STUDIES OF REDUCTIVE LITHIATIONMETHODS FOR THE PREPARATION OF ORGANOLITHIUM COMPOUNDS AND APPLICATIONS OF THE PALLADIUM CATALYZED ZINC-ENE CYCLIZATION

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Studies of Reductive Lithiation Methods for the Preparation of Organolithium Compounds and Applications of the Palladium Catalyzed Zinc-ene Cyclization

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University of Pittsburgh, 2007

There are two major methods of performing radical-anion induced reductive lithiations that result in the cleavage of carbon-heteroatom bonds to produce organolithium compounds. The conventional (PAR) method uses a stoichiometric amount of preformed aromatic radical-anion. The newer catalytic aromatic (CA) method is growing rapidly in popularity and has been claimed to be far more powerful than the PAR method. The CA method uses a large excess of lithium in the presence of a catalytic quantity of the aromatic compound, usually naphthalene or 4,4′-di-*tert*-butylbiphenyl. It is revealed here that a major disadvantage of the CA method is that at any given temperature, the method is far slower than the PAR method. One other disadvantage of the CA method is that it is very wastesful of lithium metal, the most expensive ingredient used in reductive lithiations since the aromatic can easily be recovered and recycled.

A far more surprising and significant result is that *N*-phenylaziridine not only does not require naphthalene as a catalyst during its reductive cleavage but the naphthalene is actually an inhibitor of the reductive lithiation.

In collaboration with others, a Pd-catalyzed Zn-ene cyclization, using allyl phenyl sulfones instead of allyl acetates as precursors of allylzincs, was developed for the preparation of five-membered rings bearing adjacent *cis* vinyl and CH_2ZnEt or CHZnEt groups. Also in collaboration with others, this methodology has been used for the total syntheses of the highly physiologically active prostaglandin (±)-15-deoxy-$\Delta^{12,14}$-PGJ_2 in 13 linear steps in 7.7% overall

yield and it analog 15-deoxy-9,10-*2H*-$\Delta^{12,14}$-$PGJ_{2,}$ and (−)-kainic acid, an extremely neuroexcitatory amino acid that is in great demand for medical research, in sulfone approach by 10 linear steps from commercially available D-serine methyl ester with an overall yield of 11% and in chloride approach by11 linear steps from the same starting material, but with a much higher overall yield of 48%, which is by far the highest of any kainic acid synthesis to date and it can be carried out on the largest scale to date.

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PREFACE

It is with deep appreciation that I thank my mentor, Professor Theodore Cohen, for the guidance, support, encouragement and friendship that he extended to me. It has been for me an invaluable experience to be under his tutelage. I will always remember his unmatched devotion to science, his healthy lifestyle and his confidence in me.

I would like to take this opportunity to extend my gratitude to Professors Kay M. Brummond, Billy W. Day and Irving Wender for serving on my committee. Their willingness to share their expertise and provide valuable advice is greatly appreciated. I am indebted to Dr. Fu-Tyan Lin for training me on NMR spectrometers and providing immeasurable assistance.

I would also like to thank Kai Deng for helping me get accustomed to the laboratory at the beginning of my graduate career and Justin Chalker for his close cooperation on the project of "total synthesis of (-)-kainic acid". I want to thanks Roman Ivanov, Yang Zhao, Jeananne Singletary, Charlie Karcutskie, Brianna Rossiter, Heather Butela, Joseph Whetstone and Dr. Yi-xiong Lei for their help and friendship.

Most importantly, I would like to express my deep love and appreciation to my wife, Yuhuan Chen and my parents, whose constant love, support and understanding have made this possible.

LIST OF ABBREVIATIONS

Ac	acetyl
AIBN	2,2'-azo*bis*isobutyronitrile
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
DBB	4,4'-*tert*-butylbiphenyl
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
Dibal-H	diisobutylaluminum hydride
DIPT	diisopropyl tartrate
DMAN	1-(dimethylamino)-naphthalene
DMI	1,3-dimethylimidazolidin-2-one
DMSO	dimethyl sulfoxide
GC	gas chromatography
HMPA	hexamethylphosphoramide
Im	imidazole
KHMDS	potassium *bis*(trimethylsilyl)amide
LDBB	lithium 4,4'-di-*tert*-butylbiphenylide
LDMAN	lithium 1-(dimethylamino)-naphthalenide
LN	lithium naphthalenide
L-selectride	lithium tri-*sec*-butylborohydride
NaHMDS	sodium *bis*(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
Nu	necleophile
PCC	pyridium chlorochromate
PAR	preformed aromatic radical-anion
PCC	pyridinium chlorochromate
Pf	9-phenylfluorenyl
PMB	*p*-methoxyphenyl
Sia	1,2-dimethylpropyl
TBACl	tetra-*n*-butylammonium chloride
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
Tf	trifluromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TEMPO	tetramethylpiperidinyl-1-oxy
TMEDA	*N,N,N',N*'-tetramethylethylenediamine
TMS	trimethylsilyl

1.0 CHAPTER ONE

The Catalytic Method vs the Use of Preformed Aromatic Radical-anions in the Preparation of Organolithiums by Reductive Lithiation

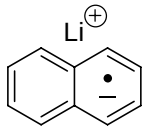
1.1 INTRODUCTION

1.1.1 Background of radical-anions

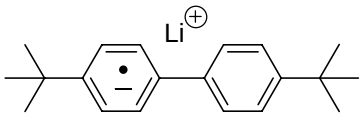
Aromatic radical-anions are formed as a result of the addition of an electron from an alkali metal atom to an aromatic hydrocarbon.[1] The electron donated by the metal is believed to occupy the lowest unoccupied π^* orbital of the aromatic compound.[1]

Several different aromatic radical-anions, such as lithium naphthalenide (LN, **1.1**), lithium 4,4'-di-*tert*-butylbiphenyl (LDBB, **1.2**) and lithium 1-(dimethylamino)-naphthalenide (LDMAN, **1.3**) are currently in use (Scheme 1.1).

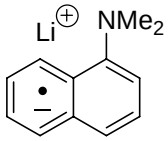
Scheme 1.1 Common aromatic radical-anion reducing agents



1.1
Lithium naphthalenide (LN)



1.2
Lithium 4,4'-di-*tert*-butylbiphenylide (LDBB)



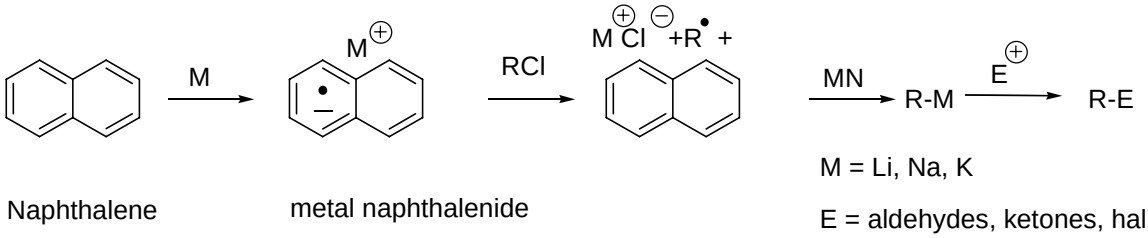
1.3
Lithium 1-(dimethylamino)-naphthalenide (LDMAN)

The aromatic compounds, naphthalene (Np), 4,4'-di-*tert*-butylbiphenyl (DBB) and 1-(dimethylamino)-naphthanlene (DMAN), usually serve as a "storehouse" for an electron. In the presence of a receptor, an electron is transferred to the receptor, which then undergoes a variety of product-forming transformations depending on its nature.

The rate of formation of aromatic radical-anions is dependent on the following factors: metal, hydrocarbon, temperature, and solvent. Screttas[1] was the first to report aromatic radical-anions formed from lithium and naphthalene in 1972. Naphthalene acts as an acceptor of lithium's electron, and the resulting radical-anion**,** LN (**1.1,** Scheme 1.2), very rapidly reduces an alkyl halide to generate an alkyl radical, which then accepts another electron from LN to form an

alkyllithium.[2] Alkylsodiums (RNa) and alkylpotassiums (RK) can also be generated by this reductive reaction,[3] but they are far too reactive to wait to be trapped with electrophiles and are immediately protonated by solvents or starting materials to give RH, along with a considerable amount of naphthalene-derived by-products. Using Li as the reductant gives the more stable alkyllithium (RLi), which then can further react with electrophiles.

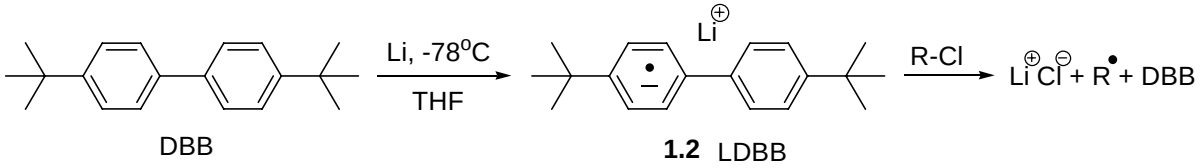
Scheme 1.2 Reductive metallation of alkyl chlorides with metal naphthalenides



There were problems with the use of LN, mainly arising from the susceptibility of naphthalene or its radical-anion to attack by the intermediate radical or the newly formed organolithium. To solve this problem, another aromatic radical-anion LDBB (**1.2**), was introduced in place of LN by Freeman.[3]

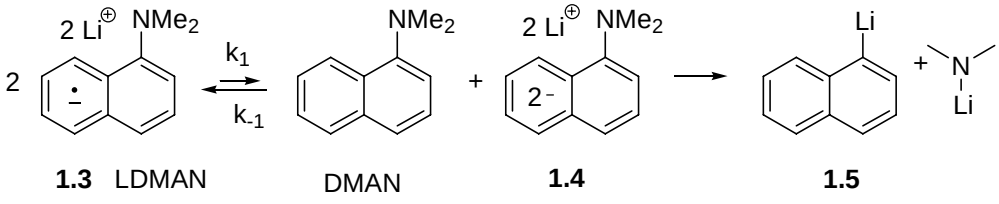
LDBB **1.2**, formed from DBB which has bulky *t*-butyl groups that effectively prevent its participation in the formation of by-products while allowing it to take part in single electron reductions, is a more powerful electron donor than LN, thus allowing reductive lithiation to be performed at a lower temperature or in a shorter time. LDBB in THF at −78 ^{o}C promotes the formation of >90% yields of carboxylic acids, derived from reductive lithiation of alkyl chlorides followed by addition of CO_2.[3] The reaction is rapid at −78 ^{o}C, and even at −100 ^{o}C, lessening even further the potential by-product problems. DBB can typically be recovered in 97% yield from these reactions.

Scheme 1.3 Formation of LDBB and its use in reductive lithiation



In 1980, a report from Cohen's laboratory indicated a solution to another problem, removal of the aromatic hydrocarbon after the reductive lithiation.[4] When lithium 1-(dimethylamino)-naphthalenide (LDMAN **1.3**) was used as the reducing agent, the basic aromatic byproduct DMAN could be removed and recovered by washing the reaction mixture with dilute acid. An additional advantage of the use of LDMAN is that it can be used in solvents other than THF, the solvent universally used in synthetic procedures involving aromatic lithium radical-anions.[5] However, reactions in the presence of LDMAN must take place below –45 °C, since above this temperature the radical-anion LDMAN decomposes to give 1-lithionaphthalene. Because of the great instability of aryl radicals, it was thought that the decomposition of LDMAN at this low temperature was probably not due to the homolytic cleavage of the bond between the ring carbon atom and the heteroatom, the usual mode in radical-anion decompositions.[6] It was postulated instead that the aromatic dianion **1.4** was generated in THF in an unfavorable equilibrium with the radical-anion **1.3,** which then was converted to the relatively more stable napthyl anion **1.5** and the dimethylamido anion (Scheme 1.4).

Scheme 1.4 Equilibrium between LDMAN and aromatic dianion 1.4 and the latter's decomposition



Aromatic radical-anions are normally prepared in THF. A variety of solvents (diethylether, benzene and dimethylether) other than THF were studied to find a more suitable

solvent. A low yield of aromatic radical-anion LDBB is obtained in dimethyl ether, but LDMAN can be obtained in as high as 80% yield at –70 ^{o}C. Little or none of the aromatic radical-anions, LDBB or LDMAN, were obtained in diethyl ether or benzene.

1.1.2 Background of reductive lithiation to produce organolithium compounds

Since its introduction in 1978,[7,8] reductive lithiation of phenyl thioethers using aromatic radical-anions has been demonstrated to be one of the most versatile methods known for generating organolithiums.[9,10] A number of other leaving groups, such as halides,[11] sulfones,[12] sulfates,[13] nitriles,[14] selenides,[15] allylic and benzylic ethers,[16,17] vinyl sulfides,[18] amines,[19] and acetals,[20] have also been used but they have been considerably less versatile than the phenylthio group. The superior versatility of compounds containing the phenylthio group as substrates for reductive lithiation arises from their almost unique ease of construction, particularly by methods involving C-C bond formation but also by the ability of the phenylthio group to enter a molecule as a nucleophile, electrophile, or radical. In addition, the substrates are almost always able to withstand the powerful nucleophiles/bases that are present in the reductive lithiation conditions. For example, alkyl halides, sulfates, sulfonates, etc. are subject to ready nucleophilic substitution, but most seriously to base induced elimination, thus limiting their use largely to the preparation of primary alkyllithiums unless an aryl or vinyl group is present to increase the rate of the reductive lithiation and favor it over competing processes.

An important advantage of reductive lithiation is that unlike the most conventional method of organolithium preparation, removal of an electrophile such as H^+, I^+, R_3Sn^+, etc. by another organolithium, it is often the case that the less stable the organolithium, the greater the ease of its generation by reductive lithiation. The reason is due to the mechanism which involves

the transfer of an electron from the aromatic radical-anion to the substrate followed by a homolytic cleavage of the bond between the organic moiety and the leaving group.[21] Since this step is rate determining, the rate of the reaction is mainly determined by the stability of the intermediate radical, rather than that of the carbanion, to which the radical is rapidly reduced. Thus, it is an extremely general method of organolithium production especially since phenyl thioethers are available by a wide variety of synthetic methods. Another considerable advantage is that the aromatic and the thiophenol are recoverable and thus a stoichiometric amount of lithium metal is the only reagent that is destroyed, making this the most economical method available since lithium is far less expensive than any organic form of lithium.

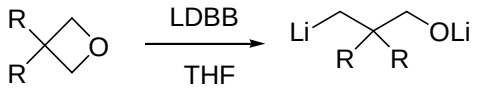
In the earliest reports of the reductive lithiation of phenyl thioethers, a stoichiometric quantity of lithium naphthalenide was used. However, in several cases, a substoichiometric quantity of naphthalene was used along with a stoichiometric quantity of lithium metal. The latter conditions were successful in reducing the amount of naphthalene that had to be removed from the desired product but the reductive lithiations required higher temperatures and longer reaction times.

Because LDMAN **1.3** decomposes to 1-lithionaphthalene **1.5** above –45 °C,[22] a "catalytic method" was devised which allowed reactions with LDMAN to be performed with good results at higher temperatures. Since DMAN and Li metal react over a period of hours to produce LDMAN while most reductive lithiations are extremely rapid, it was reasoned that DMAN would act as a conduit for electrons to the substrate undergoing reductive lithiation and that the concentration of the radical-anion **1.3** would be extremely low until the reductive lithiation is complete. Thus, the equilibrium in Scheme 1.4 would be driven even further to the left, resulting in a negligible concentration of the unstable dianion **1.4** and consequently in a very slow

decomposition of LDMAN. This reasoning is apparently correct as evidenced by the fact that the green-black color of LDMAN only became evident when all of the substrate thioether had reacted and by the ability, using the catalytic method, of performing reductive lithiations above –45 °C.

The success of the next published use of the catalytic method was more mixed. During a study in this laboratory of the reductive lithiation, using lithium 4,4'-di-*tert*-butylbiphenylide (LDBB), one of the most common aromatic radical-anions, of oxetanes **1.6** to produce organolithiums **1.7** bearing an oxyanionic group (Scheme 1.5), the catalytic aromatic method, as expected from the above results and discussion, took far longer than the method using preformed aromatic radical-anion at the same temperature.[23] However, the result led to just as a favorable outcome with **1.6** (R=Me) but with **1.6** (R=H), the production of **1.7** (R=H) was far less efficient, giving a lower yield of dianion than when preformed aromatic radical-anion was used and leading to the production of considerable 1-propanol. Undoubtedly, the propanol resulted when the intermediate anion **1.7** (R=H), during the long reaction time, removed a proton from the 2-position of the sterically unhindered oxetane, a known type of proton loss for oxetanes.[24] The steric hindrance provided by the methyl groups of **1.6** (R=Me) apparently saved it from this fate.

Scheme 1.5 Reductive lithiation of oxetanes with preformed LDBB



1.6 **1.7**

1.1.3 Using preformed aromatic radical-anions vs catalytic amounts of aromatic compounds in reductive lithiation

More recently, Yus and his co-workers introduced the use of the catalytic aromatic method (which we abbreviate CA method), in a mode somewhat different than that used previously, for the reductive lithiation of some primary alkyl chlorides and two alkyl phenyl sulfides.[25] In their work,[26,27,28] a solution of the substrate to be reduced in THF is mixed with from 1 to 5 mole % of the aromatic, usually naphthalene or 4,4'-di-*tert*-butylbiphenyl (DBB), and a large excess of lithium powder, usually a 8-14 eq. excess. In their extensive and impressive publications on this topic, they have demonstrated that a large variety of organic compounds can be reductively lithiated, and that this method eases the separation of the aromatic from the reaction product.

In a number of these papers, the claim is made that this version of the catalytic aromatic method, in which the radical-anion is continually generated and rapidly destroyed by electron transfer to the substrate, is far more powerful than the use of a stoichiometric amount of preformed aromatic radical-anion (PAR).[29,30,31] For example, “above all, the catalytic version is far more reactive, so it is possible to perform new lithiation reactions, which do not work when a lithiation-arene is used as lithiation agent” and "in the catalytic version, yields are better, reaction times are far shorter, the reactions are very clean.”

This assertion seemed unlikely to us based on the experimental results enumerated above and some other results from our laboratory, heretofore only reported in a thesis (see below). The theoretical basis also appears inconsistent with our experience that radical-anion formation is virtually always slower than the reductive lithiation, as mentioned above. Thus, in most cases the rate-determining step for the reductive lithiation would be the transfer of an electron from the surface of the metal to the aromatic catalyst. The net result would be that, as found in the

published work described above, the process of reductive lithiation would be slower at any given temperature than the process using preformed radical-anion. As again indicated above, such longer reaction times can in some cases translate into destruction of some organolithium compounds. Of course, damage is minimized in the Yus protocol in which the radical-anion formation is accelerated by supplying the lithium as a powder instead of larger chunks with less surface area and by the use of a very large excess of lithium. Nonetheless, the rate-determining step is still the electron transfer to the aromatic catalyst as evidenced by the fact that, as in the use of the catalytic method with LDMAN mentioned above, the color of the radical-anion does not appear until all of the reduction substrate has been consumed.[32]

The mechanistic explanation suggested to account for the purported superiority of the CA method is that there is a greater concentration of aromatic dianion during reduction by the CA method than that by the PAR method and that the dianion is expected to be a more powerful reducing agent. However, it seems to us that there should be a far *lower* concentration of aromatic dianion in the CA method than in the PAR method for the reasons in our earlier paper that are outlined in the discussion above pertaining to Scheme 1.4. For example, in that scheme, the concentration of dianion **1.4** is given by the expression: [**1.4**] = K [**1.3**]^2/[**DMAN**] where **1.3** is the radical-anion and **1.4** is the dianion. Thus, in the case of preformed aromatic radical-anion, the concentration of dianion is at the maximum since virtually all of the aromatic is in the form of the radical-anion and the concentration of neutral aromatic is negligible. On the other hand, in the CA method, the concentration of dianion is minimal since the rapid transfer of an electron from the slowly formed radical-anion to the substrate maintains a negligible concentration of aromatic radical-anion and virtually all of the aromatic is in the neutral form; this is clearly

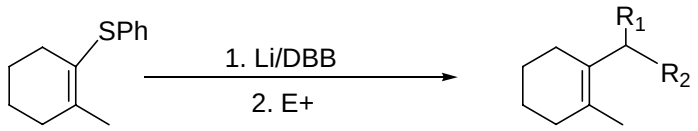
indicated by the fact that the color of the radical-anion appears only after the substrate has been consumed.

Presumably, these claims of the greater power of the CA method are at least partly responsible for the choice that most groups now make to adopt it in new work as indicated in recent reviews of Yus.[33] On the other hand, if this superiority is found to be unsubstantiated, the choice as to which of the two modes of reductive lithiation is appropriate in a given case should be made on other grounds. The present study was performed to directly compare the PAR and CA methods by conducting reactions using both methods to determine the relative advantages of each.

1.1.4 Reductive lithiation of 2-methyl-1-(phenylthio)cyclohexene

There is already evidence for decreased yields using the catalytic method rather than the PAR method in the reductive lithiation of 2-methyl-1-(phenylthio)cyclohexene **1.8,** followed by quenching with various electrophiles, as reported in the thesis of Mary Dosch Doubleday (Scheme 1.6 and Table 1.1).[34] The use of a slightly greater than stoichiometric amount of LDBB gave yields of 80%, 71%, and 71%, respectively, of products **1.9** when the vinyllithium was quenched with cyclohexanecarboxaldehyde, *n*-hexyl iodide, and allyl bromide. When the same reaction was performed using a slight excess of lithium and only 20% of the stoichiometric amount of DBB, the yields were 54%, 50%, and 52%, respectively. Thus, in this case as in those described in the introduction, preformed aromatic radical-anion gave better yields than the use of the same quantity of Li but a considerably sub-stoichiometric quantity of the aromatic hydrocarbon.

Scheme 1.6 Reductive lithiation of 2-methyl-1-(phenylthio)cyclohexene



1.8 **1.9**

Table 1.1 Reductive lithiation of 2-methyl-1-(phenylthio)cyclohexene

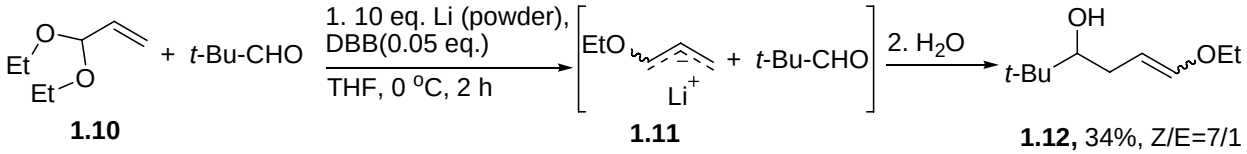
				Yield (%) of **1.9**	
Entry	E^+	R_1	R_2	PAR	Catalytic
1	*c*-$C_6H_{11}CHO$	OH	*c*-C_6H_{11}	80	54
2	$C_6H_{13}I$	H	C_5H_{11}	71	50
3	CH_2=$CHCH_2Br$	H	CH=CH_2	71	52

1.2 RESULTS AND DISCUSSION

1.2.1 Reductive lithiation of acrolein diethyl acetal

In 1994, a report appeared in which acrolein diethyl acetal **1.10** was reductively lithiated via the CA method at 0 °C in the presence of various carbonyl compounds that captured the resulting allylic lithioether (the Barbier method[35]) to give 34 to 40% yields of alcohols **1.12**. Scheme 1.7 shows one example. Significantly, it was stated that no reduction occurred at –40 °C and that if the carbonyl compound were added after the reductive lithiation, the yields were greatly reduced due to decomposition of the allyl anionic intermediate.

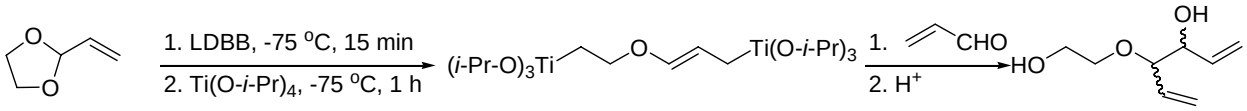
Scheme 1.7 Reductive lithiation of acrolein diethyl acetal with catalytic DBB



1.10 **1.11** **1.12,** 34%, Z/E=7/1

This caught our attention for two cogent reasons. First, a previous publication from our laboratory had reported the reductive lithiation of an analogous acrolein acetal **1.13** at -75 °C using the PAR method to deliver a far higher yield of trapped product **1.15** (Scheme 1.8). Second, the anions of allyl ethers such at **1.11** are known to undergo the Wittig rearrangement, at temperatures as low as –25 °C,[36] the probable cause of the reported instability of **1.12**, thus making it imperative to work at a lower temperature; a comparison of Schemes 1.7 and 1.8 made it appear that this would be possible only by using the PAR method, as discussed above.

Scheme 1.8 Reductive lithiation of analogous acrolein acetal with preformed LDBB



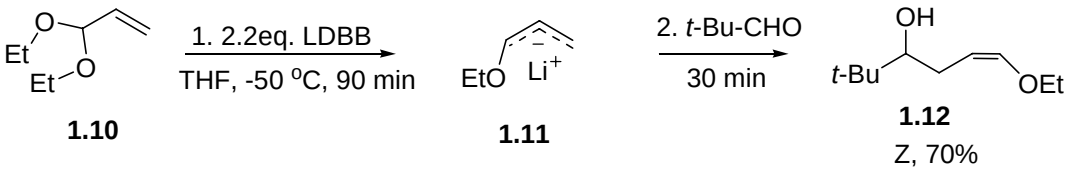
1.13 **1.14** **1.15**

50:50, 70%

Thus, the substrate **1.10** was subjected to the PAR conditions. It was found (Scheme 1.9) that the reductive cleavage occurred smoothly at –50 °C to provide the anion **1.12** which was trapped with the same aldehyde to provide a 70% yield of **1.11** with higher stereoselectivity than that reported using the CA method under the required Barbier conditions and higher temperature.[37] Attempts to cleave **1.10** with Li powder in the absence of DBB failed, indicating as expected that the aromatic indeed acts as a catalyst in this reductive lithiation. This case is an excellent demonstration that in cases in which the carbanion being produced by reductive lithiation is unstable, the use of preformed aromatic radical-anion is preferable to the catalytic method even with a large excess of lithium powder (compare Schemes 1.7 and 1.9). It seems

likely that a more recent reductive lithiation of a related acetal of acrolein[38] using the CA method could have also benefited by the use of a stoichiometric quantity of preformed LDBB.

Scheme 1.9 Reductive lithiation of acrolein diethyl acetal with preformed LDBB



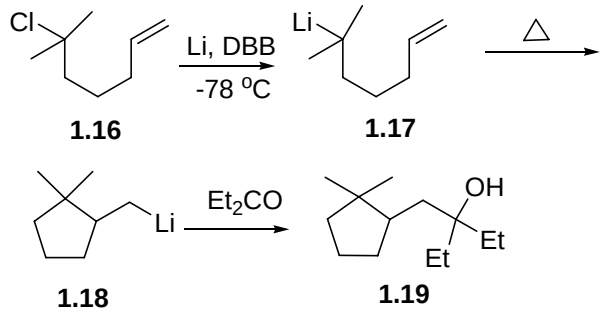
1.10 **1.11** **1.12**

Z, 70%

1.2.2 Reductive lithiation of 6-chloro-6-methyl-1-heptene

In 2002, a report appeared that the reductive lithiation of 6-chloro-6-methyl-1-heptene **1.16,** using the CA method at −78 °C, gave an anion that cyclized at higher temperatures but that the cyclization product could be trapped by 2-pentanone only under very special conditions, namely the Barbier mode at 0 °C (76% yield) or in a two-step process at −30 °C (75% yield).[39] The anion **1.17** was reported to be unstable at −78 °C.

Scheme 1.10 Reductive lithiation of 6-chloro-6-methyl-1-heptene with catalytic DBB

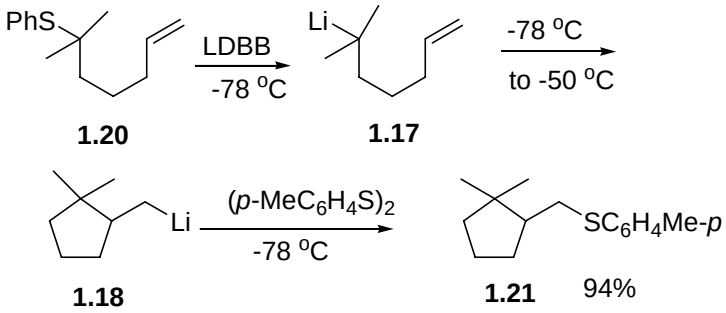


1.16 **1.17**

1.18 **1.19**

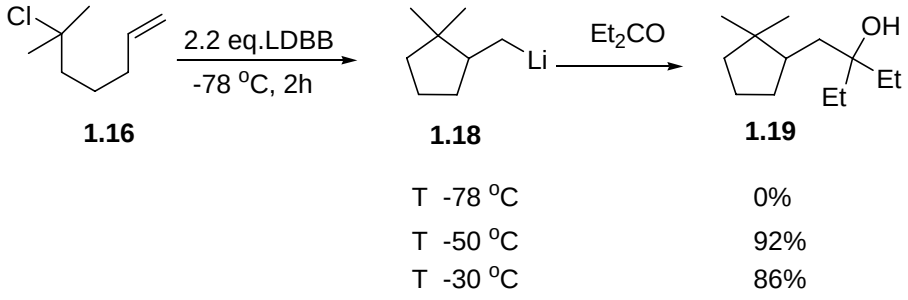
This report surprised us since it was found in our lab that reductive lithiation of the phenylthio analogue **1.20** of **1.16** at −78 °C, after cyclization by warming **1.17** to −50 °C, occurred smoothly under the usual PAR conditions to provide a 94% yield of trapped product **1.21**.[40]

Scheme 1.11 Reductive lithiation of 2-methyl-2-(6-heptenyl)phenylsulfane



In order to make a direct comparison with the published CA method, the tertiary alkyl chloride **1.16** was treated with LDBB at three temperatures and the cyclized organolithium **1.18** was treated with 3-pentanone to provide the alcohol **1.19**. From the results in Scheme 1.12, it is clear that the reductive lithiation product **1.17** of **1.16** does not cyclize at −78 °C but that it cyclizes smoothly at −50 °C to give an excellent yield of trapped product. In order to test the possibility that higher temperatures would cause destruction of the intermediate organolithiums, the experiment was repeated at −30 °C and the yield was found to drop slightly, indicating that lower temperatures are preferred for these reductive lithiations. These are generally better attainable by the PAR mode as discussed above. Once again, the importance of the presence of DBB was tested by performing the reductive lithiation at −30 °C without DBB and the yield merely fell to 53%, thus indicating that in this particular case, the catalyst is not absolutely essential.

Scheme 1.12 Reductive lithiation of 6-chloro-6-methyl-1-heptene with preformed LDBB



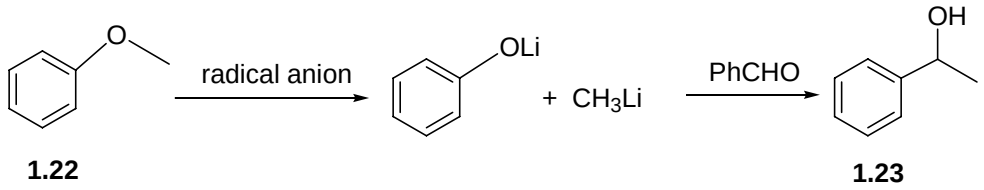
Unfortunately, this apparent comparison of the CA and PAR methods became somewhat less meaningful when a more recent paper by the Spanish group revealed that the structure **1.16** in their preliminary communication, was in error and that the real compound used was 6-chloro-6-ethyl-1-octene (terminal ethyl groups rather than methyls). Nevertheless, the results in Scheme 1.12 do indicate that tertiary organolithiums can be readily generated by reductive lithiation of the chloride using the PAR method, just as had occurred with the corresponding phenyl thioether, at very low temperatures and that this carbanion cyclizes at −50 °C to give an excellent yield of cyclized organolithium. It is also clear (Scheme 1.11) that the tertiary carbanion is not unstable at −78 °C as the corresponding tertiary carbanion from CA reductive lithiation of 6-chloro-6-ethyl-1-octene is reported to be. It seems likely that the latter carbanion does not necessarily remove a proton from the THF at that temperature as suggested, but that the hindered carbanion abstracts an α-proton from the trapping agent, 3-pentanone, instead; the alternative reaction of the carbanion with the carbonyl group would yield a very highly congested di-tertiary C-C bond.

1.2.3 Reductive lithiation of anisole

Normal dialkyl ethers are in general inactive to lithium in the presence of arene; indeed some of them (THF) are widely used as solvents in lithiation reactions. A special case is the lithiation of a phenyl alkyl ether, namely anisole, which is also resistant to Li metal under non-forcing conditions. However, a report occurred that the reductive cleavage of anisole **1.22** at the alkyl C-O bond at room temperature using CA conditions yielded 80% of **1.23**, the product of capture of the methyllithium by benzaldehyde.[41] This paper reported that 75% cleavage of anisole was observed using Li dispersion with a stoichiometric amount of DBB for reductive lithiation after

0.5 h at RT. However, 92% conversion was obtained under the same reaction conditions in the case in which a catalytic amount of the DBB and a 7-fold excess of Li were used.

Scheme 1.13 Reductive lithiation of anisole



1.22 **1.23**

This paper indicated that PAR conditions were somewhat inferior, but the comparison was not fair for two reasons. First, they used a large excess (7-fold) of lithium in the catalytic example. Second, room temperature was apparently used but it has been reported that LDBB is unstable above 0 °C.[42]

The authors suggested that in the catalytic version an arene-dianion is involved as a reducing agent instead of the corresponding radical-anion, which is the species that takes part in the stoichiometric version. However, as mentioned above, the equilibrium established with the aromatic electron carrier does not favor the formation of the dianion at a low concentration of the radical monoanion that must exist in the catalytic method.

Scheme 1.14 Equilibrium of radical-anion and dianion

$$ArH + Li \longrightarrow ArH^{\bullet-}Li^{+} \quad (1) \qquad 2ArH^{\bullet-}Li^{+} \rightleftharpoons ArH^{2-}2Li^{+} + ArH \quad (2)$$

With a low concentration of the monoanion, the equilibrium (2) in Scheme 1.14 should be driven to the left. Excess lithium might produce monoanion more rapidly, consequently driving the equilibrium (2) in Scheme 1.14 to the right, to produce more dianion. However, the generally faster process of reductive lithiation will continue to deplete concentrations of monoanion and, by doing so, decrease the concentration of the dianion. Furthermore, this paper

states that in their catalytic method, the intense blue green color of the radical-anion does not appear until after the reductive lithiation is complete. This observation indicates that there was a low concentration of radical monoanion, and consequently there must have been a low concentration of dianion during the process. This contradicts Yus's claim that the dianion is responsible for the purported superiority of the CA method.

We therefore, undertook a comparison of the two methods at 0 °C for 2 hours. The results were striking. Because LDBB is not stable above 0 ^{o}C, it is impossible to compare the PAR method and catalytic method for the reductive lithiation of anisole at room temperature. The CA method (same conditions as above but at 0 °C) yielded 30% of **1.23** while the PAR method provided 87% of **1.23** during the same time period (Table 1.2). Using 14 equivalents of Li but no DBB gave no product, indicating that the DBB is indeed a catalyst in this case. Thus, the reaction is clearly faster using preformed stoichiometric LDBB than using the catalytic method even with the use of a large excess of the metal. These results strongly suggest that the PAR method is superior to the catalytic method in reductive lithiation of anisole.

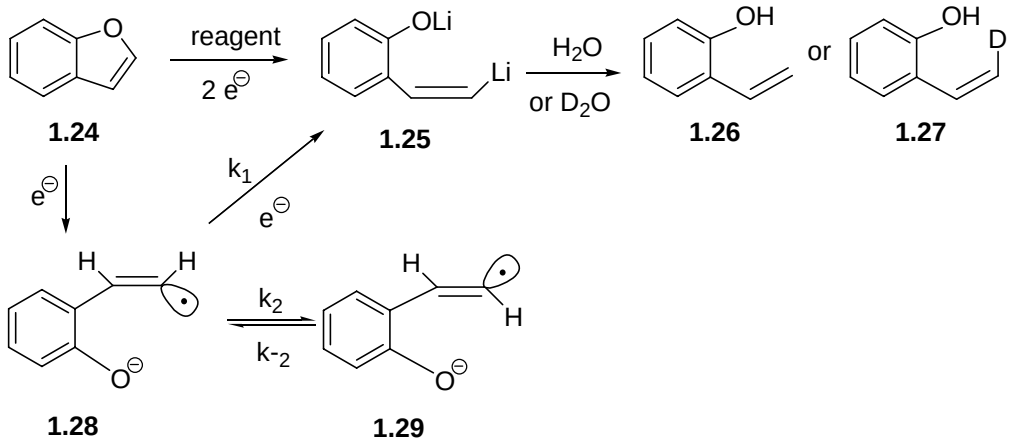
Table 1.2 Reductive lithiation of anisole

Entry	Method	Reagent	T (^{o}C)	Time	Yield (%) of **1.23**
1	CA	14 eq Li (dis.), 0.05 eq. DBB	RT	1.5 h	80
2	CA	14 eq Li (dis.), 0.05 eq. DBB	0 ^{o}C	2 h	30
3	PAR	2.0 eq. LDBB	0 ^{o}C	2 h	87
4		14 eq Li (dis.)	0 ^{o}C	2 h	0

1.2.4 Reductive lithiation of 2,3-benzofuran

The reductive lithiation of 2,3-benzofuran **1.24** with an excess of lithium in the presence of DBB was reported to give the result shown in Scheme 1.15.[43] The cleavage of the sp^2 C-O bond was stereospecific. Only the corresponding product **1.26** or **1.27** was obtained. The mechanistic explanation for the stereochemistry was that after the first C-O cleavage the reaction gave a *cis*-vinyl radical **1.28,** which has two possibilities of evolving depending on its stability: the capture of a second electron to give the dianion **1.25** or the isomerization to *trans*-radical-anion **1.29**. In Scheme 1.15, $k_1 >> k_2$, so the capture of a second electron to give the dianion **1.25** is much faster than the isomerization to the *trans*-radical-anion **1.29**. Thus, only *cis*-product was obtained. Another possible pathway, not discussed in the paper, involves only a dianion intermediate instead of a radical intermediate. In this pathway, **1.24** picks up two electrons directly to form dianion **1.25**, which, being a vinyl anion, would have a very low rate of inversion from the *cis*- to the *trans*- conformation.[44]

Scheme 1.15 Reductive lithiation of 2,3-benzofuran and its mechanism



It occurred to us that the LUMO of **1.24** may be lower in energy than that of DBB and that the electron transfer might occur directly from the Li metal to **1.24**, thus obviating the

requirement for the purported catalyst, DBB. Indeed, when the reported conditions were duplicated, but in the absence of DBB, an 91% yield of **1.26** was obtained, very close to the yield in the literature (93%) with the CA method (Table 1.3, entry 1). When the resulting anion **1.25** was quenched with D_2O, deuterated product **1.27** was obtained with a yield of 87%. It is thus doubtful that DBB serves as a catalyst when the CA method is attempted.

Table 1.3 Reductive lithiation of 2,3-benzofuran with Li metal

Entry	Reagent	T (^oC)	Time	Yield (%) of **1.26**	Yield (%) of **1.27**
1	10 eq. Li (powder), 0.1 eq. DBB	0 ^oC	45 min	93	94
2	10 eq. Li (dispersion)	0 ^oC	45 min	91	87

Doubleday[45] found evidence concerning the relative rates of isomerization and reduction of some vinyl radicals. Some inversion occurred in the reductive lithiation of the propenyl phenyl sulfides (**1.30**, R = CH_3, Scheme 1.16 and Table 1.4). Regardless of whether the starting material was pure *trans*-**1.30a** or pure *cis*-**1.30b**, a mixture of *trans*-**1.33a** and *cis*-**1.33b** was always obtained. This indicates that vinyl radicals **1.31a** and **1.31b** invert more rapidly that they capture a second electron to produce the dianions **1.32a** and **1.32b,** which would not suffer inversion. More evidence was found in the reductive lithiation of β-styryl phenyl sulfide (**1.30**, R = Ph), in which when pure *trans*-isomer was reduced and captured with electrophile, the ratio of *trans* and *cis* products was almost to 1:1. It would be expected that the *cis*-isomer of β-styryl phenyl sulfide would proceed via the same pathway to also give vinyl radical intermediates and therefore a mixture of *trans* and *cis* products after quenching with an electrophile. However,

unlike the *trans* isomer, there was no significant loss in configuration; the product contained 97-99% of the *cis*-isomer.

Scheme 1.16 Lithiation of vinyl sulfides

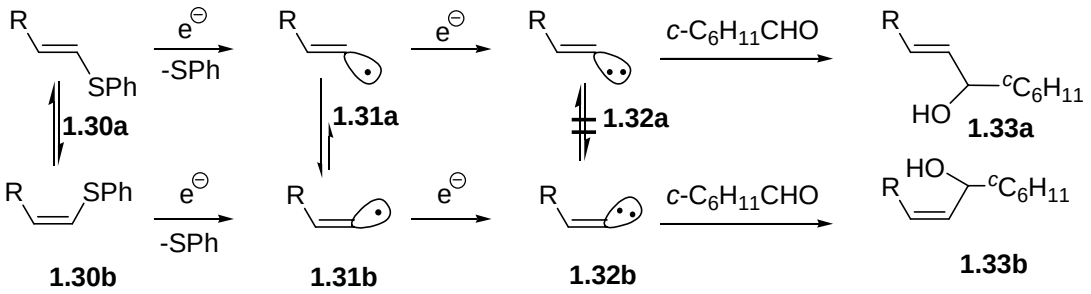


Table 1.4 Lithiation of vinyl sulfides

Starting material		**1.33a**	**1.33b**
R=CH_3	*trans* (**1.30a**)	72%	28%
R=CH_3	*cis* (**1.30b**)	45%	55%
R=Ph	*trans* (**1.30a**)	57%	43%
R=Ph	*cis* (**1.30b**)	1-3%	97-99%

A likely explaination is that in the styryl case, the equilibrium between the *trans* (**1.31a**) and the *cis* (**1.31b**) strongly favors the latter. Thus, once the cis radical is formed, it can not equilibrate to the *trans* and ends up as the *cis* anion. Indeed, recent calculations suggest that the *cis* configuration is thermodynamically more stable ($\Delta G \geq 0.80$ Kcal/mol) than the *trans* configuration for the β-styryl radical.[46]

Scheme 1.17 Isomerization of β-styryl radical

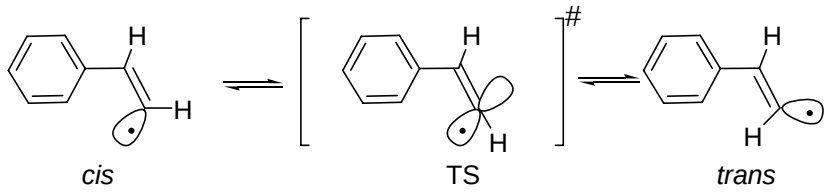


Table 1.5 Calculations of β-styryl radical

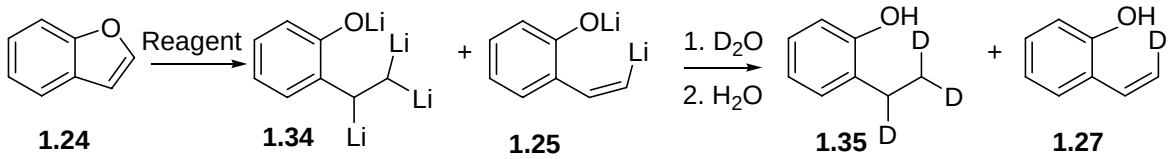
	6-31+G* B3LYP				6-311+G* B3LYP		
	ΔE	ΔH(298K)	ΔG(298K)		ΔE	ΔH(298K)	ΔG(298K)
cis->*trans*-	1.09	1.12	0.88	*cis*->*trans*-	1.07	1.11	0.80
cis->TS	3.61	3.57	3.59	*cis*->TS	3.48	3.43	3.49

It is therefore possible that the reductive lithiation of benzofuran by Yus yields the *cis* radical that remains *cis* until reduced to the carbanion, not because the reduction is faster than the isomerization of the *cis*- to the *trans*-styryl radical, but because the *cis*-styryl radical is thermodynamically more stable that the *trans*-styryl radical. However, the same stereochemical result would occur if the C-O bond cleavage occurs via the aromatic dianion. It may be that the weaker C-S bond would cleave at the radical-anion stage whereas the C-O bond would require the greater driving force of the higher energy dianion.

1.2.5 Generation of a trilithioalkyl arene in the reductive lithiation of 2,3-benzofuran

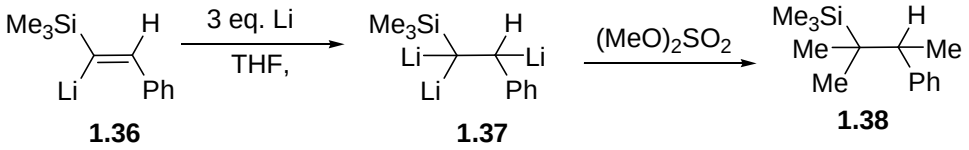
During the study of the reductive lithiation of 2,3-benzofuran when reducing agent LDBB was used, a trilithioalkylarene **1.34**, was produced as revealed by the deuteriation product **1.35**, which was obtained in 70% of yield after a separation in which the OLi group was converted to OH.

Scheme 1.18 Reductive lithiation of 2,3-benzofuran 1.24 with excess reducing agent: generation of a polylithio compound



Interestingly, the only other 1,1,2-trilithio compound **1.37** that we have been able to locate (Scheme 1.19)[47] is generated by lithiation of vinyllithium **1.36** that is remarkably analogous to **1.25** in that it too is a substituted β-lithiostyrene. Despite the presence of an anion-stablizing trimethylsilyl group in **1.37**, it appears to be far more labile than **1.34**. When the lithiation of **1.36**, was performed in THF, the yield of **1.38**, the methylation product of **1.37**, was only 3%, the major product arising from replacement of one of the terminal lithium atoms with an H, presumably from the solvent. However, when the solvent was perdeuterio THF and precautions were taken to maintain a temperature of –90 °C throughout the whole operation, the yield of **1.38** rose to 22%.

Scheme 1.19 The addition of Li metal to a vinyl lithium



1,1,2-Trilithio compound **1.34** could not be obtained from reductive lithiation of **1.24** by Li powder itself. Only intermediate **1.25** was obtained in this lithiation to give deuterated product **1.27** (Table 1.7, entry 3). 1,1,2-Trilithio compound **1.34** can be obtained in a lower yield (21%) at a higher temperature (0 °C) in the reductive lithiation of **1.24** when DBB is present (entry 4). The yield of 1,1,2-trilithio compound **1.34** decreased to 21% because of Schlenk dimerization,[48] in which radical dimerization of **1.28** occurred, and probably because the unstable 1,1,2-trilithio compound **1.34** decomposed rapidly at 0 °C. After the vinyllithium **1.25**

formed, it reacted further with 2 eq. of LDBB to generate 1,1,2-trilithio compound **1.34**, providing **1.35** in 60% yield after quenching with deuterium oxide (entry 5).

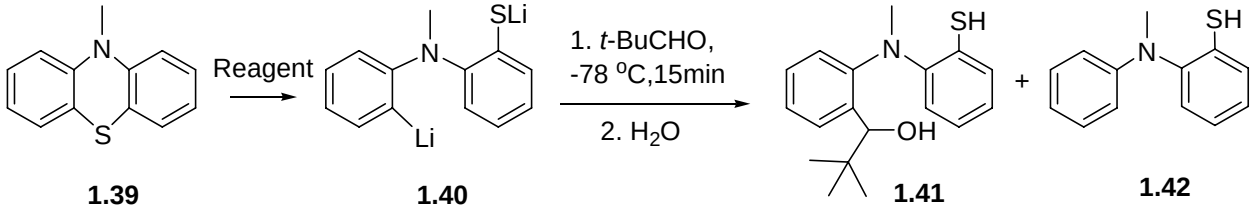
Table 1.6 Reductive lithiation of 2,3-benzofuran with excess reducing agent: generation of polylithio compounds

Entry	Reagent	T (^{o}C)	Time	Yield (%) of **1.35 : 1.27**
1	10 eq. Li, 2 eq. DBB	−78	2 h	73 : 0
2	4 eq. LDBB	−78	1.5 h	70 : 0
3	10 eq. Li	−78	6 h	0 : 50
4	10 eq. Li, 2 eq. DBB	0	2 h	21 : 0
5	2 eq. LDBB, 1 h; then 2 eq. LDBB	−78	6 h	60 : 0

1.2.6 Reductive lithiation of 10-methylphenothiazine

The cleavage of a C-S bond in the presence of arene has been used to generate organolithium compounds by S-Li exchange. Yus[49] has reported that the reaction of phenothiazine **1.39** with Li and a catalytic amount of DBB (CA method) in THF at −78 ^{o}C gave the corresponding intermediate dianion **1.40**. Presumably because the C-S bond is weaker than the C-N bond, it was broken first. In this report, when **1.40** was quenched with the electrophile trimethylacetaldehyde, at the same temperature, it led to the thiol **1.41** in 25% yield. Again, the PAR method was applied to the reductive lithiation of **1.39** in order to determine whether it is superior to the CA method in this case as well.

Scheme 1.20 Reductive lithiation of 10-methylphenothiazine



1.39 **1.40** **1.41** **1.42**

Table 1.7 Reductive lithiation of 10-methylphenothiazine

Entry	Method	Reagent	T (°C)	Time	Product	Yield (%)
1	CA	10 eq. Li (powder), 0.075 eq DBB	−78	45 min	**1.41**	25[49]
2	PAR	2.2 eq LDBB	−78	45 min	**1.41** : **1.42**	33:41
3		10 eq. Li (dispersion)	−78	45 min	**1.41** : **1.42**	50:40

In this study, the reductive lithiation of 10-methylphenothiazine **1.39** by LDBB in THF at –78 °C gave the intermediate **1.40**, which after reacting with the electrophile trimethylacetaldehyde at the same temperature, followed by final hydrolysis, led to the expected product **1.41** in a yield of 33% and reduction product **1.42** in a yield of 41%. Thus, even though less reducing agent (2.2 eq. instead of 10 eq.) was used for reductive lithiation of **1.39**, the PAR method still provided a better yield (33%) than that (25%) in the CA method.

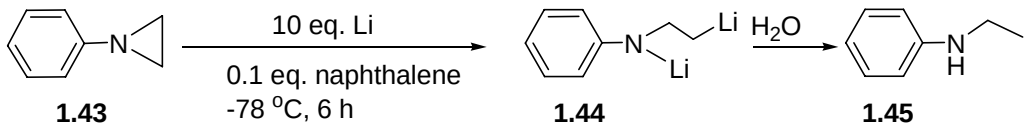
When 10-methylphenothiazine **1.39** was reduced by 10 eq. of Li, in the absence of DBB, the reaction gave product **1.41** in 50% yield and the other reduction product **1.42** in a yield of 40%. The result is better than that obtained from lithiation in the presence of DBB. Thus, the 10-methylphenothiazine **1.39** itself is probably an aromatic electron carrier in its reductive lithiation.

1.2.7 Reductive lithiation of *N*-phenylaziridine

Normally the C-N bond, in which both atoms are hybridized sp^3, is difficult to cleave in basic conditions. But it has been reported by Yus and co-workers that for *N*-phenylaziridine **1.43**, because of the ring strain, the three-membered ring can be opened by excess Li with a catalytic amount of the aromatic electron carrier naphthalene in 93% yield even at the very low temperature of –78 °C (Scheme 1.21 and entry 1, Table 1.8).[50] In this report, the claim is made that the catalytic method is more powerful than the stoichiometric method. Electrophiles other than protons were used as well.

There is a statement in that paper that aziridines do not undergo reductive opening by lithioarenes at low temperature. Since the type of aziridine and the reaction conditions were not included in the paper, we decided to directly compare the CA and PAR methods as applied to the reductive cleavage of *N*-phenylaziridine **1.43**. To our initial surprise, lithium naphthalenide (LN) did not cause the cleavage of **1.43** at the temperature and in the time reported in entry 1 of Table 1.8; only the starting material was recovered. A repetition of the literature procedure (Scheme 1.21) did indeed produce the reported result. This result appeared to support the claim that the CA method is more powerful than the PAR method. However, for the reasons stated before, it seemed highly unlikely that the method using naphthalene as a catalyst could lead to a faster reductive cleavage than the use of preformed lithium naphthalenide.

Scheme 1.21 Reductive lithiation of *N*-phenylaziridine quenching with H_2O

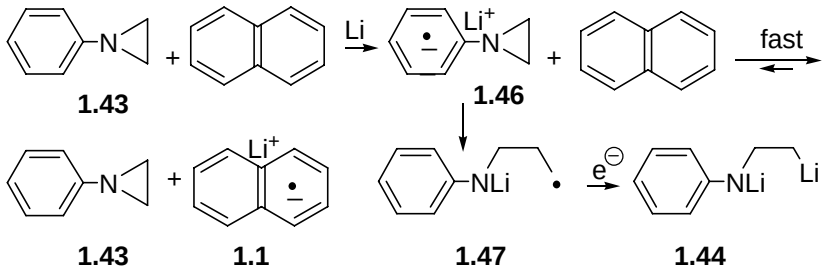


1.43 **1.44** **1.45**

A possible alternative explanation for these experimental results is illustrated in Scheme 1.22. The transfer of an electron from the surface of the lithium occurs more rapidly to the *N*-

phenylaziridine **1.43** than to the naphthalene but in the presence of the latter, the resulting radical-anion **1.46** can rapidly transfer an electron to the naphthalene to generate the more thermodynamically stable naphthalenide radical-anion LN **1.1**. In other words, the radical-anion **1.46** is the kinetic product of electron transfer from the lithium but the naphthalenide **1.1** is the thermodynamic radical-anion as indicated by the inequality of the arrows leading from **1.46** and naphthalene to **1.43** and **1.1**. Since **1.46** is the immediate precursor of the ring-opened product **1.47**, its concentration is directly proportional to the rate of ring cleavage. The higher the concentration of naphthalene, the lower is the rate of ring cleavage. By behaving as a sink for electrons, naphthalene reduces the concentration of **1.46**, and thus inhibits the reductive ring opening. If this reasoning is correct, the aziridine should open at −78 °C even in the absence of the naphthalene "catalyst." In fact, naphthalene in this specific case should behave as an inhibitor rather than a catalyst.

Scheme 1.22 Possible mechanistic explaination for results in table 1.8



This hypothesis was tested first by attempting the cleavage of **1.43** with lithium in the absence of naphthalene. The result was quantitative ring opening within the 4 hour test period at −78 °C (entry 3, Table 1-8). Thus, as predicted, naphthalene is not required and, in fact, the yield (98%) in its absence was somewhat higher than the 90% in the presence of 0.1 equivalent of naphthalene (entry 4).

Table 1.8 Reductive lithiation of N-phenylaziridine

Entry	Reagent	T (^{o}C)	Time	Yield (%)* **1.45** : **1.43**
1	10 eq. Li (powder), 0.05 eq. Np	−78	6 h	93: 0
2	2.2 eq. LN	−78	6 h	0 : 100
3	10 eq. Li (dispersion)	−78	4 h	98 : 0
4	10 eq. Li (dispersion), 0.1 eq. Np	−78	6 h	90 : 10
5	10 eq. Li (dispersion), 1.0 eq. Np	−78	6 h	76 : 24
6	10 eq. Li (dispersion), 10.1 eq Np	−78	6 h	16 : 84

*Only the yields of entries 1 and 3 were isolated yields. Other yields are from NMR. However, the recoveries are always above 97%. Thus the NMR yields in the table should be very close to the isolated yields.

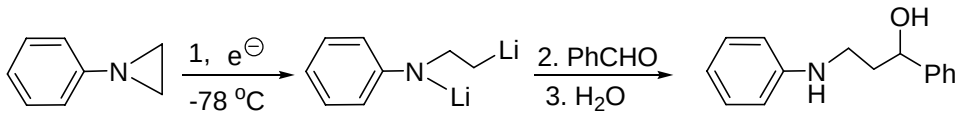
In order to test the prediction that naphthalene is an inhibitor, reductive cleavages were performed with the usual 10 equivalents of lithium in the presence of 1.0 equivalent and 10 equivalents of naphthalene. As seen in entries 3 to 6, the larger the quantity of naphthalene the lower was the yield obtained. Thus, naphthalene is indeed an inhibitor. The inability of LN to reductively cleave *N*-phenylaziridine is understandable on the basis of the unfavorable position of the equilibrium in which an electron is transferred from the naphthalenide **1.1** to **1.43** (Scheme 1.22).

The reason that *N*-phenylaziridine accepts an electron more rapidly from lithium than naphthalene does is not known but this finding is consistent with our experience that 1-(*N,N*-dimethylamino)naphthalene (DMAN) forms a lithium radical-anion *at −45 °C* somewhat faster[51]

than naphthalene does *at room temperature*. One can speculate that the amino group complexes with a lithium cation on the surface of the metal thus increasing the electrophilicity of the ring while at the same time increasing the electron donating power of the metal surface, leading to a more rapid transfer of an electron to the *pi* system of the aromatic. Some further studies of this phenomenon in the hope of finding practical applications are described below.

DBB also decreases the rate of this reaction, but because LDBB is a more powerful electron donor than LN, the effect of inhibition of DBB is not as pronounced. Preformed LDBB still gave 12% yield of reduction product **1.43** after 6 hours at –78 ^{o}C**.** In the same condition, a 66% yield of **1.45** was obtained after 6 hours when 10 eq. of Li and 10.1 eq. of DBB was used; a 100% yield of **1.45** was obtained after 6 hours when 10 eq. of Li and 1.0 eq. of DBB was used. When *N*-phenylaziridine was reduced by 2.2 eq. of LDBB, it required 53 h to produce a 62% yield of the product **1.48** of trapping with benzaldehyde. When the temperature was increased to –50 ^{o}C, *N*-phenylaziridine was reduced by 2.2 eq. of LDBB during 6 hours to produce a 92% yield of **1.45** when water was used as trapping agent; an 84% yield of **1.48** was obtained when benzaldehyde was used as trapping agent.

Scheme 1.23 Reductive lithiation of *N*-phenylaziridine quenching with PhCHO



1.43 **1.44** **1.48**

Table 1.9 Reductive lithiation of N-phenylaziridine using DBB and LDBB

Entry	Reagent	T (^{o}C)	Time	E^{+}	Product	Yield (%)
1	2.2 eq. LDBB	−78	6 h	H_2O	**1.45** : **1.43**	12 : 88
2	10 eq. Li(dispersion), 1.0 eq DBB	−78	6 h	H_2O	**1.45 : 1.43**	100 : 0
3	10 eq. Li (dispersion), 10.1 eq DBB	−78	6 h	H_2O	**1.45 : 1.43**	66 : 34
4	2.2 eq. LDBB	−50	6 h	H_2O	**1.45 : 1.43**	92 : 18
5	2.2 eq. LDBB	−78	53 h	PhCHO	**1.48**	62
6	2.2 eq. LDBB	−50	6 h	PhCHO	**1.48**	84

* Only the yields of entries 5 and 6 are isolated yield. Other yields are from NMR. However the recoveries are always above 97%. So the NMR yields in the table should be very close to the isolated yield.

1.2.8 Catalysts which are analogues of *N*-phenylaziridine

Because *N*-phenylaziridine acquires an electron from Li metal much faster than naphthalene does and the resulting radical-anion **1.46,** can transfer the electron rapidly to naphthalene, *N*-phenylaziridine could in principle catalyze the formation of LN. However, the *N*-phenylaziridine radical-anion **1.46** is unstable and easily undergoes ring opening at −78 ^{o}C. Thus, we sought catalysts that are more stable analogues of *N*-phenylaziridine for the formation of LN and LDBB. Because LN forms faster than LDBB, we used the formation of LDBB as an example to make the effect of catalysis clear (Scheme 1.24 and Table 1.10).

Li dispersion was used to provide enough surface area for the reaction and also used bis-(phenylthio)methane to quench the generated LDBB. At the end of the reaction of *bis*-(phenylthio)methane with LDBB, the color of the reaction system changed from deep blue to

yellow and phenylthiomethylithium and lithium thiophenoxide were formed. Without any catalyst, at –78 °C, after 2 hours, 0.28 eq. of LDBB was trapped by bis(phenylthio)methane (entry 1, Table 1.10). *N*-phenylazetidine **1.49** was the first to be tried as a catalyst, because it is the closest analog of *N*-phenylaziridine and it decomposes extremely slowly at –78 °C in the presence of Li, as indicated in section 1.2.9 below. However, it only gave a yield (0.25 eq., entry 2, Table 1.10) of LDBB which is very similar to that (0.28 eq.) in the absence of catalyst. Thus, other catalysts were tried. With 0.1 eq. of *N,N*-dimethylaniline **1.50** as a catalyst, 0.41 eq. of LDBB was obtained under the same conditions (entry 3, Table 1.10). When *N,N*-dimethyl-*o*-toluidine **1.51,** *o-tert*-butyl-*N,N*-dimethylaniline **1.52,** or 2,6,*N,N*-tetramethylaniline **1.53** were used as catalysts, the yields of LDBB were about twice that obtained without catalysis under the same condition (entries 4, 5 and 6, Table 1.10). Thus, these four aromatic amines did increase the rate of formation of LDBB, but only to a modest degree. They are mild catalysts for the formation of LDBB. Nevertheless, to our knowledge, these are the first catalyst ever discovered for the formation of aromatic radical-anions.

Scheme 1.24 Attempts to find catalysts for the formation of LDBB

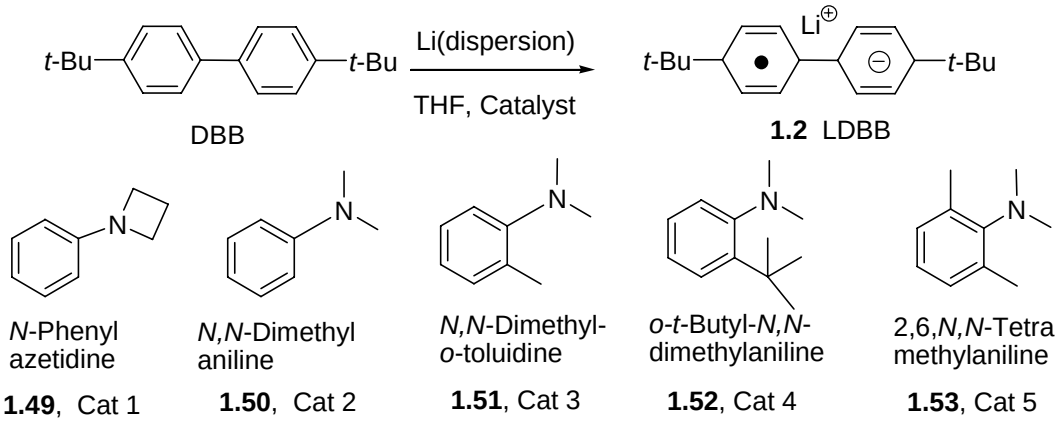


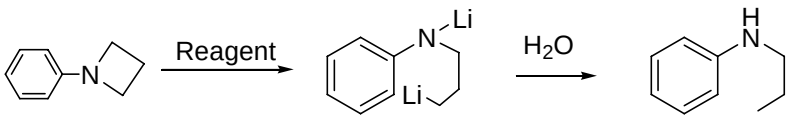
Table 1.10 Formation of LDBB in the presence of catalysts

Entry	Substrate	T (^{o}C)	Time	Li (Dis)	Catalyst	Consumption of $(PhS)_2CH_2$
1	$(PhS)_2CH_2$	−78 ^{o}C	2 h	5 eq.		0.28 eq.
2	$(PhS)_2CH_2$	−78 ^{o}C	2 h	5 eq.	0.1 eq. **1.49**	0.25 eq.
3	$(PhS)_2CH_2$	−78 ^{o}C	2 h	5 eq.	0.1 eq. **1.50**	0.41 eq.
4	$(PhS)_2CH_2$	−78 ^{o}C	2 h	5 eq.	0.1 eq. **1.51**	0.55 eq.
5	$(PhS)_2CH_2$	−78 ^{o}C	2 h	5 eq.	0.1 eq. **1.52**	0.53 eq.
6	$(PhS)_2CH_2$	−78 ^{o}C	2 h	5 eq.	0.1 eq. **1.53**	0.54 eq.

1.2.9 Reductive lithiation of *N*-phenylazetidine

Due to the decrease in ring strain, *N*-phenylazetidine **1.49** is less reactive than *N*-phenylaziridine in ring opening processes and usually needs the help of an acid catalyst to undergo this reaction.[52] However, it has been reported that the four-membered ring of *N*-phenylazetidine **1.49** can be opened by Li metal in the presence of DBB. A 90% yield was obtained by reductive lithiation of *N*-phenylaziridine in the presence of a catalytic amount of DBB after hydrolysis. Lower yields (36-44%) were obtained when the intermediate was captured by different electrophiles (*tert*-BuCHO, PhCHO, Me_2CO).

Scheme 1.25 Reductive lithiation of *N*-phenylazetidine I



1.49 **1.54** **1.55**

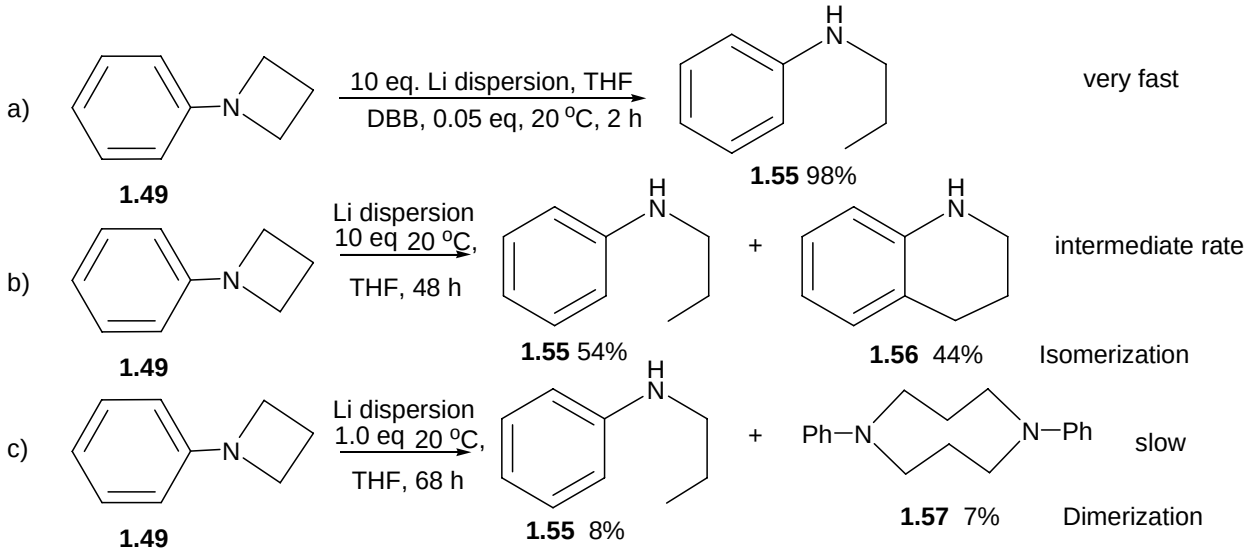
Table 1.11 Reductive lithiation of *N*-phenylazetidine

Entry	Reagent	Method	T (^{o}C)	Time	E^{+}	Yield (%) of **1.55**
1	10 eq. Li (powder), 0.05 eq. DBB	CA	−15	7 h	H_2O	90[52]
2	2.2 eq. LDBB	PAR	−15	7 h	H_2O	99

When preformed LDBB was used to open the four-membered ring, a 99% yield of protonated product **1.55** was obtained under otherwise identical conditions (Table 1.11, entry 2). This was slightly higher than the yield reported for the catalytic method using a large excess of lithium. Thus, once again the PAR method appears to be better than the CA method for reductive lithiation.

With the help of DBB, Li can open the four-membered ring of azetidine rapidly at room temperature; after 2 hours, almost all of **1.49** had been converted to reduction product **1.55** (Scheme 1.26)**.** Without DBB, Li reduced **1.49** far more slowly. All of **1.49** had been converted only after 48 hours at room temperature. However, only just over half of the product **1.55** was obtained from reduction. The remainder of the product was bicyclic isomerization product, 1,2,3,4-tetrahydroquinoline **1.56**.

Scheme 1.26 Reductive lithiation of *N*-phenylazetidine II

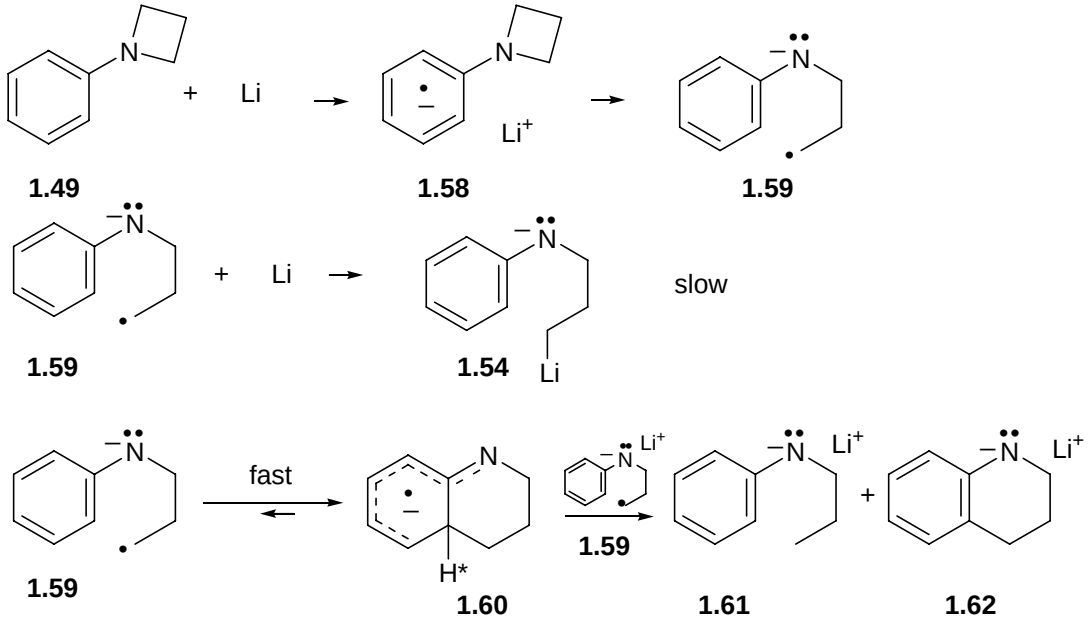


When the amount of Li was reduced to 1.0 eq. in order to try to get a greater proportion of isomerization product, the reaction was far slower. Only a little of **1.49** was converted after 68 hours at room temperature. Surprisingly, no isomerization product **1.56** was obtained but an eight-membered ring product **1.57**, a dimerization product of the starting material, was obtained in almost the same low yield as the reduction product **1.55**.

Thus, in this reductive lithiation, aromatic electron carrier DBB catalyzed the reaction and changed the manner of reaction to give a single product. Furthermore, in the absence of the catalyst DBB, two new products were generated, **1.56** when a relatively large quantity of Li was used and **1.57** when a small amount of Li was used.

Scheme 1.27 is a hypothetical mechanism for the formation of isomerization product **1.56** and it explains why the production of reduction and isomerization products **1.55** and **1.56** occur to equal extents.

Scheme 1.27 Possible mechanism for the formation of isomerization product 1.56



In this reductive lithiation, *N*-phenylazetidine **1.49** accepts one electron to produce the aromatic radical-anion **1.58**, which suffers opening of its four-membered ring to give carbon-centered radical **1.59**. There are several pathways that **1.59** can take. One pathway is to accept a second electron from Li to generate dianion **1.54**. Under these conditions in which aromatic catalyst is absent, this pathway is slower than the isomerization of **1.59** to radical-anion **1.60**, in which the *pi* electron pair of nitrogen helps to stabilize the radical**.** Based on the products **1.61** and **1.62**, the hydrogen labeled with a star in **1.60** had to leave. Because we obtained the reduction product **1.55** and isomerization product **1.56** as about a 1:1 ratio, we thought the **1.60** may have transferred the hydrogen atom to **1.59** to give one molecule of **1.61** and one molecule of **1.62.** **1.59** is a transient radical but **1.60** is a persistent radical, which is presumably far more stable than **1.59**. According to Scheme 1.27, products **1.61** and **1.62** come from selective reaction of the intermediate radical **1.59** through the radical-anion **1.60** by disproportionation.

However, we have no explanation for the absence of ring expansion product **1.56** in reaction c in which there was a deficiency of Li.

1.2.10 Conclusions

In the present work, we have demonstrated a major disadvantage of the CA method that should be weighed against its advantages in deciding whether to use that method or the PAR method, involving a stoichiometric quantity of preformed aromatic radical-anion, for performing reductive lithiations. The disadvantage of the CA method is that at any given temperature, the catalytic method is slower than that using a stoichiometric amount of preformed aromatic radical-anion. This is illustrated in all of the cases compared above but most vividly by the large decrease in yield in the reductive cleavage of anisole in going from the PAR to the CA method in experiments with the same limited duration. In some cases this lower rate may not be a highly significant disadvantage, particularly when the organolithium being produced is stable to the reaction conditions and some of the reductive lithiations that the Yus group has performed proceed in good yields. However, in cases in which the organolithium is not entirely stable to the reaction conditions, significant decreases in yield are observed in going from the PAR to the CA method. Examples are the reductive lithiation of acrolein acetals to produce allylic α-lithioethers that are capable of undergoing the Wittig rearrangement and of tertiary alkyl chlorides that can undergo elimination in the presence of the tertiary organolithium products.

Furthermore, some compounds previously believed to undergo catalytic reductive lithiation, such as 2,3-benzofuran **1.24**, pick up an electron and cleave as fast in the absence as in the presence of the aromatic catalyst. This is not surprising as the radical-anion derived from this substrate has extensive delocalization, probably greater than that in the LDBB that would be

the intermediate radical-anion if the catalytic process were indeed occurring. Moreover, a polylithio compound **1.34** was discovered in the reductive lithiation of 2,3-benzofuran **1.24** using a large excess of reducing agent.

A far more surprising and significant result is that *N*-phenylaziridine **1.43** not only does not require naphthalene as a catalyst during its reductive cleavage but the naphthalene is actually an inhibitor of the reductive lithiation. Apparently, this substrate forms a radical-anion **1.46** by reaction with lithium more rapidly than naphthalene does but the radical-anion **1.1** from naphthalene is more thermodynamically stable than that **1.46** from *N*-phenylaziridine. Thus the arene can behave as a catalyst, an unnecessary additive or an inhibitor, depending on the specific substrate.

In the reductive lithiation of *N*-phenylazetidine, the PAR method is also better than the catalytic method. Furthermore, in the absence of arene catalyst, two new reactions were found, the production of 1,2,3,4-tetrahydroquinoline **1.56** and an eight-membered ring product **1.57**.

Finally, one other disadvantage of the CA method should be mentioned. Lithium metal is the most expensive ingredient used in reductive lithiations since the arene can easily be recovered and recycled. The large excess of lithium used could become an economic liability as well as something of a safely hazard, especially in an industrial setting. The expense is especially onerous considering that the cost of lithium powder from Aldrich is almost 6 times the cost of the ribbon that we ordinarily use to make preformed radical-anion.

Based on the above work, the results of reductive lithiations of acrolein diethyl acetal, 6-chloro-6-methyl-1-heptene, anisole, 2,3-benzofuran and *N*-phenylaziridine have been published in 2006.[53]

1.3 EXPERIMENTAL SECTION

General Experimental Procedures. A dry ice/acetone bath was used to obtain a temperature of –78 °C. An ice bath was used to obtain 0 °C. Silica gel 60 (40-60 μm, Sorbent Technologies) was used for flash-column chromatography. Thin-layer chromatography was performed on glass supported 250-μm silica GF plates (Analtech). Visualization of TLC plates was accomplished with one or more of the following: 254 nm UV light; aqueous $KMnO_4$ (1%) with NaOH (0.1%) and K_2CO_3 (6%); 7% phosphomolybdic acid in ethanol; 5% anisaldehyde in ethanol containing 5% sulfuric acid and a trace amount of acetic acid.

Instrumentation. Most ^1H and ^{13}C NMR spectra were recorded on Bruker DPX-300 spectrometer operating at 300 MHz for ^1H and 75 MHz for ^{13}C at 22 ºC unless otherwise noted. Some ^1H and ^{13}C NMR spectra, and two-dimensional NMR spectra were recorded on a Bruker AM-500 spectrometer. Chemical shift data are reported in unit of δ (ppm) relative to TMS as δ = 0.0 for ^1H NMR spectra and $CDCl_3$ as internal standard: δ = 77.00 for ^{13}C NMR spectra unless indicated otherwise. Multiplicities are given as s (singlet), d (double), t (triplet), q (quartet), m (multiplet), and br (broad). Coupling constants, *J*, are reported in Hz. Infrared spectra were recorded on an IR/32 FT-IR spectrometer and are reported in wave numbers (cm^{-1}). Low and high-resolution mass spectra were recorded on a VG-70SE mass spectrometer in EI mode at 70 eV.

Materials. Commercial solvents and reagents were used as received with the following exceptions. Tetrahydrofuran (THF) and diethyl ether were distilled over sodium benzophenone ketyl. Methylene chloride and CH_3CN were distilled over CaH_2. Benzene was dried over

melting sodium. Commercial solvents and reagents were used as received with the following exceptions. Anhydrous magnesium sulfate and sodium sulfate were used as the drying reagent.

Preparation of Lithium 4,4'-di-*tert*-butylbiphenylide (LDBB) or Lithium Naphthalenide (LN)

Lithium ribbon (32 mg, 4.61 mmol) was cleaned and cut into small pieces before it was added under a heavy argon flow to a stirred solution of 4,4'-di-tert-butylbiphenyl (1064 mg, 4.00 mmol) (or naphthalene) in 10 mL of dry THF at room temperature. After approximately five minutes, the solution turned a dark green (or black) color. The flask was then cooled to 0 °C with an ice bath, and was allowed to stir at that temperature for five hours.

Reductive lithiation of acrolein diethyl acetal (1.10)

a) Reductive lithiation of 1.10 with preformed LDBB: To a stirred solution of LDBB (4.00 mmol) under an argon at -78 °C, acrolein diethyl acetal (**1.10**, 0.310 mL, 2.10 mmol) was added dropwise over a period of 5 min. Since no new spot except starting material was observed on TLC for the reaction at -78 °C, the reaction mixture was allowed to warm to -50 °C, where it was stirred for 90 min. Pivalaldehyde (180 mg, 0.23 mL, 2.10 mmol) was then added dropwise to the reaction flask and the mixture was allowed to stir at -50 °C for an additional 30 min. Cold water (10 mL) was added to quench the reaction. The resulting mixture was extracted with ether (3×20 mL), and the combined extract was dried over anhydrous $MgSO_4$, filtered and concentrated by solvent removal by rotary evaporation. Flash-column chromatography, with 10% ethyl acetate in hexanes, afforded the pure product *Z*-1-ethoxy-5,5-dimethylhex-1-ene-4-ol **1.12** (0.27 g, 70%). ^{1}H NMR ($CDCl_3$): δ 6.20 (1 H, dt, *J* = 6.0, 1.5 Hz), 4.55 (1 H, ddd, *J* = 6.9, 6.3, 6.0 Hz), 3.90 (2 H, q, *J* = 7.0 Hz), 3.31 (1 H, m), 2.28 (2 H, m), 2.02 (1 H, br s), 1.34 (3 H, t,

J = 7.0 Hz), 1.0 (9 H, s). ^{13}C NMR ($CDCl_3$) δ 146.5, 103.4, 78.9, 67.3, 34.4, 26.3, 25.2, 14.9. This spectral data is consistent with that reported in the literature.[20]

b) Reductive lithiation of 1.10 with lithium in the absence of DBB: Li (dispersion, 460 mg, 20.0 mmol) was washed with three 10.0 mL portions of hexane in a 100 mL three-necked flask under an argon. THF (10.0 mL) and acrolein dimethyl acetal (**1.10**, 260 mg, 2.00 mmol) were added under an argon at 0 °C. After the mixture had been stirred for 90 min at 0 °C, it was cooled to -78 °C, pivalaldehyde (180 mg, 0.23 mL, 2.10 mmol) was added dropwise to the reaction flask and the mixture was allowed to stir at -50 °C for an additional 30 min. Cold water (20.0 mL) was slowly added to quench the reaction. The resulting mixture was extracted with ether (3×20 mL) and the organic layer was dried over anhydrous $MgSO_4$ and concentrated by solvent removal. The residue was starting material, acrolein diethyl acetal, by crude NMR analysis.

Reductive lithiation of 6-chloro-6-methyl-1-heptene (1.16)

a) Reductive lithiation of 1.16 with preformed LDBB: To a stirred solution of LDBB (4.00 mmol) under an argon at -78 °C, 6-chloro-6-methyl-1-heptene (**1.16**, 0.270 g, 1.90 mmol) was added dropwise over a period of 5 min. The reaction mixture was allowed to warm to –50 °C, where it was stirred for 120 min. 3-Pentanone (180 mg, 2.10 mmol) was added dropwise to the reaction flask and the reaction mixture was allowed to stir at –50 °C for an additional 30 min. 10% aqueous sodium bicarbonate solution was added to quench the reaction and the reaction vessel was allowed to warm to room temperature. The resulting mixture was extracted with ether (3×20 mL) and the combined extract was dried over anhydrous $MgSO_4$, filtered and concentrated by solvent removal using rotary evaporation. Flash-column chromatography, with 5% ethyl acetate in hexanes as eluent, afforded pure 3-(2,2-dimethyl-cyclopentylmethyl)-pentan-

3-ol (**1.19,** 0.34 g, 92%). ^{1}H NMR ($CDCl_3$): ^{1}H NMR ($CDCl_3$) δ 2.0 (m, 1 H), 1.30 (m, 12 H), 0.96 (s, 3 H), 0.85 (2 t, *J* = 7.2, 6 H), 0.71 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 74.8, 44.2, 41.6, 41.0, 38.6, 31.9, 31.6, 30.9, 27.4, 21.3, 20.92, 8.0, 7.6. This compound was reported by Yus, but no spectral data were provided.

Under otherwise identical conditions, but at –78 °C instead at –50 °C, no product **1.19** was obtained.

Under otherwise identical conditions, but at -30 °C instead at –50 °C, 0.32 g (86%) of **1.19** was obtained.

b) Reductive lithiation of 1.16 with lithium in the absence of DBB: Li (dispersion, 460 mg, 20.0 mmol) was washed with three 10.0 mL portions of hexane in a 100 mL three-necked flask under an argon. THF (10.0 mL) and 6-chloro-6-methyl-1-heptene (1.16, 293 mg, 2.00 mmol) were added under argon at -30 °C. After the reaction mixture had been stirred for 2 h at -30 °C , the mixture was cooled to -78 °C and 3-pentanone (180 mg, 2.10 mmol) was added dropwise to the reaction flask and the reaction mixture was allowed to stir at -78 °C for an additional 30 min. Cold water (20 mL) was added slowly to quench the reaction and the reaction mixture was allowed to warm to RT. The resulting mixture was extracted with ether (3×20 mL) and the organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by flash-column chromatography (5% ethyl acetate in hexanes) to afford 1.19 (0.21 g , 53%).

Reductive lithiation of anisole (1.22)

a) Reductive lithiation of 1.22 with preformed LDBB: A solution of freshly prepared LDBB (4.40 mmol) in 10.0 mL of THF was cooled to 0 ^{o}C prior to the slow addition of anisole (**1.22**,

216 mg, 2.00 mmol) under argon over a period of 5 min. The reaction mixture was stirred at 0 ^{o}C for 2 h and was then cooled to -40 °C. The reaction was quenched by dropwise addition of benzaldehyde (223 mg, 2.10 mmol). After the reaction mixture had been further stirred for 30 min at –40 $^{\circ}$C, the mixture was allowed to warm to room temperature over a period of 3 h and cold water (20 mL) was added slowly. The resulting mixture was extracted with ether (3×20 mL) and the organic layer was dried over anhydrous $MgSO_4$ and concentrated by solvent removal. The residue was purified by flash-column chromatography (10% ethyl acetate in hexanes), affording 1-phenylethanol **1.23** (212 mg, 87%). ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5 H), 4.5 (q, J = 6.5, 1 H), δ 2.10 (s, 1 H), 1.47 (d, J = 6.5, 3 H); ^{13}C NMR ($CDCl_3$) δ 145.7, 128.4, 127.4, 125.3, 70.3, 25.1. This NMR data compared well with that in the reference.[41]

b) Reductive lithiation of 1.22 with lithium in the presence of DBB: Li (dispersion, 644 mg, 28.0 mmol) was washed with three 10 mL portions of hexane in a 100 mL three-necked flask under an argon. THF (10.0 mL), DBB (53.2 mg, 0.20 mmol) and anisole (**1.22**, 216 mg, 2.00 mmol) were added under an argon at 0 °C. The reaction mixture was stirred at 0 °C for 2 h before the temperature was cooled to -40 °C. The reaction was quenched by dropwise addition of benzaldehyde (223 mg, 2.10 mmol). After the reaction mixture had been further stirred for 30 min at -40 °C, the temperature was allowed to rise to room temperature over a period of 3 h and ice-water (20 mL) was added slowly. The resulting mixture was extracted with ether (3×20 mL), and the organic layer was dried over anhydrous $MgSO_4$ and concentrated by solvent removal. The residue was purified by flash-column chromatography (10% ethyl acetate in hexanes), affording 1-phenylethanol **1.23** (73.0 mg, 30%).

c) Reductive lithiation of 1.22 with lithium in the absence of DBB: Under otherwise identical conditions but with no DBB, no 1-phenylethanol **1.23** was obtained.

Reductive lithiation of 2,3-benzofuran (1.24)

a) Reductive lithiation of 1.24 with lithium dispersion (entry 2, Table 1.3): Li (dispersion, 460 mg, 20.0 mmol) was washed with three 10.0 mL portions of hexane in a 100 mL three-necked flask under an argon. THF (10.0 mL) and 2,3-benzofuran (**1.24**, 236 mg, 0.22 mL, 2.00 mmol) were added under an argon at 0 °C. After the reaction mixture had been stirred for 45 min at 0 ^{o}C, the temperature was cooled to -30 °C and cold water (20 mL) was added slowly to the resulting mixture. After 15 min, the reaction mixture was neutralized with 1.00 M hydrochloric acid (5.0 mL). The resulting mixture was extracted with ether (3×20.0 mL), and the organic layer was dried over anhydrous $MgSO_4$ and concentrated by solvent removal. The residue was purified by flash-column chromatography (10% ethyl acetate in hexanes), affording 2-vinylphenol **1.26** (214 mg, 91%). ^{1}H NMR ($CDCl_3$) δ 7.38 (dd, J_1 = 7.7, J_2 = 1.7, 1 H), 7.14 (td, J_1 = 7.7, J_2 = 1.1 Hz, 1 H), 6.92 (m, 2 H), 6.78 (dd, J_1 =7.7, J_2 = 1.1, 1 H), 5.74 (dd, J_1 = 17.7, J_2 = 1.4, 1 H), 5.36 (dd, J_1 = 13.2, J_2 = 1.4, 1 H), 5.01 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 152.6, 131.3, 128.8, 127.2, 124.8, 120.9, 115.9, 115.8. This NMR data compared well with that in the reference.[43]

When the above reaction was quenched with D_2O (0.5 mL), after the same workup procedure, 205 mg of deuterated **1.27** was obtained; yield 87% ^{1}H NMR ($CDCl_3$) δ 7.40 (dd, J_1 = 7.7, J_2 = 1.7, 1 H), 7.16 (td, J_1 = 7.7, J_2 = 1.1 Hz, 1 H), 6.97 (m, 2 H), 6.79 (dd, J_1 =7.7, J_2 = 1.1, 1 H), 5.45 (d, J = 11.2, 1 H), 5.019 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 152.7, 131.4, 128.8, 127.3, 124.8, 120.9, 115.8, 115.2 (t, J_{CD} = 23.0 Hz).

b) Reductive lithiation of 1.24 with 10 eq. of Li and 2 eq. of DBB (Entry 1, Table 1.6)**:** Li (dispersion, 140 mg, 20.0 mmol) was placed in a 100 mL three-necked flask under an argon. THF (10.0 mL), DBB (532 mg, 2.0 eq.) and 3-benzofuran (**1.24**, 236 mg, 0.22 mL, 2.00 mmol)

were added under an argon at -78 °C. After the reaction mixture had been stirred for 2 hours at that same temperature, D_2O (5 mL) was added slowly to the resulting mixture. After 15 min, the reaction mixture was neutralized with 1.0 M hydrochloric acid (5 mL). The resulting mixture was extracted with ether (3×20.0 mL), and the organic layer was dried over anhydrous $MgSO_4$ and concentrated by solvent removal. The residue was purified by flash-column chromatography (10% ethyl acetate in hexanes), affording **1.35** (183 mg, 73%). ^{1}H NMR ($CDCl_3$) δ 7.14 (dd, J_1 = 7.7, J_2 = 1.7, 1 H), 7.06 (td, J_1 = 7.7, J_2 = 1.1 Hz, 1 H), 6.87 (td, J_1 =7.7, J_2 = 1.1, 1 H), 6.74 (dd, J_1 = 17.7, J_2 = 1.4, 1 H), 5.06 (s, 1 H), 2.73 (d, J = 17.7, 1 H), 1.34 (d, J =17.7, 1 H); ^{13}C NMR ($CDCl_3$) δ 153.3, 129.9, 129.27, 126.93, 120.87, 115.12, 22.36 (t, J_{CD} =19.4), 13.26 (quintet, J_{CD} = 19.3). MS (EI) *m*/*z* (relative intensity) 125 (M^+, 35), 108 (100), 78 (20).

c) Reductive lithiation of 1.24 with 4 eq. of preformed LDBB (Entry 2, Table 1.6)**:** To 4 eq. of LDBB (made from 70 mg of lithium ribbon and 1.064 g of DBB) in a 100 mL three-necked flask at –78 ^{o}C under an argon, 2,3-benzofuran (**1.24**, 236 mg, 0.22 mL, 2.00 mmol) were added through syringe. After the reaction mixture had been stirred for 1.5 hours at the same temperature, D_2O (5 mL) was added slowly to the resulting mixture. After 15 min, the reaction mixture was neutralized with 1.0 M hydrochloric acid (5 mL). The resulting mixture was extracted with ether (3×20.0 mL), and the organic layer was dried over anhydrous $MgSO_4$ and concentrated by solvent removal. The residue was purified by flash-column chromatography (10% ethyl acetate in hexanes), affording **1.35** (167 mg, 70%).

d) Reductive lithiation of 1.24 with 10 eq. of Li (Entry 3, Table 1.6)**:** Li (dispersion, 140 mg, 20.0 mmol) and THF (10.0 mL) were in a 100 mL three-necked flask under argon, and then the reaction mixture was cooled down to –78 ^{o}C. 2,3-benzofuran (**1.24**, 236 mg, 0.22 mL, 2.00 mmol) were added under argon at –78 °C. After being stirred for 6 hours at the same

temperature, D_2O (5 mL) was added slowly to the resulting mixture. After 15 min, the reaction mixture was neutralized with 1.0 M hydrochloric acid (5 mL). The resulting mixture was extracted with ether (3×20.0 mL), and the organic layer was dried over anhydrous $MgSO_4$ and concentrated by solvent removal. The residue was purified by flash-column chromatography (10% ethyl acetate in hexanes), affording **1.27** (119 mg, 50%).

f) Reductive lithiation of 1.24 with 10 eq. of Li and 2 eq. DBB at 0 ^oC (Entry 4, Table 1.6)**:** Li (dispersion, 140 mg, 20.0 mmol), THF (10.0 mL) and DBB (532 mg, 2 eq.)were in a 100 mL three-necked flask under an argon, and after the reaction temperature was cooled to 0 ^oC, 2,3-benzofuran (**1.24**, 236 mg, 0.22 mL, 2.00 mmol) were added. After being stirred for 2 hours at the same temperature, D_2O (5 mL) was added slowly to the resulting mixture. After 15 min, the reaction mixture was neutralized with 1.0 M hydrochloric acid (5 mL). The resulting mixture was extracted with ether (3×20.0 mL), and the organic layer was dried over anhydrous $MgSO_4$ and concentrated by solvent removal. The residue was purified by flash-column chromatography (10% ethyl acetate in hexanes), affording **1.35** (50 mg, 21%).

g) Reductive lithiation of 1.24 with preformed LDBB (Entry 5, Table 1.6)**:** To 4 eq. of LDBB (made from 70 mg of lithium ribbon and 1.064 g of DBB) in a 100 mL three-necked flask at –78 ^oC under an argon, 2,3-benzofuran (**1.24**, 236 mg, 0.22 mL, 2.00 mmol) were added through syringe. After the reaction mixture had been stirred for 1 hours at the same temperature, the starting material was completely consumed when checking with TLC. 2.eq of preformed LDBB was added by syringe and the reaction mixture was stirred for 5 additional hours. D_2O (5 mL) was added slowly to the resulting mixture. After 15 min, the reaction mixture was neutralized with 1.0 M hydrochloric acid (5 mL). The resulting mixture was extracted with ether (3×20.0 mL), and the organic layer was dried over anhydrous $MgSO_4$ and concentrated by solvent

removal. The residue was purified by flash-column chromatography (10% ethyl acetate in hexanes), affording **1.35** (142 mg, 60%).

Reductive lithiation of 10-methylphenothiazine 1.39

a) Reductive lithiation of 1.39 with preformed LDBB: A solution of freshly formed LDBB (4.40 mmol) in 10.0 mL of THF was cooled to -78 ^{o}C prior to the slow addition of 10-methylphenothiazine (**1.39**, 398 mg, 2.00 mmol) under argon. The reaction mixture was stirred at the same temperature for 45 min and then quenched with pivalaldehyde (180 mg, 0.23 ml, 2.10 mmol). After the reaction mixture had been further stirred for 15 min, the temperature had been allowed to rise to 20 °C over a period of 3 h and ice-water (20 g) was slowly added. The resulting mixture was extracted with ether (3×20 mL), and the combined organic solvent was dried over anhydrous Na_2SO_4, filtered and concentrated by solvent removal with rotary evaporation. After the solvent had been removed, the crude materials were flash-column chromatography (2% ethyl acetate in hexanes) on silica gel, affording the two product **1.41 (**163 mg, 41%), 2-anilinothiophenol **1.42** (189 mg, 33%).

1.41: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (m, 1 H), 7.33 (m, 3 H), 7.10 (m, 1 H), 6.92 (m, 2 H), 6.75 (m, 1 H), 4.54 (s, 1 H), 3.11 (s, 3 H), 0.93 (s, 9 H). This NMR spectrum compared well with that in the reference.[49]

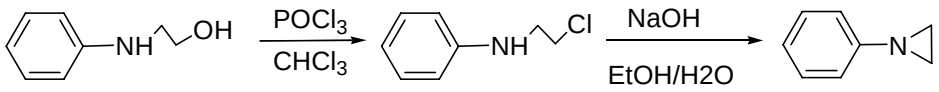
1.42: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (m, 1 H), 7.41 (m, 2 H), 7.33 (m, 2 H), 6.99 (m, 2 H), 6.82 (m, 2 H), 4.09 (s, 1 H), 3.39 (s, 3 H). This NMR spectrum compared well with that in the reference.[49]

b) Reductive lithiation 1.39 with lithium in the absence of DBB: Li (dispersion, 460 mg, 20.0 mmol) was placed in a 100 mL three-necked flask under argon, and was washed with three 10.0 mL portions of hexane. THF (10.0 mL) and 10-methylphenothiazine (**1.39**, 398 mg, 2.00 mmol)

were added under argon at –78 °C. After the reaction mixture had been stirred at the same temperature for 45 min, it was then quenched with pivalaldehyde (180 mg, 0.23 ml, 2.10 mmol). After the reaction mixture had been further stirred for 15 min at that temperature and had been allowed to rise to 20 °C over a period of 3 h, ice-water (20 g) was slowly added. The resulting mixture was extracted with ether (3×20.0 mL), and the combined organic solvent was dried over anhydrous Na_2SO_4, filtered and concentrated by solvent removal. The residue was purified by flash-column chromatography (10% ethyl acetate in hexanes), affording the two products **1.41** (159 mg, 40%), 2-anilinothiophenol **1.42** (287 mg, 50%).

Synthesis of *N*-phenylaziridine[54,55] 1.43

Scheme 1.28 Synthesis of *N*-phenylaziridine



a) *N*-(2-Chloroethyl)aniline: 2-Anilinoethanol (27.4 g, 0.200 mol) was dissolved in 17.2 mL of concentrated hydrochloric acid and the solution was evaporated under diminished pressure. The resulting 2-anilinoethanol hydrochloride was dissolved in 35.0 mL of chloroform, the solution was cooled in ice, fresh phosphoryl chloride 5.00 mL (0.054 mol) was added, and the solution was gradually heated under a reflux condenser. The temperature was maintained about 60 °C and three 5.00 mL (0.054 mol) portions of phosphoryl chloride were added in a period of 45 min. followed by the addition of 16.0 mL of (0.17 mol) phosphoryl chloride. The bath temperature was raised to 84 °C over a period of ca. 2 h. The solution was evaporated under diminished pressure (1 mm Hg) and 50.0 mL of absolute ethanol was added to it. The suspension was cooled for a day and filtered, giving colorless crystals *N*-(2-chloroethyl)aniline hydrochloride (34.6 g, 90%).

b) *N*-Phenylaziridine 1.43: A solution of 100 mL of 3.00 N sodium hydroxide and 100 mL of ethanol was placed in a 500 mL three-necked flask equipped with a stirrer, condenser and dropping funnel and the flask was immersed in a water bath held at 50 °C. To this was added dropwise and with stirring 20.0 g (0.13 mol) *N-(*2-chloroethyl)aniline hydrochloride dissolved in 100 mL ethanol. After the addition was complete the temperature of the water bath was raised to 85 °C for one hour. Next, the ethanol was removed by distillation, the residue was cooled to room temperature and extracted with ether (3×50 mL). The ethereal solution was dried over sodium sulfate, filtered and distilled until the temperature reached 82 °C. The residue was subjected to vacuum distillation. A fraction (64-65 °C at 4 mmHg) of 10.4 g *N*-phenylaziridine **1.43** (68%) was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (m, 2 H), 6.98 (m, 3 H), 2.10 (s, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.1, 128.8, 122.2, 121.0, 27.5. The yield is 61% over two steps.

Reductive lithiation of *N*-phenylaziridine (1.43)

a) General procedure for reductive lithiation of *N*-phenylaziridine (1.43) by the PAR method: A solution of freshly formed LDBB (4.40 mmol) (or lithium naphthalenide) in 10 mL of THF was cooled to −78 °C (or −50 °C) prior to the slow addition *N*-phenylaziridine (**1.43**, 238 mg, 2.00 mmol) under an argon. The reaction mixture was stirred at that temperature for 6 hours (or 53 hours) and quenched with water (or benzaldehyde). The organic layer was extracted with ether (3×20.0 mL) and the combined organic layer was dried over anhydrous Na_2SO_4. Flash-column chromatography (5% ethyl acetate in hexanes) gave product 1.45 or 1.50. Yields depend on the reaction temperature and time as shown in table 8 and 9.

b) General procedure for reductive lithiation of *N*-phenylaziridine (1.43) by the CA method: Li (dispersion, 460 mg, 20.0 mmol) was washed with four 10 mL portions of hexane in

a 100 mL three-necked flask under an argon. THF (10 mL) was added and the reaction mixture was cooled to -78 °C. *N*-Phenylaziridine (**1.43**, 238 mg, 2.00 mmol) and naphthalene (0.05 eq.) were added under an argon at the same temperature. After the mixture had been stirred for 6 hours at -78 °C, the reaction was quenched by adding ice-water (20 mL) slowly. The resulting mixture was extracted with ether (5×20 mL) and the organic layer was dried over anhydrous Na_2SO_4 and concentrated by solvent removal. The residue was purified by flash-column chromatography (5% ethyl acetate in hexanes), affording *N*-ethylaniline 1.38. Yields depend on the reaction temperature and time as shown in table 1-8 and 1-9.

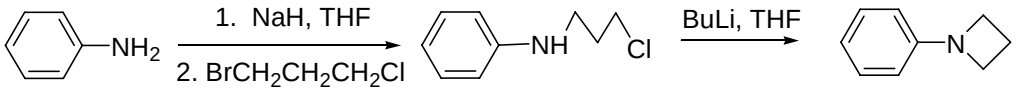
N-Ethylaniline **1.45:** ^{1}H NMR ($CDCl_3$) δ 7.36 (m, 2 H), 6.88 (m, 1 H), 6.79 (m, 2 H), 3.37 (s, 1 H), 3.11 (q, J = 7.1, 2 H), 1.21 (t, J = 7.1, 3 H); ^{13}C NMR ($CDCl_3$) δ 148.4, 129.1, 117.1, 112.6, 38.3, 14.8. The spectral data are consistent with that reported by Aldrich.

3-(*N*-anilino)-1-phenylpropane-1-ol **1.48**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 5 H), 7.18 (m, 2 H), 6.72 (t, J = 7.3, 1 H), 6.60 (d, J = 7.7, 2 H), 4.84 (dd, J = 5.3, J = 2.1, 1 H), 3.24 (t, J = 6.4, 2 H), 2.02 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.2, 144.3, 129.2, 128.5, 127.6, 125.6, 117.7, 113.2, 73.6, 41.6, 38.1. This NMR data compared well with that in the reference.[56]

Catalysis of the formation of LDBB

(a) Synthesis of *N*-phenylazetidine (1.49)[52]

Scheme 1.29 Synthesis of *N*-phenylazetidine



***N*-(3-Chloropropyl)aniline**: A solution containing aniline $PhNH_2$ (4.50 mL, 0.050 mol), NaH (1.35 g, 0.045 mol), and THF (250 mL) was heated at reflux for 2 h under an argon, the reaction mixture was cooled to –78 °C, and $BrCH_2CH_2CH_2Cl$ (5.40 mL, 0.055 mol) was added by

syringe. The mixture was allowed to warm to room temperature over a period of ca. 3 h and water was then added. Column chromatography (5% ethyl acetate in hexanes) was used to purify the product, giving *N-(*3-chloropropyl)aniline (7.20 g, 40%).

***N*-Phenylazetidine 1.49**: To a cooled (-78 °C) solution of *N*-(3-chloropropyl)aniline (17.0 g, 0.100 mol) in 100 mL THF under an argon was added a 1.6 M hexane solution of *n*-BuLi (64.0 mL). The temperature was allowed to rise to room temperature during 3 h. The reaction mixture was stirred at room temperature for 8 days. The resulting mixture was hydrolyzed with water and extracted with ether. The organic layer was dried over sodium sulfate and concentrated. The resulting residue was purified by distillation under reduced pressure (51 °C at 0.5 mm Hg) to give *N*-phenylazetidine 1.51 (5.30 g, 40%).

***N*-(3-Chloropropyl)aniline**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (m, 2 H), 6.74 (m, 1 H), 6.64 (m, 2 H), 3.65 (t, *J* = 6.3, 2 H), 3.34 (t, *J* = 6.6, 2 H), 2.09 (tt, *J* = 6.6, *J* = 6.3, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.79, 129.20, 117.35, 112.63, 42.57, 40.71, 31.80.

***N*-Phenylazetidine 1.49**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (m, 2 H), 6.74 (m, 1 H), 6.46 (m, 2 H), 3.87 (t, *J* = 7.2, 4 H), 2.35 (quintet, *J* = 7.2, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.21, 128.76, 117.19, 111.24, 52.37, 16.92. This NMR data compared well with that in the reference.

b) Synthesis of 2-*t*-butyl-*N,N*-dimethylaniline (1.52): A solution containing 2-*t*-butylaniline (1.49 g, 0.010 mol), methyl iodide (3.20 g, 0.023 mol), ethanol (100 mL), and 4.00 g sodium carbonate was heated at reflux over night, and then cooled to RT. After the solvent was removed by rotary evaporation, the crude materials were chromatographed (2% ethyl acetate in hexanes) on silica gel, affording the product 2-*t*-butyl-*N,N*-dimethylaniline (0.93 g, 53%). ^{1}H NMR (300 Hz, $CDCl_3$) δ 7.36 (m, 2 H), 7.34 (m, 1 H), 7.22 (m, 1 H), 2.60 (s, 6 H), 1.44 (s, 9 H); ^{13}C NMR (75Hz, $CDCl_3$): δ 155.13, 147.29, 126.92, 126.66, 125.53, 125.12, 47.08, 35.41, 30.88.

c) Synthesis of 2,6,*N*,*N*-tetramethylaniline (1.53): A solution containing 2,6-dimethylaniline (1.21 g, 0.010 mol), methyl iodide (3.20 g, 0.023 mol), ethanol (100 mL), and 4.00 g sodium carbonate was heated at reflux over night, and then cooled to RT. After the solvent was removed by rotary evaporation, the crude materials were chromatographed (2% ethyl acetate in hexanes) on silica gel, affording the product 2,6,*N*,*N*-tetramethylaniline (1.05 g, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (m, 3 H), 2.80 (s, 6 H), 2.29 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.62, 137.08, 128.73, 124.66, 42.43, 19.13.

d) General procedure for the formation of LDBB in the presence of catalyst: Li (dispersion) (115 mg, 5 mmol) was placed in a 100 mL three-necked flask under an argon, and was washed with three portions of 10.0 mL hexane. THF (10.0 mL), DBB (266 mg, 1.00 mmol) and 0.1 mmol of catalyst were added under an argon at –78 ^{o}C. After the mixture had been stirred for 2 h at that temperature, $(PhS)_2CH_2$ bis(phenylthio)methane (330 mg, 1.29 mmol) in 5 mL THF was dropped into the resulting mixture until the deep green color of the reaction changed to a yellow color. After the solvent of the remaining solution of $(PhS)_2CH_2$ in THF had been removing the remained $(PhS)_2CH_2$ was weighed, and the consumed $(PhS)_2CH_2$ was calculated.

Reductive lithiation of *N*-phenylazetidine 1.49

a) With preformed DBB: A solution of freshly formed LDBB (4.40 mmol) in 10 mL of THF was cooled to -15 °C prior to the slow addition of *N*-phenylazetidine (**1.49**, 266 mg, 2.0 mmol) under an argon. The reaction mixture was stirred at the same temperature for 7 hours and quenched with water. The organic layer was extracted with ether (3×20.0 mL) and the combined organic layer was dried over anhydrous Na_2SO_4. Flash-column chromatography (5% ethyl acetate in hexanes) gave *N*-propylaniline **1.55** (265 mg, 99%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (m, 2 H), 6.59 (m, 3 H), 3.60 (s, 1 H), 3.06 (t, J = 7.4, 2 H), 1.62 (m, 2 H), 0.98 (t,

J = 7.4, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.46, 129.16, 117.00, 112.63, 45.73, 22.67, 11.60. This NMR data compared well with that in the reference.[52]

b) With lithium in the presence and absence of DBB: Li (dispersion, 460 mg, 20.0 mmol) was placed in a 100 mL three-necked flask under an argon and was washed with three 10.0 mL portions of hexane. THF (10.0 mL) and *N*-phenylazetidine (**1.49**, 266 mg, 2.0 mmol) (DBB (26.6 mg) was added when it was involved) were added under an argon at room temperature. After 7 h stirring at the same temperature, water was added to the mixture. The reaction mixture was extracted with ether (3×20 mL) and the combined organic layer was dried over anhydrous Na_2SO_4. After the solvent had been removed, the crude materials were chromatographed (5% ethyl acetate in hexanes) on silica gel, affording products **1.55**, **1.56** or **1.57**. Yields depend on the amounts of Li and DBB as shown in Scheme 1.25.

1,2,3,4-Tetrahydroquinoline 1.56: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (m, 2 H), 6.60 (m, 1 H), 6.45 (m, 1 H), 3.28 (t, J = 5.6, 2 H), 2.75 (t, J =6.4, 2 H), 1.92 (tt, J =6.4, J =5.6, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.73, 129.47, 126.67, 121.40, 116.89, 114.13, 41.93, 26.92, 22.13. This NMR data compared well with Aldrich NMR spectra.

1,5-Diphenyl-1,5-diazocane 1.57: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (m, 5 H), 6.61 (m, 5 H), 3.33 (t, J = 5.6, 8 H), 1.90 (quintet, J =5.6, 4 H); MS 266(M^+), 237, 146, 130 (100), 120, 104, 91, 77, 51; m/z calcd. 266.18. This NMR data compared well with that in the reference.[57]

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2.0 CHAPTER TWO

Pd-catalyzed Zn-ene Cyclization and Its Application to the Total Synthesis of 15-Deoxy-$\Delta^{12,14}$-PGJ_2

This work was carried out in collaboration with Dr. Kai Deng

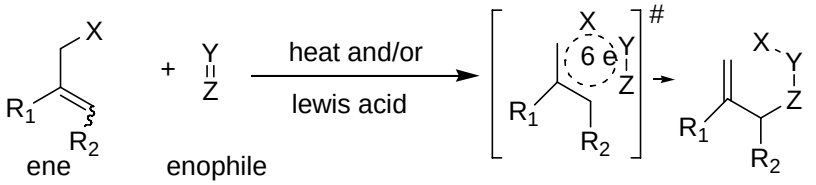
2004-2005

2.1 INTRODUCTION

2.1.1 Background for metallo-ene reactions

The ene reaction is the addition of a compound with a double bond having an allylic hydrogen (the "ene") to a compound with a multiple bond (the "enophile"). As illustrated in Scheme 2.1, the formation of 1:1 adducts by ene and enophile usually involves a cyclic six-electron transition state.[1,2]

Scheme 2.1 Ene reactions



X = H : ene reaction, X = M : metallo-ene reaction, X = Zn : Zn-ene reaction

enophile = carbonyl and thiocarbonyl compound, imine, alkene, alkyne

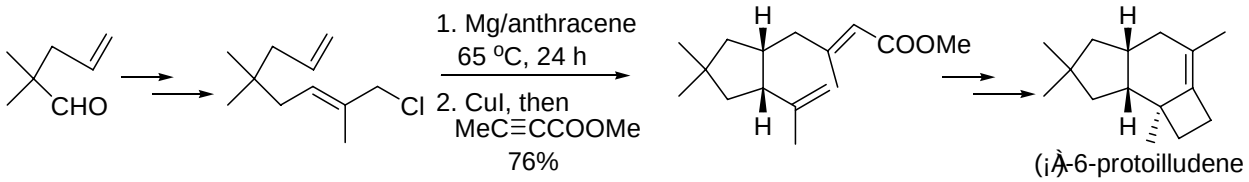
Lewis acid = BF_3¡Et_2O, $SnCl_4$, $AlEtCl_2$, $AlMe_2Cl$

When X = H, a normal ene reaction occurs. A high temperature is usually needed for such a reaction without a Lewis acid present, so it is often called the thermal ene reaction. When X = Li, Mg, Zn, B, Al, Pd, Pt or Ni, the reactions are known as metallo-ene reactions. The advantage of metallo-ene reactions are their relatively less demanding reaction conditions as compared to thermal ene reactions. Moreover, in some cases (M = Li, Mg, Zn), more functionality can be introduced simply by trapping the cyclized organometallics with various electrophiles. Since the "ene" may have different substitution patterns and the enophiles can be carbon multiple bonds or carbon heteroatom multiple bonds, the various combinations will result in a vast variety of products from ene reactions.

2.1.2 Background for Magnesium-ene Cyclizations

Magnesium-ene cyclizations[1] (intramolecular Mg-ene reactions) are well known for the syntheses of 5-membered rings in a stereoselective fashion due to the work of many chemists, especially Oppolzer. Scheme 2.2 shows the total synthesis of (±)-6-protoilludene[3] by the use of the Mg-ene cyclization as the key step to construct the cyclopentane ring stereoselectively. Treatment of allylic chloride **2.2,** with activated Mg afforded the corresponding allylmagnesium chloride, which underwent an intramolecular Mg-ene cyclization to provide a cyclopentane ring with high stereoselectivity. After the resulting cyclic primary alkylmagnesium chloride underwent transmetallation with CuI**,** the resulting cuprate was coupled with methyl 2-butynoate to generate **2.3**, which was further processed to (±)-6-protoilludene.

Scheme 2.2 Total synthesis of (±)-6-protoilludene



2.1 **2.2** **2.3** **2.4**

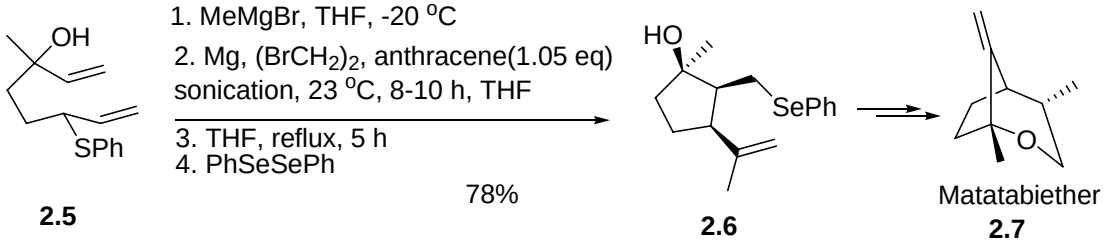
Many other superb total syntheses of natural products have been achieved by using this methodology. For examples, the syntheses of $\Delta^{9,12}$-capnellene,[4] sinularene,[5] 12-acetoxy-sinularene,[6] (+)-α-skytanthine,[7] all involve highly diastereoselective Mg-ene cyclizations as the key steps.

Recently, Cohen and co-workers developed a novel method to perform the Mg-ene cyclization by using allyl phenyl sulfides as precursors of the allylmagnesium species.[8] As illustrated in Scheme 2.3, allyl phenyl sulfide **2.5** was first treated with MeMgBr to remove the

proton on the allylic alcohol followed by the reductive allyl magnesiation using activated magnesium powder with anthracene. The Mg-ene cyclization proceeded smoothly with great stereoselectivity (*cis* : *trans* >95:1). The cyclized organomagnesium was trapped with diphenyl diselenide to produce a 78% yield of the phenyl selenide **2.6**, further elaboration of which completed the most efficient synthesis of matatabiether **2.7** to date.

Allyl phenyl sulfides are more stable than allyl halides, easier to assemble, and give no coupling product upon treatment with magnesium, thereby, making allyl phenyl sulfides superior to allyl chlorides as precursors of allylmagnesiums.

Scheme 2.3 Synthesis of matatabiether using the Mg-ene cyclization as the key step



2.5 **2.6** **2.7**

One major limitation[1] of the intramolecular Mg-ene reaction is that olefinic enophiles must be either terminally unsubstituted or strained. Another limitation[1] is that attempts to apply these cyclizations to the preparation of pyrrolidines have so far failed because of β-elimination.

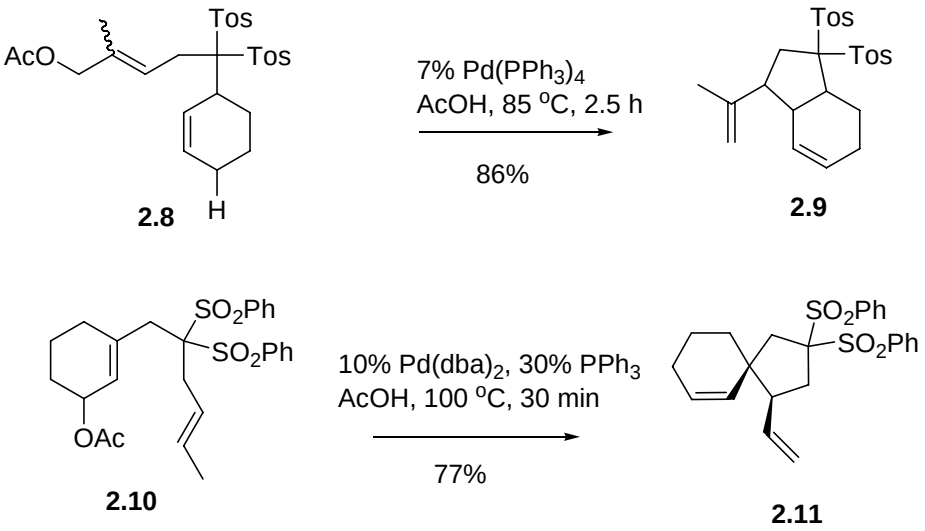
2.1.3 Background for Palladium-ene Cyclizations

Some of the limitations of the Mg-ene cyclization can be overcome by the Pd-ene cyclization. Intramolecular Pd-ene reactions have been proven to be an excellent method for the construction of 5-membered ring systems.

When allyl acetates **2.8** and **2.10** are heated in acetic acid with a catalytic amount of Pd(0),[9,10] the latter inserts into the allylic acetates to generate π-allylpalladium complexes which

undergo ene reactions efficiently to provide useful ring systems. Allyl acetates **2.8** and **2.10** were cyclized smoothly to bicyclics **2.9** and **2.11** in good yield. Moreover, since only a catalytic amount of Pd(0) is used, it is a very efficient transformation. However, the drawback of this method is that the organometallic intermediates can not be captured by reagents; instead the reaction terminates by elimination of a hydride of palladium. Thus, the reaction cannot be quenched by electrophiles to add more functionality to the cyclization products.

Scheme 2.4 Intramolecular Pd-ene reactions

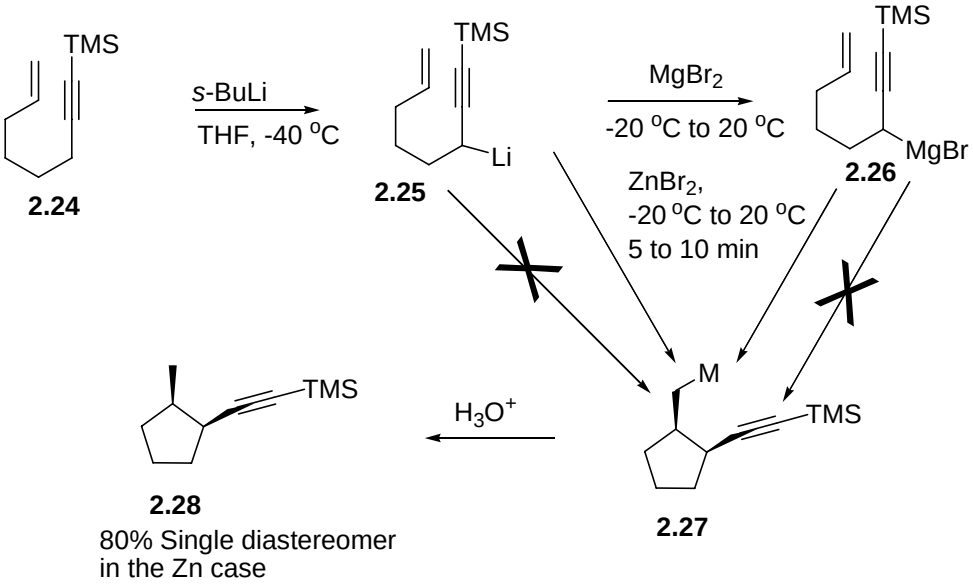


2.1.4 Background for Zinc-ene Cyclizations

Intramolecular Zn-ene cyclizations have the potential to embrace the possibility of trapping the cyclized intermediates with various electrophiles compared to Pd-ene cyclizations. However, the intramolecular Zn-ene reaction has not been widely used in organic synthesis probably due to the tedious preparation method needed for the generation of allylzincs. Traditionally, allylzincs are obtained by the transmetallation method by treating allyllithium or allylmagnesium reagents with $ZnCl_2$ or $ZnBr_2$.

As illustrated in Scheme 2.5,[11] **2.24** was cleanly metalated to **2.25** with *sec*-BuLi in THF at −40 °C. However, when **2.25** was allowed to stand for 1-2 h at 20 °C, no cyclization was observed since hydrolysis of the reaction mixture produced the starting enyne and its allenic counterpart in a 60:40 ratio. Addition of 1.0 equiv of magnesium salt to the lithium derivative to transmetalate to organomagnesium **2.26** did not lead to the cyclic product **2.27** either. However, the addition of 1.0 equiv of $ZnBr_2$ at −20 °C caused transmetalation to the organozinc and resulted in a virtually quantitative cyclization reaction after the reaction mixture was stirred for a few minutes at room temperature. In this case, the Zn-ene cyclization provided a better yield than the Li-ene cyclization and the Mg-ene cyclization.

Scheme 2.5 Zinc-ene cyclization

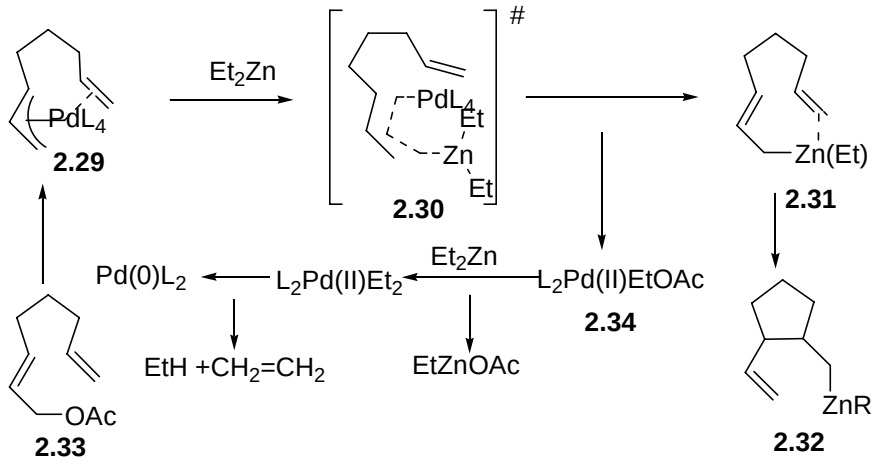


2.1.5 Background for Pd-catalyzed Zinc-ene Cyclizations

Due to the highly reactive nature of allyllithium and allylmagnesium intermediates, it is not surprising to see that this transmetalation method has poor functional group tolerance. In 1994, Oppolzer developed an excellent Pd-catalyzed Zn-ene method to overcome this limitation.[12] Palladium-catalyzed intermolecular allylation of carbonyl compounds via umpolung of π-allylpalladium by diethylzinc is known.[13] The nature of π-allylpalladium species is electrophilic.

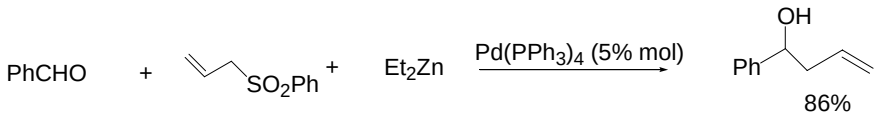
Oppolzer used this umpolung method to generate allylzincs using allyl acetates as the substrates and intramolecular Zn-ene reactions.[12] As shown in Scheme 2.6, the mechanism of this reaction is thought to involve Pd(0) insertion into the allyl acetate to generate π-allyl palladium intermediate **2.29** that undergoes transmetallation with diethylzinc through transition state **2.30** to give the corresponding allylzinc intermediate **2.31** together with ethyl palladium species **2.34**. The allylzinc **2.31** can attack the carbon-carbon multiple bond efficiently to give cyclized organozinc **2.32** capable of being trapped by electrophiles to give functionalized products. The Pd atom attached to the ethyl group undergoes PdH elimination to release ethylene and ethane and regenerate the Pd(0) catalyst. Since the elimination is the key to drive the reaction to the forward direction, the use of Me_2Zn instead of Et_2Zn causes no reaction because the methyl group has no β-hydride available to eliminate. The stereochemistry of the products was thought to be *cis* based on the C^{13} chemical shifts of the ring carbon atoms bearing the substituents in the electrophile-trapped products.[2]

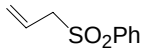
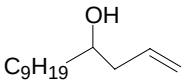
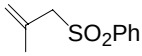
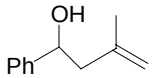
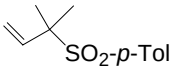
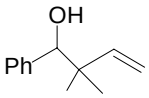
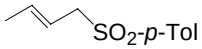
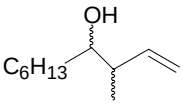
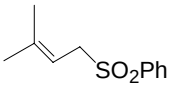
Scheme 2.6 Mechanism of palladium-catalyzed intramolecular zinc-ene reactions



Trost[14] had demonstrated that allyl phenyl sulfones could serve as substrates for allyl palladium formation, while Julia[15] had shown that allyl palladiums generated in this way could be reduced by diethylzinc to generate allylzincs capable of undergoing intermolecular addition to aldehydes (Scheme 2.7). By heating a mixture of an allyl phenyl sulfone, 5% Pd(0), 2 equivalents of Et_2Zn and PhCHO at reflux in THF, the allylzinc was produced *in situ* and attacked benzaldehyde to afford the corresponding homoallylic alcohol in good yield. As shown in Scheme 2.7, in most cases, allyl phenyl sulfones work well. Unsymmetrical allylic phenyl sulfones (entries 3 and 4) react with complete regioselectivity at their more-substituted termini in accordance with the expected behavior of allylzinc species. The reactions become slow when allyl phenyl sulfones have γ substitution (entry 4) and the reaction is completely shut down when a γ,γ-disubstituated allyl phenyl sulfone is being used (entry 5). However, it should be noted that the product expected in the latter case has almost the same steric hindrance as that formed from the allylically isomeric analogue in entry 3.

Scheme 2.7 Allyl sulfones as precursors for Pd-catalyzed allylzincation

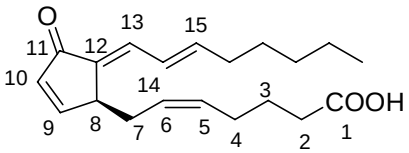


Entry	sulfone	aldehyde or ketone	product	yield
1		*n*-$C_9H_{19}CHO$		97%
2		PhCHO		88%
3		PhCHO		86%
4		*n*-$C_6H_{13}CHO$		76%
5		PhCHO	no reaction	

Due to the wide variety of methods available for producing allyl phenyl sulfones, along with their valuable feature of readily losing an α-proton to form an allyl anion that reacts with alkylating agents virtually exclusively at the α-position, it is envisioned that many substrates for Pd-catalyzed allylzincation could be constructed in a highly efficient, connective manner from allyl phenyl sulfones. Thus, instead of using allyl acetates as the precursors for Pd-catalyzed Zn-ene cyclization, using allyl phenyl sulfones would greatly increase the efficiency of substrate preparation.

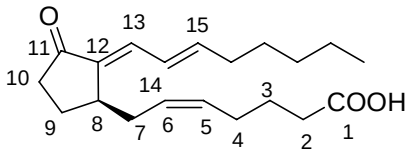
2.1.6 Background for the Total Synthesis of 15-Deoxy-$\Delta^{12,14}$-PGJ_2

Scheme 2.8 15-Deoxy-$\Delta^{12,14}$-PGJ_2 and 15-deoxy-9,10-*2H*-$\Delta^{12,14}$-PGJ_2



2.35

15-deoxy- $\Delta^{12,14}$-PGJ_2



2.36

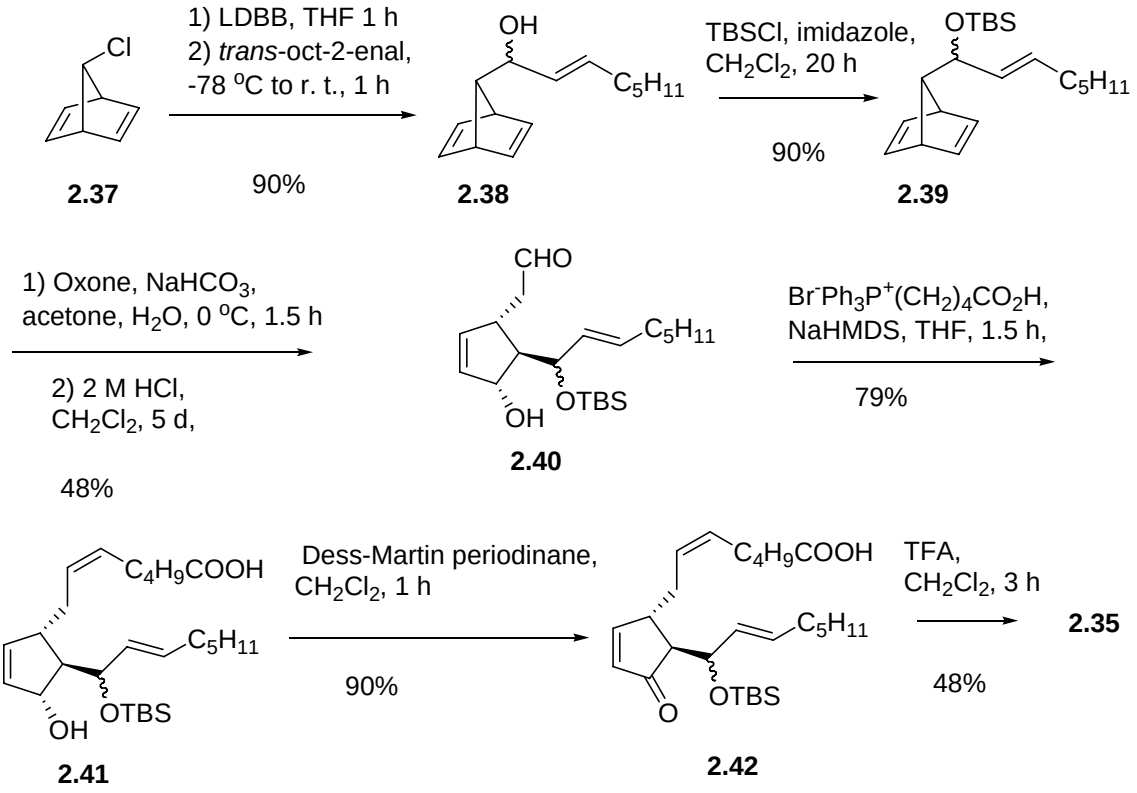
15-deoxy-9,10-*2H*- $\Delta^{12,14}$-PGJ_2

15-Deoxy- ^{12,14}-PGJ_2 (15-d-PGJ_2) **2.35** is one of the ultimate dehydration products of PGD_2.[16] PGD_2 is formed from PGH_2 which itself is synthesized from arachidonic acid by the enzyme prostaglandin synthetase. In aqueous solution, PGD_2 forms PGJ_2. It has been shown that 15d-PGJ_2 is the agonist of the peroxisome proliferator activated receptor (PPAR)-gamma. The high-affinity binding of 15d-PGJ_2 to PPARγ is believed to be responsible for the repressive effect on gene expression.[17] Moreover, 15d-PGJ_2 is a potent anti-inflammatory agent that prevents cytokine- and endotoxin-stimulated activation of peripheral and resident tissue macrophages and cytokine-induced iNOS expression by *β*-cells by the inhibition of transcriptional activation and induction of the heat shock response.[18] There is also evidence that 15-d-PGJ_2 may have anti-tumorigenic effects due to its inhibitory effects on tumor cell proliferation and angiogenesis.[19] This compound is commercially available for biological studies.[20]

Due to the obvious biological activity, 15-d-PGJ_2 has attracted considerable attention among the synthetic community and four total syntheses have been reported so far. The first total synthesis came from Sutton's group (Scheme 2.9).[21] Treating 7-chloronorbornadiene **2.37** with LDBB affords the corresponding secondary alkyllithium which adds to *trans*-oct-2-enal to provide alcohol **2.38** in excellent yield. After protection of the secondary alcohol, the key

transformation is the oxidative rearrangement caused by treating **2.39** with oxone. Subsequent acid hydrolysis gave hydroxyaldehyde **2.40**. After Wittig olefination to install the desired *cis* double bond, Dess-Martin oxidation provided enone **2.42**. Acid induced desilylation/ dehydration furnished the natural product **2.35**. This is a rather efficient racemic synthesis even though it suffers two low yield transformations. Enantioselective syntheses of (+)-**2.35** and (-)-**2.35,** via enzyme resolution of intermediates **2.40** and **2.38** respectively, were also reported in the same paper.[21] Biological tests show that the mirror image of the natural prostaglandin (-)-**2.35** is almost equi-active as an *anti*-viral agent against Sendai virus and as an effective inhibitor of NF-κB.

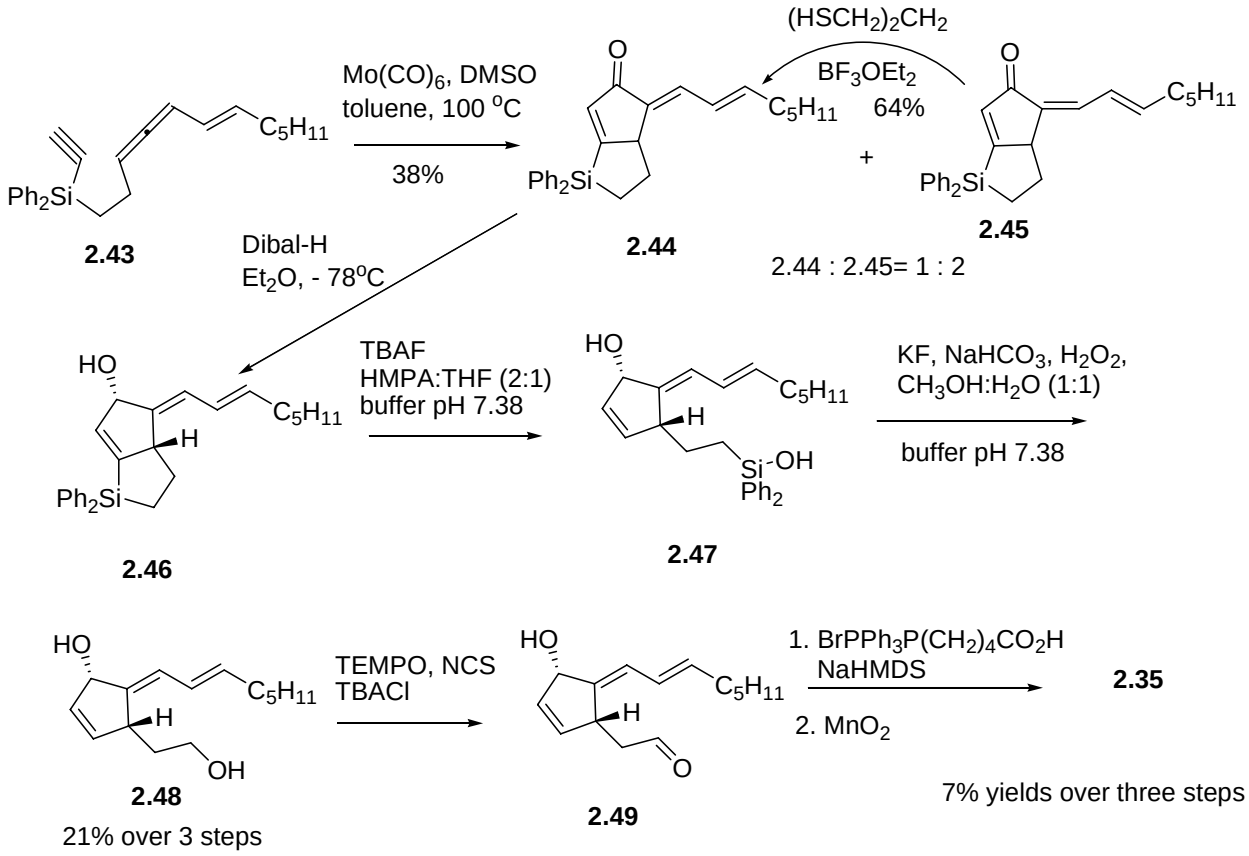
Scheme 2.9 Total synthesis of (+)-15-deoxy-$\Delta^{12,14}$-PGJ2 by Sutton



The second synthesis of 15-deoxy- ^{12,14}-PGJ_2 came from Brummond's group[22] by using an allenic [2+2+1] Pauson-Khand-type reaction in which the alkyne and allene functions were

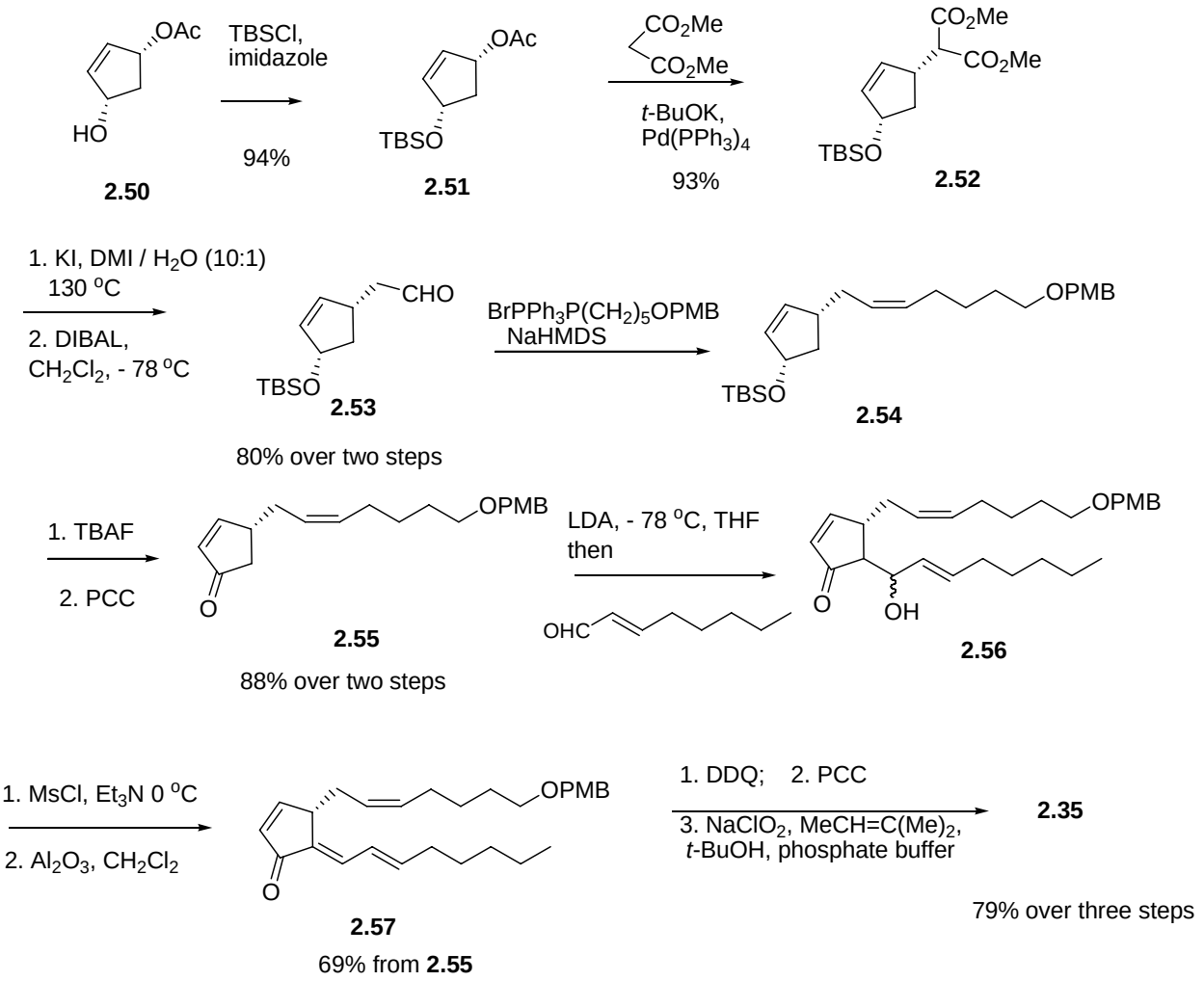
silicon-tethered. As illustrated in Scheme 2.10, compound **2.43**, prepared in 5 steps in 40% of overall yield, was subjected to Pauson-Khand reaction conditions to afford **2.44** and **2.45** in 38% yield (**2.44**:**2.45** = 1:2). The undesired enone **2.45** can be completely transformed to the desired **2.44** by using boron trifluoride and propanedithiol. Dibal-H reduction of **2.44** furnished bisallylic alcohol **2.46** which underwent a ring-opening reaction followed by oxidative desilylation to afford diol **2.48**. Selective oxidation of the primary alcohol followed by Wittig olefination and MnO_2 oxidation furnished 15-deoxy-$\Delta^{12,14}$-PGJ_2 **2.35**. Although, this synthesis suffers from several low yield steps, it was successful in unambiguously assigning the E-configuration to the C14-C15 alkene by a careful study of the 2D NMR spectrum.

Scheme 2.10 Total synthesis of 15-deoxy-Δ12,14-PGJ2 by Brummond



The third total synthesis came from Kobayashi's group (Scheme 2.11).[23] The first key step in the synthesis is palladium-catalyzed alkylation of the TBS ether **2.51** of 4-cyclopentene-1,3-diol monoacetate with an anion derived from methyl malonate to afford **2.52**. The second key transformation is the aldol reaction between the enone **2.55** and an ω-chain aldehyde to furnish aldol adduct **2.56**. The derived mesylate of **2.56** was exposed to Al_2O_3 to afford the cross-conjugated dienone **2.57**. Further transformations afforded the optical active natural product **2.35**.

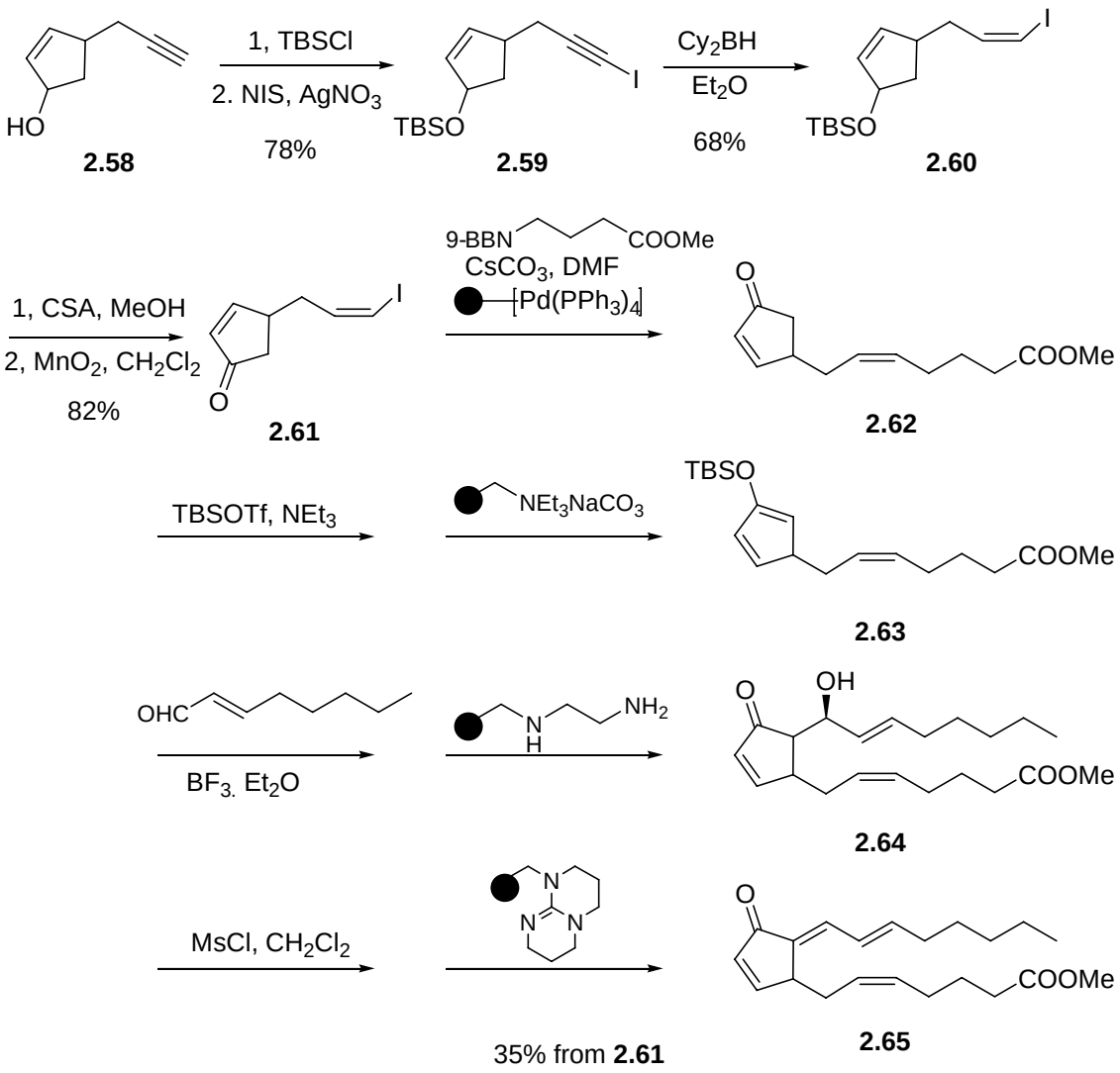
Scheme 2.11 Total synthesis of (+)-15-deoxy-$\Delta^{12,14}$-PGJ_2 by Kobayashi



Uchida and Takashi[24] just finished the fourth total synthesis last year (Scheme 2.12). The synthesis of 15-deoxy-$\Delta^{12,14}$-PGJ_2 involved the use of a vinyl iodide bearing cyclopentenone **2.61** as a key intermediate. It underwent Suzuki-Miyaura coupling and subsequent Lewis acid catalyzed aldol condensation. The *cis*-configuration of **2.60** was achieved by the reduction of alkyne **2.59**. Polymer-supported catalysts and scavengers were adapted for use in four diverse steps, in which workup and purification can be performed by simple filteration of solid-

supported reagents. Based on this methodology, they succeeded in the synthesis of 16 PGJ_2 derivatives that contain variable α and ω chains.

Scheme 2.12 Total synthesis of 15-deoxy-Δ12,14-PGJ2 by Uchida and Takashi

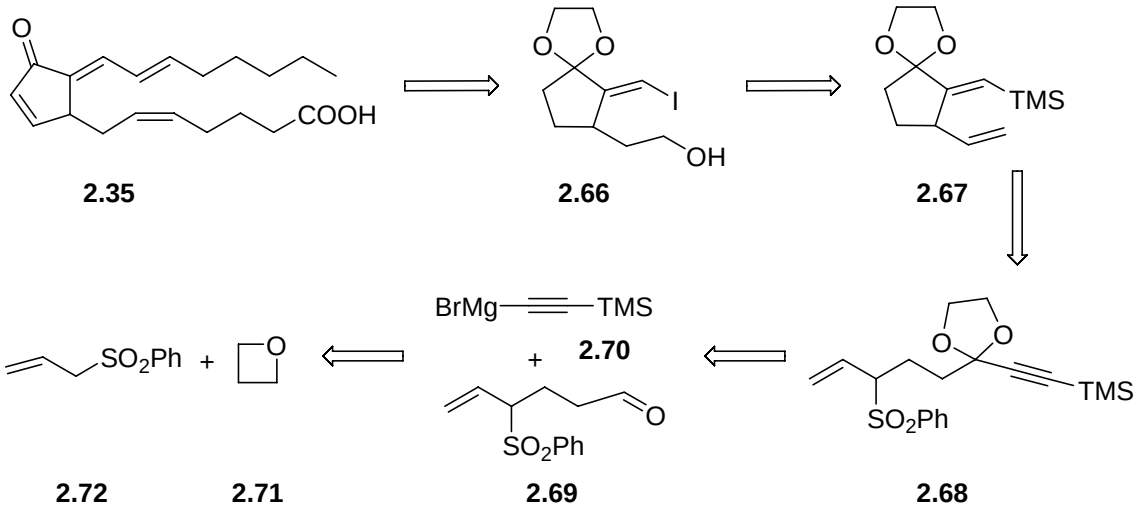


The four reported syntheses of 15-deoxy-^{12,14}-PGJ_2 share a common synthetic feature, the introduction of the double bond on the cyclopentanone ring at a very early stage of their syntheses. This is an advantage for the synthesis of 15-deoxy-^{12,14}-PGJ_2, but this method is not suitable for synthesizing 15-deoxy-9,10-*2H*-^{12,14}-PGJ_2.[25] The latter is an important

prostaglandin analog of 15-d-PGJ_2 with structural modifications intended to give it PPARγ ligand activity and resistance to metabolism.[26]

It was envisioned that 9,10-*2H*-15-deoxy-^{12,14}-PGJ_2 can serve as precursor for 15d-PGJ_2. Retrosynthetically, the double bond on the cyclopentane ring of 15d-PGJ_2 can be installed by organoselenium chemistry. The diene moiety can be constructed from Suzuki coupling reaction and the Z-double bond can be obtained by a Wittig reaction. This disconnection leads to vinyl iodide **2.66**, which can be obtained from vinyl silane **2.67** by Si-I exchange (Scheme 2.13). The 5-membered ring of vinyl silane **2.67** can in turn be prepared by Pd-catalyzed Zn-ene cyclization. The features of our retrosynthesis are: (a) both 15-deoxy-^{12,14}-PGJ_2 and 9,10-*2H*-15-deoxy-^{12,14}-PGJ_2 can be obtained by one reaction sequence; (b) stereoselective introduction of each double bond; (c) the ease in which the allyl phenyl sulfone precursor **2.68** for Pd-catalyzed Zn-ene cyclization can be assembled.

Scheme 2.13 Retrosynthetic analysis using a Zn-ene cyclization as the key step



2.2 RESULTS AND DISCUSSION

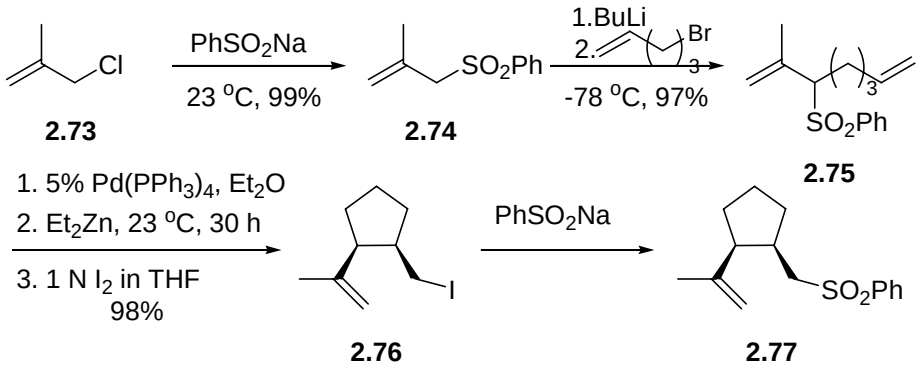
2.2.1 Pd-catalyzed Zn-ene Cyclization Utilizing Allyl Phenyl Sulfones as Precursors of Allylzincs

We now present syntheses of small molecules and natural product 15d-PGJ_2 **2.35** by preparing in a highly efficient manner the allyl sulfones required for α-alkylation and intramolecular carbozincation. Furthermore, we provide the first definitive evidence that the Pd-catalyzed Zn-ene cyclization provides *cis*-disubstitued 5-membered rings as in Mg-ene cases; this fact has some bearing on the question of whether this is a Zn-ene rather than a Pd-ene cyclization.

One example of the production of a simple allyl phenyl sulfone is illustrated by the production of methallyl phenyl sulfone **2.74**[27] by treatment of methallyl chloride with commercial $C_6H_5SO_2Na$ (Scheme 2.14**)**.[28] The allyl phenyl sulfone anion, generated by treatment of **2.74** with *n*-butyllithium, is alkylated exclusively at the α-position by 1-bromo-4-pentene to provide a high yield of cyclization substrate **2.75**. Subjecting **2.75** to 5 mol % $Pd(PPh_3)_4$ and 6 equiv of Et_2Zn affords the cyclopentane derivative, after iodination, in excellent yield as the only detectable product **2.76**. The *cis* stereochemistry of **2.76** was established by converting a sample to the corresponding sulfone **2.77**; both the ^{13}C and ^{1}H NMR spectra of the latter were identical with those reported for the same compound, the X-ray crystal structure of which had been determined.[29] This definitive evidence for the stereochemistry of the cyclization product lends strong credence to the suggestions of Oppolzer and Schröder that the main products of the Pd-catalyzed Zn-ene cyclizations are indeed rings bearing adjacent *cis* substituents. It also provides some support, albeit weak, for their contention that this is a Zn-ene

cyclization rather than a Pd-ene cyclization, followed by Zn-Pd exchange; the Pd-ene cyclization in an analogous system, although under somewhat different conditions, yields a *trans* product.[22]

Scheme 2.14 Palladium catalyzed zinc-ene reaction

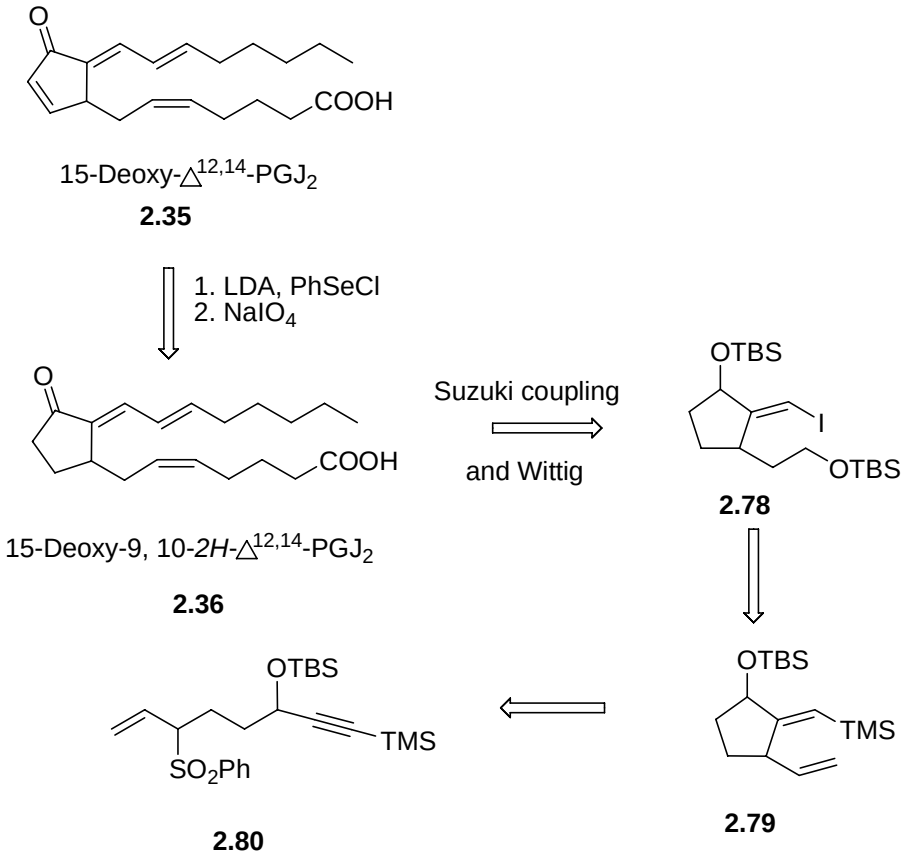


2.73 **2.74** **2.75** **2.76** **2.77**

2.2.2 Approach I to the Total Synthesis of 15-Deoxy-9,10-*2H*- ^{12,14}-PGJ$_2$

Our retrosynthetic approach to the total synthesis of 15-deoxy- ^{12,14}-PGJ$_2$ is shown in Scheme 2.15. The key reaction in the retrosynthetic analysis is the Zn-ene cyclization of substrate **2.80** to afford **2.79**. Vinylsilane **2.79** is elaborated to synthesize vinyl iodide **2.78**, which can undergo a Suzuki coupling reaction to install the desired diene side chain. A Wittig reaction can set the Z-double bond in another side chain. The approach also features late stage introduction of a double bond on the cyclopentane ring. Therefore, both 15-deoxy-9,10-2H- ^{12,14}-PGJ$_2$ **2.35** and 15-deoxy- ^{12,14}-PGJ$_2$ **2.36** should be available by this route.

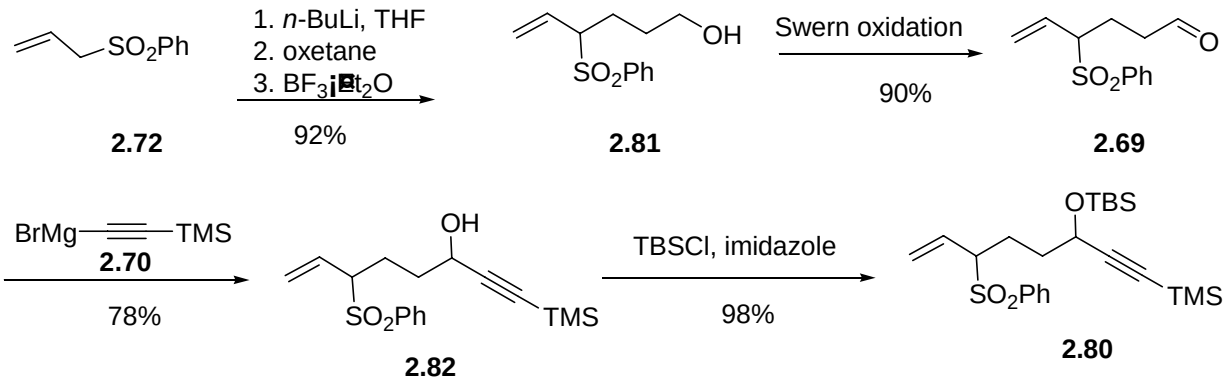
Scheme 2.15 Retrosynthetic analysis for 15-deoxy-Δ12,14-PGJ2 (approach I)



Based the original work of Kai Deng, the substrate **2.80**, capable of Zn-ene cyclization, was resynthesized from allyl phenyl sulfone **2.72** (Scheme 2.16). The latter was treated with 1.2 equiv. of *n*-BuLi in the presence of 1.2 equiv. of DMPU at –78 ^{o}C in THF. The resulted allyl carbanion reacted with oxetane highly selectively at the α-position in the presence of the Lewis acid BF_3•Et_2O to afford **2.81** in 92% yield. No product resulting from attack of the allyl carbanion on THF was observed at –78 ^{o}C. The aldehyde **2.69,** which was generated from alcohol **2.81** by Swern oxidation[30] in 90% yield, was attacked by trimethylsilylethynyl magnesium bromide **2.70** (generated by treating trimethylsilylacetylene with EtMgBr) to give

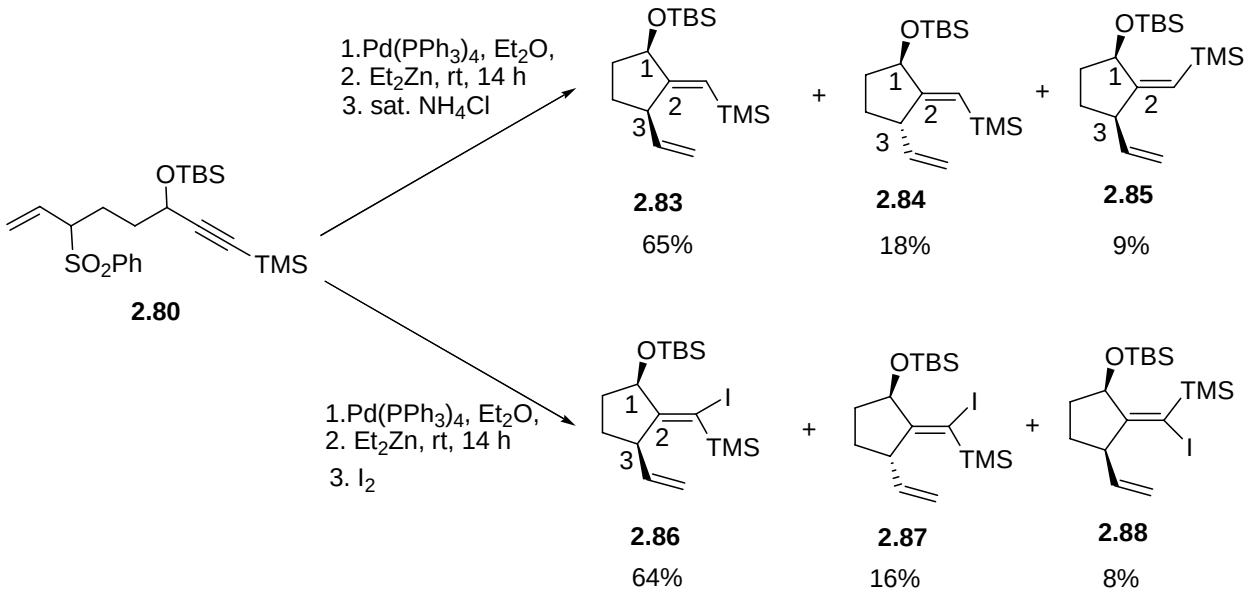
propargylic alcohol **2.82** in 78% yield. Protection of the alcohol with TBSCl in the presence of imidazole afforded cyclization precursor sulfone **2.80** in 98% yield.

Scheme 2.16 Synthesis of cyclization precursor sulfone 2.80 by Kai Deng



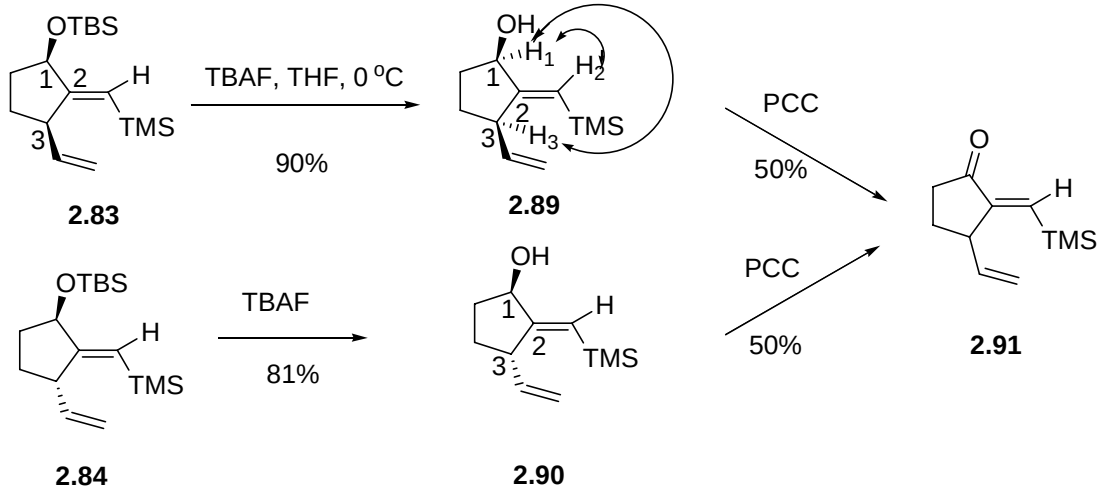
When $Pd(PPh_3)_4/Et_2Zn$ was added to allyl phenyl sulfone **2.80** in diethyl ether, Pd(0) inserted into the C-S bond and the transmetallation of Pd by Zn resulted in an allylzinc, which added to the internal alkyne enophile, resulting in cyclization (Scheme 2.17). After 14 h at room temperature, the reaction was quenched with saturated NH_4Cl aqueous solution. Three products **2.83**, **2.84**, **2.85** were isolated in 65%, 18%, and 9% yields, respectively, after purification by flash-column chromatography. When the reaction was quenched with I_2, products **2.86**, **2.87**, **2.88** were isolated in 64%, 16% and 8% yields respectively. Therefore, the stereoselectivity of cyclization of the allylzinc to the alkyne is fairly high but not complete.

Scheme 2.17 Cyclization studies of allyl phenyl sulfone 2.80 by Kai Deng



Deng assigned the stereochemistry of **2.83** based on the 2D NMR spectrum of its derivative **2.89** (Scheme 2.18). The ROESY spectrum clearly shows the cross peaks between H_1 and H_2 and H_1 and H_3. The cross peak between H_1 and H_3 indicates that the hydroxy group at C-1 and the vinyl group at C-3 are on the same side of the ring. The cross peak between H_1 and H_2 supports the *E* geometry of the vinylsilane.

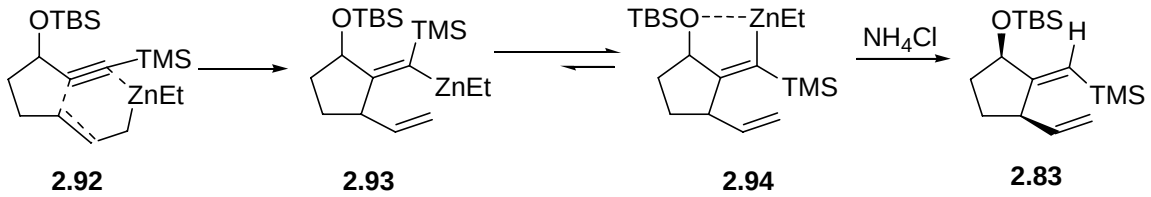
Scheme 2.18 Stereochemical proof for vinylsilanes by Kai Deng



As illustrated in Scheme 2.18, **2.83** and **2.84** were treated with TBAF to generate alcohols **2.89** and **2.90,** respectively, which were then oxidized with PCC to provide the same ketone **2.91**. This proves that alcohols **2.89** and **2.90** must have the same *E* vinylsilane geometry. Since the stereochemistry of alcohol **2.89** has been determined to have a 1,3-*cis* relationship between the two substituents, alcohol **2.90** must have the two substituents at C-1 and C-3 *trans* to each other. Compounds **2.83** and **2.84** should have the same stereochemistry as **2.89** and **2.90**, respectively, because the desilylation reactions do not involve a change of in stereochemistry.

It is interesting to note that the major products **2.83** and **2.86** appear to result from an *anti* addition of the allylzinc intermediate to the internal alkyne. The probable mechanism of formation of the vinylsilane **2.83** is shown in Scheme 2.19. Initially, vinylzinc intermediate **2.93** results from *syn* addition of the allyzinc to the internal alkyne. The silyl ether group appearently caused isomerization[31] of vinylzinc intermediate **2.93** to the more stable intermediate **2.94**, in which the oxygen atom can coordinate with the zinc. Aqueous workup provided vinylsilane **2.83** as the major product.

Scheme 2.19 Isomerization of vinylzinc

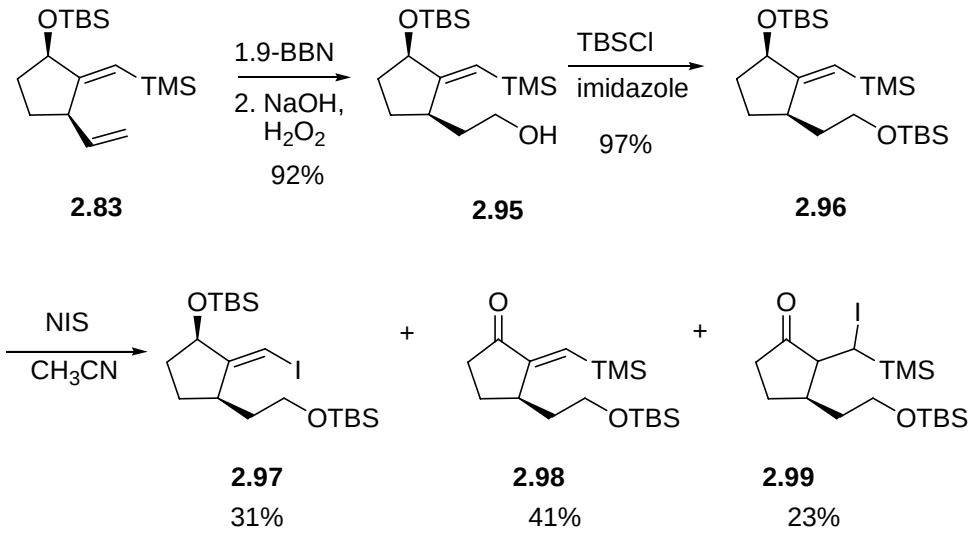


2.92 **2.93** **2.94** **2.83**

In collaboration with Deng, vinyl iodide **2.97** was synthesized as shown in Scheme 2.20. Primary alcohol **2.95** was obtained in 92% yield by hydroboration of **2.83** with 9-BBN at 0 °C followed by oxidation of the resulting alkylborane with H_2O_2. Alcohol protection of **2.95** with TBSCl and imidazole afforded vinylsilane **2.96** in 97% yield. Deng treated vinylsilane **2.96** with

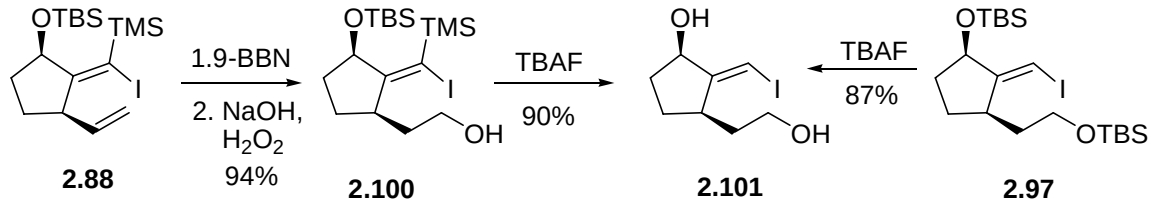
NIS[32] in CH_3CN at 0 °C to afford the desired vinyl iodide **2.97** in 31**%** yield and by-products **2.98** and **2.99** in yields of 41% and 23%, respectively.

Scheme 2.20 Synthesis of vinyl iodide 2.97 by Kai Deng and Ao Yang



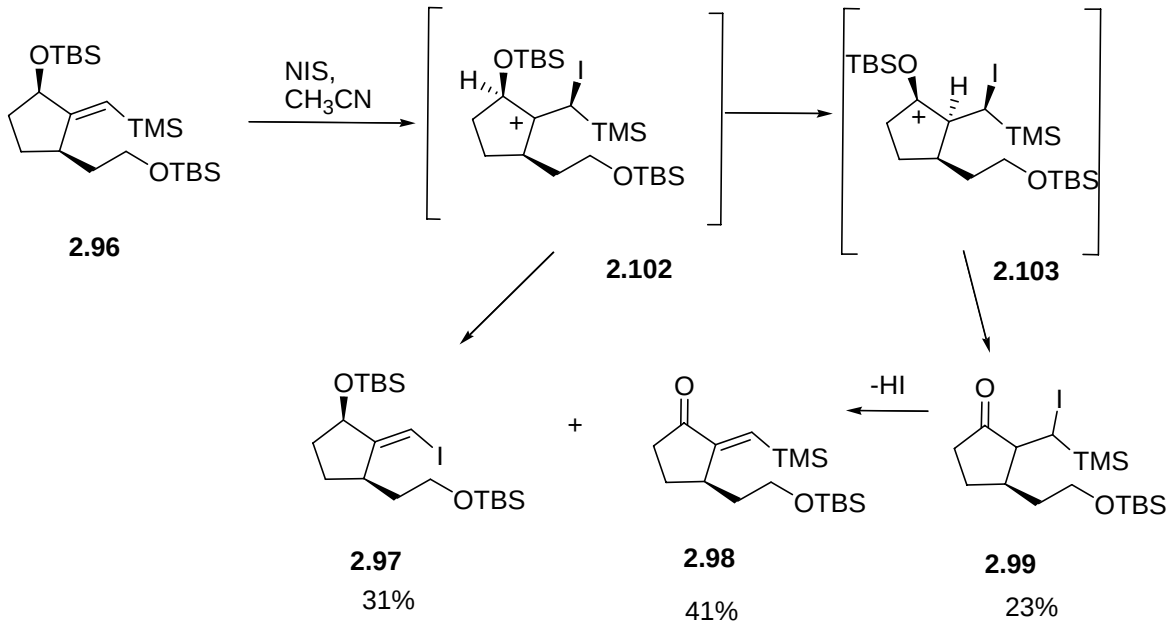
Based on the above results, the stereochemistry of compound **2.97** was determined by the following method in Deng's study. As shown in Scheme 2.21, **2.88,** which has the same stereochemical relationship at the two chiral centers as **2.97**, underwent hydroboration with 9-BBN, followed by oxidation, to provide alcohol **2.100**. Product **2.101,** from desilylation of **2.100** with TBAF, is identical to the compound obtained by desilylation of vinyl iodide **2.97**, which was obtained from **2.83** by the transformations shown in Scheme 2.20. These transformations did not change the initial stereochemistry of **2.83**. Thus, **2.97** must have the two substituents at C-1 and C-3 *Z* to each other. The double bond geometry in **2.83** is known to be *E*, thus, the vinyl iodide geometry in **2.97** must be *E*.

Scheme 2.21 Synthesis for vinyl iodide 2.102 by Kai Deng



The proposed mechanism for the iodination is shown in Scheme 2.22. The addition of I^+ across the double bond of the vinylsilane forms an intermediate cation **2.102**, which could lose TMS to react further and produce the desired vinyl iodide **2.97,** or undergo a 1,2-hydride shift to afford cation **2.103**, which is stabilized by an adjacent oxygen atom. After elimination of the TBS group, cation **2.103** affords ketone **2.99** which loses HI to produce **2.98**.

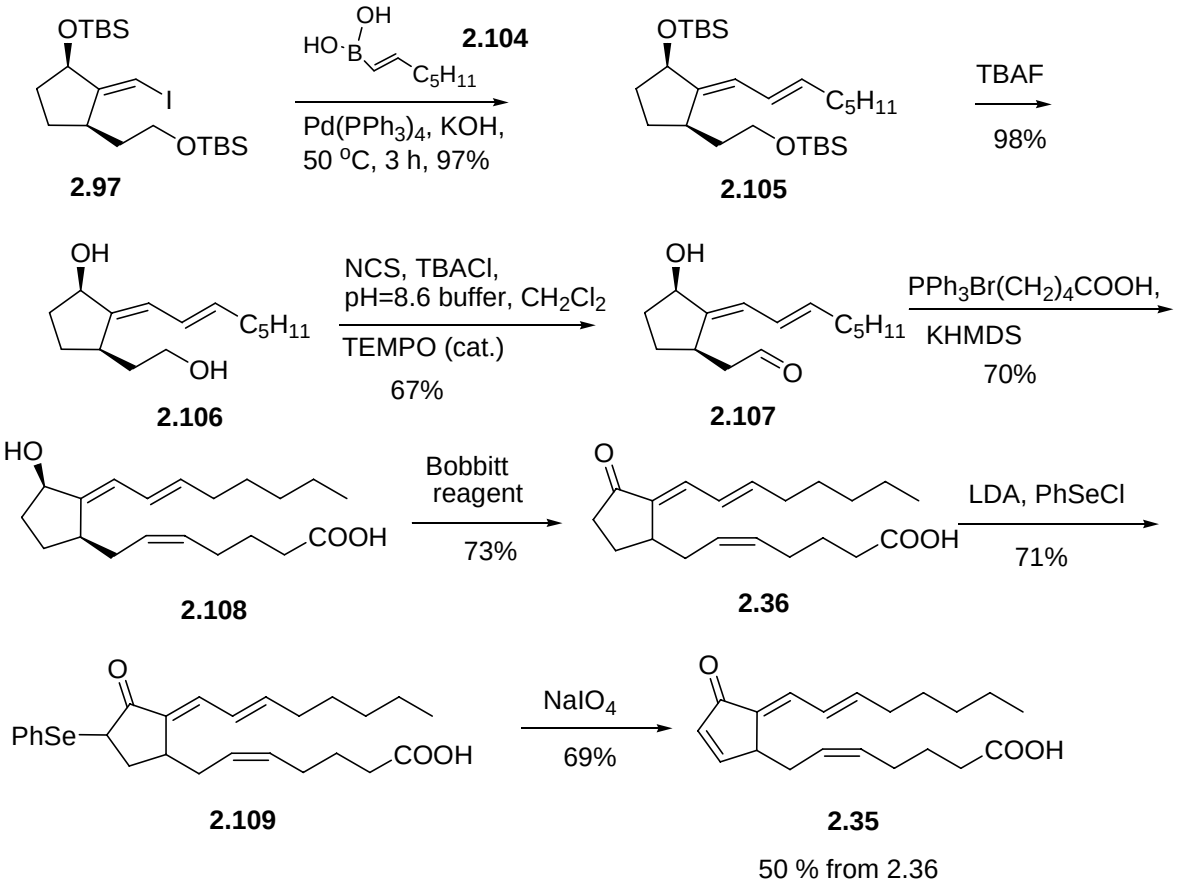
Scheme 2.22 Mechanism for the formation of vinyl iodide 2.97 by Kai Deng



In collaboration with Deng, the sythesis of 15d-PGJ_2 **2.35** was accomplished as in Scheme 2.23. Suzuki coupling[33] between vinyl iodide **2.97** and vinylboronic acid **2.104**[34] with Pd(0) catalysis afforded the desired diene **2.105** in 97% yield. Desilylation with TBAF gave a 98% yield of diol **2.106**, which underwent selective oxidation of the primary alcohol in the

presence of the secondary alcohol by NCS with TEMPO as catalyst in buffer conditions based on the methodology developed by Einhorn.[35] Deng established the *Z*-double bond with a Wittig reaction[36] of **2.107** to afford desired acid **2.108** in 70% yield and oxidated the latter to furnish 9,10-2H-15-deoxy- ^{12,14}-PGJ_2 **2.36** with Bobbitt's reagent.[37] This reagent does not require anhydrous conditions, does not involve heavy metals, and the process can be carried out conveniently.

Scheme 2.23 Total synthesis of 9,10-*2H*-15-d PGJ_2 and 15-d PGJ_2 by Kai Deng and Ao Yang



Installation of the double bond on the cyclopentanone ring was accomplished by organoselenium chemistry, which converts ketones to enones by selenoxide *syn* elimination.[38] **2.108** was treated with 2.3 equivalent of LDA at -78 °C to generate the corresponding dianion, which was quenched by PhSeCl to provide α-phenylselenyl substituted ketoacid **2.109.** The

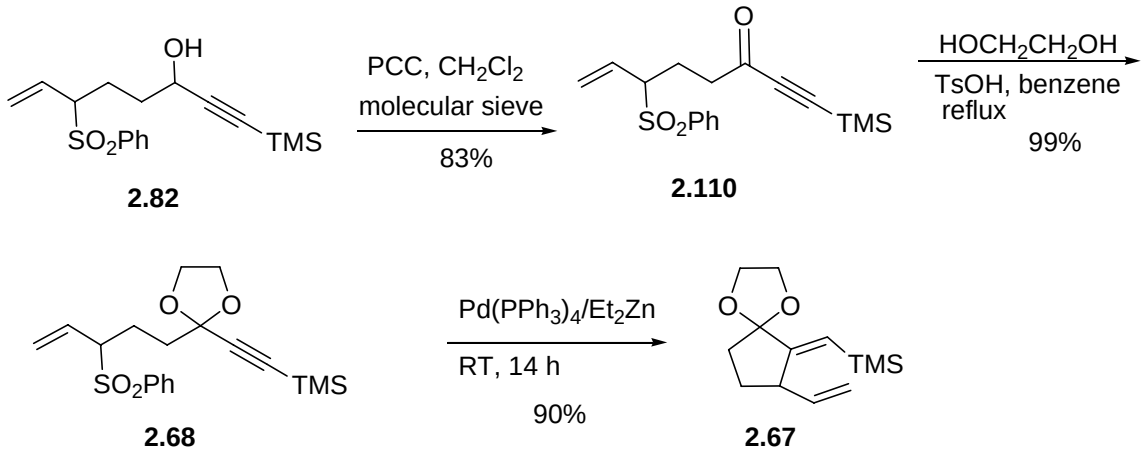
oxidation of phenylselenide to phenylselenoxide is a facile transformation for which many reagents have been employed in the literature, such as H_2O_2, *m*-CPBA, O_3, $NaIO_4$. In Scheme 2.23, $NaIO_4$ was used to oxidize the α-phenylselenyl substituted ketoacid **2.109** in aqueous methanol and subsequent elimination of the resulting α-phenylselenoxide occurred readily at room temperature to provide the desired natural product 15-d PGJ_2 **2.35** in 50% overall yield in two steps from **2.36**.

2.2.3 Approach II to the Synthesis of 15-Deoxy-9,10-2H-^{12,14}-PGJ_2

Since there was substantial trouble in the transformation from vinylsilane **2.96** to vinyl iodide **2.97** and since the stereoselectivity in the Zn-ene cyclization was not as high as desired in our first generation approach to the natural product, we set about to develop a more efficient approach II. The main feature of this approach is to introduce a ketal group at an early stage of the synthesis (Scheme 2.24).

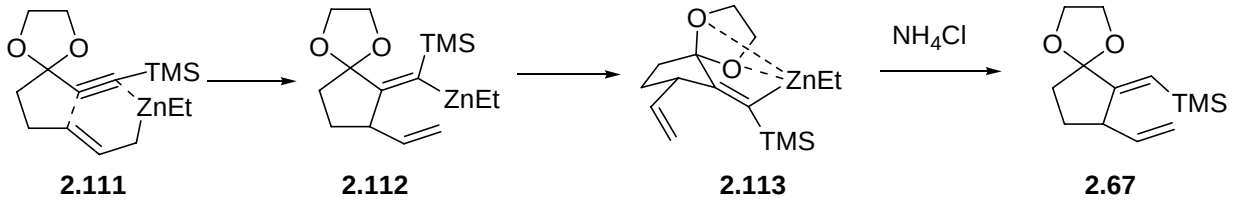
Synthesis of vinylsilane **2.67** in collaboration with Deng is illustrated in Scheme 2.24. Propargylic alcohol **2.82** was treated[39] at room temperature with PCC in CH_2Cl_2 to afford an 83% yield of the corresponding ketone **2.110**, which was converted to the desired ketal **2.68** in quantitative yield with ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid in benzene.[40] When **2.68** was subjected to $Pd(PPh_3)_4/Et_2Zn$ in Et_2O, the generated allylzinc intermediate underwent the Zn-ene cyclization smoothly. Aqueous workup afforded **2.67** in 92% yield as a single diastereomer. Compared with the poor stereoselectivity obtained in the Zn-ene cyclization in our first generation approach, the use of the ketal protecting group greatly increased the efficiency of the Zn-ene cyclization.

Scheme 2.24 Zn-ene cyclization with a ketal at the propargylic position by Kai Deng and Ao Yang



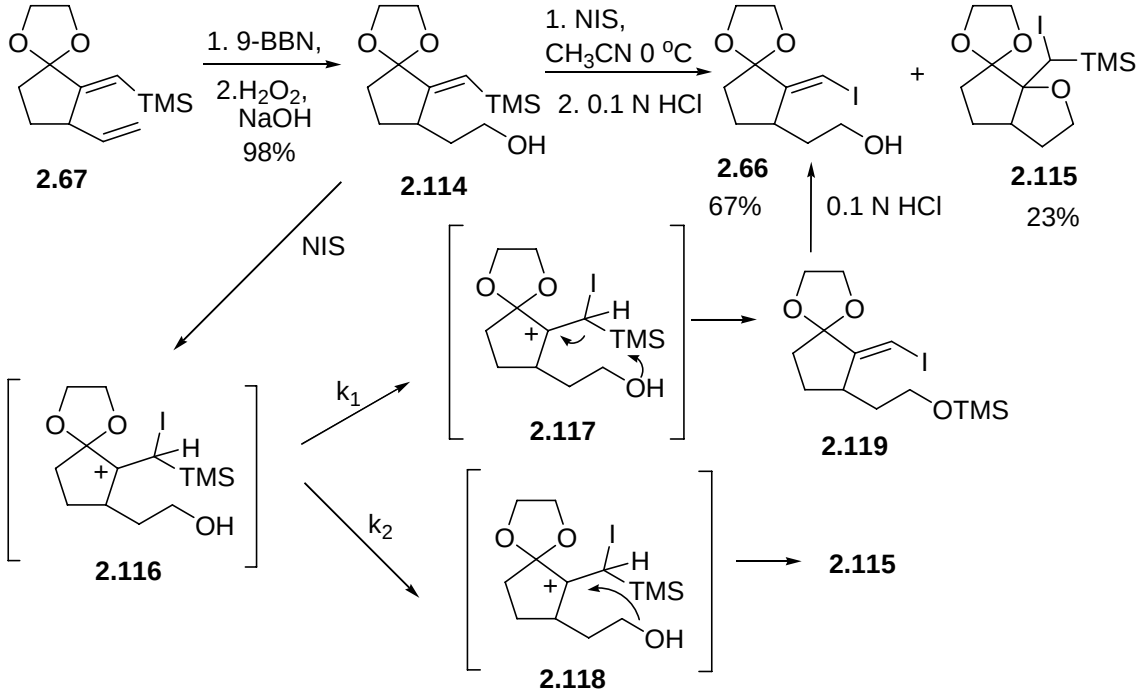
The product **2.67** also appears to result from an *anti* addition of the allylzinc intermediate to the internal alkyne. The proposed mechanism of the formation of vinylsilane **2.67,** shown in Scheme 2.25, involves an isomerization analogous to that shown in Scheme 2.19. The *cis* addition product, vinylzinc intermediate **2.112**, completely isomerizes[31] to the more stable intermediate **2.113**, in which both oxygen atoms can probably coordinate with the zinc.

Scheme 2.25 Zn-ene cyclization of 2.60 and the mechanism



In Deng's study, as shown in Scheme 2.26, hydroboration of alkene **2.67** with 9-BBN followed by oxidation with $NaOH/H_2O_2$ provided primary alcohol **2.114** in 98% yield. Si-I exchange by Deng was performed by treating alcohol **2.114** with N-iodosuccinimide in acetonitrile. The desired vinyl iodide **2.66** was generated in 67% yield together with 23% of by-product **2.115**. 0.1 N HCl was needed to wash the ether extracts of the reaction mixture in order to obtain product **2.66**. Without acid wash, three compounds, **2.66**, **2.119** and **2.115** were obtained in 31%, 34% and 23% yields, respectively, after flash-column chromatography.

Scheme 2.26 Hydroboration and Si-I exchange reactions by Kai Deng

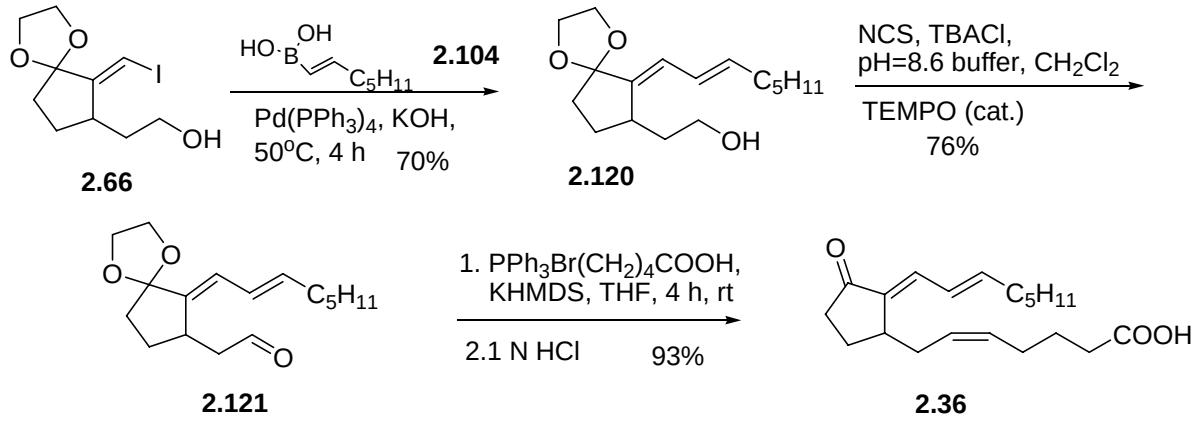


The mechanism of the reaction is proposed in Scheme 2.26. Cationic intermediate **2.116**, produced by the addition of I^+ across the vinylsilane, has three reaction pathways. The first pathway involves elimination of the TMS group by attack of an external nucleophile to afford the desired vinyl iodide **2.66**. The second pathway involves internal nucleophilic attack of the primary alcohol on the TMS group to generate the vinyl iodide **2.119**, which can be converted into the desired **2.66** by washing the ether extracts of the reaction mixture with 0.1 N HCl. The third pathway is the internal attack of the alcohol oxygen atom onto the cation itself to form a bicyclic compound **2.115** as a single diastereomer.

9,10-*2H*-15-d PGJ_2 was synthesized again by Deng and Yang. As shown in Scheme 2.27, Suzuki coupling of vinyl iodide **2.66** with *trans*-1-heptenyl boronic acid **2.104** afforded a 70% yield of diene **2.120**, which was oxidated by the TEMPO based methodology described before to afford the corresponding aldehyde **2.121**. A Wittig reaction installed the Z-olefin side

chain, followed by acid work-up to remove the ketal protecting group to reveal the desired ketone functionality, producing 9,10-2H-15-deoxy-^{12,14}-PGJ_2 **2.36** in 93% yield.

Scheme 2.27 Synthesis of 9,10-*2H*-15-d PGJ_2 by Kai Deng and Ao Yang



Compared with the first generation approach, this approach is far more efficient. The use of a ketal has the following advantages. Firstly, due to the symmetry, the formation of a ketal destroys a chiral carbon center and this provides a far cleaner Zn-ene cyclization since only two stereoisomers are possible. Secondly, the quaternary carbon center that bears the ketal group has no hydrogen atom available that could lead to by-products such as **2.98** and **2.99** which were observed in the transformation from **2.96** to **2.97** in approach I (Scheme 2.22). Thirdly, the ketal can be removed easily by simple acid work-up to reveal the ketone functionality without an additional deprotection step.

2.2.4 Conclusions

Allyl phenyl sulfones have been used as an alternative to the previously used allyl acetates for Pd-catalyzed Zn-ene cyclizations. Due to the ease of assembly of allyl phenyl sulfones, particularly in a connective fashion, the efficiency of substrate preparation is greatly increased.

The total synthesis of 15d-$\Delta^{12,14}$-PGJ_2 has been achieved using the Zn-ene cyclization as the key step. Two different approaches were attempted to synthesize 15d-9,10-2H-$\Delta^{12,14}$-PGJ_2. The first approach involved the addition of an allylzinc to an internal TMS-substituted alkyne bearing a propargylic TBSO group. Si-I exchange was used to obtain the vinyl iodide with the desired double bond geometry, but rearrangement of the intermediate cation was observed thus decreasing the yield. The overall yield is 2.0% in 15 linear steps. The second approach features the use of a ketal group at the propargylic position during the Zn-ene cyclization. A single isomer was obtained, probably due to complete isomerization of the vinylzinc intermediate mediated by the ketal group. The ketal group completely shuts down the cation rearrangement pathway that caused by-product formation during the Si-I exchange step in the previous synthesis. Moreover, the ketal protecting group was removed readily by an acid wash after the Wittig reaction without the need of an additional deprotection step. The overall efficiency is improved, giving an 8.0% yield in 13 linear steps.

2.3 EXPERIMENTAL SECTION

See the Experimental Sectional of Chapter One for general procedure, instrumentation and materials.

4-(Benzenesulfonyl)hex-5-en-1-ol (2.81)

To a stirred solution of allyl phenyl sulfone **2.72** (2.57 g, 14.14 mmol) in 60 mL of THF at –78 ºC was added *n*-BuLi (11.1 mL, 15.5 mmol, 1.40 M solution in cyclohexane). The resulting red solution was stirred at –78 ºC for 1 h followed by the addition of oxetane (21.2 mmol, 1.38 mL). Then $BF_3 \bullet Et_2O$ (21.2 mmol, 2.7 mL) was added in a dropwise fashion via a syringe. The

resulting mixture was stirred at -78 ºC for 30 min before the addition of 60 mL of saturated aqueous NH_4Cl. The reaction mixture was extracted with Et_2O (50 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and concentrated in vacuo. The residue was purified by column chromatography (50% EtOAc in hexane) to give 3.17 g of alcohol **2.81** (92% yield) as a pale yellow oil. IR (neat) 3516, 2937, 2874, 1447, 1304, 1289, 1146, 1085, 727, 690, 634. ^{1}H NMR ($CDCl_3$) δ 7.83-7.27 (m, 5 H), 5.58 (m, 1 H), 5.28 (d, *J* = 10.2 Hz, 1 H), 5.03 (d, *J* = 17.0 Hz, 1 H), 3.70-3.50 (m, 3 H), 2.25-2.05 (m, 3 H, including the OH hydrogen), 1.75-1.35 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 137.2, 133.8, 130.3, 129.3, 128.9, 124.0, 69.8, 62.0, 29.5, 23.7; MS (EI) *m*/*z* (relative intensity) 241 (M^++1, 8), 223 (4), 210 (9), 169 (49), 143 (18), 125 (9), 99 (50), 81 (100), 77 (31), 67 (17). HRMS (EI) calcd for $C_{12}H_{17}O_3S$ (M^++1): 241.0898, found 241.0908.

4-Benzenesulfonyl-hex-5-enal (2.69)

To a solution of oxalyl chloride (1.4 mL, 15.4 mmol) at –60 ºC in dichloromethane (60 mL) was added dimethylsulfoxide (2.20 mL, 30.8 mmol) and the temperature was carefully maintained below -50 ºC. After the reaction mixture was stirred for 5 min, a solution of alcohol **2.81** (2.84 g, 11.8 mmol) in CH_2Cl_2 (10 mL) was added. After the reaction mixture was stirred for 15 min between -50 ºC to -30 ºC, then 10 min at -30 ºC, Et_3N (8.4 mL, 60 mmol) was added and the reaction mixture had been stirred for another 5 min at -30 ºC before it was warmed to room temperature. After the addition of 50 mL of water, the aqueous phase was extracted with dichloromethane (30 mL × 3). The combined organic layer, after being washed sequentially with 1% HCl (20 mL), saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by column chromatography (25% ethyl acetate in hexane) to give 2.55 g of aldehyde **2.69** (90% yield) as a

yellow oil. IR (neat) 3066, 2936, 2832, 2730, 1723, 1447, 1305, 1147, 1085, 940, 722, 690, 634. ^{1}H NMR ($CDCl_3$) δ 9.67 (s, 1 H), 7.79-7.46 (m, 5 H), 5.54 (m, 1 H), 5.26 (dd, *J* = 10.2, 0 Hz, 1 H), 5.00 (dd, *J* = 17.0, 0 Hz, 1 H), 3.55 (m, 1 H), 2.59-2.49 (m, 2 H), 2.39-2.32 (m, 1 H), 1.95-1.88 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 200.5, 137.1, 134.0, 129.6, 129.2, 129.0, 124.5, 68.6, 40.4, 20.0; MS (EI) *m*/*z* (relative intensity) 239 (M^++1, 17), 210 (14), 195 (21), 143 (15), 125 (15), 97 (100), 79 (57), 69 (53). HRMS (EI) calcd for $C_{12}H_{15}O_3S$ (M^++1): 239.0742, found 239.0743.

6-Benzenesulfonyl-1-trimethylsilanyl-oct-7-en-1-yn-3-ol (2.82)

Trimethylsilylacetylene (22.8 mmol, 2.23 g) in THF (30 ml) was allowed to cool to –78 ºC and subsequently treated with EtMgBr (21 mmol, 21 mL, 1.0 M solution THF). The cooling bath was then removed and the solution was allowed to warm to room temperature. After the reaction mixture was heated at reflux for 2 h, it was allowed to cool to room temperature. In a separate flask, aldehyde **2.69** (2.50 g, 10.5 mmol) in THF (40 mL) was allowed to cool to –78 ºC under an argon with magnetic stirring and treated with $Me_3SiC{\equiv}CMgBr$ (40 mL of the solution prepared above). The solution was stirred at –78 ºC for 30 min and then was allowed to warm to –20 ºC during 1 h period before the addition of 100 mL of saturated aqueous NH_4Cl. The reaction mixture was extracted with Et_2O (150 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and concentrated in vacuo. The residue was purified by column chromatography (40% EtOAc in hexane) to give 2.76 g of **2.82** (78% yield). IR (neat) 3491, 3067, 2960, 1447, 1305, 1250, 1146, 1084, 844. ^{1}H NMR ($CDCl_3$) δ 7.82-7.46 (m, 5 H), 5.58 (m, 1 H), 5.29 (dd, *J* = 10.1, 0 Hz, 1 H), 5.06 (dd, *J* = 17.0, 0 Hz, 1 H), 4.34 (m, 1 H), 3.59 (m, 1 H), 2.41 (br, 1 H), 2.25 (m, 1 H), 1.90-1.60 (m, 3 H), 0.12 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 137.2, 133.8, 130.1, 129.4, 129.0, 124.2, 69.4, 62.1, 34.4, 23.0, -0.057; MS (EI) *m*/*z* (relative intensity)

321 (M^+-CH_3, 9), 281 (7), 253 (11), 239 (8), 135 (13), 97 (20), 84 (100), 73 (34), 58 (37). HRMS (EI) calcd for $C_{16}H_{21}O_3SiS$ (M^+-CH_3): 321.0981, found 321.0980.

6-Benzenesulfonyl-3-(*t*-Butyl-dimethyl-silanyloxy)-1-trimethylsilanyl-oct-7-en-1-yne (2.80)

To a solution of **2.82** (3.73 g, 11.1 mmol) in DMF (50 mL) was added TBSCl (2.50 g, 16.5 mmol) followed by imidazole (1.51 g, 22.2 mmol). The mixture was stirred for 12 h and then diluted with brine (30 mL). The resulting mixture was extracted with diethyl ether (70 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography on silica gel (15% ethyl acetate in hexane) to give 4.90 g (98%) of **2.80** as a yellow oil. IR (neat) 3067, 2957, 2929, 2897, 2857, 2172, 1447, 1307, 1251, 1149, 1080, 842, 779, 723. ^{1}H NMR ($CDCl_3$) δ 7.84-7.50 (m, 5 H), 5.61 (m, 1 H), 5.33 (m, 1 H), 5.10 (m, 1 H), 4.31 (m, 1 H), 3.57 (m, 1 H), 2.20 (m, 1 H), 1.90-1.50 (m, 3 H), 0.86 (s, 9 H), 0.13 (s, 9 H), 0.07 (s, 3 H), 0.009 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 137.4, 133.7, 130.1, 129.4, 128.9, 124.1, 106.9, 89.4, 69.5, 62.8, 35.2, 25.9, 23.2, 18.3, - 0.10, - 4.3, - 4.8; MS (EI) *m*/*z* (relative intensity) 393 (M^+-C_4H_9, 39), 309 (30), 289 (11), 199 (10), 135 (100), 73 (67), 59 (96). HRMS (EI) calcd for $C_{19}H_{29}O_3Si_2S$ (M^+-C_4H_9): 393.1376, found 393.1377.

Cyclization reactions

(I) Saturated aqueous NH_4Cl quenched reaction: compounds 2.83, 2.84, 2.85.

To a solution of **2.80** (2.26 g, 5.01 mmol) in Et_2O (50 mL) at room temperature was added $Pd(PPh_3)_4$ (290 mg, 0.25 mmol). The resulting solution was stirred for 5 min before Et_2Zn (23.0 mL, 25.0 mmol, 1.10 M solution in toluene) was added. The mixture was stirred for 12 h at room temperature before it was cooled to 0 ºC and quenched with 25 mL saturated NH_4Cl solution. The resulting mixture was extracted with ether (50 mL × 3). The combined organic layer was

dried over $MgSO_4$, filtered through cotton and concentrated in vacuo. The residue was purified by flash-column chromatography (5% EtOAc in hexane) to afford **2.83**, **2.84** and **2.85**, respectively, as colorless liquids.

2.83: 1.006 g, 64.4% yield, IR (neat) 2956, 2929, 2895, 2857, 1247, 1066, 835, 774. ^{1}H NMR ($CDCl_3$) δ 5.88 (m, 1H), 5.63 (s, 1 H), 4.98 (m, 2 H), 4.26 (m, 1 H), 3.21 (m, 1 H), 1.90 -1.50 (m, 4 H), 0.91 (s, 9 H), 0.09 (s, 9 H), 0.08 (s, br, 6 H); ^{13}C NMR ($CDCl_3$) δ 163.9, 143.0, 123.5, 114.0, 78.7, 44.6, 33.0, 29.7, 26.0, 18.3, -0.03, -4.3, -4.4; MS (EI) *m*/*z* (relative intensity) 310 (M^+, 7), 253 (42), 237 (45), 195 (21), 165 (41), 147 (85), 133 (56), 73 (100), 59 (39). HRMS (EI) calcd. for $C_{17}H_{34}OSi_2$ (M^+): 310.2148, found 310.2147.

2.84: 287 mg, 18.5% yield, IR (neat) 2956, 2930, 2896, 2858, 1632, 1248, 1149, 836, 775. ^{1}H NMR ($CDCl_3$) δ 5.77 (m, 1H), 5.65 (s, 1 H), 4.97 (m, 2 H), 4.34 (m, 1 H), 3.30 (m, 1 H), 1.90 - 1.70 (m, 3 H), 1.55 (m, 1 H), 0.90 (s, 9 H), 0.14 (s, 9 H), 0.133 (s, 3 H), 0.126 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 163.3, 142.7, 120.4, 113.3, 76.1, 44.1, 33.4, 27.9, 26.1, 18.5, 0.10, -4.5, -4.6; MS (EI) *m*/*z* (relative intensity) 310 (M^+, 10), 253 (50), 237 (53), 195 (34), 147 (55), 133 (59), 73 (100), 59 (38). HRMS (EI) calcd. for $C_{17}H_{34}OSi_2$ (M^+): 310.2148, found 310.2155.

2.85: 149 mg, 9.6%, IR (neat) 2956, 2930, 2896, 2858, 1630, 1248, 1072, 860, 773. ^{1}H NMR ($CDCl_3$) δ 5.78 (m, 1 H), 5.44 (s, 1 H), 4.96 (m, 2 H), 4.61 (m, 1 H), 2.93 (m, 1 H), 1.90-1.70 (m, 3 H), 1.55 (m, 1 H), 0.90 (s, 9 H), 0.14 (s, 9 H), 0.133 (s, 3 H), 0.126 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 164.5, 143.5, 125.0, 113.5, 74.0, 51.3, 35.5, 29.3, 26.1, 18.2, 0.37, -3.3, -3.8; MS (EI) *m*/*z* (relative intensity) 310 (M^+, 3.7), 253 (40), 195 (36), 147 (80), 133 (83), 73 (100), 59 (34). HRMS (EI) calcd. for $C_{17}H_{34}OSi_2$ (M^+): 310.2148, found 310.2138.

(II) I_2 quenched reaction: compounds 2.86, 2.87, 2.88.

To a solution of **2.80** (2.83 g, 6.28 mmol) in Et_2O (60 mL) at room temperature was added $Pd(PPh_3)_4$ (363 mg, 0.314 mmol). The resulting solution was stirred for 5 min before Et_2Zn (28.5 mL, 31.4 mmol, 1.10 M solution in toluene) was added. The mixture was stirred for 12 h and then I_2 (16 g, 63.0 mmol) in 30 mL THF was added. The resulting purple mixture was stirred for 30 min before the addition of 25 mL saturated $Na_2S_2O_3$ solution. The aqueous phase was extracted with ether (50 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography (5% EtOAc in hexane) to give **2.86**, **2.87** and **2.88**, as pale yellow oils.

2.86: 1.73 g, 63.3%, IR (neat) 2955, 2929, 2896, 2856, 1250, 1076, 838, 775. ^{1}H NMR ($CDCl_3$) δ 5.85 (ddd, 1 H, *J* = 17.1, 10.3, 5.7 Hz), 5.04 (m, 2 H), 4.63 (m, 1 H), 3.40 (m, 1 H), 2.00-1.40 (m, 4 H), 0.90 (s, 9 H), 0.26 (s, 9 H), 0.23 (s, 3 H), 0.12 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 163.4, 141.5, 115.0, 108.2, 83.4, 47.1, 33.8, 31.6, 26.1, 18.1, 1.1, -3.6, -3.9; MS (EI) *m*/*z* (relative intensity) 421 (M^+-CH_3, 1.1), 379 (52), 309 (13), 259 (21), 179 (46), 147 (20), 105 (25), 73 (100), 59 (24). HRMS (EI) calcd. for $C_{16}H_{30}OSi_2I$ (M^+-CH_3): 421.0880, found 421.0888.

2.87: 431 mg, 15.7%, IR (neat) 2955, 2928, 2896, 2856, 1249, 836. ^{1}H NMR ($CDCl_3$) δ 5.79 (ddd, 1 H, J = 17.2, 10.3, 4.8 Hz), 5.06 (dt, 1 H, J = 10.3, 1.7 Hz), 5.10 (dt, 1 H, J = 17.2, 1.7 Hz), 4.69 (m, 1 H), 3.54 (m, 1 H), 2.31 (m, 1 H), 1.80 - 1.60 (m, 3 H), 0.93 (s, 9 H), 0.26 (s, 9 H), 0.25 (s, 3 H), 0.17 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 163.4, 141.9, 114.9, 110.2, 83.3, 46.7, 32.6, 28.3, 26.4, 18.5, 0.71, -3.3, -3.6; MS (EI) *m*/*z* (relative intensity) 421 (M^+-CH_3, 1.2), 379 (85), 310 (29), 259 (24), 241 (27), 179 (63), 147 (17), 105 (20), 73 (100), 59 (24). HRMS (EI) calcd. for $C_{16}H_{30}OSi_2I$ (M^+-CH_3): 421.0880, found 421.0879.

2.88: 216 mg, 7.9%, IR (neat) 2956, 2929, 2897, 2857, 1250, 1070, 836. ^{1}H NMR ($CDCl_3$) δ 5.79 (ddd, 1 H, J = 17.7, 9.9, 7.7 Hz), 5.17 (dd, 1 H, J = 17.7, 0.8 Hz), 5.10 (dd, 1 H, J = 10.0,

0.7 Hz), 4.75 (m, 1 H), 3.30 (m, 1 H), 2.03 (m, 1 H), 1.87 (m, 1 H), 1.61 (m, 1 H), 0.88 (s, 9 H), 0.31 (s, 9 H), 0.12 (S, 3 H), 0.11 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 164.6, 140.3, 115.5, 112.2, 74.7, 56.1, 35.5, 29.1, 25.9, 18.1, 1.7, -3.3, -4.3; MS (EI) *m*/*z* (relative intensity) 421 (M^+-CH_3, 0.6), 379 (40), 309 (48), 259 (44), 185 (35), 147 (70), 73 (100), 59 (25). HRMS (EI) calcd for $C_{16}H_{30}OSi_2I$ (M^+-CH_3): 421.0880, found 421.0892.

2-[3-(*tert*-Butyl-dimethyl-silanyloxy)-2-(*trans*)-trimethylsilanylmethylene-cyclopentyl]-ethanol (2.95)

To a stirred solution of vinyl silane **2.83** (973 mg, 3.14 mmol) in THF (20 mL) at 0 ºC wasadded 9-BBN (14.0 mL, 7.0 mmol). The temperature of the resulting solution was allowed to rise to room temperature and the solution was stirred for 12 h before it was allowed to cool to 0 ºC. NaOH (840 mg, 21.0 mmol) in 15 mL of H_2O was added followed by the addition of H_2O_2 (7.2 mL, 63.0 mmol). The resulting mixture was allowed to stir at room temperature for 1 h before it was extracted with ether (40 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography (20% EtOAc in hexane) to afford 948 mg of **2.95** (92% yield). IR (neat) 3353 (br), 2954, 2895, 2857, 1248, 835, 774. ^{1}H NMR ($CDCl_3$) δ 5.55 (t, 1 H, J = 1.6 Hz), 4.25 (m, 1 H), 3.72 (m, 2 H), 2.66 (m, 1 H), 1.90-1.60 (m, 6 H), 0.90 (s, 9 H), 0.14 (s, 9 H), 0.092 (s, 3 H), 0.085 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.4, 122.7, 79.8, 61.4, 39.8, 37.5, 33.6, 28.2, 26.0, 18.3, 0.06, -4.2, -4.4; MS (EI) *m*/*z* (relative intensity) 328 (M^+, 0.9), 313 (0.5), 283 (5.1), 255 (43), 183 (24), 147 (52), 107 (55), 73 (100), 59 (23). HRMS (EI) calcd for $C_{17}H_{36}O_2Si_2$ (M^+): 328.2254, found 328.2254.

1-(*tert*-Butyl-dimethyl-silanyloxy)-3-[2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-2-trimethylsilanylmethylene-cyclopentane (2.96)

To a stirred solution of vinyl silane **2.95** (313 mg, 0.95 mmol) in CH_2Cl_2 (6 mL) at room temperature was added TBSCl (216 mg, 1.43 mmol) followed by the addition of imidazole (130 mg, 1.91 mmol). The resulting solution was allowed to stir for 12 h before the addition of 10 mL of brine. The reaction mixture was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography (5% EtOAc in hexane) to afford 410 mg of **2.96** (97% yield). IR (neat) 2955, 2895, 2857, 1629, 1472, 1463, 1250, 1128, 836, 774. ^{1}H NMR ($CDCl_3$) δ 5.49 (t, 1 H, J = 1.7 Hz), 4.22 (m, 1 H), 3.66 (m, 2 H), 2.64 (m, 1 H), 1.90-1.50 (m, 6 H), 0.91 (s, 9 H), 0.90 (s, 9 H), 0.13 (s, 9 H), 0.083 (s, 3 H), 0.076 (s, 3 H), 0.06 (s, br, 6 H); ^{13}C NMR ($CDCl_3$) δ 167.5, 121.4, 79.5, 62.0, 40.9, 37.4, 33.5, 27.7, 26.3, 26.2, 18.6, 18.5, 0.34, -4.0, -4.3, -5.0, -5.1; MS (EI) *m*/*z* (relative intensity) 442 (M^+, 5.4), 369 (30), 327 (17), 237 (42), 147 (100), 133 (38), 107 (23), 73 (79), 59 (17). HRMS (EI) calcd for $C_{23}H_{50}O_2Si_3$ (M^+): 442.3119, found 442.3127.

1-(tert-Butyl-dimethyl-silanyloxy)-3-[2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-2-oct-2-enylidene-cyclopentane (2.105)

To a stirred solution of vinyl iodide **2.97** (35 mg, 0.07 mmol) in THF (2 mL) was added $Pd(PPh_3)_4$ (8.2 mg, 0.007 mmol) and the resulting solution was stirred at room temperature for 5 min before the addition of a solution of *trans*-1-heptenyldihydroxyborane (40 mg, 0.28 mmol) in 2 M KOH (0.42 mL, 0.85 mmol). The resulting mixture was heated at 50 ºC for 4 h under an argon atmosphere. After the mixture was allowed to cool to room temperature, 10 mL of brine was added. The resulting mixture was extracted with Et_2O (10 mL × 3). The combined organic

layer was dried over $MgSO_4$, filtered through cotton and concentrated in vacuo. The residue was purified by flash-column chromatography (5% EtOAc in hexane) to afford **2.105** (32 mg) in 97% yield. IR (neat) 2955, 2928, 2856, 1471, 1253, 1099, 1046, 835, 774. ^{1}H NMR ($CDCl_3$) δ 6.21 (dd, 1 H, J = 15.0, 11.0 Hz), 5.97 (d, 1 H, J = 11.1 Hz), 5.63 (dt, 1 H, J = 14.6, 7.0 Hz), 4.36 (m, 1H), 3.68 (m, 2 H), 2.83 (m, 1 H), 2.10 (m, 2 H), 1.89 (m, 1 H), 1.80-1.50 (m, 5 H), 1.44-1.24 (m, 6 H), 0.92 (s, 9 H), 0.92-0.88 (m, 3 H), 0.89 (s, 3 H), 0.11-0.07 (m, 12 H); ^{13}C NMR (d_6 acetone) δ 149.1, 134.6, 127.3, 123.3, 77.2, 61.8, 40.1, 35.6, 34.4, 33.0, 31.6, 29.3, 28.4, 26.1, 26.0, 22.6, 18.4, 18.2, 14.2; MS (EI) *m*/*z* (relative intensity) 466 (M^+, 15), 334 (6), 307 (34), 277 (17), 147 (12), 133 (28), 105 (29), 91 (32), 73 (100). HRMS (EI) calcd for $C_{27}H_{54}O_2Si_2$ (M^+): 466.3662, found 466.3678.

3-(2-hydroxy-ethyl)-2-oct-2-enylidene-cyclopentanol (2.106)

To a stirred solution of diene **2.105** (266 mg, 0.57 mmol) in THF (10 mL) at – 20 ºC was added TBAF (1.4 mL, 1.4 mmol). The resulting solution was allowed to warm to room temperature and was stirred for 12 h before the addition of 10 mL of saturated NH_4Cl aqueous solution. The resulting mixture was extracted with Et_2O (15 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and concentrated in vacuo. The residue was purified by flash-column chromatography (40% EtOAc in hexane) to afford diol **2.106** (133 mg) in 98% yield. IR (neat) 3334 (br), 2960, 2926, 2855, 1462, 1054, 968. ^{1}H NMR ($CDCl_3$) δ 6.15 (m, 2 H), 5.70 (m, 1 H), 4.44 (m, 1 H), 3.74 (m, 2 H), 2.90 (m, 1 H), 2.14-1.70 (m, 6 H), 1.5-1.20 (m, 6 H), 0.89 (t, 3 H, J = 6.8 Hz); ^{13}C NMR (d_6 acetone) δ 148.1, 136.5, 126.6, 125.5, 77.4, 61.3, 38.5, 36.3, 33.8, 33.1, 31.5, 29.21, 29.16, 22.6, 14.2; MS (EI) *m*/*z* (relative intensity) 238 (M^+, 11), 220 (35), 193 (28), 165 (51), 149 (100), 121 (42), 105 (36), 91 (66), 79 (48), 67 (36), 55 (44). HRMS (EI) calcd for $C_{15}H_{26}O_2$ (M^+): 238.1933, found 238.1931.

(3-Hydroxy-2-oct-2-enylidene-cyclopentyl)-acetaldehyde (2.107)

To a solution of diol **2.106** (62 mg, 0.26 mmol) and TBACl (15 mg, 0.05 mmol) in CH_2Cl_2 (2 mL) and H_2O at pH 8.6 (carbonate buffer, 2 mL) was added NCS (121 mg, 0.91 mmol) followed by TEMPO (8 mg, 0.052 mmol). The resulting mixture was stirred at r.t. for 40 min and TLC showed the complete consumption of the starting materials. 5 mL of CH_2Cl_2 was added and the organic layer was washed with brine. The aqueous phase was extracted with CH_2Cl_2 (5 mL × 2). The combined organic layer was dried over $MgSO_4$, filtered through cotton and concentrated in vacuo. The residue was purified by flash-column chromatography (20% EtOAc in hexane)to afford aldehyde **2.107** (41 mg) in 67% yield. IR (neat) 3311 (br), 2956, 2927, 2871, 2856, 1722, 1460, 971. ^{1}H NMR ($CDCl_3$) δ 9.81 (s, 1 H), 6.17 (d, 1 H, J = 11.1 Hz), 6.06 (dd, 1 H, J = 14.3, 11.1 Hz), 5.74 (dt, 1 H, J = 14.3. 7.0 Hz), 4.45 (m, 1 H), 3.20 (m, 1 H), 2.85-2.65 (m, 2 H), 2.20-2.00 (m, 3 H), 1.87-1.60 (m, 3 H), 1.44-1.24 (m, 6 H), 0.90 (t, 3 H, J = 7.0 Hz); ^{13}C NMR (d_6 acetone) δ 202.1, 146.7, 137.3, 125.9, 125.4, 76.9, 50.3, 33.8, 33.66, 33.0, 31.5, 29.6, 29.1, 22.6, 14.1; MS (EI) *m*/*z* (relative intensity) 218 (M^+-H_2O, 17), 174 (27), 129 (64), 117 (100), 91 (64), 79 (31), 55 (27). HRMS (EI) calcd for $C_{15}H_{22}O$ (M^+-H_2O): 218.1671, found 218.1663.

7-(3-hydroxy-2-oct-2E-enylidene-cyclopentyl)-hept-5Z-enoic acid (2.108)

To a three-neck flask was added KHMDS (200 mg, 0.442 mmol) and 4-carboxybutyl triphenylphosphonium bromide (186 mg, 0.884 mmol). THF (5 mL) was introduced and the resulting red solution was stirred at room temperature for 30 min, and then cooled to –78 ^{o}C. A solution of aldehyde **2.107** (21 mg, 0.089 mmol) in THF (3 mL) was added to the above ylide solution and the resulting mixture was warmed to room temperature during 4 h before 10 mL of Et_2O was introduced. The reaction mixture was washed sequentially with HCl (1 M, 10 mL) and brine (10 mL). The ether solution was dried over $MgSO_4$, filtered and the solvent was removed

by rotary evaporation. The resulting residue was purified by flash-column chromatography (60% EtOAc in hexane) to afford **2.108** (20 mg) in 70% yield. IR (neat) 3396 (br), 2956, 2927, 2856, 1709, 1453, 1238, 968. ^{1}H NMR ($CDCl_3$, 500 MHz) δ, 6.20-6.10 (m, 2 H), 5.69 (m, 1 H), 5.45 (m, 2 H), 2.77 (m, 1 H), 2.35 (t, 3 H, *J* = 7.0 Hz), 2.21 (m, 1 H), 2.18-2.05 (m, 4 H), 1.90-1.69 (m, 6 H), 1.44-1.36 (m, 2 H), 1.44-1.23 (m, 4 H), 0.90 (t, 3 H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz) δ 178.5, 148.1, 135.8, 129.7, 129.3, 126.7, 125.0, 76.9, 39.7, 33.6, 33.25, 33.16, 32.8, 31.3, 28.9, 28.1, 26.6, 24.5, 22.4, 13.9; MS (EI) *m*/*z* (relative intensity) 302 (M^+-H_2O, 20), 175 (100), 131 (18), 119 (47), 105 (75), 91 (54), 79 (34), 67 (36), 55 (21). HRMS (EI) calcd for $C_{20}H_{28}O_2$ (M^+-H_2O): 218.1671, found 218.1663.

15-Deoxy-9,10-2H-$\Delta^{12,14}$-PGJ_2 (2.36)

To a stirred solution of hydroxy acid **2.108** (7 mg, 0.022 mmol) in CH_2Cl_2 (2 mL) was added silica gel (2.5 mg) followed by Bobbitt's reagent (7.2 mg, 0.023 mmol). The resulting mixture was stirred for 20 min and it was loaded directly on the top of silica gel for purification by flash-column chromatography (50% EtOAc in hexane). The title compound **2.36** (5.1 mg) was isolated in 73% yield. IR (neat) 3500 - 2500 (br), 2956, 2929, 2857, 1708, 1628, 1604, 1459, 1411, 1203, 974. ^{1}H NMR ($CDCl_3$) δ, 6.94 (dd, 1 H, *J* = 5.5, 3.5 Hz), 6.27-6.17 (m, 2 H), 5.50-5.40 (m, 2 H), 3.10 (m, 1 H), 2.44-2.30 (m, 4 H), 2.28-2.18 (m, 3 H), 2.13-2.06 (m, 2 H), 1.96-1.81 (m, 2 H), 1.76-1.65 (m, 2 H), 1.50-1.40 (m, 2 H), 1.33-1.18 (m, 5 H), 0.88 (t, 3 H, *J* = 6.5 Hz); ^{13}C NMR δ 208.6, 179.3, 147.2, 138.6, 133.2, 130.8, 128.3, 126.5, 39.0, 36.3, 33.55, 33.48, 32.5, 31.5, 28.5, 26.7, 24.7, 24.6, 22.6, 14.1; MS (EI) *m*/*z* (relative intensity) 318 (M^+, 32), 247 (6), 191 (100), 173 (38), 121 (48), 109 (32), 105 (21), 97 (50), 91 (47), 79 (71), 67 (39), 55 (31). HRMS (EI) calcd for $C_{20}H_{30}O_3$ (M^+): 318.2195, found 318.2184.

15-Deoxy-9,10-2H-$\Delta^{12,14}$-PGJ_2 (2.35)

To a stirred solution of THF (1.5 mL) at – 78 ºC was added $(i\text{-Pr})_2NH$ (0.025 mL, 0.17 mmol) followed by dropwise addition of *n*-BuLi (0.09 mL, 0.144 mmol). After the mixture had been stirred at – 78 ºC for 30 min, the temperature was allowed to rise to 0 ºC and the mixture was stirred at this temperature for 10 min before it was allowed to cool to –78 ºC again. The keto-acid **2.36** (20 mg, 0.063 mmol) in 2 mL THF was added in dropwise fashion and the resulting mixture was stirred at – 78 ºC for 1 h before PhSeCl (36 mg, 0.19 mmol) in THF (2 mL) was added. The reaction mixture was stirred for 2 h and then 5 mL of 1 N HCl was introduced to quench the reaction. The resulting mixture was extracted with Et_2O (10 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography (50% EtOAc in hexane) to give 21 mg of α-phenylselenyl ketoacid **2.109** (71% yield). The latter (18 mg, 0.038 mmol) was dissolved in a mixture of methanol (2 mL) and H_2O (0.6 mL) and $NaIO_4$ (16 mg, 0.076 mmol) was added. After the mixture was stirred for 10 min, TLC showed the complete consumption of the starting materials. The reaction mixture was loaded directly onto the top of a silica gel in column for purification to give 8.3 mg of 15-deoxy-9,10-2H-$\Delta^{12,14}$-PGJ_2 **2.35** (69% yield). IR (neat) 3500 - 2500 (br), 2955, 2925, 2854, 1709, 1693, 1629, 1207, 978. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.48 (ddd, 1 H, *J* = 5.9, 2.6, 0.95 Hz), 6.96 (d, 1 H, *J* = 11.4 Hz), 6.37 (dd, 1 H, *J* = 6.0, 1.8 Hz), 6.33 (ddt, 1 H, *J* = 15.0, 11.4, 1.4 Hz), 6.25 (dt, 1 H, *J* = 14.7, 7.8 Hz), 5.46 (m, 1H), 5.38 (m, 1 H), 3.59 (m, 1 H), 2.60 (m, 1 H), 2.34 (t, 2 H, *J* = 7.5 Hz), 2.36-2.29 (m, 1 H), 2.23 (q, 2 H, *J* = 6.7 Hz), 2.06 (q, 2 H, *J* = 7.1 Hz), 1.69 (p, 2 H, *J* = 7.4 Hz), 1.46 (p, 2 H, *J* = 7.1 Hz), 1.34-1.26 (m, 4 H), 0.90 (t, 3 H, *J* = 6.7 Hz); ^{13}C NMR δ 197.6, 178.5, 160.8, 147.1, 135.5, 135.1, 131.9, 131.4, 126.2, 125.7, 43.5, 33.6, 33.3, 31.5, 30.8, 28.6, 26.6, 24.5, 22.6, 14.1; MS (EI) *m*/*z*

(relative intensity) 316 (M^+, 40), 245 (58), 190 (90), 133 (93), 119 (96), 91 (85), 81 (48), 67 (53), 55 (100). HRMS (EI) calcd for $C_{20}H_{28}O_3$ (M^+): 316.2038, found 316.2034.

6-Benzenesulfonyl-1-trimethylsilanyl-oct-7-en-1-yn-3-one (2.110)

To alcohol **2.82** (10.14 g, 30.18 mmol) in CH_2Cl_2 (250 mL) was added PCC (13.02 g, 60.4 mmol), celite (11 g), and molecular sieves (4 Å, 11 g). After being stirred at room temperature for 7 h, the solution was filtered through celite and the solvent was removed by rotary evaporation. The residue was purified by flash-column chromatography (20% EtOAc in hexane) to give ketone **2.110** (8.36 g) in 83% yield. IR (neat) 3067, 2961, 2897, 1737, 1447, 1306, 1251, 1148, 1086, 1044, 846. ^{1}H NMR ($CDCl_3$) δ 7.83-7.50 (m, 5 H), 5.59 (m, 1 H), 5.31(d, J = 10.3 Hz), 5.06 (d, J = 17.0, Hz), 4.34 (m, 1 H), 3.61 (m, 1 H), 2.71-2.58 (m, 2 H), 2.44-2.38 (m, 1 H), 2.02-1.95 (m, 1 H), 0.21 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 185.6, 137.1, 133.9, 129.5, 129.3, 129.0, 124.6, 101.6, 98.9, 68.5, 41.7, 21.6, -0.73; MS (EI) *m*/*z* (relative intensity) 319 (M^+-CH_3, 2), 193 (87), 125 (75), 97 (43), 73 (100), 67 (17). HRMS (EI) calcd for $C_{16}H_{19}O_3SiS$ (M^+-CH_3): 319.0824, found 319.0811.

[2-(3-Benzenesulfonyl-pent-4-enyl)-[1,3]dioxolan-2-ylethynyl]-trimethyl-silane (2.68)

To a three-neck flask equipped with a Dean-Stark trap was added ketone **2.110** (7.74, 23.2 mmol) and 170 mL of dry benzene. After the addition of ethylene glycol (12.9 mL, 232 mmol), *p*-toluenesulfonic acid monohydrate (250 mg, 1.3 mmol) was charged as the catalyst. The resulting mixture was heated at reflux for 12 h. After the mixture was allowed to cool to room temperature, saturated $NaHCO_3$ (100 mL) was added to quench the reaction. The resulting mixture was extracted with Et_2O (100 mL × 3). The combined organic layer was dried over

$MgSO_4$, filtered through cotton and concentrated in vacuo. The residue was purified by flash-column chromatography (15% EtOAc in hexane) to give ketal **2.68** (8.58 g) in 99% yield. IR (neat) 3067, 2959, 2897, 1447, 1306, 1251, 1147, 1085, 844. ^{1}H NMR ($CDCl_3$) δ 7.84-7.49 (m, 5 H), 5.61 (m, 1 H), 5.32 (d, *J* = 10.4 Hz), 5.09 (d, *J* = 17.0, Hz), 4.06-4.01 (m, 2 H), 3.96-3.88 (m, 2 H), 3.63 (m, 1 H), 2.36 (m, 1 H), 1.99-1.81 (m, 3 H), 0.14 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 137.4, 133.7, 130.0, 129.3, 128.9, 124.2, 102.3, 102.1, 89.2, 69.3, 64.9, 64.8, 35.7, 21.7, -0.15; MS (EI) *m*/*z* (relative intensity) 363 (M^+-CH_3, 3), 295 (3), 237 (95), 169 (96), 99 (100), 73 (82). HRMS (EI) calcd for $C_{18}H_{23}O_4SiS$ (M^+-CH_3): 363.1086, found 363.1099.

Trimethyl-(7-vinyl-1,4-dioxa-spiro[4.4]non-6-ylidenemethyl)-silane (2.67)

To a stirred solution of **2.68** (8.34 g, 22.0 mmol) in Et_2O (150 mL) at room temperature were added $Pd(PPh_3)_4$ (1.27 g, 1.1 mmol). The resulting solution was stirred for 5 min before Et_2Zn (88 mL, 88 mmol, 1.00 M solution in hexane) was added. The mixture was stirred for 20 h at room temperature before it was allowed to cool to 0 ºC and the reaction was quenched with 80 mL saturated NH_4Cl solution. The reaction mixture was extracted with ether (150 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and concentrated in vacuo. The residue was purified by flash-column chromatography (5% EtOAc in hexane) to afford **2.67** (4.70 g) in 90% yield. IR (neat) 2955, 2880, 1247, 1040, 847. ^{1}H NMR ($CDCl_3$) δ 5.89 (d, 1 H, *J* = 2.1 Hz), 5.91-5.88 (ddd, 1 H, *J* = 17.1, 10.2, 6.9 Hz), 5.07-5.00 (m, 2 H), 4.11-3.91 (m, 4 H), 2.04-1.57 (m, 4 H), 0.11 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 159.6, 141.9, 125.2, 114.4, 113.9, 65.0, 64.6, 44.6, 33.9, 28.5, -0.10; MS (EI) *m*/*z* (relative intensity) 238 (M^+, 31), 207 (17), 195 (51), 169 (61), 141 (68), 125(50), 99 (61), 73 (100). HRMS (EI) calcd for $C_{13}H_{22}O_2Si$ (M^+): 238.1389, found 238.1391.

2-(6-Oct-2-enylidene-1,4-dioxa-spiro[4.4]non-7-yl)-ethanol (2.120)

To a stirred solution of vinyl iodide **2.66** (573 mg, 1.89 mmol) in THF (40 mL) was added $Pd(PPh_3)_4$ (218 mg, 0.19 mmol) and the resulting solution was stirred at room temperature for 5 min before the addition of a solution of *trans*-1-heptenyldihydroxyborane (540 mg, 3.8 mmol) in 2 M KOH (7.6 mL, 15.2 mmol). The resulting mixture was heated at 50 ºC for 4 h under an argon atmosphere. After the reaction mixture was allowed to cool to room temperature, 20 mL of brine was added. The resulting mixture was extracted with Et_2O (50 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography (20% EtOAc in hexane) to afford diene **2.120** (362 mg) in 70% yield. IR (neat) 3430 (br), 2955, 2927, 2872, 1660, 1467, 1318, 1036, 971. ^{1}H NMR ($CDCl_3$) δ 6.21-6.10 (m, 2 H), 5.80-5.70 (m, 1 H), 4.11-3.89 (m, 4 H), 3.70-3.60 (m, 2 H), 2.99 (m, 1 H), 2.14-2.03 (m2 H), 1.96-1.50 (m, 6 H), 1.45-1.18 (m, 6 H), 0.88 (t, 3 H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 143.2, 137.8, 126.4, 114.9, 65.5, 64.3, 61.1, 38.4, 35.5, 35.3, 34.8, 33.2, 31.7, 29.3, 27.2, 22.8, 14.3; MS (EI) *m*/*z* (relative intensity) 280 (M^+, 60), 235 (65), 219 (53), 191 (34), 165(100), 137 (55), 105 (80), 99 (75), 91 (82), 79 (63), 67 (33), 55 (41). HRMS (EI) calcd for $C_{17}H_{28}O_3$ (M^+) 280.2038, found 280.2046.

(6-Oct-2-enylidene-1,4-dioxa-spiro[4.4]non-7-yl)-acetaldehyde (2.121)

To a solution of alcohol **2.120** (81 mg, 0.29 mmol) and TBACl (16 mg, 0.058 mmol) in CH_2Cl_2 (4 mL) and H_2O (pH 8.6, carbonate buffer, 4 mL) was added NCS (116 mg, 0.87 mmol) followed by TEMPO (9 mg, 0.058 mmol). The resulting mixture was stirred at r.t. for 1.5 h and TLC showed complete consumption of the starting materials. 10 mL of CH_2Cl_2 was added and the organic layer was washed with brine. The aqueous phase was extracted with CH_2Cl_2 (15 mL × 2). The combined organic layer was dried over $MgSO_4$, filtered through cotton and

concentrated in vacuo. The residue was purified by flash-column chromatography (10% EtOAc in hexane) to afford **2.121** (61 mg) in 76% yield. IR (neat) 3430 (br), 2957, 2928, 2874, 2717, 1723, 1661, 1459, 1318, 1140, 1036, 970. ^{1}H NMR ($CDCl_3$) δ 9.81 (s, 1 H), 6.19 (dd, 1 H, *J* = 11.2, 2.0 Hz), 6.06 (dd, 1 H, *J* = 14.7, 11.4 Hz), 5.80 (dt, 1 H, *J* = 14.6, 7.1 Hz), 4.14-3.90 (m, 4 H), 3.34 (m, 1 H), 2.72 (ddd, 1 H, *J* = 17.4, 5.0, 0.8), 2.59 (ddd, 1 H, *J* = 17.4, 9.9, 1.9 Hz), 2.18-2.02 (m, 3 H), 1.93-1.76 (m, 2 H), 1.52-1.20 (m, 7 H), 0.89 (t, 3 H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 202.1, 141.9, 138.6, 125.6, 124.5, 114.3, 65.2, 64.2, 50.0, 34.9, 33.1, 32.6, 31.4, 29.0, 27.7, 22.6, 14.1; MS (EI) *m*/*z* (relative intensity) 278 (M^+, 89), 249 (18), 235 (100), 221 (32), 207 (54), 195 (42), 179 (37), 163(26), 137 (27), 99 (32), 79 (30), 67 (12), 55 (16). HRMS (EI) calcd for $C_{17}H_{26}O_3$ (M^+): 278.1882, found 278.1879.

15-Deoxy-9,10-2H-$\Delta^{12,14}$-PGJ_2 (2.36)

To a three-neck flask was added KHMDS (400 mg, 0.884 mmol) and 4-carboxybutyl triphenylphosphonium bromide (372 mg, 1.768 mmol). THF (5 mL) was introduced and the resulting red solution was stirred at room temperature for 30 min, and then cooled to –78 ^{o}C. A solution of aldehyde **2.121** (50 mg, 0.18 mmol) in THF (5 mL) was added to the above ylide solution and the resulting mixture was warmed to room temperature for 4 h before 20 mL of Et_2O was introduced. After the separation, the aqueous phase was extracted with Et_2O (20 mL × 2). The combined organic layer, after being washed sequentially with HCl (1 M, 30 mL) and brine (30 mL), was dried over $MgSO_4$, filtered through cotton and concentrated in vacuo. The residue was purified by flash-column chromatography (50% EtOAc in hexane) to afford **2.36** (53 mg) in 93% yield.

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3.0 CHAPTER THREE

Total Synthesis of Enantioenriched (–)-Kainic acid

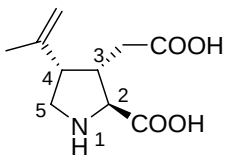
This work was carried out in collaboration with Justin Chalker

2006

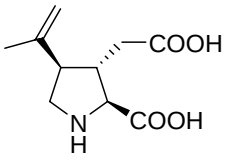
3.1 INTRODUCTION

3.1.1 Background for (−)-kainic acid

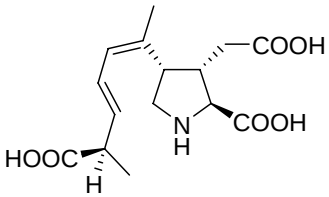
Scheme 3.1 (−)-Kainic acid and its analogs



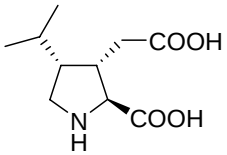
(-)-Kainic acid **3.1**



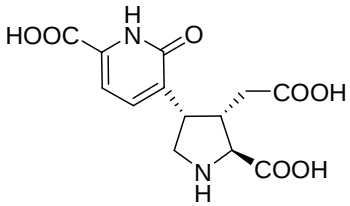
(+)-Allokainic acid **3.2**



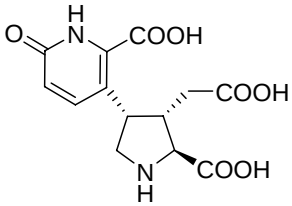
Domoic acid **3.3**



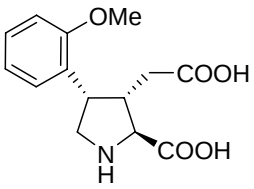
Dihydrokainic acid **3.4**



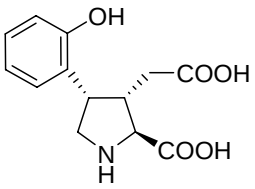
Acromellic acid A **3.5**



Acromellic acid B **3.6**



MFPA **3.7**



HFPA **3.8**

(−)-Kainic acid (KA, **3.1**), a unique non-proteinogenic pyrrolidine dicarboxylic acid, was first isolated from the marine alga *Digenea simplex* in 1953.[1] Right after its discovery, KA was assigned to have the structure of (*2S,3S,4S*)-3-carboxymethyl-4-isopropenylpyrrolidine-2-carboxylic acid by a series of classical chemical degradations and syntheses of degradative products,[2] and the relative stereochemistry of the pyrrolidine ring substituents was deduced by Morimoto's[3] chemical studies. This relative stereochemistry has been supported by X-ray evidence.[4] Moreover, its absolute stereochemistry was later provided by the rigorous assignment of Oppolzer and Thirring[5] in their concise synthesis of (−)-kainic acid (**3.1**) in 1982. A number of structurally related compounds have been discovered, including allokainic acid (**3.2**),[1] domoic

acid (**3.3**),[6] dihydrokainic acid (**3.4**),[7] acromellic acids (**3.5**, **3.6**),[8] MFPA (**3.7**),[9] HFPA (**3.8**).[10] These analogs are called kainoids with (−)-kainic acid as the parent compound.

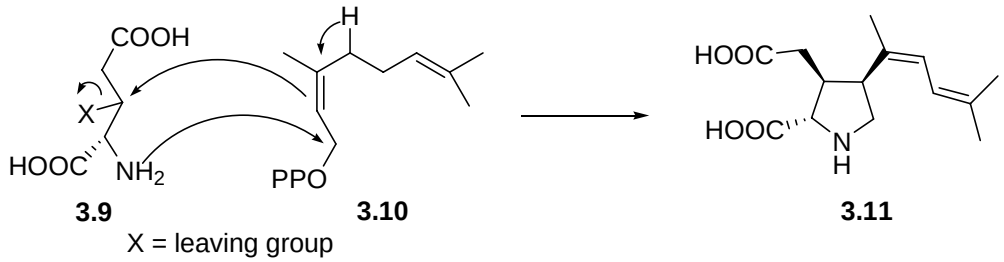
Kainic acid has attracted considerable interest largely because of it pronounced insecticidal,[11] anthelmintic[3] and neuroexcitatory properties. In fact, kainic acid (**3.1**) has been found to be 10 times more effective than santonin, a different anthelmintic, without any observable side effects.[3] In recent years, neurobiologists have made extensive use of kainic acid to simulate brain degeneration. This model is important for research on Alzheimer's disease, epilepsy and other neurological diseases as well as the aftermath of strokes.

The excitatory activity of kainic acid is thought to arise from its structural similarity to glutamic acid.[12] The neuroexcitatory potency depends on the strength of the binding at the kainite receptor, one of three types of glutamate receptors.[13] Analogs of KA also interact with the kainate type receptors to cause strong depolarization, where the nature of the C4 substituent and *cis*- stereochemistry of the C3 and C4 play an important role in the excitatory activity.[14] Among the kainoids, MFPA (**3.7**) [8] shows the most potent activity and is about 10 times more potent than kainic acid in the newborn rat spinal motoneuron, while dihydrokainic acid (**3.4**), which has no π-electron on the C-4 substituent, does not show excitatory activity. Moreover, all of the known stereoisomers of kainic acid (**3.1**) show considerably reduced biological activity compared with that of kainic acid itself.[15] These results indicate that the nature of the π-electron group on C4 and stereochemistry of the C3 and C4 substituents in the molecule have a strong effect on the depolarizing activity and kainate-type selectivity.

3.1.2 Biosynthesis

Wright and co-workers[16] has studied the biosynthesis of kainoids by investigating the biosynthesis of a derivative (**3.11**) of domoic acid. ^{13}C Labelling experiments indicated that a novel condensation of a glutamic acid derivative (**3.9**) with a geranyl pyrophosphate (**3.10**) followed by cyclization formed a proline ring (Scheme 3.2). It is likely that this route provides a general biosynthetic pathway to all the kainoids.

Scheme 3.2 Biosynthesis of a derivative of domoic acid



3.9 **3.10** **3.11**

X = leaving group

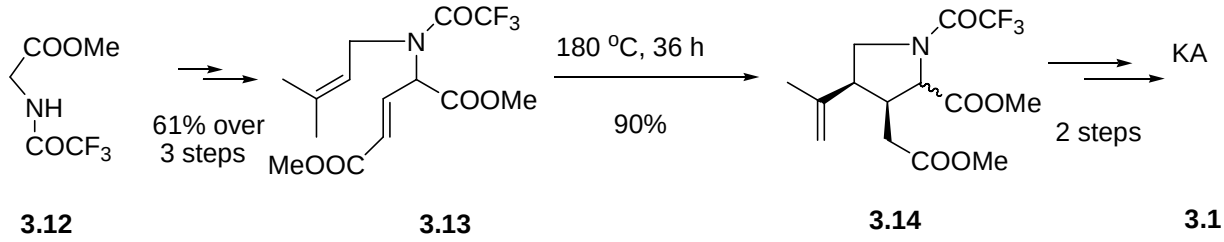
3.1.3 Background for total syntheses of (−)-kainic acid

(−)-Kainic acid was unavailable commercially for a period in late 1999 and in 2000, apparently because of the difficulty in obtaining it from natural sources and that its use as an anthilmintic has been superceded by more readily available antiworming agents.[17] An outcry from the medical community, which requires substantial amounts of it for their research, brought it back onto the market. By far the largest supplier in the kainic acid resurgence is Ocean Produce International which has developed a strain of sea algae that is far richer in (−)-kainic acid than the natural algae. Although it is usually sold in milligram quantities, one gram quantities are available at prices ranging from $6160 to $11,503 per gram.[18] An efficient, practical and scalable synthesis of it is therefore widely sought. There are over 60 publications devoted to the

synthesis of (–)-kainic acid alone, and many other reports in both academic and patent literature that focus on other kainoids and analogs of KA.

Because of its three contiguous stereocenters and high functional density, kainic acid represents a significant synthetic challenge. The first racemic synthesis of kainic acid (**3.1**) was achieved by Oppolzer[19] by an intramolecular ene reaction in 1979 (Scheme 3.3). Starting from methyl N-trifluoroacetylglycinate (**3.12**), an isomeric mixture (11% α-kainic acid,[20] 6% β-kainic acid, 8% α-allokainic acid and 14.5% β-allokainic acid) was synthesized in 41% overall yield with a thermal-ene reaction as the key step (**3.13**→**3.14**).

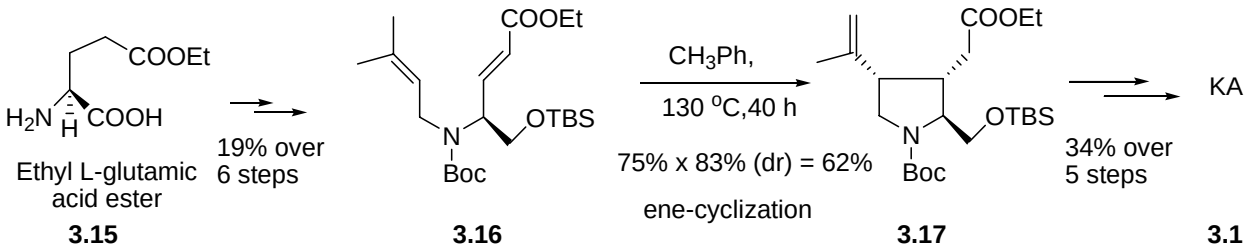
Scheme 3.3 Total synthesis of racemic kainic acid by Oppolzer



Overall 11% in 5 steps

Oppolzer and Thirring[5] later developed the first enantioselective synthesis of kainic acid (**3.1**), using a stereocontrolled intramolecular ene reaction as the key step (Scheme 3.4). Starting from L-glutamic acid, the key diene (**3.16**) was prepared in good yield. When **3.16** was heated in a sealed tube with toluene, the ene cyclization proceeded in 75% yield to furnish the desired pyrrolidine (**3.17**) under the steric control of the chiral C-2 center. GC/MS analysis of crude as well as of chromatographed **3.17** indicated the presence of three diastereomers in a ratio of 8:83:9. It thus follows that the crucial ene reaction **3.16** to **3.17** is 83% stereoselective. The relative stereochemistry of the major product of **3.17** was rigorously ascertained by conversion of this compound to (–)-kainic acid (**3.1**) in 5 straightforward steps.

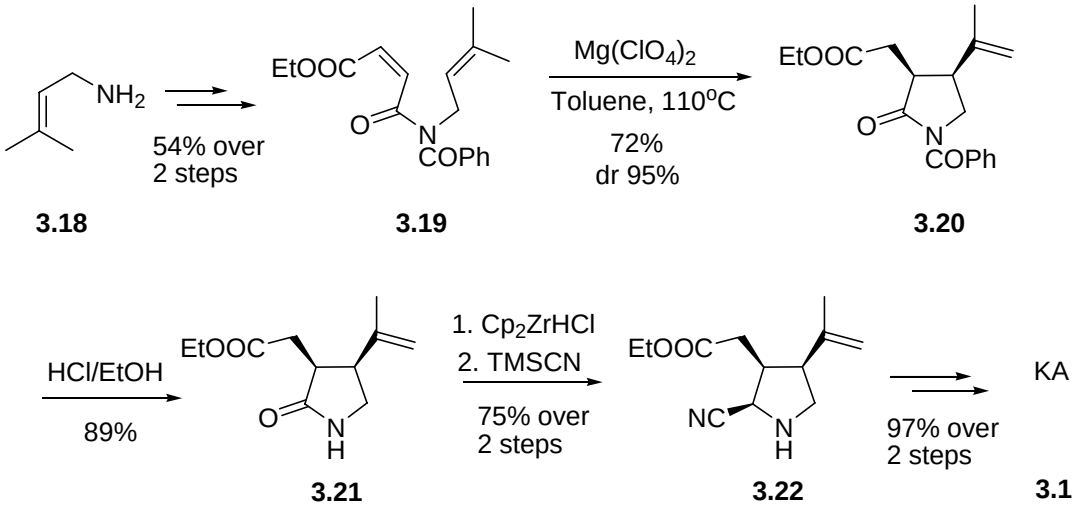
Scheme 3.4 Total synthesis of (–)-kainic acid by Oppolzer



Overall 4.8% in 12 steps

A short and efficient synthesis of kainic acid, also using the ene reaction route, has been reported by Ganem.[21] The overall yield is 21% in 8 steps, enabling preparation of 1–2 g quantities of KA (Scheme 3.5). In the key step, amide **3.19** was heated at reflux in toluene with a mild Lewis acid that induced a stereoselective ene cyclization to give predominantly the *cis*-stereoisomer **3.20** in a 72% yield with a dr > 20:1. Mild acid hydrolysis of **3.20** afforded **3.21**, which was treated with Schwartz's reagent (Cp_2ZrHCl) immediately followed by TMSCN to give the all *cis*-nitrile **3.22**. Acidic hydrolysis followed by basic C2 epimerization furnished kainic acid. Although the ene cyclization could be conducted with a chiral Lewis acid, the enantioselectivity was not high enough to lead directly to optically pure (–)-kainic acid and a resolution using the (+)-ephedrine salt was required in the final step.

Scheme 3.5 Total synthesis of racemic kainic acid by Ganem

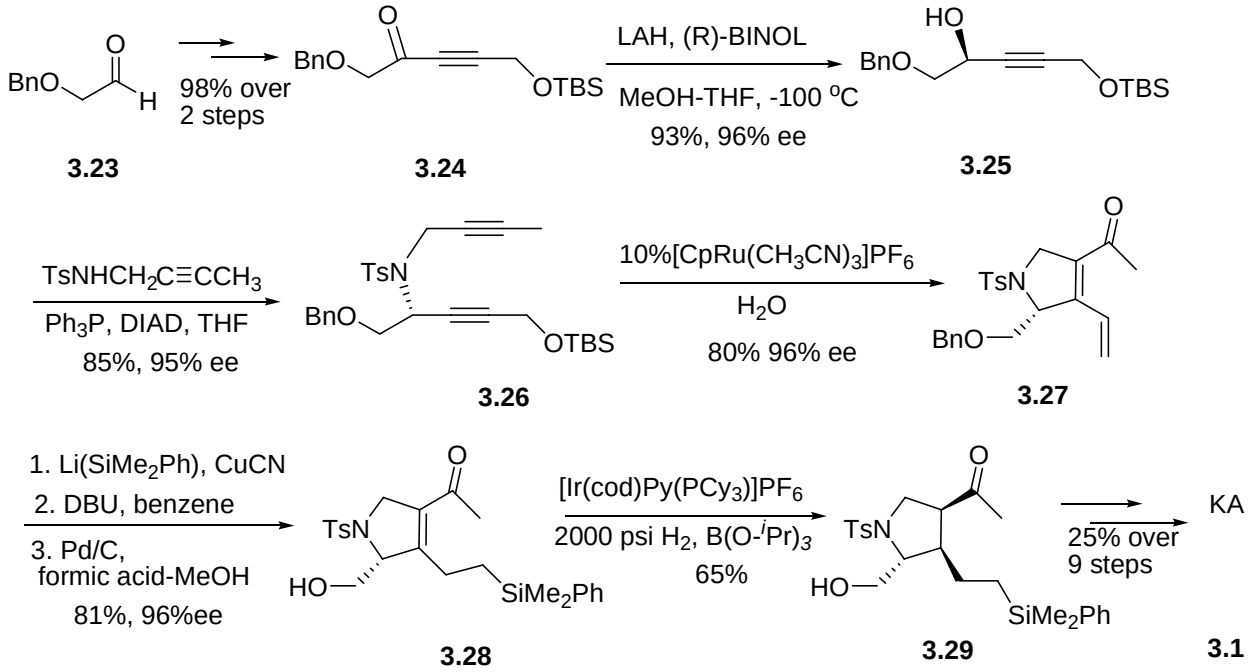


3.18 **3.19** **3.20** **3.21** **3.22** **3.1**

21% overall yield in 8 steps

Trost[22] reported a ruthenium catalyzed alkyne-propargyl alcohol cycloisomerization as a key step in the synthesis of kainic acid. Ynone **3.24** was derived from commercially available aldehyde **3.23** in 2 steps in high yield. Asymmetric reduction[23] of the ynone **3.24** using the LiAlH4/BINOL/MeOH system provided propargylic alcohol (–)-**3.25** with 95% ee. Mitsunobu reaction[24] of (–)-**3.25** with a protected propargylic amine provided a similar protected amino diynol **3.26.** When the diynol **3.26** was subjected to the standard ruthenium-catalyzed cycloisomerization conditions developed for primary propargylic alcohols (10 mol% ruthenium catalyst, 10 vol % water/acetone, malonic acid, room temperature), the cycloisomerization product **3.27** was isolated in 75% yield as a *single diastereoisomer*. **3.28** was produced from **3.27** in 3 steps. Hydrogenation of the α,β-unsaturated ketone **3.28** with Crabtree's catalyst[25] under a high pressure of hydrogen afforded **3.29** with two new chiral centers. Nine additional steps furnished enantiopure (–)-kainic acid to give a 15% overall yield for 14 linear steps.

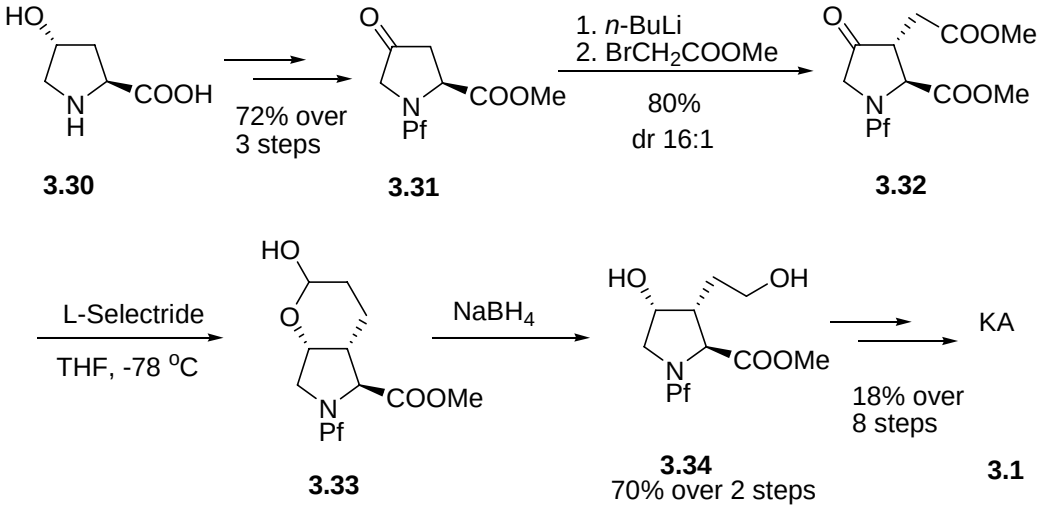
Scheme 3.6 Total synthesis of (–)-kainic acid by Trost



15% overall yield in 14 steps

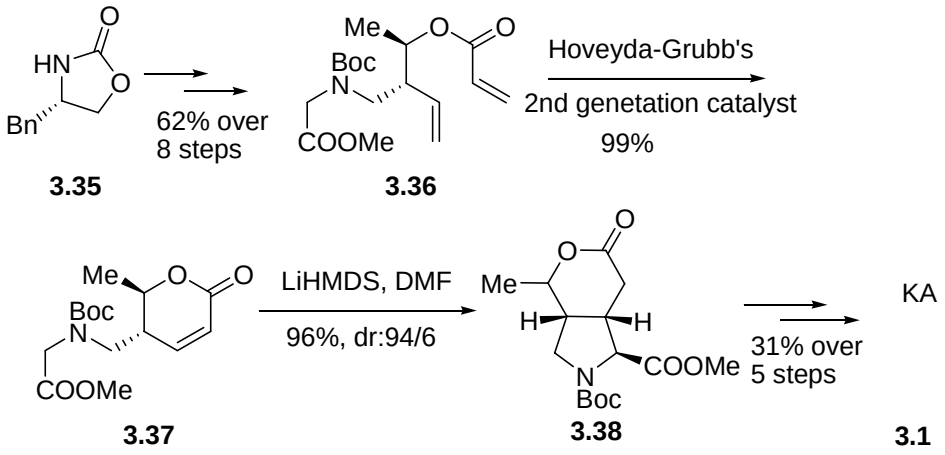
Greene[26] recently reported the modification of a pre-existing pyrrolidine ring to provide a useful entry to kainic acid. A highly stereoselective synthesis of (–)-kainic acid was achieved with a 7% overall yield in 14 steps starting from commercially available *trans*-4-hydroxy-L-proline (**3.30**). The key step was diastereoselective enolate alkylation of **3.31** (dr 16:1) in 80% yield. L-Selectride selectively reduced **3.32** to a lactol **3.33**, which could be further reduced with sodium borohydride to give diol **3.34** in 70% yield. After 8 additional steps, enantiopure (–)-kainic acid was obtained in 7.2% yield for 14 steps with stereochemical control at the three contiguous chiral centers.

Scheme 3.7 Total synthesis of (−)-kainic acid by Greene



The most recent total synthesis of kainic acid was reported by Fukuyama.[27] A fully functionalized trisubstituted pyrrolidine ring **3.38** was constructed by ring-closing metathesis of an acrylate derivative **3.36,** obtained from commercially available Evans aldol reaction reagent[28] **3.35,** in 8 steps**,** followed by an intramolecular Michael addition on to the resultant α,β-unsaturated lactone **3.37,** with high diastereoselectivity. The efficient synthetic route provided (−)-kainic acid in 13% overall yield for 15 steps. This is the first, and as of yet only, gram scale synthesis of enantiopure (−)-kainic acid.

Scheme 3.8 Total synthesis of (−)-kainic acid by Fukuyama



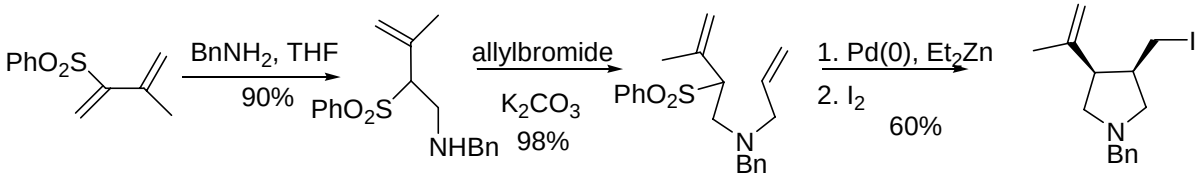
13% overall yield in 15 steps

Other strategies in the synthesis of (−)-kainic acid rely on a variety of ring closing strategies including free radical cyclization,[29,30,31,32,33] Pauson-Khand based annulation[34,35] and dipolar cycloaddition,[36,37,38,39] among others.[40,41,42]

3.1.4 Background for palladium catalyzed zinc-ene cyclization

In previous work in this laboratory, a palladium catalyzed zinc-ene cyclization was developed that allows access to a pyrrolidine skeleton with *cis*-disubstitution at C3, C4 (Scheme 3.9). Allyl phenyl sulfone **3.43** was obtained in 90% yield by adding benzylamine to unsaturated sulfone **3.42,**[43] which was produced from commercial 2-methylbut-1-en-3-yne and thiophenol in 2 steps. *N*-Allylation of **3.43** provided **3.44** in 98% yield. When **3.44** was treated with $Pd(PPh_3)_4/Et_2Zn$, the Zn-ene cyclization proceeded to afford cyclization product **3.45** in a moderate, unoptimized yield of 60% (68% based on consumed reactant) with high stereoselectivity (>40:1) as determined by GC. The lowered yield in this case may be the result of elimination of zinc allyl amide in the allylzinc intermediate.

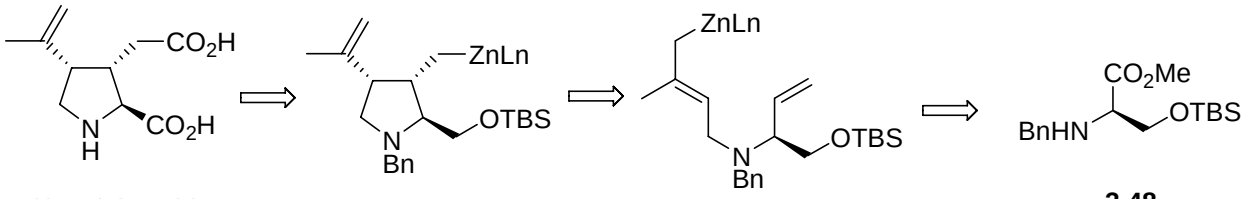
Scheme 3.9 Synthesis of a pyrrolidine derivative by Pd-catalyzed zinc-ene cyclization



3.42 **3.43** **3.44** **3.45**

A concept was developed that allow us to synthesize (–)-kainic acid in the most economical route to date with regard to the number of separate operations, the total yield, and the cost of reactants. This synthesis would be based on the new cyclization method shown above that involves the action of diethylzinc and a catalytic amount of a common palladium catalyst on an allyl phenyl sulfone containing a strategically placed terminal alkene function. The method (Scheme 3.10) to synthesize (–)-kainic acid would utilize as the enantiomeric source, a protected version (**3.48**) of the inexpensive commercial reagent D-serine methyl ester ($4/g at Aldrich).

Scheme 3.10 Retrosynthetic analysis for (–)-kainic acid



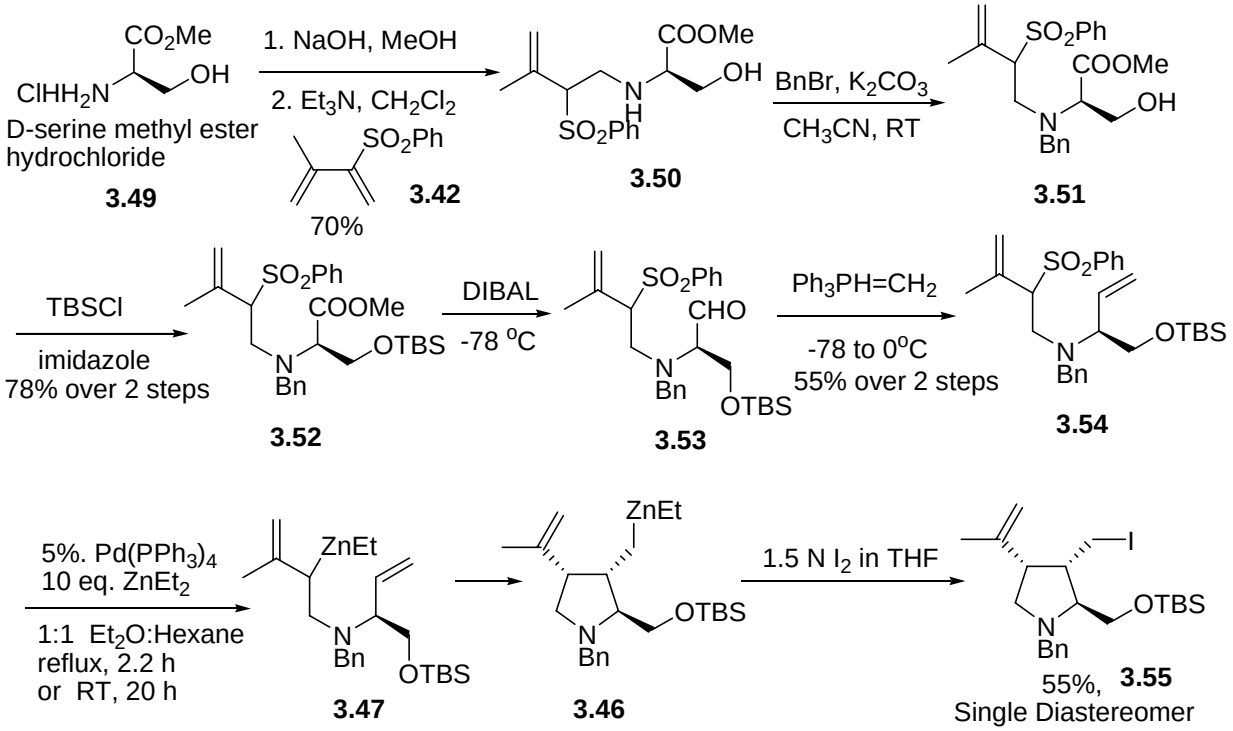
(-)-Kainic Acid **3.1** **3.46** **3.47** **3.48**

3.2 RESULTS AND DISCUSSION

3.2.1 Formal synthesis of kainic acid utilizing an allyl phenyl sulfone as the precursor of the allylzinc

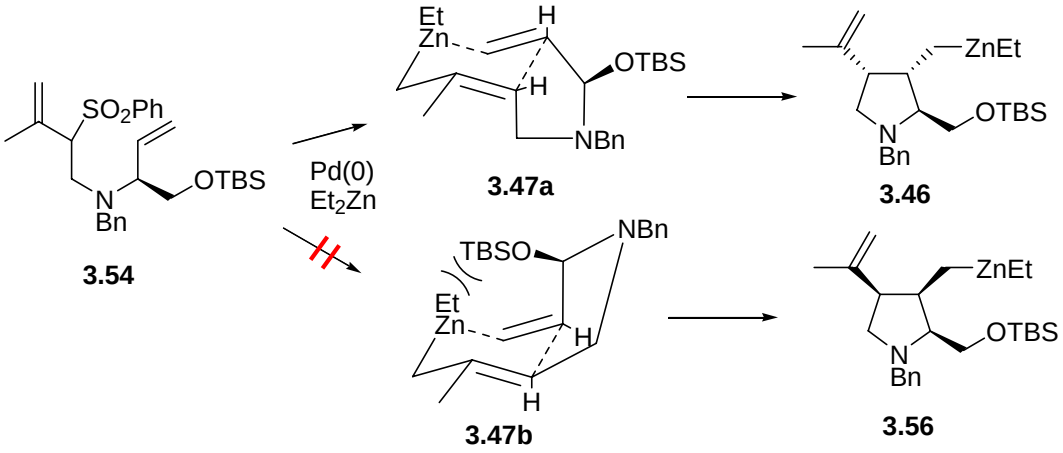
In Justin Chalker's work, pyrrolidine **3.55** was synthesized as a single diastereomer from commercial D-serine methyl ester hydrochloride (Scheme 3.11). In previous work, a primary amine was found to undergo Michael addition to unsaturated sulfone **3.42** (Scheme 3.9). However, the Michael addition of D-serine methyl ester, neutralized **3.49,** to **3.42** proved problematic and early attempts resulted in low conversion and polymerization of the diene **3.42.** Only when 2.0 equiv. of the neutralized amino acid ester, was heated at reflux in dichloromethane with unsaturated sulfone **3.42**, was the adduct **3.50** produced in 70% yield as a mixture of diastereomers. Protection of the secondary amine with benzyl bromide gave alcohol **3.51**, which was treated with TBSCl/imidazole to afford **3.52** in 78% yield over two steps, after flash-column chromatography (Scheme 3.11). In our collaboration, the ester **3.52** was reduced with DIBAL in toluene at –78 ^{o}C to provide the corresponding aldehyde **3.53**, which was immediately subjected to olefination conditions (Ph_3PCH_3Br/KHMDS) to provide the desired terminal olefin **3.54** in 55% yield. The stage was then set for the key step, Zn-ene cyclization.

Scheme 3.11 Synthesis of cyclization product 3.55 from allyl sulfone by Justin Chalker



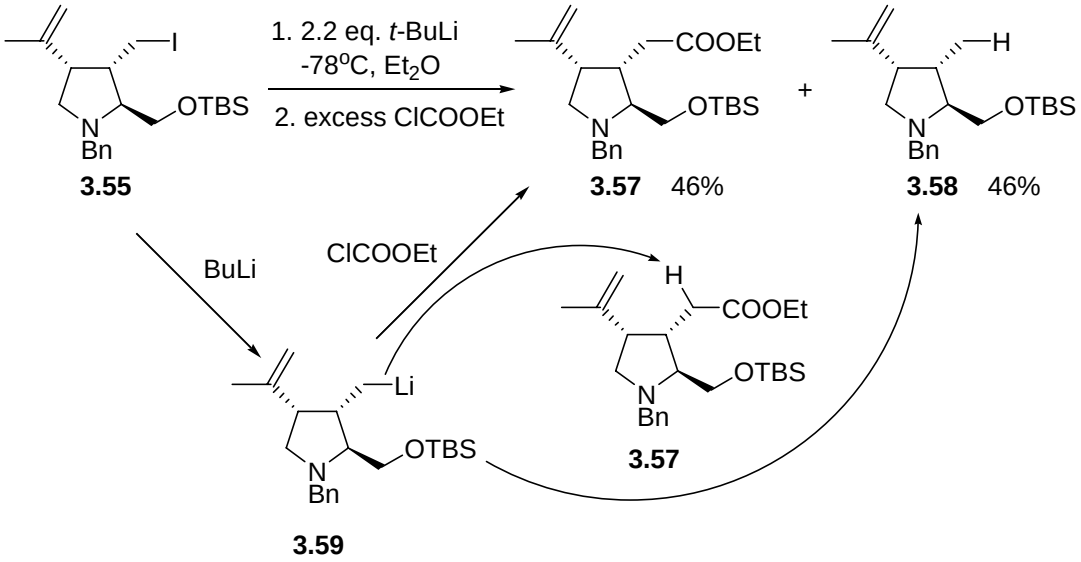
Accordingly, a solution of **3.54** in diethyl ether was heated at reflux in the presence of a catalytic amount of $Pd(PPh_3)_4$ and 10 equivalents of diethylzinc, in which excess $ZnEt_2$ was used to maintain the anhydrous and oxygen free condition for the reaction system. The palladium was added in three portions of 5% over the 20 hour reaction period since a single palladium loading never resulted in complete consumption of **3.54**. The cyclization was *entirely diastereoselective*, giving alkylzinc **3.46**, which was quenched with iodine to afford pyrrolidine **3.55** in 55% yield. The formation of **3.55** demonstrates both the high *cis*-fidelity of the zinc-ene cyclization as well as the exquisite substrate control by the TBS silyl ether in directing the formation of the desired *trans* C2-C3 isomer.[44] This stereochemical outcome is rationalized in Scheme 3.12.

Scheme 3.12 Transition state model of the Zn-ene cyclization



Though iodide **3.55** is a known precursor to kainic acid,[45] its reported conversion to kainic acid **3.1** suffers a low yielding acylation. Chalker's study showed that after lithium halogen exchange with *t*-BuLi in Et_2O at -78 ^oC and quenching with ethylchloroformate, a 1:1 mixture of desired ester **3.57** and reduced compound **3.58** was obtained (Scheme 3.13). This problem arises from self-quenching of the alkyllithium by the acidic α-proton of the product ester.[46] Other mechanisms of quenching, such as 1,5-proton transfer to give an allyllithium, were ruled out by D_2O quenching. Despite the low yielding acylation, the synthesis of **3.57** verified the stereochemical outcome of the cyclization by NMR spectra comparison.[47]

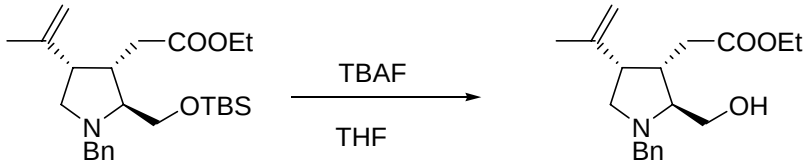
Scheme 3.13 Lithium halogen exchange



In my work, conversion of the cyclized product **3.57** to the known primary alcohol **3.60** was performed using TBAF (Scheme 3.14). Obtaining **3.60** allowed me to do a direct comparison of literature values[48] for specific rotation to determine optical purity. The optical activity of **3.60** was found to be $[\alpha]_{Na} = -38.1^{o}$, much higher than the published value of $[\alpha]_{Na} = -3.66^{o}$.[48] This big difference of optical rotation led to the suspicion that the rotation in reference[48] is unreliable, and led us to turn to chiral chromatography. HPLC on a chiral support indicated a decrease in enantiomeric purity for **3.60** by revealing two peaks (56% : 44%) while regular HPLC only gives a single peak. This, unfortunately, suggested that epimerization had occurred somewhere in the route.

The step most likely to cause a loss of optical activity was the reduction of ester **3.52** to aldehyde **3.53** since α-amino aldehydes are often susceptible to epimerization.[49]

Scheme 3.14 Deprotection of 3.57 by Ao Yang



3.57 **3.60**

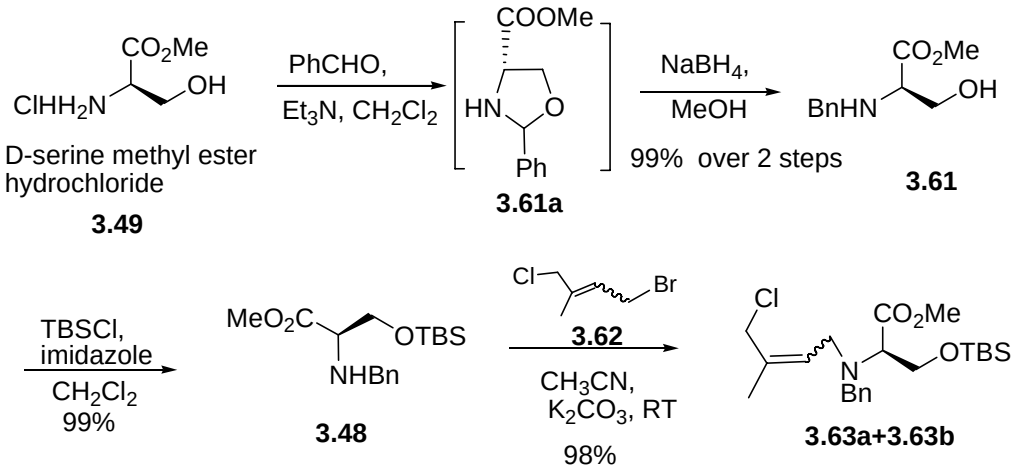
While the synthesis of kainic acid **3.1** was accomplished in a formal sense, and the suitability of the key cyclization established, there are several limitations of this first generation route. First, while unhindered primary amines typically add smoothly to diene **3.42**, an equivalent of chiral starting material (D-serine methyl ester) is wasted since it was needed in excess. Second, the reduction-olefination route to **3.54** is only achieved in moderate yield and significant epimerization was observed. Finally, the acylation route to **3.57** is unacceptably low in yield and a different end-game strategy is necessary if the route is to be amenable to a scalable process. Addressing these limitations, and motivated by the high diastereoselectivity of the zinc-ene cyclization, we revised our approach to one which is higher yielding and can be carried out on a multi-gram scale.

3.2.2 Total synthesis of kainic acid utilizing an allyl chloride as the precursor of the allylzinc

In collaboration with Chalker, allyl chloride **3.63** was synthesized utilizing chlorobromide **3.62** (Scheme 3.15). After D-serine methyl ester hydrochloride (**3.49**) was neutralized with Et_3N, the resulting primary amine was allowed to react with benzylaldehyde to produce an oxazolidine derivative **3.61a**, which was reduced selectively to **3.61** by $NaBH_4$ in MeOH (Scheme 3.15).[49]

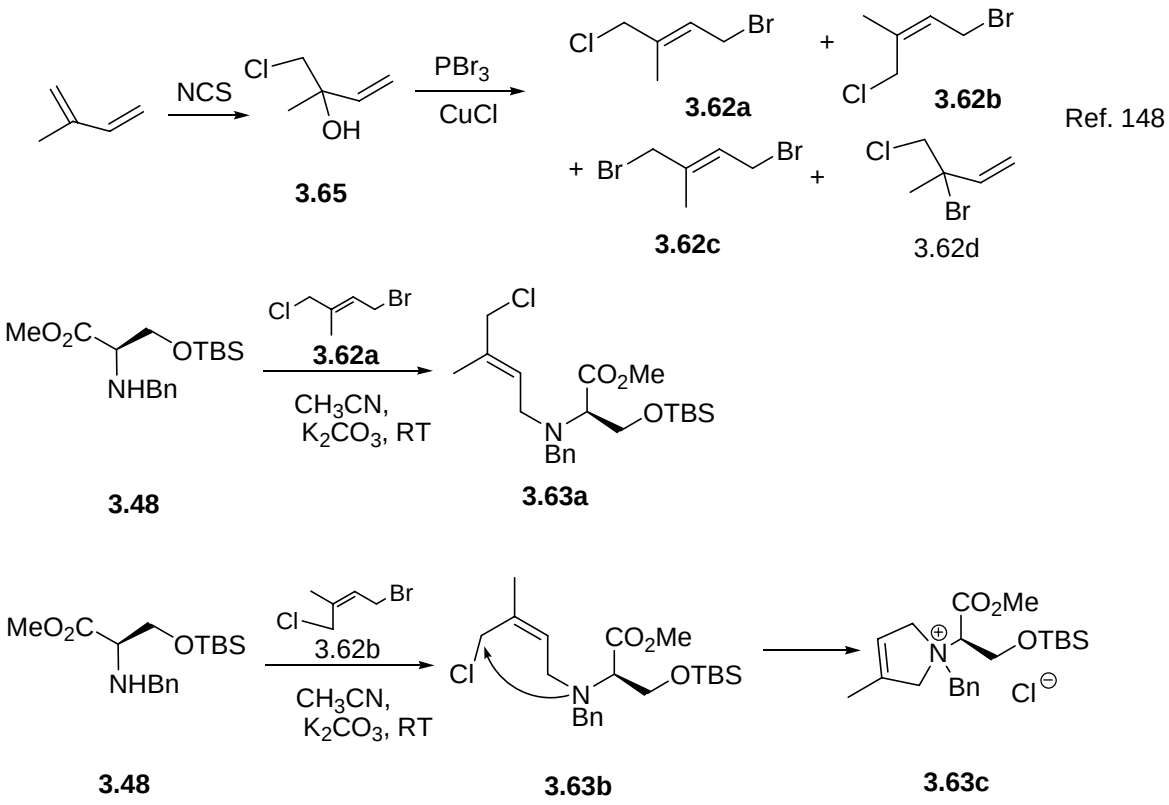
Protection of the alcohol of **3.61** was carried out easily with TBSCl and imidazole in CH_2Cl_2 to give **3.48** quantitatively.

Scheme 3.15 Synthesis of amine 3.63 by Ao Yang and Justin Chalker



Recently, Koo[50] reported that chloro bromide **3.62** could be utilized as a selective allylation reagent. The bromination of **3.65,** obtained from isoprene and *N*-chlorosuccinimide, in the presence of catalytic amount of CuCl afforded a mixture of **3.62a** and **3.62b** in a ratio around 6:1, along with trace amounts of **3.62c** and **3.62d** (Scheme 3.16)[50] and this mixture could be used directly for allylation without purification. My chemoselective allylation of **3.48** with **3.62** afforded allyl chloride **3.63**. Usually, **3.63** was obtained in a yield of about 80% and the NMR spectrum showed that it was a single isomer. Only once was **3.63** obtained in a high yield (98%), with the NMR spectrum showing that the major product was **3.63a** along with minor product **3.63b**. The explanation probably is that the *cis*-isomer **3.63b** could react further to form an ammonium salt **3.63c**, which was easily lost in the extraction or chromatography.

Scheme 3.16 Allylation of amine 2.48 by Ao Yang



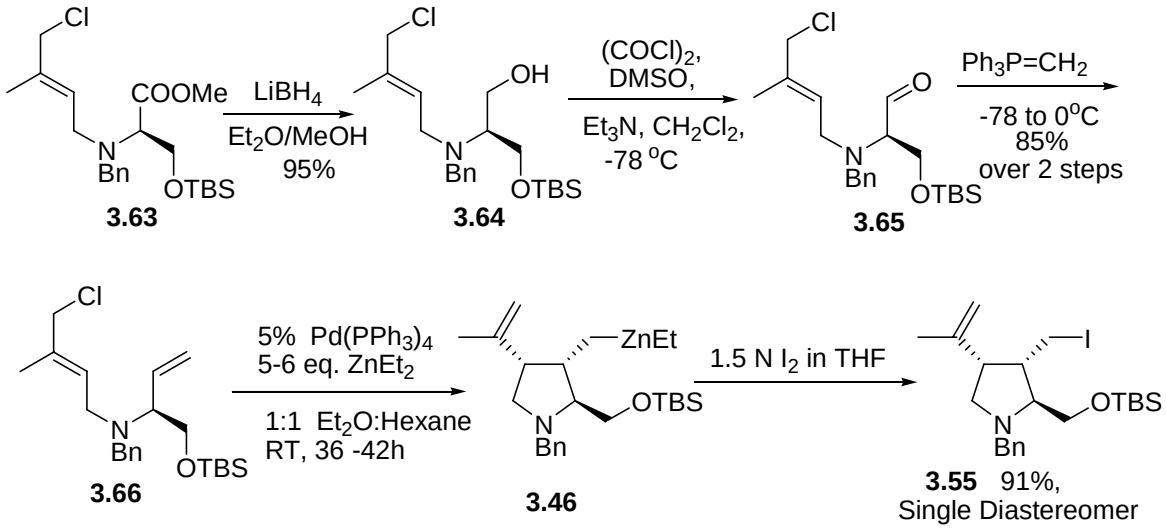
While **3.63** was originally set out as a substrate for sulfonylation by sodium benzene sulfinate to obtain the allyic isomer of sulfone **3.52**, it was apparent that an allyl chloride would be suitable in the cyclization, provided it could survive a reduction/oxidation/olefination sequence in the conversion of the methyl ester **3.63** to the terminal olefin **3.64**. Gratifyingly, the chloride survived such a manipulation and chemoselective $LiBH_4$ reduction provided alcohol **3.64** in high yield. Since the ester of **3.63** is hindered, 4 equiv. of $LiBH_4$ and 4 equiv. of MeOH[51] in Et_2O was used to reduce it to alcohol **3.64**. $NaBH_4$ in any solvent and $LiBH_4$ in THF alone did not give any reduction product in my study.

Subsequent Swern oxidation and Wittig olefination of the sensitive α-amino aldehyde provided diene **3.66** in 85% yield. Unfortunately, when I oxidized the alcohol **3.64** to the aldehyde and then reduced **3.65** back to the original alcohol **3.64**, the optical rotation revealed a

large decrease in activity $[\alpha]_{Na} = -1.4^{o}$ (c = 1.0, EtOH) compared to the original alcohol $[\alpha]_{Na} = -2.7^{o}$ (c = 1.0, EtOH), demonstrating a frustrating susceptibility to epimerization during the Swern oxidation. This epimerization occurs despite literature precedents for successfully oxidizing optically sensitive alpha-amino alcohols. For instance, Hoppe's one pot Swern oxidation, Horner-Emmons olefination proceeded with negligible loss in enantiopurity.[52]

It is also worth noting that epimerization could occur as well during the Wittig reaction of the aldehyde with Ph_3PCH_2. It has been reported that the olefination product maintained a 99% ee[53] after the Wittig reaction of Ph_3PCH_2 with an *N*-Boc amino aldehyde, which was obtained from an *N*-Boc amino ester by reduction with DIBAL-H. Thus, no epimerization occured during the olefination of an *N*-Boc amino aldehyde with Ph_3PCH_2, but of course that does not rule out epimerization during the olefination of an *N*-alkylamino aldehyde with Ph_3PCH_2.

Scheme 3.17 Synthesis of cyclization product 3.55 from an allyl chloride 3.63 by Ao Yang and Justin Chalker



Mehrotra reported that when the nitrogen was protected with two benzyl groups, the oxidation of an α-amino alcohol to an α-amino aldehyde with SO_3.pyridine-Et_3N gave 99.9%

ee.[54] However, in my experiment, the oxidation of **3.64** according to Mehrotra's procedure, followed by olefination, gave a much lower yield (around 50%), possibly because the allyl chloride reacted with Et_3N to form an ammonium salt. Moreover, the optical purity of **3.66** showed no obvious improvement.

Despite the loss in optical purity, we subjected the cyclization substrate, allyl chloride **3.66** to 5 mol% of $Pd(PPh_3)_4$ and 6 eq. of $ZnEt_2$ in a mixture of diethyl ether and hexane. After the mixture had been stirred at room temperature for 36-42 hours and quenched with iodine, pyrrolidine **3.55** was obtained in *91% yield as a single diastereomer*. It is interesting that no *β*-elimination in the intermediate allylzinc is observed in this Zn-ene cyclization. Though both the allylic sulfone **3.54** and allylic chloride **3.66** underwent the cyclization with complete diastereoselectivity, the higher yield and milder conditions of the allyl chloride **3.66** approach, room temperature and 5 mol% of Pd, instead of heating at reflux in Et_2O and 3 portions of 5 mol% of Pd for allyl sulfone **3.54**, gave a distinct advantage over the sulfone strategy. The milder cyclization conditions for allyl chloride **3.66** could be responsible for the lesser amount of elimination and this side reaction could be the reason of the lower yield in the cyclization conditions of allyl sulfone **3.54.** Furthermore, the cyclization of **3.66** could be carried out on a 10 g scale without any significant deterioration in stereoselectivity and yield. A minor amount (typically 2-5%) of uncyclized, dechlorinated material is also isolated after quenching. This material is likely the result of protic quenching of the allyl zinc intermediate when a Pd-H species is the proton source. Without excess diethylzinc as a proton scavenger, the amount of this byproduct increases significantly.

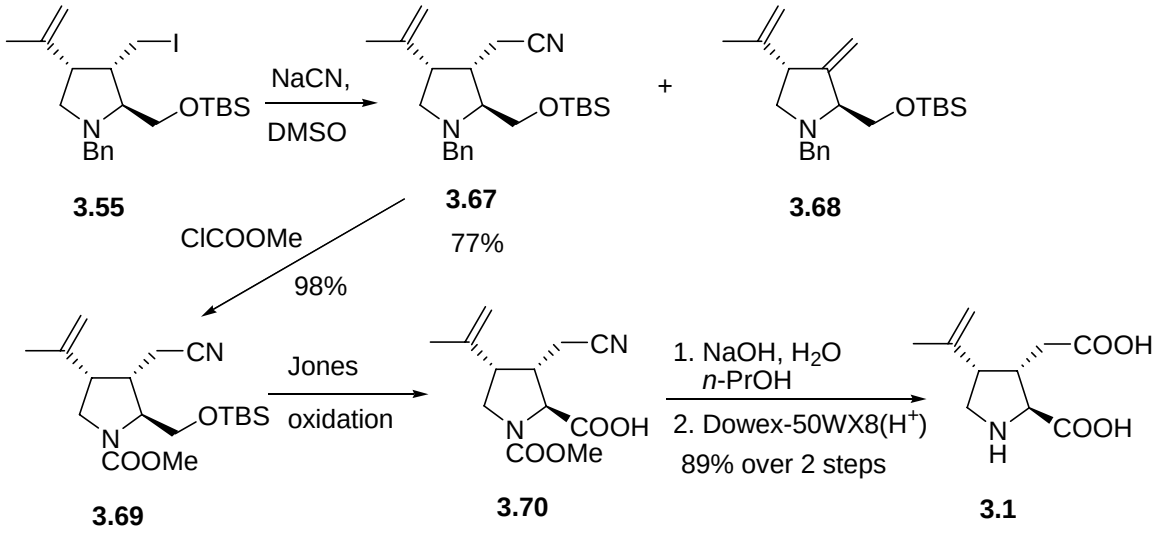
Once again, in order to check its optical purity, the primary alcohol **3.60** was produced followed the procedure in Schemes 3.13 and 3.14. HPLC on a chiral support revealed two peaks

(65:35), indicating that epimerization had occurred during this route as well. The transformation most suspect is the oxidation of alcohol **3.64** to the aldehyde **3.65**. It is thought that once formed, the labile α-amino aldehyde reacted with the Et_3N, necessary for the Swern oxidation, to form an epimerized aldehyde.

Revising the conversion of **3.55** to kainic acid **3.1**, we turned to cyanation as an alternative to the lithiation, acylation protocol (Scheme 3.18). Treatment of **3.55** with NaCN in DMSO at room temperature provided the corresponding nitrile **3.67** in 77% yield along with 23% of a mixture of elimination by-product **3.68** and some unidentified compounds. Conversion of the benzyl amine **3.67** to carbamate **3.69** proceeded in high yield both with ClCOOMe in heating at reflux in $ClCH_2CH_2Cl$ (98%) or in the presence of pure ClCOOMe at room temperature (97%). Direct Jones oxidation of the TBS silyl ether[55] provided the corresponding carboxylic acid **3.70**.

It is well known that nitriles are easily hydrolyzed in strongly acidic conditions to acids or esters.[56] However, since the C-C double bond in **3.70** is sensitive to strong acid, acidic hydrolysis was not attempted. It was found that basic hydrolysis removed the carbamate and also converted the nitrile to the corresponding carboxylate.[57] The final product, after purification by ion exchange chromatography, was spectroscopically identical to (-)-kainic acid and produced a homogenous NMR spectra when co-mixed with an authentic sample. The specific rotation was half of the literature value $[\alpha]_{Na}= -7.2^o$ (c=1.0, H_2O) vs. $[\alpha]_{Na}= -14.8^o$ (c=1.0, H_2O) (Merck Index), consistent with the e.r. observed by HPLC for compound **3.60**.

Scheme 3.18 Synthesis of partially racemized kainic acid from iodide 3.55 by Ao Yang and Justin Chalker

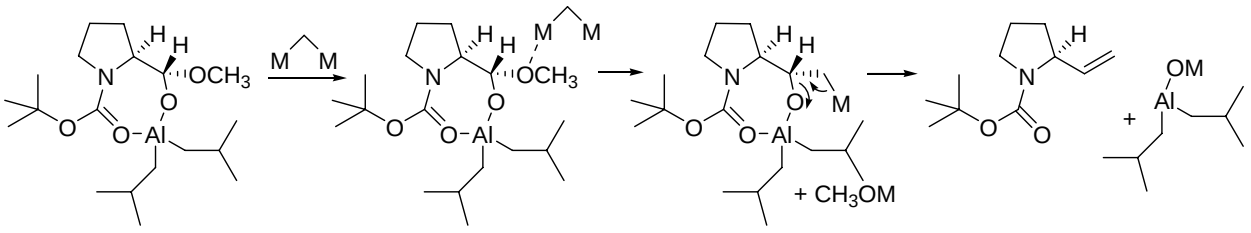


3.2.3 Conclusions

The total synthesis of (–)-kainic acid was accomplished through a highly diastereoselective zinc-ene cyclization of both an allyl sulfone and an allyl chloride substrate. The sulfone approach was 10 linear steps from commercially available D-serine methyl ester hydrochloride with an overall yield of 11%. The chloride strategy was 11 linear steps from the same starting materials, but with a much higher overall yield of 48%. This overall yield is by far the highest of any kainic acid synthesis to date and can be carried out on a multigram scale. The major problem for the allyl chloride route is the troublesome epimerization that results from the optically unstable amino aldehyde. Currently, efforts are focused on developing a new reaction sequence to convert the ester to the olefin *without passing through the stereochemically labile aldehyde.* The strategy (Scheme 3.19) uses di-Grignard reagent ($BrMgCH_2MgBr$)[58] as a potential reaction partner with the tetrahedral DIBAL adduct **3.71** of the ester. It is envisioned that after

substitution of the methoxy group, the aluminumoxide will be eliminated to afford the desired olefin.

Scheme 3.19 Proposed olefination by reaction of a di-Grignard reagent with the tetrahedral DIBAL adduct of the ester



3.71 **3.72** **3.73** **3.74** **3.75**

3.3 EXPERIMENTAL SECTION

Instrumentation. Optical rotation data were obtained from samples loaded into 100 mm cell on a Perkin-Elmer 241 polarimeter operating at the Na_D-line. See the Experimental Sectional of Chapter One for general procedure, materials and other instrumentation.

Methyl 3-hydroxy-2-(3-methyl-2-(phenylsulfonyl)but-3-enylamino)propanoate 3.50

To a solution of NaOH (2.60 g, 65.0 mmol) in MeOH (100 mL) was added D-serine methyl ester hydrochloride **3.49** (10.1 g, 65.0 mmol). The mixture was stirred for 1 hour and then filtered through a plug of silica and rinsed with methanol repeatedly. The solvent was removed under reduced pressure and replaced with CH_2Cl_2 (100 mL) and triethylamine (10 mL). Diene **3.42** (13.5 g) was added as a solution in CH_2Cl_2 (50 mL). The reaction mixture was heated at reflux for 24 hours after which time an additional 10.0 g of D-serine methyl ester was added as a solution in CH_2Cl_2 (30 mL) after neutralization with methanolic NaOH. The reaction mixture

was heated at reflux for an additional 16 hours. The solvent was removed under reduced pressure and the residue was purified by flash-column chromatography (50% EtOAc in hexane) to yield **3.50** (14.8 g, 70%) as a mixture of diastereomers. IR (ν, cm^{-1}): 3512 (br), 2953, 1735, 1447, 1304. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm, two diastereomers): δ 7.86-7.51 (m, 5 H), 5.11, 5.02 (2×s, 1 H), 4.83, 4.71 (2×s, 1 H), 3.87-3.76 (m, 2 H), 3.73 (s, 3 H), 3.67-3.43 (m, 2 H), 3.39-3.35 (t, *J* = 4.5, 1 H), 3.26-2.92 (m, 2 H), 2.68 (br s, 2 H), 1.84, 1.76 (2×s, 3 H). ^{13}C NMR (75 MHz, two diastereomers): δ 172.7, 172.6, 137.3, 137.0, 136.4, 135.6, 133.6, 128.9, 128.7, 128.6, 120.9, 120.0, 71.6, 62.7, 62.6, 62.5, 62.0, 51.9, 45.1, 44.4, 20.8, 20.2; MS (EI) *m*/*z* (relative intensity) 327 (M^+, 15), 296 (20), 268 (25), 186 (30), 132 (100), 77 (63); HRMS (EI) calcd. for $C_{15}H_{21}NO_5S$ (M^+): 327.1133, found 327.1133.

Methyl 2-(benzyl(3-methyl-2-(phenylsulfonyl)but-3-enyl)amino)-3-(*tert*-butyldimethyl silyloxy)propanoate 3.52

To the stirred solution of allyl sulfone **3.50** (255 mg, 0.78 mmol) in 8 mL of DMF, was added potassium carbonate (108 mg, 0.78 mmol) and benzyl bromide (0.10 mL, 0.91 mmol) sequentially at room temperature. The reaction mixture was heated to 65 ºC and stirred for 4.5 hours at which time an additional portion of benzyl bromide was added (0.05 mL, 0.45 mmol). The reaction mixture was stirred for an additional 12.5 hours at 65 ºC before being cooled to room temperature, diluted with diethyl ether (100 mL), washed with water (3x30 mL), dryed ($MgSO_4$), filtered. The solvent was removed under reduced pressure and the product was purified by column chromatography (40% EtOAc in hexanes) to yield 279 mg of the benzylated product **3.51** (86%). To a solution of this product **3.51** (210 mg, 0.50 mmol) in 7 mL of CH_2Cl_2 at 0 ºC was added imidazole (68 mg, 1.0 mmol) and TBSCl (85 mg, 0.55 mmol) sequentially. After being stirred at 0 ºC for 20 minutes, the reaction was quenched with saturated aqueous

$NaHCO_3$ (10 mL), and the mixture was extracted with CH_2Cl_2 (3x25 mL) and dried over $MgSO_4$. After filtration and removal of solvent under reduced pressure, the product was purified by flash-column chromatography (50% EtOAc in hexane) to give **3.52** (242 mg, 91%) as a clear oil. IR (ν, cm^{-1}): 2952, 2856, 1736, 1447. ^1H NMR ($CDCl_3$, 300 MHz, ppm, two diastereomers): δ 7.87-7.79 (m, 2 H), 7.66-7.63 (m, 1 H), 7.57-7.53 (m, 2 H), 7.33, 7.28 (m, 5 H), 5.09 (s, 1 H), 4.81, 4.79 (2×s, 1 H), 3.91-3.86 (m, 4 H), 3.81-3.64 (m, 5 H), 3.58-3.50 (m, 2 H), 3.46-3.32 (m, 1 H), 1.78, 1.75 (3 H), 0.91 (s, 9 H), 0.08 (s, 6 H). ^{13}C NMR (75 MHz, two diastereomers): δ 171.6, 171.3, 139.4, 138.9, 138.2, 136.8, 136.7, 133.3, 133.2, 128.7, 128.6, 128.5, 128.1, 128.0, 127.0, 126.9, 120.1, 120.0, 71.4, 70.9, 66.3, 64.8, 62.9, 62.3, 56.7, 56.2, 51.1, 51.0, 49.7, 25.6, 25.4, 21.0, 20.7, 17.9, -5.7, -5.8; MS (EI) *m*/*z* (relative intensity) 532 (100), 472 (20), 400 (21). HRMS (EI) calcd. for $C_{28}H_{41}NO_5SSi(M^+)$: 532.2553, found 532.2536.

_N_-Benzyl-_N_[(_S_)-1-(_tert_-butyldimethylsilyloxy)but-3-en-2-yl]-3-methyl-2-(phenylsulfonyl)-but-3-en-1-amine 3.54

To a flame dried flask was added ester **3.52** (2.51 g, 4.71 mmol) and CH_2Cl_2 (100 mL). The stirred solution was cooled to –78 ºC and DIBAL-H (1.00 M in hexane, 9.42 mL, 9.42 mmol) was added dropwise over 10 minutes so as to maintain a low internal temperature. After the mixture was stirred at -78 ºC for two hours, the reaction was carefully quenched by the dropwise addition of MeOH (2.0 mL). After 5 minutes of stirring, a 50 mL portion of saturated Rochelle's salt was added. The mixture was stirred vigorously while being warmed to room temperature over a period of 30 minutes. The resulting slurry was extracted with CH_2Cl_2 (4 x 80mL) and the organic fraction dried over Na_2SO_4 briefly. The solids were filtered and the solvent was removed at room temperature under reduced pressure. The sensitive aldehyde was used immediately without further purification. After dissolving in a 10 mL of THF, the aldehyde was

added dropwise via syringe to a preformed solution of $Ph_3P{=}CH_2$ (1.5 eq) in THF at -78ºC. The solution was warmed to room temperature over 3 hours before quenching with saturated NH_4Cl (50 mL). The resulting mixture was extracted with Et_2O (3x100 mL), dryed ($MgSO_4$), filtered, and concentrated under reduced pressure. After purification by column chromatography (7% EtOAc in hexanes), diene **3.54** was obtained as an oil (1.31 g, 55%). IR (ν, cm^{-1}): 3064, 2928, 1641, 1585. ^1H NMR ($CDCl_3$, 300 MHz, ppm, two diastereomers): δ 7.81 (d, J = 7.50, 2 H), 7.65-7.61 (m, 1 H), 7.55-7.50 (m, 2 H), 7.29-7.24 (m, 5 H), 5.87-5.75 (m, 1 H), 5.35-5.10 (m, 2 H), 5.07 (s, 1 H), 4.76 (s, 1 H), 3.84-3.62 (m, 5 H), 3.55-3.48 (m, 1 H), 3.35-3.12 (m, 2 H), 1.75 (s, 3 H), 0.95, 0.91 (2×s, 9 H), 0.09, 0.06 (2×s, 6 H). ^{13}C NMR (75 MHz, two diastereomers): δ 139.9, 139.6, 138.3, 138.2, 135.1, 134.0, 133.3, 128.7, 128.6, 128.5, 128.0, 126.7, 120.2, 120.1, 118.7, 117.8, 71.6, 71.0, 64.6, 64.5, 63.3, 55.9, 55.1, 49.2, 48.8, 25.8, 20.9, 20.6, 18.1, -5.5, -5.6; MS (EI) *m*/*z* (relative intensity) 502 (15), 501(51), 500 (100). HRMS (EI) calcd. for $C_{28}H_{41}NO_3Ssi$ (M^+): 500.2655, found 500.2645.

(*2S,3R,4S*)-1-Benzyl-2-[(*tert*-butyldimethylsilyloxy)methyl]-3-(iodomethyl)-4-(prop-1-en-2-yl)pyrrolidine 3.55

To a flame dried flask was added diene **3.54**. After dissolving in Et_2O (10 mL), $Pd(PPh_3)_4$ (21.0 mg, 0.018 mmol, Strem Chemicals) was added and the yellow suspension stirred for 5 minutes at room temperature. $ZnEt_2$ (1.00 M in hexane, 3.56 mL, 3.56 mmol) was then added at a steady rate. The reaction was heated to reflux and additional portions of palladium (21.0 mg, 0.018 mmol) were added after 7 and 19 hours. The mixture was stirred for an additional 5 hours after the final palladium dose before being cooled to 0 ºC. A 1.50 M solution of I_2 in THF was then added dropwise until a purple color persisted. The mixture was stirred an additional 30 minutes at room temperature before being diluted with 100 mL of Et_2O, washed with 40% $Na_2S_2O_3$ (3x40

mL), and dryed over $MgSO_4$. The solids were filtered and the solvent removed under reduced pressure. The product was purified by flash-column chromatography (5% EtOAc in hexane) to give **3.55** as a colorless oil (95.0 mg, 55%). $[\alpha]_{Na} = -25.0^{o}$ (c = 1.0, EtOH); IR (ν, cm^{-1}): 2928, 2856, 1648, 1471. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 7.33-7.25 (m, 5 H), 4.85 (s, 1 H), 4.60 (s, 1 H), 4.08 (d, *J* = 13.2, 1 H), 3.61 (d, *J* = 13.2, 1 H), 3.54 (dd, *J* = 5.5, 1.2, 2 H), 3.15 (dd, *J* = 9.9, 3.6, 1 H), 2.88 (dd, *J* = 8.4, 5.5, 1 H), 2.83-2.70 (m, 3 H), 2.57-2.44 (m, 2 H), 1.73 (s, 3 H), 0.90 (2, 9 H), 0.06 (s, 6 H). ^{13}C NMR (75 MHz): δ 141.8, 139.6, 128.7, 128.2, 126.8, 111.8, 71.2, 66.4, 60.4, 54.2, 48.4, 45.0, 26.0, 23.1, 18.3, 10.34, -5.26, -5.29; MS (EI) *m*/*z* (relative intensity) 487 (20), 486 (M^+, 100), 354 (8). HRMS (EI) calcd. for $C_{22}H_{36}INOSi$ (M^+): 486.1689, found 486.1669.

Ethyl 2-{(*2S,3S,4S*)-1-benzyl-2-[(*tert*-butyldimethylsilyloxy)methyl]-4-(prop-1-en-2-yl) pyrrolidin-3-yl}acetate 3.57 and **(*2S,3S,4S*)-1-benzyl-2-[(*tert*-butyldimethylsilyloxy)-methyl]-3-methyl-4-(prop-1-en-2-yl)pyrrolidine 3.58**

Iodide **3.55** (649 mg, 1.34 mmol) was dissolved in Et_2O and cooled to –78 ºC. ^{t}BuLi (1.70 M in pentane, 2.95 mmol, 1.73 mL) was then added at a steady rate. After stirring for 10 minutes at –78 ºC, ethylchloroformate (1.28 mL, 13.4 mmol) was added in one portion and stirred at –78 ºC for 15 minutes. The reaction was then quenched with saturated $NaHCO_3$ (5 mL) and warmed to room temperature. The mixture was diluted with 20 mL of H_2O and extracted with Et_2O (3x20 mL). After drying over $MgSO_4$ and filtering, the solvent was removed under reduced pressure. The product was purified by flash-column chromatography (7% EtOAc in hexane) to afford **3.57** (266 mg, 46%) and **3.58** (222 mg, 46%).

3.57: $[\alpha]_{Na} = -29.1^{o}$ (c=1.0, EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 7.39-7.20 (m, 5 H), 4.80 (s, 1 H), 4.57 (s, 1 H), 4.12 (q, *J* = 7.1, 2 H), 3.60-3.47 (m, 3 H), 3.00-2.80 (m, 2 H), 2.72-

2.64 (m, 1 H), 2.56-2.43 (m, 2 H), 2.23 (dd, *J*= 15.0, 4.9, 1 H), 2.05 (dd, *J* = 15.0, 10.2, 1 H), 1.70 (s, 3 H), 1.26 (t, *J* = 7.1, 3 H) 0.89 (s, 9 H), 0.05 (s, 6 H). ^{13}C NMR (75 MHz): δ 172.9, 142.8, 139.9, 128.7, 128.1, 126.7, 111.5, 70.8, 66.8, 60.6, 60.2, 54.8, 46.5, 39.1, 35.8, 25.9, 23.1, 18.3, 14.2., -5.4; MS (EI) *m*/*z* (relative intensity) 339 (15), 313 (15), 264 (25), 153 (35), 122, (50), 108 (65), 80 (100), 68 (95).

3.58: ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 7.35-7.20 (m, 5 H), 4.80 (s, 1 H), 4.57 (s, 1 H), 4.00 (d, *J* = 13.2, 1 H), 3.56-3.40 (m, 3 H), 2.86-2.82 (m, 1 H), 2.75-2.65 (m, 1 H), 2.53-2.42 (m, 2 H), 2.18-2.15 (m, 1 H), 2.23 (dd, *J* = 15.0, 4.9, 1 H), 2.05 (dd, *J* = 15.0, 10.2, 1 H), 1.69 (s, 3 H), 0.88 (s, 9 H), 0.08 (d, *J* = 7.2, 3 H), 0.00 (s, 3 H), -0.01 (s, 3 H); ^{13}C NMR (75 MHz): δ 172.9, 143.6, 140.0, 128.7, 128.1, 126.7, 110.2, 73.7, 66.7, 60.9, 54.6, 46.7, 37.0, 25.9, 23.1, 18.3, 16.5, -5.3, -5.4.

Ethyl 2-[(2*S*,3*S*,4*S*)-1-benzyl-2-(hydroxymethyl)-4-(prop-1-en-2-yl)pyrrolidin-3-yl]acetate 3.60

3.57 (266 mg, 0.62 mmol) was dissolved in 10 mL THF and the mixture was cooled to 0 ºC. TBAF (1.00 M in THF, 1.0 mL) was then added. The reaction mixture was stirred for 1 hour at 0 ºC before quenched with saturated $NaHCO_3$ (5 mL) and allowed to warm to room temperature. The mixture was diluted with 20 mL of H_2O and extracted with Et_2O (3x20 mL). After drying over $MgSO_4$ and filtering, the solvent was removed under reduced pressure. The product was purified by flash-column chromatography (20% EtOAc in hexane) to afford **3.60** (190 mg, 97%). $[\alpha]_{Na}$ = -38.1^{o} (c = 0.1, EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 7.35-7.25 (m, 5 H), 4.81 (s, 1 H), 4.57 (s, 1 H), 4.15 (q, *J* = 6.1, 2 H), 3.95 (d, *J* = 12.9, 1 H), 3.71-2.47 (m, 3 H), 2.95-2.91 (m, 2 H), 2.84-2.76 (m, 1 H), 2.71-2.50 (m, 2 H), , 2.26 (dd, *J* = 15.0, 4.9, 1 H), 2.11 (dd, *J* =

15.0, 10.2, 1 H), 1.70 (s, 3 H), 1.26 (t, J = 6.1, 3 H); ^{13}C NMR (75 MHz): δ 173.2, 142.3, 139.0, 128.6, 128.4, 127.2, 111.5, 71.1, 63.3, 60.5, 59.4, 54.8, 46.9, 39.4, 35.7, 23.1, 14.2.

(*R*)-*N*-Benzylserine methyl ester 3.61

To a stirred solution of D-serine methyl ester hydrochloride **3.49** (2.03 g, 12.7 mmol, purity: 98%, Aldrich) in 40 mL of anhydrous CH_2Cl_2 and 10 mL Et_3N, at room temperature was added 3.000 g of anhydrous $MgSO_4$, then 1.29 mL of anhydrous PhCHO (12.7 mmol, 1.00 eq.) under an argon. The reaction mixture had been stirred at room temperature for 24 hours before filtered through cotton, and the filtrate was concentrated under reduced pressure. The resulting solid was dissolved in 40 mL MeOH and cooled on ice-bath for 10 minutes before $NaBH_4$ (483 mg, 1.00 eq.) was added slowly in portions. After the reaction mixture had been stirred for 3 hours on ice-bath, the reaction was quenched with water (10 mL). The resulting solution was extracted with EtOAc (3 x 40 mL), and combined organic mixture was washed with brine (20 mL), dried over K_2CO_3, filtered, and concentrated under reduced pressure. Flash-column chromatography of the crude material with EtOAc afforded 2.66 g of the desired product **3.61** (99%). ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 7.37-7.21 (m, 5 H), 3.95-3.59 (m, 7 H) [including 3.72 (s, 3 H, COOCH_3)], 3.40 (dd, 1 H, J = 4.6, 1.2), 2.72 (br, s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 173.4, 139.1, 128.4, 128.2, 127.2, 62.4, 61.8, 52.0, 51.9.

Methyl (*2R*)-2-benzylamino-3-{[*tert*-bytyl(dimethyl)silyl]-oxy}propanoate 3.48

To a stirred solution of (R)-*N*-benzylserine methyl ester **3.61** (8.48 g, 40.5 mmol) in 170 mL of anhydrous CH_2Cl_2 was added 4.14 g of imidazole (60.8 mmol, 1.50 eq.), then 6.36 g of TBSCl (40.9 mmol, 1.01 eq.) on ice-bath under an argon. The reaction mixture was stirred at room temperature for 2 hours before sat. NH_4Cl (50 mL) and CH_2Cl_2 (100 mL) was added. The

aqueous solution was separated and extracted with CH_2Cl_2 (2 x 100 mL), and combined organic mixture was washed with brine (20 mL), dried over K_2CO_3, filtered, and concentrated under reduced pressure to give an oil **3.48** (12.89 g, 99%). ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 7.37-7.24 (m, 5 H), 3.94-3.69 (m, 7 H) [including 3.72 (s, 3 H, COOC*H*$_3$)], 3.41 (t, 1 H, *J* = 4.8), 2.17 (br, s, 1 H), 0.88 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 173.7, 139.8, 128.3, 128.1, 126.9, 64.5, 62.2, 52.8, 51.5, 25.7, 18.1, -5.6, -5.7.

(*R*)-Methyl 2-[benzyl(4-chloro-3-methylbut-2-enyl)amino]-3-(*tert*-butyldimethylsilyloxy)-propanoate 3.63

To a stirred solution of **3.48** (1.02 g, 3.15 mmol) in 20 mL of acetonitrile was added 0.80 g of potassium carbonate (5.89 mmol, 1.80 eq.), then 0.80 g of 1-bromo-4-chloro-3-methyl-2-butene (4.23 mmol, 1.40 eq.) at room temperature under an argon. The reaction mixture was stirred at room temperature for 24 hours before concentrated under reduced pressure before 100 mL of ethyl ether and 20 mL of water were added. The organic layer was separated and washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash-column chromatography of the crude material with 5-10% EtOAc in hexane afforded 1.31 g of the desired product **3.63** (98%). IR (v, cm^{-1}) 2952, 2856, 1736, 1692, 1462, 1256, 1198, 1108; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm, two isomers) δ 7.36-7.22 (m, 5 H), 5.71 (t, 0.2 H, *J* = 6.2), 5.57 (t, 1 H, *J* = 6.2), 4.04 (s, 2 H), 3.96-3.61 (m, 7 H) [including 3.72 (s, 3 H, COOC*H*$_3$)], 3.56 (t, 1 H, *J* = 6.2), 3.28 (d, 2 H, *J* = 6.6), 1.82 (s, 0.6 H), 1.72 (s, 3 H), 0.86 (s, 9 H), 0.06(s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 172.1, 140.0, 134.4, 128.9, 128.6, 128.2, 127.0, 64.2, 62.9,

55.9, 51.9, 51.2, 49.1, 25.8, 18.2, 14.5, -5.5; MS (EI) *m*/*z* (relative intensity) 428 (35), 426 (100). HRMS (EI) calcd. for $C_{22}H_{36}ClNO_3Si(M^+)$: 426.2231, found 426.2213.

(*S*)-2-(Benzyl(4-chloro-3-methylbut-2-enyl)amino)-3-(*tert*-butyldimethylsilyloxy)propan-1-ol 3.64

To a stirred solution of **3.63** (0.326 g, 0.77 mmol) in 20 mL of anhydrous ethyl ether was added 0.17 mL of anhydrous MeOH. The resulting mixture was stirred on ice-bath for 10 minutes before 100 mg of $LiBH_4$ (3.10 mmol, 4.00 eq.) in portions under an argon. The reaction mixture was stirred on ice-bath for 6 hours before quenched with sat. NH_4Cl (10mL) and diluted with 100 mL of ethyl ether. The organic layer was separated and washed with water (3 x 50 mL), then brine (50 mL), and dried over $MgSO_4$, filtered, concentrated under reduced pressure. Flash-column chromatography of the crude material with 20% EtOAc in hexane afforded **3.64** (0.29 g, 95%). $[\alpha]_{Na} = -2.7^o$ (c = 1.0, EtOH); IR (v, cm^{-1}) 3445 (br), 2952, 2928, 2856, 1494, 1471, 1257, 1096, 1072; ^1H NMR ($CDCl_3$, 300 MHz, ppm) δ 7.34-7.19 (m, 5 H), 5.55 (t, 1 H, *J* = 6.6), 3.98 (s, 2 H), 3.92-2.97 (m, 9 H), 1.72 (s, 3 H), 0.92 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 139.5, 134.2, 129.0, 128.8, 128.4, 127.1, 61.3, 60.9, 59.4, 54.4, 51.7, 47.6, 25.8, 18.1, 14.4, -5.6; MS (EI) *m*/*z* (relative intensity) 398 (M^+, 100). HRMS (EI) calcd. for $C_{21}H_{36}ClNO_2Si$ (M^+): 398.2245, found 398.2282.

(*S*)-*N*-Benzyl-N-(1-(*tert*-butyldimethylsilyloxy)but-3-en-2-yl)-4-chloro-3-methylbut-2-en-1-amine 3.66

To a stirred solution of oxalyl chloride (1.32 mL, 15.0 mmol., 3.0 eq.) in 100 mL of anhydrous CH_2Cl_2 was added anhydrous DMSO (2.13 mL, 30.0 mmol., 6.0 eq) at –78 ^oC under an argon. The reaction mixture was stirring at the same temperature for 10 minutes before alcohol **3.64**

(1.99 g, 5.0 mmol.) in 5mL THF was added and the mixture was stirred for 30 minutes. Et_3N (12.3 mL, 90.0 mmol., 18.0 eq.) was added and the reaction mixture was stirred for 5 additional hours at –78 ^oC before quenched with water (50 mL), and diluted with hexane (150 mL). The organic layer was separated and washed with water (100mL x 5), dried over Na_2SO_4, filtered, concentrated under reduced pressure to afford **3.65**. The residue was dissolved in 10 mL anhydrous THF, and dropped into the solution of Ph_3PCH_2 in THF (which was prepared from Ph_3PCH_3Br (2.680 g, 7.5 mmol, 1.5 eq.) and KHMDS (1.470 g, 7.5 mmol, 1.5 eq.) in 60 mL anhydrous THF by stirring at room temperature for 1 hours, then cooled to –78 ^oC on acetone-dry ice bath) under an argon. The reaction was allowed to warm from –78 ^oC to 0 ^oC in 30 minutes, and then quenched with sat. NH_4Cl, diluted with 150 mL ethyl ether. The organic layer was separated and washed with water (100 mL), then brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash-column chromatography of the crude material with 6% EtOAc in hexane afforded 1.680 g of the desired product **3.66** (85%). IR (v, cm^{-1}) 2953, 2928, 2885, 2856, 1494, 1471, 1462, 1257, 1102, 1072; ^1H NMR ($CDCl_3$, 300 MHz, ppm) δ 7.35-7.19 (m, 5 H), 5.82 (m, 1 H), 5.60 (t, 1 H, J = 6.1), 5.21 (m, 2 H), 3.96 (s, 2 H), 3.82-3.03 (m, 7 H), 1.69 (s, 3 H), 0.89 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 140.5, 135.4, 133.3, 129.8, 128.5, 128.1, 126.6, 118.0, 64.6, 63.6, 55.0, 52.0, 48.1, 25.9, 18.2, 14.4, -5.3, -5.4; MS (EI) *m*/*z* (relative intensity) 393 (M^+, 15), 358 (75), 250 (100), 236, (50), 214 (70), 146 (88), 73 (90). HRMS (EI) calcd. for $C_{22}H_{36}ClNOSi$ (M^+): 393.2255, found 393.2240.

Reduction of 3.65

3.65 (100 mg, 0.25 mmol) obtained in above procedure was dissolved in 10 mL EtOH on ice-bath, and then 100 mg $NaBH_4$ was added. The reaction mixture was stirred for 30 minutes, before quenched with sat. NH_4Cl, diluted with 50 mL ethyl ether. The organic layer was

separated and washed with water (100 mL), then brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash-column chromatography of the crude material with 20% EtOAc in hexane afforded 89 mg of **3.64** (90%). $[\alpha]_{Na} = -1.4^o$ (c = 1.0, EtOH).

(*2S, 3S, 4S*)-1-Benzyl-2-[(*tert*-butyldimethylsilyloxy)methyl]-3-(iodomethyl)-4-(prop-1-en-2-yl)pyrrolidine 3.55

To a stirred solution of diene **3.66** (464 mg, 1.18 mmol.) in 7 mL of anhydrous ethyl ether was added $Pd(PPh_3)_4$ (68.0 mg, 0.59 mmol., 5%, Strem) and diethylzinc (1.00 N in hexane, 7.06 mL, 7.06 mmol., 6.0 eq., Aldrich) at room temperature under an argon. The reaction mixture was stirred at the same temperature for 42 hours before cooled down on ice-bath, and quenched with 1.50 M I_2 (3.60 g, 14.2 mmol., 12.0 eq.) in THF (9.5 mL). The resulting purple solution was stirred on ice-bath for 30 minutes, then filtered through celite, diluted with 150 mL ethyl ether. The organic layer was separated and washed with 5% $Na_2S_2O_3$ (2 x 50 mL), then brine (50 mL), dried over $MgSO_4$, filtered, concentrated under reduced pressure. Flash-column chromatography of the crude material with 8% EtOAc in hexane afforded 523 mg of the desired product **3.55** (91%).

2-{(*2S, 3S, 4S*)-1-Benzyl-2-[(*tert*-butyldimethylsilyloxy)methyl]-4-(prop-1-en-2-yl)pyrro lidin-3-yl}acetonitrile 3.67

To a stirred solution of iodide **3.55** (523 mg, 1.08 mmol.) in 10 mL of anhydrous DMSO was added NaCN (111 mg, 2.15 mmol., 2.0 eq.) at room temperature under an argon. After stirring at the same temperature for 36 hours, the reaction was diluted with ethyl ether (300 mL) and water (100 mL). The organic layer was separated and washed with water (100 mL), 5% $NaHCO_3$ (100 mL), then brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the crude material with 12% EtOAc in hexane afforded 320 mg of

the desired product **3.67** (77%). $[\alpha]_{Na}$ = -31.7° (c = 1.5, EtOH); IR (v, cm^{-1}) 3084, 3063, 3028, 2953, 2928, 2856, 2246, 1649, 1494, 1471, 1453, 1255, 1115; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 7.33-7.23 (m, 5 H), 4.91 (s, 1 H), 4.68 (s, 1 H), 4.01 (d, 1 H, *J* = 13.2), 3.63 (d, 1 H, *J* = 13.2), 3.59-3.44 (m, 2 H), 2.93-2.76 (m, 3 H), 2.60 (dd, 1 H, *J* = 8.4, 2.6), 2.47-2.45 (m, 1 H), 2.15 (m, 2 H), 1.74 (s, 3 H), 0.90 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 141.2, 139.2, 128.6, 128.2, 126.9, 119.4, 112.5, 70.4, 65.7, 59.8, 54.3, 46.1, 39.3, 25.8, 23.2, 19.2, 18.1, -5.4, -5.5; MS (EI) *m*/*z* (relative intensity) 385 (M^+, 100), 304 (5). HRMS (EI) calcd. for $C_{23}H_{36}N_2OSi$ (M^+): 385.2675, found 385.2671.

(*2S, 3S, 4S*)-Methyl 2-[(*tert*-butyldimethylsilyloxy)methyl]-3-(cyanomethyl)-4-(prop-1-en-2-yl)pyrrolidine-1-carboxylate 3.69

To 250 mL round-button flask with a magnetic stir was added nitrile **3.67** (3.30 g, 8.58 mmol.) and methyl chloroformate (20.0 mL, 259 mmol., 30.0 eq., Aldrich) at room temperature under an argon. After stirring at the same temperature for 16 hours, the reaction mixture diluted with ethyl ether (100 mL), and then cooled down on ice-bath, quenched with 10% K_2CO_3 (350 mL). The organic layer was separated and washed with water (100 mL), then brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash-column chromatography of the crude material with 15-40% EtOAc in hexane afforded 2.86 g of the desired product **3.69** (97%). $[\alpha]_{Na}$ = -27.7° (c = 2.0, EtOH); IR (v, cm^{-1}) 3523 (br), 3085, 2951, 2929, 2885, 2857, 2247, 1701, 1649, 1450, 1382, 1256, 1216, 1132; ^{1}H NMR (DMSO, 360K, 300 MHz, ppm) δ 5.01 (d, 1 H, *J* = 1.1), 4.82 (s, 1 H), 3.80-3.78 (m, 3 H), 3.68 (s, 3 H), 3.57-3.41 (m, 2 H), 3.15 (dd, 1 H, *J* = 8.7, 7.2), 2.67 (q, 1 H, *J* = 6.8), 2.43 (dd, 2 H, *J* = 5.1, 2.4), 1.79 (s, 3 H), 0.96 (s, 9 H), 0.12 (d, 6 H, *J* = 4.5); ^{13}C NMR (DMSO, 360K, 75 MHz, ppm) δ 154.6, 140.8, 119.0, 112.7, 63.5, 62.7, 51.7,

47.3, 44.8, 25.6, 22.1, 17.7, 16.9, -5.6, -5.7 (one peak is covered by DMSO); MS (EI) *m*/*z* (relative intensity) 353(35), 337(50), 321(55), 297(25), 221(45), 208(50), 108(67), 105(100); MS (EI) *m*/*z* (relative intensity) 353 (35), 337 (60), 321 (65), 297 (33), 221 (45), 208 (48), 108 (67), 105 (100). HRMS (EI) calcd. for $C_{17}H_{29}N_2O_3Si(M^+-CH_3)$: 337.1940, found 337.1940.

(-)-Kainic acid 3.1

To a stirred solution of nitrile **3.69** (2.76 g, 7.83 mmol.) in acetone (50 mL) on ice-bath was added Jone's reagent (10.0 mL, 10.0 eq.). The resulting orange mixture was stirred on ice-bath for 10 minutes, then room temperature for 4 hours, before being quenched with isopropanol (10.0 mL), extracted with EtOAc (5 x 50 mL). The combined organic layer was washed with water (30 mL), then brine (20 mL), dried over $MgSO_4$, filtered, concentrated under reduced pressure. The residue was dissolved in DI water (15 mL) and 1-propanol (5 mL) and NaOH (6.30 g, 157 mmol., 20 eq.) was added. The resulting mixture was heated at 125 ^oC (bath temperature) for 18-24 hours under an argon, diluted with water (20 mL), and then cooled on ice-bath, neutralized with ion-exchange resin (Dowex 50wx8-100, Aldrich) to PH = 4-5. The mixture was filtered, washed with 5% NH_4OH (100 mL), and concentrated under reduced pressure to afford a yellow solid **3.1** (1.61 g, 89% yield). The crude solid was recrystallized from aqueous EtOH. mp: 200-205^oC; $[\alpha]_{Na}$ = -7.2^o (c = 1.0, H_2O); ^1H NMR (D_2O, 300 MHz, ppm) δ 4.85 (s, 1 H), 4.56 (s, 1 H), 3.88 (d, 1 H, *J* = 2.8), 3.45 (dd, 1 H, *J* = 7.4, 4.5), 3.25 (t, 1 H, *J* = 10.5), 2.86-2.76 (m, 2 H), 2.04 (ddd, 2 H, *J* = 13.9, 9.3, 6.1), 1.59 (s, 3 H); ^{13}C NMR (D_2O, 75 MHz, ppm) δ 179.7, 173.8, 140.4, 113.2, 66.0, 46.5, 46.0, 42.0, 36.0, 22.3.

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