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Matthew James Jones Date

Synthetic Studies Toward Cyclobutyl Nucleoside Analogs for the Treatment of Hepatitis C Virus

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Synthetic Studies Toward Cyclobutyl Nucleoside Analogs for the Treatment of Hepatitis C Virus

By

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B.S., University of North Georgia, 2013

Advisor: Dennis Liotta, Ph.D.

An abstract of a thesis submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
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Abstract

Synthetic Studies Toward Cyclobutyl Nucleoside Analogs for the Treatment of Hepatitis C Virus

By Matthew J. Jones

Computational evaluations of novel cyclobutyl nucleoside analogs for the targeting of the hepatitis C virus (HCV) NS5B Rdrp led to the investigation of synthetic routes towards several target molecules. This work sought to determine a viable synthetic strategy for a highly functionalized cyclobutane core that was amenable to late stage elaboration for thorough SAR studies. Several strategies were evaluated, ultimately revealing the stereoselective [2+2] ketene cycloaddition with Stericol offering the most promising route despite several late-stage difficulties stemming from the labile auxiliary. An achiral route was initially employed that failed to allow facile α-functionalization to the intermediate cyclobutanone. Instead, performing the cycloaddition with a disubstituted enol ether removed the requirement for α-functionalization, and use of the chiral Stericol would provide the added benefit of stereoselective construction of the cylcobutyl ring. Further synthetic efforts provided an advanced intermediate that would allow for the investigation of different fluorination strategies once the critical Wittig olefination stage is optimized, at which point subsequent glycosylation and phosphorylation would yield analogs suitable for testing in an HCV replicon assay.

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Introduction

1.1 Cyclobutyl Nucleoside Analogs

The discovery of oxetanocin A (Figure 1a) marked the beginning of a decades long interest in cyclobutyl nucleoside analogs.[1] Isolated from *Bacillus megaterium*, this novel analog showed potent activity against HIV, which led to the synthetic and medicinal evaluation of nucleoside analogs bearing a cyclobutane core.[2] While other oxetane-containing nucleosides were

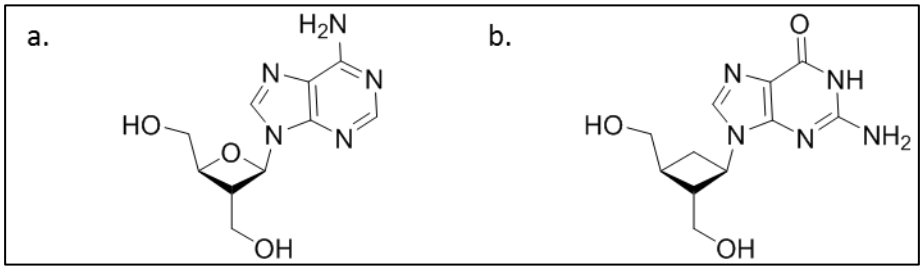
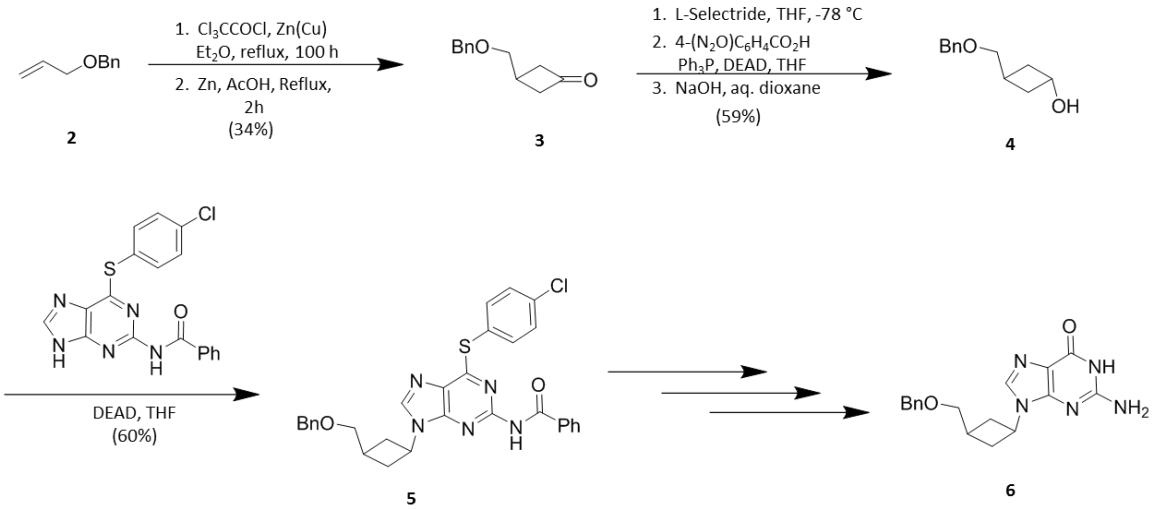


Figure 1. Structures of (a) oxetanocin-A and (b) Cyclobut-G

subsequently synthesized and studied, efforts leading to Cyclobut-G (Figure 1b) provided compelling evidence that analogs bearing the cyclobutyl carbocycle would be of great therapeutic value.[3,4,5] Towards this end, a number of synthetic approaches were undertaken to construct these analogs, chief among which is the [2+2] thermal cycloaddition with dichloroketene. Other methods have been developed, including Lewis acid-mediated cycloadditons with various ketene acetals, ring expansion of cyclopropyl precursors, ring contractions, and intramolecular cyclization, which are briefly discussed below

1.2 Synthetic Routes Towards Cyclobutyl Nucleoside Analogs

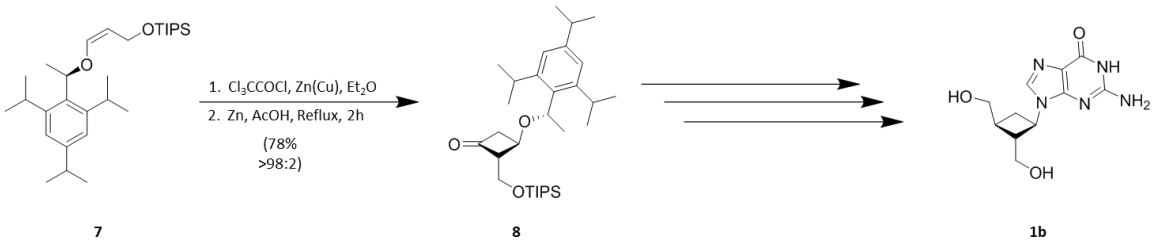
The [2+2] ketene cycloaddition has been used to generate four-membered rings since the discovery of the Staudinger synthesis, whereby a β-lactam was formed by reaction of a substituted ketene with an imine.[6] Later work investigating the synthetic utility of ketene additions revealed that the non-photochemical cycloaddition could be performed with other ketenophiles, including carbonyls to form β-lactones, alkenes to form cyclobutanones, and alkynes to form cyclobutenes. Early pioneers of this work demonstrated the perispecificity of these reactions as well as the underlying mechanistic pathways. Studies by William Brady and others during the 70's probed the utility of these cycloadditions in forming four-membered rings by reaction of olefins and vinyl ethers with *in situ* generated dichloroketene.[7,8] These reports showed that a number of cycloaddition substrates could be utilized, and his general procedure for this reaction provided the method commonly used today. This work demonstrated that the cycloaddition reaction could be performed using terminal olefins, as well as di-, tri-, and tetra-substituted alkene starting materials, though the rate of reaction



Scheme 1. Synthesis of a cyclobutyl nucleoside analog via [2+2] ketene cycloaddition

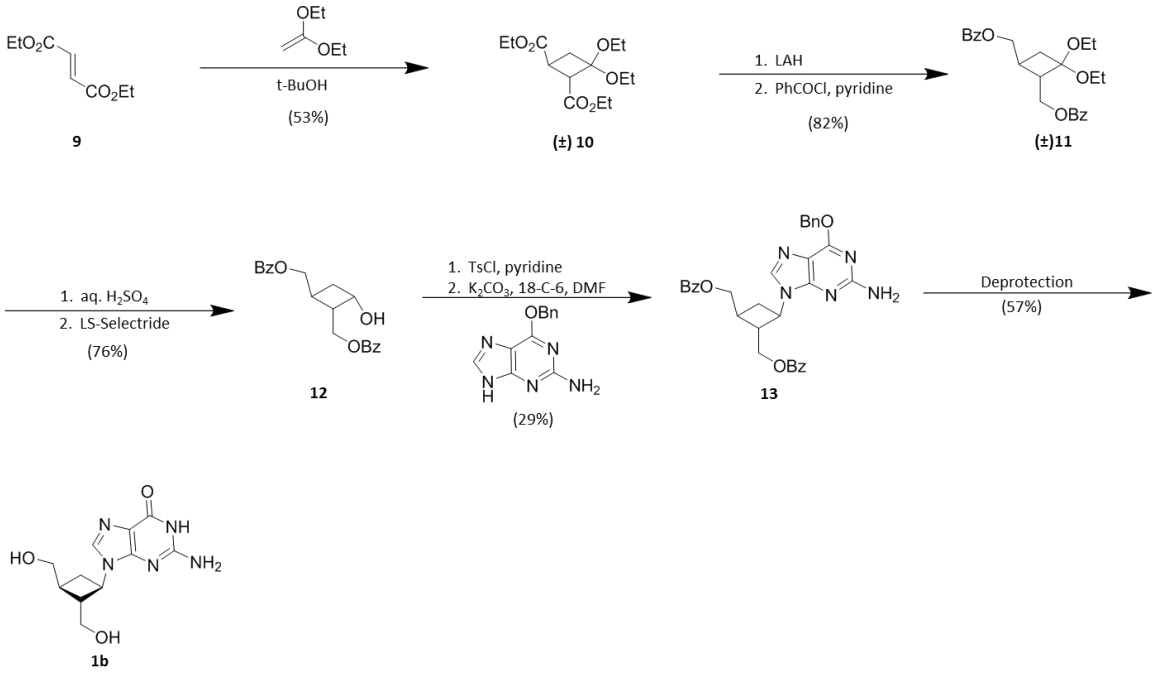
decreases with greater substitution. Additionally, it was observed that the E-olefins react less rapidly than their Z isomers. Still, this has proven to be one of the most reliable methods for construction of substituted cyclobutane rings.

Other efforts to synthesize cyclobutyl nucleoside analogs have utilized this route, including studies by Reese *et. al.* to examine analogs lacking the 2'-hydroxymethyl (Scheme 1).[9] This synthesis began with the 2+2 cycloaddition of allyl benzyl ether followed by zinc-mediated dechlorination to afford cyclobutanone 2 in 51% overall yield. The ketone was next reduced by L-Selectride to afford a 20:1 mixture of cis and trans alcohol, as hydride delivery occurs preferentially on the less hindered face of the molecule. Subjecting the mixture of alcohols to Mitsunobu conditions then allowed for isolation of the crystallized trans alcohol, which could be activated and then displaced with the desired purine base. While this analog did not display the antiviral activity hoped for, it was among the first nucleoside analogs to be made using the [2+2] cycloaddition with dichloroketene. More recently, Darses and coworkers have adapted an enantioselective dichloroketene cycloaddition using Stericol to synthesize a number of chiral cyclobutanones as well as Cyclobut-G (Scheme 2).[10] In a one-pot procedure, chiral enol ether 7 was subjected to dichloroketene, and the resulting dichloro species was subsequently de-chlorinated by refluxing in methanolic ammonium chloride to afford the α-substituted cyclobutanone.



Scheme 2. Asymmetric synthesis of Cyclobut-G via Stericol, a chiral auxiliary

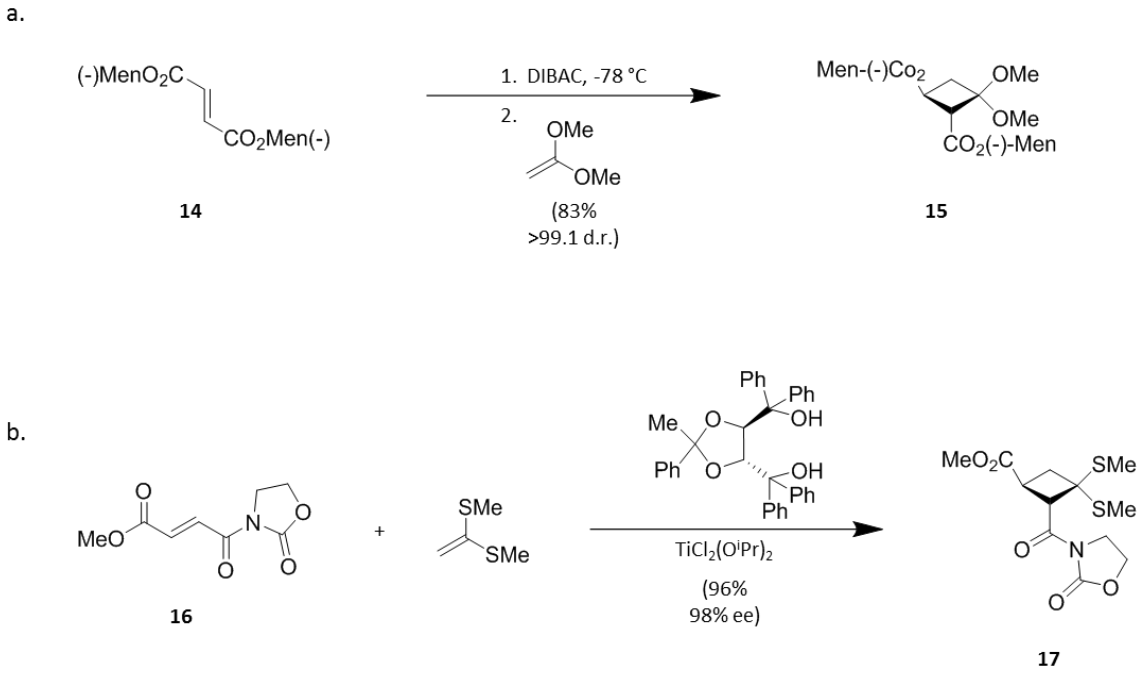
A number of [2+2] cycloaddition reactions have also been studied using instead ketene acetals, such as Bristol-Meyers Squib's (BMS) early achiral route to Cyclobut-G (BMS-180194, Scheme 3).[11] In this synthesis, a thermal [2+2] cycloaddition between diethyl fumarate and ketene diethyl acetal in t-BuOH at 84 °C furnished the racemic cyclobutane diester **11** in 53% yield. Following ester reduction, benzoylation, and acidolysis of the acetal, stereoselective reduction of the resulting ketone afforded the α-hydroxy isomer in 92% yield. The guanine base could then be appended, and racemic Cyclobut-G synthesized after two deprotection steps (5.4% yield over 11 steps). Motivated by earlier reports of asymmetric Diels-Alder cycloadditions utilizing dimenthyl fumarate, a chiral route was developed by BMS employing a Lewis acid-mediated [2+2] cycloaddition (Scheme 4a).[12] Reaction between dimenthyl fumarate and dimethyl ketene acetal in the presence of diisobutylaluminum chloride (DIBAC) afforded the cycloadduct in 83% yield and greater than 99:1 diasteromeric excess after recrystallization. Following the same synthetic transformations as the achiral route, Cyclobut-



Scheme 3. Bristol-Meyers Squib's achiral route to Cyclobut-G

G could be made on kilogram scale quantities in 35-40% overall yield over 10 steps. Around the same time, Hayashi and coworkers developed a route to enantioenriched cyclobutanones via a chiral Lewis acid-mediated cycloaddition in which the desired cycloadduct was formed in 96% yield and 98% ee (Scheme 4b).[13]

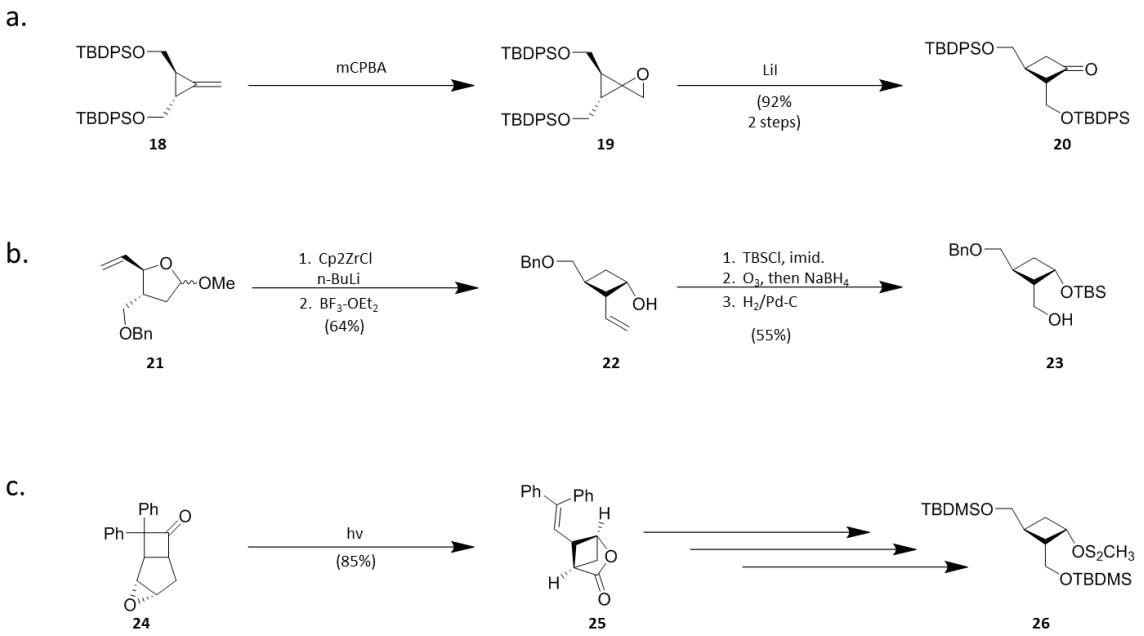
Hannick soon reported an intriguing asymmetric synthesis of the Cyclobut-G protected cyclobutanone precursor via an oxaspiropentane rearrangement using Feist's acid (Scheme 5a).[14] In this route, resolution of the chiral Feist's acid was followed by conversion to the diester and then the diol. After silylation, the methylenecyclopropane 18 was epoxidized to the oxaspiropentane, which next underwent facile rearrangement to form the optically pure,



Scheme 4. (a) Diasteroselective Lewis acid-mediated cycloaddition of dimenthyl fumarate (b) Enantioselective synthesis with a chiral Lewis acid.

protected cyclobutanone (32% overall yield). Shortly thereafter, Taguchi *et. al.* showed that another optically active precursor to Cyclobut-G could be prepared by the zirconium-mediated ring contraction of 4-vinylfuranoside (Scheme 5b).[15] By subjecting 2-deoxy-4-

vinylfuranoside to *in situ* generated zirconocene in the presence of BF_3•OEt_2, the resulting cyclic (Z)-allylic zirconium species adds intramolecularly to the oxocarbenium, yielding the cyclobutanol adduct in 64% yield. Following silylation of the secondary alcohol, ozonolysis, and reduction of the aldehyde, deprotection of the benzyl ether affords the optically pure diol. Lastly, Cotterill and Roberts reported a procedure by which photolysis of an optically active expoxidized bicyclo[3.2.0]heptanone derivative yielded a lactone intermediate that was readily converted to the cyclobutane core following methanolysis (Scheme 5c).[16]



Scheme 5. (a.) Cyclobutanone construction via a LiI-catalyzed oxaspiropentane rearrangement (b.) Synthesis of a cyclobutanol intermediate by ring-contraction promoted by zirconocene (c.) Photolytic procedure for cyclobutyl core formation.

1.3 Hepatitis C Virus

Each year, approximately 3-4 million people globally are infected with hepatitis C virus (HCV), while an estimated 350,000-500,000 deaths are attributed to complications stemming

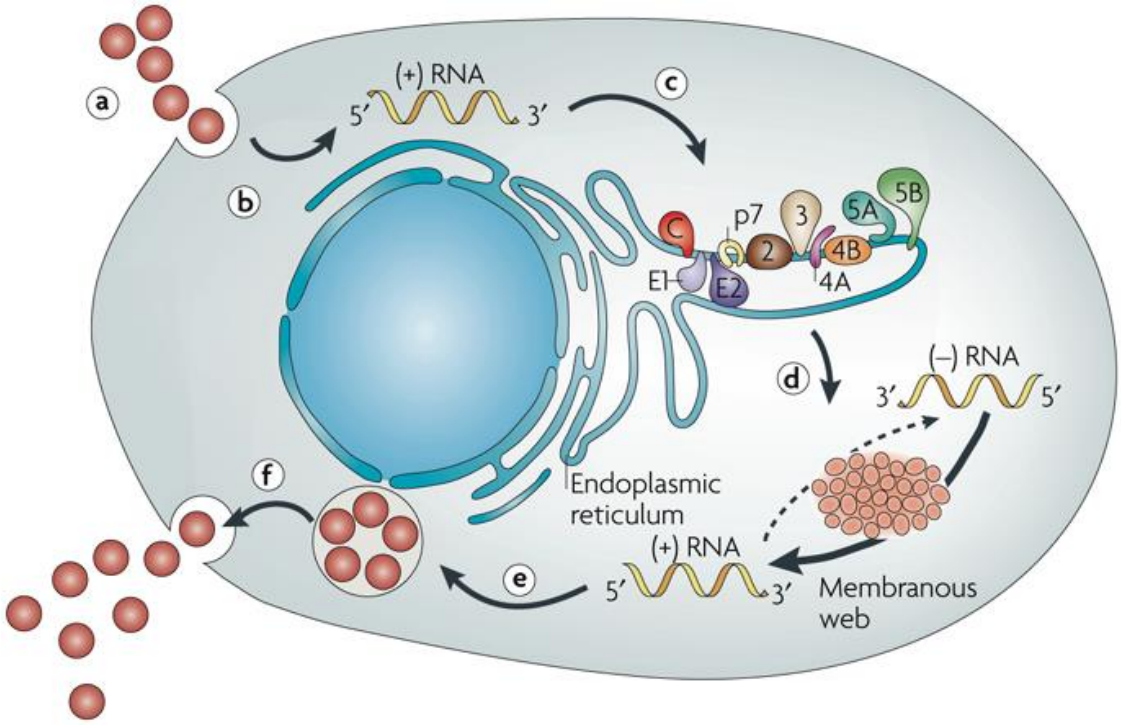


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Figure 2. Viral binding and entry (a); uncoating (b); translation of viral RNA and assembly of viral replication complex (c); RNA replication (d); assembly of daughter virion (e); viral release.

from the virus.[17] Symptomatic acute viral infection is observed in 20% of cases, and 85% of that population will progress to chronic infection, which leads to an elevated risk of cirrhosis and hepatocellular carcinoma (HCC).[18] While HCV infection has been significantly reduced in Western countries with the advent of improved screening methods, areas such as East and Central Asia, the Middle East, and North Africa have higher rates of infection, with Egypt having the highest (15-20% of the population).[19] Viral transmission occurs by contact with infected blood, primarily through unscreened blood transfusions, unsterilized medical equipment, and shared needle use among injection drug users. Perinatal transmission has been documented, and it can be spread sexually, though this is believed to be less common.[20] Additionally, coinfection with HIV has been shown to accelerate progression to liver disease.[21]

Hepatitis C virus is a member of the *Hepacivirus* genus within the family *Flaviridae*, which includes Yellow fever virus, dengue virus, and tick-borne encephalitis virus, among others, and is only known to infect humans and chimpanzees.[22] There are six major genotypes (1-6), which differ in nucleotide sequence by 30-35%.[23] Within each genotype are various subtypes, which in turn differ by 20-25% in nucleotide sequence. The viral genome consists of a 9.6 kb positive sense, single-stranded RNA (ssRNA) molecule encased by a nucleocapsid composed of core protein that is itself enclosed in a host cell-derived, double layer lipid membrane adorned with envelope glycoproteins E1 and E2.[24] Once a patient is exposed to the virus, it can associate with low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) to provide transport to the liver.[25]

Cellular entry is facilitated by host receptors, via attachment by the viral E1 and E2 proteins.[26] These surface proteins orchestrate viral attachment to the host cell, at which time clathrin-mediated endocytosis allows for cellular entry (Figure 2). Acidification of the viral-laden endosome is then postulated to effect the presentation of a viral fusion peptide. This fusion peptide can next coordinate the fusion of the viral envelope to the endosome, allowing for delivery of the viral genome to the cytosol. The viral RNA can then bind the ribosomal subunits and necessary cellular complexes, at which point the viral polyprotein will be translated. Co- and post-translational processing furnishes the mature proteins necessary for viral replication, assembly, and maturation.[27] Chief among the clinical targets of HCV, the NS5B RNA-dependent RNA polymerase (RdRp) is one of the six nonstructural proteins encoded in the viral genome and, once translated, is the catalytic unit of the viral replication complex.[28] This unit is vital to the survival and proliferation of HCV, and already success has been realized in the clinic with NS5B inhibitors.[29]

1.4 Project Goals

Our interest in cylobutyl nucleoside analogs stems from modeling work performed by Dr. Bryan Cox (Table 1). For our model, the geometry of pyrimidine nucleosides in the active site of NS5B was used as a template for docking acyclic nucleotide analogs. By shape-similarity, the highest scoring compounds are expected to reside in the same three-dimensional space and form complementary interactions like endogenous nucleotides. After modeling thousands of conformations of the proposed compounds, those with low energy conformations that displayed high degrees of shape similarity were considered for further examination. These analogs were also studied *in silico* with the cytidine monophosphate kinase enzyme (CMPK), which effects the phosphorylation of monophosphate nucleosides. It is expected that analogs with high shape similarity scores for both enzymes will be readily phosphorylated to the active nucleoside, which can then be incorporated into the replicating RNA strand. Of the analogs

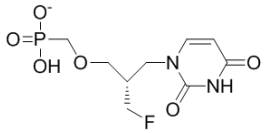
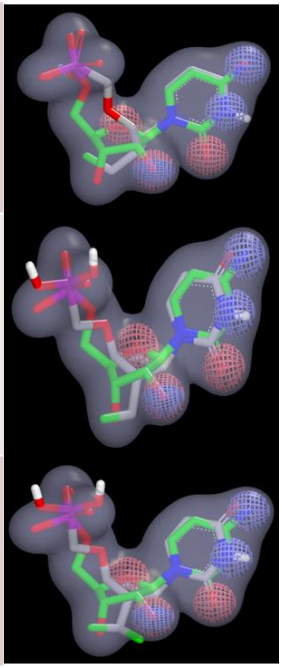
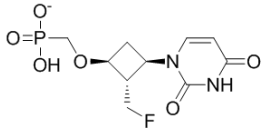
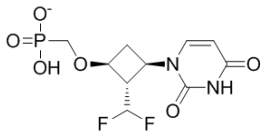
	NS5B:UT(m)P	CMPK:CD(m)P	
	**0.882**	**0.821**	
	**0.917**	**0.861**	
	**0.936**	**0.852**	

Table 1. Example docking scores for phosphonate nucleotide analogs.

studied, several cyclobutyl nucleosides were found to dock favorably to both NS5B and CMPK (Figure 3). This led to current efforts in the synthesis of novel cyclobutyl nucleoside analogs for the treatment of HCV.

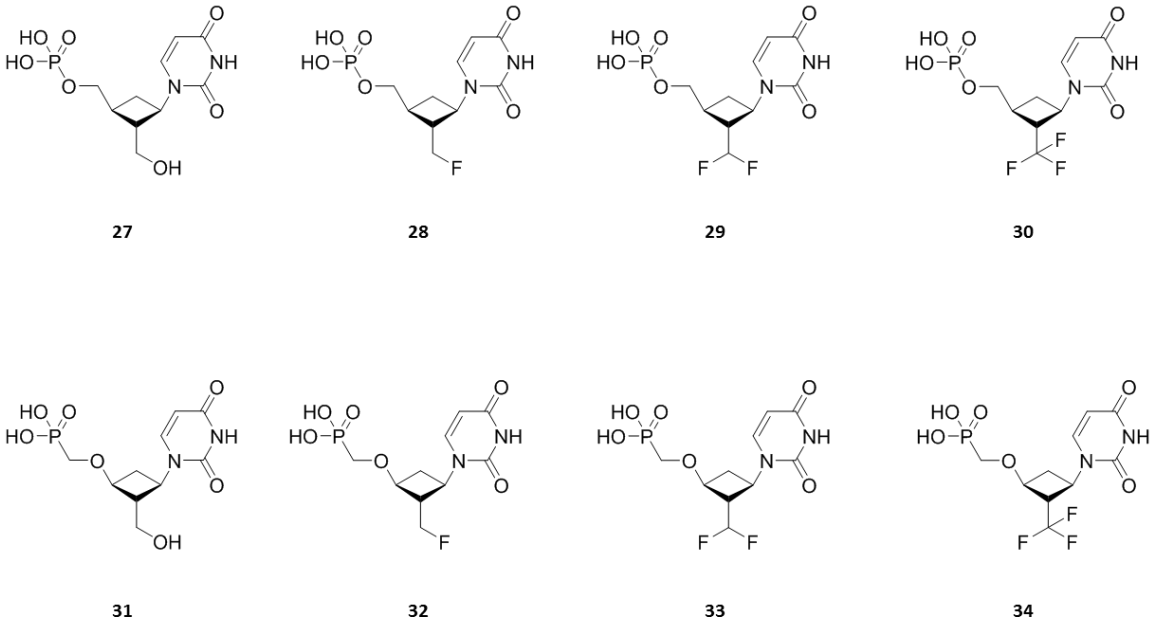


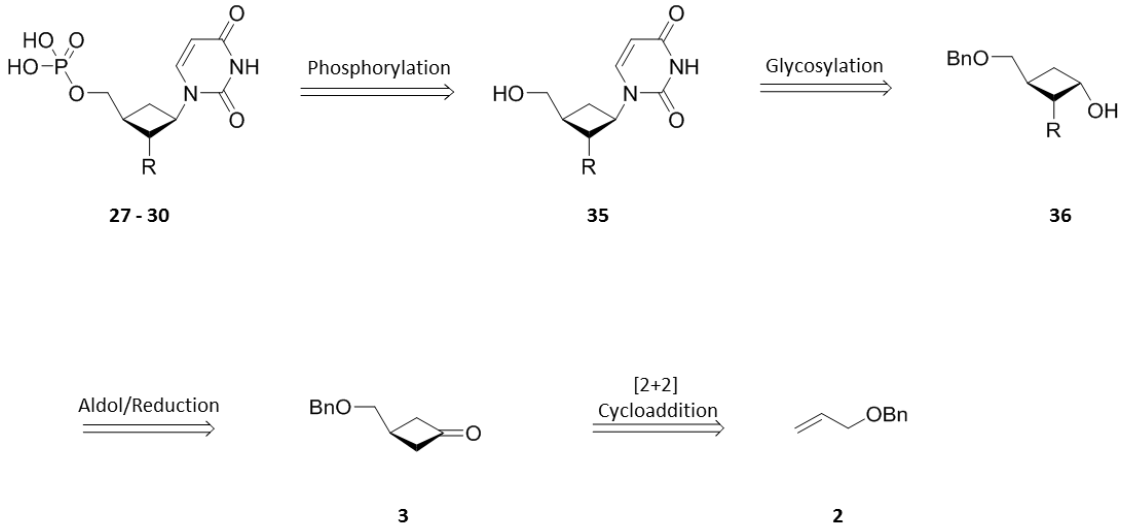
Figure 3. Target cyclobutyl analogs derived from shape-similarity model.

The goals of this project were to synthesize a set of analogs predicted computationally to bind favorably to the HCV Rdrp as well as undergo efficient phosphorylation by endogenous CMPK and to develop a synthesis that will allow for the elaboration of a diverse family of cyclobutyl nucleoside analogs for structure-activity relationship (SAR) studies.

2. Results and Discussion

2.1 Initial Synthesis Efforts via an Achiral Route

Two retrosynthetic analyses were utilized for synthesis of the phosphate series (27 – 30). The first route (Scheme 6) envisioned the target nucleoside coming from displacement of the activated alcohol by protected uridine at the 1' position and subsequent global deprotection. Alcohol 36 would arise from reduction of ketone 3 following functionalization at the α position by aldol chemistry. The starting cyclobutanone intermediate would be furnished by the [2+2] dichloroketene cycloaddition with allyl benzyl ether.



27 - 30 **35** **36**

3 **2**

Scheme 6. Retrosynthetic analyses for the construction of target analogs (R= CH_2OH, CH_2F, CHF_2, and CHF_3).

Towards the first route, synthesis began with the Williamson ether synthesis to make allyl benzyl ether in good yield (Scheme 7). The cycloaddition was next performed, though yields were generally poor. Typically, starting allyl benzyl ether remained after the prescribed 96-hour reaction time. Purification by distillation and column chromatography facilitated decomposition of the gem-dichlorocyclobutanone 38 into a brown tar, so the material was carried over to the dechlorination step crude. This provided yields of 20-32% after purification by column chromatography, however previous work on this reaction in our lab suggested the it is sensitive to the Zn(Cu) couple used. The literature provides several methods for its preparation, and after several trials, a suitable method was found. Best results are

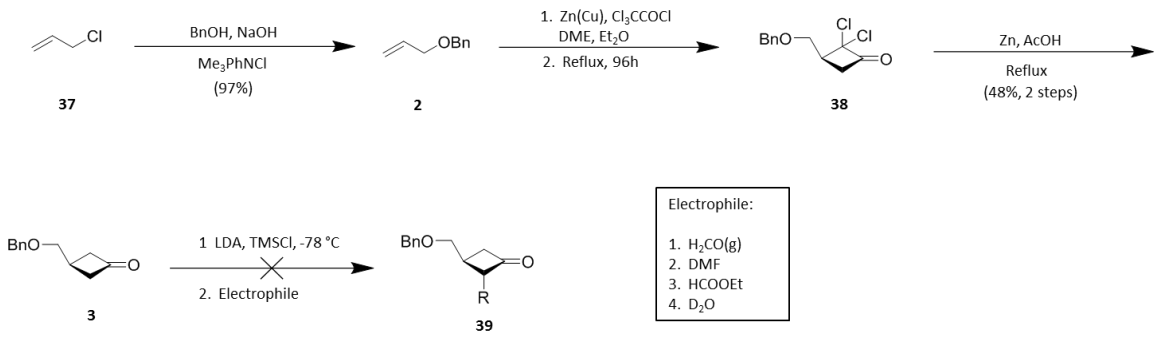
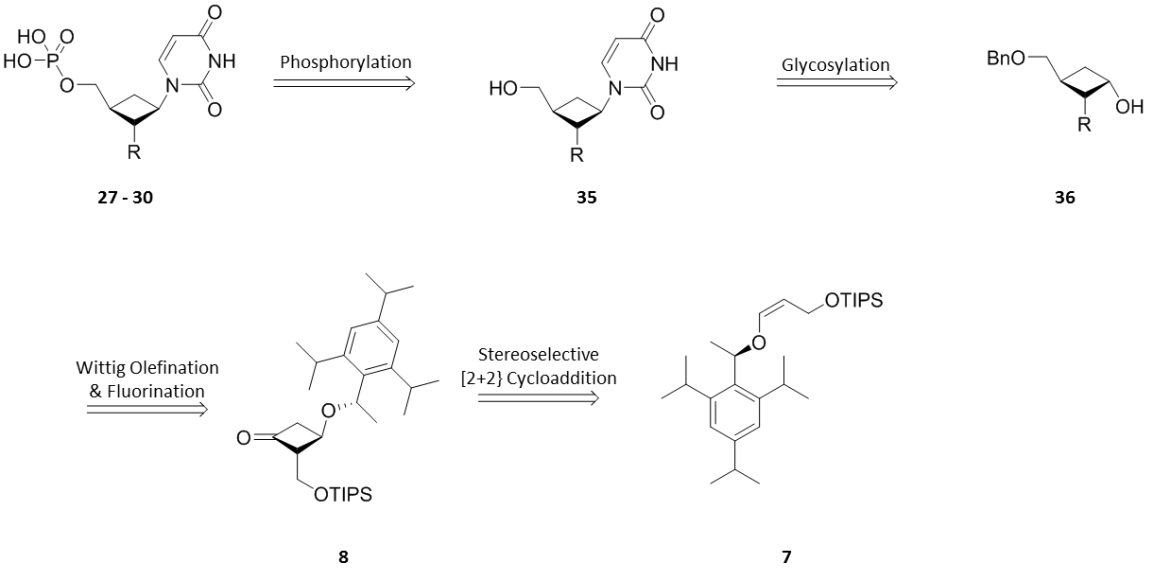


Figure 7. Synthesis of cycobutyl core and attempted functionalization.

achieved when Cu content is 28-32% of the couple, ultimately resulting in a 48% yield over two steps, which is in accordance with literature reports. Functionalization at the α position was attempted by treatment with LDA and TMSCl following a published method.[30] After addition of TMSCl to trap the enolate, formaldehyde was added by the thermal decomposition of paraformaldehyde. During addition, the formaldehyde regularly polymerized in the reaction vessel as well as the transfer needle, and neither the desired product nor starting material were observed. To rule out the possibility of insufficient electrophile entering in solution, methyl chloroformate was used, however, no product was observed and instead a complex mixture of decomposition products was obtained with no material containing the four-membered ring. To determine if decomposition was occurring prior to addition of the electrophile, a deuterium quenching study was performed. After stirring in the presence of LDA, D_2O was added and following workup, no deuterium-enriched product was observed. Instead, all starting material was consumed (by TLC), and a complex mixture containing no discernable cyclobutyl byproducts was observed by NMR. Variations on this reaction were attempted using different bases, however, each led to decomposition. Due to the difficulty in functionalization at the α position as well as the lack of stereochemical control, this route was not pursued further.

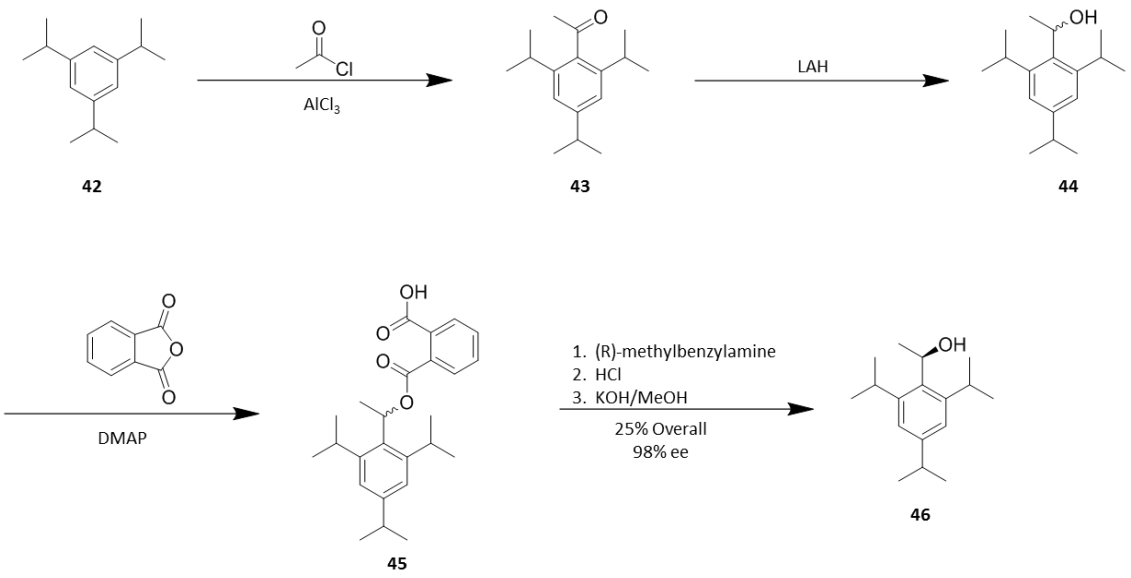
2.2 Adoption of an Asymmetric Method via Stericol

While the achiral route was investigated, an asymmetric method was found that appeared applicable to both the phosphate and phosphonate series.[10] This route (Scheme 8) instead utilizes enol ether 7 and allows for construction of the α-substituted cyclobutanone intermediate during the cycloaddition step. This "pre-functionalization" at the α position obviated the need for aldol chemistry on the strained cyclobutanone, though access to the enol



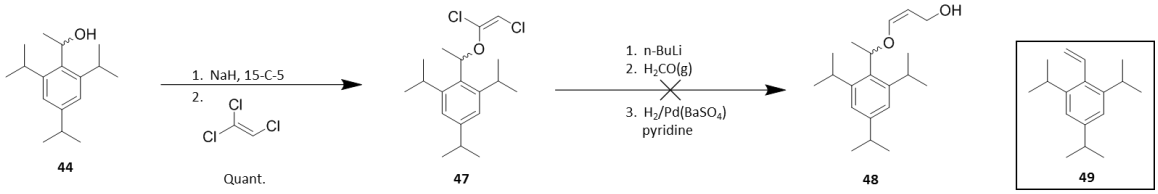
Scheme 8. Retrosynthetic analysis using enantioselective [2+2] cycloaddition method (R= CH_2OH, CH_2F, CHF_2, and CHF_3).

would eventually be desired to further functionalize both sides of the ketone for SAR studies. The chiral alcohol, Stericol, was constructed by literature methods (Scheme 9).[31] First, triisopropylbenzene was treated with acetyl chloride in the presence of $AlCl_3$ to furnish ketone 43. Following reduction by LAH, acylation with phthalic anhydride yielded acid 45. Chiral resolution using (R)-methylbenzylamine provided the chiral salt, which was then treated HCl, and then refluxed with KOH in methanol to afford the chiral alcohol in 25% overall yield and 98% ee. It should be noted that this material was quickly consumed in the next stages, so the quickly prepared racemic alcohol was then used for all further steps while this chemistry was



Scheme 9. Construction of (R)-Stericol

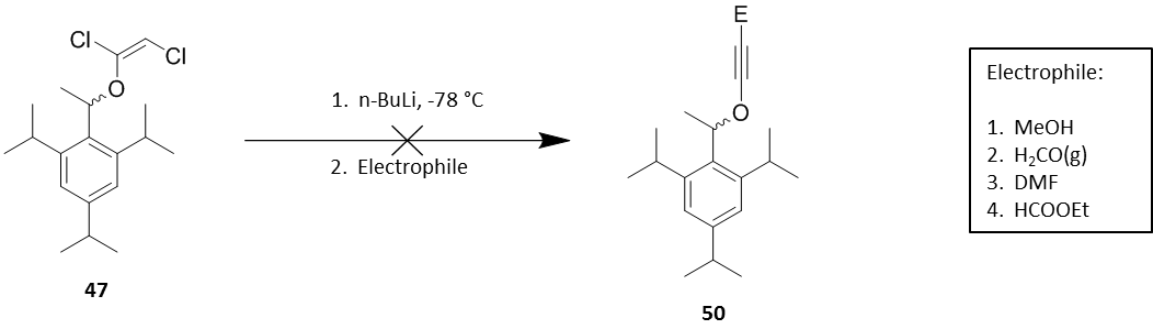
being explored (Scheme 10). The dichloroenol ether was next made, though with a modification in procedure. To avoid using KH for scale up, it was found that NaH in the presence of 15-Crown-5 led to improved yields over the published methods, even on decagram quantities. This dichlorovinyl ether was then used to form enol ether 48, though this step proved rather problematic. The first issue arose from difficulties in providing gaseous formaldehyde generated from the thermal decomposition of paraformaldehyde to the reaction vessel. Cannulas were regularly clogged by repolymerization, so an apparatus was developed using wide-diameter glass tubing. Once it was apparent that formaldehyde was added to the lithiated acetylide, quenching the remaining n-BuLi with methanol caused repolymerization of the unreacted formaldehyde in solution. This transformed the entire reaction mixture to a gelatinous solid beyond saving. This was remedied by adding first the pyridine needed for the hydrogenation step and then methanol. Hydrogenation over Pd($BaSO_4$) was then attempted, and the three-step reaction yielded only styrene derivative 49 in large quantity (79% yield).



44 47 48 49

Scheme 10. Initial attempt at forming cycloaddition starting material.

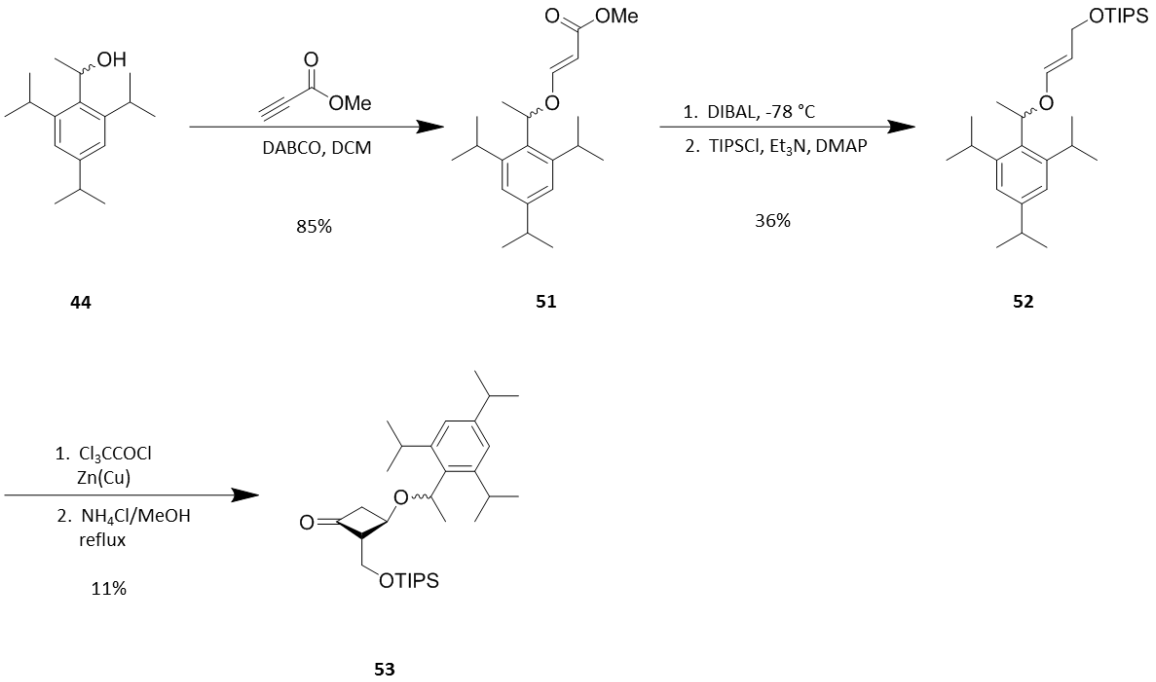
This troubling result led to an investigation of alternative routes to the desired alcohol, which would ideally be more step-wise and scalable (Scheme 11). The first attempt was to form the ynol ether by quenching the lithiated acetylide with methanol. This led to the isolation of 49, so instead we moved to isolate the propargylic alcohol, aldehyde, and ester. Every attempt led to isolation of 49, demonstrating the thermal lability of the ynol ether formed. In all instances, tracking the reaction by IR indicated successful formation of the substituted ynol ether (2100 – 2300 cm^{-1}), however it appeared that elimination upon warming was occurring and hydrogenation must immediately follow addition of the electrophile. New bottles of catalyst were purchased, as this appeared to be the problematic step in the sequence, but little to no alcohol was observed. When it could be seen by crude NMR, the reported column conditions were not sufficient to purify what little amount of alcohol was formed. Additionally, Pd-C and Lindlar's catalyst were sampled, but to no avail.



47 50

Scheme 11. Attempted synthesis of ynol ethers. In all instances, elimination occurred upon warming to room temperature.

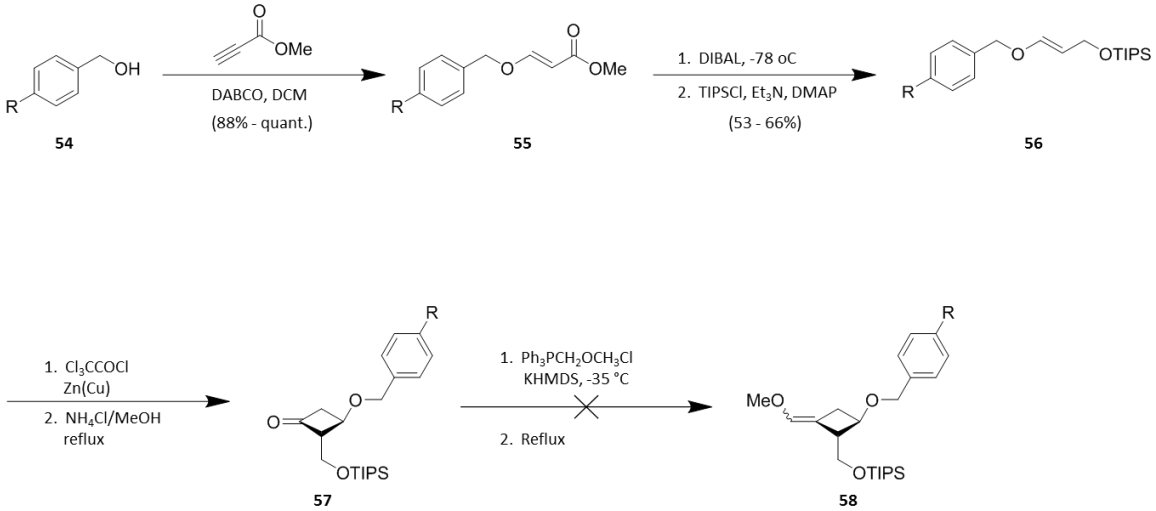
2.3 Model System Synthesis



Scheme 12. Synthesis of trans cyclobutanone.

While this reaction was being investigated, Dr. Rhonda Moore began developing an alternative route using trans-vinyl ethers (Scheme 12). Her synthetic route was then adopted to quickly generate the necessary cyclobutyl intermediates, though at the expense of an additional future step (inversion of the alcohol prior to appending the base). Stericol was treated with methyl propiolate in the presence of DABCO to afford the vinylogous carbonate 51 in 85% yield. DIBAL reduction furnished the alcohol, which was next TBS-protected. Though only small amounts of this enol ether were made, the cycloaddition was next attempted. While crude NMR showed the desired cycloadduct, purification of any material containing the chiral auxiliary remained problematic, resulting in low yields. As we continued to remedy this issue, it was decided a model system would be developed in order to generate the target molecules and study our fluorination strategy, though as the racemate.

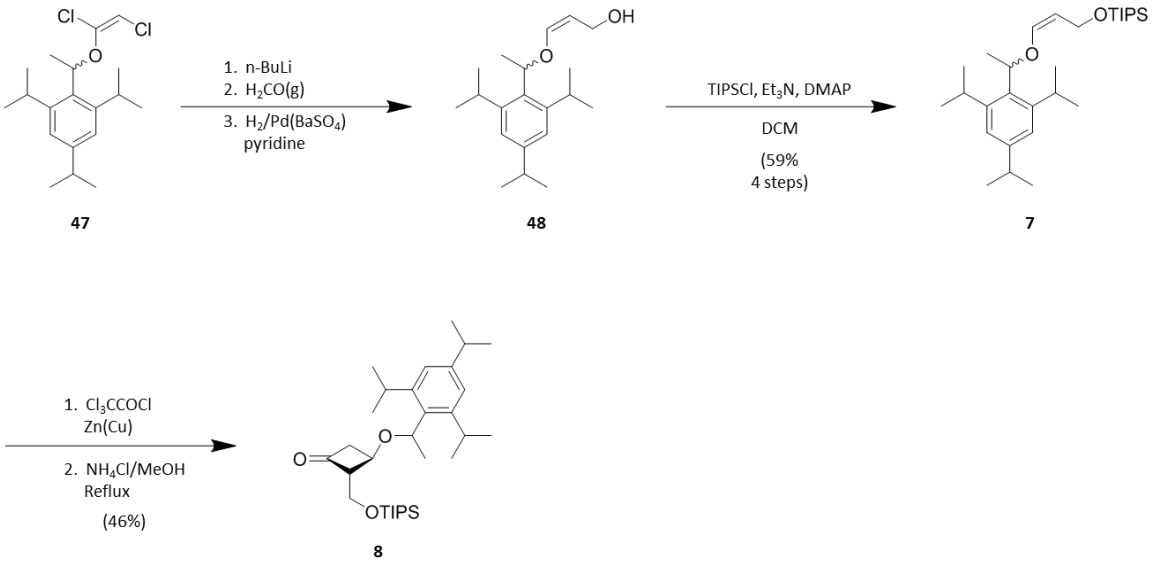
Following the same procedure as above, the vinylogous carbonates from benzyl and paramethoxybenzyl alcohol were made, followed by reduction and silylation (Scheme 13). These substrates were then subjected to cycloaddition conditions, resulting in a complex reaction mixture. Attempts at purification by column chromatography and distillation prohibited acceptable spectral confirmation of the desired cylclobutanones, though HRMS data indicated their presence, along with the mono- and di-chlorinated species. Because Dr. Moore's targets were the phosphonate analogs, treatment with L-Selectride provided a reaction mixture with the chromatographic resolution necessary for clean separation. For the phosphate targets, however, the next step was the Wittig reaction with methoxymethylphosphine. The crude mixture was carried over to this step, but no product formation was observed by NMR and HRMS. While reduction of the cyclobutanone mixture and then oxidation back to the ketone after purification could be performed to isolate the desired material, this seemed too cumbersome for a model system and was not attempted.



Scheme 13. Model system for investigation of cycloaddition conditions and later transformations (R = H, OMe).

2.4 Synthesis of an Advanced Intermediate

Fortunately, reexamination of the catalytic hydrogenation of the chiral Z-enol ether proved fruitful. After trying several new bottles of Pd($BaSO_4$) from Strem Chemicals, catalyst purchased from Sigma-Aldrich allowed for reliable generation of the desired alcohol with no



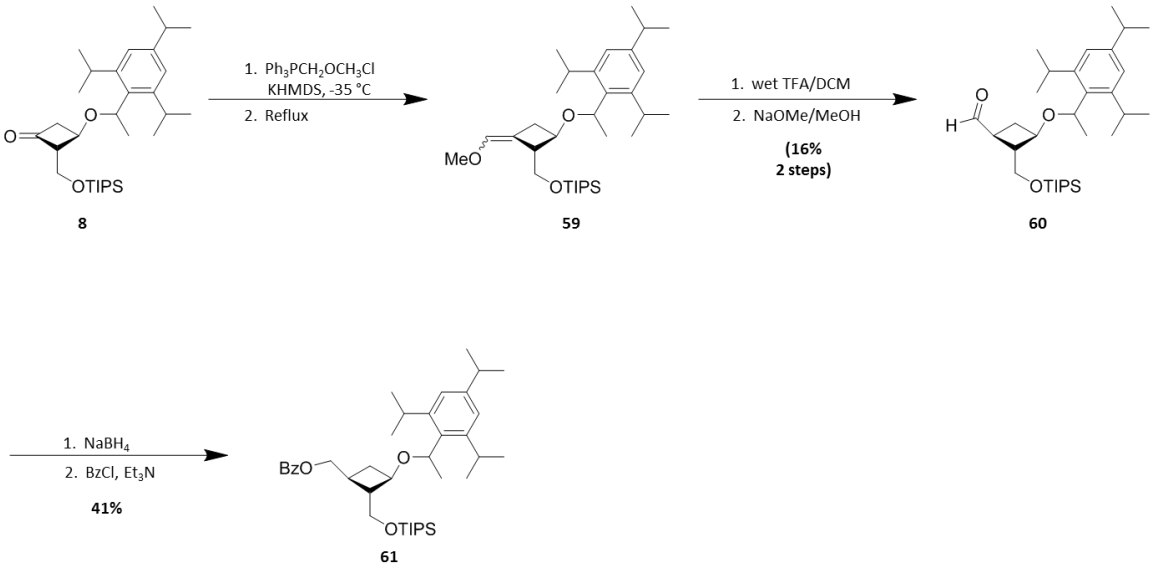
Scheme 14. Successful construction of desired cyclobutanone.

formation of styrene derivative 49. This reaction is best performed with careful temperature control and monitoring by IR. Consumption of the transient ynol ether is judged complete once IR analysis of the crude reaction mixture shows no band at 2260 cm^{-1}. Purification of the alcohol by the reported method suffers from elimination of the chiral auxiliary despite the use of ammonium hydroxide, and the styrene derivative observed in earlier stages is present as a contaminant. To bypass this issue, subjecting the crude alcohol to TIPS-protection furnishes a quick-eluting material and no observable degradation on the silica. Following this procedure, decagram scale quantities can be quickly prepared in yields comparable to those reported in the literature. (Scheme 14).

Following the successful synthesis of the requisite chiral substrate, the [2+2] cycloaddition was next performed. Unlike the previous, achiral cycloaddition, this procedure

uses a two-step, one pot method developed by Dharses et. al. Following dropwise addition of trichloroacetyl chloride to enol ether and Zn(Cu) couple and stirring at room temperature for 30 minutes, the gem-dichlorocylobutanone is cleanly dechlorinated by the addition of methanolic ammonium chloride and refluxing for 45 minutes. This cycloaddition was achieved in 32 – 46% yield, could be completed in less than 2 hours whereas over 90 hours were needed for the allyl benzyl ether substrate.

With the requisite ketone in hand, elaboration of the 3' methylol was attempted via Wittig olefination with $Ph_3PCH_2OCH_3Cl$ and KHMDS (Scheme 15). This reaction was very low yielding (approximately 39% with impurities) and difficult to purify. As with nearly every preceding step, 1,3,5-triisopropyl-2-vinylbenzene was observed before purification. Though exocyclic olefins on cyclobutane systems are known in the literature, none bear an appendage as labile as the chiral auxiliary in this system.[30] The formation of the phosphonium ylide was investigated using 2-indanone and following the same procedure, yielding the homologated



Scheme 15. Elaboration of core substituents

species in 56% yield. Because the substrate appeared to be the issue, the more nucleophilic

methoxymethyldiphenylphosphine oxide was used but disappointingly, only provided modest improvement.

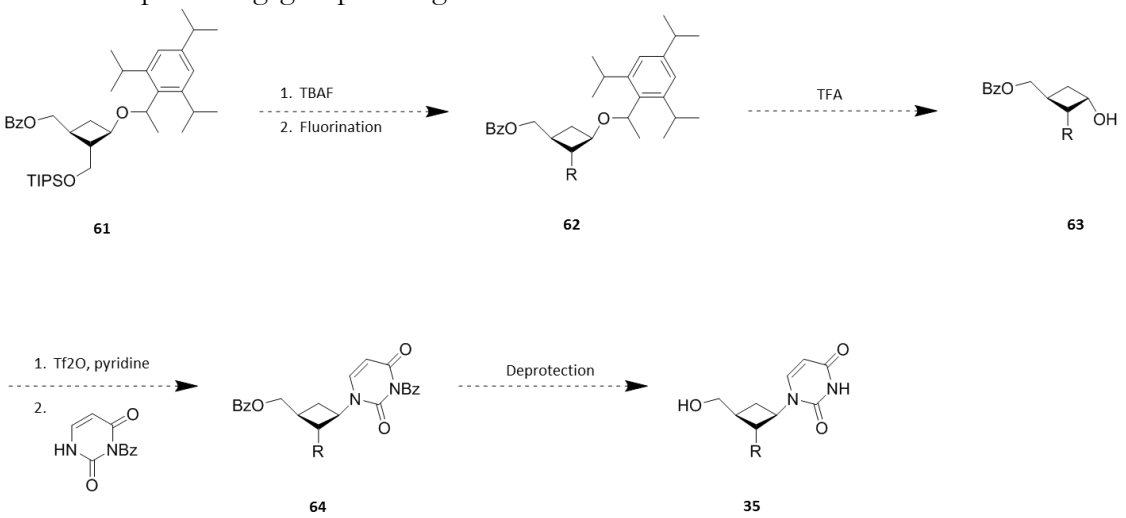
With the vinyl ether that could be made, the aldehyde was formed by acid hydrolysis and then epimerization by NaOMe/MeOH. Acidic hydrolysis of the vinyl ether also hydrolyzed the chiral ether to an extent, further diminishing yields of aldehyde. Following $NaBH_4$ reduction, the alcohol was benzyl protected (41% yield). At this stage only 21 mg of material was made, and with the number of remaining steps, greater quantities were needed. While the cycloaddition starting material could readily be made on a 10g scale, the cyclization was not as scalable. Furthermore, lower yields were observed in the homologation stages at larger scales, and useful amounts of material needed to investigate both the "glycosylation" and fluorination strategies have been unattainable.

3. Conclusions and Future Work:

Once the homologation, hydrolysis, and epimerization sequence can be achieved in greater yields, TIPS-removal will allow for investigation of the fluorination strategy (Scheme 16). Conversion to the monofluorinated intermediate can be attempted either by activation of the 2' alcohol and displacement by fluoride or treatment of the alcohol by DAST. The difluorinated analog is expected to be accessed by oxidation to the aldehyde followed by reaction with DAST.[32] Finally, the trifluorinated intermediate could be oxidized to the carboxylic acid and then treated with Deoxofluor.[33] Once appropriately fluorinated, removal of the protecting group at the 1'-position can be followed by insertion of the protected uridine base. Lastly, global deprotection and phosphorylation to the triphosphate will furnish the desired analogs for biological testing. From these assays, our model will be further evaluated and refined in order to better target NS5B. Additionally, should activity be observed, these

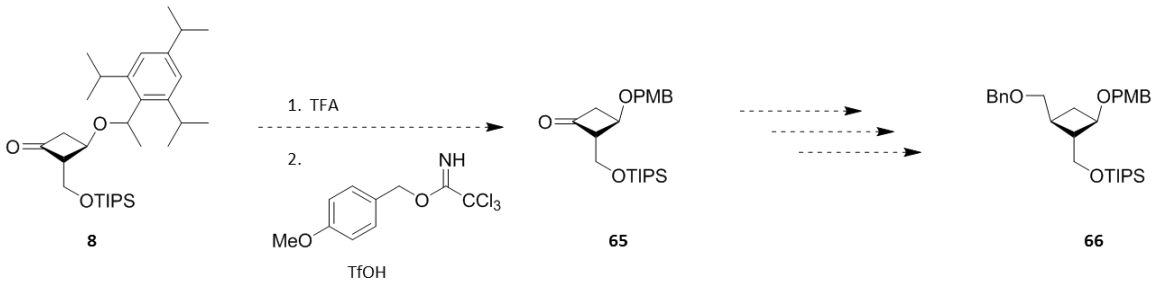
analogs can conceivably be prepared in various monophosphate pro-drug forms to enhance activity.[34]

In addition to providing stereoselectivity in the cycloaddition, Stericol was expected to serve as a protecting group during later transformations. With the host of issues during



Scheme 16. End game strategy for construction of target nucleosides (R = CH_2OH, CH_2F, CHF_2, CF_3)

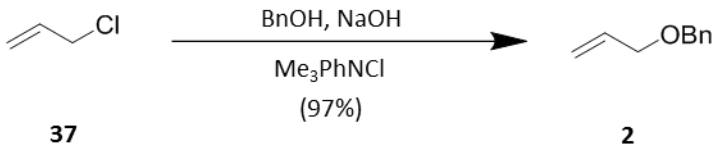
synthesis stemming from the chiral auxiliary, its removal following the stereoselective [2+2] cycloaddition may improve yields of downstream reactions. Though this adds two additional steps to an already lengthy synthesis (removal and protection) and may influence the stereochemistry of later stages, it removes the problematic acid- and base-sensitive functionality from an already labile molecule. In this way, use of benzyl, para-methoxybenzyl, and TIPS protecting groups will allow for orthogonal protection amenable to chemoselective removal and likely improved handling of the cyclobutane. Despite the unfortunate use of an additional protecting group, yields may be enhanced to an such an extent as to warrant this protection strategy.



Scheme 17. Possible protection strategy to overcome stability issues encountered with Stericol use.

4. Supporting Information

Allyl Benzyl Ether (2)

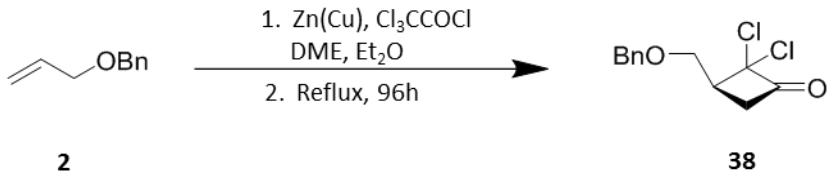


Allyl chloride (88 mL, 1.08 mol) was added to a stirring solution of NaOH (12.5 M, 65 mL), trimethylphenylammonium chloride (1.1544g, 6.73 mmol), and benzyl alcohol (14 mL, 135 mmol). After stirring overnight at room temperature, the reaction mixture was washed with H_2O (100 mL), 1N HCl (100 mL), saturated aqueous $NaHCO_3$ (100 mL), and then H_2O (100 mL) again. The organic layer was then distilled to afford allyl benzyl ether (19.6912g, 132.9 mmol, 98.4% yield) as colorless liquid: IR (Neat) 3029.87, 2853.77, 1072.27, 921.56, 735.22, 696.48 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H), 5.97 (m, 1H), 5.31 (d, J = 17.2 Hz, 1H), 5.21 (d, J = 10.4 Hz, 1H), 4.53 (s, 2H), 4.04 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 138.3, 134.7, 128.4, 127.7, 127.6, 117.1, 72.1, 71.1; HRMS (ESI) calcd for $C_{10}H_{13}O$ $(M+H)^+$ 149.09609. Found: 149.09621.

Zn-Cu couple

Zinc dust (64.6784g, 0.989 mmol) was dissolved in H_2O (100 mL) and stirred vigorously at room temperature. $CuSO_4$ (9.8074g, 61.4 mmol) was added in two portions in 50 mL H_2O each thirty seconds apart. After 1 minute of rapid stirring, solids were filtered and washed with H_2O (2 x 50 mL), acetone (2 x 50 mL), and ether (2 x 50 mL). Zn-Cu couple was dried over night under reduced pressure, affording 68.3218g of black solid.

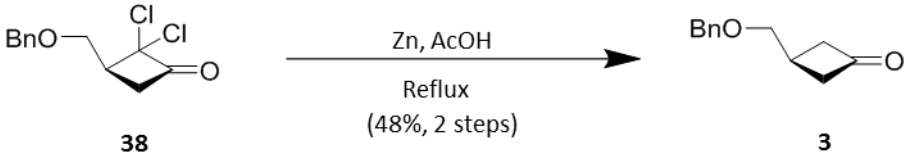
3-(Benzyloxymethyl)-2,2-dichlorocyclobutanone (38)



2 **38**

Redistilled trichloroacetyl chloride (15.5 mL, 139 mmol) was added dropwise to a stirring solution of all benzyl ether (5.5 mL, 35.6 mmol), Zn-Cu couple (13.8079 g), and 1,2-dimethoxyethane (33 mL) in diethyl ether (250 mL). After gently refluxing for 90 hours, the cooled reaction mixture was cooled and vacuum filtered. Filtrate was washed with diethyl ether (2 x 50 mL). The washings were then concentrated by rotary evaporation until approximately 50 mL of crude remained. Crude oil was stirred in pentanes for 5 minutes and decanted twice. The supernatant was next washed with water and then brine, dried over $MgSO_4$, filtered, and concentrated to afford black crude oil, which was then carried on to the next step: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 5H), 4.58 (s, 2H), 3.85 (m, 1H), 3.69 (m, 1H), 3.48-3.41 (m, 1H), 3.20-3.08 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 192.5, 137.2, 128.5, 128.0, 127.8, 87.3, 73.5, 68.9, 45.5, 45.1; HRMS (ESI) calcd for $C_{12}H_{16}O_2NCl_2$ $(M+NH_4)^+$ 276.05526. Found: 276.05530.

3-(Benzyloxymethyl)cyclobutanone (3)

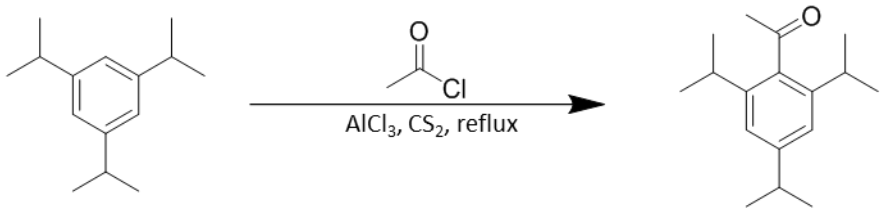


38 **3**

Crude 3-(Benzyloxymethyl)-2,2-dichlorocyclobutanone was dissolved in acetic acid (65 mL), and zinc dust (14.0026 g, 214 mmol) was added to stirring solution. The reaction mixture heated rapidly and was allowed to cool over two hours. The reaction mixture was filtered and washed with ether (100 mL, 3x). Filtrate and washings were concentrated by rotary

evaporation and carefully diluted with saturated aqueous $NaHCO_3$ before extracting with DCM (100 mL, 3x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to yield yellow oil (7.4876 g). Crude oil was purified by flash chromatography (Combiflash 40g silica column, 0 to 15% EtOAc in hexanes) to afford 3-((benzyloxy)methyl)cyclobutan-1-one as colorless oil (1.4518g, 7.63 mmol, 21.4% over 2 steps): IR (Neat) 2859.17, 1777.58, 1095.33, 1025.42, 742.22, 714.07 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 5H), 4.57 (s, 2H), 3.59 (d, J = 7.6Hz, 2H), 3.12 (m, 2H), 2.90 (m, 2H), 2.70 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 207.6, 138.0, 128.5, 127.8, 127.7, 73.2, 72.9, 50.1, 23.7; HRMS (ESI) calcd for $C_{12}H_{15}O_2$ $(M+H)^+$ 191.10673. Found: 191.10673.

1-(2,4,6-triisopropyl)ethan-1-one (43)

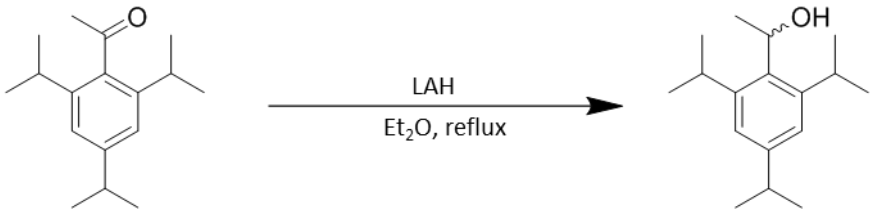


42 **43**

A solution of acetyl chloride (7.25 mL, 102 mmol) in carbon disulfide (18 mL) was added dropwise to a stirring solution of 1,3,5-triisopropylbenzene (25 mL, 103 mmol) and aluminum chloride (15.1315 g, 114 mmol) in carbon disulfide (45 mL) dropwise over 30 minutes. The reaction mixture was then refluxed for 1.5 hours, changing in color from yellow to reddish brown. Upon completion, the solution was poured into concentrated HCl (50 mL) and ice (200 g), and then extracted with ether (3 x 100 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$, water, and brine. The organic layer was then dried over Na_2SO_4, filtered, and concentrated to afford 1-(2,4,6-triisopropylphenyl)ethan-1-one (25.5844 g) as a white solid: IR (neat) 2959, 2928, 2868, 1692, 1605, 1457, 1358, 1276 cm^{-1}; ^1H NMR

(400 MHz, $CDCl_3$) δ 7.00 (s, 2H), 2.88 (sept, J = 7.2 Hz, 1H), 2.72 (sept, J = 6.8 Hz, 2H), 2.49 (s, 3H), 1.25 (d, J = 7.2 Hz, 6H), 1.24 (d, J = 6.8 Hz, 12H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 149.4, 143.1, 138.4, 121.0, 34.3, 33.9, 31.0, 24.4, 24.025; MS (M^+) m/z 247.21

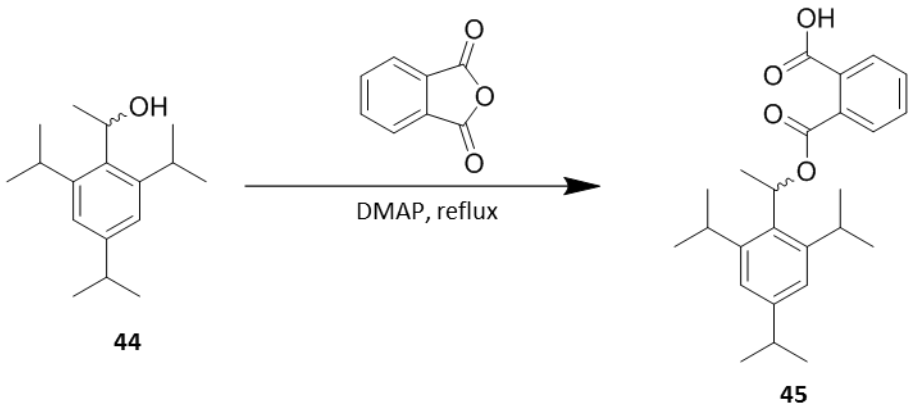
1-(2,4,6-triisopropylphenyl)ethan-1-ol (44)



43 **44**

Crude 1-(2,4,6-triisopropylphenyl)ethan-1-one (25.5844 g) was dissolved in diethyl ether (200 mL). Lithium aluminum hydride (4.0186 g, 106 mmol) was added portion wise, and then the reaction mixture was refluxed for 2.5 hours. The reaction mixture was next cooled to 0 °C followed by drop wise addition of water (18 mL). 1 N NaOH (16 mL) was next added dropwise, and the solids were filtered on a sintered glass funnel and washed with diethyl ether. The ether filtrate was then concentrated by rotary evaporation to yield 1-(2,4,6-triisopropylphenyl)ethan-1-ol (19.2081 g) as an amorphous white solid: IR (neat) 3335, 2958, 2868, 1459, 1362, 1066 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 2H), 5.52 (q, J = 6.8 Hz, 1H), 3.60 (br s, 2H), 2.86 (sept, J = 6.8 Hz, 1H), 1.98 (s, 1H), 1.60 (d, J = 6.8 Hz, 3H), 1.26 (d, J = 6.8 Hz, 3H), 1.24 (d, J = 7.2 Hz, 12H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 147.6, 135.9, 121.64, 66.1, 34.1, 29.0, 24.7, 24.6, 24.0, 23.9, 23.6; HRMS (ESI) calcd for $C_{17}H_{25}O$ $(M+H)^+$ 245.18999. Found: 245.290143.

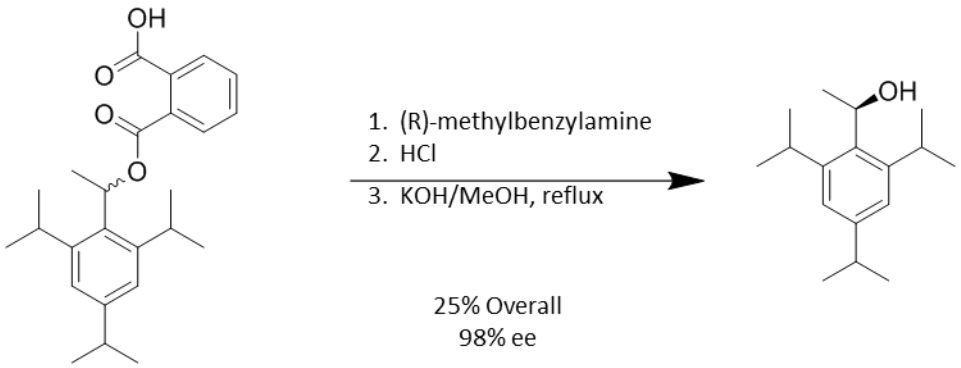
2-((1-(2,4,6-triisopropylphenyl)ethoxy)carbonyl)benzoic acid (45)



44 **45**

Crude 1-(2,4,6-triisopropylphenyl)ethan-1-ol (19.2081 g) was dissolved in pyridine (100 mL). Phthalic anhydride (17.2047 g, 116 mmol) was added, and the solution was heated to 110 °C for 2 hours. The reaction mixture was then diluted with diethyl ether (200 mL) and washed with 6N HCl (3 x 75 mL). The organic layer was then washed with water (100 mL) and brine (100 mL). After drying over Na_2SO_4, the ethereal solution was filtered and concentrated to yield 2-((1-(2,4,6-triisopropylphenyl)ethoxy)carbonyl)benzoic acid (26.5 g) as a white foam. IR (neat) 2959, 2869, 1698, 1288, 1124, 1053 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.33 (br s, 1H), 7.91 – 7.94 (m, 1H), 7.65 – 7.66 (m, 1H), 7.51-7.58 (m, 2H), 7.01 (s, 2H), 6.79 (q, J = 6.4 Hz, 1H), 3.54 (br s, 2H), 2.84 (sept, J = 6.8 Hz, 1H), 1.77 (d, J = 6.8 Hz, 3H), 1.16-1.29 (m, 18H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 172.5, 167.6, 148. 2, 134.0, 132.2, 131.7, 130.7, 129.9, 128.9, 121.0, 70.3, 34.0, 29.5, 24.6, 24.3, 23.9; HRMS (ESI) calcd for $C_{25}H_{32}O_4$ $(M)^+$ 396.2395. Found 396.30116.

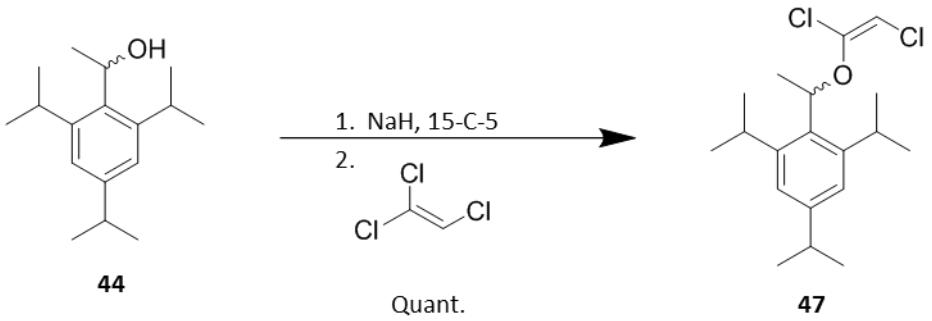
(*R*)-1-(2,4,6-triisopropylphenyl)ethan-1-ol (46)



45 **46**

To a stirring solution of 2-((1-(2,4,6-triisopropylphenyl)ethoxy)carbonyl)benzoic acid (26.5 g) in diethyl ether (800 mL), (R)-(+)-α-methylbenzylamine (3.2 mL, 25.1 mmol) was added dropwise. After stirring 3 hours, solids were filtered and washed with ether and dried under vacuum to afford 51.2 g white salt. The solids were then dissolved in ether (200 mL) and 2N HCl (100 mL), and the layers were separated. The organic layer was next dried over Na_2SO_4, filtered, and, concentrated. The white foam was next refluxed in MeOH (100 mL) and 4N KOH (75 mL) for 2.5 hours. After cooling to room temperature, the solids were filtered and dried under vacuum to afford (*R*)-1-(2,4,6-triisopropylphenyl)ethan-1-ol as a white solid (6.348g, 25.6 mmol, 25.1% yield over 4 steps, 98.3 % ee by HPLC): IR (neat) 3416, 2956, 2868, 1460, 1058 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 2H), 5.50 (q, J = 6.8 Hz, 1H), 3.63 (br s, 2H), 2.85 (sept, J = 6.8 Hz, 1H), 1.98 (s, 1H), 1.58 (d, J = 6.8 Hz, 3H), 1.27 (d, J = 6.8 Hz, 3H), 1.22 (d, J = 7.2 Hz, 12H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 148.0, 135.8, 121.6, 65.9, 34.0, 29.3, 24.8, 24.6, 24.1, 23.9, 23.6; HRMS (ESI) calcd for $C_{17}H_{28}O$ $(M)^+$ 248.20563. Found: 248.20943.

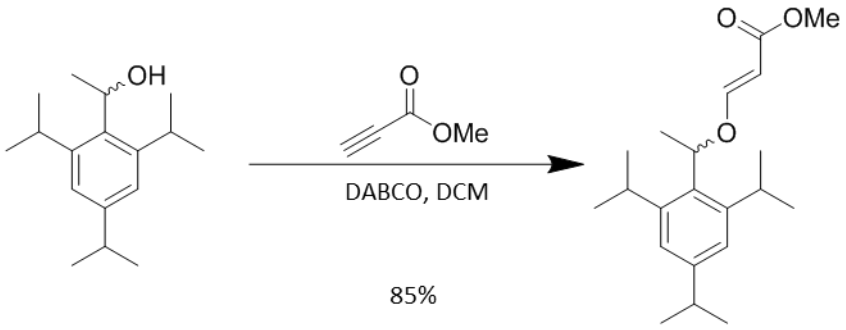
(E)-2-(1-((1,2-dichlorovinyl)oxy)ethyl)-1,3,5-triisopropylbenzene (47)



44 Quant. **47**

NaH (1.6560g, 60% w/w in oil, 41.4 mmol) was washed with pentane and dried under vacuum. THF (20 mL) was added, followed by a solution of 1-(2,4,6-triisopropylphenyl)ethan-1-ol (4.0018g, 16.1 mmol) in THF (15 mL) dropwise. 15-crown-ether (1.6 mL, 8.1 mmol) was next added, and the solution was stirred at room temperature for 2 hours. A solution of trichloroethylene (1.6 mL, 17.7 mmol) in THF (7 mL) was added dropwise, and the reaction mixture was stirred overnight. Next, the brown reaction mixture was cooled to 0 °C, and methanol (4 mL) and water (6 mL) were added slowly. The layers were separated, and the organic fraction was washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford a brown crude oil (6.6103 g). The residue was purified by flash chromatography (Combiflash 24g silica gel column, 100% hexanes) to afford (R,E)-2-(1-((1,2-dichlorovinyl)oxy)ethyl)-1,3,5-triisopropylbenzene as a colorless oil that solidified upon standing (5.2391g, 15.3 mmol, 95.1%): IR (neat) 2959, 2928, 2869, 1274, 1077, 1046 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.04 (s, 2H), 5.96 (q, J = 7.2 Hz, 1H), 5.58 (s, 1H), 3.54 (br s, 2H), 2.87 (sept, J = 6.2 Hz, 1H), 1.67 (d, J = 7.2 Hz, 3H), 1.26 (m, 18H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 148.2, 142.6, 133.3, 121.9, 98.0, 76.6, 34.0, 29.5, 24.8, 24.5, 24.1, 23.9, 21.6.

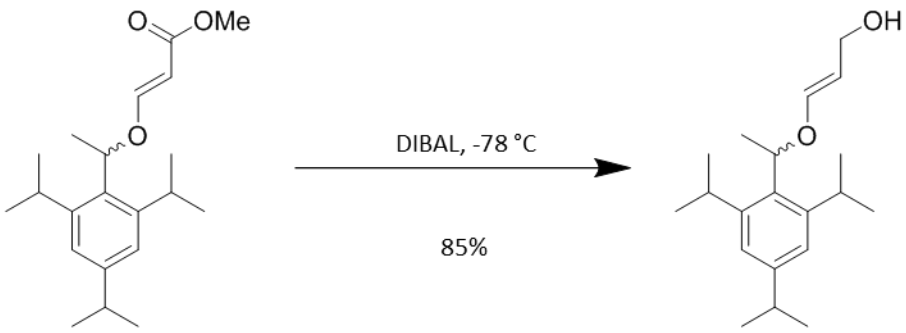
Methyl (*E*)-3-(1-(2,4,6-triisopropylphenyl)ethoxy)acrylate (51)



44 **51**

N-methylmorpholine (3.0 mL, 26.6 mmol) was added to a stirring solution of racemic Stericol (3.0297g, 12.2 mmol) and methyl propiolate (1.2 mL, 12.1 mmol) in DCM (15 mL) and stirred overnight at room temperature. The reaction mixture was next concentrated by rotary evaporation and purified on a Combiflash 80 g silica column (0 – 10% EtOAc in hexanes) to afford methyl (*E*)-3-(1-(2,4,6-triisopropylphenyl)ethoxy)acrylate (3.4363 g, 10.3 mmol, 84.7% yield) as a white solid: IR (neat) 2954, 2869, 1709, 1639, 1281, 1200, 1060 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, J=12.3 Hz, 1H), 7.02 (s, 2H), 5.61 (q, J = 6.9 Hz, 1H), 5.26 (d, J = 12.3 Hz, 1H), 3.64 (s, 3H), 3.40 (br s, 2H), 2.87 (sept, J = 6.9 Hz, 1H), 1.68 (d, J = 6.9 Hz, 3H), 1.29 – 1.19 (m, 18H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 168.5, 162.1, 148.5, 131.4, 97.3, 51.0, 34.1, 31.6, 29.3, 24.7, 24.4, 23.9, 23.8, 22.7, 22.4, 14.2; HRMS (ESI) calcd for $C_{21}H_{33}O_3$ $(M+H)^+$ 333.24218. Found: 333.24242.

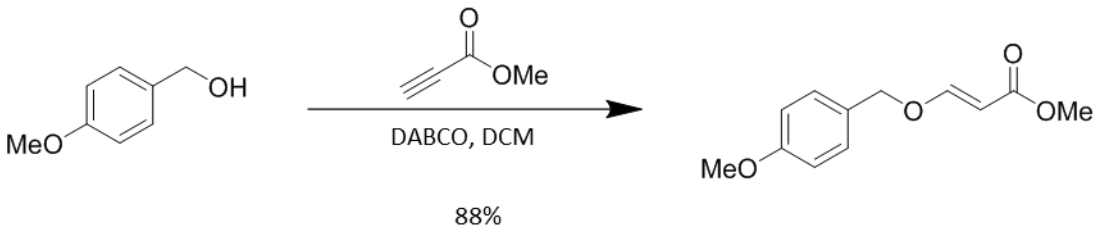
(*E*)-3-(1-(2,4,6-triisopropylphenyl)ethoxy)prop-2-en-1-ol



51

DIBAL (3.8 mL, 1.0 M in toluene, 3.8 mmol) was added dropwisely to a stirring, -78°C solution of methyl (*E*)-3-(1-(2,4,6-triisopropylphenyl)ethoxy)acrylate (0.5010 g, 1.51 mmol) in toluene (20 mL). After stirring for 7 hours at -78°C, EtOAc (20 mL) was added carefully, followed by a saturated solution of Rochelle's salt (20 mL). After stirring 2 hours, Et_2O (30 mL) was added and layers separated. The organic phase was washed with water (2 x 20 mL) and brine (20 mL). The organic phase was then dried over Na_2SO_4, filtered, and concentrated to afford 0.7141 g crude oil, which was carried to the next step without further purification: IR (neat) 3409, 2959, 2869, 1668, 1460, 1167 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.00 (s, 1H), 6.34 (d, J = 9.0 Hz, 1H), 5.42 (q, J = 5.1 Hz, 1H), 5.13 (dt, J= 7.8, 9.3 Hz, 1H), 3.96 (m, 2H), 3.68 – 3.39 (br s, 2H), 2.86 (sept, J= 5.1 Hz), 1.68 (d, J=5.1Hz, 3H), 1.63 – 1.60 (m, 18H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 148.0, 146.4, 146.0, 132.3, 121.6, 104.9, 76.1, 65.8, 56.8, 34.0, 29.1, 24.6, 23.9, 23.8, 22.5, 15.2

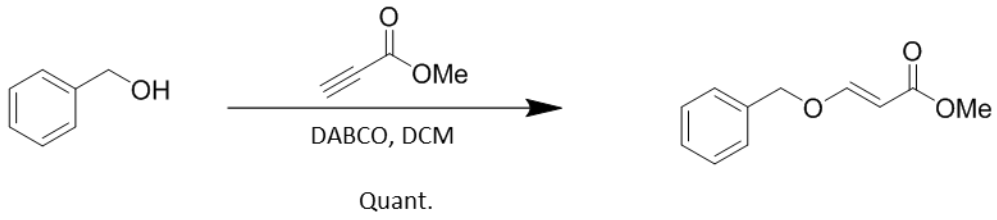
Methyl (*E*)-3-((4-((4-methoxybenzyl)oxy)benzyl)oxy)acrylate (55)



54 **55**

DABCO (0.3104 g, 2.77 mmol) was added to a stirring solution of 4-methoxybenzyl alcohol (3.4 mL, 27.0 mmol) and methyl propiolate (2.6 mL, 29.7 mmol) in DCM (60 mL). After stirring 1.5 hours, the solvent was removed by rotary evaporation and the brown crude oil purified by flash chromatography (Combiflash 80g silica column, 0-30% EtOAc in hexanes) to afford vinylogous carbonate as a clear oil (5.2817g, 88.1% yield): IR (neat) 2950, 2838, 1706, 1619, 1514, 1125 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, 1H, J=12.3 Hz), 7.28 (m, 2H), 6.91 (m, 2H), 5.31 (d, 1H, J=12.3 Hz), 4.83 (s, 2H), 3.82 (s, 3H), 3.70 (s, 3H) ^{13}C NMR (400 MHz, $CDCl_3$) δ 168.1, 162.1, 159.9, 129.5, 127.2, 114.1, 96.9, 72.8, 55.3, 51.1; HRMS (ESI) calcd for $C_{12}H_{15}O_2$ $(M+H)^+$ 191.10666. Found: 191.10673.

Methyl (E)-3-(benzyloxy)acrylate (55)



54 **55**

DABCO (0.3283g, 2.9 mmol) was added to a stirring solution of benzyl alcohol (2.8 mL, 27.0 mmol) and methyl propiolate (2.6 mL, 27.0 mmol) in DCM (60 mL). After stirring 2 hours, the solvent was removed by rotary evaporation and the crude oil was purified by column chromatography (0-20% EtOAc in hexanes) to provide 5.1719 g (26.9 mmol, 99.7%) vinylogous carbonate as clear oil: IR (neat) 1706, 1622, 1194, 1126 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, 1H, J=12.3 Hz), 7.38 (m, 5H), 6.91 (m, 2H), 5.33 (d, 1H, J=12.3 Hz), 4.91 (s, 2H), 3.71 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 168.0, 162.1, 135.2, 128.7, 128.6, 127.7, 97.1, 72.9, 51.1; HRMS calcd for $C_{11}H_{13}O_3$ $(M+H)^+$ 193.08592. Found: 193.08577.

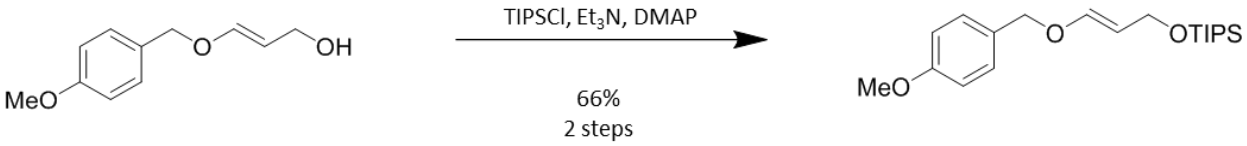
(*E*)-3-((4-methoxybenzyl)oxy)prop-2-en-1-ol

55

DIBAL (55 mL 1M in toluene, 55.0 mmol) was added dropwise to a -78°C stirring solution of methyl (E)-3-(benzyloxy)acrylate (4.9257 g, 22.2 mmol) in toluene (100 mL). After stirring for 6 hours at -78°C, the solution was allowed to warm to 0°C and subsequently quenched with EtOAc (20 mL) and a saturated solution of Rochelle's salt (100 mL). After stirring for 2 hours, diethyl ether (50 mL) was added and layers were separated. The organic phase was washed with water (2 x 50 mL) and brine (50 mL), then dried over Na_2SO_4, filtered and concentrated to afford 4.0240 g of crude alcohol, which was carried to the next step without purification: IR (neat) 3362 (br), 2935, 1650, 1613, 1513, 1246, 1167 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ

7.27 (d, 2H, J=7.2 Hz), 6.90 (d, 2H, J=7.2 Hz), 6.91 (m, 2H), 5.33 (d, 1H, J=12.3 Hz), 4.91 (s, 2H), 3.71 (s, 3H); HRMS calcd for $C_{16}H_{17}O_3$ $(M+H)^+$ 241.12231. Found: 241.12233.

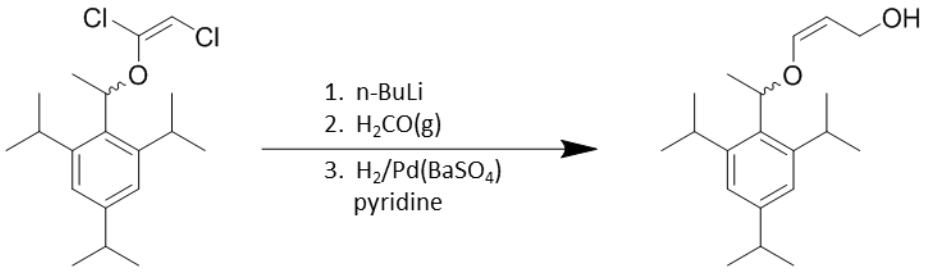
(*E*)-*tert*-butyl((3-((4-methoxybenzyl)oxy)allyl)oxy)dimethylsilane (56)



56

Triethylamine (4.2 mL, 30.3 mmol) was added to a stirring solution of crude (*E*)-3-((4-methoxybenzyl)oxy)prop-2-en-1-ol (3.9174 g, 20.2 mmol) in DCM (40 mL). DMAP (0.0284g, 0.23 mmol) was next added, followed by TBSCl (3.9995 g, 26.5 mmol). The reaction mixture was stirred overnight at room temperature. Water (50 mL) was next added, and layers were separated. The organic phase was washed with water (2 x 50 mL) and brine (50 mL) and then dried over $MgSO_4$, filtered, and concentrated. The crude oil was purified by column chromatography (0 – 20% EtOAc in hexane) to afford 4.7101 g product as colorless oil (15.3 mmol, 65.9% yield over 2 steps): IR (neat) 2930, 2856, 1651, 1514, 1302 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, 2H, J=9 Hz), 6.89 (d, 2H, J = 9.0 Hz), 6.53 (d, 1H, J = 12.9 Hz), 5.03 (dt, 1H, J=12.9, 6.9 Hz), 4.68 (s, 2H), 4.11 (dd, 2H, J = 6.9, 1.2 Hz) 3.81 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 159.5, 148.4, 129.3, 128.9, 113.9, 103.9, 70.9, 61.2, 55.3, 25.9, 18.4, -5.0); HRMS calcd for $C_{17}H_{29}O_3Si$ $(M+H)^+$ 309.18805. Found: 309.18767.

(*Z*)-3-(1-(2,4,6-triisopropylphenyl)ethoxy)prop-2-en-1-ol (48)

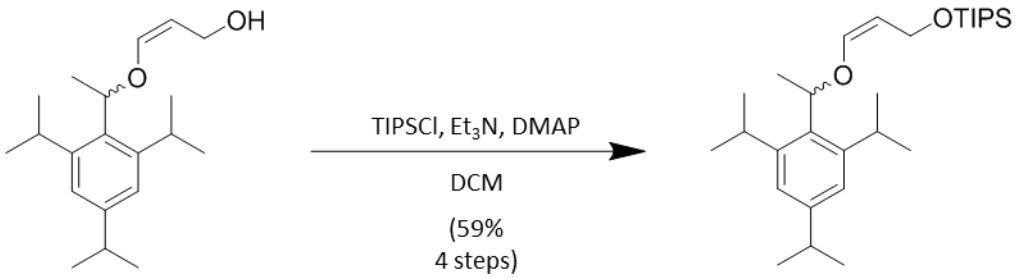


47 **48**

N-BuLi (2.5 M in hexanes, 5.5 mL, 13.6 mmol) was added dropwise to a -78°C stirring solution of dichlorovinyl ether (2.1229 g, 6.21 mmol) in THF (40 mL). After addition, the solution was warmed to -41°C and stirred for 15 minutes. Gaseous formaldehyde generated by the thermal decomposition of paraformaldehyde (1.0432 g, 34.7 mmol) was passed into the reaction vessel, and the reaction mixture was stirred for an additional 25 minutes. MeOH (1 mL) and pyridine (16 mL) were then added slowly, followed by Pd($BaSO_4$) (0.2215 g, 5% w/w, reduced). After evacuating argon and flushing with H_2 twice, the reaction mixture was hydrogenated while cooling to 0°C over 5 hours. Once IR showed no disubstituted alkyne (~2260 cm^{-1}), the reaction mixture was warmed to room temperature and filtered through a pad of Celite. Water (40 mL) was added to the filtrate and washings, and layers were separated. The aqueous phase was extracted with Et_2O (2x50 mL), and the combined organic layers were washed with sat. aq. $CuSO_4$, water, and brine. The organic phase was then dried over Na_2SO_4, filtered and concentrated to afford 2.1206 g crude alcohol, which was carried on to the next step without further purification: IR (neat) 3403, 2959, 2868, 1660, 1608, 1460, 1381 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (s, 2H), 6.08 (d, J = 6.6 Hz, 1H), 5.37 (q, J = 6.9 Hz), 4.58 (q, J= 6.3 Hz, 1H), 4.34 – 4.21 (m, 2H), 3.68 – 3.25 (m, 2H), 2.89 (sept, J = 6.3 Hz), 1.32 – 1.15 (m, 18H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 148.0, 146.4, 146.0, 132.3, 121.6, 104.9, 76.1,

65.8, 56.8, 34.0, 29.1, 24.6, 23.9, 23.8, 22.5, 15.2; HRMS calcd for $C_{20}H_{32}O_2$ $(M+Na)^+$ 327.22901. Found: 327.22945.

(*Z*)-triisopropyl((3-(1-(2,4,6-triisopropylphenyl)ethoxy)allyl)oxy)silane (7)

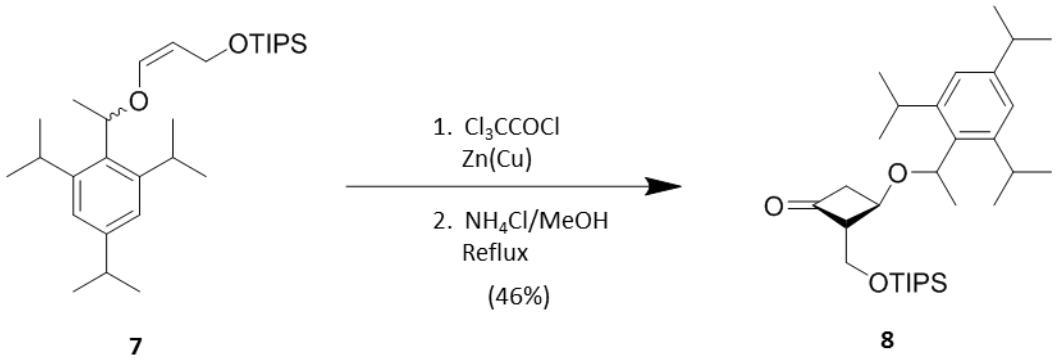


48 **7**

TIPSCl (1.7 mL, 8.05 mmol) was added to a stirring solution of crude 2-119 (2.1206 g), Et_3N (1.3 mL, 9.29 mmol), and DMAP (0.0078g, 0.06 mmol) in DCM (25 mL). After stirring overnight, water (20 mL) was added to the reaction mixture, and layers separated. The aqueous phase was extracted with DCM (2 x 20 mL), and the combined organic layers were extracted with water (30 mL) and brine (30 mL). The organics were dried over $MgSO_4$, filtered, and concentrated. The crude oil was purified by column chromatography (0-15% EtOAc in hexanes) to afford protected enol ether as colorless oil:

IR (neat) 2958, 2866, 1663, 1608, 1462 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.00 (s, 2H), 5.98-5.96 (m, 1H), 5.33 (q, J=6.9 Hz, 1H), 4.57-4.49 (m, 2H), 4.28-4.21 (m, 1H), 3.65-3.21 (m, 2H), 2.85 (sept, J=7.2Hz, 1H), 1.59 (d, J=6.9 Hz, 3H), 1.28-1.08 (m, 39H); ^{13}C (400 MHz, $CDCl_3$) δ 147.6, 144.2, 132.4 121.9, 106.5, 76.0, 57.2, 34.0, 30.0, 24.5, 24.1, 23.9, 22.3, 18.1, 11.8.

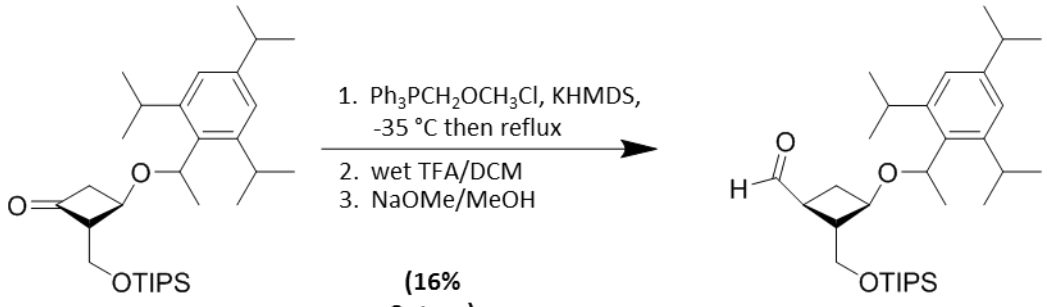
3-(1-(2,4,6-triisopropylphenyl)ethoxy)-2-(((triisopropylsilyl)oxy)methyl)cyclobutan-1-one (8)



7 **8**

Trichloroacetyl chloride (0.24 mL, 2.17 mmol) was added dropwisely over 30 minutes to a stirring solution of (*Z*)-triisopropyl((3-(1-(2,4,6-triisopropylphenyl)ethoxy)allyl)oxy)silane (0.5016 g, 1.09 mmol) and Zn(Cu) couple (1.2001 g). After stirring an additional 30 minutes at room temperature, a saturated solution of NH_4Cl in MeOH (40 mL) was added carefully. The reaction mixture was then refluxed for 45 minutes. Upon consumption of dichlorocyclobutanone as seen by TLC, the cooled reaction mixture was passed through Celite, and water added to filtrate and washings. The organic layer was removed, washed by water (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The crude ketone was purified by column chromatography (0-15% EtOAc in 2.5% Et_3N/hexane) to afford 0.2508 g pure ketone as colorless oil (0.50 mmol, 45.8%): IR (neat) 2958, 2866, 1788, 1608, 1461, 1382 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.06 (s, 1H), 6.96 (s, 1H), 5.07 (q, J = 6.9 Hz, 1H), 4.23-4.17 (m, 1H), 4.10-4.08 (m, 2H), 3.99-3.94 (m, 1H), 3.31-3.27 (m, 1H), 3.21-3.06 (m, 3H), 2.86 (sept, J=6.9 Hz, 1H), 1.57 (d, J=6.6Hz, 3H), 1.26 – 1.05 (m, 39H)

3-(1-(2,4,6-triisopropylphenyl)ethoxy)-2-(((triisopropylsilyl)oxy)methyl)cyclobutane-1-carbaldehyde (60)

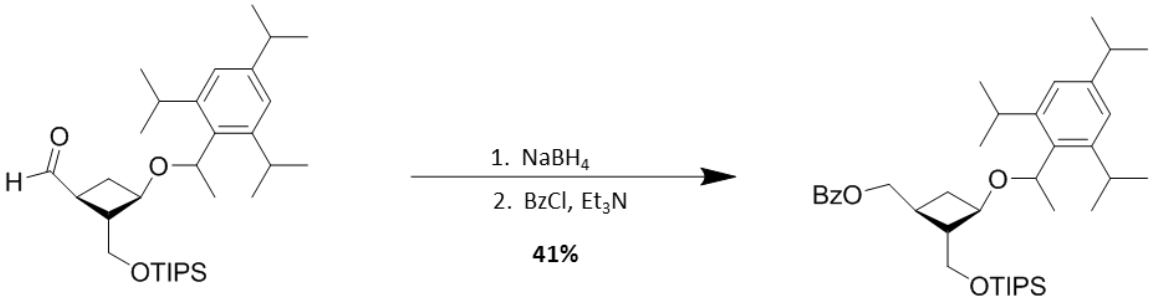


8 **60**

KHMDS (0.5 M in toluene, 13.2 ml, 6.61 mmol) was added dropwise to a stirring, -35 °C suspension of $Ph_3PCH_2OCH_3Cl$ (2.6000g, 7.55 mmol) in THF (30 mL). After stirring 10 min., reaction mixture was warmed to room temperature over 1 hr. The reaction mixture was then cooled back to -35 °C and a solution of cyclobutanone 2-202 (0.949g, 1.89 mmol) in THF (8 mL) was added dropwise. The reaction mixture was next warmed to room temperature over 1.25 hr., then refluxed for 2h. The cooled reaction mixture was quenched with aq. sat. NH_4Cl solution and extracted with Et_2O (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Purification of crude oil was attempted by flash chromatography (0-2.5% EtOAc in hexanes, pretreated with 2.0% Et_3N in hexanes) to afford 1.1859g oily mixture of enol ethers with triphenylphosphine oxide. This material was then added to a solution of trichloroacetic acid (3.0792g, 18.9 mmol) and a few drops of water in DCM (10 mL) and stirred for one hour. Saturated aqueous sodium bicarbonate was added, and the mixture was extracted with DCM (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude material was then stirred at room temperature for 24h in MeOH (10 mL) with NaOMe (0.052g,

0.967 mmol). Water was added and then extracted with diethyl ether (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by column chromatography (0-2.5% EtOAc in hexanes, pretreated with 2.0% Et3N in hexanes) to afford 0.1563g (16%) of aldehyde as colorless oil: IR (neat) 2923, 2892, 2868, 1716, 1453, 1122 cm^{-1} ; 1 H NMR (300 MHz, $CDCl_3$) δ 9.80 (d, J = 1.3 Hz, 1H), 7.01 (s, 1H), 6.96 (s, 1H), 4.87 (q, J = 6.6 Hz, 1H), 4.05−3.74 (m, 4H), 3.24−3.15 (m, 1H), 3.15−3.00 (m, 1H), 2.84 (sept, J = 6.9 Hz, 1H), 2.79−2.69 (m, 1H), 2.58−2.47 (m, 1H), 2.27−2.15 (m, 1H), 1.48 (d, J = 6.8 Hz, 3H), 1.28−1.00 (m, 39H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 202.25, 148.67 147.24, 145.23, 132.84, 123.21, 120.19, 70.82, 69.17, 67.62, 61.47, 59.23 48.42, 44.17 44.16, 40.29, 33.82, 28.78, 28.34, 28.25, 24.52, 23.90, 23.76, 23.2, 18.16, 18.09, 17.97, 11.93

3-(1-(2,4,6-triisopropylphenyl)ethoxy)-2-(((triisopropylsilyl)oxy)methyl)cyclobutyl)methanol (61)



60 **61**

$NaBH_4$ (0.0214g, 0.518 mmol) was added to a stirring solution of aldehyde (0.1338g, 0.259 mmol) in EtOH (1.3 mL). After stirring for 3 hrs., the reaction was quenched by addition of water then H3PO4 then extracted with Et2O (3x). The combined organic phases were washed with brine, dried over Na2SO4, filtered, and concentrated. The crude oil was purified by flash

chromatography (0-10% Et_2O in pentane) to afford 0.0742g (0.143 mmol, 55%) alcohol as colorless oil; IR (neat) 3391, 2962, 2878, 2862, 1463, 1108, 1084 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 7.06 (s, 1H), 6.93 (s, 1H), 4.99 (q, J = 6.8 Hz, 1H), 3.98−3.74 (m, 4H), 3.72− 3.60 (m, 1H), 3.39 (dt, J = 10.2, 1.4 Hz, 1H), 3.16−3.00 (m, 1H), 2.96 (dd, J = 9.0, 1.5 Hz, 1H), 2.84 (sept, J = 6.9 Hz, 1H), 2.76−2.60 (m, 1H), 2.33−2.20 (m, 1H), 2.16−2.05 (m, 1H), 1.75−1.62 (m, 1H), 1.55 (d, J = 6.8 Hz, 3H), 1.29−1.00 (m, 39H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 148.78, 147.07, 145.74, 133.34, 123.08, 120.21, 70.6, 69.56, 66.70, 62.37, 47.11, 39.85, 33.90, 28.73, 28.41, 28.03, 25.17, 24.82, 24.44, 24.21, 23.9, 23.76, 23.32, 17.70, 11.82

5. References

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