = 17.0, 1.6 Hz, 1H)

4.87 (app. dd, *J* = 10.1, 1.6 Hz, 1H)



196

2.31 (ddd, *J* = 9.3, 5.1, 3.8 Hz, 1H)

2.27-2.18 (m, 1H)

1.70 (ddd, *J* = 8.7, 5.1, 3.7 Hz, 1H)

0.77 (ddd, *J* = 8.0, 5.5, 3.7 Hz, 1H).

^{13}C NMR (126 MHz, C_6D_6) δ: 196.9, 138.5, 138.0, 132.2, 128.3, 128.0, 114.3, 28.8, 26.2, 17.4.

(7-Methoxybenzofuran-2-yl)(*trans*-2-ethenylcyclopropyl)methanone, 197.

To a solution of the allylic acetate **164** (100 mg, 0.331 mmol) in 1.65 mL of dichloromethane was added DBU (54.4 μL, 0.364 mmol) and then tetrakis(triphenylphosphine)palladium(0) (22.9 mg, 0.0199 mmol). The solution was stirred for ~1 h and then was applied directly to a column of silica gel prewetted with ethyl acetate in hexanes. The compound of interest was further eluted using this solvent system. The

vinylcyclopropyl ketone **197** was obtained as a colorless oil (19.2 mg, 0.0793 mmol) in 24% yield.

^{1}H NMR (400 MHz, C_6D_6) δ:

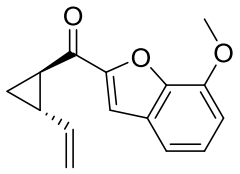
7.20 (s, 1H)

6.96 (d, *J* = 3.2 Hz, 1H)

6.95 (d, *J* = 5.6 Hz, 1H)

6.49 (dd, *J* = 5.7, 3.3 Hz, 1H)

5.14 (ddd, *J* = 17.1, 10.2, 8.5 Hz, 1H)



197

4.97 (ddd, *J* = 17.0, 1.7, 0.5 Hz, 1H)

4.83 (ddd, *J* = 10.1, 1.7, 0.5 Hz, 1H)

3.40 (s, 3H)

2.74 (ddd, *J* = 8.2, 5.1, 3.9 Hz, 1H)

2.34 (dddd, *J* = 8.5, 8.5, 6.4, 3.8 Hz, 1H)

1.65 (ddd, *J* = 8.7, 5.1, 3.7 Hz, 1H)

0.78 (ddd, *J* = 8.1, 6.4, 3.8 Hz, 1H).

^{13}C NMR (126 MHz, C_6D_6) δ: 188.3, 153.8, 146.2, 145.5, 138.2, 129.1, 124.2, 114.8, 114.4,

111.2, 108.9, 55.1, 29.1, 26.6, 17.9.

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