JYU DISSERTATIONS 611

Rajanish Reddy Pallerla

Studies Towards Synthesis of Favipiravir & Humilisin E

UNIVERSITY OF JYVÄSKYLÄ
FACULTY OF MATHEMATICS
AND SCIENCE

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ABSTRACT

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Synthetic organic chemistry has made human life easier by giving access to a variety of useful molecules. Be it academic research, industrial or medicinal applications, synthesis has paved way for accelerated growth in respective fields. The majority of drugs we use in our daily life are either natural products, analogues of natural products or mimic natural products in a certain way. Access to natural products from Nature can be laborious and inefficient, leading to a plethora of practical issues. Total synthesis bridges this gap by providing a way to access the required molecules from commercially available compounds.

The first chapter discusses the synthetic routes towards favipiravir, an antiviral with a large global demand. Motivated by COVID-19 pandemic, we became interested in addressing the chemical synthesis of this molecule. The chapter outlines the previously reported synthetic routes and describes the rationale behind the design of a shorter route.

The second chapter describes synthetic approaches towards the recently discovered tricyclic terpenoid humilisin E. Examples of natural products containing a bicyclo[3.2.0]heptane motif which constitutes the core of the humilisin E, and compiled examples from the literature for synthetic construction of this motif are reviewed. This discussion is followed by a detailed description of our own strategies to construct the bicyclo[3.2.0]heptane core of humilisin E, culminating in a successful stereocontrolled synthesis of the fully functionalized humilisin E core.

The entire thesis is summarized in chapter 3, and full experimental details are provided in chapter 4.

Keywords: total synthesis, natural products, terpenoids, pyrazines, cyclobutanes, cyclopentanes

TIIVISTELMÄ

Pallerla, Rajanish Reddy
Favipiraviirin ja humilisiini E:n synteesiin tähtääviä tutkimuksia
Jyväskylä: Jyväskylän yliopisto, 2023, 139 s.
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Synteettinen orgaaninen kemia on helpottanut ihmisten elämää antamalla käsiimme erilaisia hyödyllisiä aineita. Sekä akateemisessa tutkimuksessa että teollisissa tai lääketieteen sovellutuksissa synteesikemia on ollut tärkeä tekijä alan kasvulle. Suuri osa päivittäisessä käytössä olevista lääkeaineista on joko luonnonaineita, niiden muunnelmia, tai luonnonaineiden toimintaa matkivia aineita. Tästä huolimatta luonnonaineita on usein vaikeaa ja kallista tuottaa luonnollisista lähteistään. Luonnonaineiden kokonaissynteesi tarjoaa onnistuessaan keinon tuottaa luonnonaineita kaupallisesti saatavista lähtöaineista.

Väitöskirjan ensimmäinen kappale käsittelee viruslääke faviripaviirin synteesiä. Faviripaviirin synteesiä motivoi COVID-19-pandemian eteneminen, koska tätä lääkeainetta kaavailtiin myös koronaviruslääkkeeksi. Tässä luvussa esitellään aiemmin julkaistuja faviripaviirin synteesimenetelmiä sekä omaa yritystämme kehittää lyhyempi ja tehokkaampi synteesimenetelmä faviripaviirille.

Toisessa kappaleessa kuvataan hiljattain eristetyn trisyklisen terpenoidin, humilisiini E:n, synteesiä. Kappaleessa esitellään kirjallisuudessa eri tapoja syntetisoida humilisiini E:n rakenteessa oleva bisyklo[3.2.0]heptaaniyksikkö tai sitä vastaava rakenne. Tämän jälkeen kappaleessa kuvataan omia synteesistrategioitamme ja lopulta onnistunutta humilisiini E:n ydinrakenteen stereokontrolloitua synteesiä.

Koko väitöskirjan yhteenveto esitellään luvussa 3, ja luku 4 sisältää kuvauksen väitöskirjan kokeellisesta työstä.

Avainsanat: kokonaissynteesi, luonnonaineet, terpenoidit, pyratsiinit, syklobutaanit, syklopentaanit

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Moving to Finland during winter from one of the hottest parts of India might be a crazy thing to do. Rahul & Lasya, thank you for the help during the initial days. I will be forever grateful for treating me as family and making me feel at home.

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Jyväskylä 27.1.2023
Rajanish Reddy Pallerla

ABBREVATIONS

[O]	oxidation
°	degree
AChE	acetylcholinesterase
Ac	acetyl
AcOH	acetic acid
Ar	aryl
atm	atmosphere
AIBN	2,2′-azobis(2-methylpropionitrile)
(*S*)-BINAP	(*S*)-(-)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
Bn	benzyl
Bu	butyl
t-Bu	*tert*-butyl
i-Bu	*iso*-butyl
Bz	benzoyl
C	centigrade/celsius
CDI	1,1′-carbonyldiimidazole
d	doublet
dba	dibenzylideneacetone
DCC	N,N′-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DEE	diethyl ether
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIPEA	N,N-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMEA	dimethylethylamine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
DOWEX	ion exchange resin
Dppf	1,1′-ferrocenediyl-bis(diphenylphosphine)
dr	diastereomeric ratio
E	electrophile
equiv.	molar equivalent
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
Grubbs′ 2nd generation catalyst	(1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene) (tricyclohexylphosphine)ruthenium
HGPRT	hypoxanthine-guanine phosphoribosyltransferase
HMPA	hexamethylphospharamide

HOMO	highly occupied molecular orbital
J	coupling constant
Jones reagent	oxidant, solution of chromium trioxide in aqueous sulfuric acid
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LiTMP	lithium 2,2,6,6-tetramethylpiperidide
LUMO	lowest unoccupied molecular orbital
m	multiplet
M	molarity, mol . l^{-1}
Me	methyl
MeOH	methanol
n	linear chain
NaH	sodium hydride
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NHPI	N-hydroxyphthalimide
NMM	*N*-methylmorpholine
NMR	nuclear magnetic resonance spectroscopy
OAc	acetate
OEt	ethoxy
OMe	methoxy
Pd	palladium
Ph	phenyl
PhCl	chlorobenzene
PhMe	toluene
PIDA	(diacetoxyiodo)benzene
PIFA	(bis(trifluoroacetoxy)iodo)benzene
PPh_3	triphenylphosphine
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
i-Pr	*iso*-propyl
*p*TSA	*para*-toluenesulfonic acid
Pyr	pyridine
R	a general abbreviation for an atom or a group of atoms
Rb	round-bottomed flask
RCM	ring closing metathesis
R_f	retardation factor
RNA	ribosenucleic acid
rt	room temperature
s	singlet
SOMO	singly occupied molecular orbital
SPS	solvent purification system

TBAB	tetrabutylammonium bromide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEA	Triethylamine
Tf	triflate
TFA	Trifluoroacetic acid
TfOH	triflic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMSBr	bromotrimethylsilane
TMSCl	trimethylsilyl chloride
TMSI	trimethylsilyl iodide
T3P	propylphosphonic anhydride
UV	ultraviolet

CONTENTS

1 FAVIPIRAVIR

COVID-19 pandemic is the worst health crisis the modern world has experienced and brought the entire global community to an impasse. Corona virus disease 2019 (COVID-19) is caused by an unidentified strain of corona virus, which is named severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) by WHO[1]. Rapid increase in number of infections overwhelmed the health services around the world. The inability to fully treat COVID-19 led to an increase in death toll and inspired a global collaborative effort in finding new drugs and effective treatments. Development of vaccine for COVID-19 and repurposing existing antivirals for emergency usage was carried out simultaneously. Multiple approved antivirals used for treating SARS, MERS, HIV/AIDS and malaria were repurposed to treat intial stages of COVID-19. Remdesivir, favipiravir, hydroxychloroquine, pirfenidone, baricitinib, camostat and lopinavir/ritonavir were among the small molecule antivirals that went to clinical trials for treating COVID-19[2].

The situation in Finland during COVID-19 pandemic was concerning both in the number of rising infections and death rate. Protocols were put in place to curb the rising infections which led to the shut down of research labs in the university, including our laboratories. The time off from laboratory work coincided with the commencement of clinical studies for repurposing existing antiviral drugs. Favipiravir, with its simple structure and highly functionalized pyrazine core, appeared to us as an interesting target to synthesize and to assist the global community in case molecules of this type were needed in large quantities. A thorough literature survey revealed that several complex synthetic routes were developed for the synthesis of favipiravir. These routes developed by both academia and industry often included harsh conditions, multiple steps, low yields and allergenic or toxic intermediates. Our motive was to reduce the number of steps and access favipiravir in a shorter time in an atom economical fashion.

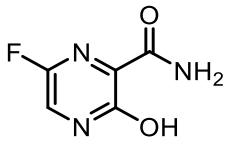
The core pyrazine ring of faviripavir was our initial starting point. The inherent acidity of the hydrogen atoms on a pyrazine ring is favourable for ortho-lithiation and subsequent substitution reactions. With methodologies available

to install a wide variety of functional groups, ortho-lithiation is an efficient way to functionalize electron deficient heteroaromatics like pyrazine[3,4]. Applying this methodology to access favipiravir seemed to be a promising way to reduce the number of steps in the synthetic route.

In the following discussion, the existing synthetic routes to faviripavir are presented. This is followed by a discussion of our synthesis designs and attempts to access favipiravir are described along with relevant literature. This chapter concludes with a summary and future prospects to be addressed.

1.1 Introduction

Favipiravir (**1.1)** (6-fluoro-3-hydroxypyrazine-2-carboxamide), sold under the trade name Avigan is a novel broad-spectrum, low molecular weight antiviral developed by Toyama Chemical Company (Figure 1). This modified pyrazine analogue was approved in Japan as an anti-influenza medicine[5], and is known to inhibit replication of influenza A and B. Favipiravir has shown activity against avian influenza and for many other RNA type viruses[6].



Favipiravir (**1.1**)

Figure 1: Small–molecule antiviral favipiravir.

Favipiravir can exist in several different tautomeric forms. Mirzaei and co-workers reported the structural analysis of favipiravir and examined the tautomeric structures of favipiravir (Figure 2) using DFT calculations[7]. Further studies involved calculation of molecular properties and subsequent docking studies on COVID-19 related enzymes. Structural analysis revealed tautomer T3 (-380891 kcal/mol) to be energetically favourable over tautomer T1 (-380886 kcal/mol) by 5 kcal/mol. The other two tautomers were less stable with energy values of -380871 kcal/mol for tautomer T2 and -380876 kcal/mol for tautomer T4. Although T3 was the most stable tautomer, tautomer T1 was the most active againt protease and polymerase macromolecules.

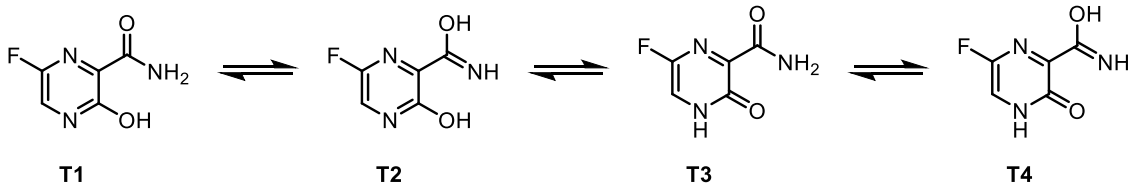


Figure 2: Tautomeric structures of favipiravir based on DFT calculations[7].

Inspite of lower energy, synthesis routes reported tautomer T1 instead of tautomer T3 as the final isolated product. The X-ray crystallographic studies (CCDC deposition number 969968) revealed the planar structure of favipiravir (tautomer T1) with the presence of an intramolecular O−H···O hydrogen bonding making a 6-membered ring as illustrated in Figure 3 [8]. The presence of favipiravir in enol form (T1) and not the energetically favourable keto form (T3) can be attributed to the presence of intramolecular hydrogen bonding. Li and co-workers reported the ^{1}H NMR of tautomer T1 in DMSO-*d*6 with the singlet at 13.41 ppm representing the hydrogen atom of hydroxyl group[9].

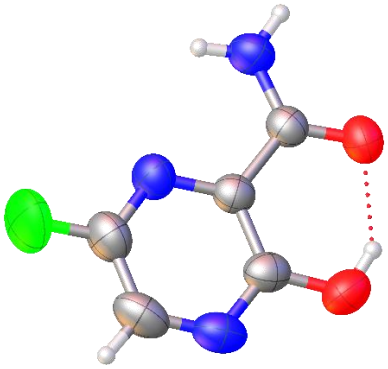


Figure 3: X-ray crystal structure of favipiravir[8].

The active form of favipiravir, the corresponding ribofuranosyl-5′-triphosphate (**1.3)** (Favipiravir-RTP), is generated intracellularly via phosphoribosylation of the prodrug favipiravir (Figure 4) and is known to inhibit RNA-dependent RNA polymerase (RdRp)[10]. Favipiravir-RTP potently binds to RdRp and inhibits RNA polymerase activity, resulting in disruption of viral transcription and replication. The unique structure of favipiravir offers various advantages in inhibiting the viral RdRp. The fluoro group improves the binding affinity with the RNA polymerase[11], and the purine nucleoside analogue replaces the purine nucleotide resulting in prevention of RNA chain elongation and subsequently causing chain termination.

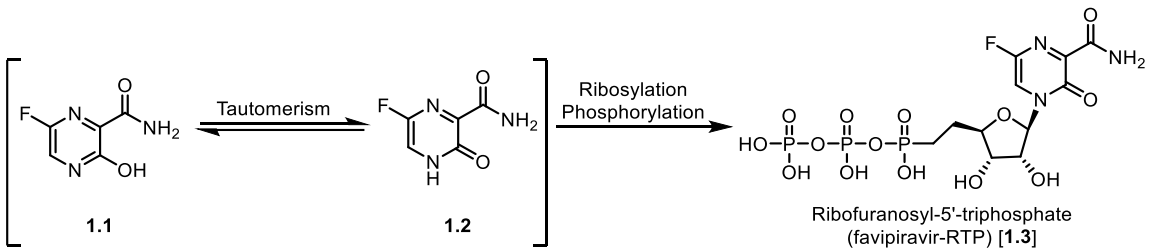


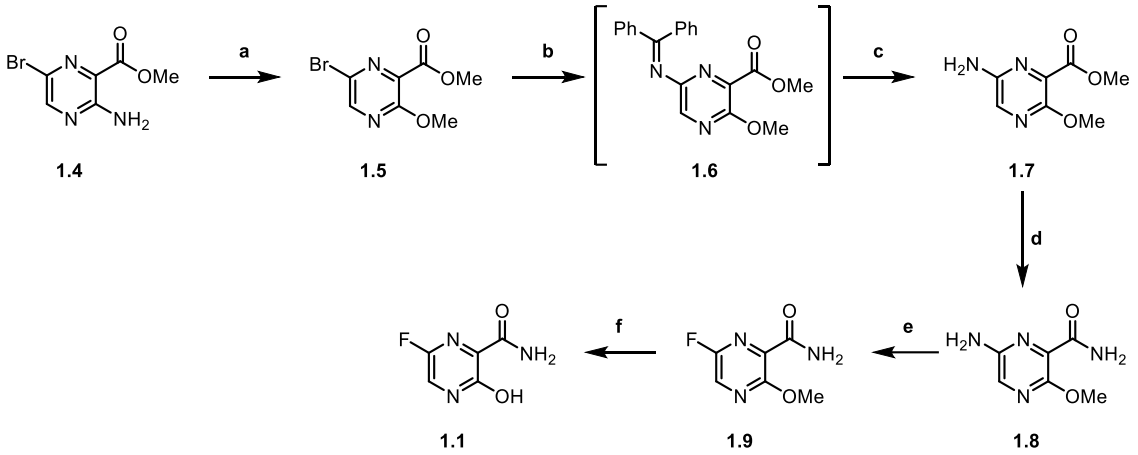
Figure 4: Metabolism of favipiravir to the active ingredient, favipiravir–RTP[10].

1.2 Reported syntheses of favipiravir

Favipiravir (**1.1**), with a molecular weight of 157, has been a complicated target to synthesize in spite of its structural simplicity. Favipiravir was first synthesized in 2000, and since then a variety of approaches have been disclosed. Reported synthesis routes to favipiravir can be divided into two categories, with one group being the routes developed by the innovator Toyama Chemical Company and the other group being routes developed by academia and generic companies.

1.2.1 Methods developed by Toyama Chemical Company

The first-generation medicinal chemistry route to favipiravir by Toyama Chemical Co. (Scheme 1) comprised six steps with an overall yield of 2%[12–14] starting from methyl 3-amino-6-bromopyrazine-2-carboxylate (**1.4)**. The synthesis begins with diazotization of **1.4** using conc. sulfuric acid and sodium nitrite followed by addition of MeOH to generate methoxy compound **1.5** in 35% yield. Subsequent cross-coupling of **1.5** with benzophenone imine was carried out using (*S*)-BINAP generating adduct **1.6**, which was then hydrolysed using 2M HCl to provide **1.7** in 43% yield over two steps. Treating methyl ester **1.7** with methanolic ammonia furnished primary amide **1.8** in 88% yield. Fluorination of **1.8** was accomplished by highly corrosive Olah reagent (sodium nitrite in 70% pyridinium hydrofluoride) with a yield of 86%, furnishing **1.9**. The final step involved *O*-demethylation using *in situ* generated TMSI to obtain favipiravir in 15% yield.

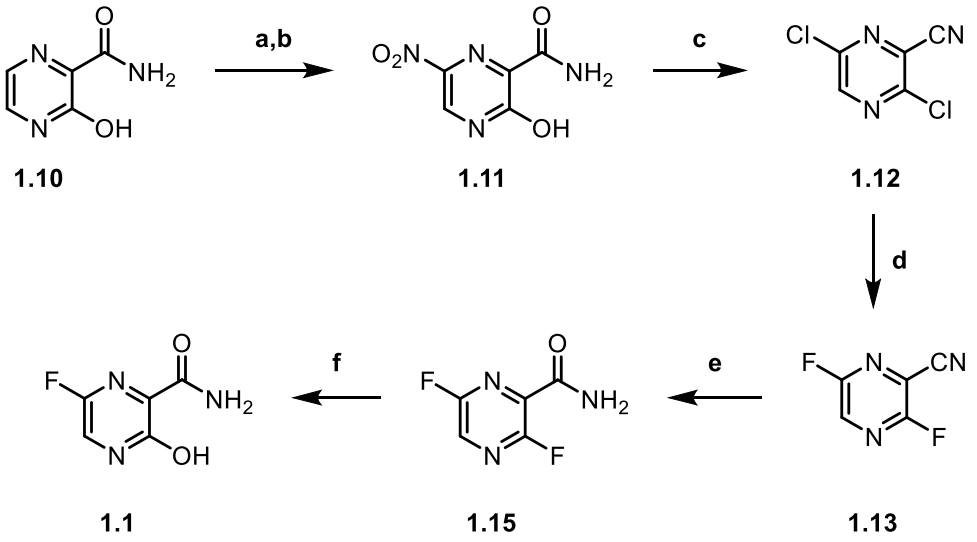


Scheme 1: First generation route to favipiravir by Toyama Chemical Co.[12–14]. Reagents and conditions: a) H_2SO_4, $NaNO_2$, MeOH, reflux, 35%; b) diphenylmethanimine, (*S*)-BINAP, *t*-BuONa, $Pd_2(dba)_3$, PhMe, 80 °C; c) 2 M HCl, THF, 43% (2-steps); d) NH_3, MeOH, 88%; e)$NaNO_2$, Pyr-HF, 86%; f) NaI, TMSCl, MeCN, 15%.

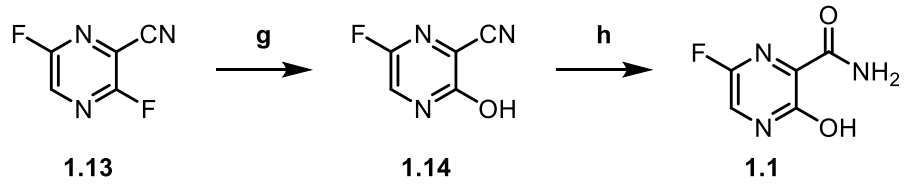
The second-generation route developed by Toyama Chemical Co. in 2001 was carried out on a multigram scale (section I of Scheme 2)[15]. The first step involved nitration of 3-hydroxypyrazine-2-carboxamide (**1.10)** using sodium nitrate in concentrated sulfuric acid, followed by neutralization with aq. NaOH to furnish product **1.11** in 65% yield. Subjecting the nitro compound **1.11** to phosphorus oxychloride and pyridine resulted in the formation of 3,6-dichloropyrazine-2-carbonitrile (**1.12)** by displacing both the nitro and hydroxyl groups with chlorine atoms along with the dehydration of amide group to nitrile in overall 77% isolated yield. Conversion of compound **1.12** to 3,6-difluoro-2-carbonitrile (**1.13)** was achieved in 79% yield using potassium fluoride and tetrabutylammonium bromide in DMSO. The nitrile group of **1.13** was hydrolyzed to amide using 12 M HCl to furnish 3,6-difluoropyrazine-2-carboxamide (**1.15)** in 82% yield. The final step included the selective 3-F group hydrolysis. This was accomplished using sodium bicarbonate in dioxane/water resulting in crystalline favipiravir with 52% yield. The synthesis of favipiravir was achieved in 5 steps with an overall yield of 17%, including chromatographic purifications and an allergenic intermediate **1.12**.

In 2009, Toyama Chemical Co. came up with an alternative route to favipiravir from 3,6-difluoropyrazine-2-carbonitrile (section II of Scheme 2)[16]. This approach involved the selective hydrolysis of the C3 fluoride using potassium acetate in aqueous DMF as the first step. The hydrolysis product **1.14** was purified in 82% yield in the form of a dicyclohexylammonium salt, which proved to be the best approach due to the high-water solubility of **1.14**. Further hydrolysis of **1.14** with aqueous hydrogen peroxide provided favipiravir in 89% yield after crystallization.

I) Second generation route by Toyama Chemical Co.

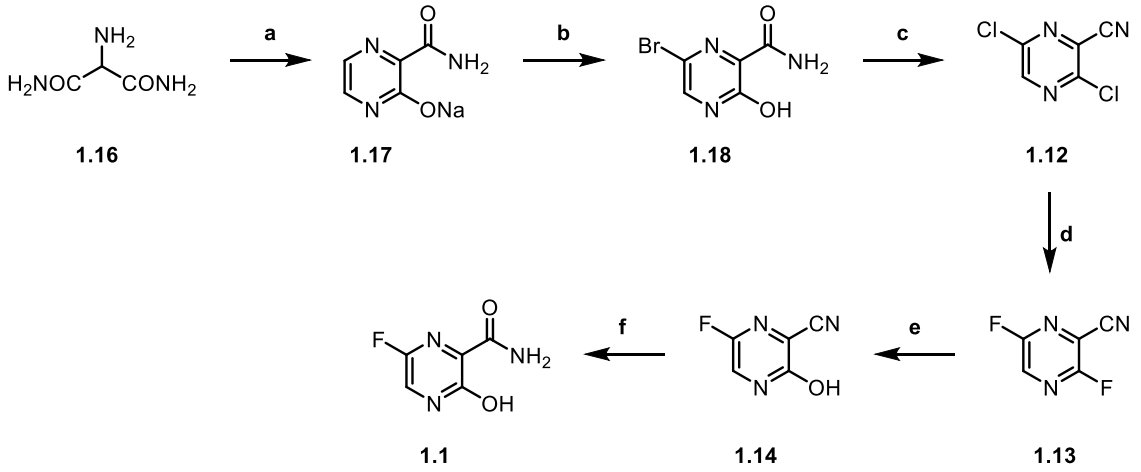


II) Alternative route to favipiravir from intermediate 1.13



Scheme 2: Second generation route to favipiravir by Toyama Chemical Co.[15,16]. Reagents and conditions: a) $NaNO_3$, Conc. H_2SO_4, 40 °C; b) aq. NaOH, 65%; c) $POCl_3$, pyridine, 100 °C, 77%; d) KF, TBAB, DMSO, 100 °C, 6 h, 79%; e) 12 M HCl, THF, 35 °C, 84%; f) $NaHCO_3$, dioxane, H_2O, 50 °C, 52%; g) KOAc, DMF, H_2O, 82%; h) H_2O_2, H_2O, 89%.

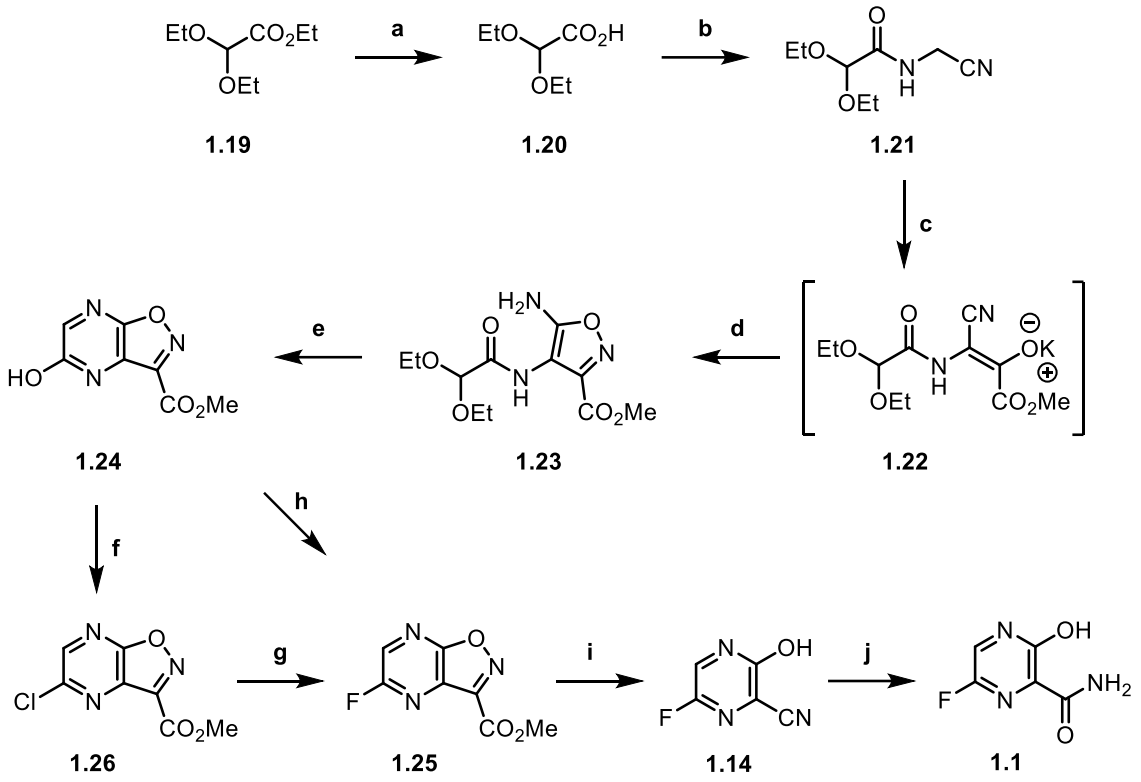
Realizing the importance of compound 3,6-dichloropyrazine-2-carbonitrile (**1.12)** in the synthesis of favipiravir, Nippon soda developed an improved route starting from 2-aminomalonic acid diamide (**1.16)** (Scheme 3)[17]. Treating compound **1.16** with glyoxal in aqueous sodium hydroxide solution resulted in the sodium salt of **1.17** in 92% yield, which was crystallized directly from the reaction mixture. Brominating sodium salt of **1.17** with molecular bromine resulted in **1.18** which was crystallized from water in 76% yield. Displacement of bromine and hydroxyl group of **1.18** with chlorine atoms was accomplished using phosphorus oxychloride and DIPEA in chlorobenzene furnishing 3,6-dichloropyrazine-2-carbonitrile (**1.12)** in 83% yield. The dichloro compound **1.12** was converted to difluoro compound **1.13** using KF and TBAB in DMSO with 92% yield. Further selective 3-F hydrolysis and nitrile hydrolysis to amide were accomplished using sodium acetate and concentrated sulfuric acid in two steps. This approach establishes a three-step route to 3,6-dichloropyrazine-2-carbonitrile (**1.12)**, and utilizes the conditions outlined in Scheme 3 to complete the synthesis of favipiravir. Overall yield of the scalable six-step second-generation route to favipiravir from compound **1.16** was 33%.



Scheme 3: Improved route to favipiravir by Nippon Soda[17]. Reagents and conditions: a) glyoxal, aq. NaOH, 92%; b) Br_2, MeOH/MeCN, 76%; c) $POCl_3$, DIPEA, PhCl, 100 °C, 83%; d) KF, TBAB, DMSO, 100 °C, 6 h, 79%; e) KOAc, DMF, H_2O, 82%; f) H_2O_2, H_2O, 89%.

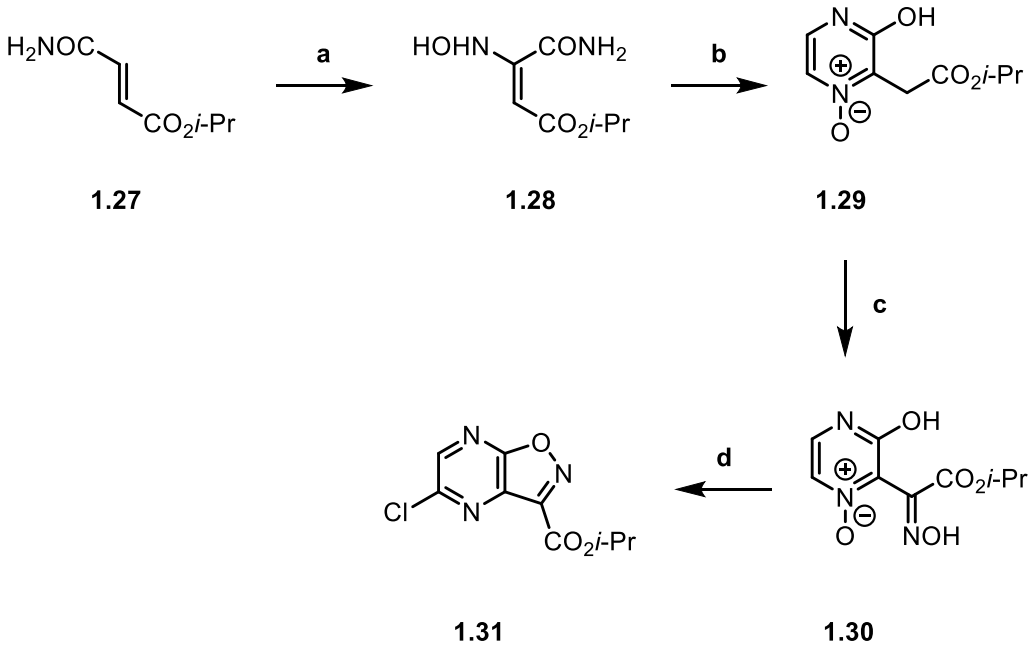
The third-generation route by Toyama Chemical Co. in 2013[18–20] was longer but made use of simple and inexpensive starting materials to make the core pyrazine ring system (Scheme 4). The strategy was to mask the ortho amide and hydroxyl functional groups as an isoxazole. The patent reports the first steps in kilogram scale while final steps were reported in gram scale.

Synthesis started by saponification of diethoxyacetate **1.19** to give diethoxyacetic acid (**1.20)** in 95% yield. The next step involved a CDI mediated acid amine coupling with amino-acetonitrile obtaining product **1.21** in 60% yield. Reaction of **1.21** with dimethyl oxalate with potassium *tert*-butoxide resulted in intermediate **1.22**, which was further treated with hydroxylamine hydrochloride and trifluoroacetic acid to furnish the oxazole **1.23** in 48% yield over two steps. Pyrazine ring was established by hydrolysis of acetal group using *p*-TSA to generate **1.24** in 58% yield. Replacing the hydroxyl group of **1.24** with a chloride using phosphorus oxychloride and triethyl amine hydrochloride resulted in compound **1.25** in 89% yield. At this stage various esters were synthesized, which gave differing yields in further steps and resulting in ease of operation. The fluorination of **1.25** was carried out with KF in DMSO to yield **1.26** in 84% yield. Addition of 1-chloro-2,4-dinitrobenzene resulted in cleaner reactions by acting as sink for excess fluorides. An alternate route where **1.24** was directly converted to the fluorinated compound **1.26** was reported with an isolated yield of 44% by using 2,2-difluoro-1,3-dimethylimidazolidine. The final steps include oxazole ring opening with aqueous sodium hydroxide resulting in nitrile **1.14**, after purification by an ion-exchange resin. Final hydrolysis of nitrile group was carried out with basic hydrogen peroxide to obtain favipiravir. The authors were able to crystallize favipiravir as its dicyclohexylamine salt resulting in 99.0% pure favipiravir.



Scheme 4: Third generation route to favipiravir by Toyama Chemical Co.[18–20]. Reagents and conditions: a) aq. NaOH, 70 °C, 95%; b) amino-acetonitrile, CDI, Et_3N, MeCN, 60 %; c) dimethyl oxalate, *t*-BuOK, THF; d) $NH_2OH.HCl$, TFA, MeOH, reflux, 48% (2-steps); e) *p*-TSA-H_2O, AcOH, 77 °C, 58%; f) $POCl_3$, Et_3N-HCl. 85 °C, 89%; g) KF, DMSO, 80 °C, 84%; h) 2,2-difluoro-1,3-dimethylimidazolidine, MeCN, 44%; i) NaOH, THF/H_2O, 90%; j) NaOH, H_2O_2, 84%.

Toyama Chemical Co. also reported a four-step synthetic route to intermediate **1.31** using maleic amide-ester **1.27** as the starting material (Scheme 5)[18–20]. Ester-amide **1.28** was obtained by Michael addition of hydroxylamine to **1.27** in aqueous isopropanol with an isolated yield of 59% after crystallization. Condensation of **1.28** using aqueous glyoxal solution along with sodium carbonate solution resulted in pyrazine *N*-oxide **1.29** in 62% yield after crystallization. The *N*-oxide **1.29** was further converted to oxime **1.30** using isoamyl nitrite and acetyl chloride with an 88% yield after crystallization from reaction mixture. Final step involving the ring closure and chlorination was accomplished on treatment of **1.30** with phosphoros oxychloride affording isopropyl ester **1.31** in 49% yield. Although the yields have been moderate in most of the steps, the advantage is in the isolation of products. All the products are crystalline, and several products were directly crystallized from the reaction mixture.



Scheme 5: Alternate route to intermediate **1.31** by Toyama Chemical Co.[18–20]. Reagents and conditions: a) aq. NH_2OH, *i*-PrOH, 59%; b) glyoxal, aq. Na_2CO_3, *i*-PrOH, 41 °C, 62%; c) isoamyl nitrite, CH_3COCl, *i*-PrOH, 88%; d) $POCl_3$, PhMe/DMF, 70 °C, 49%.

In summary the innovative routes developed by Toyama Chemical Company included significant developments from first-generation synthesis route to the third-generation synthesis route in terms of yields, separation, and scalability.

The first-generation route focused mainly on obtaining small quantities of compound for various screening studies and initial testing. Unfortunately, this was not appropriate for scaling up due to the use of highly corrosive reagents, expensive catalysts, and purification hurdles.

The second-generation route provided a six-step scalable route to favipiravir owing to the contributions from both Toyama Chemical Co.[15,16] and Nippon Soda[17]. The overall yield of favipiravir has been increased to 33% on a scale as compared to the first-generation route. The Nippon Soda route provides a short and scalable route to 3,6-dichloropyrazine-2-carbonitrile (**1.12)** (Scheme 3)[17] from inexpensive and commercially available diamide **1.16** in three-steps. This was followed by Toyama Chemical Co. route (**1.12** → **1.13** → **1.14** → **1.1**, Scheme 2) which involves purification of intermediate **1.14** as a dicyclohexylamine salt[16]. The only drawback of this route was the late-stage intermediate 3,6-difluoropyrazine-2-carbonitrile (**1.13)**, which was reported to be volatile and have high skin irritancy requiring special equipment and handling techniques.

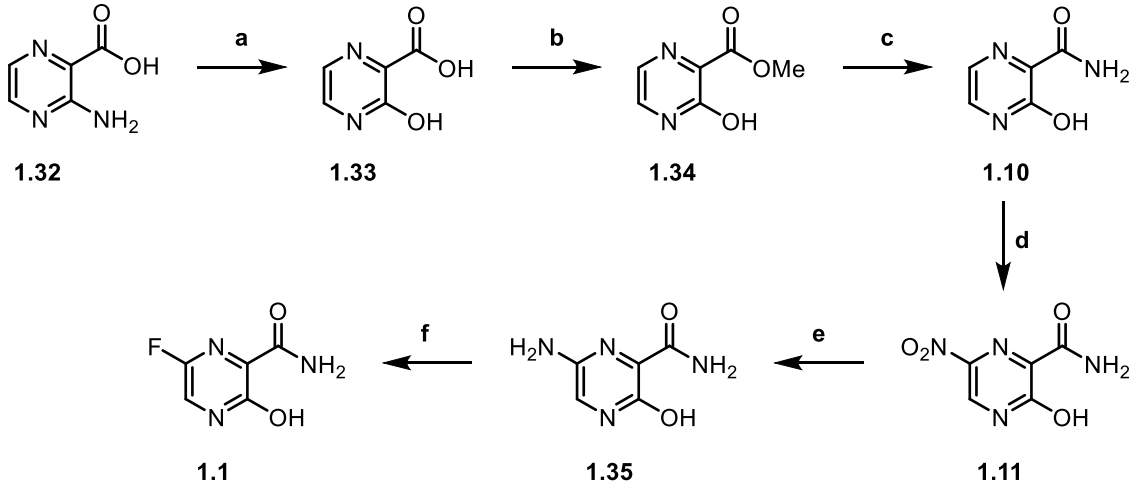
The third-generation route has an overall yield of 9% with nine-steps (Scheme 4) or 10% (Scheme 4 & Scheme 5). Due to modest yields and length of the synthesis, this has not been an attractive route to synthesize favipiravir. Most of the compounds reported were liquids and required vacuum distillation. This

approach has an advantage from the safety point of view. It skips the difluoro intermediate **1.13** reported to be volatile and a skin irritant, thereby eliminating the need for special equipment.

1.2.2 Methods developed by academic laboratories and generic companies

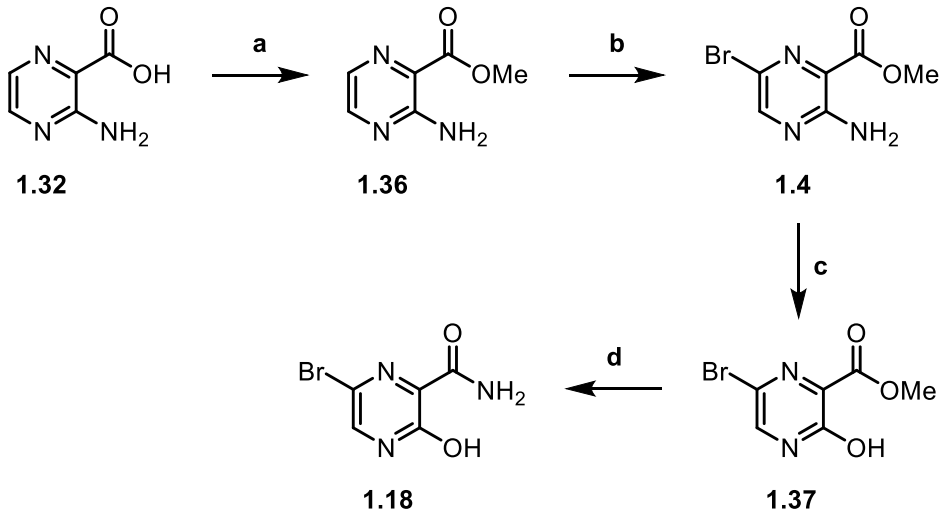
A variety of synthetic routes have been developed by generic companies and academic laboratories all over the world. Some of these focus on making key intermediates, but a range of syntheses have been developed for the full synthesis of favipiravir using a wide range of commercially available starting materials.

In 2012, Zhang and co-workers from Shandong Qidu Pharmaceutical company patented a short route to favipiravir starting from 3-aminopyrazine-2-carboxylic acid (**1.32)** (Scheme 6)[21]. Nitration of **1.10** as described in Scheme 6 gave the nitro compound **1.11** in 76% yield. Hydrogenation of **1.11** over Pd/C gave the corresponding amine **1.35** in 65% yield after crystallization. Treatment of amine **1.35** with 70% pyridinium hydrofluoride and sodium nitrite furnished favipiravir in 70% yield after an aqueous workup. No information regarding the purity of favipiravir was mentioned and the three-step route from **1.10** to favipiravir had an overall yield of 34%.



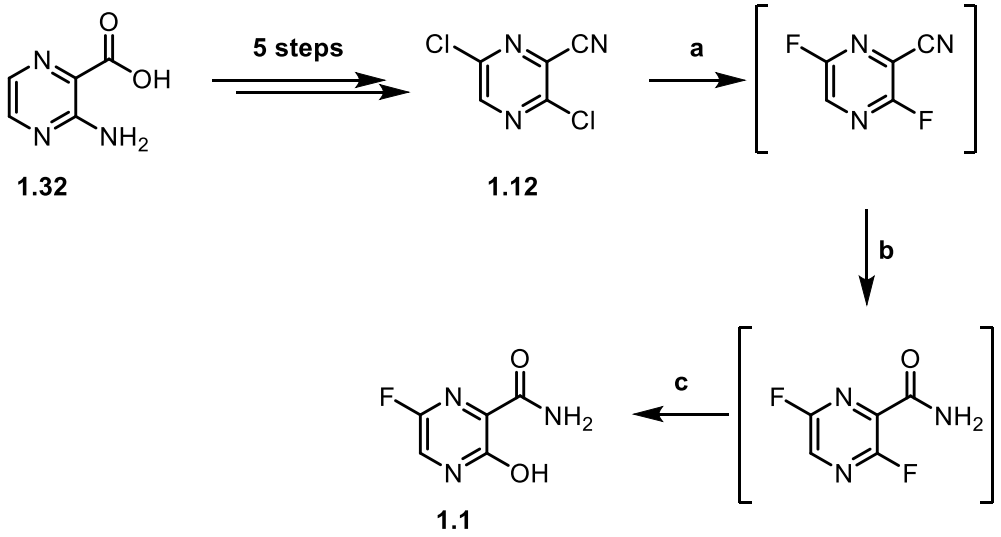
Scheme 6: Synthesis route to favipiravir by Zhang and co-workers[21]. Reagents and conditions: a) 1 M HCl, $NaNO_2$, 0 °C, 90%; b) H_2SO_4, MeOH, 40 °C, 92%; $NH_3.H_2O$, MeOH, rt, 95%; d) H_2SO_4, HNO_3, -5 °C, 76%; e) H_2, 5% Pd/C, AcOH, 10 °C, 65%; f) $NaNO_2$, 70% Pyr-HF, -20 °C, 70%.

A route from Zhang and co-workers in year 2013 (Scheme 7)[22] arrives at the intermediate **1.18** of Nippon Soda synthesis (Scheme 3) starting from 3-amino-2-pyrazinecarboxylic acid (**1.32)**. Esterification of **1.32** was followed by bromination using NBS, diazotization, hydrolysis and amide formation resulted in the required intermediate **1.18**.



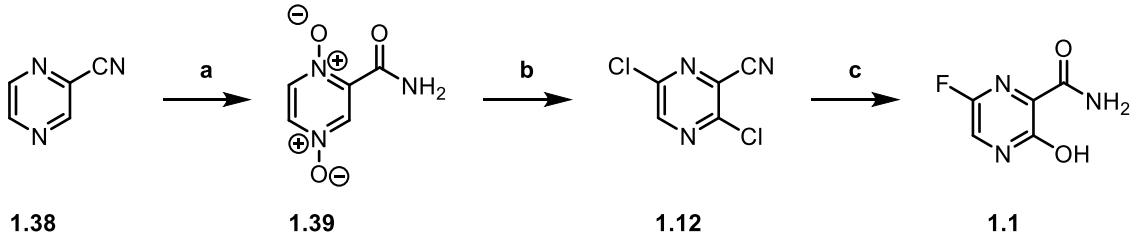
Scheme 7: Route to intermediate **1.18** by Zhang and co–workers[22]. Reagents and conditions: a) H_2SO_4, MeOH, 0 °, 8 h, 70%; b) NBS, MeCN, rt, 24 h, 87%; c) H_2SO_4, $NaNO_2$, H_2O, rt, 2 h, 93%; d) $NH_3.H_2O$, rt, 3 h, 94%.

A key method involving one-pot conversion of 3,6-dichloro-2-pyrazinecarbonitrile (**1.12)** to favipiravir has been developed by Liu and co-workers. This procedure avoids the isolation of volatile 3,6-difluoro-2-pyrazinecarbonitrile (**1.13)** which is a known skin irritant (Scheme 8)[9]. The optimized yield turned out to be 60% over three steps.



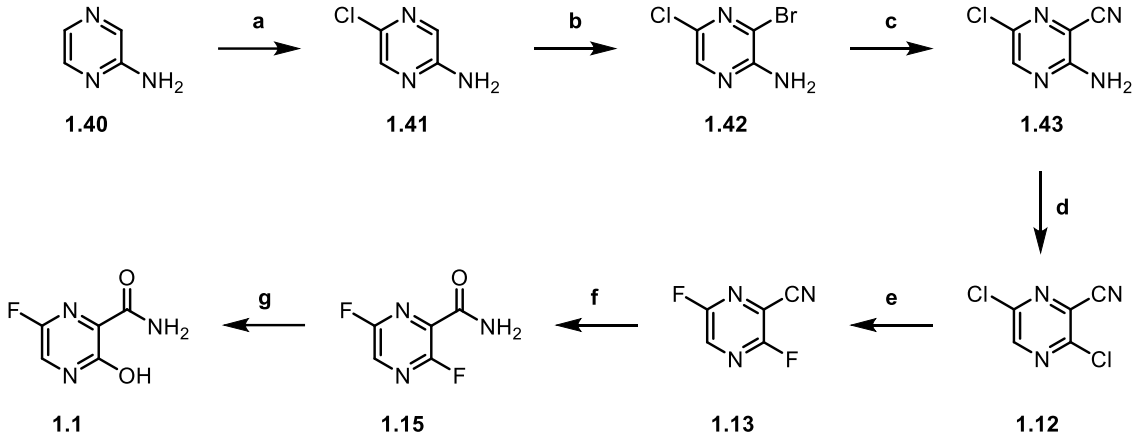
Scheme 8: One-pot conversion of 3,6-dichloro-2-pyrazinecarbonitrile to favipiravir[9]. Reagents and conditions: a) KF, TBAB, DMSO, 50 °C; b) K_2CO3, H_2O_2, DMSO, 25 °C; c) $NaHCO_3$, H2O, 50 °C, 60% (3-steps).

A report by Li revealed the synthesis of 3,6-dichloro-2-pyrazinecarbonitrile (**1.12)** in 2 steps starting form Pyrazine-2-carbonitrile (**1.38)** (Scheme 9)[23]. The scheme involves the generation of bis-*N*-oxide **1.39** followed by subsequent chlorination to generate **1.12**.



Scheme 9: Two-step route to 3,6-dichloro-2-pyrazinecarbonitrile[23]. Reagents and conditions: a) 30% H_2O_2, AcOH, reflux, 57%; b) $POCl_3$, Et_3N, reflux, 45%; c) i. KF, TBAB, DMSO, 50 °C; ii. K_2CO3, H_2O_2, DMSO, 25 °C; iii. $NaHCO_3$, H2O, 50 °C, 60% (3-steps).

Xie and co-workers developed a four-step synthesis of **1.12** starting from 2-aminopyrazine (**1.40)** (Scheme 10)[24]. Chlorination of 2-aminopyrazine using TSA followed by bromination via NBS gave compound **1.42**. Palladium catalyzed cyanation mediated by CuI followed by conversion of amine to chloride using *t*-butyl nitrite and titanium tetrachloride resulted **1.12** in 48% yield over four steps. The intermediate **1.12** was then converted to favipiravir over 3 steps to complete the synthesis.

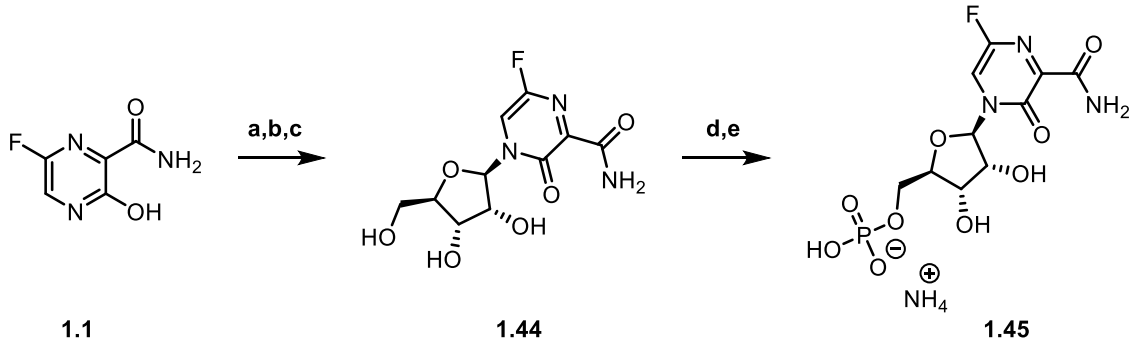


Scheme 10: Four-step route to 3,6-dichloro-2-pyrazinecarbonitrile by Xie and co-workers[24]. Reagents and conditions: a) TSA (*N*-chloro-*N*-methoxy-4-toluenesulfonamide), MeCN, 80%; b) NBS, DCM, 87%; c) NaCN, CuI, $Pd(PPh_3)_4$, DMF, 85%; d) *t*-butyl nitrite, DCM, $TiCl_4$, 81%; e) KF, TBAB, DMSO, 60%; f) Conc. HCl, THF, 75%; g) $NaHCO_3$, 1,4-dioxane, H_2O, 82%.

In summary, these reports present the synthesis of favipiravir from a variety of starting materials such as pyrazine-2-carbonitrile **(1.38)**, 3-aminopyrazine-2-carboxylic acid **(1.32)**, 2-aminopyrazine **(1.40)**, and 3-hydroxypyrazine-2-carboxamide **(1.10)**. Though many of these academic routes involve issues with scaling up and product purity, two of these methods stand out for the significant advances they reported in the synthesis of key intermediates and favipiravir. One of them is the three-step favipiravir synthesis starting from 3-hydroxypyrazine-2-carboxamide (**1.10)** (Scheme 6) and the other being one-pot conversion of 3,6-dichloropyrazine-2-carbonitrile to favipiravir avoiding the isolation of volatile intermediate **1.13** (Scheme 8).

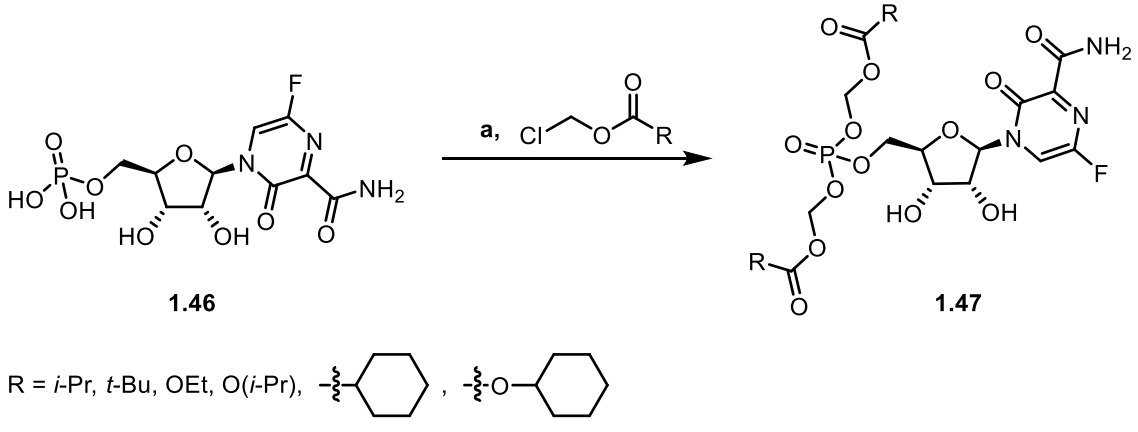
1.3 Modifications to favipiravir

A report in 2013 by Naesens and co-workers describes the transformation of favipiravir to its active metabolite favipiravir-RTP to be the key limiting step in the antiviral action mechanism[25]. This discovery paved way for various modifications to be applied to favipiravir. One such attempt was at the preparation of favipiravir derivatives based on monosaccharides. Successful synthesis of favipiravir ribonucleoside and its 5′-monophosphate **1.44** (Scheme 11) followed by various chemical stability studies revealed the remarkable labile nature of the derivatives[26]. It was observed that even under very mild conditions the nucleoside bond was prone to cleavage along with the decomposition of the heterocyclic fragment.[26]



Scheme 11: Monosaccharide based favipiravir derivatives[26]. Reagents and conditions: a) $O(SiMe_3)_2$, $(NH_4)_2SO_4$, 140 °C, 1 h; b) 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose $SnCl_4$, MeCN, rt, 7 h; c) Bu_2SnO, MeOH, 80 °C, 24 h, 40%; d) $POCl_3$, pyridine, H_2O–MeCN, 0 °C, 20 min; e) NH_4HCO_3, H_2O, 0 °C, 30 min, 50%.

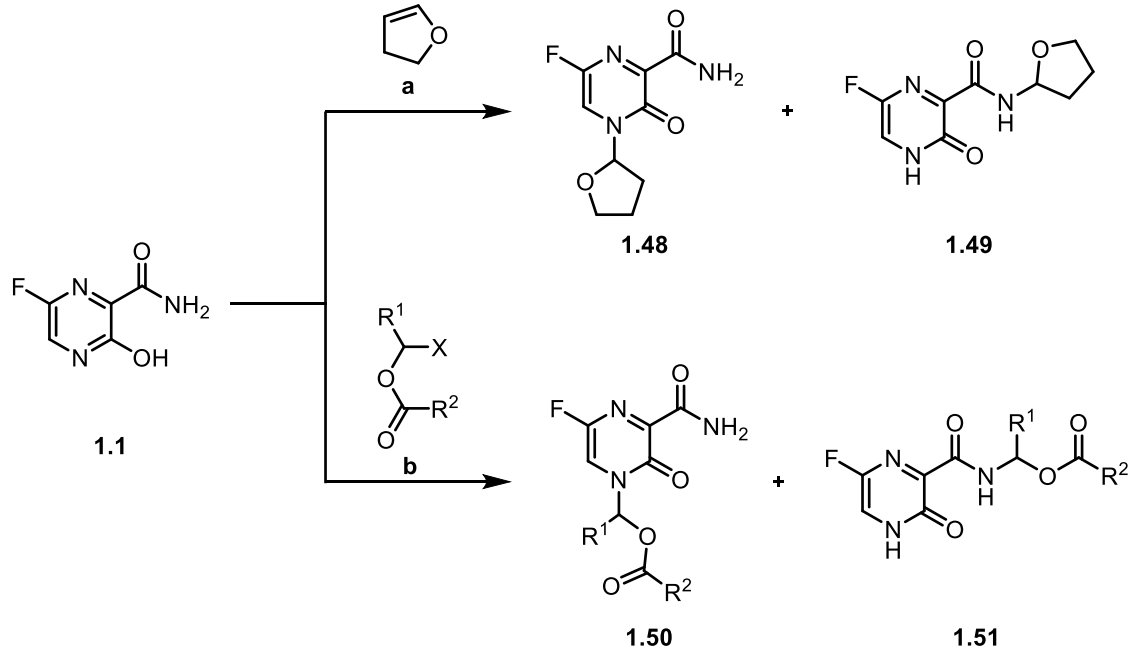
Alkylation of phosphate moiety resulted in more stable derivatives of favipiravir ribosides with comparable antiviral activity (Scheme 12)[27].



Scheme 12: Alkylated derivatives of favipiravir ribonucleosides[27]. Reagents and conditions: a) Et_3N, N_2 atm, DMF, rt, 13-27%.

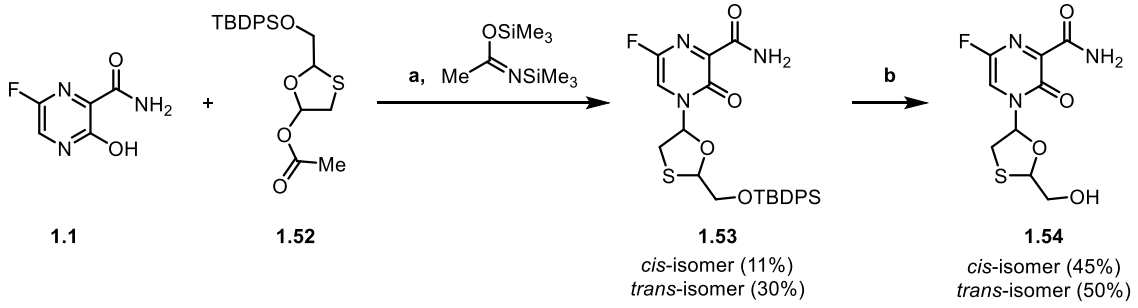
Mimicking the glucosidic bond formation in the riboside triphosphate, modifications were attempted to the pyrazine ring nitrogen of favipiravir by treatment with various esters (Scheme 13). Synthesized compounds had better

pharmacokinetic characteristics and strong antiviral activity against H1N1 influenza virus in comparison to favipiravir[28]. Substitution of amide group in the reaction resulted in unwanted byproducts. (Competing side reaction of amide group substitution resulted in undesired byproducts **1.49**, **1.51**.)



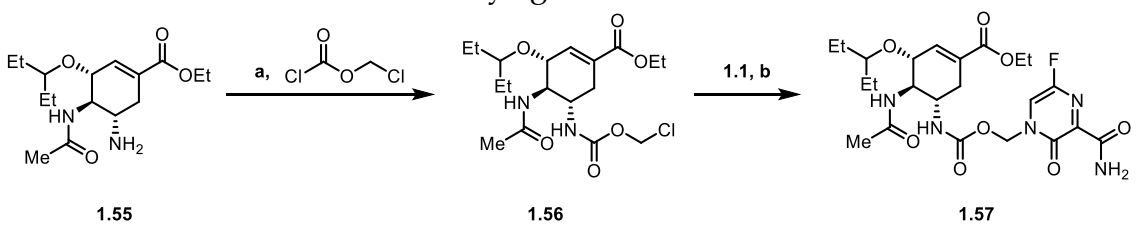
Scheme 13: Modification to favipiravir by Li and co-workers[28]. Reagents and conditions: a) PPTS, THF, rt, 72 h; b) Et_3N, N_2 atm, DMF, rt, 24 h.

An interesting discovery has been made when favipiravir was modified using oxathiolane derivative **1.52** (Scheme 14). The *cis* and *trans* isomers of 2-(hydroxymethyl)oxathiolane-containing derivative formed exhibited activity against H1N1 influenza virus and HIV respectively[29].



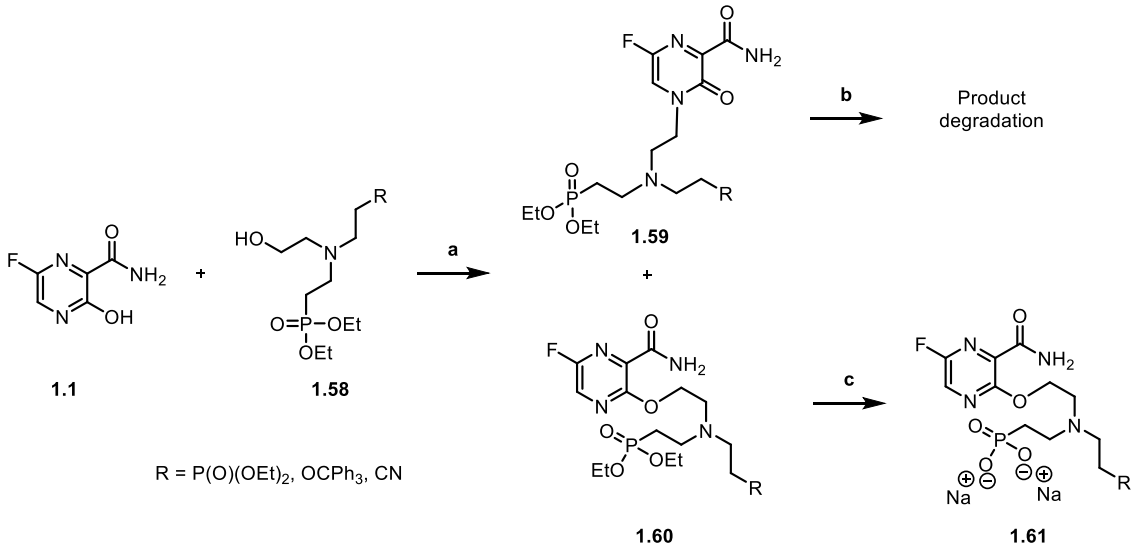
Scheme 14: Oxathiolane based derivatives of favipiravir[29]. Reagents and conditions: a) $SnCl_4$, N_2 atm, MeCN, rt, 20 min; b) NH_4F, MeOH, rt, 8h.

Combining favipiravir and another antiviral drug oseltamivir **1.55** in one molecule (Scheme 15) manufactured a synergistic effect. The resulting compound **1.57** had enhanced antiviral activity against H5N2 influenza virus[30].



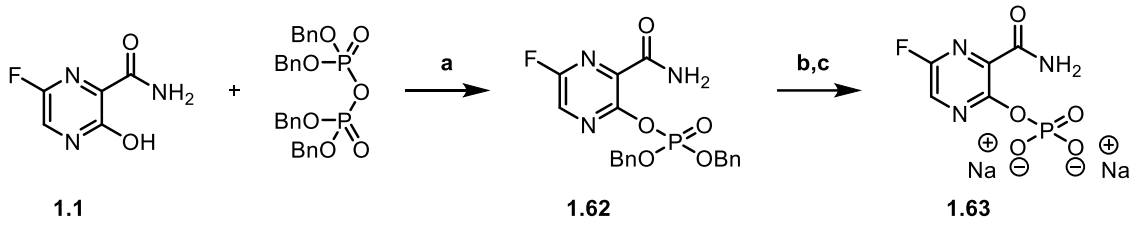
Scheme 15: Derivatizing favipiravir using oseltamivir[30]. Reagents and conditions: a) DMEA, MeCN, rt, 3 h; b) **1.1**, K_2CO_3, MeCN, reflux, 5 h, 69%.

Alkylation of favipiravir with nitrogen-containing acyclic phosphonates **1.58** under Mitsunobu conditions led to the generation of *N*- and *O*-regioisomers **1.59** and **1.60**. Obtained *N*-isomers were unstable under the deprotection conditions (Scheme 16). However, few of the *O*-regioisomers **1.60** exhibited selective inhibition of human enzymes HGPRT and PfHGXPRT. When the nitrogen-containing acyclic phosphonates were replaced by oxygen-containing acyclic phosphonates as alkylating agents, *O*-alkylation products of favipiravir were obtained exclusively[31].



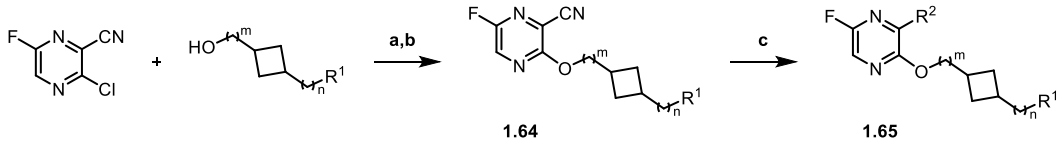
Scheme 16: Alkylation of favipiravir with acyclic phosphonates[31]. Reagents and conditions: a) PPh_3, DIAD, PhMe, 60 °C, 10 min, 73-94%; b) i. TMSBr, pyridine, rt, 48 h; ii. DOWEX; c) i. TMSBr, pyridine, rt, 48 h; ii. DOWEX, 26-92%.

Wu and co-workers reported the synthesis of favipiravir phosphate **1.63** (Scheme 17), with enhanced solubility and pharmacokinetic properties[32].



Scheme 17: Synthesis of favipiravir phosphate **1.63**[32]. Reagents and conditions: a) 60% NaH, DMF, rt, 3 h, 36%; b) TMSBr, DCM, rt, 4 h; c) NaOH, H_2O, 80%.

Further trials towards derivatization of favipiravir involved substituted cyclobutanes. A series of such cyclobutane-containing favipiravir derivatives **1.65** (Scheme 18) were active against various influenza virus strains[33].



m,n = 0, 1
R^1 = OH, CO_2Me; R^2 = $C(O)NH_2$, $C(NH)NH_2$, C(NH)NHOH

Scheme 18: Substituted cyclobutane based favipiravir derivatives[33]. Reagents and conditions: a) SO_2Cl_2, Et_3N, DCM, 0 °C, 5 h; b) NaH, DMF, 130 °C, 25 h; c) NH_4Cl or $NH_2OH.HCl$, NaOH, MeOH, rt.

1.4 Our retrosynthesis

Our retrosynthetic analysis presented in Figure 5 focused on minimizing the number of steps required to make **1.1**. Our short synthesis plan involved making the intermediate cores **1.66** and **1.67** from commercially available starting materials. Using 2,5-dichloropyrazine (**1.68)**, the first approach involved installation of an ester functionality at the ortho position using an ortho-lithiation strategy to arrive at intermediate **1.66**. While the second approach involved carbamoylation of **1.68** using Minisci reaction to obtain the required intermediate **1.67**. Our plan also included exploring the synthesis of 2,5-dichloropyrazine (**1.68)** from 2,5-diketopiperazine (**1.69)**, which was cheap and abundant for industrial scale synthesis.

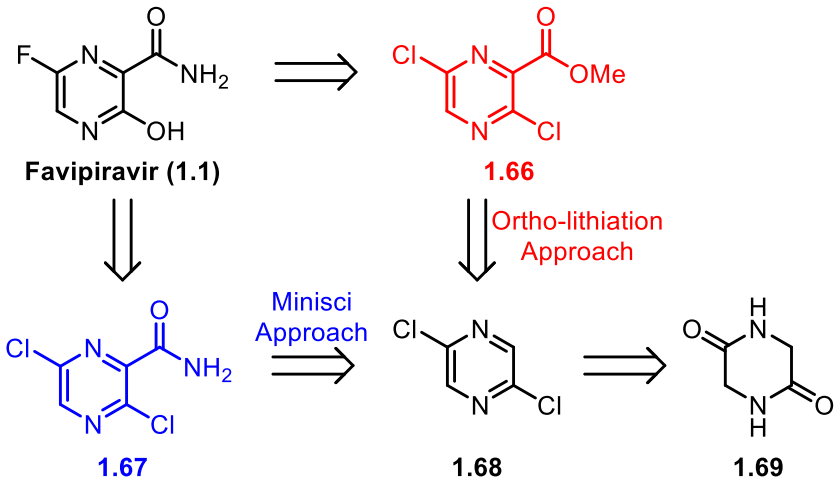


Figure 5: Retrosynthetic analysis for favipiravir.

1.5 Studies towards synthesis of favipiravir

With definite target molecule and defined synthetic plan in hand, the synthesis of **1.1** was divided in three phases. The plan to arrive at favipiravir was based on selectively functionalizing 2,5-dichloropyrazine (**1.68**) using either ortho-lithiation or Minisci reaction (Figure 6). Thus, the emphasis was on synthesizing 2,5-dichloropyrazine (**1.68**) in a reliable and efficient way and constituted the first phase of our synthesis plan. The second and third phases concentrated on ortho-lithiation and Minisci strategies to get to the planned intermediates **1.66** & **1.67** respectively. This section follows a similar sequence explaining the relevant literature and work done in all three phases.

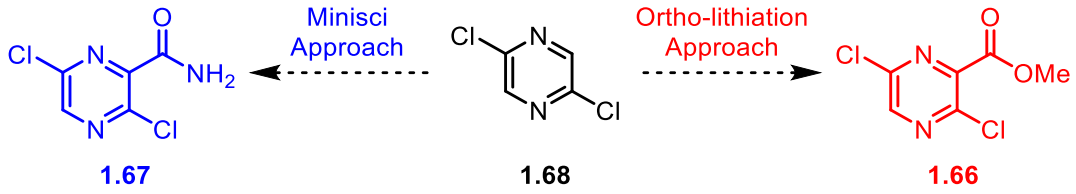


Figure 6: Synthesis plan illustrating functionalization of 2,5-dichloropyrazine (**1.68**).

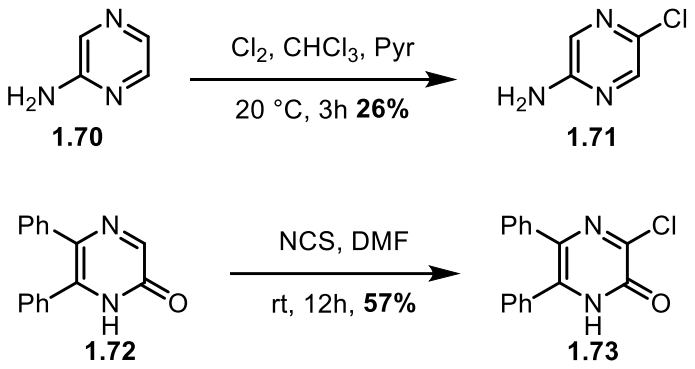
1.5.1 Synthesis of 2,5-dichloropyrazine

The following section describes the procedures reported in literature to synthesize monochloro- and dichloropyrazine compounds. The literature survey is then succeeded by details of our attempts at synthesizing 2,5-dichloropyrazine (**1.68**).

1.5.1.1 Literature survey of synthesis of 2,5-dichloropyrazine

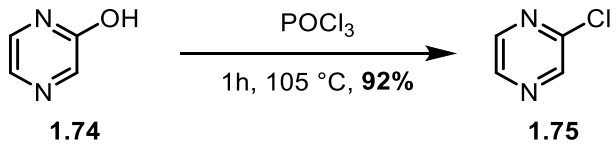
Pyrazine and substituted pyrazines comprise the core of several natural products and pharmaceuticals used in our day-to-day life[34]. Halopyrazines makeup a key class of intermediates due to their relative ease of displacing the halogen atoms to incorporate various functionalities. Chloropyrazines with high availability and better reactivity are preferred over other halopyrazines as ideal starting materials.

Although the mono- and dihalopyrazines are structurally relatively simple heterocycles, their synthesis is surprisingly challenging. Direct nuclear halogenation of pyrazine ring required elevated temperatures and harsh conditions to install multiple halogen atoms onto the pyrazine ring. The earliest published protocols to make chloropyrazine involved vapor phase chlorination of pyrazine at 400 °C in a steel tube. The presence of activated carbon or copper chloride allowed the chlorination to take place at lower temperatures. However, employing a higher chlorine to pyrazine ratio at 580 °C resulted in the formation of tetrachloropyrazine[35]. Other routes involving elemental chlorine[36] and *N*-chlorosuccinimide[37] as chlorine source are illustrated in Scheme 19.



Scheme 19: Examples of chlorination of substituted pyrazines from the literature using elemental chlorine and NCS[35–37].

A traditional approach to prepare chloropyrazine involved treating hydroxypyrazine (**1.74**) with phosphorus oxychloride as shown in Scheme 20[38].

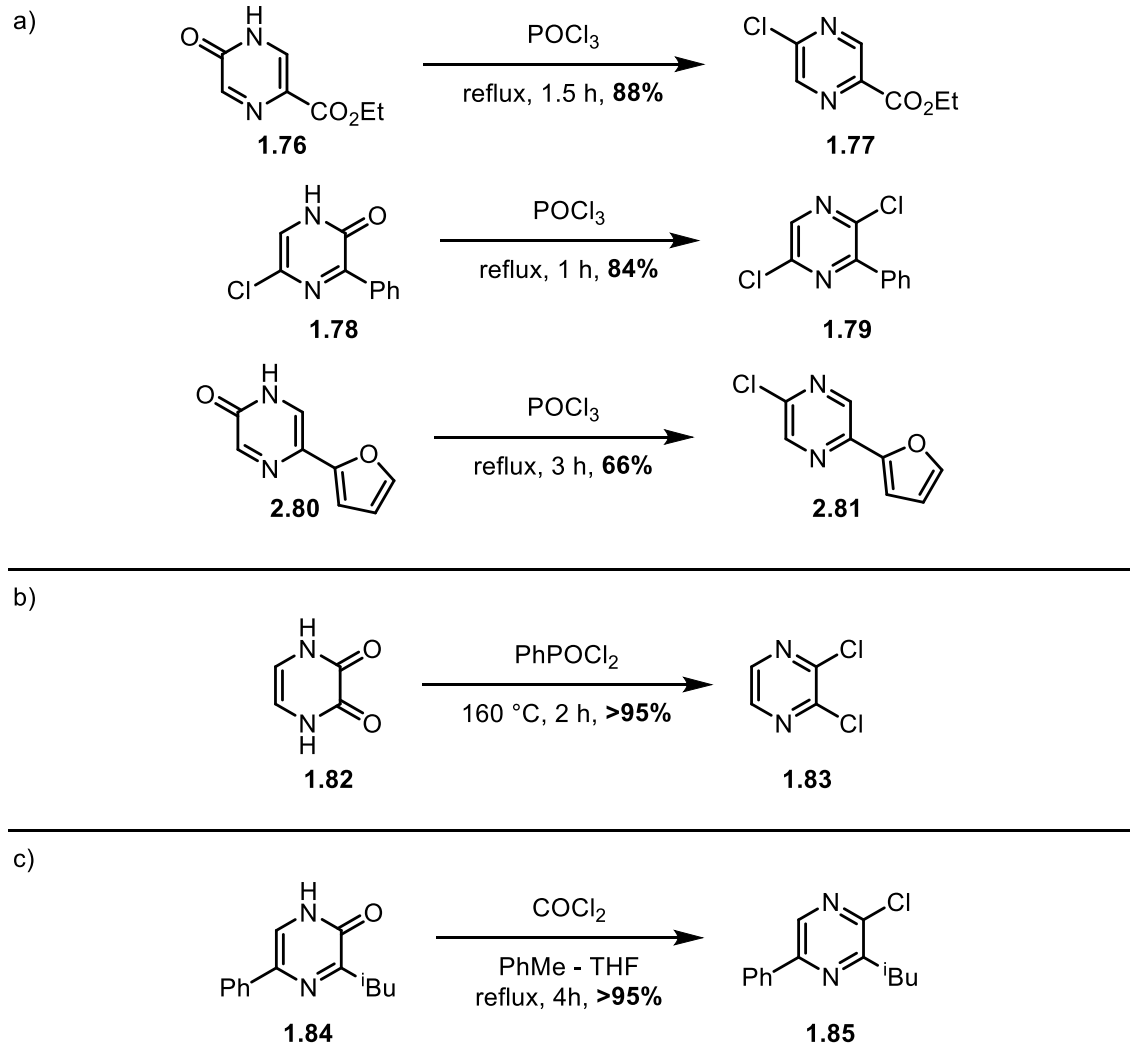


Scheme 20: Preparation of chloropyrazine[38].

Alternative methods to make chloropyrazines involved treatment of tautomeric pyrazinones or pyrazine *N*-oxides with phosphorus oxychloride, while other halopyrazines required either a direct halogenation procedure or transhalogenation of chloropyrazines.

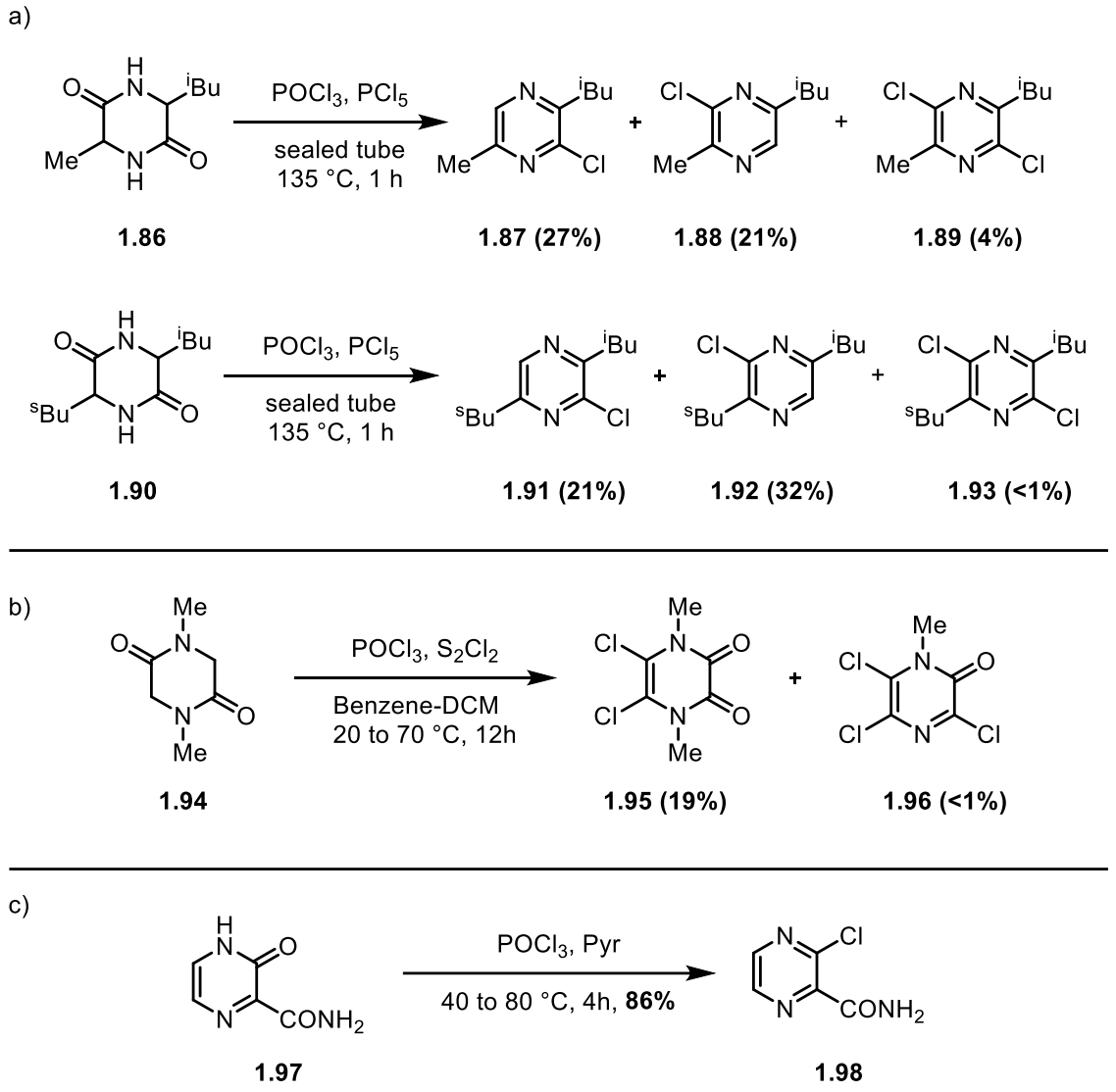
1.5.1.1.1 Chloropyrazines from pyrazinones

Chloropyrazines from pyrazinones can be made by using various chlorinating reagents like phosphorus oxychloride[39–41], phenylphosphonic dichloride[42] and phosgene[43] as shown in Scheme 21.



Scheme 21: Examples of chlorination of pyrazinones from the literature using a) phosphorus oxychloride[39–41], b) phenylphosphonic dichloride[42] and c) phosgene[43].

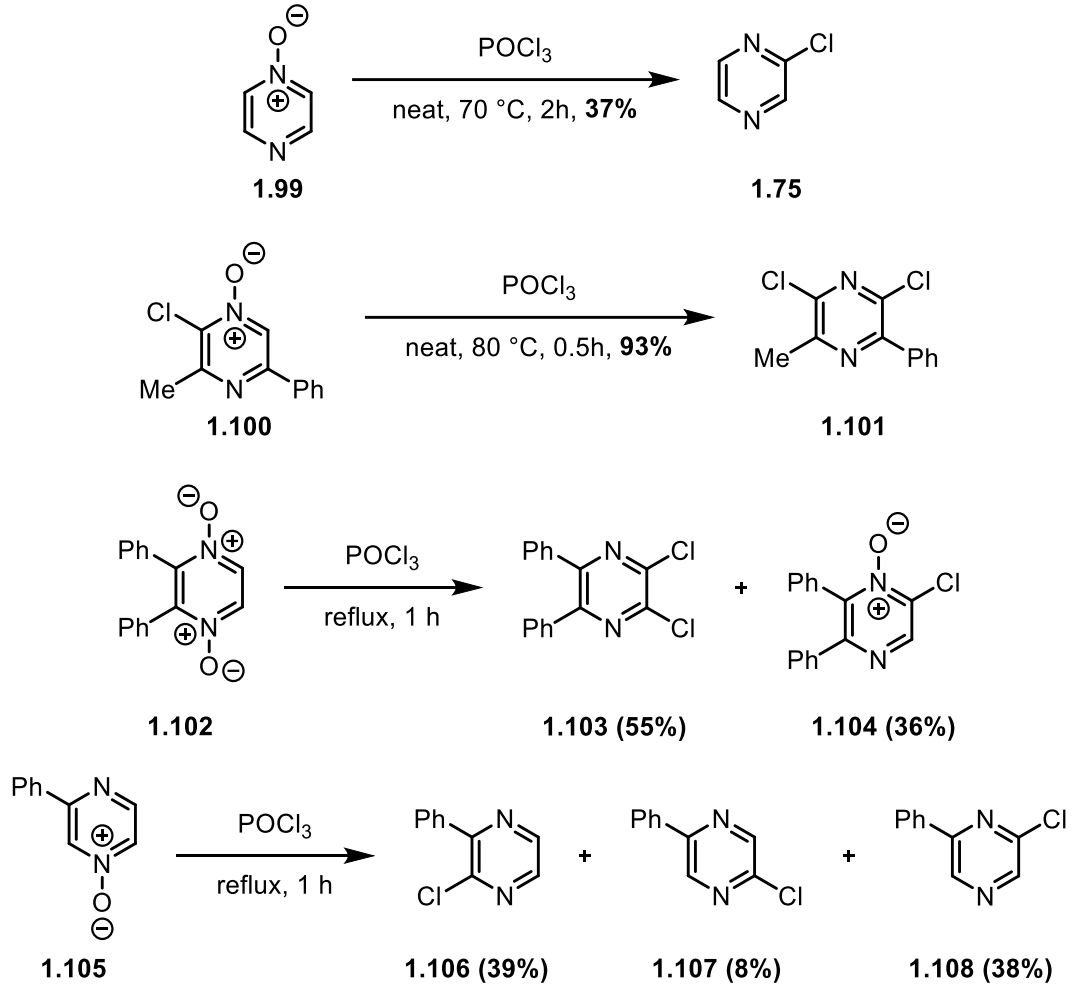
Although phosphorus oxychloride with pyrazinone results in the formation of the desired chloropyrazine, it is also used in combination with phosphorus pentachloride[44] or sulfur monochloride[45] or with a tertiary amine base[46] (Scheme 22). A mixture of reagents is typically used, if the reaction with neat phosphorus oxychloride is either too slow or additional chlorination of pyrazine ring is needed.



Scheme 22: Examples of chlorination of pyrazinones from literature using a mixture of chlorinating reagents[44–46].

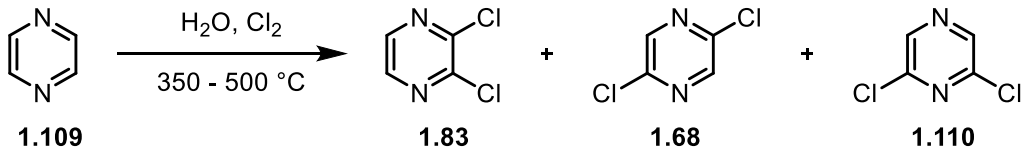
1.5.1.1.2 Chloropyrazines from pyrazine-*N*-oxides

Generating chloropyridine by treating pyridine *N*-oxide with $POCl_3$ is a well-known reaction[47]. Likewise, the procedure has been applied to pyrazine *N*-oxides to generate chloropyrazines[48–51]. Scheme 23 illustrates few reactions involving preparation of chloropyrazines from pyrazine *N*-oxides.



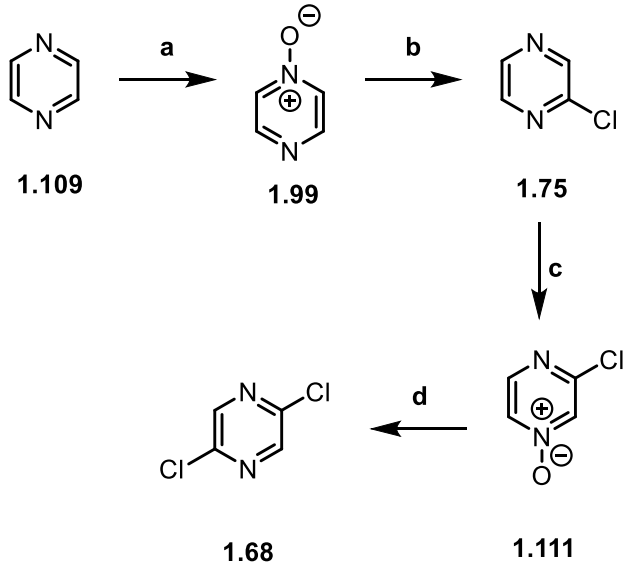
Scheme 23: Examples of chlorination of pyrazine *N*–oxides[48–51].

A literature survey suggested numerous procedures to synthesize chloropyrazine in presence of various substituents and functionalities[35]. Further focus on synthesis of dichloropyrazines revealed the necessity of extremely harsh conditions starting from pyrazine. A simple Reaxys search for 2,5-dichloropyrazine resulted in a multitude of patents and reports utilizing very high temperatures furnishing all possible regioisomers as shown in Scheme 24.



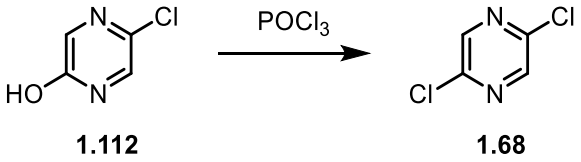
Scheme 24: Dichlorination of pyrazine using elemental chlorine.

Klein and co-workers[52] reported a four-step synthesis to **1.68** starting from pyrazine. As shown in Scheme 25, the route included sequential formation of *N*-oxide using peracids followed by chlorination using phosphorus oxychloride.



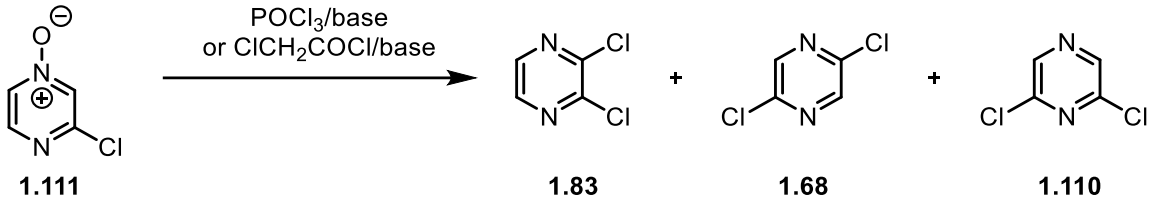
Scheme 25: Four-step route to 2,5–dichloropyrazine[52] reported by Klein and co-workers. Reagents and conditions: a) AcOH, 30% H_2O_2, 95 °C, 8 h, 60%; b) $POCl_3$, reflux, 0.5 h, 25%; c) AcOH, 30% H_2O_2, 75 °C, 17 h, 49%; d) $POCl_3$, reflux, 1 h, 64.2%.

Bernardi and co-workers repeated the procedure reported by Klein and co-workers to find out that the final chlorination step did not result in 2,5-dichloropyrazine rather gave rise to 2,3-dichloro and 2,6-dichloropyrazine compounds (**1.83** & **1.110**)[53]. The Bernardi group confirmed this result by preparing an authentic sample of 2,5-dichloropyrazine by treating 2-hydroxy-5-chloropyrazine (**1.112)** with phosphorus oxychloride as shown in Scheme 26 to compare the spectroscopic data.



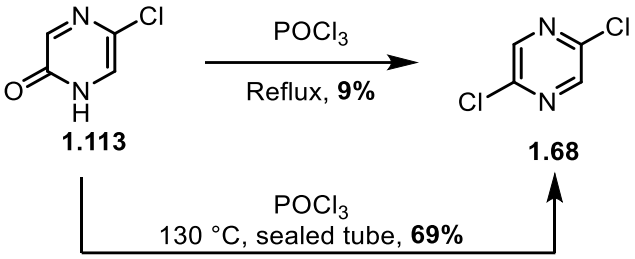
Scheme 26: Synthesis of 2,5–dichloropyrazine from 2-hydroxy-5-chloropyrazine[53].

Sato and co-workers reported on the regioselective synthesis of chloropyrazines from 3-substituted pyrazine-1-oxides[54]. Attempts to synthesize **1.68** starting from 3-chloropyrazine-1-oxides (Scheme 27) has been mentioned under various reaction conditions. On treating 3-chloropyrazine-1-oxides with phosphorus oxychloride in presence of base resulted in 2,3-dichloropyrazine (**1.83)** as the major product, whereas substituting phosphorus oxychloride with chloroacetyl chloride produced 2,6-dichloropyrazine (**1.110)** as the major product. In both the cases 2,5-dichloropyrazine (**1.68)** was obtained in negligible amounts.



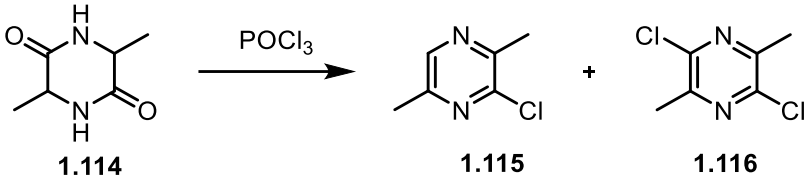
Scheme 27: Chlorination of 3-chloropyrazine-1-oxide[54] reported by Sato and co-workers

Synthesis of **1.68** from 5-chloro-1,2-dihydro-2-oxopyrazine[55] (**1.113)** using phosphorus oxychloride gave 9% yield, whereas the same experiment in a sealed tube at high temperatures gave a much-improved yield of 69% (Scheme 28).



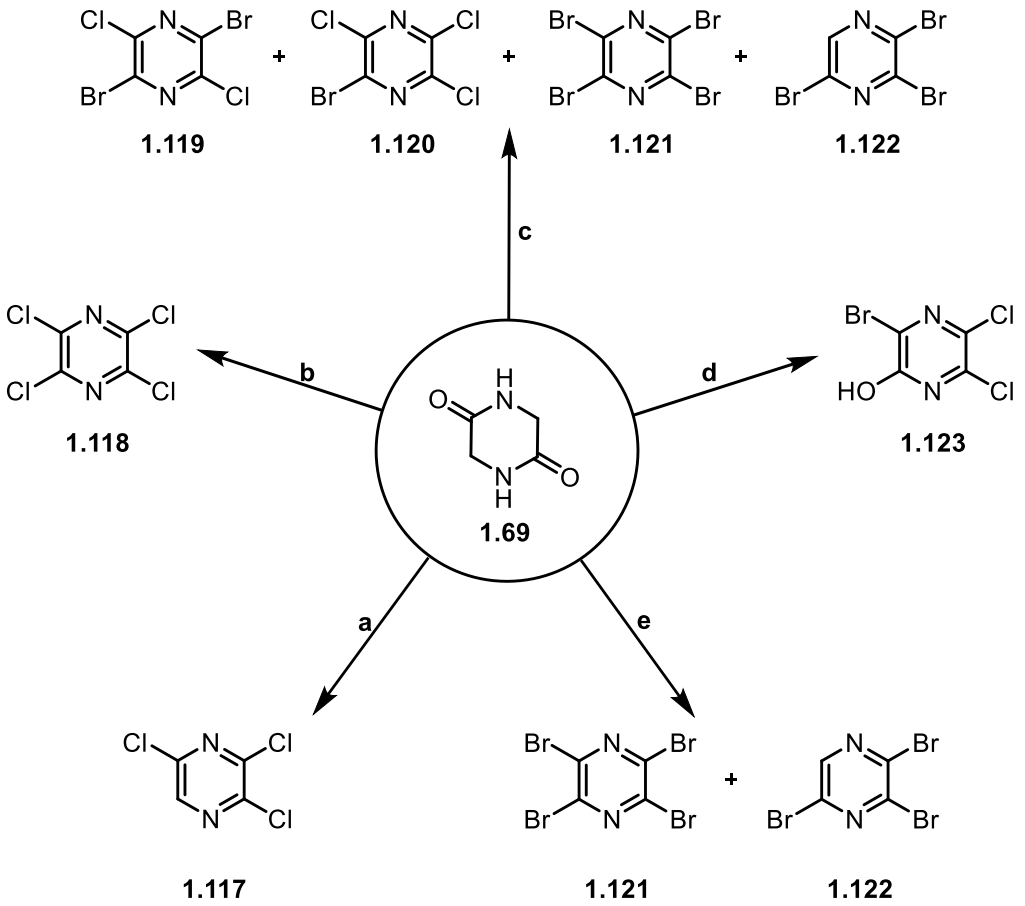
Scheme 28: Synthesis of 2,5–dichloropyrazine reported by Tuntiwachwuttikal and co-workers[55].

Alternative approaches to halopyrazines have become a necessity due to the harsh reaction conditions. One such approach was to use 2,5-diketopiperazines along with phosphorus oxychloride. Treatment of compound **1.114** with phosphorus oxychloride resulted in mono and dichlorinated pyrazines **1.115** & **1.116** as shown in Scheme 29[35].



Scheme 29: Conversion of substituted diketopiperazines to substituted dihalopyrazines[35].

Yudin and co-workers[56] reported a detailed study on the reaction of 2,5-diketopiperazine (**1.69**) with various chlorinating and brominating agents as shown in Scheme 30. In each case the resulting products were either tri- or tetra-halogenated pyrazines.



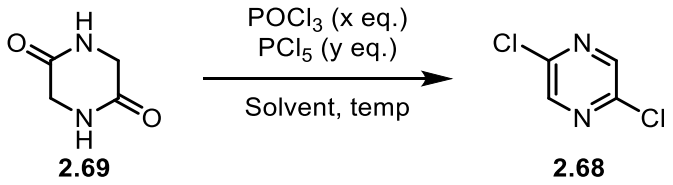
Scheme 30: Reagents and conditions: a) $POCl_3$, PCl_5, Cl_2, rt; b) $POCl_3$, PCl_5, Cl_2, 20 °C to 104 °C; c) $POCl_3$, PCl_5, Br_2, 40 °C to 104 °C; d) $POCl_3$, PCl_5, Br_2, rt; e) PBr_5, Br_2, DMSO, 40 °C to 80 °C.

1.5.1.2 Experimental results and discussion

With limited literature precedents, we started by trying to find a reasonable method to synthesize **1.68** from 2,5-diketopiperazine (**1.69**). Our initial attempts included the treatment of **1.69** with phosphorus oxychloride and phosphorus pentachloride. Reactions at elevated temperatures always resulted in a black sticky tar, whereas reaction at room temperature yielded the required product in 20% yield.

Optimizing the reaction conditions with respect to equivalents of phosphorus oxychloride, phosphorus pentachloride, solvent, temperature, and their subsequent yields have been mentioned in Table 1.

Table 1: Optimization of reaction conditions for 2,5-dichloropyrazine synthesis.



Entry	$POCl_3$ (eq.)	PCl_5 (eq.)	Solvent	Temperature (°C)	Yield (%)	Observation
1	5	0	neat	Reflux	-	Black tar
2	5	0	neat	60	-	Black tar
3	5	0	neat	rt	-	No reaction
4	13	2.5	neat	rt	20%	-
5	5	2.5	Sulfolane	rt	15%	-
6	5	2.5	MeCN	rt	-	No reaction
7	5	2.5	DCM	rt	-	No reaction

Despite our elaborate optimization attempts, the yield did not improve and stayed at around 20%. Unsuccessful optimization efforts can be attributed to differences in solubility of starting material and product coupled with corrosive chlorinating agents made it difficult to monitor the reaction effectively. Yet, this was a milder one step procedure compared to the reported protocols to synthesize 2,5-dichloropyrazine (**1.68**).

Failed attempts at synthesizing 2,5-dichloropyrazine (1.68) using multiple chlorination methods led us to focus on functionalization of pyrazine core. The first strategy to be utilized was the ortho-lithiation strategy.

1.5.2 Ortho-lithiation strategy

A brief description of various methodologies reported in literature to functionalize pyrazine core is mentioned, followed by a detailed literature study on directed metalation (ortho-lithiation) of pyrazines. Our attempts at functionalizing the pyrazine core by utilizing ortho-lithiation methodology are described below, after the survey of the literature.

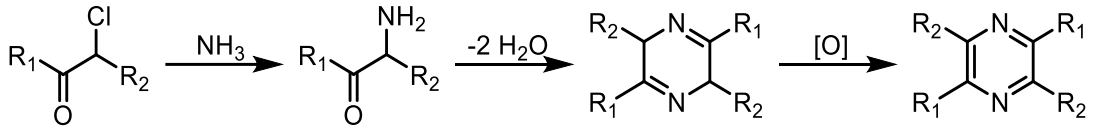
1.5.2.1 Functionalization of pyrazines: a brief survey of the literature

Substituted pyrazines make up the core of a plethora of important natural products and pharmaceutical agents[57,58]. Methodologies to synthesize polyfunctionalized pyrazines have always been limited increasing the need to develop new and efficient procedures to make substituted pyrazines. With growing importance of substituted pyrazines in synthesis, numerous protocols were developed targeting each position on the pyrazine ring for functionalization. Key methodologies to access functionalized pyrazines include construction of the pyrazine ring, nucleophilic aromatic substitution, transition-metal catalyzed

cross-coupling and direct metalation. Forthcoming sections will concentrate on directed metalation of pyrazines, while the other methodologies are briefly discussed.

1.5.2.1.1 Synthesis of the pyrazine ring

Self-condensation of amino ketones has been the general protocol to synthesize pyrazines with the limitation of being able to synthesize symmetrically substituted pyrazines. Reported in 1876, the Staedel-Rugheimer pyrazine synthesis[35] is the oldest procedure to make pyrazine ring (Scheme 31). This method involves self-condensation of α-amino ketones to form a dihydropyrazine intermediate which was subsequently oxidized to pyrazine ring. Various methods to generate α-amino carbonyl compounds with wide range of substituents make them desired for self-condensation reactions to form pyrazine rings.



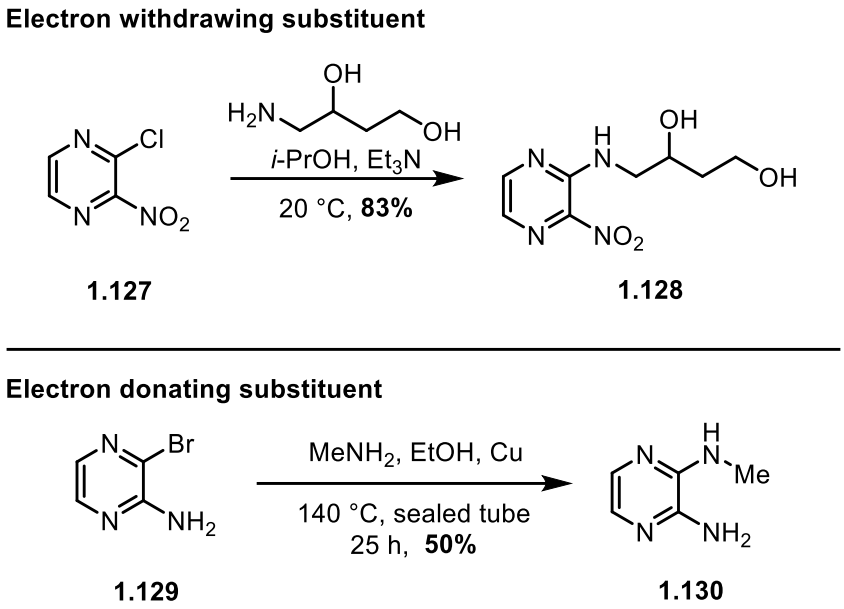
1.123 **1.124** **1.125** **1.126**

Scheme 31: The Staedel-Rugheimer pyrazine synthesis[35].

Several methodologies developed over time rely on condensation chemistry with an expansion in the scope of starting materials. The reaction of α,β-dicarbonyl compounds with α,β-diamines has been largely used owing to its ability to generate unsymmetrically substituted pyrazines[59,60]. Development of other methodologies has become a necessity due to the limited substituent scope.

1.5.2.1.2 Nucleophilic aromatic substitution

Pyrazines and halogenated pyrazines are prone to undergo nucleophilic aromatic substitution reactions due to their high electron-deficient nature[61,62]. The nature of nucleophile and type of substituents present on the pyrazine ring have a pronounced effect on the reactivity, while the position or type of halogen atom has little to no effect. Amines, alcohols, and thiols are common heteroatom nucleophiles to take part in the nucleophilic aromatic substitution of halogenated pyrazines. The most common reaction includes halopyrazines with different amines to generate amine substituted products. As mentioned above, the electronic nature of substituents on the pyrazine ring has a pronounced effect, with electron withdrawing substituents accelerating the reaction whereas electron donating substituents slowing the reaction or needing forcing conditions as shown in Scheme 32[63,64]. This observation justifies the facile nature of reaction and the necessity of an electron deficient system.

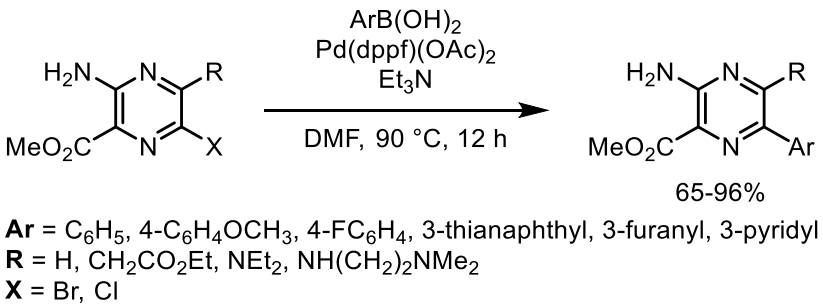


Scheme 32: Nucleophilic aromatic substitution of halopyrazines bearing electron donating and electron withdrawing substituents[63,64].

1.5.2.1.3 Transition metal catalyzed cross-coupling

Transition metal catalyzed cross-couplings are one of the most frequently utilized reactions in organic chemistry. Though these reactions are very useful to generate diverse and complex entities required in organic synthesis, the scope with respect to pyrazine motifs has been limited. This situation has been steadily improving with the development of better catalytic systems and easy access to halopyrazines from commercial sources.

The first report involving a halopyrazine as a coupling partner in Suzuki reaction was reported by Thompson and co-workers in 1988[65]. Optimization of catalysts and reaction conditions led to the coupling of bromopyrazines with a wide range of arylboronic acids (electron poor, electron rich, heteroaryl) in very good yields (Scheme 33)[65].



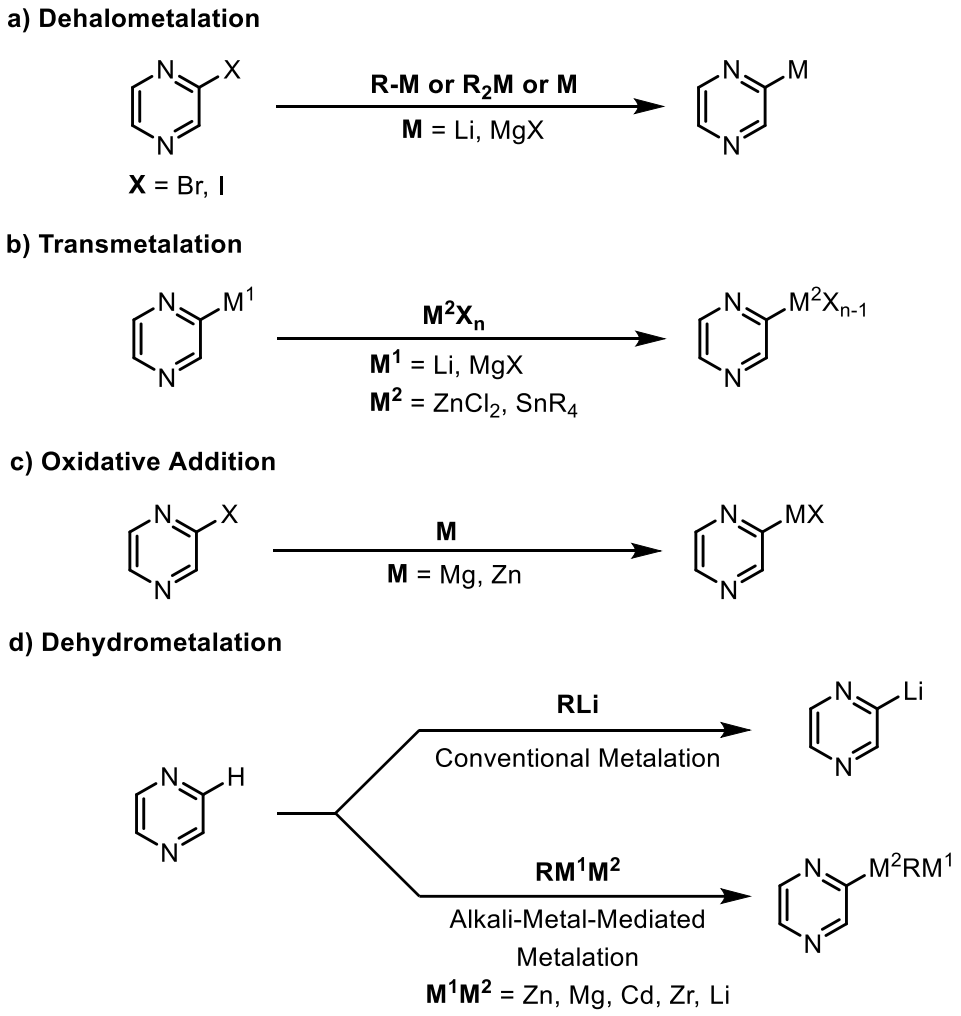
Scheme 33: Suzuki reaction of a pyrazine substrate[65] reported by Thompson and co-workers.

Further studies reported the compatibility of various arylboronic acids with the Suzuki reaction and the role of electronic nature of arylboronic acids in determining the reactivity of coupling partner[66]. The availability of

halopyrazines, large scope of coupling partners and high functional group tolerance has made Suzuki reaction an important pathway to generate functionalized pyrazine scaffolds. Over time, the pyrazine core has been successfully used in various coupling reactions such as the Buchwald-Hartwig, Kumada, Negishi, Heck, Sonogashira, and Stille couplings[67].

1.5.2.1.4 Metalation

Synthetic methodologies to functionalize pyrazine ring with electrophiles are nonexistent due to the highly electron-deficient nature of the pyrazine core. In other words, regioselective functionalization of pyrazine ring can be achieved by reacting the electrophile with a specifically metalated pyrazine. With the focus on generating metalated pyrazines, various synthetic protocols have been developed over the decades. The developed methodologies include dehydrometalation (directed metalation), dehalometalation, transmetalation and oxidative addition. Scheme 34 illustrates the different types of metalations developed.



Scheme 34: Methodologies for generating organometallic intermediates of pyrazine.

Dehalometalation is a non-deprotonative halogen-metal exchange developed extensively using bromo and iodo derivatives of pyridine. Inspite of having a wide scope with halopyridines, this method lacks the applicability in case of halopyrazines due to the difficulty in the synthesis of heavy halogenated pyrazine compounds.

Transmetalation reaction occurs when a more electropositive metal M2 replaces a less electropositive metal M1. Bases involving a highly electropositive metal like lithium are commonly used to make lithiated derivatives via deprotonation of substrate, which are further used to access various organometallic species by utilizing transmetalation reactions.

Achieving metalated species by oxidative addition is a well-known procedure and is possible by reaction of a metal like magnesium with haloderivatives. The requirement of active metals due to the presence of basic nitrogen ring atoms in heteroaromatics makes this procedure difficult to use.

A labile carbon-metal bond is widely used to establish a variety of functionalities and generate substituted moieties. Dehydrometalation or direct metalation is one such useful method to generate the highly reactive carbon-metal bond. Conventional metalation is a method in which highly reactive electropositive metal such as lithium is commonly used to generate highly polar and labile carbon-lithium bonds. Extremely high reactivity of lithio-derivatives generated requires the use of low reaction temperature and is incompatible with a large variety of functional groups. Recent research has led to the development of alternative metalating reagents involving a mixture of compounds with alkali metal as a key component and is termed as alkali-metal-mediated metalations. The following section discusses about the direct metalation of pyrazines and substituted pyrazines in detail.

1.5.2.2 Dehydrometalation or directed metalation

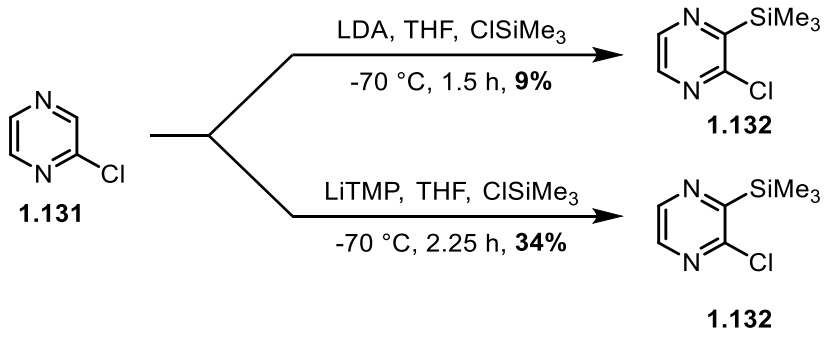
Dehydrometalation or directed metalation of pyrazine followed by quenching with electrophiles is a well-established methodology to install a wide range of electrophiles onto the pyrazine ring. Higher acidity of ring hydrogens and the symmetrical structure of pyrazine makes metalation at α position of nitrogen atom very favorable. The presence of lone pair of electrons on the ring nitrogen atoms has an added advantage of coordinating with the metal of the base and assisting in disaggregation of the base used thereby enhancing the reactivity of the base. Despite the ring nitrogen atoms of pyrazine being less chelating, the ring hydrogens are acidic enough to facilitate deprotonation using non-nucleophilic bases.

With pyrazines, the metalated species generated is stabilized by the electron-withdrawing nature of the ring nitrogen. The presence of electron-withdrawing nitrogen atoms in the ring makes the pyrazine ring highly electron deficient and prone to nucleophilic addition reactions. Hence the use of

nucleophilic bases (alkyl lithiums) is ignored and non-nucleophilic bases (LDA, LiTMP, etc) are preferred for the metalation of pyrazine substrates.

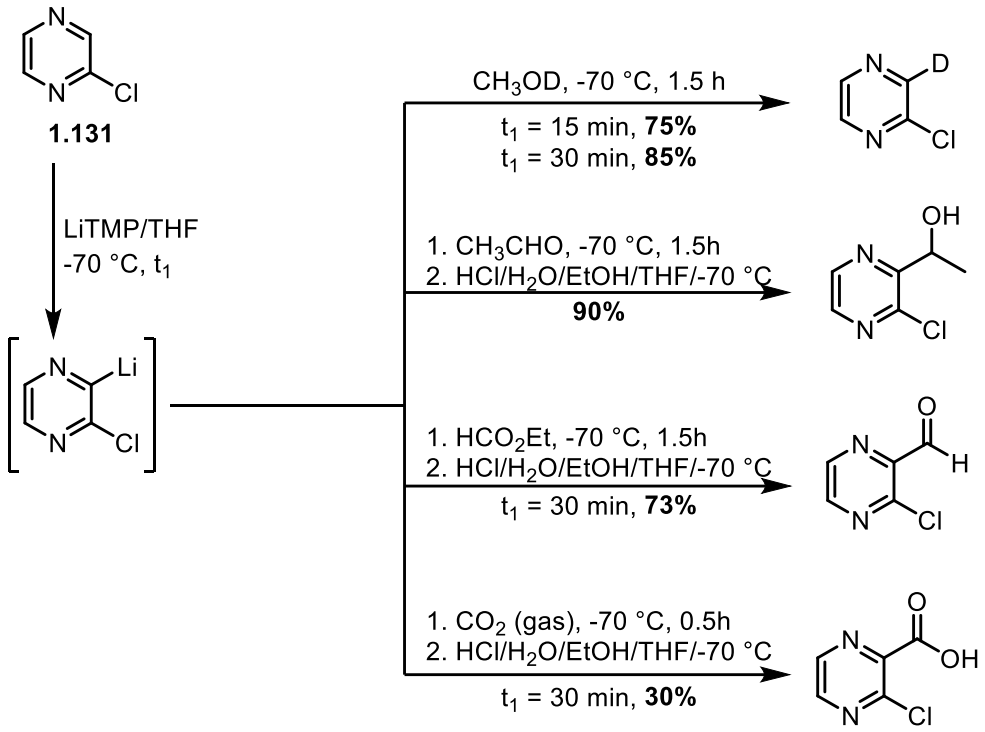
1.5.2.2.1 Lithiation

The metalation of pyrazine has been noticed and reported as a side reaction taking place during nucleophilic substitution reactions of pyrazine with alkyllithium reagents. Similar instances have also been noted during the metalation of alkylpyrazine substrates[68]. With reports mentioning similar metalations in case of electron-deficient heterocycles like pyridine and diazines[69], Queguiner and co-workers worked on developing a methodology for direct metalation of pyrazine ring. Synthesis of 2,3-disubstituted pyrazines by ortho-lithiation of chloropyrazine (**1.131**)[70] was first reported by Queguiner and co-workers in 1988. Initial attempts to metalate chloropyrazine have been carried out using an "equilibrium shift" protocol. This protocol requires the presence of quenching electrophile in the reaction medium from the start of the reaction, generating the metalated products in low yields (Scheme 35). Equilibrium shift procedure suffers with the scope of electrophiles, limiting to those that are immune to react with lithium alkylamides.



Scheme 35: Ortho-lithiation of chloropyrazine using the "equilibrium shift" procedure reported by Queguiner and co-workers[70].

Transitioning from the equilibrium shift protocol to a stepwise protocol resulted in higher yields with a broader scope of electrophiles as illustrated in Scheme 36[70]. Further studies by Queguiner and co-workers led to the advancement of methodologies compatible with a wide range of diazines and highly substituted pyrazines[4,71–76].

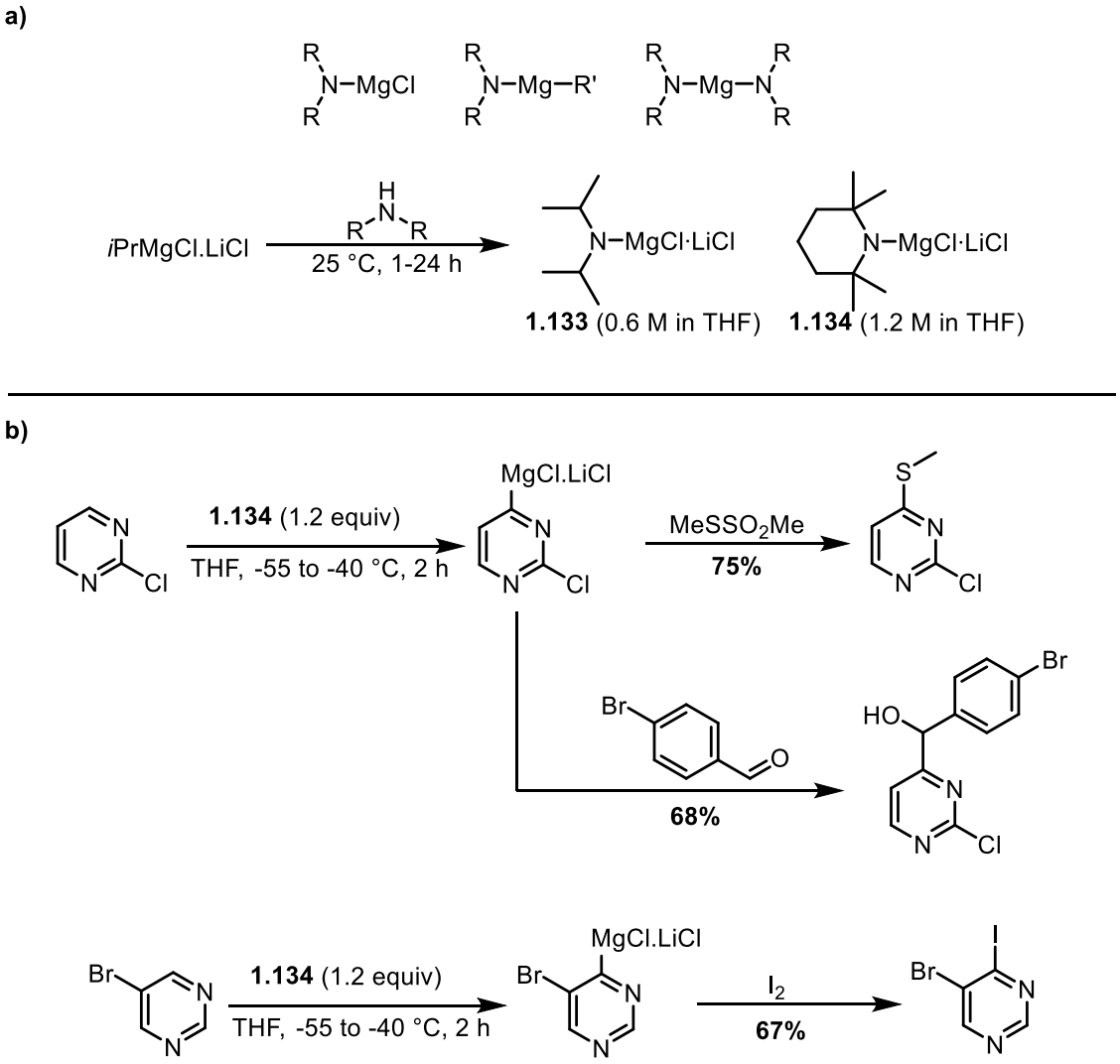


Scheme 36: Ortho-lithiation of chloropyrazine using "stepwise" procedure reported by Queguiner and co-workers[70].

Although hindered non-nucleophilic bases, such as LDA or LiTMP allow reliable deprotonation of a variety of pyrazines and substituted pyrazines, the high reactivity of the lithiated species generated renders them prone to side reactions. Regioselectivity issues can also arise as lithiation may take place at multiple sites, and under both kinetic and thermodynamic control[77].

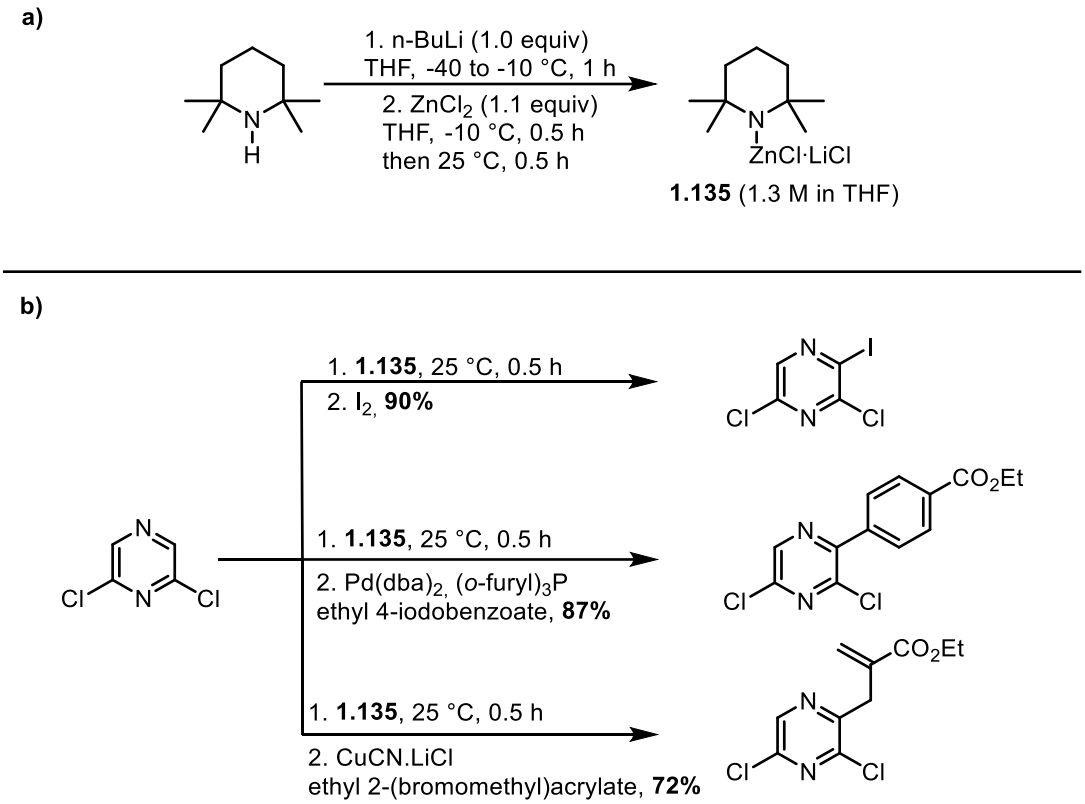
1.5.2.2.2 Alkali metal mediated metalation

To evade the restrictions imposed by lithium alkylamides, a new class of metalating agents have been discovered and reported by several groups[78–80]. Methodologies utilizing magnesium amides (Scheme 37) to achieve directed metalation of heterocyclic compounds have been reported. But low solubility of magnesium amides coupled with the necessity to use a large excess of base for higher conversions led to decline in its synthetic utility. Marked increase in reactivity of alkylmagnesium chlorides on addition of lithium chloride in magnesium-bromine exchange reaction[81,82] led Knochel and co-workers towards implementing the methodology to magnesium amides and generate a better metalating reagent. With reports mentioning LiTMP to be an effective metalating reagent with pyrazines, Knochel and co-workers reported a mixed Mg/Li amide by reaction of TMP with iPrMgCl.LiCl (Scheme 37)[83]. The generated reagent turned out to be better soluble, with a shelf life of up to 6 months in solution. Various aromatic and heteroaromatic compounds have been functionalized under mild conditions and illustrated in Scheme 37[83].



Scheme 37: a) Magnesium amides and Knochel's route to the mixed Mg/Li amide metalating reagent. b) Examples utilizing **1.134** to functionalize halopyrimidines[83].

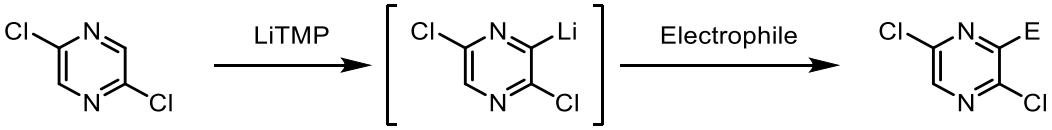
Further studies in the development of alkali metal mediated metalating reagents led to the development of the mixed Zn/Li amide TMPZnCl·LiCl (**1.135**) (Scheme 38)[84]. These zinc-based reagents, developed in-house in the Knochel group, were utilized in functionalizing a variety of heteroaromatic compounds[84–88] and there by generating their corresponding zincated species, which were used in cross coupling reactions or quenched with electrophiles respectively[84] (Scheme 38). Directed metalation remains as the prominent methodology to functionalize pyrazines, halopyrazines and other various mono and di-substituted pyrazines.



Scheme 38: a) Synthesis of Knochel's mixed Zn/Li amide metalating reagent. b) Examples of functionalization of 2,6-dichloropyrazine using reagent **1.135**[84].

1.5.2.3 Experimental results of the ortho-lithiation strategy

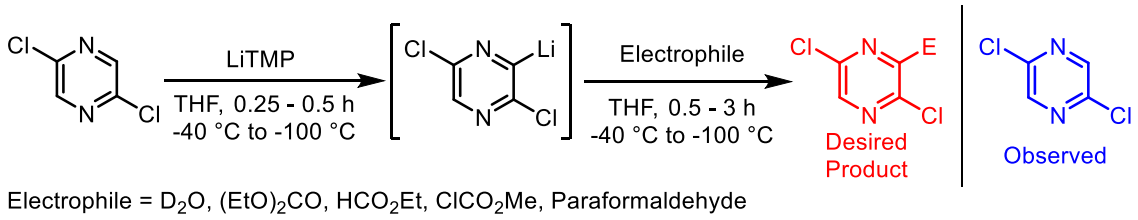
Following the reports available on ortho-lithiation of monohalo and dihalopyrazines, we have set our goals to functionalize 2,5-dichloropyrazine and establish an ester moiety. As shown in Scheme 39, the plan consisted of generating a metalated 2,5-dichloropyrazine species using a non–nucleophilic lithiated base (LiTMP), followed by quenching it with an electrophile to generate a 3-substituted-2,5-dichloropyrazine.



Scheme 39: Ortho-lithiation approach to functionalize 2,5-dichloropyrazine.

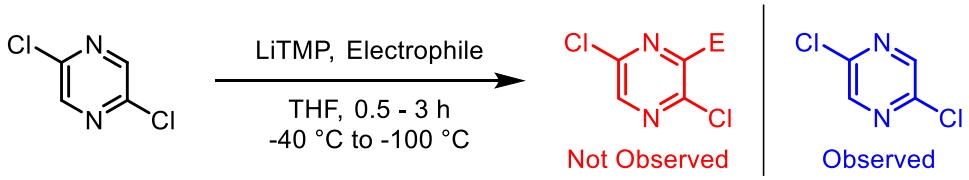
The stepwise protocol by Queguiner and co-workers[70] involved the generation of the lithiated species of substituted pyrazine and then quenching it with an electrophile. Following this methodology, lithiation of 2,5–dichloropyrazine was carried out using LiTMP as base at very low temperatures (-40 °C to -100 °C) followed by slow addition of an electrophile. The reaction mixture turned dark brown immediately on addition of 2,5–dichloropyrazine to a solution containing LiTMP. Further addition of electrophile did not change the appearance of the

reaction mixture. Workup of the reaction followed by purification by column chromatography resulted in the recovery of starting material. Optimization with respect to temperature ranging from -40 °C to -100 °C and with a variety of electrophiles did not give the desired product (Scheme 40).



Scheme 40: Functionalization of 2,5-dichloropyrazine using "stepwise" protocol.

The immediate color change of the reaction mixture to dark brown on addition of 2,5-dicholorpyrazine to a solution of LiTMP, prompted us to try out the equilibrium shift protocol also reported by Queguiner group[70]. In this procedure, electrophile is present in the reaction mixture before the addition of starting material. Lithiation of 2,5-dichloropyrazine using LiTMP, also resulted in a dark brown reaction mixture almost immediately. Purification of the reaction mixture by column chromatography resulted in the recovery of starting material. The presence of an electrophile in the reaction medium from the start did not have any impact on the reaction (Scheme 41). We were unable to replicate the reported results of functionalizing 2,5-dichloropyrazine using Knochel's mixed Zn/Li amide metalating reagent **1.135**[89]. Hence further functionalization attempts with the mixed Zn/Li amide reagent **1.135** were abandoned.

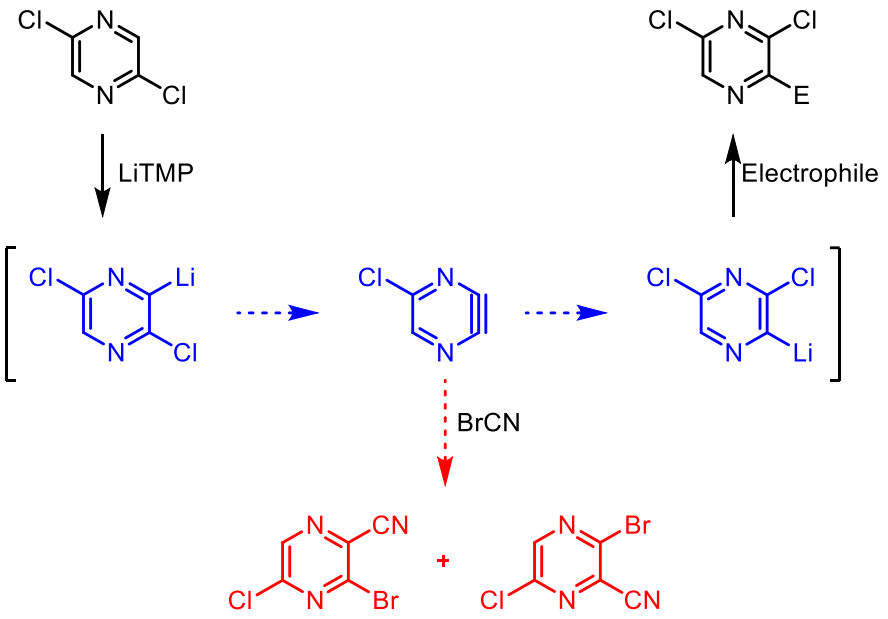


Scheme 41: Functionalization of 2,5-dichloropyrazine using "equilibrium shift" protocol.

Comparing the NMR data of starting material to that of the recovered one after reaction showed a slight peak shift in 1H NMR. Literature revealed that the ^{1}H NMR peaks of 2,3-dichloro (^{1}H NMR in $CDCl_3$: δ 8.33 ppm (s, 2H))[54] , 2,5-dichloro (^{1}H NMR in $CDCl_3$: δ 8.40 ppm (s, 2H))[54], and 2,6-dichloropyrazine (^{1}H NMR in $CDCl_3$: δ 8.53 ppm (s, 2H))[54] being very close to each other.

With a suspicion on the stability of the generated lithiated species and with the possibility of a halogen rearrangement, we decided to study and determine the possibility of a rearrangement as shown in Scheme 42. With the hypothesis in hand, we embarked on finding a valid proof to support the hypothesis. We generated a lithiated species of 2,5-dichloropyrazine following equilibrium shift procedure with the highly reactive electrophile cyanogen bromide in the system to quench the hypothesized intermediate. Numerous attempts and several

purifications by column chromatography resulted in mixtures with a complex ^{1}H NMR spectra, thus resulting in inconclusive data to support the hypothesis.

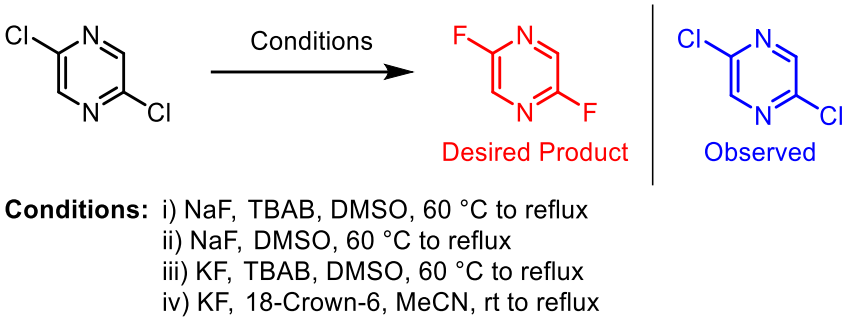


Scheme 42: Possible rearrangements and reactions of lithiated 2,5-dichloropyrazine.

As a final attempt, we repeated the ortho-lithiation experiment of 2,5-dichloropyrazine with methylchloroformate ($ClCO_2Me$) as an electrophile using equilibrium shift porotocol (Scheme 41). ^{1}H NMR of the purified crude in CD_2Cl_2 had a singlet peak at 8.39 ppm. We then spiked the same NMR sample with commercially available 2,3-dichloropyrazine & 2,6-dichloropyrazine and measured the ^{1}H NMR. 2,3-dichloropyrazine and 2,6-dichloropyrazine displayed singlet peaks at 8.32 ppm and 8.52 ppm respectively. This affirms the absence of halogen rearrangement as hypothesized.

With considerable amount of time spent on optimizing the lithiation of 2,5-dichloropyrazine and with concerns over the stability of the lithiated species generated, we changed our starting material from 2,5-dichloropyrazine to 2,5-difluoropyrazine for implementing the same strategy.

With the aim of scaling up the reaction and avoiding highly corrosive reagents, we opted for fluorination procedures that utilize sodium fluoride and potassium fluoride. With ample literature procedures for the use of NaF and KF as fluorinating reagents, we started to convert 2,5-dichloropyrazine to 2,5-difluoropyrazine. A wide range of conditions using KF, NaF along with TBAB, 18-Crown-6 at various temperatures were attempted (Scheme 43). Multiple attempts with various reaction conditions resulted in the recovery of 2,5-dichloropyrazine and did not yield 2,5-difluoropyrazine as expected.



Scheme 43: Synthesis attempts towards 2,5-difluoropyrazine.

Functionalization of 2,5-dichloropyrazine using ortho-lithiation strategy was a key step in our planned synthesis of Favipiravir. Substitution in the pyrazine ring with an electrophile using this strategy never returned reliable results, which made us change the starting material from 2,5-dichloropyrazine to 2,5-difluoropyrazine, but unfortunately the synthesis of 2,5-dichloropyrazine was not successful either. Despite the negative results, this approach has highlighted our lack of knowledge and understanding about the metalation of 2,5-dichloropyrazine and subsequent substitution reactions. In contrast, metalation of 2,3-dichloropyrazine and 2,6-dichloropyrazine are well documented resulting in literature gap related to the stability and reactivity of metalated 2,5–dichloropyrazine species.

Failure in functionalizing 2,5-dichloropyrazine core using ortho-lithiation strategy led us to pursue alternative methods. The second strategy we came up to functionalize pyrazine core is by utilizing Minisci reaction.

1.5.3 Minisci reaction strategy

The following section describes the Minisci reaction in general and examples of Minisci reactions using pyrazines. The literature survey is then followed by the results of experimental attempts at functionalizing pyrazine core using Minisci reaction.

Free radicals represent an unusual odd-electron species which possess a distinct feature of combining electrophilicity and nucleophilicity at the same reaction center. The single electron is in a common molecular orbital termed as SOMO (Singly Occupied Molecular Orbital). Thus, the reactivity of free radicals is governed by orbital interactions instead of coulombic interactions as in the case of polar reactions[90]. Being located in between the HOMO and the LUMO energetically, overlap of SOMO with either frontier orbitals is favorable. A dominant SOMO-HOMO interaction attributes the radical an electrophilic character, and a dominant SOMO-LUMO interaction ascribes the nucleophilic character to the radicals[90].

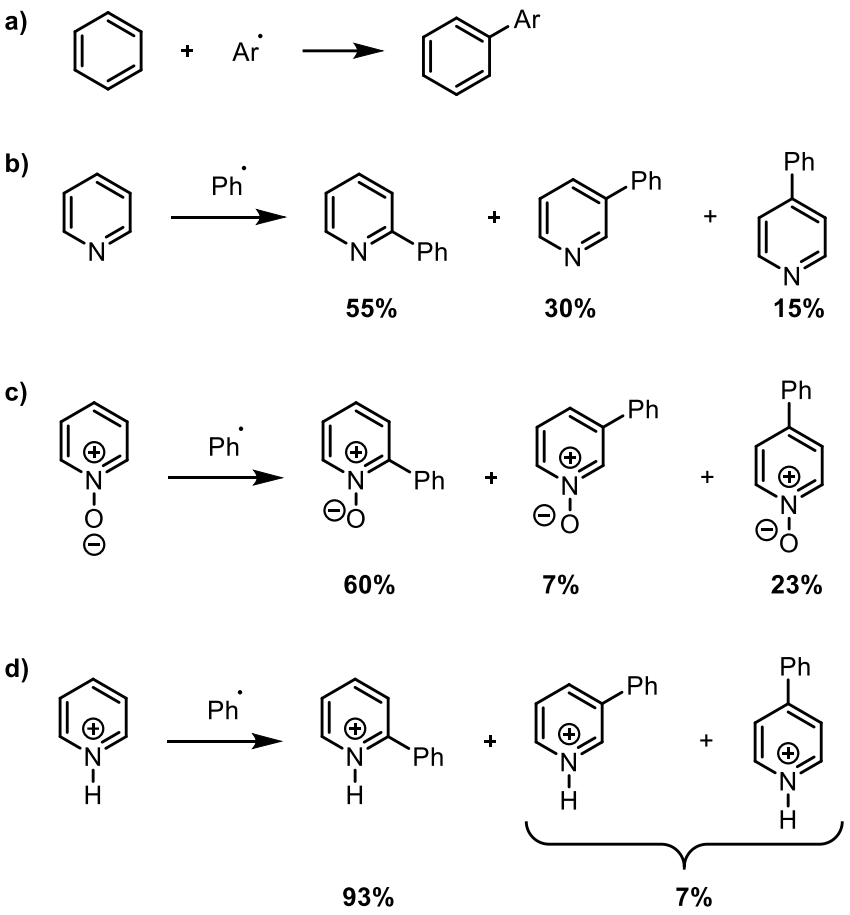
Free radicals and their reactions were infamous for their regioselectivity issues in organic chemistry for a long time[91]. Free radicals attracted interest from theoretical chemists due to their peculiar properties followed by industrial chemists due to their importance in basic chemical industries for vinyl

polymerization, chlorination of methane, etc. The use of structurally simple molecules did not give rise to selectivity issues in the case of industrial applications. Rather the complexity of structures in organic chemistry combined with the unreliable selectivity made free radical reactions less appealing to organic chemists.

With a growing number of small molecule drugs containing an aromatic heterocycle core, the need for developing a library of molecules for clinical and pharmacological testing intensified. However, derivatization of electron-deficient heteroaromatic bases like pyrazines, pyrimidines, and pyridazines has not always been straightforward with direct functionalization methods[92]. A comprehensive, but underrated methodology often ignored is the tendency of heteroaromatic bases to react with radicals. Methodologies that include radical addition are expected to be suitable to expand the required heteroarenes, yet this reactivity is rarely employed in synthesis[93]. Usually this has been justified by citing unpredictable regioselectivity, frequent low yields, and complex mixture of products. Although this reasoning is suitable in some cases, the main issue arises from the improper and incomplete understanding of the factors controlling the selectivity and reactivity of radicals and heteroarenes.

1.5.3.1 The Minisci reaction

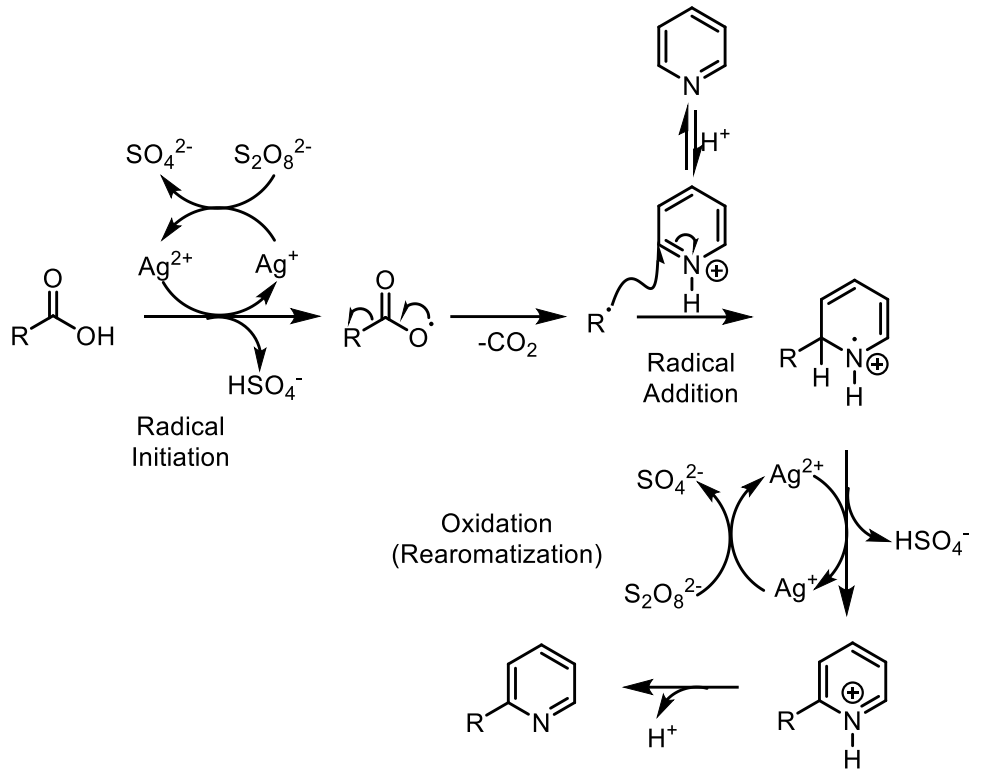
The Gomberg-Bachmann reaction[94] developed in the 1920s is an example of homolytic aromatic substitution, where an aryl radical is added to an aromatic system to generate biaryls (Scheme 44). Reactions dating to early 1890´s involved addition of aryl radicals to heteroaromatic systems such as pyridine[95–98]. Very little progress has been achieved over the next 50 years to develop the methodology required to successfully integrate it with mainstream synthesis for organic chemists. Even though the methodology to generate phenyl radicals has been expanded significantly, the efficiency and regioselectivity of reaction with pyridine was not optimized resulting in multiple regioisomers with low yields (Scheme 44)[93]. With studies aimed at understanding and controlling the regioselectivity of radical addition reactions, it was found that the regioselectivity of addition of phenyl radical to pyridine can be controlled by using pyridine-*N*-oxide instead of pyridine[99](Scheme 44). Lynch, Chang, and Dou[100–102] reported the role of acidity of the reaction medium on the regioselectivity and rate of radical addition to heteroarenes. This study established that the N-protonation of the heteroaromatic base amplifies the rate of the reaction and tilts the regioselectivity compared to that of neutral bases (pyridine, pyrazine, thiazole, quinoline, isoquinoline, *N*-methylimidazole, quinoxaline, benzothiazole, pyrimidine, *N*-methylbenzimidazole)[103] (Scheme 44).



Scheme 44: a) Gomberg-Bachmann biaryl synthesis[94]; Radical phenylation of b) pyridine[93]; c) pyridine-*N*-oxide[99]; d) protonated pyridine[103].

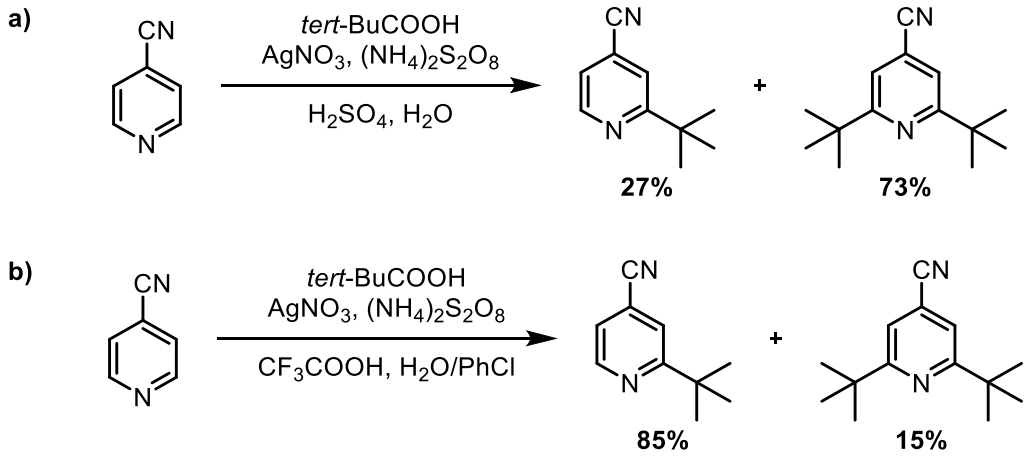
1.5.3.1.1 Alkylation

In 1971, Minisci reported a silver catalyzed decarboxylation of carboxylic acids with peroxydisulfate to generate alkyl radicals. This methodology involves homolytic alkylation of heteroarenes and illustrates the effect of acidic conditions on the reaction (Scheme 45)[104]. Henceforth the reaction scope has seen a staggering growth and the methodology evolved to be the most useful method to functionalize electron-deficient heteroaromatic bases. Thus, all kinds of homolytic substitution reactions of protonated heteroaromatics are known as "Minisci Reactions". The Minisci reactions constitute a versatile method of heteroarene CH-functionalization. The reaction mechanism (Scheme 45)[104] involves the addition of alkyl radical to the protonated heteroarene to give an aminyl radical cation which is then oxidized to form the corresponding alkylated heteroarene under reaction conditions.



Scheme 45: Mechanism illustrating alkylation of protonated pyridine (molecules 2014).

The Minisci reaction shows parallel reactivity patterns with Friedel-Crafts-alkylation with inverted reactivity and selectivity as more electron-deficient heteroarene reacts faster[103]. Due to the electron donating effect of the alkyl group, radical alkylation of heteroarene results in a slight increase of LUMO energy. Despite the increase in LUMO energy, it is not enough to warrant polyalkylation of heteroarenes as the energy increase is not sufficient to hinder consecutive reactions. Punta et al., also reported the conditions favoring monoalkylation over polyalkylation[103]. The use of a two-phase system as reaction medium favors monoalkylation, as the more lipophilic alkylated compound is extracted into the aqueous phase (Scheme 46) thereby arresting polyalkylation of heteroarene.

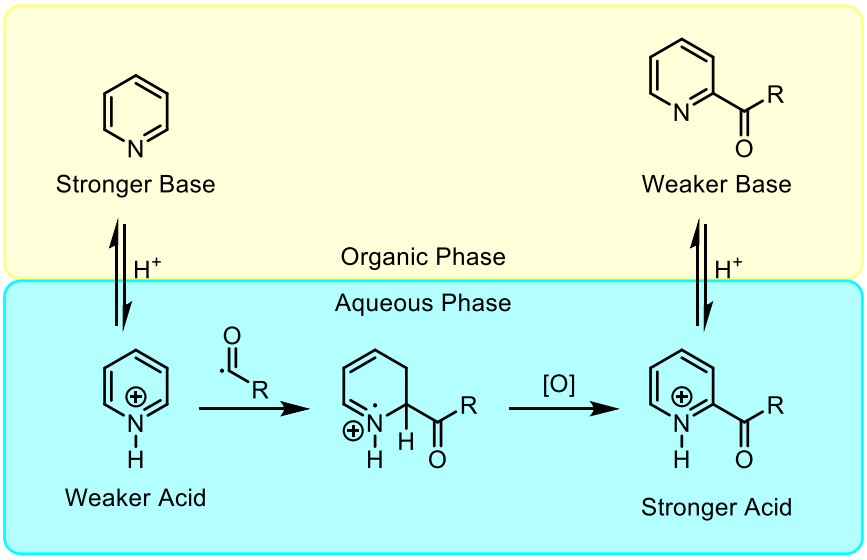


Scheme 46: Alkylation of 4-substituted pyridine a) in aqueous medium; b) in two-phase system.

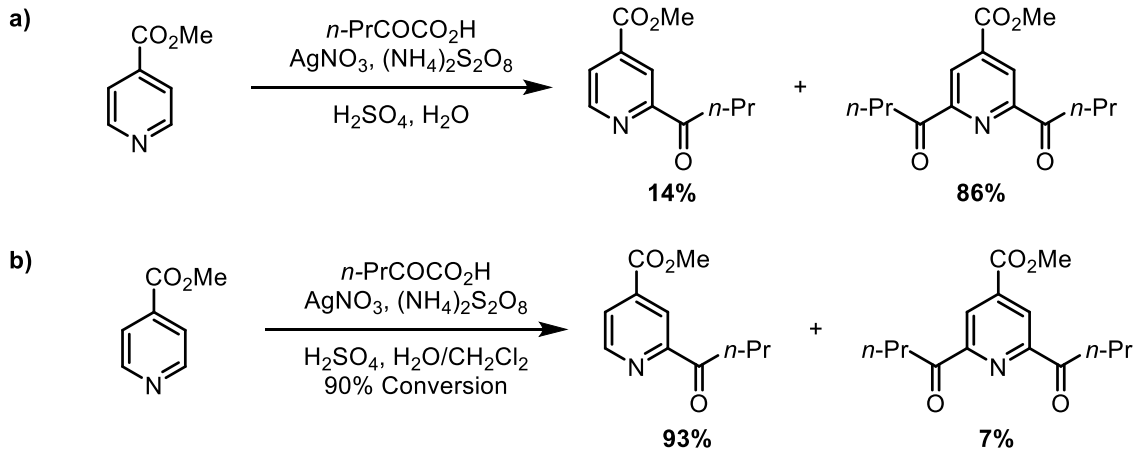
1.5.3.1.2 Acylation

In an electrophilic process such as the Friedel-Crafts reaction, acylation is much more selective than alkylation, as the incoming acyl group deactivates the aromatic ring for further acylation whereas the incoming alkyl group activates the aromatic ring for further alkylation resulting in polyalkylated products. Importantly, in a radical process such as the Minisci reaction, the reactivity and selectivity patterns are inverted compared to Friedel-Crafts reaction[89]. Addition of acyl radical to a protonated heteroarene increases the electron-deficient nature of heteroarene and activates the ring for further radical additions by lowering the LUMO energy. Hence, arresting monosubstitution by carbonyl radicals in the presence of multiple reactive centers has been a major limitation unless the reaction centers are blocked by various substituents/groups. With monosubstitution of heteroarenes by carbonyl radicals being a synthetic interest, developing a methodology to overcome polysubstitution has become a necessity. Apparent change in the basic character of starting heteroarene on acylation led to the development of a two-phase reaction medium to overcome polysubstitution[105–110]. In a two-phase system, monoacylation of heteroarene decreases the basicity and increases the amount of unprotonated species resulting in *in situ* extraction to the organic layer, whereas the protonated heteroarene is in the aqueous phase reacting with the radicals generated. Section I of Scheme 47 illustrates the principle mentioned using a general acylation mechanism of pyridine. Section II of Scheme 47 is an example of acylation of methyl isonicotinate in both aqueous please and a two-phase system[103].

I) Acylation of pyridine in a two-phase system



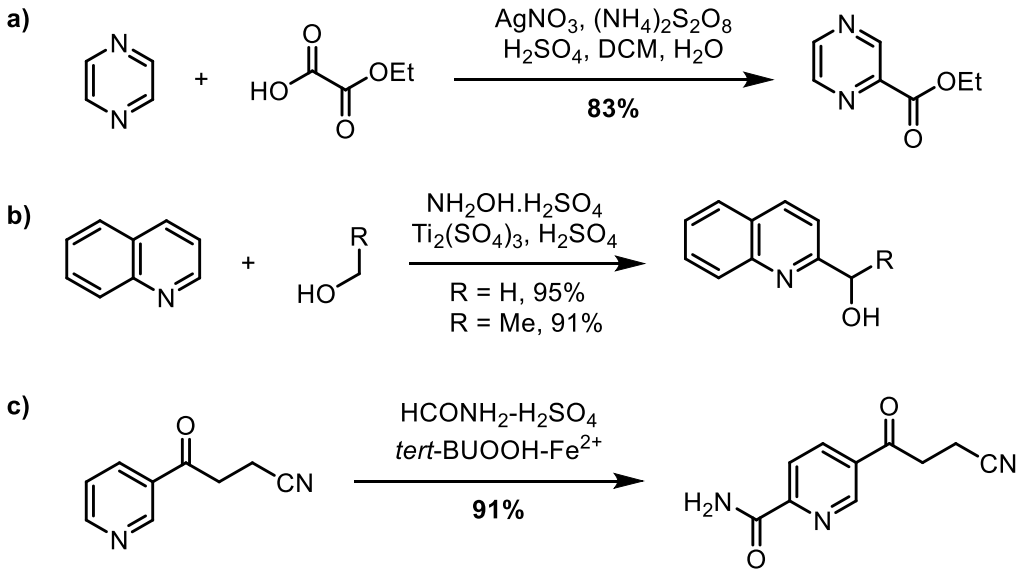
II) Acylation of methyl isonicotinate in a) aqueous medium and b) two-phase medium



Scheme 47: I) A mechanism showing radical acylation of pyridine in a two-phase system. II) acylation of methyl isonicotinate[103] in a) aqueous medium; b) two-phase system.

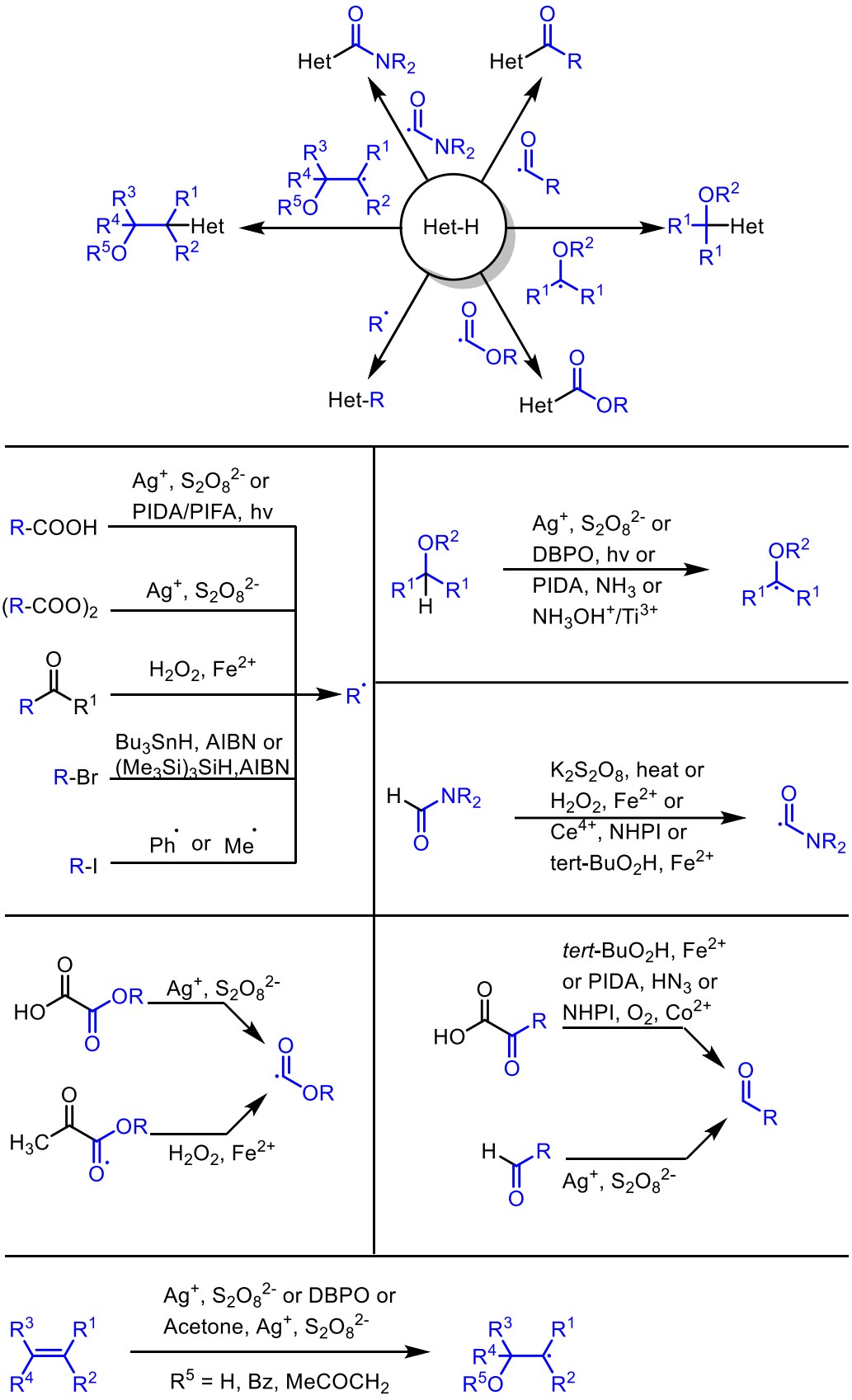
1.5.3.1.3 Versatility of Minisci reaction

Apart from alkylation and acylation, a variety of functionalizations of heteroarenes via the Minisci reaction have been developed. Hydroxyalkylated heteroarenes are generated by using alcohols as carbon centered radicals. Oxalic acid monoesters result in hydroxycarbonylation, and carbamoylation can be achieved by generating a carbon centered radical from formamide (Scheme 48)[103].



Scheme 48: Functionalization of heteroarenes a) hydroxycarbonylation; b) hydroxyalkylation; c) carbamoylation.

Utilization of aryl radicals has been limited by the fact that their generation from aromatic carboxylic acids by oxidative decarboxylation is often impractical[103]. Several alternative sources were designed and developed to generate aryl radicals. Methodologies involving generation of aryl radicals from arylboronic acids[111] and aryldiazonium salts[112] were developed with tolerance towards a wide range of functional groups. Overtime huge progress has been made in expanding the scope of the reaction with development of various radical generating protocols, and systems to enhance regioselectivity. Understanding the rate constants for radical addition, and mechanistic investigations of Minisci reaction have been accomplished[91,93,95,96,113,114] along with computational studies predicting the regioselectivity[92]. The versatility of the Minisci reaction is illustrated in Scheme 49.



Scheme 49: Versatility of Minisci reaction and variety of methods for radical generation.

1.5.3.2 Scope and limitations

The Minisci reactions include a variety of transformations resulting in a diverse set of functionalizations of corresponding heteroaromatic bases. The potential scope of Minisci reactions is based on heterocyclic base and the radical partner, along with apparent limitations.

Heterocyclic cores have become a key component in drug development and thus methodologies focusing on selective CH-functionalization of heterocycles are of extreme importance. The compatibility of a broad range of heteroaromatic bases (5-membered, 6-membered, 6,5-bicyclic, 6,6-bicyclic heteroaromatics) along with a few non-basic heteroaromatics makes a compelling case for using Minisci reaction. The ability of late-stage functionalization using radical intermediates makes Minisci reaction an attractive option for medicinal and industrial chemists[93,115]. The availability of various radical precursors with efficient radical generating protocols opened new avenues to reach late-stage transformations of heteroaromatic bases. Both these factors combined render the Minisci reaction a versatile tool to functionalize and transform all chemical substrates containing a heteroaromatic core. Figure 7 illustrates examples involving late-stage functionalization by Minisci reaction[116–118].

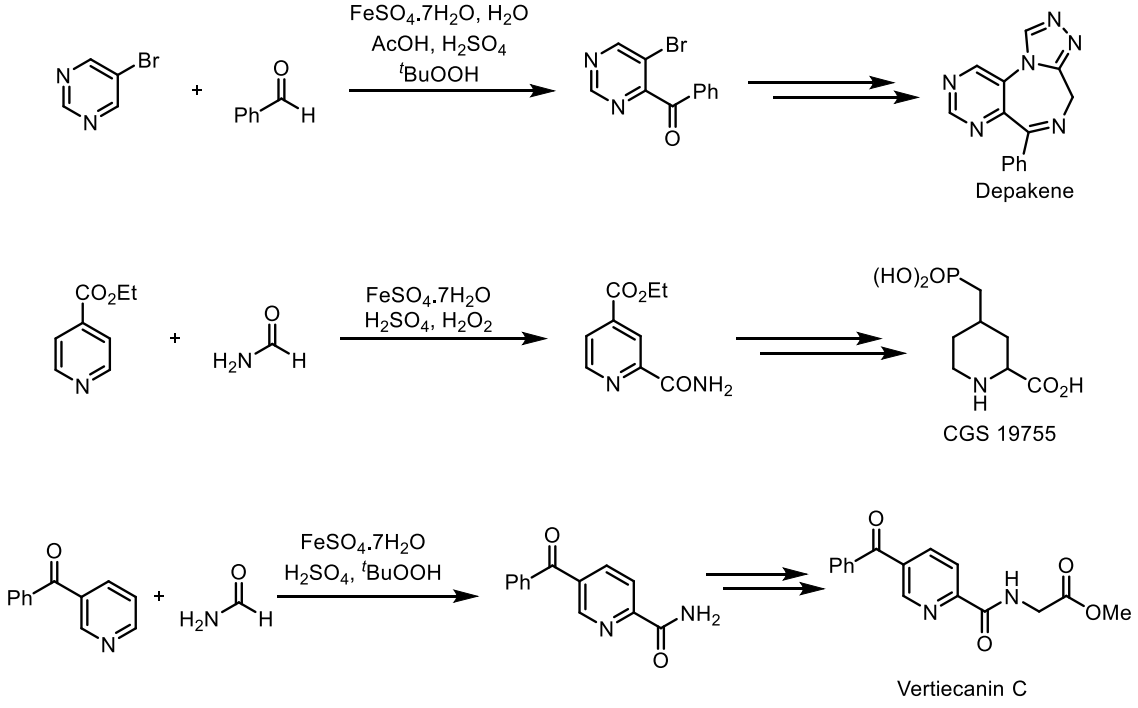


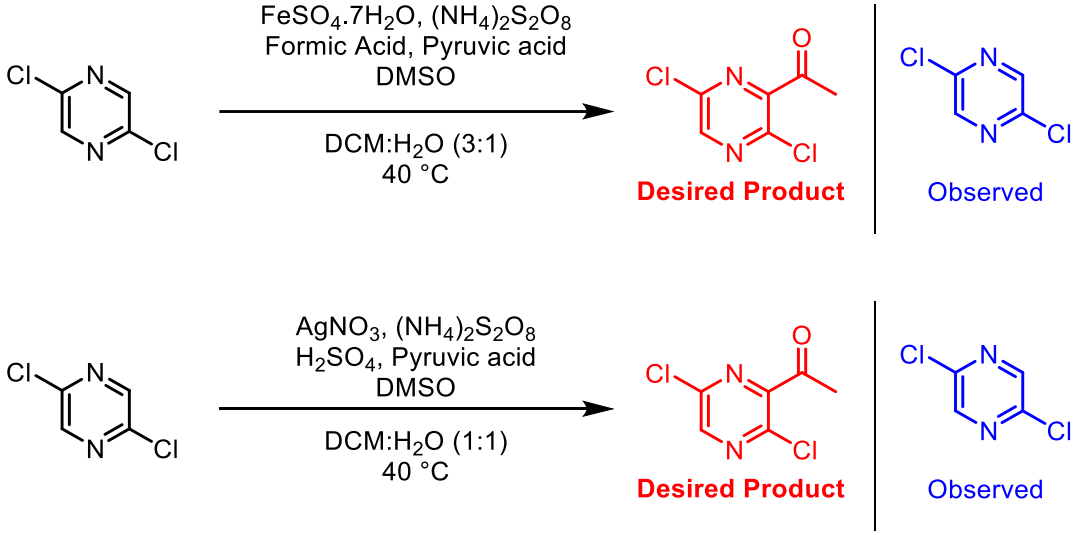
Figure 7: Synthesis examples utilizing Minisci reaction[116–118].

The Minisci reaction has three main limitations. The first one involves regioselectivity of the reaction when more than once positions are available to react. Even though it is handy for medicinal chemists, it is a roadblock for other chemists working with the reaction. The second one involves the modest yields (<50%) in most of the cases. The third one is a combination of both the issues

mentioned before. Low yields with multiple regioisomeric products require a purification step which can be tedious and challenging.

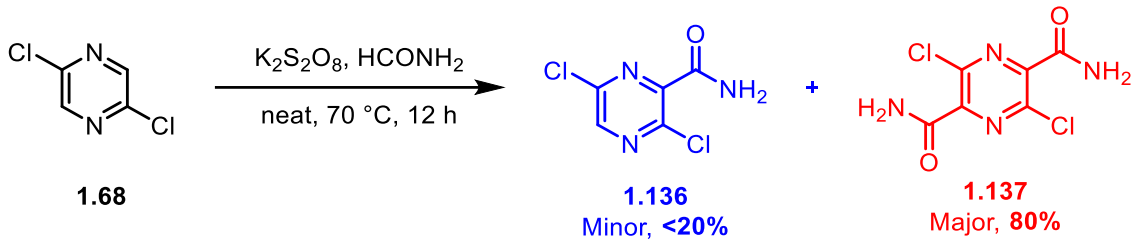
1.5.3.3 Experimental results of Minisci reaction strategy

The availability of methodologies aimed at tuning the regioselectivity of Minisci reaction assisted in sorting out the procedures to attempt functionalization of 2,5-dichloropyrazine. Easy access to large amounts of pyruvic acid made it an attractive choice to try out and optimize the reaction conditions. Reaction of 2,5-dichloropyrazine with pyruvic acid under Minisci reaction conditions (Scheme 50) did not yield the expected product. Instead, the starting material was recovered. Tweaking the reaction conditions (with respect to equivalents of reagents used, reaction temperature, solvent ratio) to find an optimal set of control parameters to arrive at the expected product were not successful.



Scheme 50: Functionalization of 2,5-dichloropyrazine using Minisci reaction conditions.

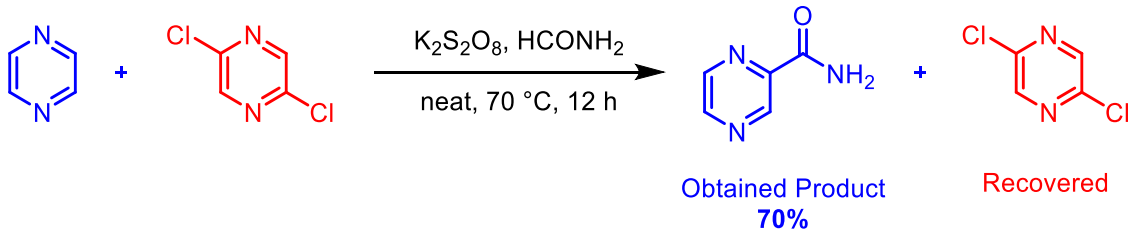
Exploring the literature revealed a solvent free procedure for carbamoylation of pyrazine and several other substituted pyrazines[119]. The protocol consisted of heating the heteroaromatic compound with Potasium persulfate with formamide resulting in installing an amide group onto the heteroaromatic ring. Replicating the same procedure with 2,5-dichloropyrazine resulted in the expected product **1.136** along with a disubstituted byproduct **1.137** (Scheme 51). Repeating the experiment produced the required monosubstituted product **1.136** as the minor one (<20% yield) and the disubstituted product **1.137** as the major one (80% Yield).



Scheme 51: Carbamoylation of 2,5-dichloropyrazine.

Replicating the same procedure in the presence of a solvent (chlorobenzene, DMSO, 1,4-dioxane, DCE, hexane, 1:1 mixture of DCM:Hexane) resulted either in the disubstituted product **1.137** or in the recovery of unreacted starting material.

In contrast to the results obtained with 2,5-dichloropyrazine, the desired monosubstitution was the major reaction pathway in a competition experiment with pyrazine in 70% yield (Scheme 52). Minisci reaction proceeds with the protonation of the heteroaromatic base followed by nucleophilic radical addition. Hence the observed result can be justified based on the ease of protonation of both the pyrazine and 2,5-dichloropyrazine. Pyrazine with a higher pK_a value is expected to be protonated faster than 2,5-dichloropyrazine in the same medium, giving rise to carbamoylation of pyrazine and recovery of 2,5-dichloropyrazine. Monosubstitution in case of pyrazine can be attributed to weak electron withdrawing nature of the amide group. Incoming amide group does not affect the electron deficient nature of pyrazine significantly to undergo additional substitution resulting in monosubstituted pyrazine. In contrast, in case of 2,5-dichloropyrazine, the incoming amide group coupled with two additional chloro substituents makes the pyrazine ring electron deficient to undergo additional substitution resulting in disubstituted compound.



Scheme 52: Competition experiment for carbamoylation under Minisci conditions.

The Minisci reaction is a versatile way to establish wide range of functionalities over electron deficient heterocycles. 2,5-dichloropyrazine turned out to be either too reactive or too unreactive under the Minisci reaction conditions, giving either a disubstituted product, or no product at all. Attempts to further functionalize 2,5-dichloropyrazine have been ineffective. The observed disubstitution during the carbamoylation reaction can be attributed to the higher susceptibility of monosubstituted product to additional nucleophilic attack due to the increased electron deficiency of the heteroaromatic ring.

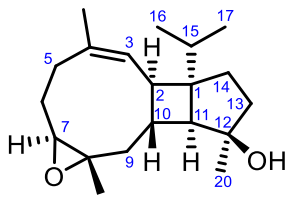
1.6 Conclusion and outlook

Repurposing approved antivirals for treatment of early stage COVID-19 infections increased the demand for favipiravir. With an aim to reduce the number of steps in the synthesis and make the synthesis more efficient, we have designed multiple approaches to assemble the functionalities on to the pyrazine ring in minimal number of steps. Unfortunately, the strategies employed in generating the intermediates required for making favipiravir were unsuccessful. Initial attempts at functionalization of 2,5-dichloropyrazine by ortho-lithiation resulted in recovery of starting material. Optimization of reaction conditions and using various lithiated bases did not yield any favourable results either. Lack of literature utilizing 2,5-dichloropyrazine to generate metalated species contributed to our lack of understanding the mechanistic aspects involved. Although the Minisci reaction is highly utilized and reported in functionalization of electron deficient heteroaromatics, its application to functionalize 2,5-dichloropyrazine was not fruitful initially. While the carbamoylation of 2,5-dichloropyrazine was successful, poor regioselectivity resulted in an undesired disubstituted compound as the major product. This observed selectivity favouring disubstituted product can be attributed to the highly electron deficient nature of monosubstituted 2,5-dichloropyrazine over 2,5-dichloropyrazine. In summary, these strategies were unsuccessful with 2,5-dichloropyrazine but are reported to work well with chloropyrazines making it an interesting path to pursue. Improving the regioselectivity of the Minisci addition to 2,5-dichloropyrazine and investigating the stability and reactivity of metalated 2,5-dichloropyrazine species will make an interesting puzzle to solve in future.

2 HUMILISIN E

2.1 Isolation and structure

In 2021, Li group reported the isolation, structure, and absolute configuration of humilisin E (Figure 8)[120]. A library of four new cembranoids (humilisins A–D), two unique diterpenoids (humilisins E and F), and eight other related compounds were isolated from soft coral species *Sinularia humilis* found in South China sea.



Humilisin E **(2.1)**

Figure 8: Structure of humilisin E[120].

Humilisin E consists of a tricyclic ring system with cyclobutane ring sandwiched between a cyclopentane and a cyclononane moiety. There are seven stereogenic centers of which five are contiguous stereocenters. All the four carbons of the cyclobutane ring are stereogenic centers with one being a hindered quaternary stereocenter bearing an isopropyl group. The nine-membered ring system bears an epoxide along with a trisubstituted olefin. These distinct structural features of humilisin E make it an appealing target for synthetic organic chemists. The absence of information about biosynthetic pathway of humilisin E along with the prospect of developing a methodology needed to assemble the unprecedented, fused ring structure provides justification for a total synthesis attempt.

2.2 Retrosynthesis and synthesis target

Natural products are an integral part of medicinal & industrial chemistry owing to their frequent utility in our everyday life. The natural products targeted for total synthesis are usually based on their biological activity and industrial utility. Although these reasons are compelling enough, often the structural complexity and chemical diversity drives the discovery process. The rationale behind undertaking a total synthesis of a molecule can be attributed to understanding the reaction pathways along with discovering novel methodologies to access unique and complex structural moieties.

Humilisin E was introduced as an assignment for an advanced level synthetic organic chemistry course, and I never imagined that it would be a part of my dissertation. The distinct structural features, in particular the complex assembly of the three fused rings, along with the inherent complexity of the the entire molecule was enough to draw our attention despite having no reported biological activity or industrial use. The absence of similar skeletal structures in literature motivated us to attempt the total synthesis of humilisin E and develop novel methodologies to synthesize highly constrained and sterically hindered systems.

Retrosynthesis is a process of breaking down a complex molecule into individual components which are easily accessible from commercially available compounds. At first glance it is quite evident that the complex stereogenic centers and sterically bulky groups of humilisin E are part of A & B rings, while the nine-membered C ring is simpler in comparison. A minimal risk synthesis design involves the installation of complex bits in earlier stages followed by simple straight forward steps in later stages. Following this minimum risk strategy, we have decided to install the five contiguous stereocenters of A & B rings in earlier stages and then continue with the construction of C ring.

Retrosynthetic design of humilisin E as shown in Figure 9 involved disconnecting the trisubstituted olefin on C ring (C3-C4 disconnection) based on ring closing metathesis reaction leading to intermediate **2.2**. Functional group transformations to **2.2** guides us to compound **2.3**, which can be further disconnected by olefination step (C7-C8 disconnection) to the bicyclo[3.2.0]heptane skeleton **2.4**. The bicyclic fragment **2.4** consists of fused A & B rings with all the complex stereocenters we envisioned to install in early stages. Hence our primary target for the total synthesis of humilisin E was to assemble the bicyclo[3.2.0]heptane skeleton with suitable handles necessary to install the nine-membered C ring. The next section includes a literature survey of natural products containing bicyclo[3.2.0]heptane skeleton and various methods reported to generate the fused skeleton. The subsequent sections describe our strategies at generating the bicyclic core, conclusions, and future prospects.

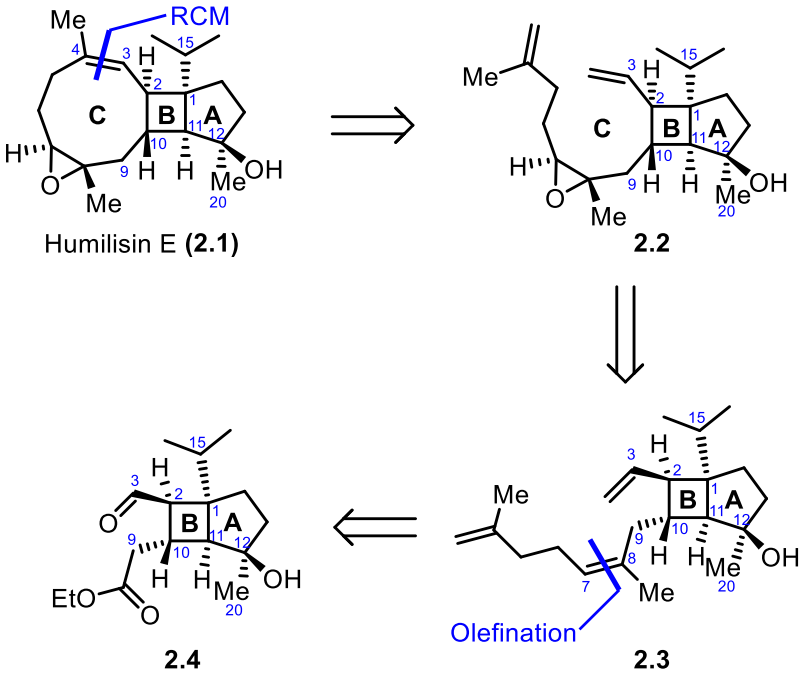
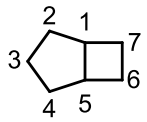


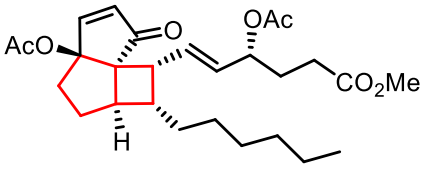
Figure 9: Retrosynthetic design to bicyclo[3.2.0]heptane skeleton.

2.3 Bicyclo[3.2.0]heptane motif

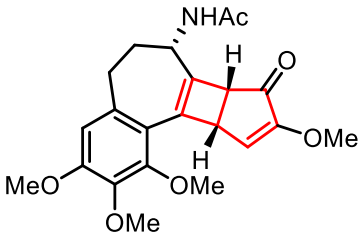
The bicyclo[3.2.0]heptane skeleton (Figure 10) is an uncommon molecular architecture that intrigues synthetic organic chemists. Although there are a range of natural products[121] and therapeutic agents[122,123] with the bicyclo[3.2.0]heptane skeleton, these systems are not so prevalent in nature. Some of the analogues with this structural skeleton are found to have cytotoxic, antimicrobial, anticancer and AChE inhibition activities[124]. The ring strain of the system provides an impetus for a wide range of skeletal isomerizations[123,125] or ring expansions[123], which has extensive utility in organic synthesis. The structural versatility along with the ability to access a wide range of cyclic & bicyclic systems makes the bicyclo[3.2.0]heptane fascinating for organic chemists.



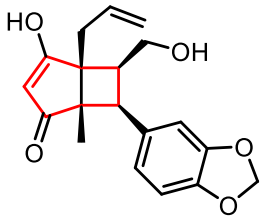
Bicyclo[3.2.0]Heptane



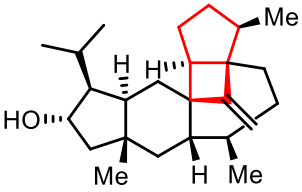
Tricycloclavulone



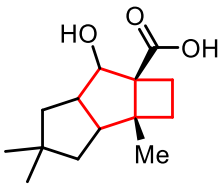
β-Lumicolchicine



AcheE Inhibitor



Astellatol

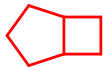


(–)-Sulcatine G

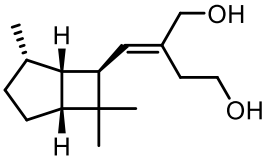
Figure 10: Natural products containing bicyclo[3.2.0]heptane skeleton.

2.3.1 Natural products with bicyclo[3.2.0]heptane skeleton

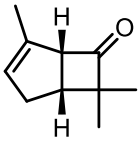
Natural products comprising of bicyclo[3.2.0]heptane skeleton can be subdivided into categories based on further ring fusions at different positions. Figure 11 illustrates naked and various fused skeletons along with the isolated and reported examples of natural products.



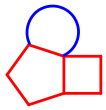
Naked skeleton



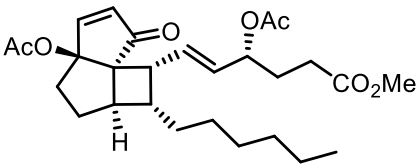
Raikovenal



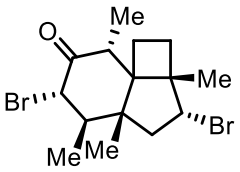
Filifolone



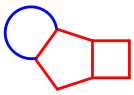
1,2-Fused skeleton



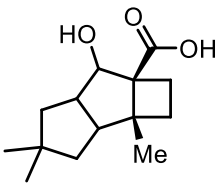
Tricycloclavulone



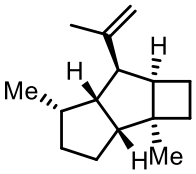
Perforatone



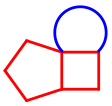
2,3-Fused skeleton



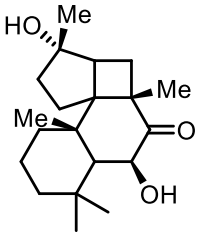
(–)-Sulcatine G



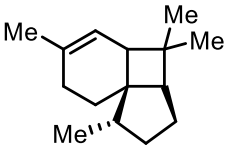
Kelsoene



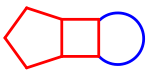
1,7-Fused skeleton



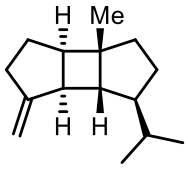
6,13-dihydroxy-7-haplopanone



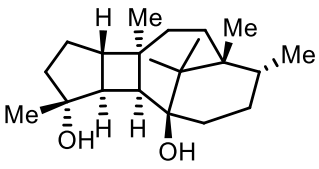
Italicene



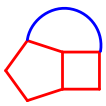
6,7-Fused skeleton



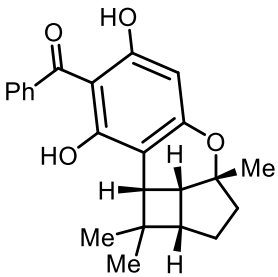
Prespatane



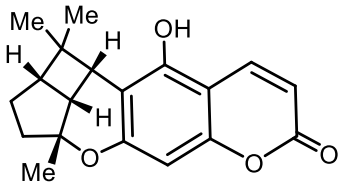
Rigidol



2,7-Fused skeleton



Clusiacyclol A



Eriobrucinol

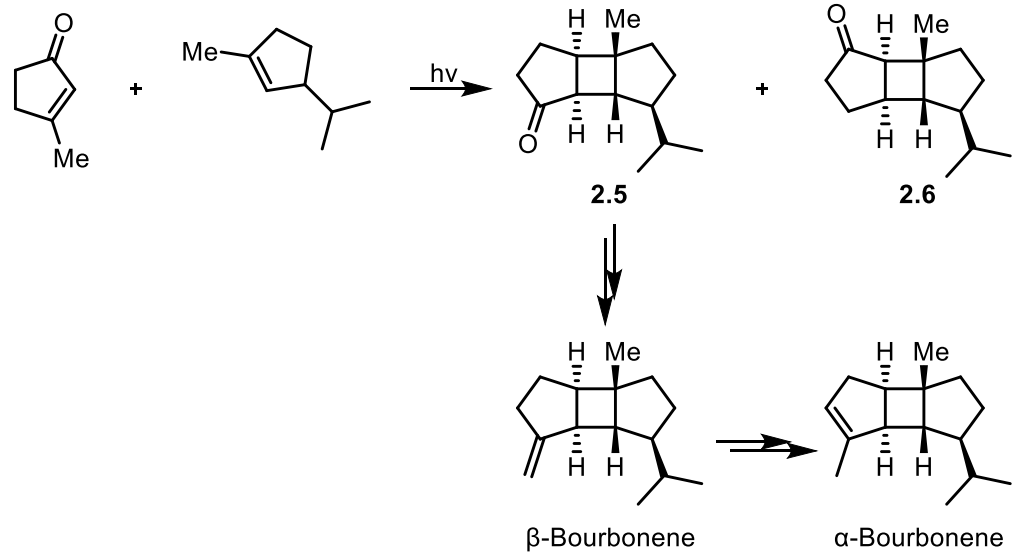
Figure 11: Natural products with naked and fused bicyclo[3.2.0]heptane skeleton.

2.3.2 Synthetic methodologies to generate bicyclo[3.2.0]heptane skeleton

The typical procedure to construct bicyclo[3.2.0]heptane skeleton is to utilize the photochemical [2+2] cycloaddition. Various intermolecular and intramolecular versions of photochemical [2+2] cycloadditions have been reported and utilized in organic synthesis. Apart from the photochemical methodologies, thermal and metal catalyzed [2+2] cycloadditions have also been developed to access a wide range of highly functionalized & substituted bicyclo[3.2.0]heptane skeletons[121]. The mechanistic aspects of photochemical [2+2] cycloadditions and Lewis acid/transition metal-catalyzed [2+2] cycloadditions have been subjected to extensive studies and have been discussed in several reviews[126–128]. Hence, this section does not focus on the mechanistic aspects of [2+2] cycloaddition, but instead describes the various methodologies employed to construct the bicyclic skeleton along with their usage in total synthesis of natural products.

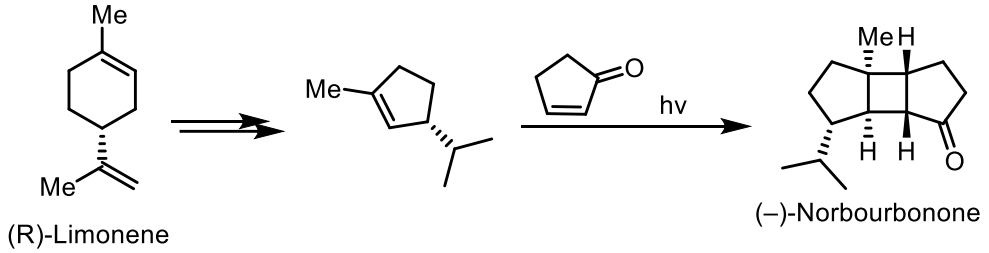
2.3.2.1 Intermolecular photochemical [2+2] cycloaddition

Intermolecular photochemical [2+2] cycloaddition is one of the most utilized methods to synthesize all kinds of molecular architectures containing a four-membered ring. In the synthesis of α and β-bourbonene, this methodology has been used to generate the precursors of the target molecules. Photochemical [2+2] cycloaddition of 1-methyl-3-isopropylcyclopentene with cyclopentenone resulted in the cycloadduct **2.5** along with its regioisomer **2.6** in 1:1 ratio (Scheme 53). Further transformations of **2.5** led to the target molecules α- and β-bourbonene[129,130].



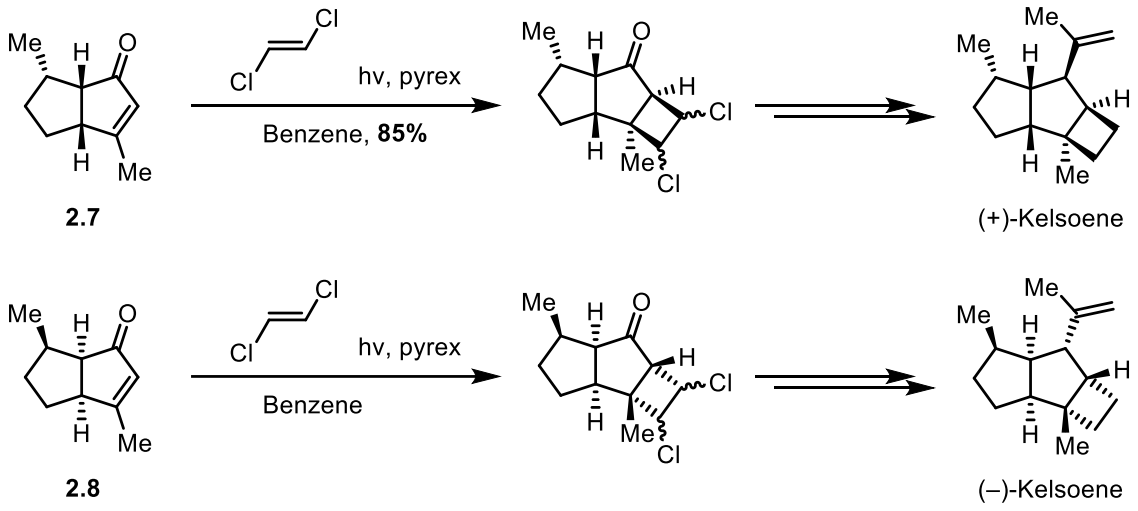
Scheme 53: Synthesis of α- and β-bourbonene via intermolecular [2+2] photocycloaddition [129,130].

Wickberg and co-workers[131] employed similar procedure to synthesize (–)-norbourbonone from (*R*)-limonene and cyclopentanone (Scheme 54). Later, the asymmetric total synthesis of (–)-β-bourbonene was accomplished by Koga and co-workers by photochemical [2+2] cycloaddition[132].



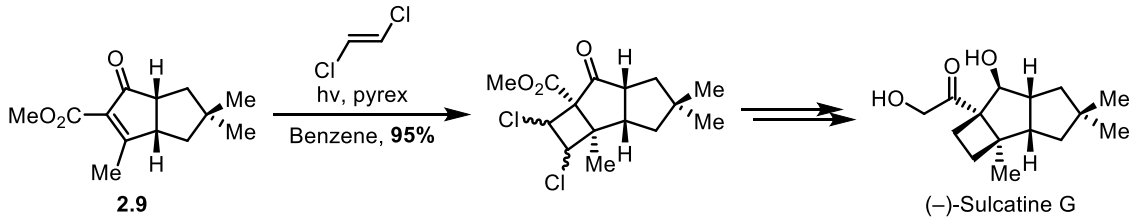
Scheme 54: Synthesis of (–)-norbourbonone by Wickberg and co-workers[131].

In the synthesis of (+) and (–)-kelsoene, the key step to generate the tricyclic skeleton was an intermolecular [2+2] photocycloaddition. Mehta and co-workers reported the total synthesis of racemic kelsoene[133] along with the total syntheses of (+) and (–)-kelsoene[134]. The synthetic approach to the tricyclic precursor of kelsoene was based on a [2+2] photochemical cycloaddition of *trans*-1,2-dichloroethylene with optically pure diquinanes **2.7** and **2.8** (Scheme 55.). Further transformations of the tricyclic intermediates resulted in (+)-kelsoene and (–)-kelsoene respectively. Reports by Orellana[135] and Jones[136] on the total synthesis of kelsoene involved [2+2] photocycloaddition of ethylene with diquinanes to access the tricyclic intermediate.



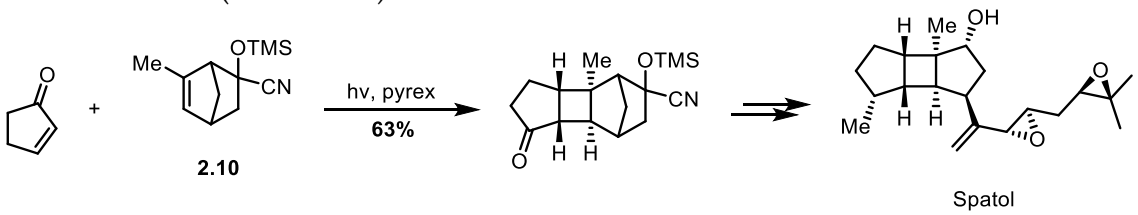
Scheme 55: Synthesis of (+)-kelsoene and (–)-kelsoene via intermolecular [2+2] photocycloaddition.[134].

Total synthesis of tricyclic sesquiterpene (–)-sulcatine G has been accomplished by [2+2] photocycloaddition of *trans*-1,2-dichloroethylene with functionalized optically active diquinane **2.9** (Scheme 56)[137,138].



Scheme 56: Synthesis route to (–)-sulcatine G via intermolecular [2+2] photocycloaddition.[137,138].

Total synthesis of spatol and spatane derivatives involved [2+2] cycloaddition as the key step to construct the tricyclic core. Salomon and co-workers built the tricyclic core by [2+2] photocycloaddition of cyclopentenone with norbornene derivative **2.10** (Scheme 57)[139].

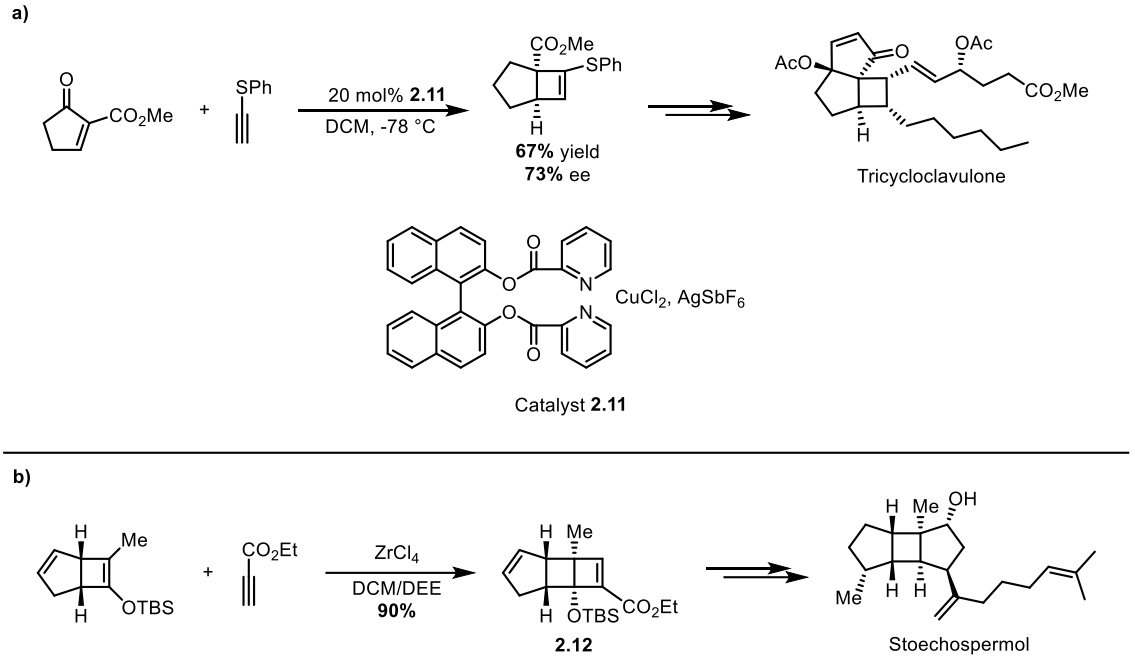


Scheme 57: Salomon and co-workers' approach towards spatol and spatane derivatives[139].

Syntheses of hippolachnin A by Carriera[140], spatadiene by Dauben and Kowalczyk[141,142], along with spatol and stoechospermol[143,144] all include intermolecular photochemical [2+2] cycloaddition as the key step to assemble the core.

2.3.2.2 Lewis acid-catalyzed [2+2] cycloaddition

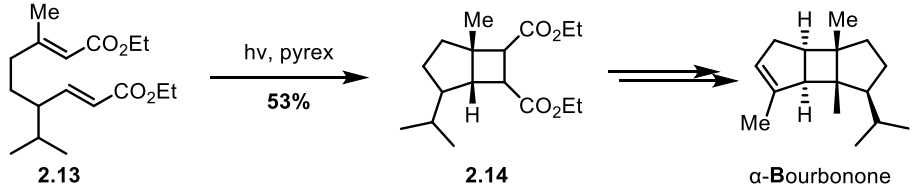
Total synthesis of (+)-tricycloclavulone[145,146] was achieved by Iguchi and co-workers, based on an enantioselective intermolecular [2+2] cycloaddition of 2-methoxycarbonyl-2-cyclopenten-1-one and phenylthioacetylene catalysed by a chiral copper catalyst **2.11** (Scheme 58). Lewis acid-catalyzed [2+2] cycloaddition has also been implemented in accessing the skeleton **2.12** of stoechospermol as shown in Scheme 58 using zirconium tetrachloride[147,148].



Scheme 58: Intermolecular Lewis Acid catalyzed [2+2] cycloaddition approach towards synthesis of a) tricycloclavulone[145,146] b) stoechospermol[147,148].

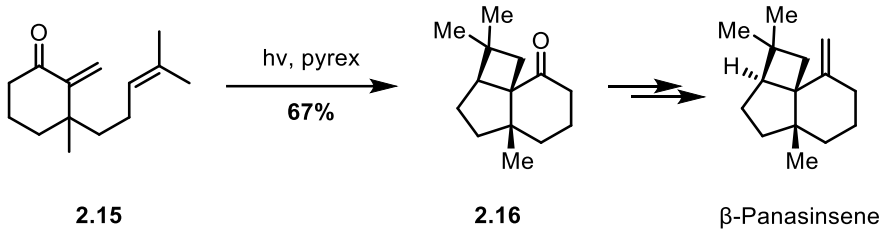
2.3.2.3 Intramolecular photochemical [2+2] cycloaddition

Intramolecular reactions are preferred over intermolecular [2+2] cycloadditions owing to reliable and better regio- & stereoselectivity. Intramolecular photochemical [2+2] cycloaddition of 1,6-dienes is a common and simple method to generate bicyclo[3.2.0]heptane systems. In the synthesis of α-bourbonone by Brown and co-workers, photolysis of 1,6-diene **2.13** resulted in the bicyclo[3.2.0]heptane precursor **2.14**, which was then transformed to α-bourbonone[149] (Scheme 59).



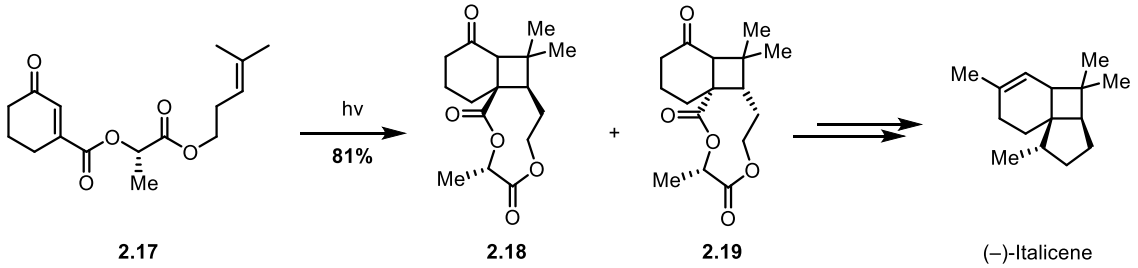
Scheme 59: Intramolecular [2+2] photocycloaddition towards the synthesis of α-bourbonone[149].

The same methodology has been applied to the synthesis of α- and β-panasinsene[150,151]. Intramolecular [2+2] cycloaddition of enone **2.15** resulted in intermediate **2.16**, which was subsequently converted to α- and β-panasinsene (Scheme 60).



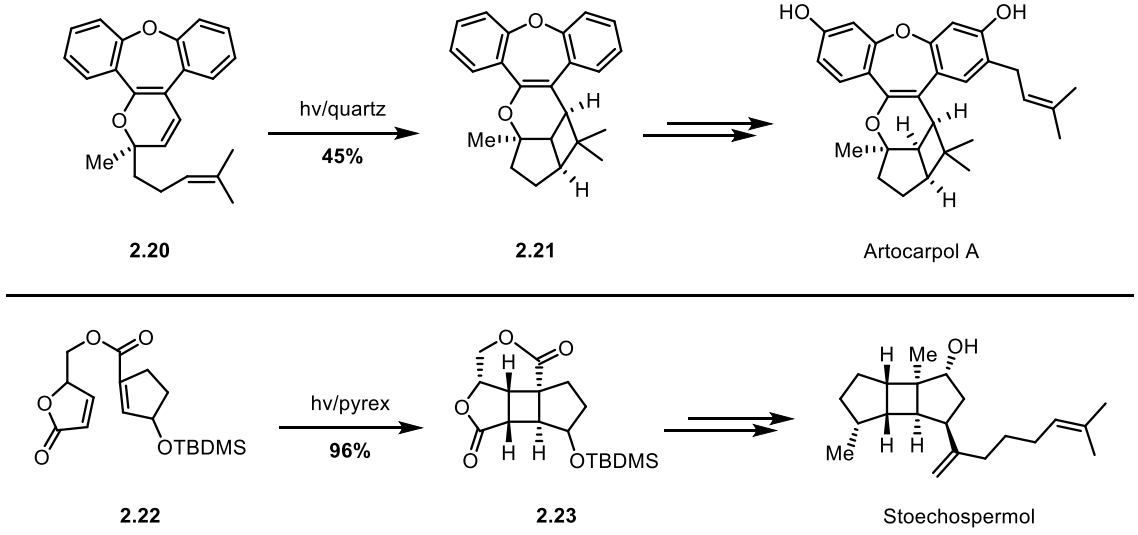
Scheme 60: Synthesis of α- and β-panasinsene via intramolecular [2+2] photocycloaddition.[150,151].

Optically pure compound **2.17**, underwent a highly regio- and diastereoselective intramolecular [2+2] photocycloaddition resulting in a 97:3 ratio of cycloadducts **2.18** and **2.19** (Scheme 61). The cycloadduct **2.18** has been further modified to complete the synthesis of (–)-italicene[152].



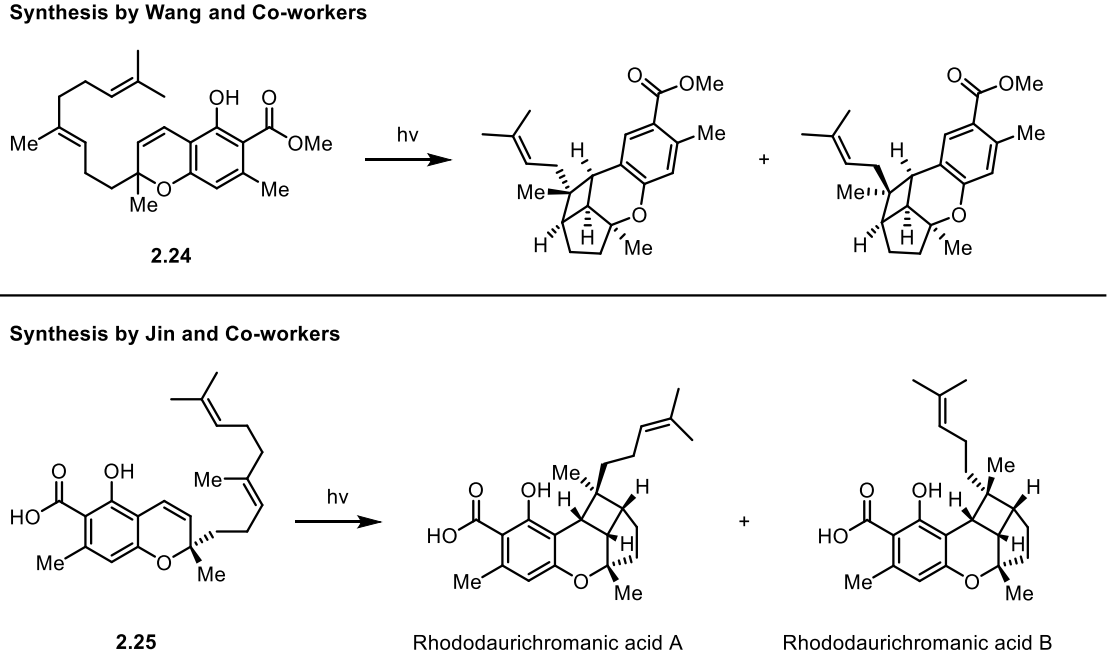
Scheme 61: Synthesis of (–)-italicene[152].

Polycyclic ring system of precursor **2.21** to artocarpol A[153] has been built using a [2+2] cycloaddition reaction of compound **2.20** (Scheme 62). Koga and co-workers reported an asymmetric total synthesis of (+)-stoechospermol with an intramolecular [2+2] photocycloaddition of compound **2.22** (Scheme 62) as the key step to establish the tricyclic ring system **2.23**[154,155]. Utilizing the same methodology, Koga and co-workers also reported the synthesis of (+)-spatol[156].



Scheme 62: Synthesis of artocarpol A[153] and stoechospermol[154,155].

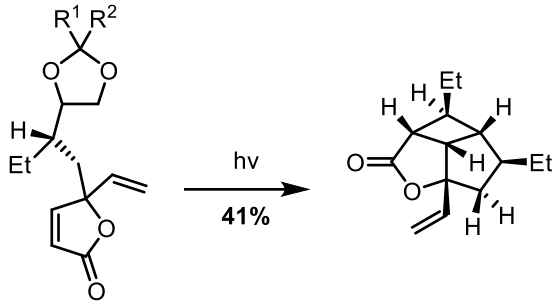
Wang and co-workers[157] synthesized rhododaurichromanic acids A and B by intramolecular [2+2] photocycloaddition of ester **2.24** (Scheme 63). Jin and co-workers utilized daurichromenic acid **2.25** as the starting material (Scheme 63) and synthesized rhododaurichromanic acids A and B by using same strategy[158].



Scheme 63: Synthetic approaches towards rhododaurichromanic acids A and B[157,158].

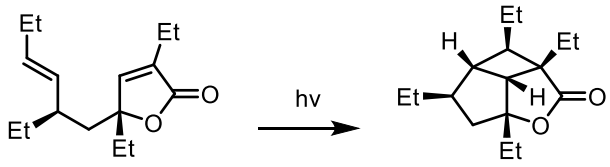
Synthesizing the core of hippolachnin A using intramolecular [2+2] photocycloaddition has been reported by multiple groups. Ghosh and co-workers reported the synthesis of enantiomerically pure form of tricyclic lactone **2.27** from butenolide **2.26** (Scheme 64) which forms the core structure of hippolachnin A[159]. Wu et al. and Tang et al. arrived at the tricyclic lactone **2.29** from butenolide **2.28**[160] (Scheme 64). Tricyclic lactone **2.29** is an advanced intermediate in synthesis of hippolachnin A by Wood & Brown[149] . Tang and co-workers accomplished the biomimetic total synthesis of hippolachnin A by intramolecular [2+2] photocycloaddition of furan derivative **2.30** (Scheme 64)[161].

Ghosh and co-workers' approach towards hippolachnin A



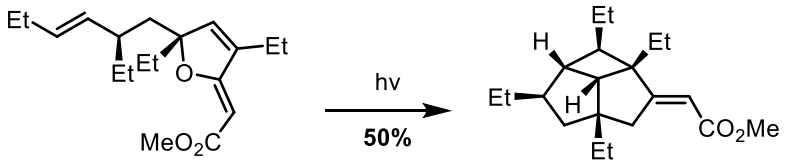
2.26 **2.27**

Wu's group & Tang's group approach towards hippolachnin A



2.28 **2.29**

Tang and co-workers approach towards hippolachnin A



2.30 Hippolachnin A

Scheme 64: Different approaches towards synthesis of hippolachnin A[149,159-161].

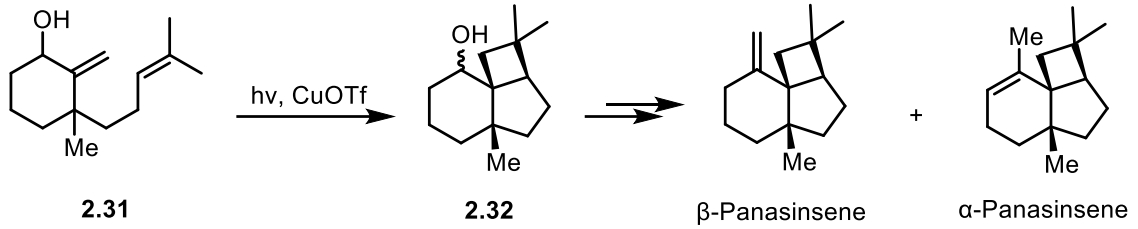
Further examples of intramolecular [2+2] photocycloaddition as the key step in total synthesis of natural products include the total syntheses bielschowskysin[162-166] , isocomene[167] and ginkgolide B[168,169]. In all cases, the [2+2] cycloaddition was highly regio- and stereoselective.

2.3.2.4 CuOTf-catalyzed [2+2] cycloaddition

Simple alkenes lack the ability to reach the excited state and undergo photocycloaddition through direct irradiation. To enable the use of alkenes and allylic alcohols in photocycloadditions, addition of transition metal salts as catalysts has been successfully applied. Copper (I) trifluoromethanesulfonate (CuOTf) has been the most suitable catalyst among a wide range of transition metal salts investigated[170] and this catalyst applied in the total synthesis of various natural products.

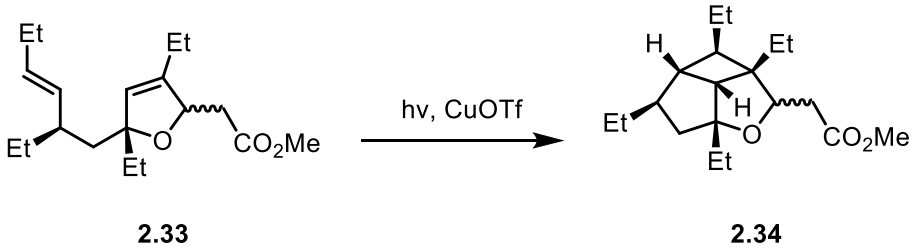
CuOTf-catalyzed intramolecular [2+2] photocycloaddition of 1,6-heptadienols has been a reliable methodology to construct bicyclo[3.2.0]heptane

skeletons and used accordingly in the total synthesis of α- and β-panasinsene[150]. The key step in the synthesis involved CuOTf catalysed cycloaddition of dienol **2.31** to construct the tricyclic ring skeleton **2.32**, which was then converted to α- and β-panasinsene (Scheme 65).



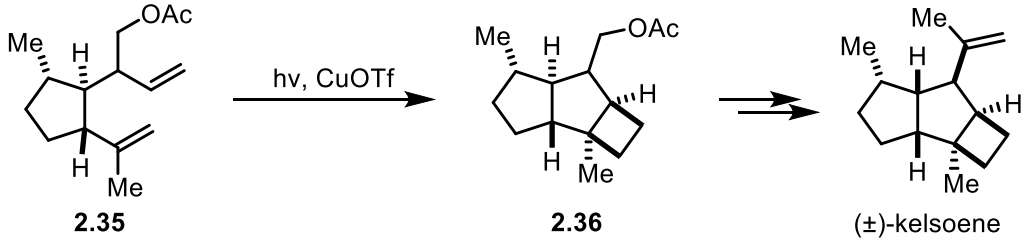
Scheme 65: CuOTf-catalyzed [2+2] cycloaddition approach towards α- and β-panasinsene[150].

Formal total synthesis of hippolachnin A was accomplished by Wu and co-workers[160] by generating the tricyclic intermediate **2.34** by CuOTf-catalysed [2+2] cycloaddition of dihydrofuran derivative **2.33** (Scheme 66). The tricyclic intermediate **2.34** was transformed to hippolachnin A by Carreira and co-workers.[140]



Scheme 66: Synthesis of intermediate 2.34 used in formal total synthesis of hippolachnin A by Wu and co-workers[160].

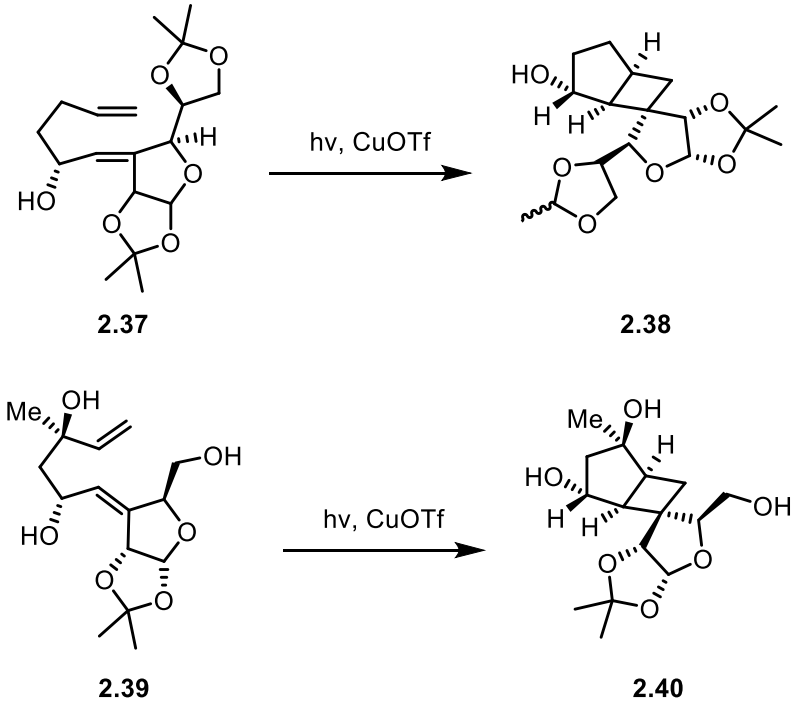
Bach and co-workers utilized the same methodology to achieve the total synthesis of sesquiterpene kelsoene. Irradiating cyclopentane derivative **2.35** in presence of CuOTf resulted in a [2+2] cycloaddition product **2.36** (Scheme 67). Further manipulations of tricyclic intermediate **2.36** has resulted in total synthesis of (±)-kelsoene[171].



Scheme 67: CuOTf-catalyzed [2+2] cycloaddition approach towards (±)-kelsoene[171].

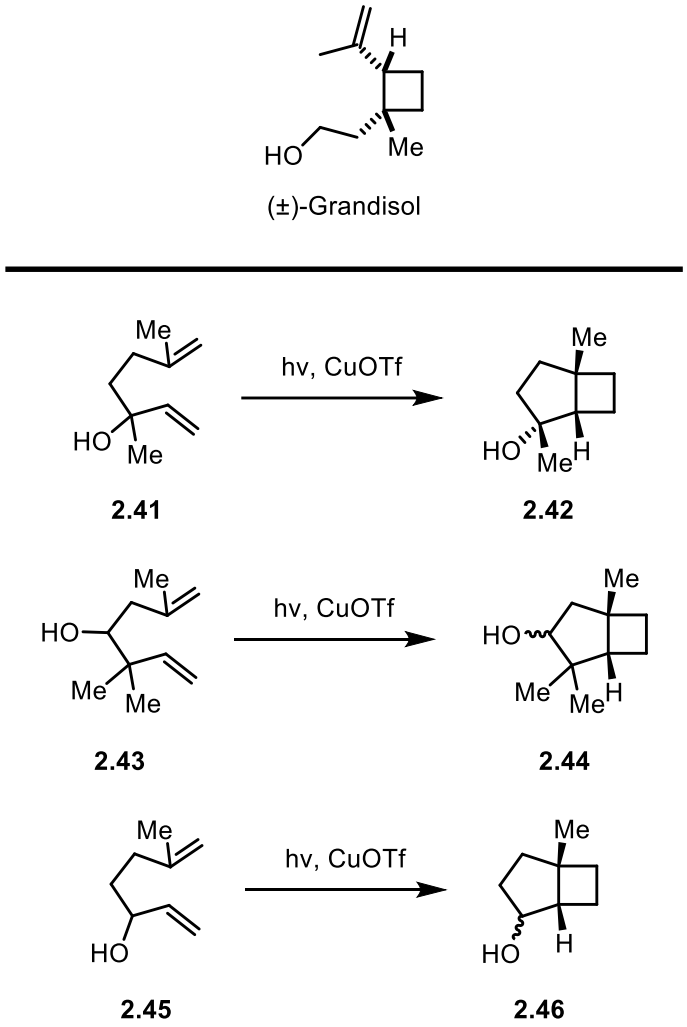
Intramolecular CuOTf-catalyzed [2+2] photocycloaddition methodology has been employed in the total synthesis of diterpene beilschowskysin to generate the desired [3.2.0]heptane system with full stereochemical control. Ghosh and co-workers reported two different routes employing CuOTf-catalyzed

photocycloaddition as the key step to arrive at the bicyclo[3.2.0]heptane intermediates **2.38**[172] and **2.40**[173] (Scheme 68).



Scheme 68: Synthesis of bicyclo[3.2.0]heptane intermediates towards total synthesis of beilschowskysin by Ghosh and co-workers[172,173].

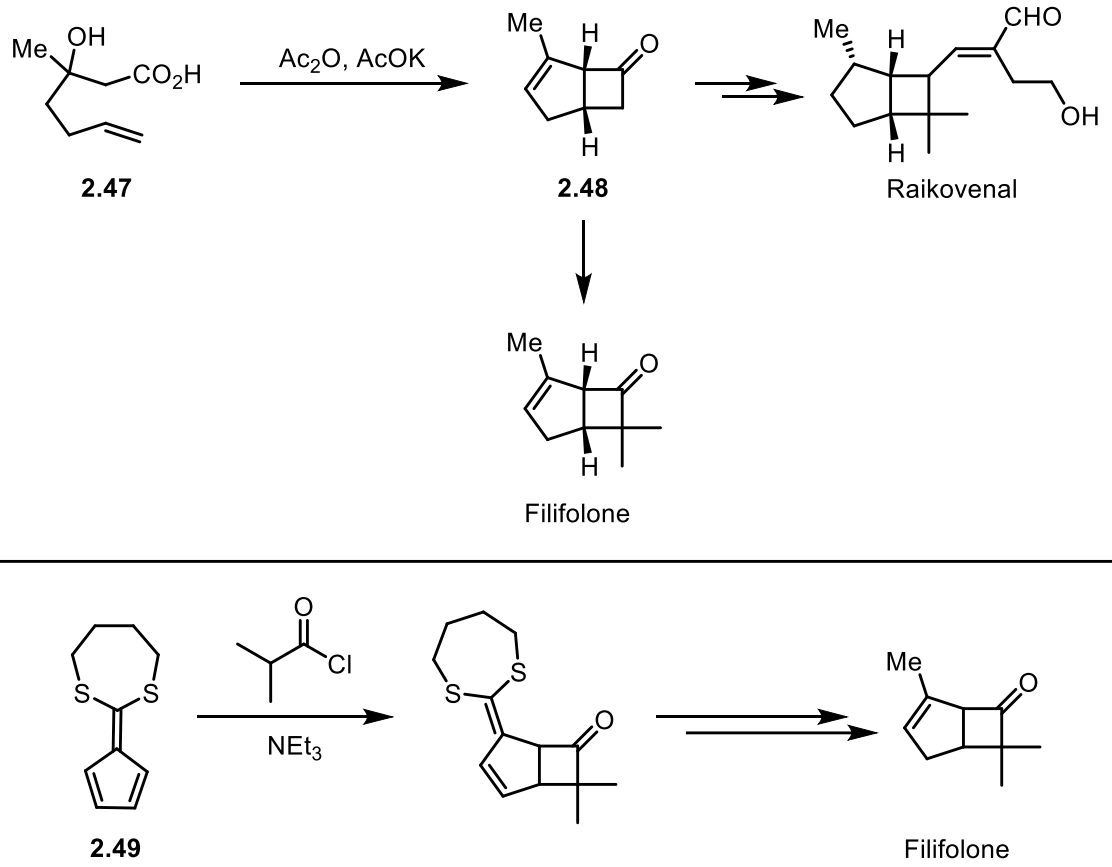
Grandisol (Scheme 69) has been a subject to multiple synthetic approaches using the CuOTf-catalysed cycloaddition methodology. Rosini and co-workers achieved the total synthesis by CuOTf-catalyzed photocycloaddition of 1,6-heptadienols **2.41** and **2.43** generating bicyclo[3.2.0]heptane intermediates **2.42** and **2.44** respectively (Scheme 69). Cleavage of five membered ring of intermediates **2.42** and **2.44** resulted in (±)-grandisol[174,175]. Rosini group also reported the synthesis of both the enantiomers of grandisol by resolution of bicyclo intermediate **2.42**[176,177]. Racemic synthesis of grandisol by Mattay and co-workers involved intramolecular CuOTf-catalyzed [2+2] photocycloaddition of 1,6-heptadienol **2.45** to generate the bicyclic skeleton **2.46** and then proceeding to complete the synthesis[178] (Scheme 69). By using enantiomerically pure dienol, Mattay and co-workers also accomplished enantioselective total synthesis of (+)- and (–)-grandisol.



Scheme 69: (±)-Grandisol and different intermediates involved in racemic and enantioselectivetotal syntheses of grandisol[174–178] by using CuOTf-catalyzed cycloaddition method.

2.3.2.5 Other methodologies

Other methodologies to construct the bicyclo[3.2.0]heptane core include [2+2] cycloaddition of a ketene and an alkene. This has been achieved by generating a ketene *in situ* followed by thermal cycloaddition with an alkene. This protocol has been successfully applied in the total synthesis of raikovenal and filifolone[179–183] . Rosini and co-workers reported the synthesis of both raikovenal and filifolone starting from 3-hydroxy-3-methyl-6-heptenoic acid (**2.47**) (Scheme 70). Treating **2.47** with potassium acetate and acetic anhydride generates a ketene *in situ* which undergoes [2+2] cycloaddition with the alkene generating 4-methylbicyclo[3.2.0]hept-3-en-6-one (**2.48**). Further manipulations of **2.48** resulted in the successful syntheses of raikovenal and filifolone. Dreiding's group[184] reported the synthesis of filifolone by [2+2] cycloaddition of olefin **2.49** to dimethylketene followed by further manipulations (Scheme 70). Treating isobutyryl chloride with triethylamine yielded the required dimethylketene in situ.



Scheme 70: Synthesis approaches towards filifolone and raikovenal[179–184].

Apart from these approaches, a variety of other methodologies have been developed to construct the bicyclo[3.2.0]heptane framework. Lewis acid-catalyzed thermal cycloaddition[185], gold(I)-catalyzed cycloaddition of allene-alkenes[186], thermal cyclization of keteneiminium-alkenes[187,188] and ketene-allenes[189] are a few reported methodologies. Apart from these, cobalt-catalyzed intramolecular cycloadditions of bis(enones)[190], gold(I)-catalyzed enyne cycloisomerizations[125], photochemical[191,192] and electrochemical[193–195] methodologies have also been reported. Although these new methodologies can construct the bicyclic framework, they are yet to be used in a total synthesis of natural products containing a bicyclo[3.2.0]heptane framework.

2.4 Synthesis of the bicyclic core of humilisin E

The bicyclo[3.2.0]heptane system of humilisin E is highlighted in Figure 12, along with the ideal and alternative bicyclic intermediates that can be utilized in the construction of 9-membered ring.

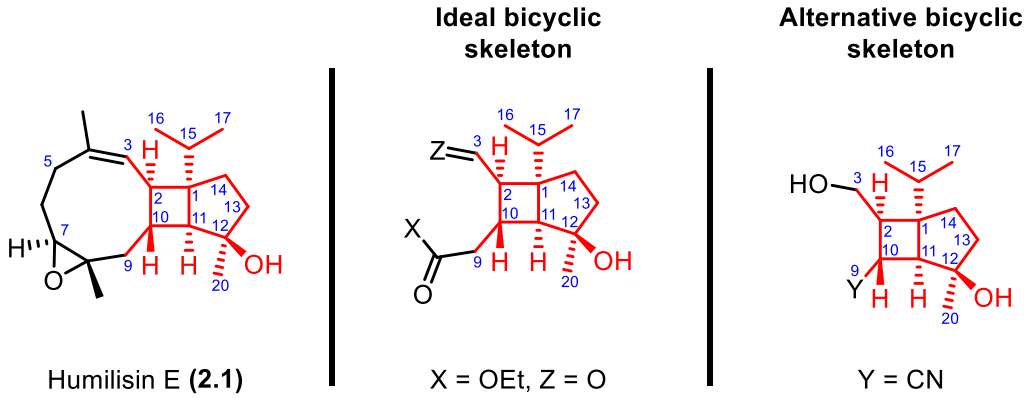


Figure 12: Illustration of bicyclo[3.2.0]heptane skeleton of humilisin E along with ideal and alternative bicyclic intermediates.

2.4.1 Intramolecular [2+2] cycloaddition strategy

The bicyclic AB ring fragment consists of a bicyclo[3.2.0]heptane skeleton. With [2+2] photocycloaddition being a straightforward method to assemble this skeleton, our thought was instantly directed towards a [2+2] cycloaddition strategy involving a cyclopentenone moiety with an olefinic counterpart. The chemical literature reveals several successful total syntheses attempts utilizing intermolecular [2+2] photocycloaddition strategy to assemble the bicyclo[3.2.0]heptane skeleton. The structural complexity of humilisin E along with sterically demanding groups rendered this approach very risky, as the intermolecular [2+2] cycloaddition might be very challenging to control in terms of regio- and stereoselectivity. This made us focus on a more controlled intramolecular approach which was expected to guide the regioselectivity as desired. An intramolecular [2+2] cycloaddition strategy basically involves having both the olefinic fragments in a single molecule. The next step was to design an intermediate that can execute two different roles. The first role includes holding both the olefinic parts together for [2+2] cycloaddition and the second one is the ability to modify into a suitable handle for further transformations. Figure 13 illustrates a general representation of an intermediate that would realize the mentioned criteria.

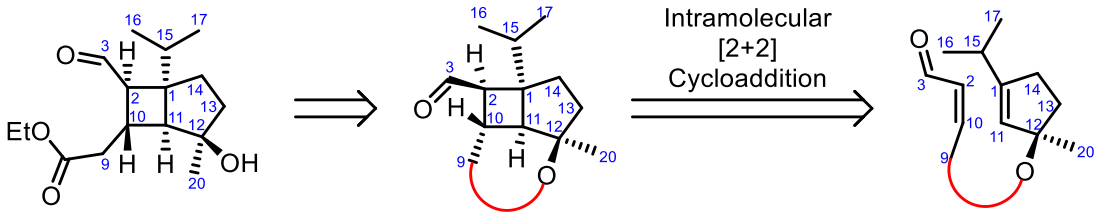
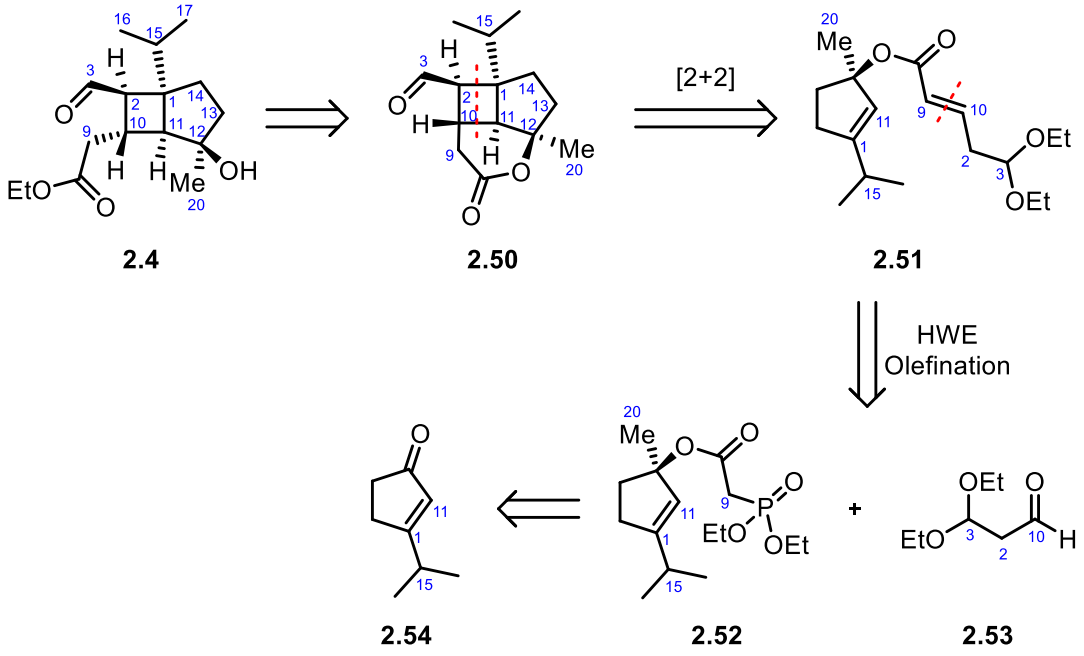


Figure 13: Representation of intramolecular [2+2] cycloaddition strategy. The final [2+2] cycloaddition could take place via either a photochemical or an iminium-catalyzed[196] route.

2.4.1.1 Strategy involving an ester tether

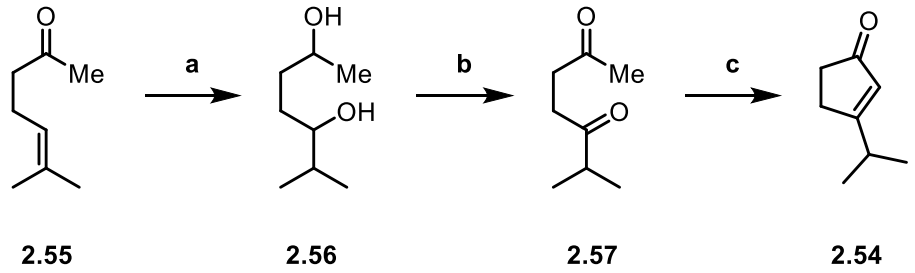
The first design was based on utilizing an ester group as a tether holding the olefinic components together. It was a simple and efficient design to access the intermediate **2.4**. The retrosynthesis plan to make the intermediate with an ester tether is depicted in Scheme 71. We arrived at an ester tethered intermediate **2.51** which can undergo intramolecular [2+2] cycloaddition to assemble the skeleton and then generate the required handle by simple hydrolysis of ester. Compound **2.51** can be accessed by HWE olefination (C9-C10 disconnection) of **2.53** and functionalized 3-alkylcyclopent-2-en-1-one.



Scheme 71: Retrosynthetic plan of intramolecular [2+2] cycloaddition using an ester tether.

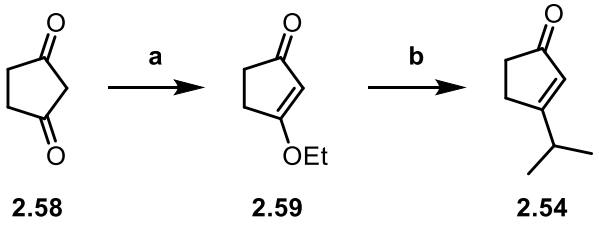
Experimental work started with the synthesis of 3-isopropylcyclopent-2-en-1-one (**2.54**) due to its commercial unavailability. Hydroboration of 2-methyl-2-hepten-6-one (**2.55**) with borane in THF followed by oxidation using alkaline hydrogen peroxide furnished diol **2.56** in quantitative yields. Further oxidation of diol **2.56** to diketone **2.57** using Jones reagent was low yielding due to incomplete oxidation of diol **2.56**. Aldol condensation of diketone **2.57** to generate **2.54** was sluggish with 45% yield. Low yields coupled with the unacceptably high

quantities of chromium waste generated made this an impractical route to synthesize 3-isopropylcyclopent-2-en-1-one (**2.54**) (Scheme 72), and an alternative route was developed later on (Scheme 73) However, accessing the required aldehyde **2.53** was straightforward involving a DIBAL-H reduction of commercially available ethyl 3,3-diethoxypropanoate[197].



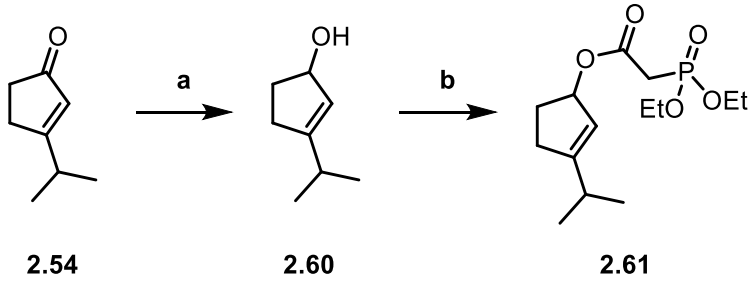
Scheme 72: Preparation of enone **2.54** by aldol reaction. Reagents and conditions: a) i. BH_3-THF complex, 0 °C to rt, 4h, ii. 3N aq. NaOH, 30% H_2O_2, 0 °C to rt, 17h, 99%; b) Jones oxidation, 18%; c) 2% aq. NaOH, EtOH, reflux, 6h, 45%.

Scheme 73 shows an alternative approach to synthesize **2.53** from cyclopentane-1,3-dione (**2.58**). Refluxing diketone **2.58** with *p*-TSA in ethanol resulted in 3-ethoxycyclopent-2-en-1-one (**2.59**) in 91% yield[198]. We opted for a Cu-catalyzed 1,4-addition of *i*PrMgCl to **2.59** to arrive at the required enone **2.54** in 83% yield.



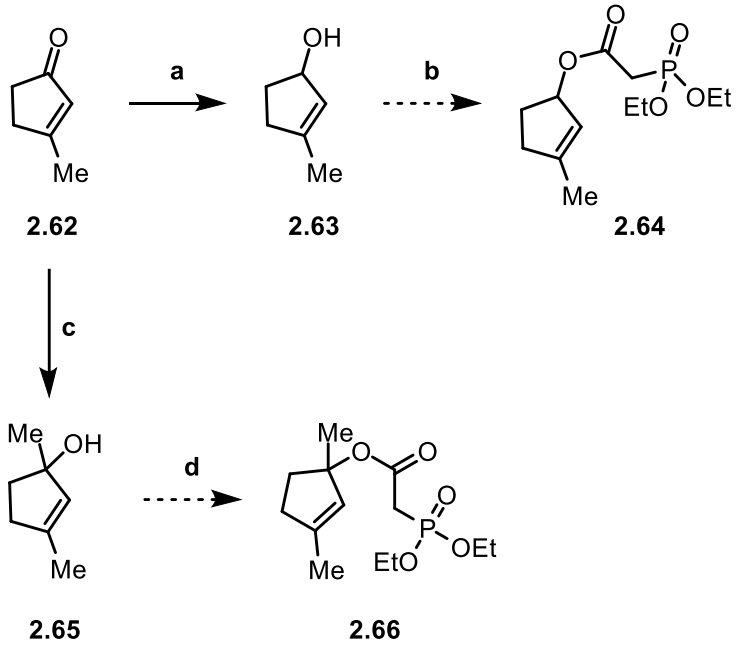
Scheme 73: Preparation of enone **2.54** by Cu-catalyzed 1,4-addition. Reagents and conditions: a) *p*-TSA, EtOH, reflux, 17h, 91%; b) CuBr.Me_2S, *i*PrMgCl, HMPA, TMSCl, THF, -78 °C, 3h, 83%.

With enone **2.54** at our disposal, our focus was on the precursor for HWE olefination. Reduction of enone **2.54** using LAH furnished the secondary alcohol **2.60** (volatile and acid sensitive) in 62% yield. Esterification of **2.60** with 2-(diethoxyphosphoryl)acetic acid in presence of T3P was slow with 20% yield of **2.61** after 3 days. Further optimization efforts failed in enhancing the yield (Scheme 74).



Scheme 74: Preparation of ester **2.61**. Reagents and conditions: a) LAH, DEE, 0 °C to rt, 2 h, 62%; b) 2-(diethoxyphosphoryl)acetic acid, T3P, DIPEA, PhMe, rt, 72 h, 20%.

To try and optimize the esterification reaction further, we temporarily switched from 3-isopropylcyclopent-2-en-1-one (**2.54**) to 3-methylcyclopent-2-en-1-one (**2.62**), which was inexpensive and commercially available. Scheme 75 illustrates our efforts towards generating a HWE olefination precursor using enone **2.62**. Luche reduction of 3-methylcyclopent-2-en-1-one (**2.62**) resulted in a highly volatile and extremely unstable secondary alcohol **2.63**. Crude alcohol **2.63** was subjected to a wide range of coupling conditions to generate **2.64**. Unfortunately, all our trials resulted in the recovery of starting alcohol **2.63**. The next attempt involved methylating enone **2.62** using MeLi producing tertiary alcohol **2.65** in 85% yield. Tertiary alcohol **2.65** was less volatile, and somewhat surprisingly, more stable compared to the secondary alcohol **2.63**. Unfortunately, the tertiary alcohol **2.65** was unreactive, and esterification using T3P and 2-(diethoxyphosphoryl)acetic acid never progressed to furnish the desired product **2.66**. Unreactivity, instability and low yields of various intermediates in the synthesis plan led us to abandon this approach and search for new possibilities.

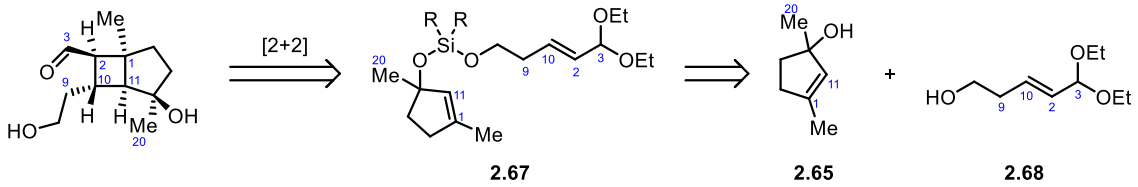


Scheme 75: Synthetic attempts to prepare esters **2.64** & **2.66**. Reagents and conditions: a) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0 °C, 1 h, >99%; b) 2-(diethoxyphosphoryl)acetic acid and i. DCC, DMAP, DCM, rt, 19 h or ii. T3P, DIPEA, PhMe, rt, 48 h or iii. PPh_3, DIAD, THF, rt, 12 h or iv. PPh_3, DEAD, THF, rt, 18 h; c) MeLi, DEE, -78 °C, 2 h, 85%; d) 2-(diethoxyphosphoryl)acetic acid, T3P, DIPEA, PhMe, rt, 24 h.

2.4.1.2 Strategy involving a silicon tether

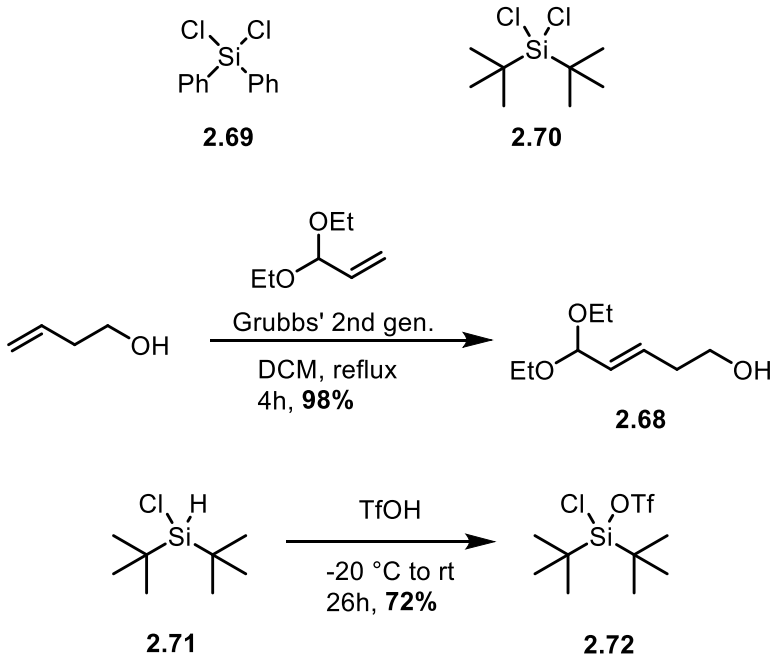
Intramolecular reactions possess superior rates as well as generally better regio- and stereoselectivities over intermolecular reactions, and these properties render them important in complex molecule synthesis. Transforming an intermolecular reaction to an intramolecular variant has added advantages and is preferred in organic synthesis. The use of temporary tethers facilitates this transformation and aid in numerous cycloaddition reactions. Easy availability and inert nature of

silicon derivatives in reactions along with selective and mild removal procedures made silicon-based tethers attractive. Use of silicon tethers in cycloaddition reactions along with other reactions has been compiled elegantly in several reviews[199,200] and this acted as a solid reference for our silicon tethered strategy. Retrosynthetic plan involves generation of bicyclo[3.2.0]heptane fragment by [2+2] cycloaddition reaction of silicon tethered intermediate **2.67** as shown in Scheme 76. Intermediate **2.67** can be assembled from smaller and easily available components as required.



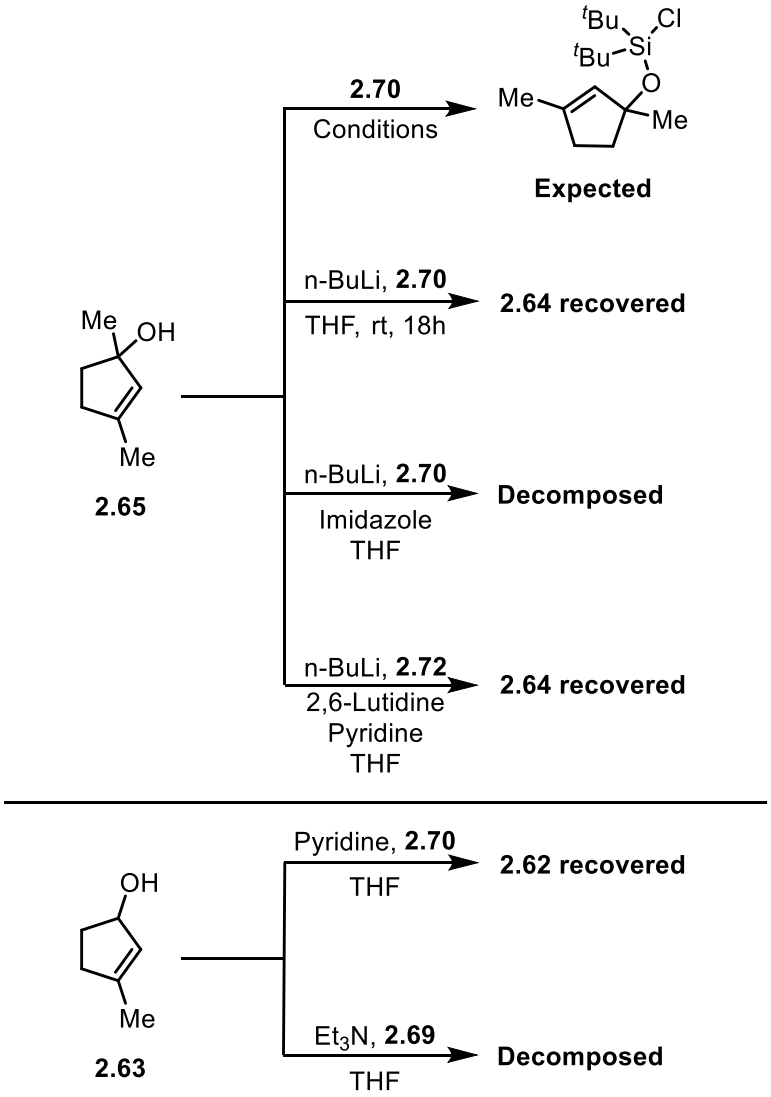
Scheme 76: Retrosynthetic plan of intramolecular [2+2] cycloaddition using a silicon tether.

Synthesizing the required components to assemble the intermediate **2.67** was straightforward. Tertiary alcohol **2.65** was prepared as shown in Scheme 75. Cross-metathesis of 3,3-diethoxyprop-1-ene with but-3-en-1-ol using Grubbs' second-generation catalyst furnished the required primary alcohol **2.68** in 98% yield. Dichlorodiphenylsilane (**2.69**) and di-tert-butyldichlorosilane (**2.70**) were commercially available and are used without any further purifications. Di-tert-butylchlorosilane (**2.71**) was treated with trifluoromethanesulfonic acid to generate di-tert-butylchlorosilyl trifluoromethanesulfonate (**2.72**) in 72% yield after vacuum distillation (Scheme 77).



Scheme 77: Synthesis of intermediates **2.68** & **2.72**.

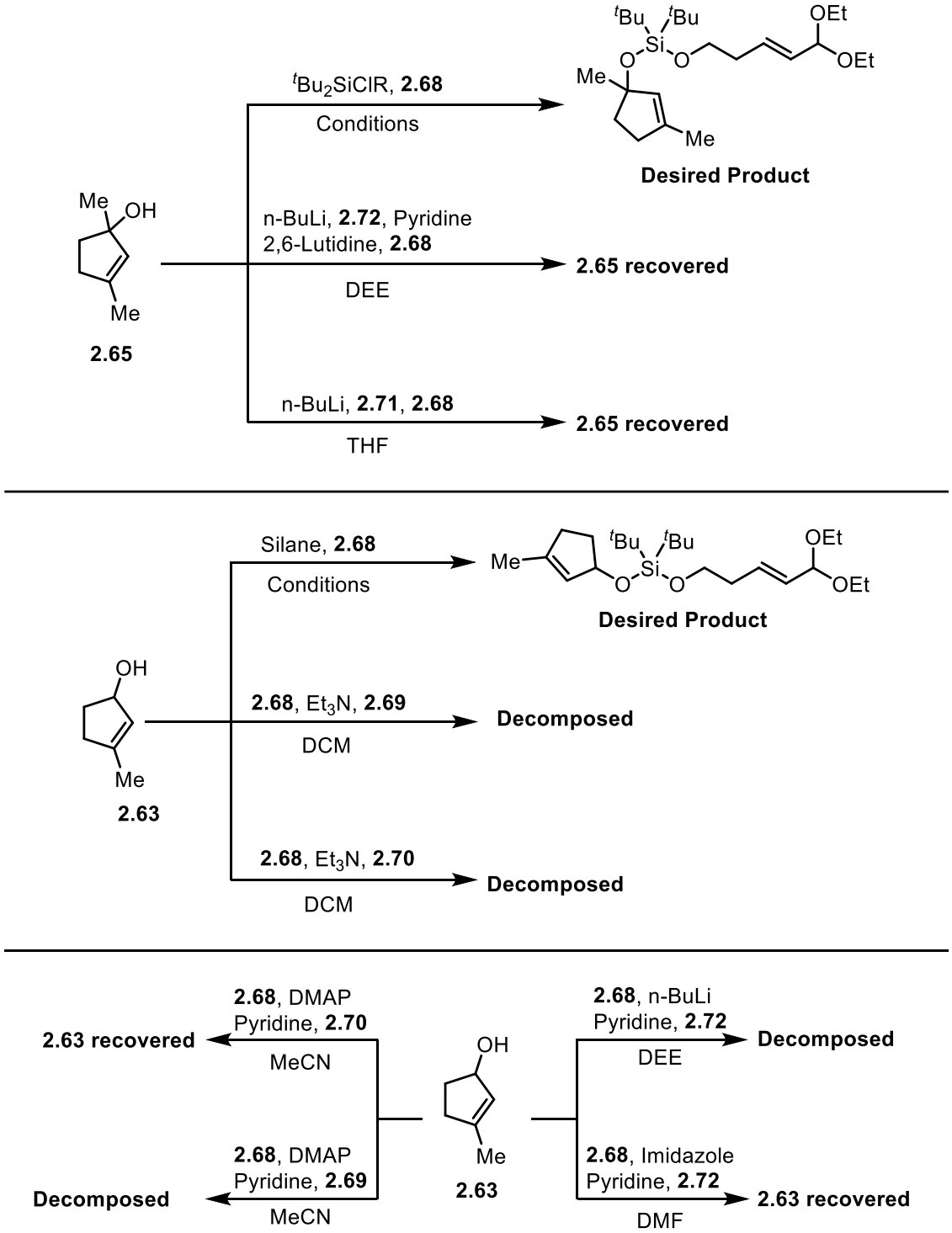
Trials to silylate the tertiary alcohol **2.65** with the available silanes was not fruitful. Treatment of alcohol **2.65** with a base and silane resulted in either dark sticky tar (decomposition) or the recovery of starting material on numerous attempts. Excess of additional base has also been added to avoid degradation of alcohol by acid generated in the reaction medium. The results of trials using various bases and silanes has been depicted in Scheme 78. With tertiary alcohol **2.65** being not reactive enough, we have switched to secondary alcohol **2.63** and tried to optimize the reaction conditions. Unfortunately, reactions of secondary alcohol **2.63** with diphenylsilane **2.69** resulted in black tar (decomposition), while reactions with di-*tert*-butylsilane **2.70** led to the recovery of starting material (Scheme 78).



Scheme 78: Attempts to prepare silyl protected alcohols from **2.63** & **2.65**.

With little success in previous attempts, we now moved to a one-pot procedure to assemble the silicon tether. Tertiary alcohol **2.65** and primary alcohol **2.68** were treated with a base in presence of various silanes to generate a silicon tethered intermediate. Exhaustive experimental trials using different protocols, additional

bases were futile. Repeating the protocols by replacing tertiary alcohol **2.65** with secondary alcohol **2.63** was of no use. Under several different conditions, either the starting alcohol was recovered, or decomposition was observed leaving a dark brown tar which was very difficult to characterize. Scheme 79 illustrates the results of the experiments undertaken to generate a silicon tethered intermediate.



Scheme 79: Attempts to prepare silyl tethers from alcohols **2.63** & **2.65**.

Inability to generate an intermediate holding both the olefinic components together for an intramolecular reaction pathway prompted us to abandon intramolecular [2+2] cycloaddition strategy and opt for alternative strategies.

2.4.2 Intramolecular Michael addition strategy

Bicyclo[3.2.0]heptane skeleton of humilisin E is structurally unique owing to the presence of a quaternary carbon (C1) bearing a sterically demanding isopropyl group. The complexity is further enhanced by a tertiary carbon center (C11) adjacent to the quaternary center. Attempts to establish both quaternary and tertiary carbon centers with high steric density in a single step is always a gamble. Realizing this, we have opted for a stepwise approach to establish the sterically demanding centers one by one. As illustrated in Figure 14, we have opted for a stepwise pathway to establish the tertiary carbon center first, followed by the quaternary carbon center.

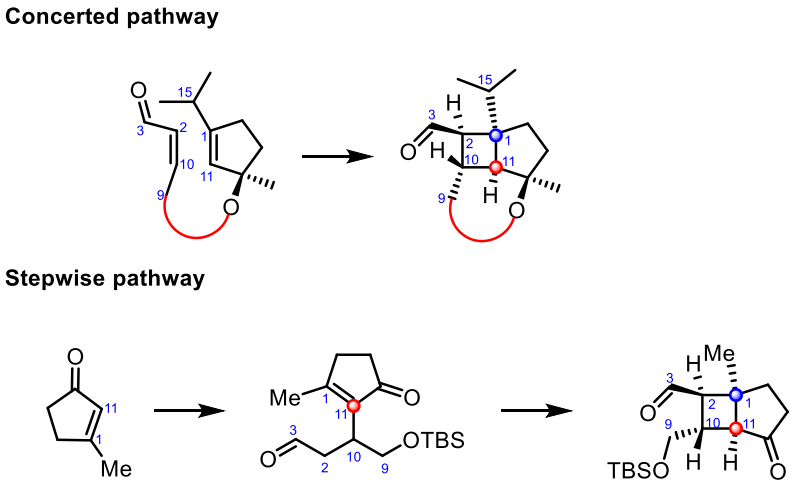
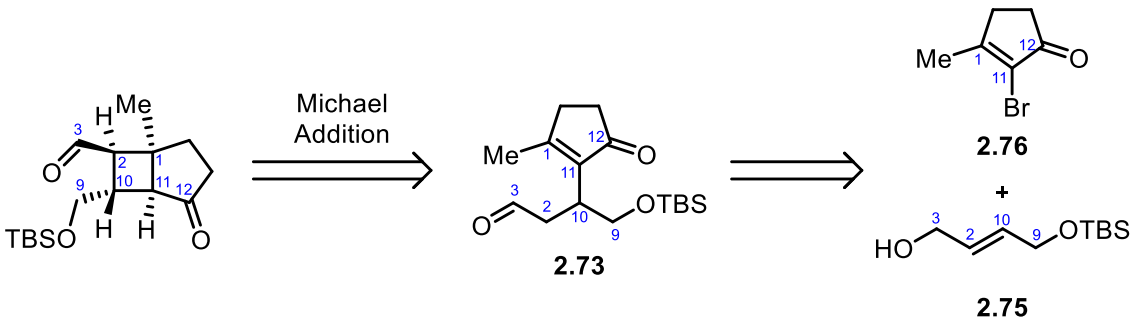


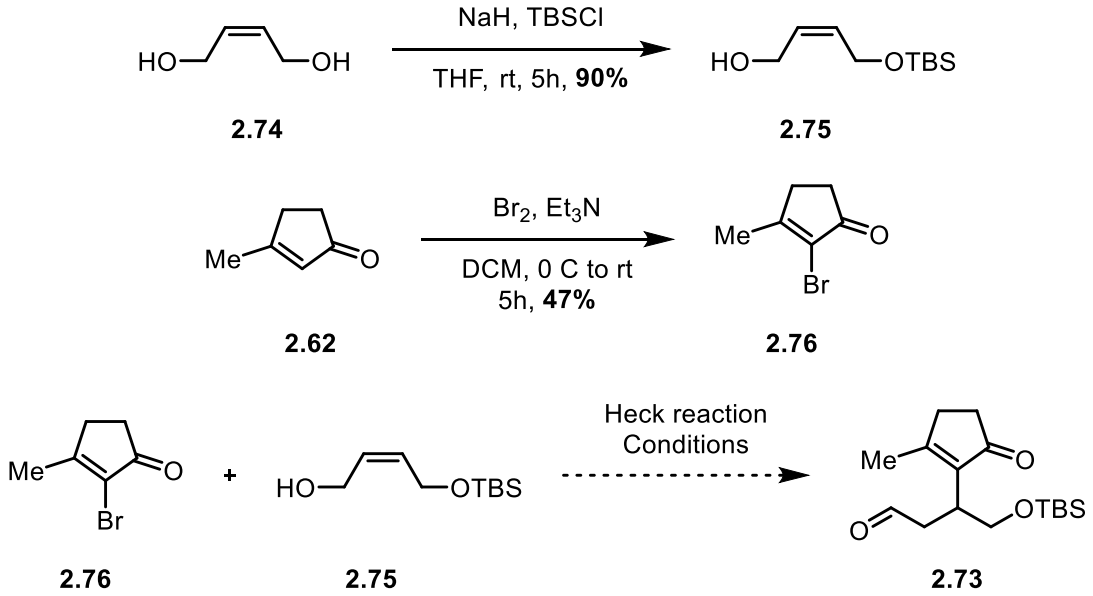
Figure 14: Illustration of concerted and stepwise pathways to establish consecutive stereocenters of the humilisin E core.

The new retrosynthetic design as depicted in Scheme 80 utilizes intramolecular Michael addition as the key step to assemble the skeleton. The core assembly was to be accomplished from compound **2.73** by Michael addition. A Heck coupling of an allylic alcohol and a vinyl bromide would result in the required intermediate **2.73**.



Scheme 80: Retrosynthetic plan based on intramolecular Michael addition reaction.

As shown in Scheme 81, monoprotection of diol **2.74** with NaH and TBSCl produced monosilylated allylic alcohol **2.75** in 90% yield. Bromination of 3-methylcyclopent-2-en-1-one (**2.62**) in presence of triethylamine resulted in the required vinyl bromide species **2.76**. Preliminary Heck cross coupling attempts to generate intermediate **2.73** were unsuccessful. We were unable to isolate even trace amounts of intermediate **2.73** for characterization following exhaustive chromatographic purifications. Considering the issues encountered with generating intermediate **2.73** and unaware of its stability, we decided to abandon this approach and go forward with a much safer epoxynitrile cyclization strategy.



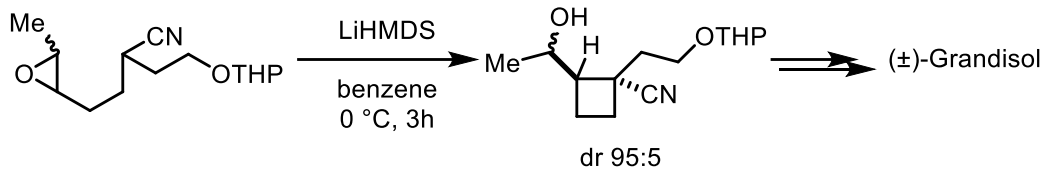
Heck reaction conditions:

1) K_2CO_3, PPh_3, $Pd(OAc)_2$, MeCN, reflux, 24h
2) Et_3N, $Pd(PPh_3)_4$, MeCN, reflux, 22h
3) TBAB, K_2CO_3, $Pd(OAc)_2$, DMF, 60 °C, 24h
4) Bu_4NHSO_4, $Pd(OAc)_2$, Ag_2CO_3, MeCN, rt, 24h

Scheme 81: Synthetic attempts towards realizing intramolecular Michael addition strategy.

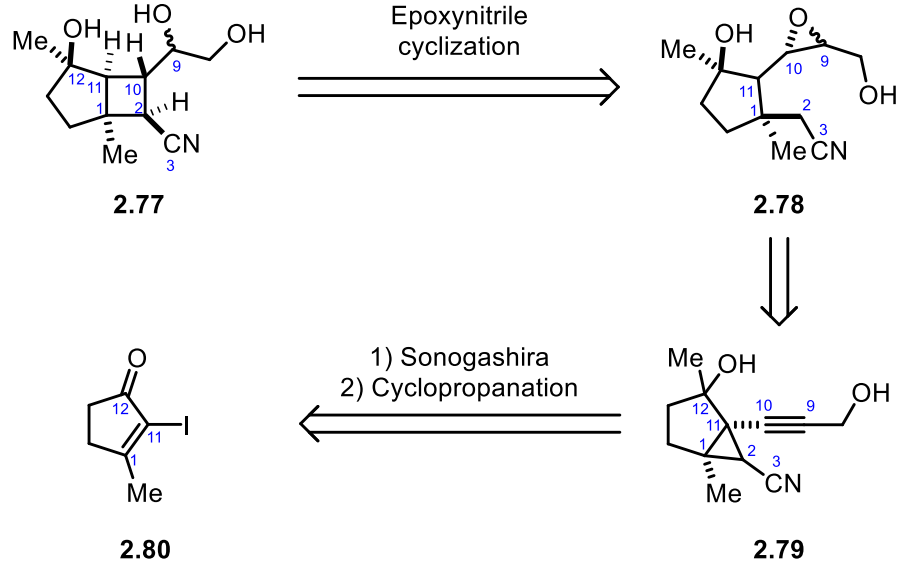
2.4.3 Epoxynitrile cyclization strategy

After the failure of all the previous strategies, we therefore turned to cyclobutane syntheses that were known to be exceptionally reliable in view of literature precedents. Stork *et al.* reported in 1974 a selective transformation, called the epoxynitrile cyclization, to construct functionally substituted cycloalkanes, including cyclobutanes[201,202]. The transformation involves the intramolecular attack of a highly nucleophilic nitrile anion to an epoxide, generating a new C–C bond and a ring of various sizes. Interestingly, the epoxynitrile cyclization always prefers formation of cyclobutane over cyclopentane even when both sides of the oxirane ring are equally substituted and is applied in the synthesis of (±)-grandisol[202] (Scheme 82).



Scheme 82: Synthesis of (±)-grandisol by Stork *et al.* utilizing epoxynitrile cyclization[202].

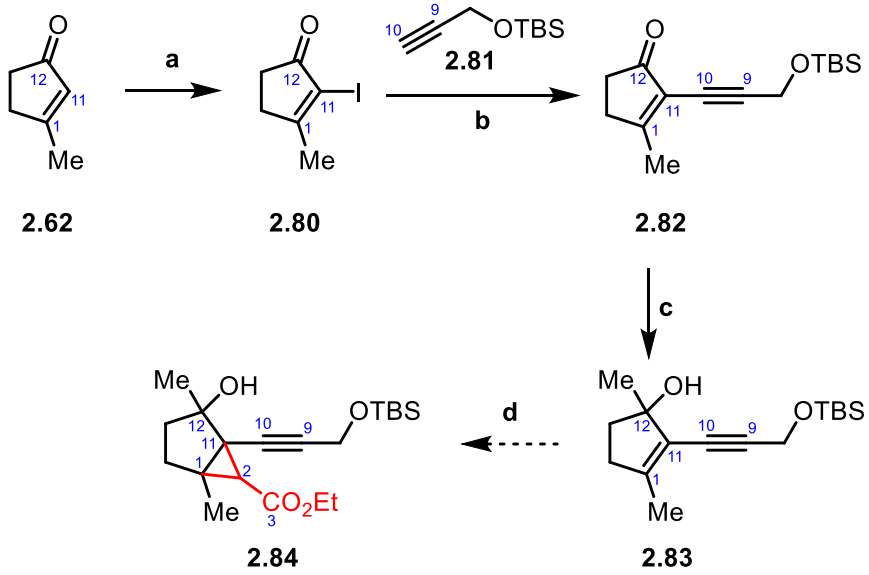
Based on this transformation, we came up with a plan to install the epoxide component and the nitrile component on the adjacent carbons of the cyclopentanone ring, thereby facilitating the cyclization to generate the four-membered ring. Scheme 83 illustrates the required intermediate **2.78** for epoxynitrile cyclization and the retrosynthetic plan to arrive at the intermediate **2.78**. In this model study, the isopropyl group at C1 was replaced by a methyl group as the starting materials were more readily available. The basic idea was that the C12 OH group could be used to direct both the cyclopropanation as well as the epoxidation reactions, thereby controlling the stereochemistry.



Scheme 83: Retrosynthetic plan to generate intermediate **2.78** for epoxy-nitrile cyclization.

The design involved a cyclopropane ring opening, reduction of the alkyne, and an epoxidation step to establish the epoxy nitrile intermediate **2.78** starting from **2.79**. Access to compound **2.79** can be achieved starting from 2-iodo-3-methyl-cyclopent-2-en-1-one **2.80**.

The synthesis towards the intermediate **2.78** started by iodination of commercially available 3-methyl-cyclopent-2-en-1-one **2.62** to generate compound **2.80** in 54% yield. Sonogashira coupling of iodide **2.80** and TBS protected propargyl alcohol **2.81** proceeded well with 98% isolated yield resulting in compound **2.82**. Methylation of compound **2.82** using MeMgBr produced the intermediate **2.83** required for cyclopropanation (Scheme 84).

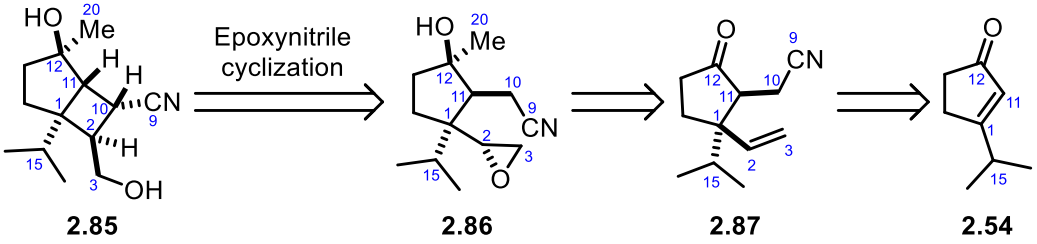


Scheme 84: Attempts towards preparation of intermediate **2.84**. Reagents and conditions: a) I_2, pyridine/DCM (1:4), rt, 60 h, 54%; b) **2.81**, $PdCl_2(PPh_3)_2$, CuI, iPr_2NH, THF, rt, 5 h, 98%; c) MeMgBr, DEE, -50 °C to rt, 16 h, 83%; d) $Pd(OAc)_2$, ethyl diazoacetate, DCM, rt, 20 h.

Metal-catalyzed decomposition of ethyl diazoacetate generated the required carbene *in situ* for insertion to compound **2.83**. Multiple attempts at establishing the cyclopropane ring by carbene insertion turned out to be futile and did not result in the required intermediate **2.84**. A quick literature survey revealed that the cyclopropanation of allylic alcohols using diazocompounds suffers with competing O–H insertion, leading us to survey alternative intermediates[203].

Following the minimal risk approach, we decided to establish the sterically demanding quaternary carbon (C1) and then move on to other stereocenters (C11, C12, C2, C10) in a step-wise manner. A new approach utilizing the inherent reactivity of the cyclopentenone **2.54** was designed (Scheme 85). Specifically, the Cu-catalyzed 1,4-addition to the enone **2.54** should generate an intermediate enolate, which would then be alkylated by bromoacetonitrile. The latter alkylation was expected to take place from the vinyl-substituted side as it is less hindered. In addition, the cuprate addition could also be catalyzed by chiral ligands, opening the possibility of enantioselective synthesis[204–206].

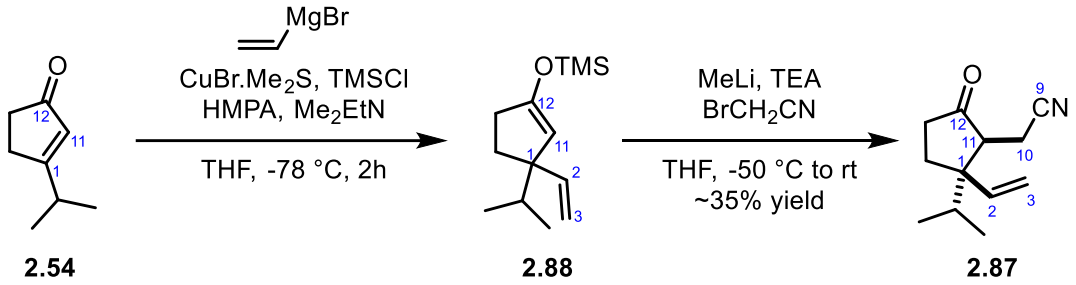
Addition of MeLi or MeMgX was then expected to provide the tertiary alcohol with the required stereochemistry at C12, as the C11 substituent would disfavor attack syn to the cyanomethyl group. Finally, epoxidation of the vinyl group should lead us to the precursor **2.86** that is now primed for epoxynitrile cyclization to generate the desired core **2.85**.



Scheme 85: Retrosynthetic plan to synthesize bicyclic intermediate **2.85** using epoxy-nitrile cyclization.

Efforts to synthesize the bicyclic intermediate **2.85** started with synthesizing 3-isopropylcyclopent-2-en-1-one (**2.54**) from cyclopentane-1,3-dione (**2.58**) as shown in Scheme 73. Cu-catalyzed 1,4-addition of vinyl magnesium bromide to enone **2.54** followed by isolation of enolate as silyl enol ether **2.88** (Scheme 86). The generated silyl enol ether **2.88** is remarkably stable and can be purified by silica gel column chromatography.

Several attempts were made to alkylate **2.88**. In the end, the most reliable method involved treatment of silyl enol ether **2.88** with MeLi in presence of TEA to generate the lithium enolate, followed by addition of bromoacetonitrile. This protocol furnished nitrile **2.87** (9:1 mixture of diastereomers) in 35% yield. Although low yielding, this step establishes the relative stereochemistry at C1 and C11. The sluggishness of the alkylation is certainly attributed to the steric hindrance at C11 due to its proximity to a crowded quaternary center, which may also explain the remarkable stability of the silyl enol ether **2.88**.



Scheme 86: Synthesis scheme for ketonitrile **2.87**.

Compound **2.87** was isolated as an inseparable mixture of diastereomers (9:1) with **2.87** being the major one. The relative stereochemistry of compound **2.87** was confirmed by 1D-NOE experiments by irradiating the highlighted protons at C10 and C2 as shown in Figure 15 and analyzing the NOE enhancements.

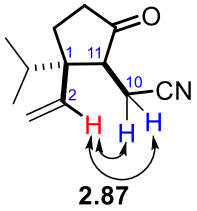
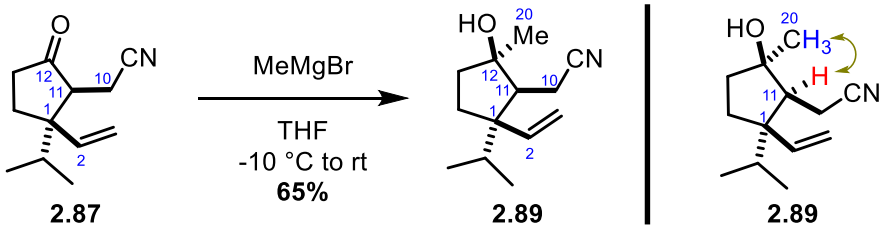


Figure 15: Illustration of 1D-NOE interactions in compound **2.87**.

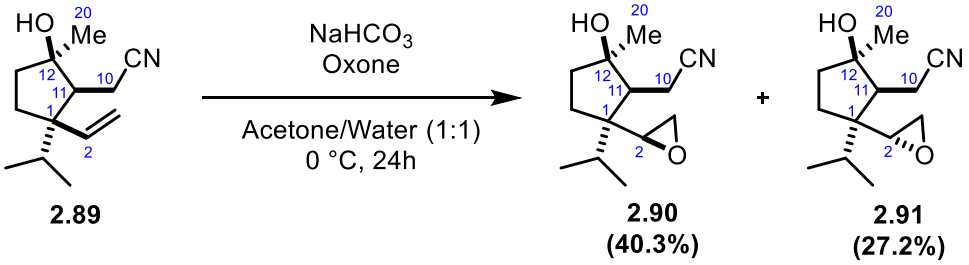
Methylation of compound **2.87** using MeMgBr furnished the tertiary alcohol **2.89** in moderate yield but with excellent stereoselectivity (>20:1). The relative stereochemistry of the tertiary alcohol was determined by 1D-NOE experiments irradiating the highlighted protons at C20 and C11 as shown in Scheme 87.



Scheme 87: Synthesis scheme of tertiary alcohol **2.89** and corresponding 1D-NOE interactions observed in 1D ^{1}H NMR NOE experiments.

We then turned to the critical epoxidation reaction. The commonly employed epoxidation procedures using *m*CPBA or TBHP were unsuccessful in epoxidation of the olefin **2.89**. Multiple attemps all resulted in the recovery of starting material. Anticipating the steric bulk around the olefin again to be the main culprit, we turned towards epoxidation reagents which are highly reactive but sterically small, such as dimethyl dioxirane (DMDO). Gratifyingly, epoxidation of the tertiary alcohol **2.89** using *in situ* generated DMDO resulted in a mixture of separable diastereomeric epoxides **2.90** and **2.91** (Scheme 88).

Although the epoxidation provided a mixture of diastereomers, these stereoisomers were readily separable. It turned out that the first eluting isomer **2.90** was the major diastereomer, with undesired stereochemistry at C2, and the second isomer **2.91** is the minor diastereomer with the desired relative stereochemistry at C2.



Scheme 88: Synthesis scheme of compound **2.90** & **2.91**.

Establishment of the relative stereochemistry of these epoxides was initially fraught with difficulties. The NMR spectroscopy data of both the diastereomers

was almost identical with minor differences. 1D-NOE data also clearly identified very similar contacts in both isomers (Figure 16), making it difficult to assign the relative stereochemistry of the epoxide in compounds **2.90** and **2.91**. The key difference between both the diastereomers included the presence of a singlet at 3.05 ppm in 1H NMR of compound **2.90**. This peak did not exhibit a cross-peak in HSQC spectrum, indicating it was likely resulting from a OH group. This peak was absent in compound **2.91**. Additionally, epoxide **2.90** was a white solid and non-polar compared to compound **2.91**, which was a colorless oil. These differences made us speculate that diastereomer **2.90** possesses an intramolecular hydrogen bond.

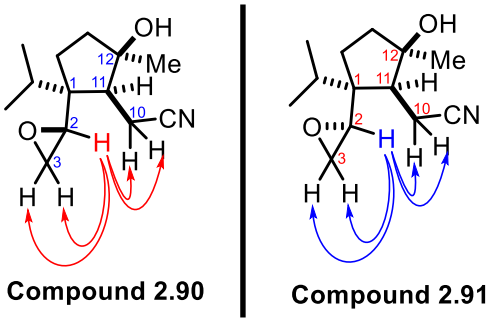


Figure 16: Illustration of 1D-NOE interactions in compounds **2.90 & 2.91**.

Based on this speculation, a conformational analysis was carried out by Monte Carlo conformational search using initially force field (OPLS4) method on both the expected diastereomers. Further optimization and energy calculations for selected conformations was carried out by DFT (M06-2X/6-311G++**) method. The optimized structures of both the diastereomers are illustrated in Figure 17. These calculations confirmed that only in **2.90** an intramolecular hydrogen bonding pattern is feasible for geometric reasons, and also confirmed the relative stereochemistry. Thus, from these conformational studies, the relative stereochemistry at C2 in epoxide diastereomers **2.90** and **2.91** has been established, and the compound **2.91** would then be the desired isomer for the cyclization step. Final confirmation of the stereochemistry was obtained by single-crystal X-ray characterization of epoxide **2.90** (Figure 17). The details of the X-ray characterization are included in the experimental section (Figure 21).

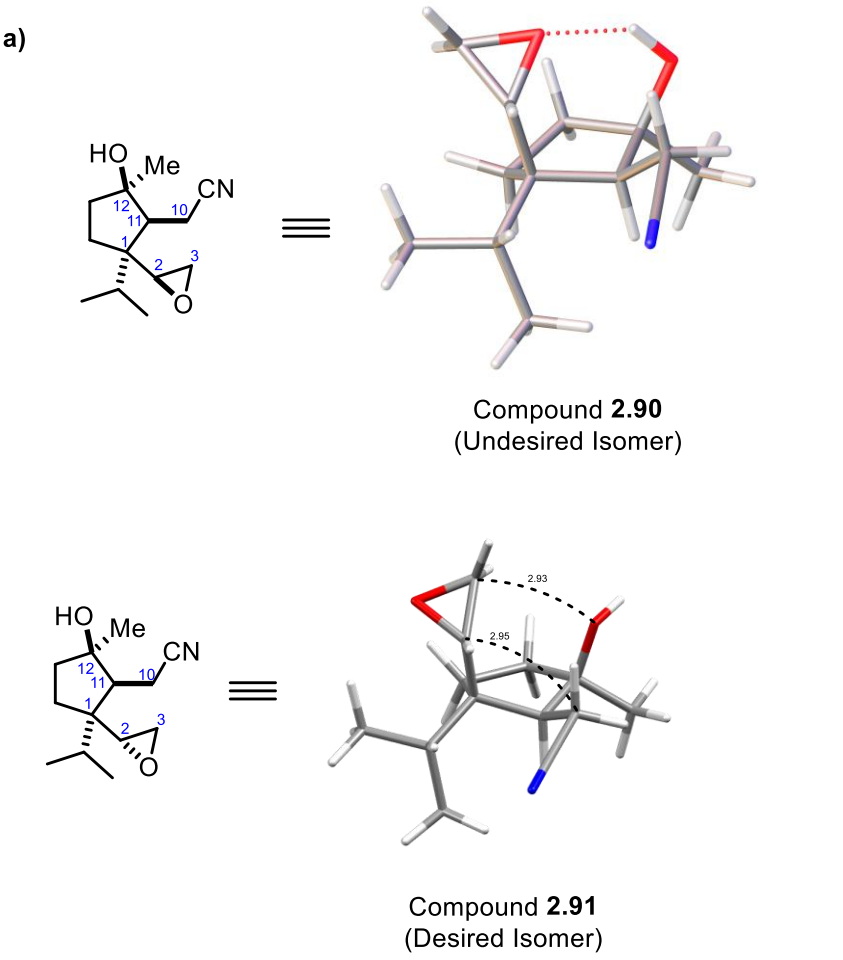
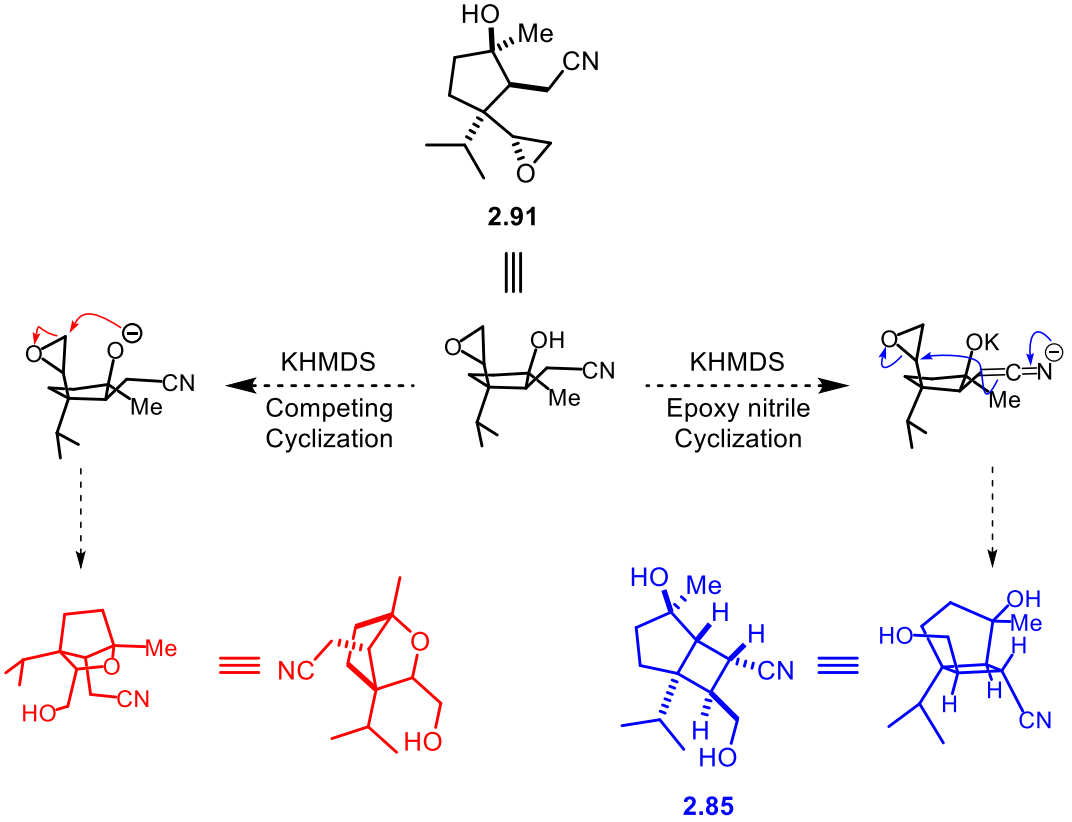


Figure 17: a) Lowest-energy optimized conformations of compounds **2.90** & **2.91** calculated using DFT method M06-2X and basis set 6-311G++**. b) X-ray structure of compound **2.90**.

These computations, however, revealed a potential risk in the synthesis plan which we did not anticipate. In compound **2.91**, the tertiary hydroxyl group

at C12 stands at striking distance to the terminal epoxide carbon (C3). Indeed, the computed distances between the potentially nucleophilic oxygen at C12 and the desired C10 carbon to their respective epoxide carbons are nearly equal (2.93 & 2.95 Å, see Figure 17a). The preceding epoxy nitrile cyclizations reported by Stork[201,202] utilized bases such as KHMDS, NaHMDS or LiHMDS to generate the nitrile anion. We were concerned that subjecting compound **2.91** to similar reaction conditions might result in rapid deprotonation of the tertiary alcohol and undesired cyclization to generate a bicyclic ether as shown in Scheme 89.

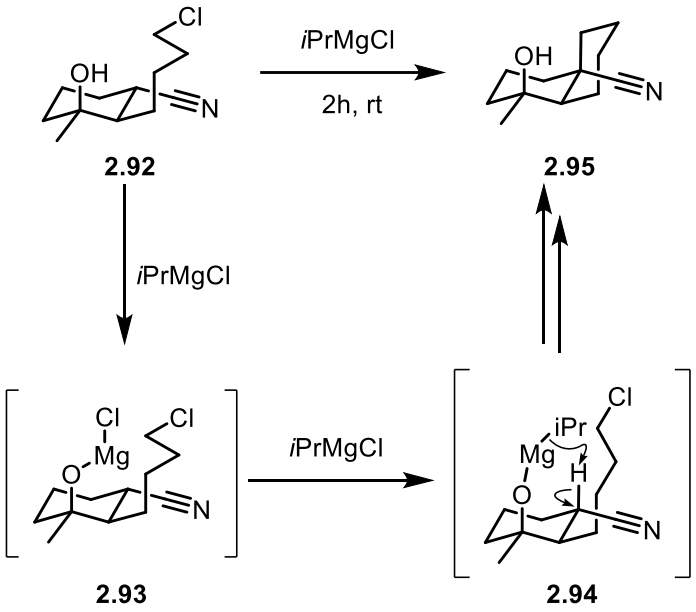


Scheme 89: Possible cyclization reactions of epoxynitrile **2.91** on treating with KHMDS.

Protection of tertiary alcohol to prevent the competing alkoxide attack on epoxide seemed like a safe way to move forward. However, all attempts to silylate the tertiary alcohol (TMSOTf, 2,6-lutidine) were unsuccessful, resulting in recovery of the starting material. The observed reluctance of tertiary alcohol towards protection can be attributed to the steric crowding around the alcohol as evidenced by the computational structures.

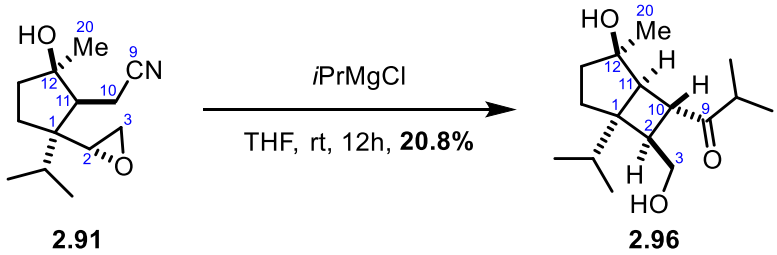
A literature survey revealed that the Fleming group has carried out extensive studies on generation of *C*-metalated nitriles using alkyl magnesium chlorides and subsequent alkylation, acylation, and cyclization reactions with suitable electrophiles[207–213]. A report on generation of *C*-metalated nitriles using alkyl magnesium halides followed by cyclization[213] caught our attention due to its similarity to the γ-hydroxynitrile system in compound **2.91**. As shown in Scheme 90, treatment of γ-hydroxynitrile with excess isopropyl magnesium chloride resulted in generation of a *C*-metalated nitrile followed by cyclization.

Addition of iPrMgCl to γ-hydroxynitrile **2.92** generates a chloromagnesium alkoxide **2.93**[212]. The alkoxide **2.93,** in the presence of excess iPrMgCl, undergoes a halogen-alkyl exchange generating an alkylmagnesium alkoxide **2.94**. Internally directed deprotonation of **2.94** generates a *C*-metalated nitrile followed by cyclization to give compound **2.95**.



Scheme 90: Mechanism of C-metalation and subsequent cyclization of γ-hydroxynitriles reported by Fleming and co-workers[213].

We thus followed the same procedure[213]. To our delight, treating epoxide **2.91** with excess *i*PrMgCl (6 equiv.) resulted in the desired bicyclo[3.2.0] skeleton **2.96** (Scheme 91). The connectivity and relative stereochemistry was revealed by 1D and 2D-NMR spectroscopic methods (COSY, HSQC, HMBC) which established the formation of the desired bicyclo[3.2.0]heptane skeleton along with an additional isopropyl group. The formation of the isopropyl ketone at C9 can be attributed to the nucleophilic addition of isopropylmagnesium reagent to nitrile and subsequent hydrolysis, resulting in a ketone.



Scheme 91: Synthesis scheme of bicyclo compound **2.96**.

Spin-spin coupling constants of the synthesized bicyclo[3.2.0]heptane intermediate **2.96** were calculated from 1H NMR spectrum and compared to the reported values for humilisin E. Coupling constants corresponding to H11-H10 ($J_{H11\text{-}H10}$) was found to be 5.9 Hz, while the reported H11-H10 coupling constant

($J_{H11-H10}$) for humilisin E was 6.5 Hz (Figure 18). Similarly, H10-H2 coupling constant (J_{H10-H2}) was 7.9 Hz in case of compound **2.96** and 9.0 Hz in case of humilisin E. The near similar coupling constants served as an additional confirmation for the formation of the desired bicyclic system.

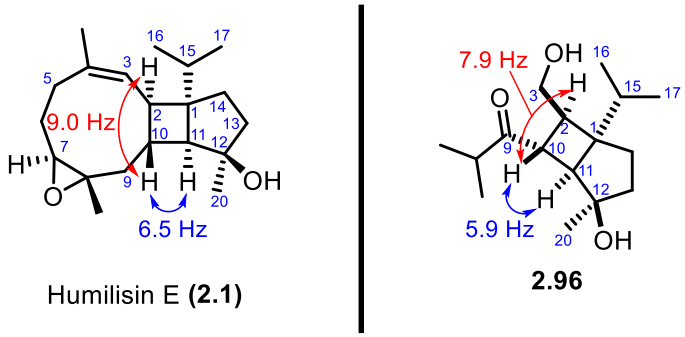
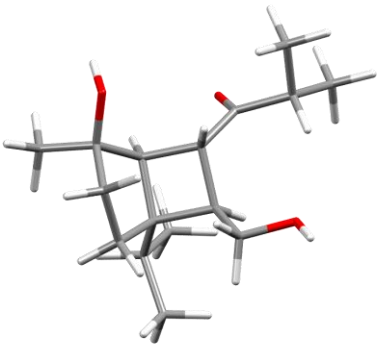
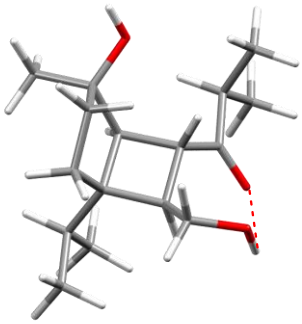


Figure 18: Illustration of humilisin E and compound **2.96** highlighting spin interactions of H11-H10 and H10-H2.

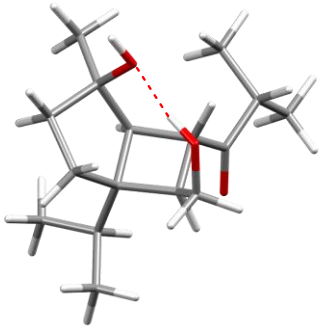
Conformational analysis of compound **2.96** was carried out by Monte Carlo conformational search using initially force field (OPLS4) method. Four different conformations containing i) no hydrogen bonding (**C1**), ii) hydrogen bonding from primary alcohol to carbonyl group (**C2**), iii) hydrogen bonding from primary alcohol to tertiary alcohol (**C3**), and iv) hydrogen bonding from tertiary alcohol to primary alcohol (**C4**) were selected and subjected to further studies. Optimization and energy calculations for the four selected confirmations was carried out by DFT (M06-2X/6-311G++**) method. The optimized structures of the four different confirmations **C1**, **C2**, **C3** and **C4** are illustrated in Figure 19. The calculated energies of all four optimized confirmations are all very close to each other. The lowest energy conformation in solution is **C1** with no intramolecular hydrogen bonding, followed by conformations **C2**, **C3** and **C4** in increasing order. Although the calculations point towards confirmation **C1** to be the most stable one with no intramolecular hydrogen bonding, the ^{1}H NMR of compound **2.96** in CD_2Cl_2 contains a broad singlet corresponding to one of the hydroxyl hydrogens' indicating the presence of intramolecular hydrogen bonding and suggesting that **C2, C3** or **C4,** or an ensemble of these structures, is more likely to be present in solution.



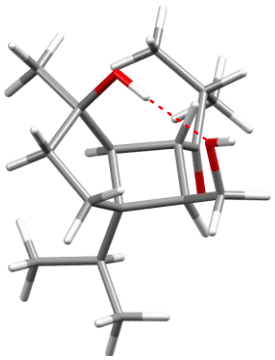
Conformation C1
Relative energy: 0 kJ/mol



Conformation C2
Relative energy: 0.81 kJ/mol



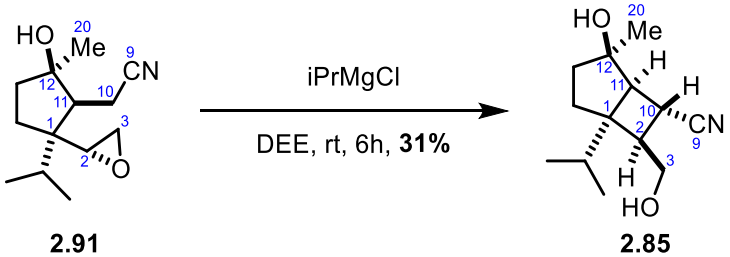
Conformation C3
Relative energy: 2.21 kJ/mol



Conformation C4
Relative energy: 5.21 kJ/mol

Figure 19: Lowest-energy optimized conformations of compound **2.96** and their respective relative energy values calculated using DFT method M06-2X and basis set 6-311G++**.

To eliminate the undesired nucleophilic addition of *i*PrMgCl to the C9 nitrile group, we repeated the cyclization with epoxide **2.91** and 3 equivalents of *i*PrMgCl resulting in the formation of desired bicyclo[3.2.0] skeleton **2.85** (Scheme 92). The connectivity and relative stereochemistry was revealed by 1D and 2D-NMR spectroscopic methods (COSY, HSQC, HMBC) which established the formation of the desired bicyclo[3.2.0]heptane skeleton with the nitrile group intact.



2.91 **2.85**

Scheme 92: Synthesis scheme of bicyclo compound **2.85**.

As with the intermediate **2.96**, spin-spin coupling constants of the synthesized bicyclo[3.2.0]heptane intermediate **2.85** were calculated from 1H NMR spectrum and compared to the reported values for humilisin E. Coupling constants corresponding to H11-H10 ($J_{H11\text{-}H10}$) was found to be 5.8 Hz, while the reported H11-H10 coupling constant ($J_{H11\text{-}H10}$) for humilisin E was 6.5 Hz (Figure 20). Similarly, H10-H2 coupling constant ($J_{H10\text{-}H2}$) was 8.3 Hz in case of compound **2.85** and 9.0 Hz in case of humilisin E. The relative stereochemistry was determined by selective 1D ^{1}H NMR NOE experiments. Selectively irradiating H3 hydrogens revealed interactions with hydrogens H10, H14 and H13 determining the relative stereochemistry of the cyclized product **2.85**.

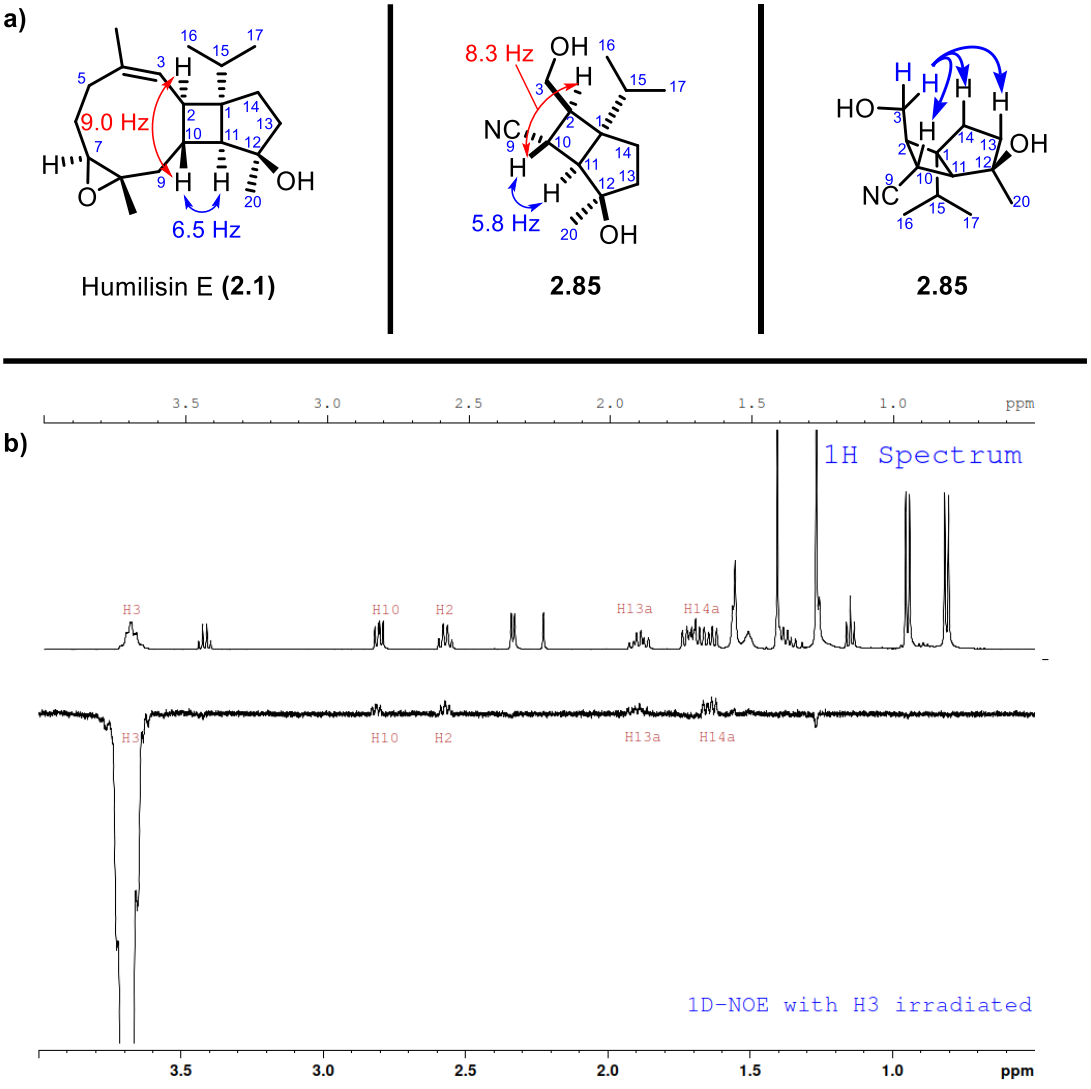


Figure 20: a) Illustration of humilisin E and compound **2.85** highlighting spin interactions of H11-H10, H10-H2 and 1D-NOE interactions. b) Overlay of ^{1}H spectrum of compound **2.85** with 1D-NOE interactions.

In conclusion, the epoxynitrile cyclization strategy designed to construct the bicyclo[3.2.0]heptane framework was fruitful. The intention of establishing the quaternary center at earlier stages proved to be important as the steric bulk

helped in directing the incoming groups to result in desired relative stereochemistry.

2.5 Conclusion and outlook

Nature is full of organic molecules with complex structures and diverse functionalities that are always a source of challenge for the synthetic organic chemist. Humilisin E belongs to a unique class of natural products that offer immense potential to discover and develop novel methodologies to access highly strained and densely functionalized systems[214–217]. With a target of generating the complex core of humilisin E, we started our journey with a short and efficient strategy to assemble the core. The first strategy to utilize intramolecular [2+2] cycloaddition via iminium catalysis to establish the required contiguous stereocenters and assemble the bicyclo[3.2.0]heptane skeleton was not succesful. Highly unstable intermediates in ester-based tethers for [2+2] cycloaddition proved to be a major road-block prompting us to shift towards a silicon-based tethers holding the olefin moieties together. Generation of silicon tethers failed due to unreactivity and instability of intermediates involved. An intramolecular Michael addition strategy based on establishing the required stereocenters in a step-wise manner failed as well.

Among the methodologies reported to construct 4-membered rings, epoxy nitrile cyclizations were found to be reliable. Based on this methodology, a new synthesis plan was designed involving Sonogashira coupling and cyclopropanation. Although Sonogashira coupling worked, cyclopropanation in presence of a tertiary alcohol proved to be difficult prompting us to change the path. Back to the drawing board, we came up with a 7-step synthesis plan involving Cu-catalyzed 1,4-addition followed by 1,3-alkylation establishing the contiguous quaternary and tertiary stereocenters with required relative stereochemistry. Functionalization from this point on were straight forward resulting in required relative stereochemistry. Epoxidation by DMDO followed by cyclization using excess of *i*PrMgCl established the required bicyclo[3.2.0]heptane.

The target of assembling the required bicyclo[3.2.0]heptane skeleton with handles for construction of 9-membered ring of Humilisin E has been achieved. Despite the success, there are a few steps in the synthesis plan which are low yielding. Optimization of low-yielding steps to facilitate scaling up, followed by construction of 9-membered ring to complete the total synthesis of Humilisin E will be a key challenge in the future to work on.

3 SUMMARY OF THE THESIS

Irrespective of the field we consider, access to new materials has led to generational changes and made human life easier by leaps and bounds. The ability to synthesize new materials is an important skill. Speaking from an organic chemistry perspective, ability to synthesize complex molecules is an essential skill to master. This dissertation is an attempt to use the synthesis knowledge and make useful molecules.

Favipiravir is a simple looking yet synthetically complicated molecule used as an antiviral. Our approach was to simplify the synthesis route to favipiravir enabling faster production when required. Attempts to develop a reliable and efficient protocol to synthesize 2,5-dichloropyrazine has been met with limited success starting from cheaply available 2,5-diketopiperazine. Solubility of 2,5-diketopiperazine has proved to be an obstacle in optimizing the reaction with $POCl_3$. With our focus being the functionalization of 2,5-dichloropyrazine towards favipiravir, we attempted to establish a suitable substituent using ortho-lithiation strategy with no success. Whereas the Minisci strategy was partially successful and the formation of undesired disubstituted product can be justified by the electronic factors involved. In summary, developing an optimized protocol to synthesize 2,5-dichloropyrazine from 2,5-diketopiperazione followed by understanding the stability of metalated 2,5-dichloropyrazine species require an in-depth study. And our attempts at developing a short and efficient route to favipiravir has left us with numerous issues to address.

Humilisin E is a unique molecule with a highly strained fused ring system with sterically demanding groups. Our initial approaches to construct the bicyclo[3.2.0]heptane core was met with issues involving instability and unreactivity of several intermediates. Although the epoxynitrile cyclization approach was successful in generating the required core, this design plagues with low yields in multiple steps while establishing the required diastereoselectivity. Optimization of the low yielding steps should make this route reliable and efficient in our efforts to complete the total synthesis of humilisin E. In short, an efficient route towards total synthesis of humilisin E will

act as a precedent towards constructing highly strained and sterically demanding natural products.

Organic synthesis has seen tremendous growth with new and efficient methodologies being discovered over time. Yet, nature reminds us of our infancy by producing unique and complex molecules with ease. We may never be as efficient as nature in synthesizing molecules, but each result we produce takes us closer to achieving that efficiency and makes an infinitesimal change in the field of synthesis.

4 EXPERIMENTAL SECTION

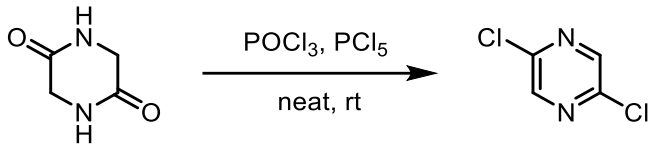
4.1 General Information

All reactions were carried out under an argon atmosphere in oven-dried glassware. When required, nonaqueous reagents were transferred under argon *via* syringe or cannula and dried prior to use. Tetrahydrofuran, toluene, acetonitrile, dichloromethane, and diethyl ether were obtained by passing deoxygenated solvents through activated alumina columns (MBraun SPS-800 Series solvent purification system). Vinyl magnesium chloride, ^{i}PrMgCl, n-BuLi and MeLi were titrated before each use (CAUTION: n-BuLi and MeLi are pyrophoric, and its handling requires proper air and moisture sensitive techniques). Other solvents and reagents were used as obtained from supplier, unless otherwise noted. Analytical TLC was performed using Merck silica gel F254 (230-400 mesh) plates and analyzed by UV light or by staining upon heating with $KMnO_4$ solution (1 g $KMnO_4$, 6.7 g K_2CO_3, 1.7 mL 1M NaOH, 100 mL H_2O), vanillin solution (6 g vanillin, 5 mL conc. H_2SO_4, 3 mL glacial acetic acid, 250 mL EtOH), or ninhydrin solution (0.3 g of ninhydrin, 100 mL of EtOH, 2 mL of AcOH). For silica gel chromatography, the flash chromatography technique with Merck silica gel 60 (230-400 mesh) and CombiFlash R_f 200 with Redisep Gold columns (20–40 µm spherical silica, 400–632 mesh) were used. All solvents were HPLC grade unless otherwise mentioned. Degassing of solvents was carried out by purging with argon gas for 30 minutes. The ^{1}H NMR and ^{13}C NMR spectra were recorded in either $CDCl_3$, CD_2Cl_2, CD_3CN, $(CD_3)_2CO$, or $(CD_3)_2SO$ on Bruker Avance 500, or 300 MHz spectrometers. The chemical shifts were reported in ppm relative to (organometallics 2010 29 9 2176-2179 ref) $CHCl_3$ (δ 7.26), $CDHCl_2$ (δ 5.32), CHD_2CN (δ 1.94), CD_3CD_2HCO (δ 2.05), CD_3CD_2HSO (δ 2.50), C_6HD_5 (δ 7.16) or CHD_2OD (δ 3.31) for ^{1}H NMR. For the ^{13}C NMR spectra, $CDCl_3$ (δ 77.16), CD_2Cl_2 (δ 53.84), CD_3CN (δ 118.26), $(CD_3)_2CO$ (δ 29.84), or $(CD_3)_2SO$ (δ 39.52), C_6D_6 (δ 128.06) were used as the internal standards. High resolution mass spectrometric data were measured using Agilent Technologies 6560 Ion Mobility ESI-Q-TOF

LC/MS. Melting points (mp) were determined in open capillaries using Stuart melting point apparatus. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer.

4.2 Favipiravir synthesis

4.2.1 2,5-dichloropyrazine (1.68)

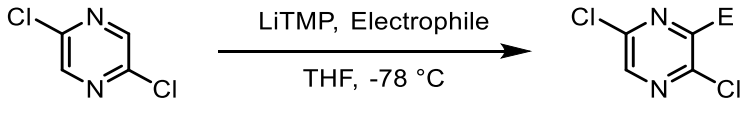


1.69 **1.68**

2,5-diketopiperazine **1.69** (0.2 g, 1.75 mmol, 1.0 equiv) was added to an RB followed by the addition of $POCl_3$ (2.12 mL, 22.79 mmol, 13.0 equiv) & PCl_5 (0.92 g, 4.38 mmol, 2.5 equiv) and the reaction mixture was let to stir at rt. After 18 h, the reaction mixture was added dropwise to crushed ice with rapid stirring. Aqueous phase was extracted with DCM (3x10 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated to give crude 2,5-dichloropyrazine **1.68** (0.052 g, 0.35 mmol, 20%) as yellow oil. The crude was pure and did not need any further purification. The spectral data of **1.68** matched with the commercially procured 2,5-dichloropyrazine.

R_f (EtOAC-hexane 30:70) = 0.71
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.39 (s, 2H)
^{13}C NMR (75 MHz, $CDCl_3$): δ 147.7, 143.9

4.2.2 Lithiation of 2,5-dichloropyrazine



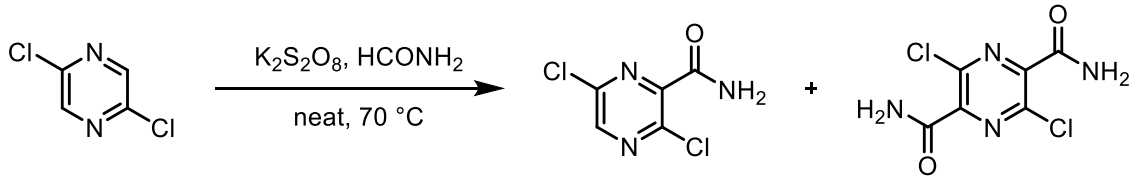
1.68

<u>*Equilibrium Shift Procedure:*</u> A freshly prepared solution of LiTMP in THF (1.1 equiv), was added to an RB and cooled to -78 °C. To this solution electrophile (1.5 equiv) was added followed by addition of 2,5-dichloropyrazine **1.68** (1.0 equiv). The reaction mixture was let to stir at -78 °C for 2 to 5 hours, followed by stirring at rt for 2-12 hours. Sat. aq. NH_4Cl (10 mL) was added, and the aqueous layer was extracted with DCM (3x10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated.

Stepwise Procedure: A freshly prepared solution of LiTMP in THF (1.1 equiv), was added to an RB and cooled to -78 °C. To this solution 2,5-dichloropyrazine **1.68** (1.0 equiv) was added and let to stir at -78 °C for 0.5 h. Electrophile (1.5 equiv) in THF was added dropwise. The reaction mixture was let to stir at -78 °C for 1 to 3 hours, followed by stirring at rt for 1-12 hours. Sat. aq. NH_4Cl (10 mL) was added, and the aqueous layer was extracted with DCM (3x10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated.

Note: Lithiation of 2,5-dichloropyrazine **1.68** was performed using both the general procedures mentioned above. Irrespective of the temperature, time, and electrophile, the reaction always led to brown sticky mixture and unreacted starting material.

4.2.3 Minisci reaction of 2,5-dichloropyrazine



1.68 **1.136** **1.137**

To a mixture of $K_2S_2O_8$ (0.498 g, 1.85 mmol, 1.1 equiv) and $HCONH_2$ (1.33 mL, 33.56 mmol, 20 equiv) in a dry RB, 2,5-dichloropyrazine **1.68** (0.25 g, 1.68 mmol, 1.0 equiv) was added and the reaction mixture was heated to 70 °C and let to stir at 70 °C for 12 h. The mixture was then allowed to cool to rt. Water (20 mL) was added to the mixture and filtered through a sintered glass filter (yellow precipitate observed). Aqueous phase was extracted with DCM (3x15 mL). The combined organic phases were washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated to give compound **1.136** (0.061 g, 0.31 mmol, 19%) as an off white solid. The yellow precipitate observed was dissolved in DMF, concentrated, and dried under vacuum to give **1.137** as an off-white solid.

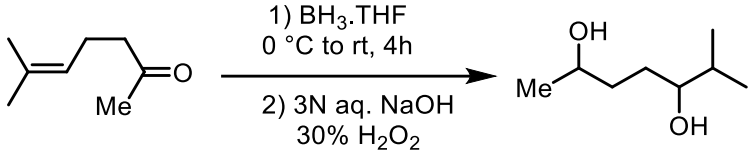
Note: Compound **1.137** was not soluble in water and common organic solvents. It was soluble only in DMF and DMSO.

Compound **1.136**
R_f (EtOAC-hexane 50:50) = 0.4; IR (film, cm^{-1}): 3500, 2960, 1690, 1260, 1087; mp 145-146 °C
^1H NMR (300 MHz, $CDCl_3$): δ 8.55 (s, 1H), 7.31 (bs, 1H), 5.86 (br s, 1H)
^{13}C NMR (75 MHz, $CDCl_3$): δ 163.0, 146.6, 146.1, 145.3, 141.5
HRMS (ESI^+): m/z calculated for $[C_5H_4Cl_2N_3O]^+$ = 191.9726, found 191.9717, Δ = -4.7 ppm

Compound **1.137**
IR (film, cm^{-1}): 3418, 3287, 3218, 3153, 1667, 1584, 1284, 1095; mp 266-269 °C (sublimes)
Anal. Calcd (%) for $C_6H_4Cl_2N_4O_2$: C, 30.7; N, 23.8; H, 1.7. Found: C, 30.8, N, 23.3, H, 2.2
^{1}H NMR (300 MHz, DMF-*d7*): δ 8.40 (s, 2H), 8.14 (s, 2H)
^{13}C NMR (75 MHz, DMF-*d7*): δ 165.1, 148.8, 143.5

4.3 Humilisin E synthesis

4.3.1 6-methylheptane-2,5-diol (2.56)

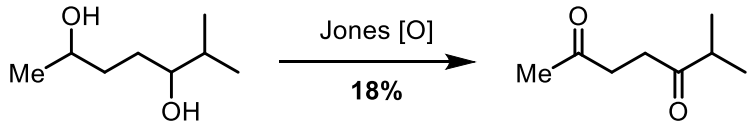


2.55 **2.56**

A solution of **2.55** (1.17 ml, 7.92 mmol, 1 equiv) in dry THF (10 mL) was cooled to 0 °C using an ice bath, followed by dropwise addition of borane THF solution (7.92 mL of 1M solution, 7.92 mmol, 1 equiv). The mixture was stirred at 0 °C for 1 h and at rt for 3 h. The mixture was then cooled to 0 °C and 3 mL H_2O, 4 mL 3N aq. NaOH solution and 4 mL 30% H_2O_2 solution were added dropwise. Let to stir at 0 °C for 1 h and at rt for 16 h. The layers were separated, and the aqueous layer was extracted with DEE (3x30 mL). The combined organic phases were washed with brine (40 mL), dried (Na_2SO_4), filtered and concentrated to give crude diol **2.56** as colorless oil (1.1 g, 7.52 mmol, 95%). No purification required for subsequent oxidation step. The spectral data of **2.56** match those reported in the literature[218].

R_f (EtOAC-hexane 70:30) = 0.2; IR (film, cm^{-1}): 3370, 1340, 1050
^{1}H NMR (300 MHz, $CDCl_3$): δ 3.76-3.70 (m, 1H), 3.52 (br s, 1H), 3.31-3.26 (m, 1H), 2.7 (br s, 1H), 1.64-1.37 (m, 5H), 1.14 (d, *J* = 6.3 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 6H)
^{13}C NMR (75 MHz, $CDCl_3$): δ 76.7, 68.4, 36.5, 33.9, 30.9, 23.8, 18.8, 17.6

4.3.2 6-methylheptane-2,5-dione (2.57)



2.56 **2.57**

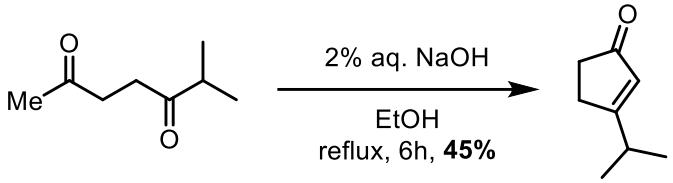
A solution of 2.83 g of CrO_3 in water (10 mL) was cooled to 0 °C. 3 mL conc. H_2SO_4 was added dropwise and stirred at 0 °C until deep orange-red colored solution was obtained. This prepared solution was added dropwise to a solution of diol

2.56 (1.48 g, 10.12 mmol, 1.0 equiv) in acetone (20 mL) at 0 °C. After stirring at 0 °C for 2 h, 3 mL isopropyl alcohol was added and the mixture was filtered through celite. Diluted with water and extracted with DEE (3x40 mL). Combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated to give diketone **2.57** (0.26 g, 1.8 mmol, 18%) as a colorless oil after purification. The spectral data of **2.57** match those reported in the literature[219].

R_f (EtOAc-hexane 20:80) = 0.5; IR (film, cm^{-1}): 2970, 1707, 1358
^1H NMR (300 MHz, $CDCl_3$): δ 2.65 (s, 4H), 2.59-2.56 (m, 1H), 1.06 (s, 3H), 1.05 (d, *J* = 7.0 Hz, 6H)
^{13}C NMR (75 MHz, $CDCl_3$): δ 213.3, 207.4, 40.7, 36.8, 33.7, 29.9, 18.1

4.3.3 3-isopropylcyclopent-2-en-1-one (2.54)

Method 01:

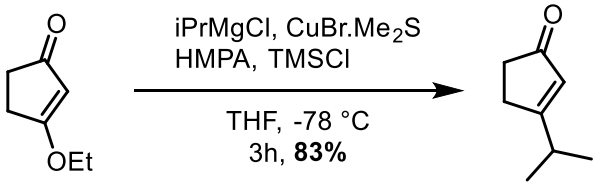


2.57 **2.54**

To a solutipon of diketone **2.57** (0.12 g, 0.86 mmol, 1 equiv) and 2% aq. NaOH solution (5 mL), ethanol (5 mL) was added and heated to reflux. The reaction mixture was cooled to rt after 6 h and diluted with water (10 mL). The phases were separated, and aqueous phase was extracted with DEE (3x10 mL). Combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated to give crude enone **2.54** (0.047 g, 0.38 mmol, 45%) as a yellow oil. The spectral data of **2.54** match those reported in the literature[220].

R_f (EtOAc-hexane 4:6) = 0.5; IR (film, cm^{-1}): 2964, 2931, 1706, 1608, 1175
^1H NMR (300 MHz, $CDCl_3$): δ 5.83 (d, *J* = 1.2 Hz, 1H), 2.56-2.51 (m, 3H), 2.32-2.29 (m, 2H), 1.10 (d, *J* = 7.0 Hz, 6H)
^{13}C NMR (75 MHz, $CDCl_3$): δ 210.0, 188.3, 127.6, 35.2, 32.0, 29.3, 20.7

Method 02:



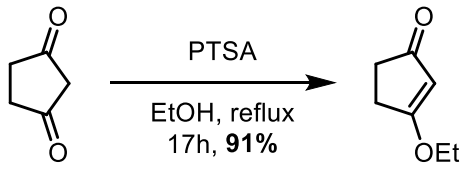
2.59 **2.54**

To vacuum dried CuBr.Me_2S (0.26 g, 1.25 mmol, 0.05 equiv), dry THF (100 mL) was added and the resulting suspension was cooled to -78 °C. A solution of iPrMgCl in THF (2 M, 17.48 mL, 35.0 mmol, 1.4 equiv) and HMPA (10.4 mL, 60 mmol, 2.4 equiv) were added dropwise and the mixture was let to stir at -78 °C for 15 minutes. A solution containing **2.59** (3.15 g, 25 mmol, 1 equiv), and

TMSCl (6.4 mL, 50 mmol, 2 equiv) in dry THF (10 mL) was added dropwise using a dropping funnel. The mixture was let to stir at -78 °C and monitored by TLC. The reaction was quenched with 2N HCl solution (50 mL). Layers were separated and aqueous layer extracted with DEE (3x75 mL). Combined organic layers were washed with sat. aq. $NaHCO_3$ solution (100 mL) to remove the copper salts followed by sat. aq. NH_4Cl solution (100 mL). Organic phase washed with brine (75 mL), dried (Na_2SO_4), filtered and concentrated to give yellow oil. Purification by column chromatography (40:60 pentane-DEE) resulted in 3-isopropylcyclopent-2-en-1-one **2.54** (2.59 g, 20.85 mmol, 83.51%) as a colourless oil. The spectral data of **2.54** match those reported in the literature[220].

R_f (EtOAc-hexane 4:6) = 0.5; IR (film, cm^{-1}): 2964, 2931, 1706, 1608, 1175
^1H NMR (300 MHz, $CDCl_3$): δ 5.83 (d, *J* = 1.2 Hz, 1H), 2.56-2.51 (m, 3H), 2.32-2.29 (m, 2H), 1.10 (d, *J* = 7.0 Hz, 6H)
^{13}C NMR (75 MHz, $CDCl_3$): δ 210.0, 188.3, 127.6, 35.2, 32.0, 29.3, 20.7

4.3.4 3-ethoxycyclopent-2-en-1-one (2.59)

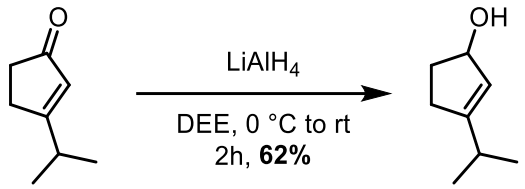


2.58 **2.59**

To a solution of diketone **2.58** (2.5 g, 25.48 mmol, 1 equiv) and EtOH (50 mL), was added PTSA (0.97 g, 5.1 mmol, 0.2 equiv) and heated to reflux. The mixture was cooled to rt after 17 h and diluted with 100 mL EtOAc. The combined organic layers were washed with sat. aq. Na_2CO_3 solution (1x80 mL) and brine (1x80 mL). The solution was dried (Na_2SO_4), filtered and concentrated to give 3-ethoxycyclopent-2-en-1-one **2.59** (2.93 g, 23.2 mmol, 91%) as a colorless oil. No purification was required to continue for the next step. The spectral data of **2.59** match those reported in the literature[221].

R_f (EtOAc-DCM 2:6) = 0.27; IR (film, cm^{-1}): 2978, 1670, 1560, 1440, 1160
^1H NMR (300 MHz, $CDCl_3$): δ 5.20 (s, 1H), 3.98 (q, *J* = 6.9 Hz, 2H), 2.55-2.51 (m, 2H), 2.36-2.33 (m, 2H), 1.33 (t, *J* = 7.0 Hz, 3H)
13C NMR (75 MHz, $CDCl_3$): δ 205.2, 189.3, 103.8, 66.9, 33.8, 28.8, 14.2

4.3.5 3- isopropylcyclopent-2-en-1-ol (2.60)



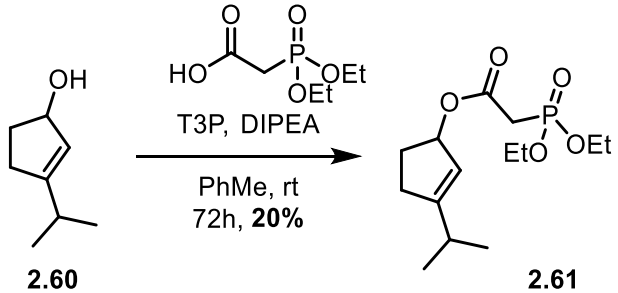
2.54 **2.60**

A slurry of $LiAlH_4$ (0.017 g, 0.44 mmol, 0.5 equiv) and dry DEE (5 mL) was prepared and cooled to -5 °C. A solution of Enone **2.54** (0.11 g, 0.89 mmol, 1 equiv) in DEE (2 mL) was added dropwise to the reaction mixture. The mixture was let to stir at rt. The reaction was quenched after 2 hours using H_2O (2 mL) and 3N NaOH solution (2 mL). The phases were separated, and the aqueous layer was extracted with DEE (3x10 mL). The combined organic layers were washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated to give the alcohol **2.60** (0.07 g, 0.55 mmol, 62%) as a colorless oil. The spectral data of **2.60** match those reported in the literature[220].

Note: The alcohol **2.60** was unstable and degraded significantly over silica. As such, the alcohol was used without further purification. Also, the compound **2.60** was volatile and acid sensitive.

R_f (EtOAc-hexane 40:60) = 0.5 ($KMnO_4$ Stain); IR (film, cm^{-1}): 3336, 2960, 2931, 1711, 1681, 1466, 1024
^1H NMR (300 MHz, C_6D_6): δ 5.45 (p, J = 1.7 Hz, 1H), 4.79 (br s, 1H), 2.35-1.94 (m, 5H), 1.76-1.69 (m, 1H), 0.96 (dd, J_1 = 4.6 Hz, J_2 = 6.8 Hz, 6H)
^{13}C NMR (75 MHz, C_6D_6): δ 154.3, 125.8, 77.4, 34.3, 31.6, 30.1, 21.5, 21.4

4.3.6 Phosphonate 2.61



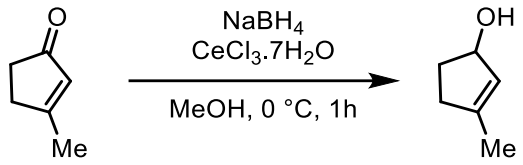
2.60 **2.61**

To a mixture of alcohol **2.60** (0.07 g, 0.55 mmol, 1 equiv) in dry toluene (5 mL), DIPEA (0.25 mL, 1.44 mmol, 2.6 equiv), 2-(diethoxyphosphoryl)acetic acid (114 mg, 0.58 mmol, 1.05 equiv), and T3P (0.43 mL, 0.72 mmol, 1.3 equiv) were added. The mixture was stirred at rt for 72 h and was diluted with water (5 mL) after 72 h. The phases were separated, and aqueous layer was extracted with EtOAc (3x5 mL). Combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography (40:60

Hexane-EtOAc) resulted in compound **2.61** (0.032 g, 0.11 mmol, 20%) as a colorless oil.

R_f (EtOAc-hexane 70:30) = 0.35; IR (film, cm^{-1}): 2980, 2933, 1726, 1444, 1374, 1331, 1253, 1108, 1020, 824
^1H NMR (300 MHz, CD_3CN): δ 5.63 (s, 1H), 5.43 (s, 1H), 4.07 (q, J = 6.8 Hz, 4H),2.92 (s, 1H), 2.85 (s, 1H), 2.51-2.22 (m, 5H), 1.27 (t, J = 7.0 Hz, 6H), 1.06 (dd, J_1 = 1.4 Hz, J_2 = 6.8 Hz 6H)
^{13}C NMR (75 MHz, CD_3CN): δ 160.2, 120.8, 82.9, 63.3, 36.0, 34.2, 32.1, 30.9, 30.7, 21.5, 16.7
HRMS (ESI^+): m/z calculated for $[C_{14}H_{25}O_5PNa]^+$ = 327.1332, found 327.1340, Δ = 2.4 ppm

4.3.7 3- methylcyclopent-2-en-1-ol (2.63)



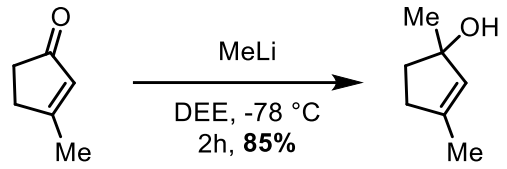
2.62 **2.63**

To vacuum dried $CeCl_3.7H_2O$ (0.45 g, 1.21 mmol, 1.2 equiv), a solution of enone **2.62** (0.1 g, 1.01 mmol, 1 equiv) in methanol (15 mL) was added and the resulting suspension was cooled to -78 °C. After stirring for 15 minutes at -78 °C, $NaBH_4$ (0.046 g, 1.21 mmol, 1.2 equiv) was added in portions. The cold bath was removed and the reaction mixture was allowed to warm to 0 °C. The mixture was stirred at 0 °C for 1 h and then warmed to rt. Sat. aq. NH_4Cl solution (5 mL) was added. The phases were separated, and the aqueous layer was extracted with EtOAc (3x5 mL). Combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated to give the alcohol **2.63** as colorless oil (0.1 g, 1 mmol, >99%). Crude alcohol **2.63** was used without purification. The spectral data of **2.63** match those reported in the literature[222].

Note: The alcohol **2.63** was highly volatile and acid sensitive. A highly nonpolar spot was visible on TLC indicating the degradation of alcohol **2.63** by elimination of water.

R_f (EtOAc-hexane 40:60) = 0.42; IR (film, cm^{-1}): 3325, 2965, 2928, 1709, 1644
^1H NMR (300 MHz, CD_3CN): δ 5.37 (s, 1H), 4.68 (bs, 1H), 2.62-2.58 (m, 1H), 2.40-2.30 (m, 1H), 2.26-2.17 (m, 2H), 1.74 (s, 3H)
^{13}C NMR (75 MHz, CD_3CN): δ 145.0, 129.1, 77.9, 35.7, 35.0, 16.8

4.3.8 1,3- dimethylcyclopent-2-en-1-ol (2.65)



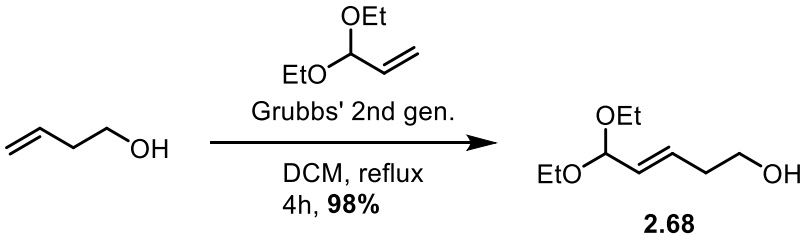
2.62 **2.65**

A solution of enone **2.62** (0.485 g, 5.05 mmol, 1 equiv) in dry DEE (30 mL) was cooled to -78 °C, followed by dropwise addition of MeLi (1.6 M in DEE, 4.73 mL, 7.6 mmol, 1.5 equiv). The resulting mixture was let to stir at -78 °C for 0.5 h. After warming the mixture to rt and stirring for 2 h, 10 mL sat. aq. NH_4Cl (15 mL) was added. The phases were separated, and aqueous layer was extracted with DEE (3x15 mL). Combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated to give tertiary alcohol **2.65** (0.48 g, 4.28 mmol, 85%) as colorless oil. The crude can be used without any purification. The spectral data of **2.65** match those reported in the literature[223].

Note: The crude was suitable to use without any purification. The alcohol was volatile and highly acid sensitive.

R_f (EtOAc-hexane 20:80) = 0.5; IR (film, cm^{-1}): 3398, 3049, 2966, 2916, 1967, 1674, 1264, 733
^1H NMR (300 MHz, C_6D_6): δ 5.27 (s, 1H), 1.91-1.81 (m, 4H), 1.53 (s, 3H), 1.34 (s, 3H)
^{13}C NMR (75 MHz, C_6D_6): δ 141.7. 133.3. 83.3. 41.1. 35.5. 28.1. 16.6

4.3.9 Acetal 2.68



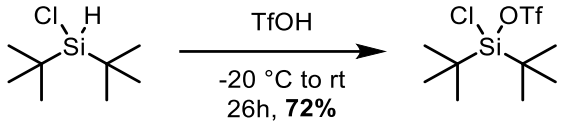
2.68

A solution of dry degassed DCM (50 mL), but-3-en-1-ol (0.84 mg, 11.6 mmol, 1 equiv) and 3,3-diethoxyprop-1-ene (5.31 mL, 34.8 mmol, 3 equiv) was degassed followed by addition of Grubbs' second-generation catalyst (0.197 g, 232 mmol, 0.02 equiv). The reaction vessel was flushed with argon and heated to reflux. The reaction mixture was cooled to rt and concentrated. The crude was then subjected to flash column chromatography (50:50 DEE-Hexane) to give compound **2.68** (2 g, 11.48 mmol, 99%) as a colorless oil.

R_f (EtOAc-hexane 40:60) = 0.6; IR (film, cm^{-1}): 3426, 3052, 2930, 1338, 1047, 733

1H NMR (300 MHz, $CDCl_3$): δ 5.81-5.71 (m, 1H), 5.56-5.49 (m, 1H), 4.78 (d, *J* = 5.2 Hz, 1H), 3.62-3.52 (m, 4H), 3.49-3.38 (m, 2H), 2.30-2.23 (m, 2H), 1.14 (t, *J* = 7.0 Hz, 6H)
13C NMR (75 MHz, $CDCl_3$): δ 130.8, 129.7, 101.4, 61.3, 60.9, 35.3, 15.0
HRMS (ESI^+): m/z calculated for $[C_9H_{18}O_3Na]^+$ = 197.1148, found 197.1154, Δ = 3.0 ppm

4.3.10 Triflate 2.72

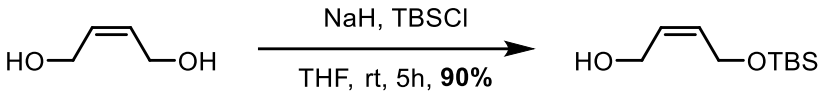


2.71 **2.72**

To a precooled (-20 °C) silane **2.71** (4.42 g, 24.72 mmol, 1 equiv), triflic acid (4.38 mL, 49.45 mmol, 2 equiv) was added dropwise using a dropping funnel and stirred at rt for 2 h. The crude was then subjected to vacuum distillation to get compound **2.72** (5.8 g, 17.75 mmol, 72%) as colorless liquid. The spectral data of **2.72** match those reported in the literature[224].

1H NMR (300 MHz, $CDCl_3$): δ 1.19 (s, 18H)

4.3.11 Protected allyl alcohol 2.75

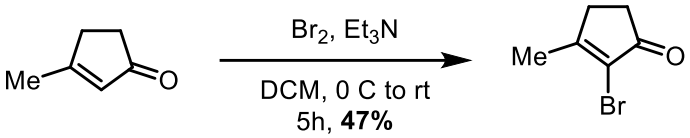


2.74 **2.75**

A suspension of NaH (0.485 g, 12.14 mmol, 1 equiv) in dry THF (20 mL) was cooled to 0 °C, followed by dropwise addition of diol **2.74** (1.07 g, 12.14 mmol, 1 equiv). After stirring at rt for 1 h, TBSCl (1.83 g, 12.14 mmol, 1 equiv) in 10 mL dry THF was added dropwise. After stirring the mixture at rt for 4 h, sat. aq. NH_4Cl solution (20 mL) was added. The phases were separated, and aqueous layer was extracted with DEE (3x30 mL). Combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography (20:80 EtOAc-Hexane) gave compound **2.75** (2.2 g, 10.87 mmol, 89%) as a colorless oil. The spectral data of **2.75** match those reported in the literature[225].

R_f (EtOAc-hexane 40:60) = 0.5; IR (film, cm^{-1}): 3740, 2930, 2865, 1456
1H NMR (300 MHz, $CDCl_3$): δ 5.70-5.58 (m, 2H), 4.23-4.21 (m, 2H), 4.16-4.14 (m, 2H), 2.53 (bs, 1H), 0.88 (s, 9H), 0.06 (s, 3H)
13C NMR (75 MHz, $CDCl_3$): δ 131.2, 130.1, 59.6, 58.7, 25.9, 18.3, -5.1

4.3.12 2- bromo-3-methylcyclopent-2-en-1-one (2.76)

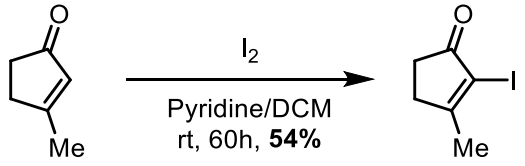


2.62 **2.76**

A solution of enone **2.62** (0.971 mg, 10.1 mmol, 1 equiv) in dry DCM (10 mL) was cooled to 0 °C, followed by dropwise addition of bromine (0.78 mL, 15.15 mmol, 1.5 equiv) using a dropping funnel and the mixture was stirred at 0 °C for 2 h. Triethylamine (1.55 mL, 11.11 mmol, 1.1 equiv) was added dropwise and stirred at rt for 2.5 h. 0.1N HCl solution (10 mL) was added, and the phases were separated. Organic layer was washed with sat. aq. $NaHCO_3$ solution (20 mL), dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography followed by recrystallization using 1:2 EtOAc-Hexane gave compound **2.76** (0.82 g, 4.7 mmol, 47%) as white solid. The spectral data of **2.76** match those reported in the literature[226].

R_f (EtOAc-hexane 30:70) = 0.69; IR (film, cm^{-1}): 1699, 1613, 951, 587
^1H NMR (300 MHz, $CDCl_3$): δ 2.66-2.64 (m, 2H), 2.55-2.52 (m, 2H), 2.18 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$): δ 201.4, 173.3, 123.3, 33.4, 32.3, 19.1

4.3.13 2-iodo-3-methylcyclopent-2-en-1-one (2.80)

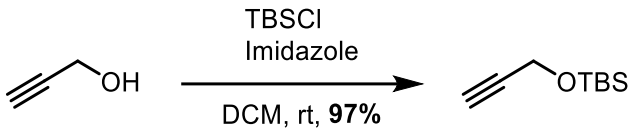


2.62 **2.80**

To a solution of enone **2.62** (1.46 g, 15.2 mmol, 1 equiv), dry DCM (120 mL), and pyridine (30 mL), iodine (8.5 g, 33.4 mmol, 2.2 equiv) was added and the dark mixture was stirred at rt for 48 h. Sat. aq. $Na_2S_2O_3$ solution (100 mL) was added to the reaction mixture and the phases were separated. The organic layer was washed with 2N HCl solution (100 mL), brine (100 mL), dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography (25:75 EtOAc-Hexane) gave the compound **2.80** (1.8 g, 8.11 mmol, 54%) as a white solid. The spectral data of **2.80** match those reported in the literature[227].

R_f (EtOAc-hexane 30:70) = 0.68; IR (film, cm^{-1}): 1682, 1594, 1371, 1137, 581
^1H NMR (300 MHz, $CDCl_3$): δ 2.75-2.73 (m, 2H), 2.58-2.56 (m, 2H), 2.21 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$): δ 203.6, 179.7, 102.8, 34.4, 33.3, 22.1

4.3.14 Protected propargyl alcohol 2.81

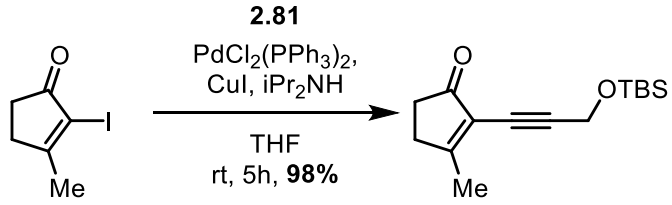


2.81

A solution of propargyl alcohol (1.93 g, 34.35 mmol, 1 equiv) in dry DCM (50 mL) was cooled to 0 °C. Imidazole (4.68 g, 68.71 mmol, 2 equiv) was added followed by TBSCl (5.18 g, 34.35 mmol, 1 equiv). The mixture was stirred at rt for 1.5 h, and diluted with water (50 mL). The phases were separated, and organic layer was washed with sat. aq. NH_4Cl solution (50 mL), brine (50 mL), dried (Na_2SO_4), filtered and concentrated to give compound **2.81** (5.65 g, 33.17 mmol, 97%) as colorless oil. Purification by flash column chromatography was not necessary. The spectral data of **2.81** match those reported in the literature[228].

R_f (EtOAc-hexane 20:80) = 0.9 ($KMnO_4$ stain); IR (film, cm^{-1}): 3309, 2930, 2858, 1255, 1089, 833
^1H NMR (300 MHz, $CDCl_3$): δ 4.30 (d, *J* = 2.4 Hz, 2H), 2.37 (t, *J* = 2.4 Hz, 1H), 0.90 (s, 9H), 0.12 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$): δ 82.3, 72.8, 51.5, 25.7, 18.2, -5.2

4.3.15 Enynone 2.82



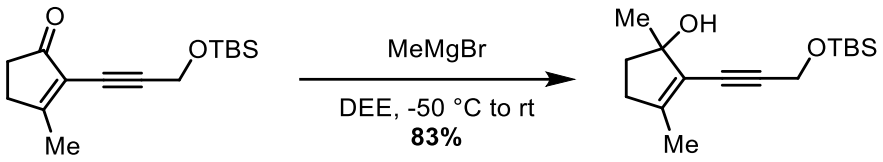
2.80 **2.82**

A solution of degassed dry THF (25 mL), CuI (22 mg, 0.112 mmol, 0.05 equiv), $Pd(PPh)_3Cl_2$ (80 mg, 0.112 mmol, 0.05 equiv) and compound **2.80** (0.5 g, 2.25 mmol, 1.0 equiv) was degassed for 20 minutes. Alcohol **2.81** (0.575 mg, 3.38 mmol, 1.5 equiv) was added and the mixture was cooled to 0 °C. Diisopropyl amine (2.3 mL, 15.76 mmol, 7 equiv) in degassed THF was added dropwise. Reaction mixture was stirred at 0 °C for 0.5 h and then at rt for 5 h. The mixture was filtered through celite, washed with sat. aq. NH_4Cl solution (20 mL), 2N HCl solution (20 mL), sat. aq. $NaHCO_3$ solution (20 mL) and brine (20 mL). It was then dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography (25:75 EtOAc-Hexane) gave compound **2.82** (0.583 g, 2.20 mmol, 98%) as colorless oil.

R_f (EtOAc-hexane 40:60) = 0.54; IR (film, cm^{-1}): 2943, 2920, 1690, 1350, 1079, 826
^1H NMR (300 MHz, $CDCl_3$): δ 4.53 (s, 2H), 2.65-2.61 (m, 2H), 2.48-2.44 (m, 2H), 2.23 (s, 3H), 0.91 (s, 9H), 0.13 (s, 6H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 205.5, 179.7, 125.9, 96.7, 75.3, 52.4, 34.8, 32.0, 25.9, 19.0, 18.4, -4.9
HRMS (ESI$^+$): m/z calculated for $[C_{15}H_{24}O_2SiNa]^+$ = 287.1438, found 287.1448, Δ = 3.5 ppm

4.3.16 Alcohol 2.83

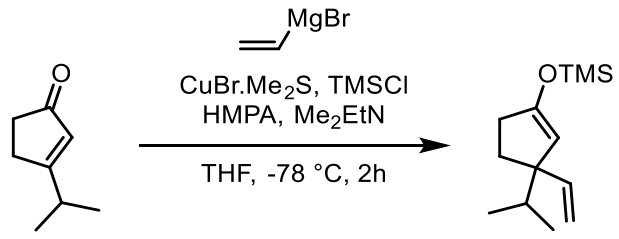


2.82 **2.83**

A solution of compound **2.82** (0.1 g, 0.38 mmol, 1.0 equiv) in dry DEE (8 mL) was cooled to -50 °C. A solution of MeMgBr solution in DEE (3 M, 0.14 mL, 0.42 mmol, 1.1 equiv) was added dropwise to the reaction mixture and stirred from -50 °C to rt overnight. Sat. aq. K_2CO_3 solution (5 mL) was added to the reaction mixture and the phases were separated. Aqueous layer was extracted with DEE (3x5 mL). The combined organic layers were washed with brine (15 mL), dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography (40:60 DEE:Pentane) resulted in compound **2.83** (0.09 g, 0.32 mmol, 83%) as a colorless oil.

R_f (EtOAc-hexane 40:60) = 0.4; IR (film, cm^{-1}): 3367, 2956, 2929, 2857, 1365, 1254, 1084, 836, 814
^{1}H NMR (300 MHz, THF-*d*8): δ 4.49 (s, 2H), 3.65 (s, 1H), 2.46-2.14 (m, 2H), 1.90-1.88 (m, 2H), 1.80 (s, 3H), 1.27 (s, 3H), 0.91 (s, 9H), 0.13 (s, 6H)
^{13}C NMR (75 MHz, THF-*d*8): δ 166.0, 158.9, 121.1, 82.0, 62.4, 35.3, 34.2, 31.8, 30.7, 30.5, 21.3, 16.4, -4.9
HRMS (ESI$^+$): m/z calculated for $[C_{16}H_{28}O_2SiNa]^+$ = 303.1751, found 303.1763, Δ = 4.0 ppm

4.3.17 Enolsilane 2.88



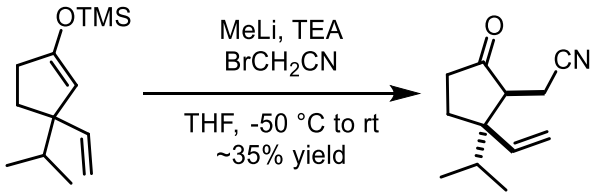
2.54 **2.88**

To a 3-neck Rb, CuBr.Me_2S (0.033 g, 0.161 mmol, 0.1 equiv) was added and dried under vacuum. Subsequently, dry THF (15 mL) was added and cooled to -78 °C. Vinylmagnesium bromide in THF solution (1 M, 2.9 mL, 2.90 mmol, 1.8 equiv) and HMPA (1.0 mL, 5.80 mmol, 3.6 equiv) were added dropwise and the mixture

was stirred at -78 °C for 15 minutes. A mixture of enone **2.54** (0.20 g, 1.61 mmol, 1.0 equiv) and TMSCl (0.61 mL, 4.83 mmol, 3.0 equiv) in dry THF (5 mL) was added dropwise to the reaction vessel. The mixture was stirred at -78 °C for 2 h and then diluted with 10 mL of pentane followed by addition of N,N-dimethylethylamine (0.68 mL, 4.83 mmol, 3.0 equiv). Mixture was filtered through celite, washed with water (10 mL), brine (10 mL), dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography (1:99 DEE-Pentane) gave silyl enol ether **2.88** (0.36 g, 1.60 mmol, >99%) as a colorless oil. The silyl enol ether degraded during storage and was used immediately.

R_f (EtOAc-hexane 10:90) = 0.9 ($KMnO_4$ stain); IR (film, cm^{-1}): 2957, 2926, 1249, 1091, 867, 839, 755
^1H NMR (300 MHz, $CDCl_3$): δ 5.88 (dd, J_1 = 9.8 Hz, J_2 = 17.8 Hz, 1H), 4.95 (dd, J_1 = 1.8 Hz, J_2 = 6.0 Hz, 1H), 4.91 (s, 1H), 4.58 (t, J = 1.5 Hz, 1H), 2.34-2.13 (m, 2H), 1.85-1.57 (m, 3H), 0.83 (dd, J_1 = 2.7 Hz, J_2 = 6.8 Hz, 6H), 0.23 (s, 9H)
^{13}C NMR (75 MHz, $CDCl_3$): δ 154.7, 145.4, 111.1, 106.9, 55.6, 36.8, 32.9, 31.7, 18.3, 18.1, 0.1

4.3.18 Nitrile 2.87



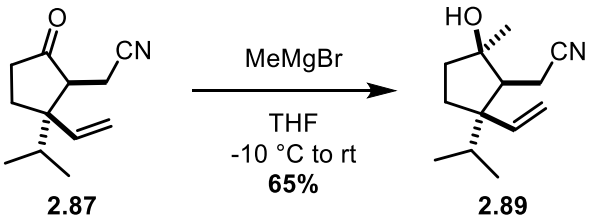
2.88 **2.87**

A solution of silyl enol ether **2.88** (0.33 g, 1.47 mmol, 1 equiv) in dry THF (3 mL) was cooled to 0 °C. A solution of MeLi in DEE (1.6 M, 1.10 mL, 1.76 mmol, 1.2 equiv) was added dropwise and the resulting mixture was stirred for 0.5 h. The reaction mixture was cooled to -20 °C and a mixture of HMPA (0.25 mL, 1.47 mmol, 1 equiv), bromoacetonitrile (0.15 mL, 2.21 mmol, 1.5 equiv) in 2 mL dry THF was added dropwise. The reaction mixture was stirred from -20 °C to rt over 16 h. Sat. aq. NH_4Cl solution (5 mL) was added to the reaction medium, and the phases were separated. The aqueous layer was extracted with DEE (3x5 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography (30:70 DEE-Pentane) gave the compound **2.87** (0.1 g, 0.52 mmol, 35%) as colorless oil.

R_f (EtOAc-hexane 30:70) = 0.5 ($KMnO_4$ stain); IR (film, cm^{-1}): 2305, 1743, 1420, 1264, 732, 703
^1H NMR (500 MHz, C_6D_6): δ 4.99 (dd, J_1 = 11.1 Hz, J_2 = 17.5 Hz, 1H), 4.80 (d, J = 11.0 Hz, 1H), 4.52 (d, J = 17.5 Hz, 1H), 2.22 (dd, J_1 = 5.0 Hz, J_2 = 17.4 Hz, 1H), 1.93 (dd, J_1 = 5.2 Hz, J_2 = 8.8 Hz, 1H), 1.68 (m, 3H), 1.59 (dd, J_1 = 8.9 Hz, J_2 = 17.6 Hz,

1H), 1.31-1.27 (m, 1H), 1.09-1.02 (m, 1H), 0.66 (d, *J* = 6.8 Hz, 3H), 0.59 (d, *J* = 6.8 Hz, 3H)
^{13}C NMR (125 MHz, C_6D_6): δ 212.8, 138.5, 118.7, 116.4, 52.4, 51.7, 33.9, 32.0, 23.1, 17.9, 17.0, 12.6
HRMS (ESI$^+$): m/z calculated for $[C_{12}H_{17}NONa]^+$ = 214.1202, found 214.1203, Δ = 0.5 ppm

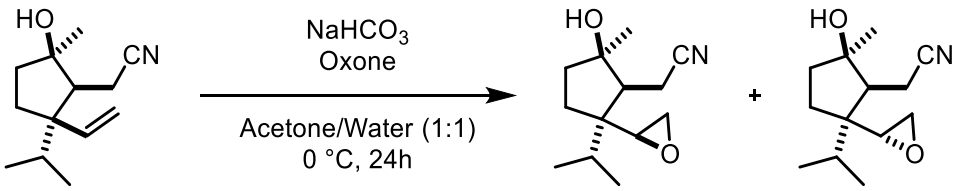
4.3.19 Alcohol 2.89



Compound **2.87** (0.10 g, 0.52 mmol, 1 equiv) was dissolved in dry THF (5 mL) and the reaction mixture was cooled to -10 °C. 3M MeMgBr in DEE solution (0.2 mL, 0.63 mmol, 1.20 equiv) was added dropwise and the reaction was let to stir from -10 °C to rt overnight. Sat. aq. NH_4Cl (5 mL) was added and the phases were separated. Aqueous layer was extracted with DEE (3x5 mL). Combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated to give crude compound **2.89** (0.07 g, 0.38 mmol, 65%) as colorless oil.

R_f (EtOAc-hexane 30:70) = 0.4 ($KMnO_4$ stain); IR (film, cm^{-1}): 3054, 2967, 2306, 1764, 1381, 1264, 732
^{1}H NMR (500 MHz, C_6D_6): δ 5.47 (dd, J_1 = 11.1 Hz, J_2 = 17.6 Hz, 1H), 4.93 (d, *J* = 17.4 Hz, 1H), 4.85 (d, *J* = 11.0 Hz, 1H), 2.10 (dd, J_1 = 7.9 Hz, J_2 = 17.1 Hz, 1H), 1.86 (dd, J_1 = 6.5 Hz, J_2 = 17.1 Hz, 1H), 1.68 (t, *J* = 7.1 Hz, 1H), 1.59-1.37 (m, 5H), 1.20-1.14 (m, 1H), 1.10 (s, 3H), 0.68 (d, *J* = 6.8 Hz, 3H), 0.65 (d, *J* = 6.8 Hz, 3H)
^{13}C NMR (125 MHz, C_6D_6): δ 141.7, 120.2. 114.9, 79.8, 54.0, 51.6, 40.7, 33.3, 28.0, 27.1, 18.4, 17.3, 13.1
HRMS (ESI$^+$): m/z calculated for $[C_{13}H_{22}NO]^+$ = 208.1696, found 208.1690, Δ = -2.9 ppm

4.3.20 Epoxides 2.90 & 2.91



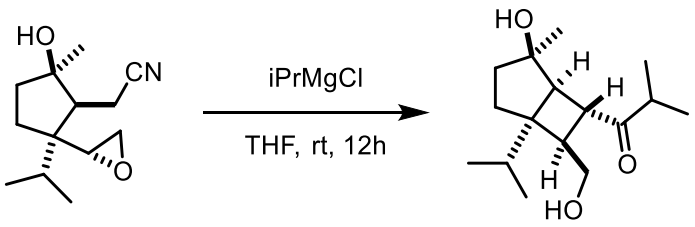
2.89 **2.90 (40.3%)** **2.91 (27.2%)**

A solution of **2.89** (0.11 g, 0.53 mmol, 1.0 equiv) and $NaHCO_3$ (0.215 g, 2.57 mmol, 4.8 equiv), in acetone/water (1:1, 3 mL) was cooled to 0 °C. Oxone (0.33 g, 0.53 mmol, 1.0 equiv) was added to the solution and the reaction mixture was stirred at 0 °C for 24 hours. Sat. aq. $Na_2S_2O_3$ solution (3 mL) was added, and the phases were separated. The aqueous layer was extracted with DEE (3x5 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (40:60 DEE:Pentane) resulted in two diastereomers with the undesired epoxide **2.90** (0.048 g, 0.21 mmol, 40%) as an off-white solid and desired epoxide **2.91** (0.033 g, 0.15 mmol, 27%) as colorless oil.

Epoxide **2.90**:
R_f (EtOAc-hexane 30:70) = 0.3 ($KMnO_4$ stain); IR (film, cm^{-1}): 2279, 1391, 1329, 1161, 811, 516, 490
^1H NMR (500 MHz, C_6D_6): δ 3.05 (br s, 1H), 2.59 (t, J = 3.5 Hz, 1H), 2.28 (dd, J_1 = 9.9 Hz, J_2 = 17.4 Hz, 1H), 2.15 (dd, J_1 = 5.4 Hz, J_2 = 17.4 Hz, 1H), 2.11 (t, J = 4.2 Hz, 1H), 2.00 (t, J = 3.5 Hz, 1H), 1.82-1.75 (m, 2H), 1.43 (dd, J_1 = 7.7 Hz, J_2 = 12.8 Hz, 1H), 1.11 (s, 3H), 1.07 (dd, J_1 = 4.3 Hz, J_2 = 12.8 Hz, 1H), 0.75 (dd, J_1 = 7.9 Hz, J_2 = 13.3 Hz, 1H), 0.57 (d, J = 6.8 Hz, 3H), 0.53 (dd, J_1 = 7.6 Hz, J_2 = 13.6 Hz, 1H), 0.49 (d, J = 6.8 Hz, 3H)
^{13}C NMR (125 MHz, C_6D_6): δ 120.1, 78.7, 54.1, 51.3, 50.0, 46.2, 39.9, 34.0, 24.2, 20.4, 18.5, 17.5, 12.8
HRMS (ESI^+): m/z calculated for $[C_{13}H_{22}NO_2]^+$ = 224.1645, found 224.1643, Δ = -0.9 ppm

Epoxide **2.91**:
R_f (EtOAc-hexane 30:70) = 0.15 ($KMnO_4$ stain); IR (film, cm^{-1}): 2279, 1391, 1329, 1161, 811, 516, 490
^1H NMR (400 MHz, C_6D_6): δ 2.53 (dd, J_1 = 2.7 Hz, J_2 = 3.9 Hz, 1H), 2.49 (dd, J_1 = 2.8 Hz, J_2 = 4.9 Hz, 1H), 2.25 (dd, J_1 = 4.2 Hz, J_2 = 4.8 Hz, 1H), 2.05 (dd, J_1 = 8.6 Hz, J_2 = 17.1 Hz, 1H), 1.92 (dd, J_1 = 6.4 Hz, J_2 = 17.1 Hz, 1H), 1.60 (dd, J_1 = 6.4 Hz, J_2 = 8.5 Hz, 1H), 1.55 (dd, J_1 = 6.7 Hz, J_2 = 13.4 Hz, 1H), 1.13-1.04 (m, 4H), 0.98 (s, 3H), 0.89 (d, J = 6.7 Hz, 3H), 0.79 (d, J = 6.7 Hz, 3H)
^{13}C NMR (100 MHz, C_6D_6): δ 120.3, 79.9, 53.1, 51.2, 50.3, 43.2, 40.9, 37.6, 27.1, 24.3, 18.6, 12.9
HRMS (ESI^+): m/z calculated for $[C_{13}H_{22}NO_2Na]^+$ = 246.1465, found 246.1442, Δ = –9.3 ppm

4.3.21 Ketodiol 2.96



2.91 **2.96**

A solution of compound **2.91** (0.04 g, 0.18 mmol, 1 equiv) in dry THF (2 mL) was cooled to 0 °C using an ice bath. *i*PrMgCl in THF (2 M, 0.54 mL, 1.07 mmol, 6 equiv) was added to the solution dropwise at 0 °C. After addition *i*PrMgCl, the ice bath was removed, the reaction mixture was allowed to warm to rt, and the mixture was stirred for 16 hours after which time sat. aq. NH_4Cl solution (3 mL) was added. Phases were separated and the aqueous layer was extracted with DEE (3x5 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (70:30 DEE:pentane) resulted in compound **2.96** (0.01 g, 0.04 mmol, 21%) as a colourless oil.

R_f (EtOAc-hexane 50:50) = 0.3 ($KMnO_4$ stain); IR (film, cm^{-1}): 3446, 2959, 2925, 2873, 1738, 1692, 1465, 1384, 1369

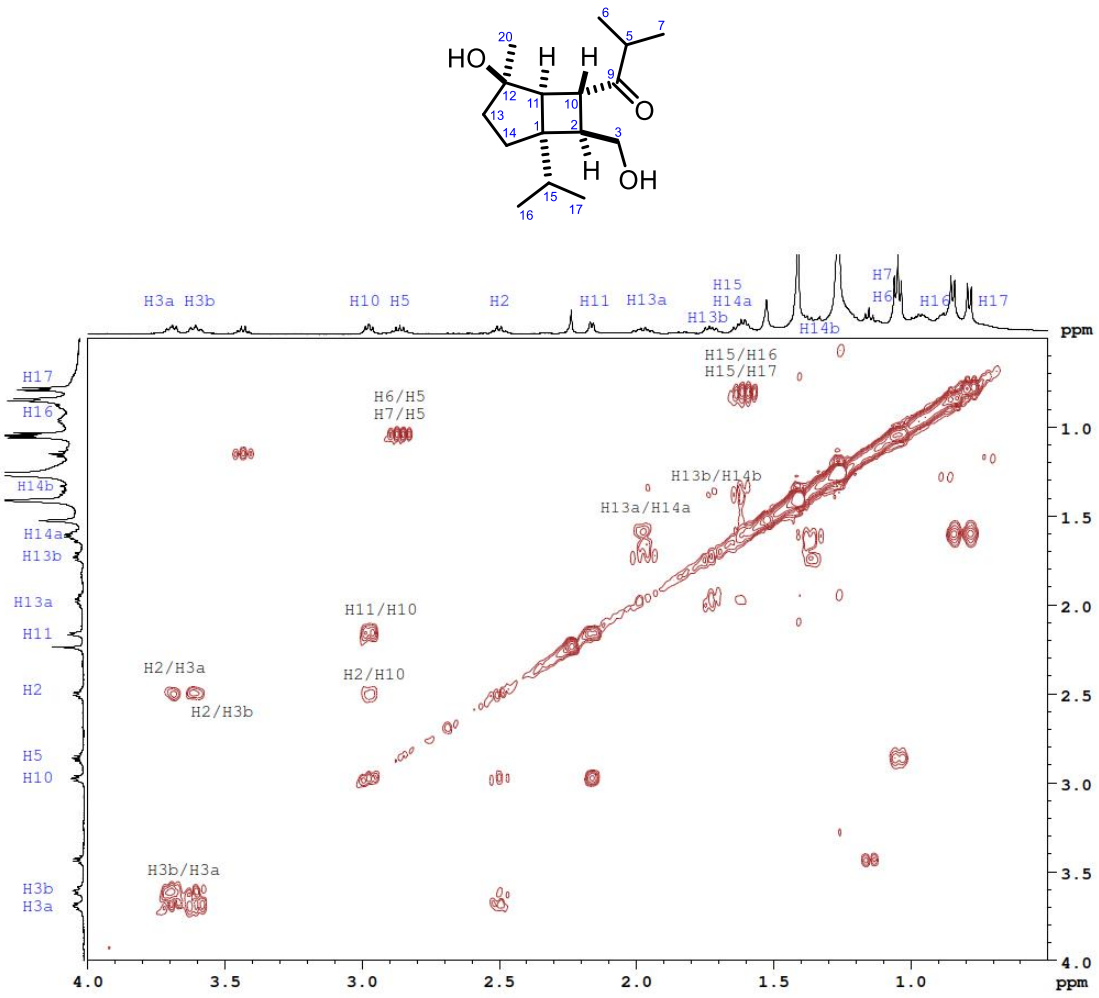
^1H NMR (500 MHz, CD_2Cl_2): δ 3.69 (dd, J_1 = 7.0 Hz, J_2 = 10.3 Hz, 1H), 3.60 (dd, J_1 = 8.5 Hz, J_2 = 10.1 Hz, 1H), 2.97 (dd, J_1 = 6.0 Hz, J_2 = 7.9 Hz, 1H), 2.86 (d, J = 6.8 Hz, 1H), 2.49 (q, J = 7.7 Hz, 1H), 2.16 (d, J = 5.7 Hz, 1H), 2.00-1.94 (m, 1H), 1.72 (q, J = 6.9 Hz, 1H), 1.64-1.57 (m, 2H), 1.38-1.33 (m, 1H), 1.04 (t, J = 6.4 Hz, 6H), 0.84 (d, J = 6.8 Hz, 3H), 0.78 (d, J = 6.8 Hz, 3H)

^{13}C NMR (125 MHz, CD_2Cl_2): δ 218.6 (derived from HMBC), 78.6, 63.3, 52.1, 50.5, 43.5, 41.0, 40.3, 38.0, 37.1, 28.7, 27.2, 18.9, 18.5, 18.1, 17.2

HRMS (ESI^+): m/z calculated for $[C_{16}H_{28}O_3Na]^+$ = 291.1931, found 291.1933, Δ = 0.7 ppm

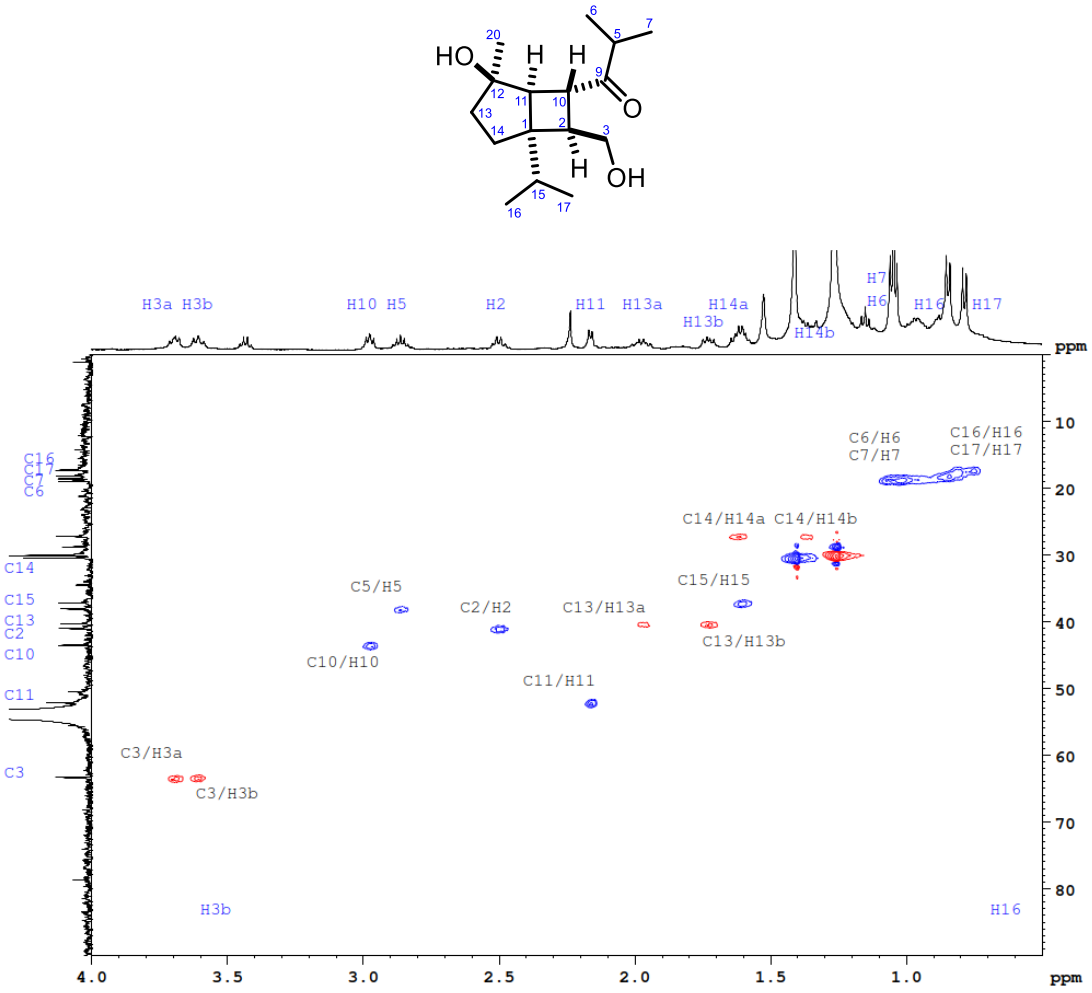
^{1}H-^{1}H-COSY Spectrum of ketodiol 2.96

The ^{1}H-^{1}H-COSY spectrum of compound **2.96** was measured at room temperature on a 500MHz NMR spectrometer by dissolving the compound in deuterated DCM. The correlations between hydrogens H3/H2/H10/H11 helped in establishing the spin system of the 4-membered ring, while the correlations of H13/H14, H15/H16/H17, and H5/H6/H7 helped in determining the remaining spin systems present in the molecule.

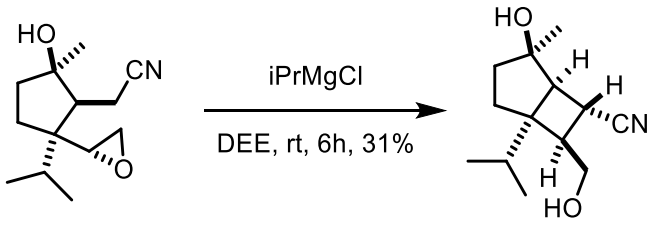


HSQC Spectrum of ketodiol 2.96

The phase sensitive HSQC spectrum of compound **2.96** was measured at room temperature on a 500 MHz NMR spectrometer by dissolving the compound in deuterated DCM. This spectrum helped us in constructing the core structure and identifying the carbon-hydrogen connections.



4.3.22 Humilisin E core 2.85



2.91 **2.85**

A solution of **2.91** (0.023 g, 0.1 mmol, 1 equiv) in dry DEE (2 mL) was cooled to 0 °C using an ice bath. To this solution, a solution of *i*PrMgCl in THF (2 M, 0.15 mL, 0.3 mmol, 3 equiv) was added dropwise at 0 °C. After the addition, the ice bath was removed, the reaction mixture was allowed to stir for 6 h at rt, after which time sat. aq. NH_4Cl solution (3 mL) was added. The phases were separated and the aqueous layer was extracted with DEE (3x5 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (70:30 DEE:Pentane) resulted in compound **2.85** (0.0072 g, 0.032 mmol, 31%) as a colourless oil.

R_f (EtOAc-hexane 50:50) = 0.3 ($KMnO_4$ stain); IR (film, cm^{-1}): 3400, 2959, 2874, 2235, 1466, 1387, 952, 708, 677

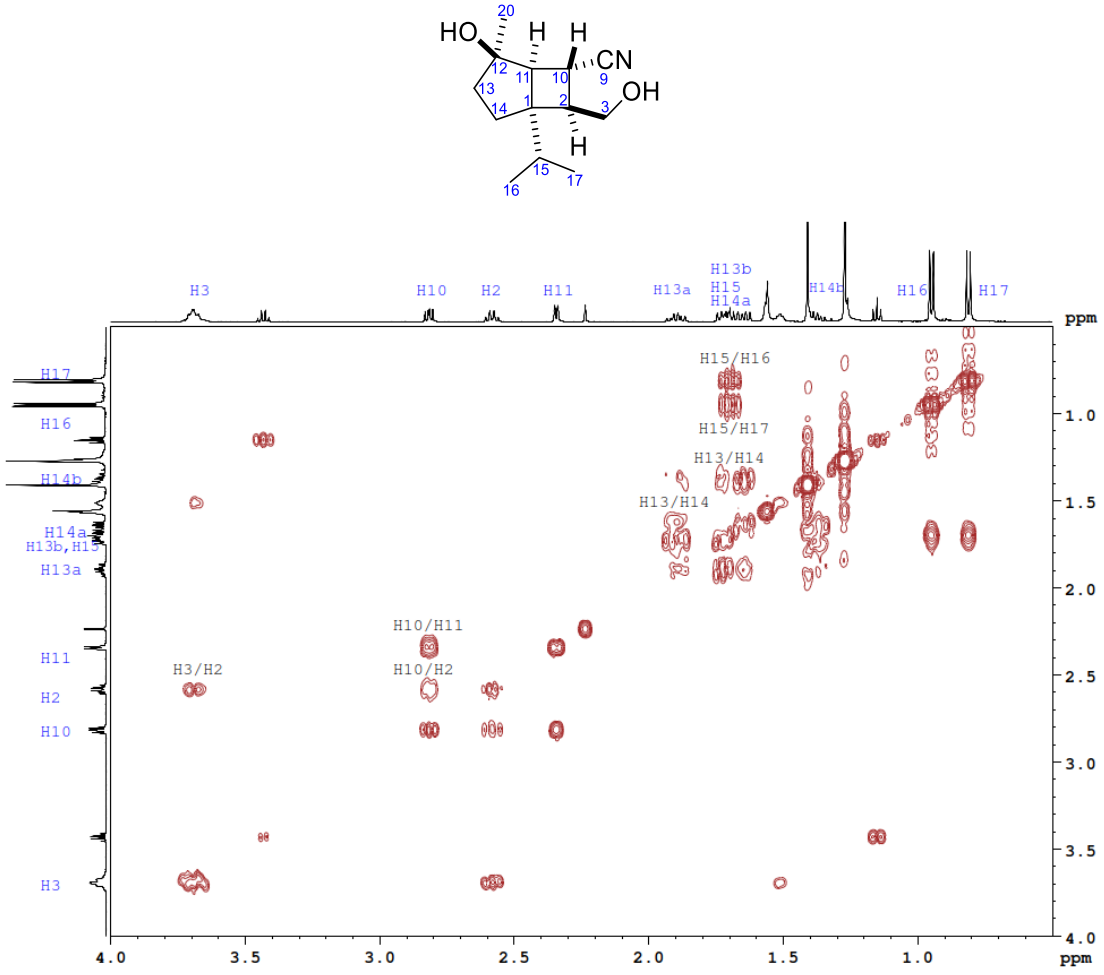
^1H NMR (500 MHz, CD_2Cl_2): δ 3.72-3.67 (m, 2H), 2.81 (dd, J_1 = 5.9 Hz, J_2 = 8.3 Hz, 1H), 2.34 (d, J = 5.8 Hz, 1H), 1.89 (dt, J_1 = 7.9 Hz, J_2 = J_3 = 13.0 Hz, 1H), 1.74-1.62 (m, 3H), 1.38-1.32 (m, 1H), 1.27 (s, 3H), 0.94 (d, J = 6.8 Hz, 3H), 0.81 (d, J = 6.8 Hz, 3H)

^{13}C NMR (125 MHz, CD_2Cl_2): δ 122.9, 78.2, 62.4, 53.5, 52.7, 43.8, 39.5, 37.3, 28.4, 27.5, 20.8, 18.0, 17.1

HRMS (ESI^+): m/z calculated for $[C_{13}H_{21}O_2NNa]^+$ = 246.1465, found 246.1459, Δ = -2.4 ppm

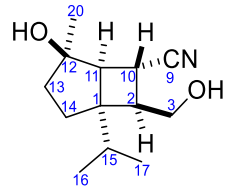
^{1}H-^{1}H-COSY Spectrum of humilisin E core 2.85

The ^{1}H-^{1}H-COSY spectrum of compound **2.85** was measured at room temperature on a 500 MHz NMR spectrometer by dissolving the compound in deuterated DCM. The correlations between hydrogens H3/H2/H10/H11 helped in establishing the spin system of the 4-membered ring, while the correlations of H13/H14, H15/H16/H17, and H5/H6/H7 helped in determining the remaining spin systems present in the molecule.

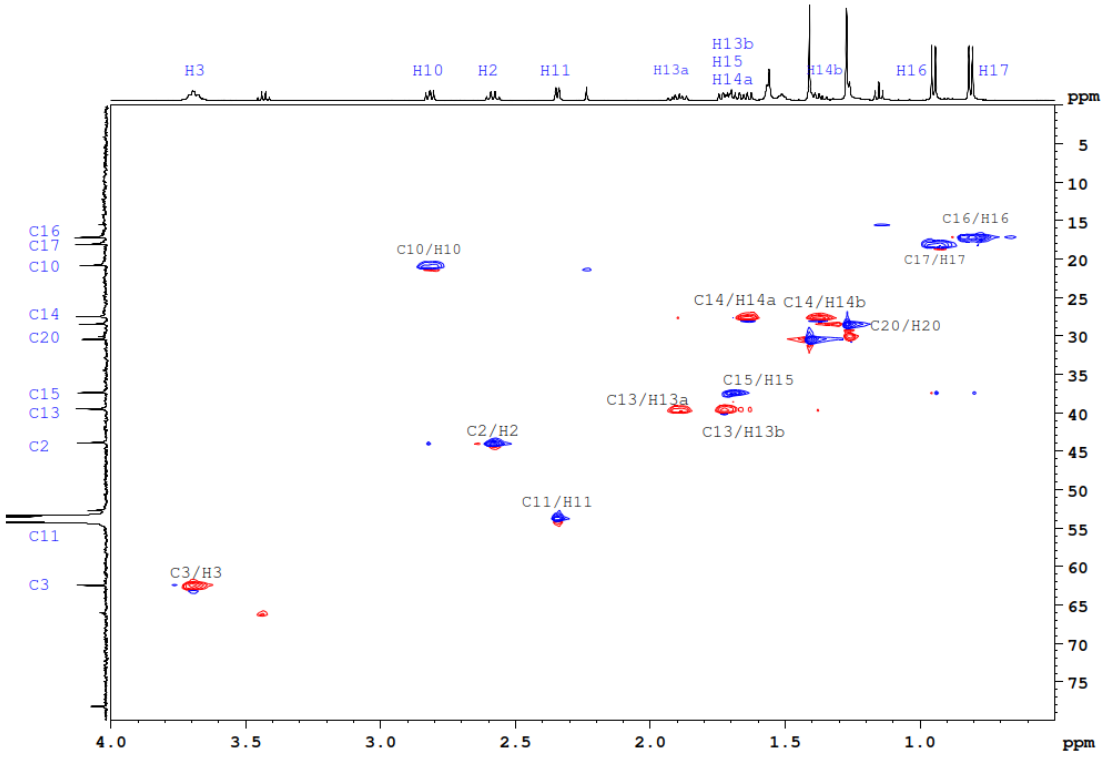


HSQC Spectrum of humilisin E core 2.85

The phase sensitive HSQC spectrum of compound **2.85** was measured at room temperature on a 500 MHz NMR spectrometer by dissolving the compound in deuterated DCM. This spectrum helped us in assignment of the key signals and identifying the carbon-hydrogen connections.

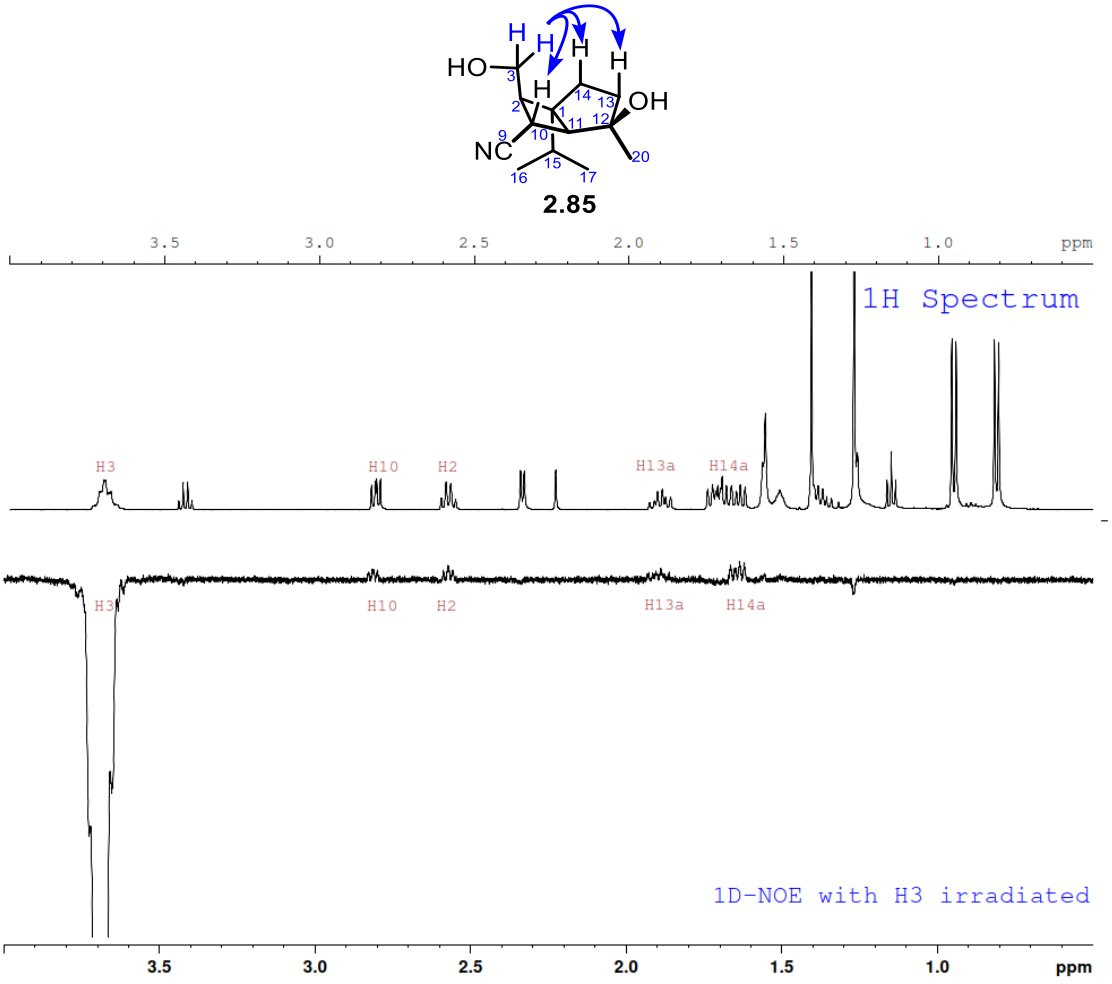


2.85



1D-NOE interactions of humilisin E core 2.85

The relative stereochemistry was determined by selective 1D ^{1}H NMR NOE experiments. Selectively irradiating the H3 protons (which are nearly overlapping) revealed NOE interactions with hydrogens H10, H14 and H13 helping us determine the relative stereochemistry of the cyclized product **2.85**.



4.4 X-ray data

The X-ray structure of epoxide **2.90** was determined by Mr. Anton Bannykh and Prof. Kari Rissanen using the instrument XtaLAB Synergy R diffractometer equipped with Hypix-Arc 100 HPC detector. The data reduction and absorption correction were made by program CrysAlisPro(version 1.171.42.80a, **2023**, Rigaku Oxford Diffraction). The structure was solved by using SHELXT[229] intrinsic phasic method, in OleX 2-1.5[230], and refined with SHELXL[231] least squares method. The structure was drawn with Mercury 2022.3.0 showing thermal ellipsoids at 50% probability level.

4.4.1 Epoxide 2.90

Identification Code	**2.90**
Empirical formula	$C_{13}H_{21}NO_2$
Formula weight	223.31
Temperature/K	120.00(10)
Crystal system	Orthorhombic
Space group	Pbca
a, b, c (Å)	11.7976(3), 9.0605(2), 22.6373(5)
α, β, γ (°)	90, 90, 90
Volume (Å^3)	2419.75(10)
Z	8
ρ_{calc} g/cm^3	1.226
μ/mm^{-1}	0.649
F(000)	976.0
Crystal size/mm^3	0.275 x 0.19 x 0.129

Data collection & Refinement	
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	7.81 to 133.498
Index ranges	-13 ≤ h ≤ 14, -10 ≤ k ≤ 10, -25 ≤ l ≤ 26
Reflections collected	14560
Independent reflections	2146 [R_{int} = 0.0538, R_{sigma} = 0.0360]
Data/restraints/parameters	2146/0/149
Goodness-of-fit on F^2	1.093
Final R indexes [I>=2σ (I)]	R_1 = 0.0806, wR_2 = 0.2372
Final R indexes [all data]	R_1 = 0.0851, wR_2 = 0.2410
Largest diff. peak/hole / e Å^{-3}	0.62/-0.33
Absorption correction	Gaussian mode

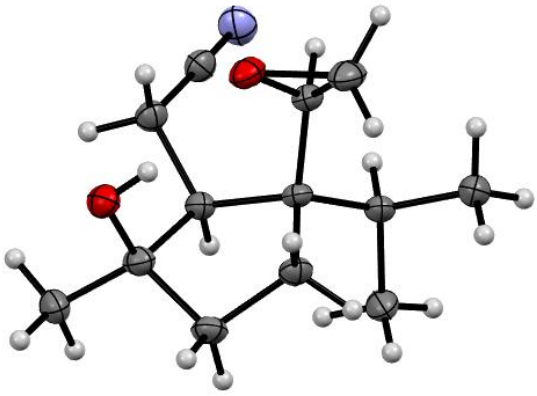


Figure 21: ORTEP-figure of the crystal structure of **2.90**. Single crystal of compound used in X-ray diffraction was obtained by slow evaporation of **2.90** solution in Et_2O-Pentane. The thermal displacement parameters are shown at 50% probability level.

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