Abstract

Nuckols, Michel Christian. Progress Toward the Synthesis of Apomorphine: Chiral Auxiliary Mediated Interception of an Intramolecularly Formed N-Acyl Iminium Ion. (Under the direction of Daniel L. Comins.)

Glaucine, which contains an aporphine skeleton, has been previously synthesized utilizing an intermolecular approach to form an iminium ion for the Pictet-Spengler reaction. A diastereomeric excess of 79% resulted as mediated by a chiral auxiliary. Progress was made in attempting to increase the diastereomeric excess by using an intramolecular approach to iminium ion formation. Apomorphine is a suitable platform on which to demonstrate the asymmetric interception of a chiral N-acyl iminium ion generated by intramolecular means.

Several routes to this end were explored. These routes included the use of an intramolecular variant on the previously published work, Grubbs’ metathesis and Horner-Wadsworth-Emmons among others. While no route proved successful in the end, understanding of the formation of aporphine skeletons was expanded upon.
Progress Toward the Synthesis of Apomorphine: 
Chiral Auxiliary Mediated Interception of an 
Intramolecularly Formed N-Acyl Iminium Ion

by

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Dedication

Early in my graduate career cancer took the life of my mother Mary Agnes Whitaker Nuckols. Not only was she a loving mother, she instilled in me a sense of curiosity for understanding and critical thinking. Mom’s death emphasized the importance of strong ties to my family and to my wife’s as well, especially as we begin our own family with the birth of our son, John Alexander.

So it is to my family that I dedicate this work. I thank them endlessly for all their support through this arduous and daedal journey.
Biography

Michel Christian Nuckols was born on April 8, 1975 in Virginia to Mary and Chris Nuckols. He has an older sister Angela. He grew up in Salem, Virginia going to NorthCross School where his interest in math and sciences was sparked. This led him to begin studying chemical engineering at Virginia Tech in 1993. Courses and research opportunities in chemistry intrigued him to leave engineering and pursue a chemistry degree instead. He graduated in 1997 with a bachelor’s degree. In May of 1998 he began working with Dr. Comins at North Carolina State where he matriculated that fall to pursue a Ph.D. In the fall of 1998 he met Molly, who would become his wife in March of 2001. Their first child, John Alexander, was born in September of 2003. Michel began his professional career as a lecturer of organic chemistry for the spring of 2004 at North Carolina State University while exploring permanent employment.
Acknowledgements

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I’d like to thank my parents; they were my first teachers. And thank you to my family who have provided support in all that I do. A special thank you to the Molnar family for their love and encouragement.

My gratitude especially goes to the graduate faculty of North Carolina State University’s chemistry department who expanded my scope of thinking. In particular I’d like to thank the members of my research committee: Dr. Bumgardner, Dr. Burton, Dr. Purrington, Dr. Wang and Dr. Whitesell. A big thank you goes to my advisor, Dr. Comins. He put up with the research group’s boisterous nature and kept us all on task. I thank him also for encouragement and persistence when the chemistry seemed most bleak.

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# Table of Contents

List of Figures .......................................................................................................................... vi

List of Schemes ....................................................................................................................... vii

List of Tables............................................................................................................................. x

1 Chiral Drugs ........................................................................................................................... 1

2 Chiral Auxiliaries ................................................................................................................... 3

3 Trans-2-(α-cumyl)cyclohexanol, TCC .................................................................................. 4

4 Uses of TCC as a chiral auxiliary........................................................................................... 5

5 Toward the Pictet-Spengler Reaction..................................................................................... 9

6 Introduction to Apomorphine............................................................................................... 15

7 Initial retrosynthesis and attempt ......................................................................................... 18

8 Redirection toward Corytuberine .......................................................................................... 27

9 Horner-Wadsworth-Emmons approaches ............................................................................ 32

10 Grubbs’ ............................................................................................................................... 35

11 Intramolecular Horner Reaction......................................................................................... 40

12 Intramolecular Suzuki and Ullmann approaches ............................................................... 46

13 Intramolecular Stille attempts ............................................................................................ 55

Conclusions ............................................................................................................................. 58

General Experimental.............................................................................................................. 61

Experimental Section .............................................................................................................. 62

Appendix 1 HOMOs of sample biaryl ions............................................................................. 98

Appendix 2 $^1$H, $^{13}$C, and $^{31}$P NMR spectra ...................................................................... 102

References ............................................................................................................................. 189
List of Figures

Figure 1 (R)-Thalomide, isomer believed responsible for positive clinical effects ............... 1
Figure 2 Chiral auxiliaries: Evan’s oxazolidone, pseudoephedrine and (-)-8-phenylmenthol . 4
Figure 3 Synthetic utility of the dihydropyridone............................................................... 8
Figure 4 (S)-camptothecin................................................................................................. 8
Figure 5 Proposed conformer of N-acyliminium salt responsible for (-)-laudanosine ........... 13
Figure 6 Intramolecular Pictet-Spengler substrate and projected iminium ion................. 14
Figure 7 Abbot’s Uprima web page for non-US medical professionals .............................. 16
Figure 8 Apomorphine, the aporphine skeleton and morphine......................................... 16
Figure 9 Ortho methoxy biaryl system .............................................................................. 22
Figure 10 Intermediate iminium ions for (-)-laudanosine, (+)-glaucine and (-)-xylopinine ... 26
Figure 11 (+)-Corytuberine and (+)-O,O-diethylcorytuberine ....................................... 27
Figure 12 Some phenanthrene alkaloids ............................................................................ 31
Figure 13 Grubbs' catalyst used ........................................................................................ 39
Figure 14 Disadvantageous conformational biases from Agami ....................................... 39
Figure 15 Unfavorable equilibrium.................................................................................... 46
Figure 16 Diastereomeric products of the Horner reaction................................................. 49
Figure 17 Schematic TLC of elimination of Horner adducts to Z- and E-olefins ............... 49
Figure 18 Intramolecular hydrogen bonding in the anti adduct with literature precedence ... 51
List of Schemes

Scheme 1 Synthesis of racemic TCC ................................................................. 5
Scheme 2 Enzymatic resolution of racemic TCC ................................................. 5
Scheme 3 Synthesis of asymmetric N-H dihydropyridones ................................ 6
Scheme 4 Some alkaloid syntheses using chiral N-acylpyridinium salt chemistry 7
Scheme 5 Liebskind’s use of (-)-TCC in the synthesis of dihydropinidine .......... 8
Scheme 6 Nucleophilic additions to other N-acyliminium ions .......................... 9
Scheme 7 The Pictet-Spengler reaction ................................................................ 9
Scheme 8 Corey’s enantioselective Pictet-Spengler in the synthesis of Ecteinascidin 743... 10
Scheme 9 Asymmetric Pictet-Spengler reaction in the synthesis of Yohimbine ...... 11
Scheme 10 Kooren’s enantioselective Pictet-Spengler reaction ........................... 11
Scheme 11 Silveira’s diastereoselective modified Pictet-Spengler ...................... 12
Scheme 12 Comins’ previous use of a chiral auxiliary in a Pictet-Spengler reaction 12
Scheme 13 Asymmetric Pictet-Spengler reaction common to (+)-glaucine and (-)-xylopine ................................................................................................................................ 13
Scheme 14 Mechanism for acidic conversion of morphine to apomorphine ........ 17
Scheme 15 The first synthesis of racemic apomorphine, by Neumeyer ................. 18
Scheme 16 Retrosynthetic analysis for apomorphine ........................................... 19
Scheme 17 Reduction of bromocinnamic acid ..................................................... 20
Scheme 18 Curtius rearrangement with DPPA and TCC alcohol ......................... 20
Scheme 19 Directed metalation on veratreraldehyde .......................................... 21
Scheme 20 One pot aryl boronation and Suzuki reaction ..................................... 22
Scheme 21 Formation of aryl boronic acid by lithium halogen exchange ............ 23
Scheme 22 Suzuki coupling .................................................................................................... 24
Scheme 23 Levine reaction ................................................................................................. 24
Scheme 24 Attempted Pictet-Spengler reactions ................................................................. 25
Scheme 25 Synthesis of activated A-ring segment 208 ......................................................... 28
Scheme 26 Attempted boronic acid formation ..................................................................... 29
Scheme 27 Directed lithiation to pinacol boronate ester 210 ................................................. 29
Scheme 28 Suzuki and Levine reactions .............................................................................. 30
Scheme 29 Phenanthrene formation .................................................................................... 31
Scheme 30 New proposed route to the formation requisite iminium ion ............................... 32
Scheme 31 First HWE retrosynthetic approach .................................................................. 33
Scheme 32 Failed phosphorylmethyl installation ................................................................. 33
Scheme 33 Duel HWE approach ......................................................................................... 34
Scheme 34 Synthesis of symmetrical carbamate 401 .......................................................... 35
Scheme 35 Kinderman’s cyclic enecarbamates by Grubbs’ metathesis ............................... 35
Scheme 36 Retrosynthetic scheme to Grubbs’ substrate ...................................................... 36
Scheme 37 $N$-vinyl formation with acetal ............................................................................. 37
Scheme 38 Chosen route to $N$-vinyl carbamate 505 ............................................................ 38
Scheme 39 Suzuki and Wittig to Grubbs’ substrate 504 ....................................................... 38
Scheme 40 Horner reaction to close the ten-membered ring ............................................... 41
Scheme 41 Triazine formation ............................................................................................. 42
Scheme 42 Diphenylphosphine oxide treatment of triazine to give 603 ............................... 42
Scheme 43 Mechanism of forming 603 .............................................................................. 43
Scheme 44 Amide formation with TCC chloroformate ....................................................... 43
Scheme 45 Suzuki reaction with aryl bromide 602

Scheme 46 Ring closure to β-hydroxy phosphine oxide 609

Scheme 47 Retrosynthesis for Horner reaction followed by Suzuki

Scheme 48 Intermolecular Horner reaction

Scheme 49 Newman projections for elimination with potassium hydride

Scheme 50 Attempted Suzuki ring closures

Scheme 51 Intramolecular Suzuki on intermediate 703

Scheme 52 Lithium-halogen exchange attempts

Scheme 53 Other intramolecular aryl-aryl bond forming attempts

Scheme 54 Directed metalation to stannyl aldehyde and attempted Horner

Scheme 55 Final retrosynthetic route

Scheme 56 Synthesis of the intramolecular Stille substrate 802
## List of Tables

Table 1 Some chiral drugs................................................................. 2

Table 2 Attempted conditions to affect Pictet-Spengler ....................... 25

Table 3 Conditions tried for intramolecular Suzuki.................................... 52

Table 4 Ring closure trials via biaryl formation ........................................ 54
1 Chiral Drugs

“Thalidomide 1 was first marketed in several countries as a clinically effective sedative hypnotic in 1956 [and for the relief of morning sickness for pregnant women in the 1960’s]. Unexpected potent teratogenic side effects, leading to birth defects such as limb reduction, produced one of the most notorious medical disasters of modern medical history. Thalidomide was withdrawn from the market in 1962.”

![Thalidomide structure](image)

Figure 1 (R)-Thalidomide, isomer believed responsible for positive clinical effects

Although thalidomide wasn’t marketed in the US, it was one of (if not) the first experiences the general public had with the concept of stereochemistry. However

“Chirality in drugs is as old as the first natural-product therapeutic agents. Isolated as products of biological synthesis, drugs such as quinine and morphine always have been available as single enantiomers. But as products of synthetic chemistry, chiral drugs until recently have had to be manufactured and used usually as racemates. Now, single-enantiomer drugs have a commanding presence in the global pharmaceutical landscape. The top two drugs in terms of global sales--Lipitor and Zocor, with combined sales of almost $14 billion in 2002--are single-enantiomer small-molecule drugs. Last year [2002], worldwide sales of single-enantiomer drugs reached more than $159 billion.”

This represents a 20% increase over the $133 billion in 2000.
The importance of optically pure pharmaceuticals can be seen in Table 1, which lists a number of drugs with some descriptions about the need for optical purity.

Table 1 Some chiral drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuterol</td>
<td>Anti-asthmatic inhalant, (D)-Albuterol may actually provoke airway constriction, (L)-Albuterol avoids side effects.</td>
</tr>
<tr>
<td>Allegra</td>
<td>Allergy medication, pure isomer of a metabolite of Seldane, life-threatening heart rhythm disorders of Seldane are avoided.</td>
</tr>
<tr>
<td>Clarinex</td>
<td>Allergy medication, pure isomer from a metabolite of Claritin, enhanced potency as single isomer.</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Depression medication, pure isomer of Prozac, improved efficacy, new indications (eating disorders), adverse side effects minimized (anxiety and sexual dysfunction).</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Reaches therapeutic concentrations in blood in 12 minutes versus 30 minutes for racemic mixture, marketed as fast acting, (patent refused versus the racemic mixture).</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>(S)-isomer: NSAID (non-steroidal antiinflammatory drug) (R)-isomer toothpaste additive to prevent periodontal disease.</td>
</tr>
<tr>
<td>Nexium</td>
<td>Treats gastroesophageal reflux disease (GERD), (S)-isomer of Prilosec, increased efficacy and symptom relief.</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>HIV/AIDS drug.</td>
</tr>
<tr>
<td>Viracept</td>
<td>HIV/AIDS drug.</td>
</tr>
<tr>
<td>Zyrtec</td>
<td>Allergy medication, single isomer of Cetirizine.</td>
</tr>
</tbody>
</table>

The importance of having enantiomerically pure drugs in the market place emphasizes the stress on the need for synthetic routes to these compounds in their optically pure form. While some drugs can be isolated in their optically pure form from natural sources, such as morphine, many more are not available from natural sources and still others are in such scarce amounts naturally that demand could not be filled or isolation would be prohibitively expensive, Taxol® (Paclitaxel) for example.
2 Chiral Auxiliaries

So how, then, can optically pure compounds be produced on both the laboratory scale of milligrams and on the industrial scale of multi-ton? There are several ways to this end: starting with chiral raw materials known as the chiral pool; resolution, which involves separating a racemic mixture into optically pure enantiomers; biological asymmetric methods that entail using enzymes to produce the desired stereochemistry; and chemical asymmetric techniques such as chiral catalysts and chiral auxiliaries. For example Lonza Exclusive Synthesis “prefer[s] to design syntheses that do not require a resolution at the end,” and instead for some commercial-scale reactions “Lonza uses chiral auxiliaries to direct chiral transformations.”

A chiral auxiliary is a molecule with asymmetric centers used to influence the stereochemical outcome of a reaction. It is covalently bonded to the substrate in much the same way as a protecting group. Rather than being able to take advantage of what Woodward defined as absolute asymmetric synthesis, also what Danishefsky called stereochemical correlation, in which two molecules that already contain a stereocenter(s) are joined resulting in new relative stereochemistry, the chiral auxiliary exerts stereocontrol in another manner. This other approach was called relative asymmetric induction by Bartlett and has been described well by Nicolaou and Sorensen:

“…when addressing the synthesis of a molecule that contains multiple stereocenters in proximity, it is often possible to exploit preexisting asymmetry for the purpose of establishing new asymmetry. Stereochemical control in this sense is referred to as relative asymmetric induction because a stereocenter already present in the substrate
molecule guides the introduction of a new stereocenter; the newly introduced asymmetric elements bear a specific relationship to previously existing ones.”

This relative asymmetric induction is the principle that was to be taken advantage of in the research presented here (*vide infra*): the substrate would have no preexisting asymmetry without the chiral auxiliary; therefore the new stereochemistry to be installed in the substrate would be fashioned by the proximal chiral auxiliary.

Several well known chiral auxiliaries are shown below: Evan’s oxazolidinone 2 for alkylation from Evans,9 pseudoephedrine 3 for alkylation of its amides used by Meyers,10 and (-)-8-phenylmenthol 4 from Corey and Ensley for a myriad of reactions including Diels-Alder, [2+2] cycloaddition, ene, 1,2- and 1,4-addition, and cyclopropanation.11

![Figure 2 Chiral auxiliaries: Evan’s oxazolidone, pseudoephedrine and (-)-8-phenylmenthol](image)

**3** *Trans*-2-(α-cumyl)cyclohexanol, TCC

The use of a chiral auxiliary and the expansion of its utility toward more reactions is the goal of the research presented in this dissertation. The chiral auxiliary to be expanded upon here is *trans*-2-(α-cumyl)cyclohexanol 7 and will be referred to as TCC. For a chiral auxiliary to have any utility it must be available with some degree of optical purity, the higher the better. Optically enriched (+) and (-)-TCC have been prepared in the past in five and six steps respectively. However it can be made as a racemic mixture in one step from addition of an α-cumyl anion to cyclohexene oxide, Scheme 1. Highly enantiomerically
enriched (+) and (-)-TCC can then be obtained by enzymatic resolution using *Candida rugosa* (Amano AY30), Scheme 2.\(^{12}\) TCC is also commercially available as either antipode from Aldrich chemical company. The short synthesis and availability in either optical form gives TCC an advantage over the structurally similar 8-phenylmenthol (4).\(^ {13}\)

### Scheme 1 Synthesis of racemic TCC

\[
\begin{align*}
\text{5} & \xrightarrow{n-\text{BuLi}} \text{6} \\
\text{6} & \xrightarrow{\text{KOH} / \text{EtOH}} \text{7}
\end{align*}
\]

(+)-7 (1\(^S\), 2\(^R\)) 82% ee

(-)-7 (1\(^R\), 2\(^S\)) >98% ee

### Scheme 2 Enzymatic resolution of racemic TCC

\[
\begin{align*}
(+)-7 (1\(^S\), 2\(^R\)) & \xrightarrow{\text{lipase AY 30}} \text{8} \\
(+)-7 (1\(^S\), 2\(^R\)) & \xrightarrow{1) \text{KOH} / \text{EtOH}} (+)-7 (1\(^S\), 2\(^R\)) >98% ee \\
(+)-7 (1\(^S\), 2\(^R\)) & \xrightarrow{2) \text{lipase AY 30}} (-)-7 (1\(^R\), 2\(^S\)) >98% ee \\
(+)-7 (1\(^S\), 2\(^R\)) & \xrightarrow{3) \text{KOH} / \text{EtOH}} (-)-7 (1\(^R\), 2\(^S\)) >98% ee
\end{align*}
\]

4 Uses of TCC as a chiral auxiliary

In the Comins research group, 2-alkyl and 2-aryl-2,3-dihydro-4-pyridones 14 have been shown to be chemically desirable as chiral building blocks. As shown in Scheme 3, homochiral *N*-acylpyridinium salts of the type 11 are formed from 4-methoxy-3-(triisopropylsilyl)pyridine 9 and the chloroformate 10 of enantiomerically pure TCC.
Addition of Gringard reagents or metallo enolates to these in situ formed salts gives dihydropyridine 12. Subsequent acidic hydrolysis provides dihydropyridones 13 in high yields and diastereoselectivity. The chiral auxiliary is removed by basic hydrolysis and protodesilylation to provide vinylogous amides of the type 14 when using enantiopure (+)-TCC as the chiral auxiliary. The utility of the asymmetric dihydropyridone obtained from the N-acylpyridinium salt has been expressed in the numerous alkaloid syntheses shown in Scheme 4, among others.

Scheme 3 Synthesis of asymmetric N-H dihydropyridones
Scheme 4 Some alkaloid syntheses using chiral N-acylpyridinium salt chemistry

The diversity of this utility is illustrated in Figure 3. The enone moiety can be used as a Michael acceptor or 1,2 addition can be effected. The C-5 position is susceptible to electrophilic substitution while the C-3 position can be alkylated. The C-2 substituent is forced axial, due to $A^{(1,3)}$ strain, giving the heterocycle a conformational bias which can influence the stereochemical outcome of further reactions.$^{14}$
In addition to its role in producing asymmetric dihydropyridones, the use of TCC as a chiral auxiliary has been extended to the shortest asymmetric synthesis of (S)-camptothecin.\textsuperscript{15} Camptothecin, \textsuperscript{17}, Figure 4, is a pentacyclic alkaloid and is an important lead compound for the preparation of selective anticancer drugs.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{(S)-camptothecin}
\end{figure}

TCC has also found use in the labs of Liebeskind. Using enantiocontrolled synthesis of disubstituted piperdines by chiral auxiliary-induced desymmetrization, (-)-dihydropinidine \textsuperscript{20} was synthesized with (-)-TCC.\textsuperscript{16}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme5.png}
\caption{Liebskind’s use of (-)-TCC in the synthesis of dihydropinidine}
\end{figure}
5 Toward the Pictet-Spengler Reaction

To expand the scope of adding nucleophiles to $N$-acyliminium ions, it was determined (unpublished work) if asymmetric induction could be obtained with other $N$-acyliminium ions 21. The addition of nucleophiles to $N$-acyl salts was briefly investigated resulting in poor diastereoselectivity (4-30% de), Scheme 6. It was reasoned that the factors, such as $\pi-\pi$ interactions, that influence chirality transfer from a cyclohexyl-based chiral auxiliary to a pyridinium ring weren’t present in these non-aromatic $N$-acyliminium ions.25

\[
\text{CO}_2\text{R}^* \quad \text{CO}_2\text{R}^*
\]

\[
\text{Nu} \quad \text{Nu}
\]

\[
n = 0,1
\]

\[
\text{R}^* = (-)-8\text{-phenylmenthyl}
\]

Scheme 6 Nucleophilic additions to other $N$-acyliminium ions

It was reasoned that intramolecular addition to similar $N$-acyliminium ions could result in better stereocontrol, hence the use of the Pictet-Spengler reaction. A very simple and generic Pictet-Spengler is shown in Scheme 7.
The Pictet-Spengler reaction has proven to be a powerful synthetic tool for the construction of 1,2,3,4-tetrahydroisoquinolines 25 from a phenethylamine unit 23 and an aldehyde under acidic conditions (23 to 25). The reaction was first reported in 1911.17

The reaction has been successfully employed in a large number of alkaloid syntheses,18,19 including its use in the late stages of the total synthesis of Ecteinascidin 743 by Corey. It should noted that this intermolecular reaction is enantioselective, Scheme 8.20

Diastereoselective Pictet-Spengler reactions, in which both reacting moieties are on the same molecule, have been successfully used in alkaloid synthesis where the existing asymmetry is used to influence the stereochemistry of the newly formed tetrahydroisoquinoline. This strategy was employed in the total synthesis of Yohimbine21 33, Scheme 9, and in the total synthesis of Ajmaline 34.22 However, the purpose of this research was to use relative asymmetric induction (vide supra) provided only by a chiral auxiliary.

Scheme 8 Corey’s enantioselective Pictet-Spengler in the synthesis of Ecteinascidin 743
Scheme 9 Asymmetric Pictet-Spengler reaction in the synthesis of Yohimbine.

In addition to Comins’ use of a chiral auxiliary to influence the stereochemical outcome of a Pictet-Spengler (vide supra), Koomen and coworkers\textsuperscript{23} reported using a chiral sulfoxide 35 as an auxiliary in an enantioselective Pictet-Spengler reaction, Scheme 10. Silveira and coworkers\textsuperscript{24} demonstrated the use of a rather modified Pictet-Spengler with $\alpha$-chloro-$\alpha$-phenylseleno propionate 37 as an aldehyde surrogate and phenethyl amine 38. However, to achieve high diastereomeric ratios, each reactant must have a pendant chiral auxiliary, an example of absolute asymmetric synthesis, Scheme 11.

Scheme 10 Koemen’s enantioselective Pictet-Spengler reaction
To influence the stereochemical outcome of a Pictet-Spengler reaction an approach like that depicted in Scheme 12 was taken. A chiral auxiliary would be attached to the substrate with a carbamate linkage on the phenethylamine moiety $40$. This pendent asymmetric center would then dictate the orientation of the alkyl group in $42$.

Using this approach and (-)-8-phenylmenthol as the chiral auxiliary, only modest diastereoselectivity was produced giving the unnatural $(R)$-(-)-laudanosine, $44$. The observed stereochemical outcome was consistent with the rationalization depicted in structure $43$, Figure 5.
Figure 5 Proposed conformer of $N$-acyliminium salt responsible for (-)-laudanosine

With the unnatural stereochemistry and only 63% ee obtained for laudanosine (44), the use of (+)-TCC was pursued to synthesize (+)-glaucine (48) and (-)-xylopinine (49) which are arrived at through a common intermediate 47, Scheme 13.25

Scheme 13 Asymmetric Pictet-Spengler reaction common to (+)-glaucine and (-)-xylopinine

In the hopes of increasing the diastereomeric excess it was envisioned that having both entities of the Pictet-Spengler reaction on the same molecule 50 would prove
advantageous. In this case, the electrophilic methyl vinyl ether, the activated carbonyl surrogate, and the nucleophilic $N$-acyl nitrogen would be joined. In the course of the reaction, the formation of the iminium ion 51 brings the nucleophilic aromatic ring and the electrophilic iminium ion to a common molecule. Joining the reaction partners prior to iminium ion formation should eliminate some degrees of freedom from the $N$-acyliminium ion prior to nucleophilic attack therefore increasing the diastereoselectivity due to a more ordered system, Figure 6.

![Figure 6 Intramolecular Pictet-Spengler substrate and projected iminium ion](image-url)
6 Introduction to Apomorphine

The candidate target for this approach is apomorphine. Apomorphine (101) is a semisynthetic alkaloid obtained by treating morphine (102) with acid as first reported by Mathiessen and Wright in 1869 in their paper entitled “Researches into the chemical constitutions of the opium bases. Part 1. On the action of hydrochloric acid on morphia.” Since this seminal paper, a large body of clinical research has been amassed on its use as a powerful emetic,27 as a sedative,28 in the management of alcoholism,29 and in treating a variety of other medical conditions30 including Parkinson’s disease.31 In the 1960’s it was demonstrated that apomorphine is a dopamine receptor agonist and “evidence that derangement of [dopamine] function may play a role in various neurological, psychiatric and other disorders… has renewed interest in clinical and pharmacological research.”32 In 1951 investigations began in the use of apomorphine to treat Parkinson’s disease.33 “As a dopamine D2 agonist, apomorphine represents a significant advance in the treatment of well-defined motor fluctuations in Parkinson’s disease.”34 It is known that apomorphine acts on the central nervous system for treatment of erectile dysfunction (ED)35 and has recently been marketed outside the United States by Abbott to treat ED under the trade name Uprima,36 Figure 7. Prior to their merger, governmental regulators are requiring pharmaceutical manufacturers Pfizer and Pharmacia to sell off an apomorphine nasal spray for erectile dysfunction.37 In an interesting result, Lal noted that apomorphine had an effect on the number of yawns in a group of subjects, less yawning with lower doses and more with higher doses. This indicates that lower doses are presynaptic while higher doses are postsynaptic.38
“Accordingly, most investigations on the effect of apomorphine of the psychopathology of schizophrenia have used doses compatible with a postsynaptic site of action.”

In 1902 Pschorr elucidated apomorphine’s structure and subsequently its stereochemistry was determined to be 6a-R in 1955 by Corrodi and Hardegger. Neumeyer accomplished the first total synthesis of racemic apomorphine from isoquinoline and vanillin in 1970 and Saari resolved the mixture in 1973. Subsequently, it was also determined that the R enantiomer was responsible for the observed dopaminergic activity.
As shown by Matthiessen and Wright, the treatment of morphine with strong acid will provide apomorphine. Scheme 14 shows a series of concerted intramolecular mechanisms can be drawn to rationalize the transformation and it is noteworthy that the reaction is stereospecific.

Neumeyer’s first synthesis of racemic apomorphine hinged on a Pschorr cyclization of intermediate which was obtained from Reissert anion and modified benzyl chloride, Scheme 15.
7 Initial retrosynthesis and attempt

For the research presented here, the total synthesis of (-)-apomorphine was envisioned arising from Pictet-Spengler cyclization of 121, Scheme 16, simultaneously forming the aporphine skeleton and setting the single stereocenter. Intermediates 122 and 123 are derived from retrosynthetic scission of the biphenyl bond in 121 and could be used in a Suzuki coupling. Directed lithiation would supply 122 from veratraldehyde (124) and the carbamate moiety of 123 would be installed by a Curtius reaction on 3-bromohydrocinnamic acid from commercially available 3-bromocinnamic acid (125).
The synthesis commenced with a reduction of commercially available 3-bromocinnamic acid over 5% Pt/C with balloon pressure hydrogen in absolute ethanol, Scheme 17. This led to complete reduction of the double bond by $^1$H-NMR. However, rather than the carboxylic acid being recovered it was converted to the ethyl ester 126 in 70% yield. In an effort to circumvent the additional step of saponification, the reduction was attempted in ethyl acetate. While the reduction did occur it was considerably slower and required additional catalyst. Saponification in methanol/water with potassium hydroxide, followed by acid-base extraction led to the desired 3-bromohydrocinnamic acid in an overall 70% yield. It was not until a large-scale reaction was run that partial reduction of the aryl bromide was recognized. The resulting hydrobromic acid was clearly the catalyst for the ester formation in the alcoholic solvent. Vacuum distillation to separate the two esters proved to be a useful method of purification. Saponification of the distilled ester gave the 3-bromohydrocinnamic acid (128).
It was later discovered that using acetic acid for the solvent prevented any observable loss of bromine. This meant that in acetic acid the intermediate ester was avoided thus eliminating the saponification step and increasing yields of \textbf{128}.

Curtius reaction\textsuperscript{45} on 3-bromohydrocinnamic acid in refluxing toluene with triethylamine, diphenylphosphoryl azide (DPPA)\textsuperscript{46} and the racemic chiral auxiliary TCC alcohol led to a modest 41\% of the TCC carbamate \textbf{129}, Scheme 18. Chromatography was difficult due to similar R\textsubscript{f} values of the carbamate and the TCC alcohol but was overcome by using slow elution and lower polarity eluent. Yields were improved to 76\% and the TCC carbamate was isolated and used initially as a thick oil. However, on standing for long periods of time, 1-2 weeks, crystals began to form and it was found that the oil could be crystallized from hot hexanes.
The iodobenzaldehyde coupling partner 122, Scheme 19, was formed through a directed lithiation procedure using the lithium amide of \( N,N,N' \)-trimethylethylenediamine to protect veratraldehyde as the \( \alpha \)-amino-alkoxy anion.\(^{47}\) This was then converted to the thermodynamic dianion 130 by stirring at room temperature overnight with three equivalents of phenyl lithium.\(^{47}\) After adding iodine as the electrophile, iodoaldehyde 122 was isolated in moderate yield.\(^{48}\)

\[
\begin{align*}
124 & \xrightarrow{1)} \text{ LiN} & & \xrightarrow{2)} \text{ PhLi} & & \xrightarrow{3)} \text{ I}_2 \\
\text{THF} & & & & & \text{75\%}
\end{align*}
\]

Scheme 19 Directed metalation on veratraldehyde

Shown in Scheme 20 is the first key step of the synthesis. The Suzuki coupling was attempted using a one-pot procedure\(^{49}\) between the two aryl halides 122 and 129, first catalytically converting 129 to the pinacol boronate ester and coupling it to 122. Although low, yields were a reproducible 15-16\% yield in DMF and poor reactivity was observed in other solvents. Even attempts at isolating the catalytically converted aryl bromide as the pinacol boronate proved fruitless (129 to 132).
Although this synthetic pathway proved unfulfilling, an interesting and characteristic $^1$H-NMR shift of the ortho methoxy group of the biphenyl moiety in 133 was observed. The methoxy signal shifted nearly one-half of one ppm from 122 (~3.95 ppm to ~3.5 ppm). This is due to the biphenyl rings not being coplanar and the protons of the methoxy group sitting directly over the adjacent $\pi$-system, see Figure 9. Having a shift in such an intense peak served as a touchstone of a successful coupling.

At this point a new approach to synthesize the biaryl system was taken. The aryl bromide of the TCC carbamate 129, Scheme 21, could be lithiated via lithium halogen
exchange and reacted with a trialkoxy boronate as noted in literature.\textsuperscript{50} This required first deprotonation of the carbamate at reduced temperatures (–20 to –78 °C) followed by cooling to –100 °C for lithium halogen exchange with tertiary butyl lithium.\textsuperscript{51} The dianion was treated with excess triisopropyl borate and the reaction was allowed to slowly warm to room temperature. An aqueous workup delivers the desired aryl boronic acid \textsuperscript{135} in repeatable yields of 88\% on a scale over one gram. Isolation of this compound was unique in that 3 to 7\% methanol was needed in the eluent to move it on silica. Therefore other organics could easily be washed from the radial PLC plate before beginning to move the product from the origin. The boronic acid \textsuperscript{135} was a hard foam when dried and resisted crystallization.

![Scheme 21 Formation of aryl boronic acid by lithium halogen exchange](image)

Suzuki coupling of the boronic acid \textsuperscript{135} and iodobenzaldehyde \textsuperscript{122}, Scheme 22, was fruitful with different palladium catalysts as well as different solvents and solvent systems.\textsuperscript{52} Isolated yields varied from 40 to 80\%. Palladium catalysts used for this reaction were Pd(PPh\textsubscript{3})\textsubscript{4} and PdCl\textsubscript{2}(dppf) [dppf = 1,1'-Bis(diphenylphosphino)ferrocene]. Solvents included DME, DMF and ethanol/DME mixtures. Reactions were run on scales upward of one gram and the desired compound \textsuperscript{133} was isolated in modest yield of 57\%. Best results were seen with PdCl\textsubscript{2}(dppf), DMF, >90 °C on 15 mg scale at >80\% yield.
The biphenyl benzaldehyde 133, Scheme 23, was then submitted to the Levine reaction with the phosphorous ylide of methoxymethyltriphenylphosphonium chloride. This reaction was often complete upon addition of the aldehyde to the deep red colored ylide. The methyl vinyl ether 136 was isolated was approximately a 3:2 E/Z mixture as determined by $^1$H-NMR.

With the intramolecular Pictet-Spengler precursor 136 in hand it was submitted to both Lewis acid and proton sources, Scheme 24. Following Comins’ success with (-)-laudanosine, (+)-glaucine, and (-)-xylopinine, attempts were made toward Pictet-Spengler
cyclization to provide aporphine 137. However, all attempts to this end were unsuccessful, see Table 2. With the exception of small amounts of starting material and hydrolyzed vinyl ether, no other identifiable materials were isolated.

![Scheme 24 Attempted Pictet-Spengler reactions](image)

Table 2 Attempted conditions to affect Pictet-Spengler

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Other</th>
<th>Entry</th>
<th>Reagent</th>
<th>Solvent</th>
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</thead>
<tbody>
<tr>
<td>1</td>
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<td>anh. DCM</td>
<td>rt</td>
<td>8</td>
<td>Amberlyst 15</td>
<td>MeCN</td>
<td>rt to reflux</td>
</tr>
<tr>
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<td>anh. PhH</td>
<td>rt</td>
<td>9</td>
<td>Amberlyst XN-1010</td>
<td>MeCN</td>
<td>rt to reflux</td>
</tr>
<tr>
<td>3</td>
<td>TFA 3 eq</td>
<td>anh. DCM</td>
<td>rt</td>
<td>10</td>
<td>Dowex 50WX8-200</td>
<td>MeCN</td>
<td>rt to reflux</td>
</tr>
<tr>
<td>4</td>
<td>CSA 3eq</td>
<td>anh. PhH</td>
<td>rt to reflux</td>
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<td>tol.</td>
<td>rt to reflux</td>
</tr>
<tr>
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<td>BF₃·OEt₂ 3eq</td>
<td>anh. PhH</td>
<td>rt</td>
<td>12</td>
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<td>tol.</td>
<td>rt to reflux</td>
</tr>
<tr>
<td>6</td>
<td>TFA 3 eq</td>
<td>tol.</td>
<td>rt</td>
<td>13</td>
<td>Dowex 50WX8-200</td>
<td>tol.</td>
<td>rt to reflux</td>
</tr>
<tr>
<td>7</td>
<td>TFA 3 eq</td>
<td>MeCN</td>
<td>rt</td>
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</tr>
</tbody>
</table>

Comparing this data relative to the previously published data, an obvious difference is apparent. The aryl ring of the phenethylamine moiety in 136 lacked activation by electron donating groups as it would become the A-ring of apomorphine. Further review of the literature surrounding Pictet-Spengler reactions shows a propensity toward success when activated rings are used and poor yields when unactivated rings are present.¹⁸,⁵⁴ Silveira also notes that the Pictet-Spengler “shows some disadvantages in terms of product yields when the starting β-phenethylamines lack activating hydroxyl or alkoxy groups at the position.
para to the ring closure, because drastic conditions are usually required to effect the cyclization.” The current synthetic approach also demands an unprecedented motif of an unactivated ring attacking an iminium ion (if it is indeed formed) in the presence of an activated ring. A potential cause for the lack of reaction could also be the strain associated in forming the initial ten-membered ring.

![Diagram of iminium ions](image)

**Figure 10 Intermediate iminium ions for (-)-laudanosine, (+)-glaucine and (-)-xylopinine**

Assuming formation of the ten-membered iminium ion, one could also look at the HOMO of the intermediate iminium. Molecular orbital calculations (AM1) from MacSpartan (See Appendix 1) indicate that for the iminium ions with the aryl-aryl bond in place, almost regardless of the substitution patterns on the A- and/or D-rings, there is a significant contribution to the HOMO on the D-ring. This would indicate that electron releasing groups on the A-ring should aid in attack on the iminium ion, assuming that it is indeed formed.
8 Redirection toward Corytuberine

With this information in hand a similar target to apomorphine was sought. (+)-Corytuberine 201, Figure 11, is another aporphine alkaloid whose \( O,O \)-dimethyl analogue 202 synthesis could be completed in a manner similar to that attempted for apomorphine. Importantly, its phenethyl moiety would contain the desired electron releasing groups on the A-ring.

\[
\begin{align*}
\text{HO} & \quad \text{HO} \\
\text{O} & \quad \text{O} \\
\text{Me} & \quad \text{Me} \\
\text{H} & \quad \text{H} \\
\text{N} & \quad \text{N}
\end{align*}
\]

Figure 11 (+)-Corytuberine and (+)-\( O,O \)-dimethylcorytuberine

The synthesis of 3-bromo-4,5-dimethoxycinnamic acid 206, produced in three steps from vanillin, would commence the pathway towards 202, Scheme 25. Following Magetich’s bromination procedure\textsuperscript{55}, methylation with iodomethane and potassium carbonate, Doebner-Knoevenagel\textsuperscript{56} with malonic acid, and finally reduction in acetic acid afforded hydrocinnamic acid 207. Curtius reaction on 207 proceeded smoothly furnishing carbamate 208 in 68% yield.
Scheme 25 Synthesis of activated A-ring segment 208

Up to this point the synthesis proceeded smoothly, but after numerous attempts at deprotonation followed by lithium halogen exchange to provide boronic acid 209, only 12% yield and 80% debrominated starting material were isolated. This could be due to the instability associated with forming the dianion on the electron rich ring. Lithium halogen exchange proceeded to 92% but the source of protonation was unclear, Scheme 26.
The inability to produce $209$ in a reasonable yield led to a more convergent path that would save a step in the overall route to $O,O$-dimethylcorytuberine: simply switch coupling partners for the Suzuki, Scheme 27. Rather than forming the iodobenzaldehyde from directed lithiation, the dianion could be quenched with a trialkyl borate. Making the boronic acid proved illusive, yet utilizing isopropyl pinacol boronate, the pinacol boronate $210$ could be made in 25% yield after recrystallization albeit on a 1.7-gram scale, Scheme 27.

Note: Isopropyl pinacol boronate, 2-isoproxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, ($i$-PrOBPin) could be made or bought with the same results obtained. It is prepared by gently heating triisopropyl borate with one equivalent of pinacol in hexanes followed by azeotroping off the isopropyl alcohol with the hexanes solvent. Vacuum distillation provided material identical by NMR to that purchased from Aldrich.
Suzuki coupling to give the tetramethoxybiphenyl 211 succeeded in modest yields on small scale (75mg) yet poor results were seen on larger scale (763mg) leading to substantial loss of boronate to give veratraldehyde. Conditions different from those used in the apomorphine attempts were chosen due to the electron rich nature of both coupling partners. The small amounts of 211 were enough to push through the Levine reaction to vinyl ether 212, Scheme 28.

![Scheme 28 Suzuki and Levine reactions](image)

Submitting 212 to Pictet-Spengler conditions of proton sources or Lewis acids led quickly and exclusively to phenanthrene 213, Scheme 29. Proton sources and Lewis acids used were TFA, BF$_3$·OEt$_2$, POCl$_3$, and TMS-Tf. Formation of 213 can simply be rationalized by protonation (or Lewis acid coordination) of the vinyl ether, followed by attack of the activated phenethyl ring on the oxonium ion 214. Efforts toward $O,O$-dimethylcorytuberine were exhausted and this pathway was quickly abandoned.
This obviously facile reaction does however lend itself to the synthesis of phenanthrene alkaloids. These alkaloids are a small group of optically inactive bases with some pharmacological and chemotaxonomic properties. In this group are three closely related alkaloids uvariopsine, stephenanthrine and argentinine.$^{58}$

With the method used above these and other structurally similar alkaloids could easily be synthesized especially with the activating groups on the A-ring. Unnatural analogues would also be easily accessible if it were so desired.
9 Horner-Wadsworth-Emmons approaches

At this point new thinking was required: an iminium ion is necessary to set the stereochemistry and a ten-membered ring with an enecarbamate moiety could be protonated to affect this end (301 to 302).

Moving in this direction, two similar Horner-Wadsworth-Emmons approaches were briefly examined as shown in Scheme 31. A sequential biaryl formation - Horner-Wadsworth-Emmons approach could quickly be set up from the in-hand TCC carbamate 129 which lacks only the N-diethylphosphorylmethyl moiety.
First, attempting to make the N-diethylphosphorylmethyl\textsuperscript{59} species \textbf{303} via Arbusov type reaction from the apomorphine carbamate fragment \textbf{129} ironically led to Pictet-Spengler products, Scheme 32. Using the dimethylcorytuberine carbamate \textbf{209} led to similar results, as would be expected.

\textbf{Scheme 31} First HWE retrosynthetic approach

\textbf{Scheme 32} Failed phosphorylmethyl installation
The second HWE approach involved a symmetric carbamate 401 that would be taken through two sequential HWE reactions to desymmetrize the carbamate as shown in Scheme 33. Deprotecting benzyl amine 402 and carbamate formation should give 401. A HWE reaction followed by a reduction to supply 303 will offer passage into the Suzuki - HWE sequence.

The carbamate 401 could be made in three steps without the necessity for intermediate purification, Scheme 34. Bisphosphonate 402 was obtained in near quantitative yield followed by removal of the N-benzyl group using catalytic hydrogenation to give secondary amine 404 in good yield. Using the chloroformate of the chiral auxiliary with powdered molecular sieves as an acid sponge, 61 carbamate 401 was obtained in good yield. Attempts toward Horner-Wadsworth-Emmons reactions between 401 and 3-bromobenzaldehyde were met with failure using NaHMDS, KHMDS or LDA.
At about the same time that the HWE attempts ended, Kinderman published what he called “the first examples of ring-closing metathesis of olefinic enamides to obtain the corresponding cyclic enamides,” Scheme 35. This introduced the option of closing the necessary ten-membered ring using Grubbs’ catalyst, providing a new pathway to the elusive apomorphine.

Scheme 35 Kinderman’s cyclic enecarbamates by Grubbs’ metathesis
A Suzuki reaction followed by a Wittig reaction would provide the N-vinyl styrene 504 from 505 and 210. Altering the TCC carbamate 129 to the N-vinyl carbamate 505 would give entry to a Grubbs’ closure, Scheme 36.

![Scheme 36 Retrosynthetic scheme to Grubbs’ substrate](image)

The first approach to modifying TCC carbamate 129 used acetal (acetaldehyde diethyl acetal) and catalytic camphorsulfonic acid to form the N-vinyl moiety. This was a straightforward synthetic step that for some reason resisted yielding product except on very small scales ~20-25 mg, Scheme 37
An alternate route to produce the necessary $N$-vinylcarbamate 505 for the ring closing metathesis was developed. Submitting 3-bromobenzaldehyde to a Henry reaction\textsuperscript{64} gave nitrostyrene 507. Following reduction procedures from Kabalka,\textsuperscript{65} using \textit{in situ}-generated borane-THF complex, furnishes amine 508, which could be distilled\textsuperscript{66} in a 54\% yield. The gauntlet that 508 would be forced into would not allow purification until the fourth step. Treating 3-bromophenethylamine (508) with acetaldehyde gave imine 509 which was exposed, without purification, to phosgene to make chloroethylcarbamoyl chloride 510 which, upon distillation, eliminated HCl to give semi pure vinyl carbamoyl chloride 511.\textsuperscript{67} Lithium TCC alkoxide was added to 511 to produce vinyl carbamate 505 in an overall acceptable yield for the sequence.
Next, Suzuki coupling of 505 with pinacol boronate 210, followed by Wittig olefination furnished vinyl styrene 504, Scheme 39. In the Suzuki reaction there was enough loss of the N-vinyl group to cause concern but, with one step to the linchpin olefination, low yields (20-50%) were acceptable. Wittig reaction to the styrene proceeded smoothly in 61-87%.

Scheme 39 Suzuki and Wittig to Grubbs’ substrate 504
Efforts to form the ten-membered ring through Grubbs’ catalyzed ring metathesis were not successful as monitored by $^1$H-NMR. (CD$_2$Cl$_2$ 5-10 mol% Grubbs’ catalyst 512 50-60 °C) This was likely due to the strain in adopting a conformation appropriate for ring closure.

Fürstner$^{68}$ notes: “Due to the inherent strain of medium-sized rings, eight- to eleven-membered cycloalkenes are excellent substrates for ROMP but constitute particularly challenging targets for RCM. If preexisting conformational constraints, however, force the substrates to adopt a favorable conformation for ring closure, even this class of compounds is within reach, as witnessed by a rapidly growing number of successful applications.” Agami reported lower activity in substrate 513 toward RCM due to a 5 kcal mol$^{-1}$ difference in the stability of conformers as determined AM1 calculations,$^{69}$ Figure 14.

![Figure 13: Grubbs' catalyst used](image)

![Figure 14: Disadvantageous conformational biases from Agami](image)
11 Intramolecular Horner Reaction

Moving away from the Grubbs’ metathesis, the next approach that was an intramolecular Horner reaction to form the ten-membered ring, a modification from the earlier HWE efforts. This required a significantly different approach from the previous HWE routes.

In a retrosynthetic manner, the requisite olefin \textbf{301} would arise from an intramolecular Horner reaction using the Suzuki coupling product of \textbf{210} and \textbf{602}. Diphenylphosphine oxide \textbf{602} would be generated from the TCC chloroformate \textbf{10} and the secondary amine \textbf{603} generated from the action of diphenylphosphine oxide on triazine \textbf{604}, a product of phenethyl amine \textbf{508} and paraformaldehyde.
Scheme 40 Horner reaction to close the ten-membered ring

This route was originally approached in the same way that the double HWE route was attempted (Scheme 34, 403 to 402). It was hoped that the combination of one equivalent each of phenethyl amine 508, paraformaldehyde and diphenylphosphine oxide would react in the same fashion as observed when diethylphosphate was used with benzyl amine. Instead, when analyzing the ¹H-NMR and ¹³C-NMR only a portion of the needed signals was present. Upon careful repetition and checking of materials the same result occurred. After going through a number of possible reactions (dimerization, etc.), the triazine seemed the most plausible and literature precedent supported the notion.⁷⁰ Treatment of phenethyl amine 508 with excess
paraformaldehyde in methylene chloride or with aqueous formaldehyde quickly leads to the triazine 604, Scheme 41.

![Scheme 41 Triazine formation](image)

Obtaining triazine 604 proved simple and quick with a fast reaction and purification consisting only of filtering. Reacting the triazine in refluxing toluene with one equivalent of diphenylphosphine oxide70 led to the secondary amine 603 in good yield, Scheme 42.

![Scheme 42 Diphenylphosphine oxide treatment of triazine to give 603](image)

In this reaction, the triazine is acting as a surrogate for the imine until thermally opened to be attacked by a tautomer of the phosphine oxide. A proton transfer completes the mechanism presented in Scheme 43.
The amine could be carried on crude or purified by radial PLC and subsequently recrystallized from diethyl ether, as it appeared to make little difference in the later steps. Combining the secondary amine \( \text{603} \) with one equivalent of triethylamine and one equivalent of TCC chloroformate \( \text{10} \) in methylene chloride quickly gave the desired carbamate \( \text{602} \), Scheme 44. The workup for this reaction was to remove the methylene chloride and wash the product from the resultant triethylamine hydrochloride salt with excess ether followed by radial PLC.

The diphenylphosphine oxide carbamate \( \text{602} \) had a \(^1\text{H-NMR} \) that was made exceedingly difficult by rotomers in CDCl\(_3\), C\(_6\)D\(_6\), and \( d_8 \)-dioxane. At elevated temperatures
in all solvents peaks could be seen to “shift” as they began to broaden and merge but never fully coalesce. The same observation was made in the $^{31}$P-NMR.

Carrying on 602 it is now the aryl bromide synthetic handle that will be taken advantage of in the Suzuki reaction with the pinacol boronate 210 to finally give the crucial Horner reaction precursor. Just as before the Suzuki reaction proved to be a robust synthetic step, easily giving the desired biaryl system 601. This actually turned out to be one of the cleanest Suzuki reactions that was run, presumably due to the lack of the N-H from the carbamate in the first two routes or an N-vinyl carbamate from the Grubbs’ route that could have potentially interfered with the catalyst. In addition to it being a clean reaction, it was less tedious to carry out. The method used was to simply combine the aryl halide 602, aryl boronate 210, a catalytic amount of tetrakis(triphenylphosphine)palladium followed by dimethoxyethane and aqueous Na$_2$CO$_3$ and heat to ~90 °C overnight giving an 85% yield after purification, Scheme 45. The Suzuki product showed the expected shift of the ortho methoxy protons from 3.95 ppm to ~3.55 ppm in the $^1$H-NMR as well as retaining complicating rotomers.

![Scheme 45 Suzuki reaction with aryl bromide 602](image-url)
Next compound 601 was submitted to intramolecular Horner conditions analogous to those worked out on an intermolecular study.\textsuperscript{71} The intermolecular reactions demonstrated the characteristic yellow color of the phosphoryl enolate as well as the high polarity of the β-hydroxy phosphine oxide (R\textsubscript{f} ~ 0.2 in 50% EtOAc/Hex). Adding a slight excess of LDA to 601 at −78 °C gave the expected yellow color and which faded slowly upon warming. Monitoring the reaction by TLC a faint spot with a higher R\textsubscript{f} was observed yet a heavy starting material spot remained. Following a standard ethereal workup the crude \textsuperscript{1}H-NMR was inconclusive besides confirming starting material. Isolating the new spot and recovering the remaining starting material gave a near quantitative mass recovery with ~10% attributed to the new material. The \textsuperscript{1}H-NMR indicated a large number of aromatic protons indicating that the phosphine oxide had not eliminated to the olefin just as in the intermolecular experiments. Also, the \textsuperscript{31}P-NMR showed a phosphorous signal.

![Scheme 46 Ring closure to β-hydroxy phosphine oxide 609](image)

Although the new material suspected of being 609 gave a \textsuperscript{1}H-NMR that was anything but conclusive, it was exposed to KH in DMF. Disappointingly the reaction with KH quickly gave back 601 by TLC and \textsuperscript{1}H-NMR, yet it did confirm that 609 had been formed.
Apparently an equilibrium must set up between the phosphorylenolate \textbf{610} and the β-alkoxy phosphine oxide \textbf{611}, favoring the former.

![Unfavorable equilibrium](image)

**Figure 15 Unfavorable equilibrium**

### 12 Intramolecular Suzuki and Ullmann approaches

This reversal of fortune, a mere elimination away from the needed enecarbamate, did at least give some proof that the ten-membered ring could be formed. While the intramolecular Horner showed that it couldn’t complete the task, perhaps using an intramolecular Suzuki reaction to close the ring after an intermolecular Horner would work, Scheme 47.
The path to the intramolecular Suzuki would actually change little in the first steps starting with diphenylphosphine oxide 602 and iodoaldehyde 122 to produce β-hydroxy phosphine oxide 702. The open-chain enecarbamate would arise from elimination of 702 and would be closed by a one-pot catalytic conversion an aryl halide of 701 to an aryl boronate followed by Suzuki aryl-aryl bond formation.

Generation of the phosphoryl enolate of 602 with LDA at –78 °C in THF followed by addition of a slight excess of iodoaldehyde 122 either as a solution in THF or as a neat solid provided β-hydroxy phosphine oxide 702, Scheme 48.
Monitoring the progress of the reaction originally by TLC was misleading for two reasons. First, as benzaldehydes are intense chromaphores, even extremely dilute samples will yield a dark spot on a TLC plate under short-wave UV light. Therefore the slight excess added to the reaction always showed up heavy, incorrectly giving the impression that the reaction was not proceeding. Second, the product ended up having the same \( R_f \) as the starting material even using a co-spot. So initial uncertainty was set in by the TLC and then by the crude \(^1\)H-NMR that showed an aldehydic proton signal that seemed to be a significant constituent of the crude mixture. Also the remainder of the crude \(^1\)H-NMR resembled a cross section of the Himalayan mountain range!

Submitting the crude mixture of 702 to purification by radial PLC gave back iodoaldehyde 122 in an amount relative to the excess added. As the very polar material that followed progressed down the plate it divided in two major bands giving what turned out to be the expected products as a diastereomers: \( \text{syn-702} \) and \( \text{anti-702} \), the Horner adducts, Figure 16. This was shown by independent elimination (\textit{vide infra}) with potassium hydride and subsequent high-resolution mass spectrometry.
In the body of work described here, the $^1$H-NMR spectra of the Horner adducts were two of the most complex, decorated by intricate $^1$H-$^1$H coupling compounded by $^1$H-$^{31}$P splitting and rotomers.

The relative stereochemistry of the two adducts was first determined indirectly in three separate elimination experiments with potassium hydride: one a purified mixture of the syn and anti adducts; two and three run side-by-side each one of the purified diastereomers. In the mixture of adducts two higher $R_f$ and more intense spots formed but the higher $R_f$ spot forming significantly faster than the other. The separated diastereomers showed the same difference in rate with the higher $R_f$ material developing faster from the lower $R_f$ adduct.

Figure 17 Schematic TLC of elimination of Horner adducts to Z- and E-olefins
Based on Newman projections of the *syn* and *anti* adducts it would be predicted that the *syn* diastereomer should eliminate faster as a σ-bond rotation isn’t required for *syn* elimination, Scheme 49. And this is the case as determined by the coupling constants of the vinyl protons of the resultant olefins: *E*-701: \( J = 14 \) Hz and *Z*-701: \( J = 9 \) Hz.

![Scheme 49 Newman projections for elimination with potassium hydride](image)

The \( ^1H \)-NMR of a later Horner adduct (with strikingly similar \( ^1H \)-NMR spectra to those discussed above) was examined to further confirm the relative stereochemistry of the separated \( \beta \)-hydroxy phosphine oxides. A sample of what was believed to be *anti*-801 was shaken with D\(_2\)O. This deuterium exchange experiment showed the vicinal coupling constant of the two C-H’s was found to be \( J = 2.4 \) Hz. This would indicate a dihedral angle of \( \sim 60^\circ \) based on the Karplus curve. But this is in direct contrast to the belief that this sample was the *anti* \( \beta \)-hydroxy phosphine oxide and assuming the Newman projections were the dominant
conformer. As it turned out, the sample was indeed the *anti* diastereomer, however an intramolecular hydrogen bond formed between the hydroxyl proton and the phosphoryl oxygen, Figure 18. This was supported by an amazing calculated (AM1) difference in energy between the non-hydrogen bonded and the hydrogen bonded of ~94 kcal/mol favoring the hydrogen bonded conformer. Literature precedent was also found with a crystal structure of a similar compound showing the same type of intramolecular hydrogen bonding between hydroxyl and phosphoryl groups.72

![Figure 18 Intramolecular hydrogen bonding in the *anti* adduct with literature precedence](image)

Instilled with confidence that the proper $E/Z$ assignments were given to the enecarbamates, experiments commenced to bring about the essential aryl-aryl bond. Hoping to find success where it couldn’t be found before, the $E$ olefin was subjected to Suzuki conditions. (Scheme 50)
Table 3 Conditions tried for intramolecular Suzuki

<table>
<thead>
<tr>
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<th>Scale</th>
<th>Cat</th>
<th>Additive</th>
<th>Boron</th>
<th>Solvent</th>
<th>Temp</th>
<th>Time</th>
<th>Result</th>
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<td>TEA</td>
<td>HBPin</td>
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<td>Mostly SM and decomposition</td>
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<td>TEA</td>
<td>HBPin</td>
<td>MeCN</td>
<td>81 °C</td>
<td>15 h</td>
<td>16% BPin-Br + SM</td>
</tr>
<tr>
<td>3</td>
<td>21 mg</td>
<td>PdCl2(dppf)</td>
<td>TEA</td>
<td>HBPin</td>
<td>MeCN</td>
<td>81 °C</td>
<td>15 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>10 mg</td>
<td>PdCl2(dppf)</td>
<td>TEA</td>
<td>HBPin</td>
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<td>43 mg</td>
<td>PdCl2(dppf)</td>
<td>KOAc (freshly melted)</td>
<td>(PinB)2</td>
<td>DMSO</td>
<td>100 °C</td>
<td>6 h</td>
<td>21% SM 39% BPin-Br 30% No I</td>
</tr>
<tr>
<td>7</td>
<td>63 mg</td>
<td>PdCl2(dppf)</td>
<td>KOAc (freshly melted)</td>
<td>(PinB)2</td>
<td>DMSO</td>
<td>100 °C</td>
<td>8 h</td>
<td>66% SM 8% BPin-Br</td>
</tr>
</tbody>
</table>

The attempts to cyclize \( E-701 \) to \( 301 \) in one pot are summarized in, Table 3. While no product was found small amounts of reduced aryl iodide were recovered and an intermediate was isolated where the aryl iodide moiety was converted to the aryl pinacol boronate (BPin-Br), \( 703 \). As the molecular weights of the starting material \( 701 \) and \( 703 \) differ by <0.2 AMU, this outcome was confirmed by HRMS. The TLC showed a bright blue spot for \( 703 \) with a lower R\(_f\). This was at least promising that first catalytic cycle was occurring albeit very low yielding.

Compound \( 703 \) was subjected to what was thought to be the best Suzuki conditions found for the intermolecular systems: tetrakis(triphenylphosphine)palladium, aqueous
sodium carbonate in refluxing dimethoxyethane. The reaction’s appearance resembled that of other successful reactions, clear yellow and no Pd-black on the flask for the first few hours. TLC showed only starting material. The reaction was allowed to go overnight and decomposed.

While these Suzuki reactions were being attempted, a couple of lithium-halogen exchange reactions were tried with little hope for success. In both trials 1 equivalent of \( t \)-butyllithium was added to dihalide \( E-701 \) in THF at \(-100 \) °C. In the first trial (10 mg starting material) isopropyl pinacol boronate was added quickly after the \( t \)-butyllithium (~1 min) resulting in 45% reduced bromide \( 704 \) and <28% impure \( 705 \) both by low resolution mass spectrometry, Scheme 52.

In the second (30 mg starting material) the isopropyl pinacol boronate was in the flask prior to lithium halogen exchange giving ~30% recovered \( E-701 \) and ~50% of what appeared to be reduced halide \( 704 \).
Additional attempts at cyclizing dihalide \( E-701 \) included a Stille-type method,\(^\text{75}\) Ulmann couplings with copper (I) thiophenecarboxylate (CuTC),\(^\text{76}\) and freshly prepared\(^\text{77}\) copper bronze, Scheme 53.\(^\text{78}\) The use of copper bronze proved modestly effective at coupling bromobenzene and iodoaldehyde 122 as observed by the shift of the \textit{ortho} methoxy proton signal but none of these endeavors hinted toward success in cyclizing dihalide \( E-701 \).

**Table 4 Ring closure trials via biaryl formation**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Type</th>
<th>Metal</th>
<th>Solvent</th>
<th>Temp</th>
<th>Other</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Stille</td>
<td>Pd(PPh(_3))(_4)</td>
<td>1,4-dioxane</td>
<td>100 °C</td>
<td>Sn(_2)Me(_6)</td>
<td>Anh. LiCl</td>
</tr>
<tr>
<td>2</td>
<td>Ullmann</td>
<td>CuTC</td>
<td>NMP</td>
<td>r.t. - 100 °C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Ullmann</td>
<td>CuTC</td>
<td>NMP</td>
<td>r.t. - 100 °C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Ullmann</td>
<td>Cu bronze</td>
<td>DMF</td>
<td>210 °C</td>
<td>Sealed tube</td>
<td>48 hrs</td>
</tr>
<tr>
<td>5</td>
<td>Ullmann</td>
<td>Cu bronze</td>
<td>DMF</td>
<td>210 °C</td>
<td>Sealed tube</td>
<td>48 hrs</td>
</tr>
<tr>
<td>6</td>
<td>Ullmann</td>
<td>Cu bronze</td>
<td>DME</td>
<td>210 °C</td>
<td>Sealed tube</td>
<td>48 hrs</td>
</tr>
<tr>
<td>7</td>
<td>Ullmann</td>
<td>Cu bronze</td>
<td>Pyridine</td>
<td>210 °C</td>
<td>Sealed tube</td>
<td>48 hrs</td>
</tr>
</tbody>
</table>
13 Intramolecular Stille attempts

Another attempt was taken with the existing material in hand to set up an intramolecular Stille. Conducting the directed metalation of veratraldehyde and quenching with tri-\(n\)-butyltin chloride gave stannyl aldehyde\(^{79}\) \textbf{706}. Attempting the Horner reaction with \textbf{602} normal and inverse additions failed, Scheme 54.

![Scheme 54 Directed metalation to stannyl aldehyde and attempted Horner](image)

The final path attempted would set its sights on an intramolecular Stille reaction and encompass a similar route to those previously described. The final ring closure would be set up with an aryl trimethyl tin moiety installed early on in the route by a triple lithium halogen exchange on triazine \textbf{604} quenched with trimethyl tin chloride.
Generation of the trianion of 604 with 3 equivalents of n-butylithium proceeded smoothly at –78 °C, a deep red color persisted. In the hood, trimethyltin chloride was carefully weighed out next to the stirring trianion and added as a solid. As it slowly dissolved the red color dissipated. After a standard ethereal workup the crude stannyl triazine 804 was carried on to the next reaction without purification, Scheme 56. As before refluxing toluene and diphenylphosphine oxide gave the secondary amine, which was purified by radial PLC to
give a 73% yield. The amine was reacted with TCC chloroformate to supply the stannyl-Horner piece 803.

An interesting anomaly was observed in the Horner reaction with the stannyl phosphine oxide 803 and 122. Upon warming the reaction to room temperature the syn adduct eliminated to give the E olefin and only a trace of the Z olefin was seen in the crude \(^1\)H-NMR. As it turned out this would be a serendipitous convenience cutting out a tight separation between Horner adducts or olefins, and the elimination with potassium hydride.

Following a Stille macrocyclization by Nicolaou\(^80\) with tetrakis palladium in toluene only resulted in 50% recovery of starting material and no other identifiable material. No reaction was seen using tetrakis palladium with CuI in DMF. And when using Pd\(_2\)(dba) with
CuI in DMF many products were observed on 3 mg scale. Multiple products were also seen using bis(triphenylphosphine) palladium dichloride with TEA and CuI in DMF. While high dilution was used in these reactions, it is possible that intermolecular reactions took place.

**Conclusions**

It was shown through multiple and sequential analytical techniques that the desired compounds described above were all synthesized in satisfactory yields to continue on with further synthetic steps. Numerous potential precursors to apomorphine were successfully synthesized and subjected to conditions under which desired reactions were not observed despite literature precedence or following solid chemical intuition.

Met with failure, the endeavors in each path pursued to apomorphine told us much about each system used. In the original route it was believed that the phenethyl ring needed to be more electron rich for the Pictet-Spengler reaction to work. It turns out that having activating groups on that ring forces the reaction through another path as shown by isolation of the phenanthrene. This may well indicate that forming a ten-membered ring in this manner would always be fruitless. Even though the carbamate nitrogen may be more nucleophilic, the proximity of the aromatic ring to the oxonium ion would effectively increase its nucleophilicity toward the oxonium ion, thus leading to a phenanthrene.

It is still unclear as to exactly why the Horner-Wadsworth-Emmons reactions failed using the symmetrical carbamate. One thought on the matter is that with two phosphate groups on the molecule the nucleophilicity of the phospharyl enolate was sacrificed to its basicity due the further presence of acidic protons. Regardless this would later lead to the more successful Horner reactions.
The robust and widespread use of olefin metathesis with Grubbs’ catalyst displayed its potential application to the synthesizing the desired enecarbamate. However with only scarce literature precedence for the formation of smaller rings containing eneamides, it may have been a case of not overcoming conformational bias that prevented success with olefin metathesis. In addition, the olefin metathesis is a reversible process resulting in the more thermodynamically stable olefin, which could favor the starting material over the product.

The intramolecular Horner route came very close to working when the conditions of the final step to form the cyclic enecarbamate caused the reaction to revert back one step, presumably a victim of thermodynamic stability of reaction intermediates.

Prior installation of the enecarbamate by intermolecular Horner reaction followed by closing the ring with an aryl-aryl bond formation with a Suzuki, Ullman or Stille reaction was thought to be the surefire reaction to bring about apomorphine. But due to unseen reasons these dependable carbon-carbon bond-forming reactions couldn’t bring ultimate victory.

While apomorphine proved illusive by these methods, the label of failure won’t be applied. The crusade of chemistry rarely produces the expected treasures on the first or second or even later expeditions. The goal of science is to answer a posed hypothesis with objectively interpreted results and apply that knowledge to refining accuracy of future hypotheses.

This paper was opened with a brief description of the importance of chiral drugs and that chiral auxiliaries are one method of producing this type of pharmaceutical. While another use for TCC wasn’t found here expanding the applications of existing chiral
auxiliaries might lead to new, cheaper and safer drugs that have become the cornerstone of American medical might.
General Experimental.

All reactions were performed in oven dried or flamed dried glassware under argon or nitrogen atmosphere and stirred magnetically. Tetrahydrofuran (THF), ether, and toluene were distilled from sodium/benzophenone ketyl prior to use. Triethylamine, diisopropylamine, and benzene were distilled from calcium hydride and stored under argon over 4 Å molecular sieves. Other reagents and solvents from commercial sources were stored under argon and used directly. Melting points were obtained from a Thomas-Hoover capillary melting point apparatus and are uncorrected. Radial preparative layer chromatography (radial PLC) was performed on a Chromatotron (Harrison Associates, Palo Alto, CA) using glass plates coated with 1, 2 or 4 mm layers of Kieselgel 60 PF254 containing gypsum. High-resolution mass spectroscopy analyses (HRMS) were performed at North Carolina State University. NMR spectra were obtained using a Varian Gemini GN-300 (300 MHz), Varian Mercury 300 (300 MHz), or Varian Mercury 400 (400 MHz) spectrometer. Chemical shifts are in δ units (ppm) with TMS (0.0 ppm) used as an internal standard for 1H NMR and the CDCl3 absorption (77.23 ppm) for 13C NMR spectra, 31P NMR were not referenced and only used as a qualitative measure of purity. IR spectra were recorded on a Perkin-Elmer 1430 spectrometer. HPLC was performed using a Waters and Assoc. (Miliford, MA) 600E multi-solvent delivery system with a 486 tunable detector equipped with a µ-Porisil analytical column.
Experimental Section

3-(3-Bromophenyl)propionic acid (128).

To 3-bromocinnamic acid (3.182 g, 14.014 mmol) in a 250 mL round bottom flask was added approximately 75 mL of glacial acetic acid. The mixture was heated gently to dissolve the starting material and argon was flushed through the flask. The catalyst, 5% wt. Pt on activated carbon (200 mg), was added and the flask was flushed liberally with hydrogen. The reaction was stirred vigorously under balloon pressure hydrogen for 16 h at which point $^1$H NMR showed a 93.4:6.6 ratio of product to starting material. The catalyst was removed by filtration and the solvent was removed by rotary evaporation. The crude product was recrystallized as a white solid from hot hexanes/ethyl acetate (99:1). Two crops: 2.907 g, 90.6%; mp 67 – 69 °C (Lit$^{81}$ 74.5-75 °C); IR (thin film, neat, NaCl) 3030, 2919, 2716, 2658, 2615, 1706, 1597, 1567, 1441, 1312, 1261, 1216, 921, 865, 790 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.68 (t, 2H, $J = 7.2$ Hz), 2.93 (t, 2H, 7.2 Hz) 7.10-7.19 (m, 2H), 7.33-7.37 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 30.30, 35.46, 122.77, 127.17, 129.77, 130.34, 131.59, 142.60, 179.02.
[2-(3-Bromophenyl)ethyl]carbamic acid 2-(1-methyl-1-phenylethyl)cyclohexyl ester (129).

A 10 mL solution of toluene containing 128 (668 mg, 2.878 mmol), triethylamine (0.441 mL, 3.166 mmol) and diphenylphosphoryl azide (0.682 mL, 3.166 mmol) was gently refluxed under argon for 2 h. The reaction was allowed to cool slightly and racemic TCC alcohol (723 mg, 3.310 mmol) was added as a solid. The reaction mixture was then refluxed overnight. The heating bath was removed and the reaction cooled and concentrated by rotary evaporation. The dark brown oil was taken up in ethyl acetate and run through a plug of silica gel and washed with excess ethyl acetate. The ethyl acetate was removed by rotary evaporation and the light brown oil purified by radial PLC (silica gel, hexanes/ethyl acetate, 85:15) to give 129 (971 mg, 76%) as a colorless oil which could be recrystallized from hot hexanes, mp 87-89 °C; IR (thin film, neat, NaCl) 3345, 2932, 2858, 1713, 1515, 1248, 1028, 853 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.04 – 1.34 (m, 12H), 1.66 – 1.75 (m, 2H), 1.95 – 2.00 (m, 1H), 2.69 (bs, 2H), 3.25 (10º m, 2H, J = 6.8 Hz), 3.65 (bs, 1H), 4.55 (dt, 1H, J = 3.6 Hz, J = 10.4 Hz), 7.02 – 7.38 (m, 9H); ¹³C NMR (750 MHz, CDCl₃) δ 24.39, 24.97, 26.29, 27.24, 28.46, 34.06, 35.95, 39.94, 41.85, 51.71, 75.53, 122.83, 124.88, 125.62, 127.68, 127.85, 129.80, 130.34, 132.05, 141.53, 152.58, 155.80; HRMS Calc for C₂₄H₃₀BrNO₂: 444.1538. Found 444.1522.
To a 100 mL round bottom flask containing 129 (1.500 g, 3.375 mmol) dissolved in 25 mL of freshly distilled THF at 0 ºC was added methyl lithium (0.94M, 3.6 mL, 3.375 mmol) and stirred for 30 min at 0 ºC. The reaction mixture was cooled to −95 to −100 ºC with a liquid nitrogen/methanol bath and t-butyl lithium (1.6 M, 4.22 mL, 6.751 mmol) was added drop wise resulting in a yellow deep color. This was stirred at −95 to −100 ºC for 2 h. Triisopropyl borate (3.12 mL, 13.501 mmol) was added causing the yellow color to quickly fade. The reaction mixture was allowed to warm slowly to room temperature and was quenched with HCl (1.2 M, ~15 mL) and stirred overnight. The reaction mixture was neutralized with saturated NaHCO₃ and extracted twice with ether. The combined organic layers were washed with water, brine, dried over MgSO₄ and concentrated. Purification by radial PLC (silica gel, hexanes/ethyl acetate 80:20 to hexanes/ethyl acetate 80:20 plus 5% methanol) gave 135 (1.22g, 88%) as a hard foam.
2-Iodo-3,4-dimethoxybenzaldehyde (122).

To a 250 mL round bottom flask containing \(N,N,N'\)-trimethylethylenediamine (1.04 mL, 8.001 mmol) dissolved in 25 mL anhydrous benzene was added \(n\)-butyllithium (2.25 M, 3.26 mL, 7.334 mmol) at 0 – 5 °C. The cooling bath was removed and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was cooled to 0 – 5 °C and veratraldehyde (1.108 g, 6.667 mmol) was added via cannula as a solution in minimal benzene (~1.5 mL, quantitated with two 0.5 mL portions of anhydrous benzene). This was allowed to warm and stir at room temperature for 30 min at which point it was cooled to 0 – 5 °C and phenyllithium (1.45 M, 13.8 mL, 20.00 mmol) was added dropwise and stirred for 11 h at room temperature. Freshly distilled THF, 25 mL, was added and the reaction mixture was cooled to −78 °C. Iodine (10.15 g, 40.0 mmol) was added and the reaction mixture was allowed to warm slowly to room temperature. A solution of 10% aq Na\(_2\)S\(_2\)O\(_3\) was added with vigorous stirring until the iodine color no longer persisted. Aqueous 10% HCl was added and the reaction mixture was extracted twice with ether. The combined organic layers were washed with water, brine, dried over MgSO\(_4\) and concentrated. Crude 122 was purified by radial PLC (silica gel, hexanes/ethyl acetate 80:20) giving 122 (1.55 g, 86%) which was recrystallized from hexanes/ethyl acetate (99:1) giving pure 122 (1.46 g, 75%), mp 75-77 °C (Lit\(^{48}\) 77-78 °C); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 3.87 (s, 3H), 3.96 (s, 3H), 6.97 (d, 1H, \(J = 8\))
Hz), 7.73 (d, 1H, J = 8 Hz), 10.02 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 56.5, 60.7, 100.6, 112.1, 127.7, 129.1, 148.9, 158.0, 195.3.

[2-[2',3'-Dimethoxy-6'-(2-methoxyvinyl)biphenyl-3-yl]ethyl]carbamic acid 2-(1-methyl-1-phenylethyl)cyclohexyl ester (133).

To a 10 mL round bottomed flask was added boronic acid 135 (61 mg, 0.1485 mmol), iodoaldehyde 122 (43 mg, 0.1485 mmol), palladium tetrakis(triphenylphosphine) (17 mg, 0.01485 mmol) followed by 8 mL DME which was subsequently degassed with an argon stream for approx 10 min. Aqueous sodium carbonate (2 M, 0.163 mL, 1.26 mmol) was added and the reaction mixture was gently refluxed overnight. After cooling, a standard ethereal workup followed by radial PLC (silica gel, ethyl acetate/hexanes 5-20%) gave 48 mg (78%) of 133. $^1$H NMR (400 MHz, CDCl$_3$) δ 1.00-1.35 (m, 12H), 1.63-1.73 (m, 2H), 1.40-1.99 (m, 1H), 2.76 (t, 2H, J = 6.8 Hz), 3.25-3.36 (m, 2H), 3.55 (s, 3H), 3.75 (bs, 1H), 3.98 (s, 3H), 4.57 (dt, 1H, J = 4.4 Hz, J = 10.2 Hz), 7.00-7.28 (m, 9H), 7.38 (t, 1H, J = 7.2 Hz), 7.83 (d, 1H, J = 8.8Hz), 9.58 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 24.5, 24.9, 26.2, 27.2, 28.2, 29.9, 34.0, 36.3, 39.9, 42.1, 51.6, 56.2, 61.0, 75.3, 111.5, 124.8, 125.6, 127.8, 128.4, 128.6, 128.9, 131.1, 133.5, 138.9, 140.5, 146.3, 152.5, 155.8, 157.8, 191.2; IR (thin film, neat, NaCl) 3354, 2931, 2856, 1707, 1684, 1584, 1508, 1482, 1458, 1303, 1253, 1208, 1117, 1033, 911 cm$^{-1}$; HRMS calcd for C$_{33}$H$_{39}$NO$_5$: 530.2906, Found 530.2904.
{2-[2',3'-Dimethoxy-6'-(2-methoxyvinyl)biphenyl-3-yl]ethyl}carbamic acid 2-(1-methyl-1-phenylethyl)cyclohexyl ester (136).

In a 10 mL round bottomed flask was dissolved (methoxymethyl) triphenylphosphonium chloride (35 mg, 0.102 mmol) in 8 mL freshly distilled diethyl ether and was cooled below 0 ºC. Phenyllithium (1.41 M, 0.072 mL, 0.102 mmol) was added resulting in a deep orange to red color. The solution was stirred for 15 min. In a separate flask was dissolved aldehyde 133 (18 mg, 0.034 mmol) in 5 mL of fresh ether. The aldehyde solution was added via syringe to the Wittig reagent, and the reaction mixture was allowed to warm to room temperature. The reaction was quenched with saturated aqueous sodium bicarbonate followed by a standard ethereal workup and purification by radial PLC (silica gel, ethyl acetate/hexanes 10 – 20%) to give 17 mg (89%) of 136. IR (thin film, neat, NaCl) 2931.3, 1712.5, 1639.2, 1481.1, 1248.7, 1122.4, 1037.5, 764.6, 701.0 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.03- 1.29 (m, 12H), 1.60-1.72 (m, 2H), 1.92-1.99 (m, 1H), 2.73 (t, 2H, J = 7.2 Hz), 3.25 (m, 1H, J = 6.8 Hz), 3.27 (m, 1H, J = 6.8 Hz), 3.43 (s, 2H, methyl of vinyl ether: E isomer), 3.48 (s, 1H, methyl of vinyl ether: Z isomer), 3.50 (s, 2H, C11-OCH₃ E isomer), 3.71 (s, 1H, C11-OCH₃ Z isomer), 3.74 (bs, 1H, NH), 3.89 (s, 2H, C10-OCH₃ E isomer), 3.90 (s, 1H, C10-OCH₃ Z isomer), 4.57 (dt, 1H, J = 4.0 Hz, J = 10.0 Hz), 4.78 (d, 0.4H, J = 7.2 Hz, vinyl proton Z isomer), 5.40 (d, 0.6H, J = 12.8 Hz, vinyl proton E isomer), 5.93 (d, 0.4H, J = 7.2 Hz, vinyl proton Z isomer), 6.74 (d, 0.6H, J = 12.8 Hz, vinyl proton E isomer), 6.87 (d, 0.6H, J = 8.4 Hz).
Hz, D-ring Ar-H, $E$ isomer), 6.91 (d, 0.4H, $J = 8.8$ Hz, D-ring Ar-H $Z$ isomer), 7.02-7.16 (m, 4H), 7.15 (d, 0.6H, $J = 8.8$ Hz, D-ring Ar-H), 7.18-7.26 (m, 3H), 7.26-7.30 (m, 1H), 7.34 (t, 1H, $J = 8.0$ Hz), 7.84 (d, 0.4H, $J = 8.8$ Hz, D-ring Ar-H $Z$ isomer); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 24.6, 25.0, 26.3, 27.3, 28.2, 34.1, 36.3, 40.0, 42.3, 51.8, 56.2, 56.6, 60.8, 75.3, 77.5, 100.1, 103.4, 104.2, 111.6, 112.1, 120.3, 124.9, 125.1, 125.6, 127.6, 127.9, 128.3, 128.6, 130.9, 137.2, 147.0, 148.0, 152.5, 155.8.

3-Bromo-4-hydroxy-5-methoxybenzaldehyde (204).

In a 50 mL round bottom flask vanillin (10.104 g, 66.408 mmol) was dissolved in 25 mL of acetic acid. Bromine (10.613 g, 66.408 mmol, 3.40 mL) was slowly added via syringe and the reaction mixture was stirred for 2.5 h. The solid product was filtered, the mother liquor was concentrated to about half its volume, and additional product was filtered. This process was repeated once more. The three combined portions of product were washed with water and recrystallized from acetic acid to give 12.01 g (78%) of 204 as a white solid, mp 158-160 °C (Lit$^{82}$ 163-164 °C); IR (thin film, neat, NaCl) 3299, 3104, 3074, 2975, 2942, 2849, 1674, 1590, 1424, 1354, 1291, 1154, 1046, 855, 830 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.99 (s, 3H), 6.47 (s, 1H), 7.37 (d, 1H, $J = 1.8$ Hz), 7.64 (d, 1H, $J = 1.8$ Hz), 9.79 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 56.86, 108.24, 108.40, 130.27, 130.32, 147.90, 149.10, 189.88; HRMS calcd for C$_8$H$_7$BrO$_3$ 229.9579, found 229.9581.
3-Bromo-4,5-dimethoxybenzaldehyde (205).

In a 250 mL round bottom flask was added 204 (11.987 g, 51.88 mmol), K₂CO₃ (28.64 g, 207 mmol) and 75 mL DMSO. Methyl iodide (8.103 g, 57.069 mmol, 3.55 mL) was added dropwise. The reaction mixture was stirred at room temperature for 1 h at which point 150 mL of cold water was added and the reaction was extracted with ether (2 x 125 mL). The combined organic layers were washed with brine and dried over MgSO₄ and concentrated to give 205 as a white solid, 12.03 g (95%), 56-58 ºC (Lit 82 61-62 ºC). This material was very clean and could be carried on crude. IR (thin film, neat, NaCl) 2940, 2832, 1696, 1588, 1567, 1485, 1416, 1385, 1279, 1137, 1045, 997 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 3.94 (s, 3H), 3.95 (s, 3H), 7.39 (d, 1H, J =1.8 Hz), 7.65 (d, 1H, J = 1.8), 9.85 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 56.47, 61.06, 110.29, 118.15, 128.98, 133.26, 152.00, 154.40, 190.11; HRMS calcd for C₉H₇BrO₃ 243.9735, found 245.9747.

3-(3-Bromo-4,5-dimethoxyphenyl)acrylic acid (206).

In a 250 mL round bottom flask was dissolved 205 (1.326 g, 5.412 mmol) in 25 mL pyridine followed by malonic acid (1.126 g, 10.824 mmol) and pyrrolidine (0.058 g, 0.812 mmol,
0.068 mL). The reaction mixture was heated overnight at 65 °C. It was allowed to cool, and ether was added followed by slow addition of 6 M HCl until pH < 2. The layers were separated and the reaction mixture was extracted twice with ether. The combined organic layers were washed with water and brine and dried over MgSO₄ and concentrated to give 206 as a white solid, 1.53g (98%); mp 134-136 °C. This material was very clean and could be carried on crude. IR (thin film, neat, NaCl): 2978, 2940, 1693, 1683, 1633, 1489, 1423, 1310, 1275, 1222, 1146, 1046, 999, 846 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 3.90 (s, 3H), 3.91 (s, 3H), 6.36 (d, 1H, J = 15.9Hz), 7.01 (d, 1H, 1.5Hz), 7.36 (d, 1H, J = 2.1 Hz), 7.66 (d, 1H, J = 15.9 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 56.4, 60.1, 111.0, 117.8, 118.4, 125.7, 131.3, 145.6, 148.8, 154.1, 172.4; HRMS calcd for C₁₁H₁₁BrO₄ 285.9841, found 285.9854

3-(3-Bromo-4,5-dimethoxyphenyl)propionic acid (207).

In a 250 mL round bottom flask was dissolved 206 (1.530 g, 5.331 mmol) in 50 mL acetic acid. The flask was flushed with argon and 5% Pd/C (565 mg, 0.267 mmol) was added. Balloon pressure hydrogen was constantly applied. After ~40 h the catalyst was removed and another aliquot of 5% Pd/C (565 mg, 0.267 mmol) was added. When the reaction was complete by ¹H NMR, the catalyst was filtered off. The reaction mixture was concentrated and taken up in ether and washed twice with 10% NaOH. The basic layer was then washed twice with ether and acidified with conc. HCl. This now acidic layer containing the precipitated product was washed with ether. The combined ether layers containing the
product was washed with water and brine and dried with MgSO₄, and concentrated to give 207 as a white solid, 1.22 g (79%). This material was very clean and could be carried on crude or recrystallized from hot hexanes. mp: 114-116 °C; IR (thin film, neat, NaCl) 3005, 2967, 2939, 2833, 1706, 1595, 1567, 1493, 1459, 1429, 1282, 1216, 1142, 1046, 993, 844 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.67 (t, 2H, J = 7.5 Hz), 2.88 (t, 2H, J = 7.8 Hz), 3.82 (s, 3H) 3.84 (s, 3H), 6.70 (d, 1H, J = 2.4 Hz), 6.97 (d, 1H, J = 2.4 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 30.31, 35.65, 56.29, 60.77, 112.13, 117.81, 124.43, 137.59, 145.16, 153.80, 178.89; HRMS calcd for C₁₁H₁₃BrO₄ 287.9997, found 288.0013.

Br Br
H
N
O
O
Ph

207

208

[2-(3-Bromo-4,5-dimethoxyphenyl)ethyl]carbamic acid 2-(1-methyl-1-phenylethyl)cyclohexyl ester (208).

A solution of toluene, ~10 mL, containing 207 (146 mg, 0.505 mmol), triethylamine (0.092 mL, 0.656 mmol) and diphenylphosphoryl azide (0.141 mL, 0.656 mmol) was gently refluxed under argon for 2 h. The reaction mixture was allowed to cool slightly and racemic TCC alcohol (165 mg, 0.758 mmol) was added as a solid. The reaction mixture was then refluxed overnight. The heating bath was removed and the reaction mixture was allowed to cool and was concentrated by rotary evaporation. The dark brown oil was taken up in ethyl acetate and run through a plug of silica and washed with excess ethyl acetate. The ethyl acetate was removed by rotary evaporation and the light brown oil purified by radial PLC (silica gel, hexanes/ethyl acetate 85:15) to give 208 (170 mg, 66%) as a colorless oil. IR (thin
film, neat, NaCl) 3422, 3381, 3359, 3087, 3057, 2935, 2860, 1711, 1598, 1564, 1513, 1492, 1463, 1451, 1414, 1369, 1301, 1271, 1240, 1141, 1048, 1005, 819, 766 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.00-1.33 (m, 12H), 1.60-1.73 (m, 2H), 1.92-2.02 (m, 1H), 2.62 (t, 2H, J = 6.9 Hz), 3.22 (m, 2H, J = 6 Hz), 3.80 (s, 3H), 3.81 (s, 3H), 3.85 (m, 1H), 4.55 (m, 1H), 6.64 (s, 1H), 6.91 (s, 1H), 7.04 (t, 1H, J = 6.9 Hz), 7.16-7.33 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 24.5, 24.7, 26.0, 27.0, 27.9, 33.8, 35.6, 39.7, 41.6, 51.4, 56.0, 60.4, 75.2, 112.2, 117.5, 124.6, 125.3, 127.6, 136.2, 114.9, 152.1, 153.5, 155.6; HRMS calcd for C₂₆H₃₄BrNO₄ 503.1671, found 503.1666.

3,4-Dimethoxy-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)benzaldehyde (210).

To a 100 mL round bottom flask containing N,N,N'-trimethylethylenediamine (0.820 mL, 6.304 mmol) dissolved in 15 mL anhydrous benzene was added n-butyllithium (2.57 M, 2.25 mL, 5.779 mmol) at 0 – 5 ℃. The cooling bath was removed and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was cooled to 0 – 5 ℃ and veratraldehyde (0.873 g, 5.253 mmol) was added via cannula as a solution in minimal benzene (~1.5 mL, quantitated with two 0.5 mL portions of anhydrous benzene). The reaction mixture was allowed to warm and stir at room temperature for 30 min, at which point it was cooled to 0 – 5 ℃ and phenyllithium (1.32 M, 11.94 mL, 15.76 mmol) was added dropwise and stirred for 11 h at room temperature. Freshly distilled THF, 25 mL, was added and the reaction mixture was cooled to –78 ℃. Isopropyl pinacol boronate (5.865 g,
31.52 mmol, 6.43 mL) was added and the reaction mixture was allow to warm slowly to room temperature. Aqueous 10% HCl was added and the reaction mixture was stirred for 30 min and finally extracted twice with ether. The combined organic layers were washed with water, brine, dried over MgSO₄ and concentrated. Crude 210 was purified by radial PLC (silica gel, hexanes/ethyl acetate 80:20) to give impure fractions, 1.22 g (80%), that could be carried on to the next step. Portions could be recrystallized in low yield from n-heptane for characterization: mp 81-82 °C; IR (thin film, neat, NaCl) 2975, 2937, 2822, 1679, 1567, 1485, 1454, 1371, 1338, 1306, 1276, 1236, 1213, 1151, 1137, 1110, 1066, 1042, 958, 874, 850, 810, 782, 740, 672 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.45 (s, 12H), 3.84 (s, 3H), 3.92 (s, 3H), 6.99 (d, 1H, J = 8.4 Hz), 7.54 (d, 1H, J = 8 Hz), 9.79 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 25.1, 56.1, 61.6, 84.6, 94.6, 112.5, 130.7, 133.7, 152.8, 157.6, 191.6; HRMS calcd for C₁₅H₂₁BO₅ 293.1560, found 293.1567.

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[2-(6'-Formyl-5,6,2',3'-tetramethoxybiphenyl-3-yl)ethyl]carbamic acid 2-(1-methyl-1-phenylethyl)cyclohexyl ester (211).
In a 25 mL round bottom flask was dissolved 209 (64 mg, 0.126 mmol) in 5 mL of degassed anhydrous benzene. In ~1 mL of degassed ethanol, boronate 210 (37 mg, 0.126 mmol) was dissolved. Solid Pd(PPh₃)₄ (29 mg, 0.0253 mmol) was added to the benzene solution followed by aqueous Na₂CO₃ (2 M, 0.133 mL, 0.266 mmol) and the boronate solution was then added and completed with ~1 mL ethanol. The yellow reaction mixture was heated at 80 – 85 °C for 48 h. The reaction mixture was filtered through Celite, and a standard ethereal workup was performed to give a red oil. Crude 211 was purified by radial PLC (silica gel, hexanes/ethyl acetate 90:10) to give 49 mg (66%) of pure 211. IR (thin film, neat, NaCl) 3384, 3087, 3057, 2940, 2861, 2758, 1711, 1689, 1587, 1491, 1463, 1426, 1393, 1369, 1305, 1276, 1214, 1144, 1090, 1040, 1009, 946, 905, 851, 815, 769, 736, 703 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.05-1.28 (m, 12H), 1.62-1.71 (m, 2H), 1.90-2.00 (m, 1H), 2.65-2.75 (m, 2H), 3.18-3.35 (m, 2H), 3.57 (s, 3H), 3.64 (s, 3H), 3.78 (m, 1H), 3.89 (s, 3H), 3.96 (s, 3H), 4.55 (dt, 1H, J = 3.2 Hz, J = 10 Hz), 6.58 (s, 1H), 6.78 (s, 1H), 7.04 (d, 1H, J = 8.8 Hz), 7.04 (m, 1H), 7.18-7.26 (m, 4H), 7.81 (d, 1H, J = 8.8 Hz), 9.55 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 24.5, 24.8, 26.1, 27.1, 28.1, 34.0, 36.1, 39.8, 42.1, 51.6, 55.9, 56.1, 60.5, 60.9, 75.2, 111.5, 113.0, 123.5, 124.4, 124.8, 125.5, 127.7, 128.1, 134.4, 136.6, 145.6, 146.4, 152.4, 152.7, 155.7, 157.7, 191.0; HRMS calcd for C₃₅H₄₃NO₇ 589.3040, found 589.3030.
{2-[5,6,2',3'-Tetramethoxy-6'-{(2-methoxyvinyl)biphenyl-3-yl}ethyl]carbamic acid 2-(1-methyl-1-phenylethyl)cyclohexyl ester (212).}

In a 25 mL round bottomed flask was dissolved (methoxymethyl)triphenylphosphonium chloride (24 mg, 0.0712 mmol) in 5 mL of freshly distilled diethyl ether and was cooled below 0 ºC. Phenyllithium (1.8 M, 0.04 mL, 0.0712 mmol) was added resulting in a deep orange to red color. This was stirred for 15 min. In a separate flask was dissolved aldehyde 211 (14 mg, 0.024 mmol) in 5 mL of dry ether. The aldehyde solution was added via syringe to the Wittig reagent and the reaction mixture was allowed to warm to room temperature. The reaction was quenched with saturated aqueous sodium bicarbonate followed by a standard ethereal workup. Purification by radial PLC (silica gel, ethyl acetate/hexanes 10 – 20%) gave 13 mg (88%) of 212. IR (thin film, neat, NaCl) 3421, 3386, 3375, 2934, 2860, 2834, 2250, 1713, 1704, 1649, 1584, 1510, 1486, 1460, 1408, 1250, 1143, 1101, 1040, 912 cm\(^{-1}\); \(^{1}\)H NMR (400 MHz CDCl\(_3\)) \(\delta\) 1.00-1.35 (m, 12H), 1.60-1.74 (m, 2H), 1.91-1.99 (m, 1H), 2.65-2.71 (m, 2H), 3.16-3.37 (m, 2H), 3.43 (s, 1.6H, methyl of vinyl ether: \(E\) isomer), 3.60 (s, 3H), 3.63 (s, 3H), 3.70 (s, 1.4H, methyl of vinyl ether: \(Z\) isomer), 3.74 (m, 1H), 3.88 (s, 3H), 3.89 (s, 3H), 4.57 (dt, 1H, \(J = 4\) Hz, \(J = 10\) Hz), 4.73 (dd, 0.45H, \(J = 1.6\) Hz, \(J = 7.2\) Hz, vinyl proton: \(Z\) isomer), 5.37 (dd, 0.55H, \(J = 4.8\) Hz, \(J = 12.8\) Hz, vinyl proton: \(E\) isomer), 5.91 (d, 0.45H, \(J = 7.2\) Hz, vinyl proton: \(Z\) isomer), 6.48 (s, 1H, A-ring Ar-H), 6.71 (s, 1H, A-ring Ar-H), 6.74 (dd, 0.55H, \(J = 1.6\) Hz, \(J = 12.8\) Hz, vinyl proton: \(E\) isomer), 6.88 (d, 0.55H, \(J =
8.8 Hz, D-ring Ar-H, $E$ isomer), 6.92 (d, 0.45H, $J = 8.8$ Hz, D-ring Ar-H, $Z$ isomer), 7.05 (m, 1H), 7.11 (d, 0.55H, $J = 8.8$ Hz, D-ring Ar-H, $E$ isomer), 7.19-7.29 (m, 4H), 7.87 (d, 0.45H, $J = 8.8$ Hz, D-ring Ar-H, $Z$ isomer); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 24.5, 24.6, 25.0, 26.3, 27.2, 28.2, 34.1, 36.2, 40.0, 42.2, 51.8, 56.0, 56.8, 60.6, 60.8, 75.3, 103.3, 104.1, 111.7, 112.0, 112.2, 119.7, 123.4, 123.5, 124.7, 124.9, 125.6, 127.9, 128.1, 128.8, 131.5, 134.2, 147.0, 148.1, 150.8, 151.0, 152.5, 152.8, 155.8; HRMS calcd for C$_{37}$H$_{47}$NO$_7$ 617.3353, found 617.3392.

[2-(3,4,5,6-Tetramethoxyphenanthren-1-yl)ethyl]carbamic acid 2-(1-methyl-1-phenylethyl)cyclohexyl ester (213).

In 5 mL of anhydrous methylene chloride was dissolved 212 (23 mg, 0.0372 mmol).

Trifluoroacetic acid (0.005 mL, 0.07 mmol) was added at –78 °C. The reaction mixture was allowed to stir at ~ – 20 °C overnight and then at room temperature overnight. No starting material remained by TLC. Standard ethereal workup gave 24 mg of crude product.

Purification by radial PLC (silica gel, ethyl acetate/hexanes 10 – 20%) gave 13 mg (60%) 213, as the sole isolable product. IR (thin film, neat, NaCl) 3419, 29.34, 2858, 1711, 1588, 1508, 1458, 145, 1275, 1251, 1148, 1110, 1070, 1032, 986, 823, 765 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.10-1.38 (m, 12H), 1.60-1.78 (m, 2H), 1.95-2.03 (m, 1H), 3.10-3.20 (m, 2H), 3.26-3.45 (m, 2H), 3.65 (s, 3H), 3.68 (s, 3H), 3.75-3.83 (m, 1H), 3.99 (s, 3H), 4.00 (s,
3H), 4.60 (dt, 1H, J = 4 Hz, J = 9.6 Hz), 7.00 (t, 1H, J = 7.2 Hz), 7.11 (s, 1H), 7.17 (t, 2H, J = 7.6 Hz), 7.22-7.65 (m, 2H), 7.30 (d, 1H, J = 8.4 Hz), 7.41 (d, 1H, J = 9.2 Hz), 7.48 (d, 1H, J = 8.8 Hz), 7.58 (d, 1H, J = 8.8 Hz); 13C NMR (100 MHz, CDCl3) δ 24.4, 25.0, 26.3, 27.2, 28.5, 34.1, 40.0, 42.1, 51.7, 57.2, 61.0, 75.4, 114.2, 115.7, 120.4, 122.2, 123.0, 123.3, 124.8, 125.2, 125.6, 127.9, 152.6; HRMS calcd for C36H43NO6 585.3090, found 585.3113.

![Chemical structure diagram]

{[Benzyl(diethoxyphosphorylmethyl)amino]methyl}phosphonic acid diethyl ester (402).

To a 25 mL round bottomed flask was added benzylamine (1 mL, 981 mg, 9.154 mmol) and diethyl phosphite (2.36 mL, 2.53 g, 18.31 mmol) and was cooled to 0 ºC. Formaldehyde (aqueous 37 wt%, 2.23 mL, 27.46 mmol) was added drop wise resulting in a white mixture about two-thirds of the way through the addition. The cooling bath was removed and the reaction mixture was stirred at room temperature for 30 min followed by heating at reflux for 1 h. The reaction mixture was concentrated in vacuo to a runny oil in nearly quantitative yield. The product 402 was sufficiently pure to carry on crude or could be purified by chromatography. IR (thin film, neat, NaCl) 3468, 3345, 2983, 2930, 2909, 2869, 2856, 1678, 1452, 1392, 1236, 1163, 1027, 960 cm⁻¹; ¹H NMR (400 MHz, CDCl3) δ 1.31 (t, 12H, J = 6.8 Hz), 3.17 (d, 4H, J = 9.2 Hz), 3.97 (s, 2H), 4.11 (pq, 8H, J = 1.6 Hz, J = 6.8 Hz), 7.23-7.40 (m, 5H); ¹³C NMR (100 MHz CDCl3) δ 16.5 (t, J = 3 Hz), 49.6 (dd, J = 7.6 Hz, J = 43.8 Hz), 61.0, 62.0, 127.5, 128.3, 129.3, 138.1; ³¹P NMR (162 MHz, CDCl3) δ 25.8; HRMS calcd for C_{17}H_{31}NO_{6}P_{2} [M+H] 408.1705, found 408.1726.
{{((Diethoxyphosphorylmethyl)amino)methyl}phosphonic acid diethyl ester (404).}

Crude 402 (3.73 g, 9.154 mmol) was dissolved in absolute ethanol and palladium (10% on carbon, ~100 mg, ~0.1 mmol, ~1 mol %) was added. This was shaken on a Paar shaker under 40-psi hydrogen at room temperature for 48 h. The reaction mixture was filtered to give 2.45 g (85%), of 404. The secondary amine was sufficiently pure to carry on to the next step. IR (thin film, neat, NaCl) 3456, 2988, 2934, 1682, 1553, 1479, 1444, 1394, 1241, 1164, 1098, 1047, 1028, 976, 874, 854, 794 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.34 (t, 12H, \(J = 6.8\) Hz), 1.55 (bs, 1H), 3.12 (d, 4H, \(J = 10.8\) Hz), 4.15 (pq, 8H, \(J = 2.4\) Hz, \(J = 6.8\) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 16.6 (t, \(J = 3\) Hz), 45.9 (dd, \(J = 12.9\) Hz, \(J = 153.2\) Hz), 62.2; \(^{31}\)P NMR (162 MHz, CDCl\(_3\)) \(\delta\) 26.0; HRMS calcd for C\(_{10}\)H\(_{25}\)NO\(_6\)P\(_2\) [M+H] 318.1235, found 318.1236.

{{((Diethoxyphosphorylmethyl)-[2-(1-methyl-1-phenylethyl)cyclohexyloxycarbonyl]amino)methyl}phosphonic acid diethyl ester (401).}

In a 50 mL round bottomed flask was dissolved the crude amine 404 (2.45 g, 7.723 mmol) in 20 mL of methylene chloride. Powdered molecular sieves (3.5 g) were added. TCC chloroformate 10 (2.168 g, 7.723 mmol) was added as an oil and quantitated with a small amount of methylene chloride. The reaction mixture was stirred overnight at room
temperature and was filtered through Celite and purified by chromatography (ethyl acetate/hexanes 20 – 50 %) to give 3.61 g (90%) of 401. $^1$H NMR (400 MHz, CDCl$_3$) δ 1.06-1.42 (m, 21H), 1.55-1.75 (m, 3H), 1.78-1.85 (m, 1H), 1.88-1.94 (m, 1H), 2.12 (dt, 1H, $J = 3.6$ Hz, $J = 11.2$ Hz), 2.64 (dd, 1H, $J = 10.8$ Hz, $J = 16.4$ Hz), 3.06 (dd, 1H, $J = 5.2$ Hz, $J = 16.4$ Hz), 3.49 (dd, 1H, $J = 6.8$ Hz, $J = 17.2$ Hz), 4.01 (quintet, 4H, $J = 7.6$ Hz), 4.18 (quintet, 4H, $J = 7.6$ Hz), 4.27 (dd, 1H, $J = 12.8$ Hz, $J = 16$ Hz), 4.72 (dt, 1H, $J = 4.4$ Hz, $J = 10.8$ Hz), 7.14 (m, 1H), 7.25-7.33 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 16.7, 23.8, 24.9, 26.2, 27.3, 29.2, 33.8, 39.8, 40.5 (d, $J = 13.7$ Hz), 42.1 (d, $J = 13.7$ Hz), 51.3, 62.3 (m), 125.1, 125.3, 128.5, 152.8; $^{31}$P NMR (162 MHz, CDCl$_3$) δ 23.8 (q, $J = 8.6$ Hz); HRMS calcd for C$_{26}$H$_{45}$NO$_8$P$_2$ [M+H] 562.2699, found 562.2709.

![405](image) → ![507](image)

1-Bromo-3-(2-nitrovinyl)benzene (507).

To a 100 mL round bottom flask containing 30 mL of MeOH was added 3-bromobenzaldehyde (4.761 g, 25.731 mmol, 3.00 mL) and nitromethane (1.571 g, 25.731 mmol, 1.39 mL) and was cooled to – 5 °C with a water/acetone/CO$_2$ bath. Aqueous sodium hydroxide (2.57 mL, 27.017 mmol, 10.5 M) was added dropwise and the reaction mixture was stirred at or below 0 °C for 10 min, followed by 1 h at room temperature giving a white, then yellow precipitate. Then 30 mL of half and half crushed ice/water was added and the reaction mixture was stirred until all of the solids dissolved, ~ 15 min. The solution was poured into ~40 mL of rapidly stirred 3.24 M HCl. The solid yellow product was filtered and
dried under vacuum to give a quantitative crude yield of 507, sufficiently pure enough to carry on without purification. It could be recrystallized from ethanol: mp: 58-61 °C; IR (thin film, neat, NaCl) 3112, 3051, 1636, 1556, 1515, 1471, 1417, 1340, 1283, 1225, 1194, 1073, 963, 894, 838, 785, 751, 712 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.32 (t, 1H, \(J = 8\) Hz), 7.47 (d, 1H, \(J = 7.6\) Hz), 7.55 (d, 1H, \(J = 14\) Hz), 7.61 (dt, 1H, \(J = 1\) Hz, \(J = 8\) Hz), 7.67 (s, 1H), 7.90 (d, 1H, \(J = 14\) Hz); \(^1^3\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 123.6, 127.9, 131.1, 131.9, 132.3, 135.1, 137.6, 138.3; HRMS calcld for C\(_8\)H\(_6\)BrNO\(_2\) 226.9582, found 226.9574.

![Chemical structure](attachment:image.png)

2-(3-Bromophenyl)ethylamine (508).

A nitrogen flushed 1000 mL 3-neck round bottom flask with large magnetic stir bar and reflux condenser was charged with NaBH\(_4\) (3.147 g, 83.192 mmol) and 150 mL of freshly distilled THF and was cooled to 0 °C. BF\(_3\)·OEt\(_2\) (14.914 g, 105.08 mmol, 13.32 mL) was added slowly via syringe resulting in mild bubbling from the reaction. The reaction mixture was stirred at 0 °C for 10 min then at room temperature for 15 min giving a white slurry. Nitrostyrene 507 (3.994 g, 17.514 mmol) was added as a solution in 15 mL of THF, and quantified with 2 x 15 mL THF. The reaction mixture was heated to reflux and the yellow color of the styrene dissipated after the first 20 min of the 6 h of refluxing. (Note: after about 4 h of refluxing the reaction mixture changed in appearance. It began as a “homogeneous” slurry, evenly suspended. Later more clear patches could be seen. Almost like an overcast day going to a partly sunny day. The solids also sank quickly if stirring was stopped.) In a 1000 mL Erlenmeyer flask was combined 200 mL of water, 200 mL of ice and 150 mL of
3.24 M HCl with a large magnetic stir bar. The reaction mixture was slowly poured into the acid solution with rapid stirring giving vigorous bubbling. This was heated at 65 – 70 °C for 1.5 h. The acid solution was allowed to cool and was extracted with diethyl ether (2 x 200 mL) and was basified with concentrated NaOH then saturated with NaCl. This base layer was then extracted with diethyl ether (2 x 250 mL). The combined ether layers were dried over MgSO₄ and concentrated to 3.018 g crude product. The dark orange oil was vacuum distilled (87 – 89 °C, ~1 mmHg) to give 1.894 g (54% yield) of 508. IR (thin film, neat, NaCl) 3361, 3299, 3058, 2967, 2867, 1567, 1474, 1428, 1384, 1328, 1201, 1167, 1072, 997, 881, 852, 781 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.67 (bs, 2H), 2.73 (t, 2H, J = 6.8 Hz), 2.97 (t, 2H, J = 6.8 Hz), 7.10-7.20 (m, 2H), 7.30-7.36 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 39.6, 43.4, 122.8, 127.7, 129.6, 130.3, 132.1, 142.3; HRMS calcd for C₈H₁₂BrN [M+H] 200.0075, found 200.0064.

![Chemical structure](image.png)

[2-(3-Bromophenyl)ethyl]vinylcarbamic acid 2-(1-methyl-1-phenylethyl)cyclohexyl ester (505).

2-(3-Bromophenyl)ethylamine (508) (610 mg, 3.049 mmol) was dissolved in ~0.7 mL of diethyl ether under an argon atmosphere in a 2 dram vial. Magnesium sulfate (630 mg, 5.18 mmol) was added and cooled to 0 °C. Acetaldehyde (148 mg, 3.354 mmol, 188 µL) was quickly added via syringe. This was allowed to stir at 0 °C for 30 min. The crude imine was gravity filtered through celite and concentrated to a clear oil which was taken up in ~4 mL of
anhydrous benzene. Triethylamine (339 mg, 3.354 mmol, 467 µL) was added and cooled to 0 °C followed by addition of phosgene (1.76 mL, 3.354 mmol, 1.9 M in toluene). The cooling bath was removed after ~7 min and the reaction mixture was stirred at room temperature for 2 h. The mixture was diluted with diethyl ether causing the TEA·HCl to precipitate. The reaction mixture was filtered, concentrated to half its original volume and filtered once more and concentrated to give the crude chloroethyl carbamoyl chloride as a light brown oil. This was bulb-to-bulb distilled (up to 160 °C, ~1 mmHg) giving 555 mg (63% yield) of the N-vinyl carbamoyl chloride as a clear oil. (This material must be used immediately as crystals form that do not dissolve in THF. What the crystals were was unclear.) In a 25 round bottom flask was dissolved (±)-TCC alcohol (462 mg, 2.115 mmol) and triphenylmethane (4 mg, 0.0192 mmol) in ~ 6 mL of fresh THF and was cooled to 0 °C. n-Butyllithium (2.35 M in hexanes) was added until a red color persisted (~ 1.09 mL). The N-vinyl carbamoyl chloride was added via syringe as a solution in 5 mL of THF. The reaction mixture was stirred at 0 °C for 30 min then overnight at room temperature. The reaction was quenched with saturated aq. NH₄Cl followed by the addition of water to dissolve remaining solids. The reaction mixture was extracted with ether (2 x 30 mL). The organic layer was then washed with brine, dried over magnesium sulfate and concentrated to a light yellow oil. The crude product was purified by radial PLC (silica gel, ethyl acetate/hexanes) to give 595 mg (66% yield) of 505. IR (thin film, neat, NaCl) 2933, 2860, 1703, 1629, 1598, 1568, 1495, 1469, 1445, 1425, 1388, 1368, 1353, 1186, 1112, 1074, 1024, 971, 836, 765 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.93-1.35 (m, 11H), 1.62-1.78 (m, 2H), 1.89 (d, 1H, J = 10 Hz), 2.11 (m, 1H), 2.48 (m, 1.5H), 2.76 (m, 1.5H), 3.65 (dm, 1H, J = 10.8 Hz, J = 8 Hz), 3.96 (d, 0.5H, J = 9.2 Hz), 4.15 (d, 0.5H, J = 16 Hz), 4.22 (d, 0.5H, J = 16 Hz), 4.27 (d, 0.5H, J = 9.2 Hz), 4.76 (m, 1H), 5.95
(dd, 0.5H, $J = 9.2$ Hz, $J = 16$ Hz), 6.92-7.36 (m, 9.5H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 23.3, 24.9, 25.0, 26.2, 27.1, 27.4, 28.3, 29.9, 32.6, 32.7, 33.6, 33.9, 39.8, 39.9, 43.1, 44.2, 51.4, 51.5, 76.7, 77.2, 90.7, 91.3, 122.7, 125.1, 125.3, 127.8, 128.3, 128.5, 129.5, 129.6, 129.7, 130.2, 130.3, 132.0, 132.1, 132.3, 132.8, 141.4, 152.0, 152.7; HRMS calcd for C$_{26}$H$_{32}$BrNO$_2$ [M+H] $^{19}$ 470.1695, found 470.1683.

[2-(3-Bromophenyl)ethyl]vinylcarbamic acid 2-(1-methyl-1-phenylethyl)cyclohexyl ester (505).

*Alternative synthesis*

To a 2 dram vial containing carbamate 129 (20 mg, 0.0450 mmol) and a catalytic amount of camphorsulfonic acid was added 500 µL acetal and was heated to 60 °C for 40 min. The reaction mixture was cooled and filtered through a silica plug with excess 10% ethyl acetate/hexanes. The solution was concentrated and heated to 200 – 230 °C for 1 h. The crude reaction mixture was purified by radial PLC (silica gel, 10% ethyl acetate/hexanes) to give 13 mg (62%) of 505 colorless oil.
[2-(6'-Formyl-2',3'-dimethoxybiphenyl-3-yl)ethyl]vinylcarbamic acid 2-(1-methyl-1-phenylethyl)cyclohexyl ester (514).

In a 4 dram vial N-vinyl carbamate 505 (68 mg, 0.1442 mmol) was dissolved in 3 mL of dimethoxylethane and was vigorously degassed with argon. Pinacol boronate 210 (42 mg, 0.1442 mmol) was dissolved in ~1 mL of ethanol and was degassed with argon. Tetrakis(triphenylphosphine)palladium was added to the carbamate solution quickly resulting in a dark brown color. Aqueous sodium carbonate (0.151 mL, 2.0 M) was then added followed by the boronate solution. An immediate TLC showed product formation as well as reduction of the boronate to veratraldehyde. The reaction mixture was stirred overnight at 70 °C. The reaction mixture was allowed to cool to room temperature and water was added. It was then extracted with ether (2 x 15 mL). The organic layer was then dried over magnesium sulfate and concentrated. The crude product was purified by radial PLC (silica gel, ethyl acetate/hexanes) to give 36 mg (45% yield) of 514 as a colorless oil. IR (thin film, neat, NaCl) 3535, 3386, 3355, 2937, 2860, 1700, 1630, 1585, 1483, 1424, 1390, 1344, 1304, 1258, 1189, 1116, 1036, 973, 953, 940, 815, 765, 735 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.00-1.38 (m, 11H), 1.62-1.77 (m, 2H), 1.78-1.93 (m, 1H), 2.04-2.16 (m, 1H), 2.60 (s, 1.5H), 2.84
(t, 1.5H, J = 8 Hz), 3.55 (m, 3H), 3.67 (m, 1H, J = 8 Hz), 3.92 (d, 0.5H, J = 9.2 Hz), 3.99 (m, 3H), 4.10-4.27 (m, 1.5H), 4.72-4.84 (m, 1H), 5.96 (dd, 0.5H, J = 9.6 Hz, J = 15.2 Hz), 6.95 (m, 10.5H), 7.80-7.90 (m, 1H), 9.60 (m, 1H); 13C NMR (100 MHz, CDCl3) \( \delta \) 23.9, 24.9, 25.1, 26.1, 26.2, 27.2, 27.4, 28.3, 29.3, 33.0, 33.3, 33.9, 39.9, 43.5, 44.7, 51.4, 51.7, 56.3, 61.0, 76.7, 77.1, 90.7, 91.3, 111.5, 124.8, 125.1, 125.3, 128.2, 128.3, 128.6, 128.7, 128.8, 130.8, 131.1, 131.3, 132.4, 132.9, 133.5, 139.0, 140.6, 146.3, 152.0, 152.5, 157.9, 191.3, 191.5; HRMS calcd for C35H41NO5 [M+H] 556.3063, found 556.3079.

[2-(2',3'-Dimethoxy-6'-vinylbiphenyl-3-yl)ethyl]vinylcarbamic acid 2-(1-methyl-1-phenylethyl)cyclohexyl ester (504).

A slurry of methyltriphenylphosphonium bromide (131 mg, 0.3671 mmol) in THF was treated with \( n \)-butyllithium (0.444 mL, 0.3617 mmol, 2.4 M in hexanes) at 0 °C giving a yellow color. The aldehyde 514 was dissolved THF at 0 °C, treated with the Wittig reagent, and was allowed to warm to room temperature. A standard ethereal workup followed by radial PLC (silica gel, ethyl acetate/hexanes) gave 22 mg (61% yield) of 504. IR (thin film, neat, NaCl) 3441, 2931, 2858, 16971629, 1595, 1480, 1448, 1417, 1389, 1293, 1256, 1189, 1121, 1110, 1030, 993, 904, 811, 766 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl3) \( \delta \) 1.00-1.37 (m, 11), 1.63-1.96 (m, 3), 2.10 (dt, 1H, J = 3.3 Hz, J = 11.4 Hz), 2.51-2.75 (m, 1.5H), 2.76-2.96 (m, 1.5H), 3.53 (m, 3H), 3.66 (t, 1H, J = 8.1 Hz), 3.92 (m, 3H), 4.11-4.29 (m, 1.5H), 4.72-4.92 (m, 1H), 5.02 (t, 1H, J = 11.4 Hz), 5.53 (dd, 1H, J = 11.1 Hz, J = 17.4 Hz), 5.98 (dd, 0.5H, J
= 9 Hz, J = 15.9 Hz), 6.36 (m, 1H), 6.90-7.45 (m, 12H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 24.3, 24.9, 25.2, 26.1, 26.2, 27.2, 27.4, 28.2, 28.9, 29.9, 33.1, 33.4, 34.0, 40.0, 43.7, 44.8, 51.5, 51.7, 56.1, 60.8, 90.7, 91.3, 111.8, 113.0, 121.1, 125.2, 125.3, 12.7, 127.8, 128.3, 128.6, 131.0, 132.4, 133.0, 135.4, 136.6, 138.6, 146.6; HRMS calcd for C$_{36}$H$_{43}$NO$_4$ [M+H] 554.3270, found 554.3293.

$^{13}$N

$^{13}$N

Br

Br

Br

Br

NH

2

508

604

1,3,5-Tris-[2-(3-bromophenyl)ethyl]-[1,3,5]triazinane (604).

2-(3-Bromo-phenyl)-ethylamine 508 (906 mg, 4.528 mmol) was dissolved in ~10 mL of methylene chloride. Solid paraformaldehyde (407 mg, 13.54 mmol) was added and stirred at room temperature for 4 h. The reaction mixture was filtered and concentrated. Crude 604 could be carried on to the next reaction or purified by radial PLC (silica gel, 50% ethyl acetate/hexanes) to give 873 mg (91% yield) of 604. IR (thin film, neat, NaCl) 3057, 3011, 2932, 2853, 2813, 1677, 1595, 1567, 1474, 1425, 1362, 1295, 1217, 1202, 1150, 1120, 1095, 1071, 1038, 998, 905, 891, 849, 778 cm$^{-1}$; $^1$H NMR (400 MHz CDCl$_3$) δ 2.70 (m, 12H), 3.41 (bs, 6H), 7.10-7.17 (m, 6H), 7.31-7.38 (m, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 34.4, 54.2, 74.5, 122.6, 127.7, 129.4, 130.2, 132.0, 142.9; HRMS calcd for C$_{27}$H$_{30}$Br$_3$N$_3$ 632.9990, found 632.9967.
[2-(3-Bromophenyl)ethyl](diphenylphosphinoylmethyl)amine (603).

Triazine 604 (525 mg, 0.8255 mmol) was dissolved in 20 mL of freshly distilled toluene followed by addition of diphenylphosphine oxide (500 mg, 2.476 mmol). The reaction mixture was gently refluxed for 4 h then concentrated to a yellow oil. The crude product 603, in near quantitative yield, was carried on without further purifcation. It could also be recrystallized from ether. mp: 75-77 °C; IR (thin film, neat, NaCl) 3427, 3300, 3055, 2927, 2851, 2805, 1592, 1564, 1472, 1436, 1366, 1183, 1120, 1105, 1071, 1028, 997, 852, 780, 746, 717 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.36 (bs, 1H), 2.69 (t, 2H, J = 7.2 Hz), 2.92 (t, 2H, J = 7.2 Hz), 3.46 (d, 2H, J_H-P = 8 Hz), 7.02 (d, 1H, J = 8 Hz), 7.09 (t, 1H, J = 8 Hz), 7.27 (t, 1H, J = 1.6 Hz), 7.30 (dt, 1H, J = 7.6 Hz, J = 1.6 Hz), 7.40-7.48 (m, 4H), 7.49-7.55 (m, 2H), 7.71-7.78 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 35.9, 49.6 (d, J = 80 Hz), 52.7 (d, J = 13Hz), 122.6, 127.6, 128.8 (d, J = 11 Hz), 129.5, 130.2, 131.3 (d, J = 9 Hz), 131.5, 131.9, 132.2 (d, J = 2 Hz), 142.4; ³¹P NMR (162 MHz, CDCl₃) δ 30.1.
[2-(3-Bromophenyl)ethyl](diphenylphosphinoylmethyl)carbamic acid 2-(1-methyl-1-phenylethyl)cyclohexyl ester (602).

Amine 603 (1.025 g, 2.476 mmol) was dissolved in ~10 mL of methylene chloride followed by addition of triethylamine (250 mg, 2.476 mmol, 345 µL) and (+)-TCC chloroformate 10 (693 mg, 2.476 mmol). The reaction mixture was stirred for 4 h at room temperature and was slowly concentrated to avoid bumping due to the TEA·HCl. The crude reaction mixture was taken up in excess ether and the TEA·HCl was filtered off. The crude product was purified by radial PLC (silica gel, 20–50 % ethyl acetate/hexanes) to give 1.303 g (80% yield) of 602. IR (thin film, neat, NaCl) 3058, 2964, 2933, 2860, 1692, 1595, 1567, 1472, 1424, 1371, 1260, 1193, 1260, 1193, 1118, 1109, 1073, 1029, 975, 837, 764, 717 cm⁻¹; ¹H NMR (400 MHz, C₆D₆, 22 °C) δ 0.70-1.10 (m, 8.6H), 1.22 (s, 0.7H), 1.39 (t, 2H, J = 13 Hz), 1.49 (s, 0.7H), 1.50-1.79 (m, 2H), 1.90 (td, 1H, J = 3 Hz, J = 10.8 Hz), 2.38-2.51 (m, 2H), 3.54-3.95 (m, 1.2H), 4.53 (dd, 0.8H, J = 3.6 Hz, J = 15.6 Hz), 4.76 (td, 1H, J = 10.4 Hz, J =3 Hz, J =4 Hz), 6.72 (t, 1.3H, J = 8 Hz), 6.85-7.02 (m, 6.7H), 7.03-7.17 (m, 6H), 7.32 (m, 0.7H), 7.44 (s, 0.2H), 7.63-7.77 (m, 0.9H), 7.84-7.93 (m, 1.5H), 8.07-8.15 (m, 1.5H); ¹H NMR (400 MHz CDCl₃, 50 °C) δ 0.91-1.27 (m, 10H), 1.45-1.94 (m, 4H), 2.00 (m, 1H), 2.40-2.64 (m, 2H), 2.70-2.87 (m, 1H), 3.09-3.21 (m, 1H), 3.45-3.55 (m, 0.33H), 3.65-3.75 (m, 0.33H), 3.83 (dd, 0.67H, J = 6.4 Hz, J = 16.0 Hz), 4.48-4.65 (m, 1.67H), 6.83-7.99 (series of multiplets, 19H); ¹³C NMR (100 MHz, CDCl₃, 50 °C) δ 22.2, 24.4, 24.8, 26.2, 27.2, 28.7, 30.8, 33.2, 34.4, 33.6, 33.8,
39.6, 39.8, 45.7, 46.6, 47.4, 47.9, 49.4, 51.2, 51.4, 77.0, 122.6, 125.1, 127.8, 128.3, 128.7, 128.8, 129.5, 130.1, 130.5, 131.1, 131.5, 131.6, 131.8, 132.1, 132.2, 141.5, 152.3, 153.5, 155.4; $^{31}$P NMR (162 MHz, CDCl$_3$) δ 28.9 (s, 0.3P), 31.5 (s, 0.7P); HRMS calcd for C$_{37}$H$_{41}$BrNO$_3$P 658.2086, found 658.2112.

[2-(3-Bromophenyl)ethyl]-[1-(diphenylphosphinoyl)-2-hydroxy-2-(2-iodo-3,4-dimethoxyphenyl)ethyl]carbamic acid 2-(1-methyl-1-phenylethyl)cyclohexyl ester (702).

Phosphine oxide 602 (183 mg, 0.278 mmol) in 5 mL of THF in a 25 mL round bottom flask at –78 °C was treated with LDA prepared from $n$-butyllithium (1.34 mL, 0.334 mmol, 0.248 M in hexanes) and diisopropylamine (0.779 mL, 0.389 mmol, 0.50 M in hexanes) resulting in a characteristic yellow phosphoryl anion. Deprotonation continued for 30 min at which point benzaldehyde 122 (81 mg, 0.278 mmol) was added as a solid and dissolved over ~2 min. The reaction mixture was allowed to come to room temperature over about 1 h and then stirred for 30 min. The reaction was quenched with saturated aqueous NaHCO$_3$, followed by a
standard ethereal workup, and radial PLC (silica gel, ethyl acetate/hexanes) to give two diastereomeric products \textit{syn-702} and \textit{anti-702} each in 42% yield.

\textbf{Syn:} $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ Characteristic signals: PCH Rotomer 1 (70%) 5.35 (ddd, 0.7H, $J^4 = 2.9$ Hz, $J^3 = 10.3$ Hz, $J^{2(H-P)} = 20.1$ Hz); Rotomer 2 (30%) 5.45 (ddd, 0.7H, $J^4 = 2.9$ Hz, $J^3 = 10.3$ Hz, $J^{2(H-P)} = 20.1$ Hz); HRMS calcd for C$_{46}$H$_{50}$BrINO$_6$P 950.1682, found 950.1664.

\textbf{Anti:} $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ Characteristic peaks 5.27 (0.3H), 5.36 (0.7H), 5.41 (0.7H), 5.49 (0.3H); HRMS calcd for C$_{46}$H$_{50}$BrINO$_6$P 950.1682, found 950.1661.

\begin{figure}[h]
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\includegraphics[width=0.5\textwidth]{syn-702.png}
\caption{\textit{syn-702}}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{E-701.png}
\caption{\textit{E-701}}
\end{figure}

[2-(3-Bromophenyl)ethyl]-[2-(2-iodo-3,4-dimethoxyphenyl)vinyl]carbamic acid 2-(1-methyl-1-phenylethyl)cyclohexyl ester (\textit{E-701}).

In a 2 dram vial containing \textit{syn 702} (18 mg, 0.0189 mmol) dissolved in ~1.5 mL of dry dimethylformamide was added excess dry potassium hydride (~1 mg,) and was stirred at room temperature. After ~10 min the starting material was consumed by TLC. Diethyl ether was added followed by slow addition of saturated aqueous NaHCO$_3$. After a standard ethereal workup, 12 mg (86% yield) of clean crude \textit{E-701} was obtained. IR (thin film, neat, NaCl) 3087, 3059, 2963, 2936, 2860, 2253, 1703, 1642, 1587, 1569, 1479, 1446, 1405, 1370, 1325, 1293, 1260, 1241, 1180, 1141, 1113, 1088, 1073, 1031, 972, 951, 947, 910, 874, 853, 821, 779, 764, 732 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.90-1.37 (m, 11H), 1.64-1.78 (m,
2H), 1.80-1.96 (m, 1H), 2.09-2.20 (m, 1H), 2.56-2.68 (m, 1.5H), 2.87-2.98 (m, 1.5H), 3.65-
3.79 (m, 0.5), 3.80-3.94 (m, 6.5H), 4.75-4.88 (m, 1H), 5.89 (d, 0.5H, J = 14 Hz), 5.98 (d,
0.5H, J = 14.8 Hz), 6.17 (d, 0.5H, J = 14.8 Hz), 6.76 (t, 0.5H, J = 7.2 Hz), 6.86-6.91 (m,
1.5H), 7.02-7.25 (m, 5.5H), 7.27-7.39 (m, 3.5), 7.53 (s, 0.5H); $^{13}$C NMR (100 MHz, CDCl$_3$
$\delta$ 23.1, 23.9, 24.8, 25.0, 26.1, 27.1, 27.2, 29.1, 29.9, 32.8, 33.5, 34.0, 39.7, 44.3, 45.5, 51.5,
51.7, 56.3, 56.4, 60.4, 60.5, 77.0, 112.5, 112.7, 113.0, 113.3, 121.1, 121.3, 125.0, 125.2,
125.3, 125.4, 127.8, 128.0, 128.3, 128.4, 129.7, 129.8, 130.2, 130.3, 132.2, 132.3, 141.2,
152.0, 152.6; HRMS calcd for C$_{34}$H$_{39}$BrNO$_4$ 731.1107, found 731.1127.

![Chemical Structure](image)

[2-(3-Bromophenyl)ethyl]-[2-(2-iodo-3,4-dimethoxyphenyl)vinyl]carbamic acid 2-(1-
methyl-1-phenylethyl)cyclohexyl ester (Z-701).

In a 2 dram vial containing syn-702 (21 mg, 0.0221 mmol) dissolved in ~1.5 mL of
dimethylformamide was added excess dry potassium hydride (~1 mg,) and was stirred at
room temperature. After ~45 min the starting material was consumed by TLC. Ether was
added followed by slow addition of saturated aqueous NaHCO$_3$. After a standard ethereal
workup 15 mg (94% yield) of clean crude Z-701 was obtained. IR (thin film, neat, NaCl)
3086, 3057, 2964, 2937, 2860, 2251, 1944, 1702, 1647, 1570, 1479, 1447, 1412, 1390, 1340,
1287, 1267, 1205, 1151, 1111, 1086, 1074, 1032, 969, 911, 871, 852, 799, 766, 734 cm$^{-1}$; $^1$H
NMR (400 MHz, CDCl$_3$) $\delta$ 1.10-1.38 (m, 10), 1.61-1.95 (m, 4H), 2.12 (t, 1H, J = 11.2 Hz),
2.23-2.41 (m, 1H), 2.56 (t, 1H, \( J = 8 \) Hz), 3.19-3.28 (m, 1H), 3.41-3.52 (m, 1H), 3.581 (m, 6H), 4.78 (m, 1H), 5.41 (dd, 1.2H, \( J = 9.2 \) Hz, \( J = 24 \) Hz), 5.70 (d, 0.4H, \( J = 10.0 \) Hz), 6.58 (d, 0.4H, \( J = 10.0 \) Hz), 6.77-7.35 (m, 11H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 24.2, 24.9, 25.5, 26.1, 27.2, 27.4, 28.0, 28.9, 33.4, 33.8, 33.9, 40.0, 45.9, 47.0, 51.1, 51.4, 56.2, 56.3, 60.5, 77.1, 112.0, 112.2, 117.9, 118.5, 112.4, 125.1, 125.3, 125.8, 126.1, 126.4, 127.1, 127.7, 128.3, 129.4, 130.0, 131.8, 132.0, 141.3, 149.0, 151.5, 152.1, 154.2; HRMS calcd for C\(_{34}\)H\(_{39}\)BrINO\(_4\) 731.1107, found 731.1108.

(Diphenylphosphinoylmethyl)-[2-(6'-formyl-2',3'-dimethoxybiphenyl-3-yl)ethyl]carbamic acid 2-(1-methyl-1-phenylethyl)cyclohexyl ester (601).

To aryl bromide 602 (46 mg, 0.070 mmol) in a 6 dram vial was added pinacol boronate 210 (22.5 mg, 0.077mmol), tetrakis(triphenylphosphine)palladium and was flushed with argon. Approximately 3.5 mL of dimethoxyethane was added followed by aqueous Na\(_2\)CO\(_3\) (0.30 mL, 0.595 mmol, 2 M). The reaction mixture was gently refluxed for 2 h. Following a standard ethereal workup and radial PLC (silica gel, ethyl acetate/hexanes) 44 mg (85% yield) of 601 was isolated. IR (thin film, neat, NaCl) 2933, 2857, 1684, 1584, 1482, 1464, 1439, 1422, 1393, 1302, 1258, 1192, 1117, 0033, 913, 764, 732 cm\(^{-1}\); \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 0.89-1.31 (m, 11H), 1.35-1.78 (m, 3H), 1.89-2.10 (m, 1H), 2.55 (s, 1H), 2.62-2.74 (m, 0.7H), 2.81-2.91 (m, 1H), 3.08 (d, 0.3H, \( J = 16 \) Hz), 3.17-3.27 (m, 0.7H), 3.40-3.50 (m, 0.6H), 3.51 (s, 3H), 3.69 (bs, 0.3H), 3.76 (dd, 0.7H, \( J = 6.4 \) Hz, \( J = 16.0 \) Hz), 3.97 (s, 3H),
4.52-4.65 (m, 1.7H), 6.85-7.20 (m, 8H), 7.27-7.62 (m, 9H), 7.75-7.99 (m, 4H), 9.57 (s, 1H);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 21.9, 24.9, 26.1, 26.2, 27.0, 27.3, 28.2, 29.9, 31.0, 33.2, 33.6, 33.9, 34.0, 39.6, 39.7, 46.3, 46.6, 47.4, 48.2, 50.1, 51.2, 51.4, 56.3, 61.0, 77.1, 111.5, 124.7, 125.1, 125.2, 128.2, 128.5, 128.7, 128.9, 131.0, 131.2, 131.6, 131.7, 131.9, 132.3, 132.4, 138.8, 140.7, 146.4, 152.3, 157.9, 191.3; $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ Rotomer 1 60% 31.4, Rotomer 2 40% 28.6; HRMS calcd for C$_{46}$H$_{50}$NO$_6$P [M+H] 744.3454, found 744.3458.

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\end{array}$

1,3,5-Tris-[2-(3-trimethylstannanylphenyl)ethyl]-[1,3,5]triazinane (804).

Triazine 604 (67 mg, 0.1053 mmol) was dissolved in 5 mL of freshly distilled THF and cooled to $-78^\circ$C in a 6-dram vial. $n$-Butyllithium (0.136 mL, 0.3266 mmol, 2.4 M in hexanes) was added giving a deep orange color. After stirring the trianion for 5 min trimethylstannanyl chloride (65 mg, 0.3266 mmol) was added as a solid and dissolved over about 5 min at which time the orange color had dissipated. The addition of water and a standard ethereal workup gave 78 mg (83% yield) clean, crude 804. This crude product was carried on to the next step without purification. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.30 (s, 27H), 2.77 (m, 12), 3.50 (bs, 6), 7.15-7.42 (m, 12); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ –9.3, 34.9, 54.9, 74.8, 128.3, 128.9, 133.8, 136.4, 140.0, 142.5; HRMS calcd for C$_{36}$H$_{57}$N$_3$Sn$_3$ 891.1618, found 891.1604.
(Diphenylphosphinoymethyl)-[2-(3-trimethylstannanylphenyl)ethyl]amine (805).

Crude stannyl triazine 804 (63 mg, 0.0709 mmol) was dissolved in 5 mL of freshly distilled toluene and diphenylphosphine oxide (43 mg, 0.2128 mmol) was added. The reaction mixture was gently refluxed for 1.5 h. The reaction mixture was concentrated to a bright yellow oil and purified by radial PLC (silica gel, 50% ethyl acetate/hexanes) to give 77 mg (73% yield) of 805. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.26 (s, 9H), 2.74 (t, 2H, $J = 7.6$ Hz), 2.95 (t, 2H, $J = 7.6$ Hz), 3.50 (d, 2H, $J = 8$ Hz), 7.08 (m, 1H), 7.20-7.26 (m, 2H), 7.32 (m, 1H), 7.41-7.48 (m, 4H), 7.52 (m, 2H), 7.73-7.80 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$–9.3, 36.4, 49.2, 50.0, 53.2, 53.3, 128.3, 128.8, 128.9, 131.4, 131.5, 131.9, 132.2, 133.9, 136.4, 139.4, 142.6; $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ 30.1.
(Diphenylphosphinoylmethyl)-[2-(3-trimethylstannanylphenyl)ethyl]carbamic acid 2-(1-methyl-1-phenylethyl)cyclohexyl ester (803).

Amine 805 (77 mg, 0.1546 mmol) was dissolved in ~3 mL of methylene chloride followed by addition of triethylamine (17 mg, 0.170 mmol, 24 µL) and the chloroformate 10 (43 mg, 0.1546 mmol). The reaction mixture was stirred for 4 h at room temperature and was slowly concentrated to avoid bumping due to the TEA·HCl. The crude reaction mixture was taken up in excess ether and the TEA·HCl was filtered away. The product was purified by radial PLC (silica gel, ethyl acetate/hexanes 20–50 %) to give 87 mg (76% yield) of 803. IR (thin film, neat, NaCl) 3056, 2962, 2926, 2858, 1687, 1590, 1468, 1438, 1422, 1369, 1286, 1256, 1239, 1191, 1117, 1101, 1029, 975, 834, 764, 764, 715 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.30 (s, 9H), 0.9-1.45 (m, 11H), 1.51-1.75 (m, 3H), 1.90-2.11 (m, 1H), 2.49-2.69 (m, 2H), 2.77-2.89 (m, 1H), 3.26 (m, 0.7H), 3.45 (m, 0.3H), 3.65-3.80 (m, 1H), 4.55 (td, 1H, J = 11.2 Hz, J =4.0 Hz), 4.59-4.67 (m, 1H), 6.88-7.62 (m, 16H), 7.79 (m, 1.5H), 7.98 (m, 1.5H); ¹³C NMR (100 MHz, CDCl₃) δ −9.2, 21.8, 24.9, 25.3, 26.2, 26.3, 27.1, 27.3, 27.9, 31.1, 33.2, 33.7, 34.2, 39.5, 39.2, 45.6, 46.4, 46.6, 47.3, 48.3, 49.8, 51.2, 51.4, 76.4, 76.9, 125.0, 125.2, 128.3, 128.7, 128.8, 128.9, 129.2, 129.3, 131.0, 131.1, 131.2, 131.6, 131.7, 131.8, 131.9, 132.1, 132.2, 132.3, 133.9, 136.6, 138.5, 142.3, 152.1, 153.7, 155.5; ³¹P NMR (162 MHz,
CDCl₃ δ 28.8 (0.66P), 31.5 (0.33P); HRMS calcd for C₄₀H₅₀NO₃PSn 744.2629, found 744.2640.

[2-(2-Iodo-3,4-dimethoxyphenyl)vinyl]-[2-(3-trimethylstannanylphenyl)ethyl]carbamic acid 2-(1-methyl-1-phenylethyl)cyclohexyl ester (802).

Phosphine oxide 803 (88 mg, 0.1186 mmol) in ~5 mL of freshly distilled THF at –78 °C was treated with LDA prepared from n-butyllithium (0.103 mL, 0.2372 mmol, 2.3 M in hexanes) and diisopropylamine (24 mg, 0.2372 mmol, 33 µL) resulting in a characteristic yellow phosphoryl anion. Deprotonation continued for 30 min at which point benzaldehyde 122 (81 mg, 0.278 mmol) was added as a solid. The reaction mixture was allowed to come to room temperature over about 1.5 h and then stirred for 30 min. A standard ethereal workup and radial PLC (silica gel, ethyl acetate/hexanes) gave 45 mg (46% yield) of E-802 and 66 mg (54% yield) horner adduct anti-801. IR (thin film, neat, NaCl) 2933, 2859, 1702, 1641, 1585, 1479, 1446, 1403, 1324, 1292, 1240, 1180, 1115, 1095, 1030, 943, 764 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.30 (s, 9H), 1.00-1.41 (m, 11H), 1.62-1.98 (m, 3H), 2.00-2.22 (m, 1H), 2.64-3.14 (m, 3H), 3.66-3.82 (m, 1H), 3.89 (m, 6H), 4.86 (m, 1H), 5.86 (d, 0.5H, J = 14 Hz), 6.07 (d, 0.5H, J = 14.4 Hz), 6.18 (d, 0.5H, J = 14 Hz), 6.77 (t, 0.5H, J = 7.6 Hz), 6.90 (m, 1.5H), 7.03-7.15 (m, 2H), 7.16-7.53 (m, 7.5H); ¹³C NMR (100 MHz, CDCl₃) δ –9.194, 23.9, 24.5, 24.8, 24.9, 26.2, 27.3, 28.8, 29.2, 33.2, 33.5, 33.7, 39.8, 39.9, 45.0, 46.1, 51.8, 56.4,
60.5, 77.2, 112.5, 112.8, 113.1, 113.4, 121.1, 121.2, 125.0, 125.3, 125.4, 125.6, 128.0, 128.1, 128.3, 128.5, 129.1, 129.2, 134.1, 134.5, 136.6, 136.8, 138.5, 142.7, 142.8, 149.0, 150.9, 152.1, 152.6, 153.3; HRMS calcd for C$_{37}$H$_{48}$INO$_4$Sn 817.1650, found 817.1646.
Appendix 1 HOMOs of sample biaryl ions
Appendix 2 $^1$H, $^{13}$C, and $^{31}$P NMR spectra
Br-CO₂H

128
E-701
801
CDCl$_3$ + D$_2$O
186
References

3 http://www.pharmacy.umaryland.edu/courses/PHAR531/lectures/chiral_drugs.html
5 Woodward, R. B. Pure & Appl. Chem. 1968, 17, 519 (see page 520-521).
13 In its 2000-2001 chemical catalog, Aldrich chemical company sells one mole of optically pure (+)- or (-)-TCC, (-)-8-phenylmenthol, and (+)-8-phenylmenthol as the chloroacetate for $18.90, $30.60 and $13.60 respectively.
17 Pictet, A., Spengler, T. Ber 1911, 44, 2030.


http://www.uprima.net 12/02/02


Li, W., Burgess, K. *Tetrahedron Lett.* 1999, 40, 6527. Dr. Burgess kindly provided experimental procedures and spectra for this chemical transformation.


56 Doebner, O. *Ber.* **1900**, *33*, 2140.


71 The intermolecular Horner work was done on a similar compound to 602 only without a halogen for the Horner piece and veratraldehyde as the electrophile.


79 $^1$H- and $^{13}$C-NMR spectra of the isolated product matched what would be expected. However HRMS returned a mass 1 AMU less than that required.

