INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps. Each original is also photographed in one exposure and is included in reduced form at the back of the book.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.
Studies directed toward the synthesis of Strychnos alkaloids:
Stereoselective synthesis of dehydrotubifoline

Michoud, Christophe, Ph.D.
The Ohio State University, 1993
STUDIES DIRECTED TOWARD THE SYNTHESIS OF STRYCHNOS ALKALOIDS:
STEREOSELECTIVE SYNTHESIS OF DEHYDROTUBIFOLINE.

DISSERTATION

Presented in Partial Fulfillment of the Requirements for
the Degree Doctor of Philosophy in the Graduate
School of the Ohio State University

By

Christophe Michoud

The Ohio State University
1993

Dissertation Committee:
Dr. Viresh H. Rawal
Dr. David J. Hart
Dr. Leo A. Paquette

Approved by
Adviser
Department of Chemistry
To My Parents
ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to Dr. Viresh Rawal for his support and guidance during the course of this work. His communicative enthusiasm for chemistry, and his encouragement have been of great help. I wish also to thank Dr. Jean Huet from ESCIL, who helped to organize my coming to the States.

To the members of the Rawal group, I express my gratitude. Stimulating discussions have often contributed to the advancement of our research projects.

I would like to acknowledge O. Cottrell and C. Engelman for recording $^1$H and $^{13}$C NMR spectra, and providing useful information about NMR experiments.

Finally, a lot of thanks should go to my friends in Columbus, who contributed to making my stay in the States more enjoyable.
VITA

April 29, 1965 ................................................................. Born, Voirol, France

1984 ........................................................................................................ Baccalauréat C, Lycee Edouart Herriot, Voirol, France

1984-1986 ............................................................................................... Math Sup.- Math Spe., Lycee Champollion, Grenoble, France

1986-1988 ............................................................................................... ESCIL, Lyon, France

1988-1990 ............................................................................................... Teaching Assistant, The Ohio State University, Columbus

1991-1992 ............................................................................................... Rohm and Haas Industrial Fellow, The Ohio State University

1992-1993 ............................................................................................... Research Associate, The Ohio State University, Columbus

PUBLICATIONS


FIELD OF STUDY

Major Field: Chemistry
Studies in Organic Chemistry
**TABLE OF CONTENTS**

DEDICATION...................................................................................................................................................ii

ACKNOWLEDGEMENT..................................................................................................................................iii

VITA.............................................................................................................................................................iv

LIST OF TABLES.......................................................................................................................................viii

LIST OF FIGURES.....................................................................................................................................ix

LIST OF SCHEMES...................................................................................................................................xii

<table>
<thead>
<tr>
<th>CHAPTER</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. The Heck Reaction: Recent Application in Synthesis</td>
<td></td>
</tr>
<tr>
<td>1- Introduction.................................................................01</td>
<td></td>
</tr>
<tr>
<td>2- Intramolecular Coupling Reactions.............................03</td>
<td></td>
</tr>
<tr>
<td>2.1- Unactivated Olefins.................................................04</td>
<td></td>
</tr>
<tr>
<td>2.2- Activated Olefins.......................................................07</td>
<td></td>
</tr>
<tr>
<td>3- Carbocyclizations........................................................11</td>
<td></td>
</tr>
<tr>
<td>3.1- 5-Membered Ring......................................................11</td>
<td></td>
</tr>
<tr>
<td>3.2- 6-Membered Ring......................................................15</td>
<td></td>
</tr>
<tr>
<td>3.3- Polycyclization.........................................................19</td>
<td></td>
</tr>
<tr>
<td>4- Heterocyclizations........................................................20</td>
<td></td>
</tr>
<tr>
<td>4.1- Oxygen Heterocycles................................................21</td>
<td></td>
</tr>
<tr>
<td>4.2- Nitrogen Heterocycles..............................................23</td>
<td></td>
</tr>
<tr>
<td>5- Conclusion.........................................................................28</td>
<td></td>
</tr>
</tbody>
</table>
II. Background and Synthetic Studies
   Background.................................................................29
   Synthetic Studies.........................................................31

III. Retrosynthetic Analysis and Model Studies
   Synthetic Strategy.........................................................48
   Model Studies..............................................................51

IV. Total Synthesis of Dehydrotubifoline.................................68

EXPERIMENTAL.................................................................................................................................94
LIST OF REFERENCES........................................................................................................................132
APPENDICES
   $^1$NMR and $^{13}$C NMR Spectra of Selected Compounds.................................142
# LIST OF TABLES

<table>
<thead>
<tr>
<th>TABLE</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. N-Alkylation of 261 with 2,3-Dibromopropene</td>
<td>64</td>
</tr>
<tr>
<td>2. Alkylation of Ortho-Nitrophenyl Acetonitrile</td>
<td>72</td>
</tr>
<tr>
<td>3. Preparation of 307, Reaction Conditions</td>
<td>80</td>
</tr>
<tr>
<td>4. Hydrolysis of Bis-carbamate 318</td>
<td>86</td>
</tr>
<tr>
<td>5. $^{13}$C NMR of Dehydrorubifoline</td>
<td>92</td>
</tr>
</tbody>
</table>
LIST OF FIGURES

FIGURE PAGE

1. Examples of Strychnos Alkaloids ................................................................. 29
2. Model Compounds for the Heck Cyclization ............................................. 53
3. 6-Exo versus 7-Endo Cyclization ................................................................. 56
4. NOE Experiments on Bicycles 240 and 241 .............................................. 58
5. Aspidosperma and Strychnos Skeletons .................................................... 83
6. Spectroscopic Data of Tetracycle 318......................................................... 84
7. Spectroscopic Data of Pentacycle 327......................................................... 88
8. $^1$H NMR Spectrum of 227 ..................................................................... 143
9. $^{13}$C NMR Spectrum of 227 .................................................................... 144
10. $^1$HNMR Spectrum of 229 .................................................................... 145
11. $^{13}$C NMR Spectrum of 229 .................................................................... 146
12. $^1$HNMR Spectrum of 218 .................................................................... 147
13. $^{13}$C NMR Spectrum of 218 .................................................................... 148
14. $^1$H NMR Spectrum of 230 .................................................................... 149
15. $^{13}$C NMR Spectrum of 230 .................................................................... 150
16. $^1$H NMR Spectrum of 219 .................................................................... 151
17. $^{13}$C NMR Spectrum of 219 .................................................................... 152
18. $^1$H NMR Spectrum of 220 .................................................................... 153
<table>
<thead>
<tr>
<th></th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>$^{13}$C NMR Spectrum of 220</td>
<td>154</td>
</tr>
<tr>
<td>20</td>
<td>$^1$H NMR Spectrum of 240</td>
<td>155</td>
</tr>
<tr>
<td>21</td>
<td>$^{13}$C NMR Spectrum of 240</td>
<td>156</td>
</tr>
<tr>
<td>22</td>
<td>$^1$H NMR Spectrum of 241</td>
<td>157</td>
</tr>
<tr>
<td>23</td>
<td>$^{13}$C NMR Spectrum of 241</td>
<td>158</td>
</tr>
<tr>
<td>24</td>
<td>$^1$H NMR Spectrum of 244</td>
<td>159</td>
</tr>
<tr>
<td>25</td>
<td>$^{13}$C NMR Spectrum of 244</td>
<td>160</td>
</tr>
<tr>
<td>26</td>
<td>$^1$H NMR Spectrum of 246</td>
<td>161</td>
</tr>
<tr>
<td>27</td>
<td>$^{13}$C NMR Spectrum of 246</td>
<td>162</td>
</tr>
<tr>
<td>28</td>
<td>$^1$H NMR Spectrum of 245</td>
<td>163</td>
</tr>
<tr>
<td>29</td>
<td>$^{13}$C NMR Spectrum of 245</td>
<td>164</td>
</tr>
<tr>
<td>30</td>
<td>$^1$H NMR Spectrum of 247</td>
<td>165</td>
</tr>
<tr>
<td>31</td>
<td>$^{13}$C NMR Spectrum of 247</td>
<td>166</td>
</tr>
<tr>
<td>32</td>
<td>$^1$H NMR Spectrum of 249</td>
<td>167</td>
</tr>
<tr>
<td>33</td>
<td>$^{13}$C NMR Spectrum of 249</td>
<td>168</td>
</tr>
<tr>
<td>34</td>
<td>$^1$H NMR Spectrum of 250</td>
<td>169</td>
</tr>
<tr>
<td>35</td>
<td>$^{13}$C NMR Spectrum of 250</td>
<td>170</td>
</tr>
<tr>
<td>36</td>
<td>$^1$H NMR Spectrum of 256</td>
<td>171</td>
</tr>
<tr>
<td>37</td>
<td>$^{13}$C NMR Spectrum of 256</td>
<td>172</td>
</tr>
<tr>
<td>38</td>
<td>$^1$H NMR Spectrum of 258</td>
<td>173</td>
</tr>
<tr>
<td>39</td>
<td>$^{13}$C NMR Spectrum of 258</td>
<td>174</td>
</tr>
<tr>
<td>40</td>
<td>$^1$H NMR Spectrum of 262</td>
<td>175</td>
</tr>
<tr>
<td>41</td>
<td>$^{13}$C NMR Spectrum of 262</td>
<td>176</td>
</tr>
<tr>
<td>42</td>
<td>$^1$H NMR Spectrum of 268</td>
<td>177</td>
</tr>
<tr>
<td>43</td>
<td>$^{13}$C NMR Spectrum of 268</td>
<td>178</td>
</tr>
<tr>
<td>44</td>
<td>$^1$H NMR Spectrum of 263</td>
<td>179</td>
</tr>
<tr>
<td>Page</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>$^{13}$C NMR Spectrum of 263</td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>$^1$H NMR Spectrum of 279</td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>$^{13}$C NMR Spectrum of 279</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>$^1$H NMR Spectrum of 280</td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>$^{13}$C NMR Spectrum of 280</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>$^1$H NMR Spectrum of 282</td>
<td></td>
</tr>
<tr>
<td>51</td>
<td>$^{13}$C NMR Spectrum of 282</td>
<td></td>
</tr>
<tr>
<td>52</td>
<td>$^1$H NMR Spectrum of 299</td>
<td></td>
</tr>
<tr>
<td>53</td>
<td>$^{13}$C NMR Spectrum of 299</td>
<td></td>
</tr>
<tr>
<td>54</td>
<td>$^1$H NMR Spectrum of 300</td>
<td></td>
</tr>
<tr>
<td>55</td>
<td>$^{13}$C NMR Spectrum of 300</td>
<td></td>
</tr>
<tr>
<td>56</td>
<td>$^1$H NMR Spectrum of 307</td>
<td></td>
</tr>
<tr>
<td>57</td>
<td>$^{13}$C NMR Spectrum of 307</td>
<td></td>
</tr>
<tr>
<td>58</td>
<td>$^1$H NMR Spectrum of 318</td>
<td></td>
</tr>
<tr>
<td>59</td>
<td>$^{13}$C NMR Spectrum of 318</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>$^1$H NMR Spectrum of 324</td>
<td></td>
</tr>
<tr>
<td>61</td>
<td>$^{13}$C NMR Spectrum of 324</td>
<td></td>
</tr>
<tr>
<td>62</td>
<td>$^1$H NMR Spectrum of 325</td>
<td></td>
</tr>
<tr>
<td>63</td>
<td>$^{13}$C NMR Spectrum of 325</td>
<td></td>
</tr>
<tr>
<td>64</td>
<td>$^1$H NMR Spectrum of 327</td>
<td></td>
</tr>
<tr>
<td>65</td>
<td>$^1$H NMR COSY Spectrum of 327</td>
<td></td>
</tr>
<tr>
<td>66</td>
<td>$^{13}$C NMR Spectrum of 327</td>
<td></td>
</tr>
<tr>
<td>67</td>
<td>$^1$H NMR Spectrum of 344</td>
<td></td>
</tr>
<tr>
<td>68</td>
<td>$^{13}$C NMR Spectrum of 344</td>
<td></td>
</tr>
<tr>
<td>69</td>
<td>$^1$H NMR Spectrum of 123</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>$^{13}$C NMR Spectrum of 123</td>
<td></td>
</tr>
</tbody>
</table>
## LIST OF SCHEMES

<table>
<thead>
<tr>
<th>SCHEME</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mechanism of the Heck Reaction</td>
<td>2</td>
</tr>
<tr>
<td>2. Intermediates in the Heck Reaction of Linear Alkenes</td>
<td>4</td>
</tr>
<tr>
<td>3. Michael Arylation</td>
<td>8</td>
</tr>
<tr>
<td>4. Palladium Mediated C-Glycoside Formation</td>
<td>10</td>
</tr>
<tr>
<td>5. An Asymmetric Heck Cyclization</td>
<td>15</td>
</tr>
<tr>
<td>6. Gore's Cyclopentanation Reaction</td>
<td>15</td>
</tr>
<tr>
<td>7. Exo versus Endo Cyclization</td>
<td>18</td>
</tr>
<tr>
<td>8. Overman's Tazettine Synthesis - Boat versus Chair</td>
<td>22</td>
</tr>
<tr>
<td>9. Overman's Asymmetric Heck Cyclization</td>
<td>27</td>
</tr>
<tr>
<td>10. Biosynthesis of Strychnos Alkaloids</td>
<td>30</td>
</tr>
<tr>
<td>11. Woodward's Synthesis of Strychnine</td>
<td>34</td>
</tr>
<tr>
<td>12. Magnus' Synthesis of Strychnine</td>
<td>35</td>
</tr>
<tr>
<td>14. Harley-Mason's Syntheses of Tubifoline and Condyfoline</td>
<td>37</td>
</tr>
<tr>
<td>15. Ban's Approach to Stemmadenine</td>
<td>38</td>
</tr>
<tr>
<td>16. Takano's Synthesis of Dehydrotubifoline</td>
<td>39</td>
</tr>
<tr>
<td>17. Kim's Approach to Strychnine</td>
<td>40</td>
</tr>
<tr>
<td>18. Vollhardt's Approach to Strychnine</td>
<td>41</td>
</tr>
<tr>
<td>19. Overman's Synthesis of Dehydrotubifoline</td>
<td>42</td>
</tr>
<tr>
<td>Chapter</td>
<td>Title</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>20.</td>
<td>Kraus' Approach to Strychnine</td>
</tr>
<tr>
<td>21.</td>
<td>Bosch's Second Synthesis of Tubifoliidine</td>
</tr>
<tr>
<td>22.</td>
<td>Kuehne's Synthesis of Tubotaiwine</td>
</tr>
<tr>
<td>23.</td>
<td>Vercauteren's Synthesis of 19-Hydroxytubotaiwine</td>
</tr>
<tr>
<td>24.</td>
<td>Retrosynthetic Analysis of Strychnine</td>
</tr>
<tr>
<td>25.</td>
<td>Regiochemistry of the Coupling Process: Endo vs Exo</td>
</tr>
<tr>
<td>26.</td>
<td>Preparation of Vinyl Bromide 218</td>
</tr>
<tr>
<td>27.</td>
<td>Reduction of Pd(OAc)$_2$ by PPh$_3$</td>
</tr>
<tr>
<td>28.</td>
<td>Heck Cyclization of Vinyl Bromide 218</td>
</tr>
<tr>
<td>29.</td>
<td>Syntheses of Vinyl Iodides 219 and 220</td>
</tr>
<tr>
<td>30.</td>
<td>Preparation of Vinyl Iodides 234 and 237</td>
</tr>
<tr>
<td>31.</td>
<td>Heck Cyclization of Vinyl Iodides 219 and 220</td>
</tr>
<tr>
<td>32.</td>
<td>Preparation of 245, First Route</td>
</tr>
<tr>
<td>33.</td>
<td>Preparation of 245, Second Route</td>
</tr>
<tr>
<td>34.</td>
<td>Regiochemistry of the $\beta$-Elimination Step</td>
</tr>
<tr>
<td>35.</td>
<td>Palladium Assisted Synthesis of 2-Methyl-Indole</td>
</tr>
<tr>
<td>36.</td>
<td>Model Studies–Construction of the Indole Nucleus</td>
</tr>
<tr>
<td>37.</td>
<td>Synthesis of Aniline Derivative 258</td>
</tr>
<tr>
<td>38.</td>
<td>Double Cyclization</td>
</tr>
<tr>
<td>39.</td>
<td>Retrosynthesis of Dehydrotubifoline</td>
</tr>
<tr>
<td>40.</td>
<td>Cyclopropyl-iminium Ion Rearrangement</td>
</tr>
<tr>
<td>41.</td>
<td>Stevens' Formal Synthesis of Aspidospermine</td>
</tr>
<tr>
<td>42.</td>
<td>Synthesis of Cyclopropyl-Imine 281</td>
</tr>
<tr>
<td>43.</td>
<td>TMSI Promoted Cyclopropyl-Iminium Ion Rearrangement</td>
</tr>
<tr>
<td>44.</td>
<td>Attempted Intermolecular Cycloadditions</td>
</tr>
<tr>
<td>45.</td>
<td>Preparation of Carbamate 299</td>
</tr>
</tbody>
</table>
46. Preparation of Dienamides from α,β-unsaturated Aldehydes........................................79
47. Preparation of Dienamide 3 0 7.........................................................................................80
48. Diels-Alder Cycloaddition of Dienamide 3 0 7.................................................................83
49. TMSI Promoted Hydrolysis of Carbamates-Mechanism..............................................85
50. Our First Approach to Dehydrotubifoline and Akuammicine......................................87
51. Heck Cyclization of Indoline Carbamate 3 2 5..............................................................88
52. Inversion of Alkene Geometry via an Exo-mode Cyclization.........................................89
53. Formation of 3 2 7-Mechanism......................................................................................89
54. Heck Cyclopropanation.................................................................................................90
55. Final Steps in the Synthesis of Dehydrotubifoline.........................................................92
Chapter I

The Heck Reaction: Recent Applications in Synthesis

I. Introduction

The palladium mediated coupling reaction of an aryl or vinyl halide with an alkene — the Heck reaction— was first reported by Heck\textsuperscript{1} in 1968. Although some interesting extensions of this reaction were reported by Heck\textsuperscript{2-4} and others\textsuperscript{5} in the subsequent years, it was not until the last decade that a considerable amount of investigation has extended the scope of this transformation.\textsuperscript{6,7} Not surprisingly, the Heck reaction is now used extensively in organic synthesis.\textsuperscript{7} The objective of the present chapter is to review the recent applications of the Heck reaction in organic synthesis. This survey of the literature will discuss intermolecular and intramolecular Heck coupling reactions, including carbocyclizations and heterocyclizations.

The basic mechanism of the Heck reaction involves four steps\textsuperscript{3,4} (Scheme 1):

1. **Palladium Insertion:** An oxidative addition of Pd(0) into the sp\textsuperscript{2} carbon-halide (or triflate) bond forms a vinyl (or aryl) palladium (II) species. This complex can also be generated from a vinyl (or aryl) mercury acetate upon treatment with a Pd(II) salt (transmetallation).\textsuperscript{1}

2. **Complexation:** The Pd(II) intermediate reacts with the alkene to afford a π-complex.

3. **Addition:** The π-complex collapses by 1,2-syn-addition to create a new carbon-carbon bond and a σ-palladium-carbon bond.

4. **β-Elimination:** The palladium σ-adduct decomposes with elimination of palladium hydride and product formation. The elimination of HX from HPdX ensures the regeneration of the active Pd(0) catalyst.

1
This general mechanism provides a useful framework for the discussion of various aspects of the reaction. The Pd(0) catalyst is usually generated in situ by reduction of a stable palladium II complex, most often Pd(OAc)$_2$. The reduction is induced by the alkene in solution or by a phosphine ligand. The regeneration of the active catalyst from HPdX is promoted by a base. Commonly used bases include tertiary amines, acetates, carbonates or bicarbonates. A polar solvent is often mandatory to keep the catalyst in solution. Dimethylformamide (DMF) and acetonitrile are both used extensively, although dimethylsulfoxide (DMSO), tetrahydrofuran (THF) and hexamethylphosphoramide (HMPA) are used occasionally. In cases where non-coordinating solvents like toluene are employed, more ligand has to be added to solubilize the catalyst. The Heck olefination reaction can be applied to various organic halides, triflates, diazonium salts, carboxylic acid chlorides, sulfonyl chlorides and sulfinate salts. This chapter will be limited to the Heck reactions of organic bromides, iodides, and triflates, as most synthetically useful applications have been obtained with these derivatives. Alkyl halides (or triflates) with
β-hydrogen generally undergo β-elimination of palladium hydride under the conditions of the Heck reaction. Consequently, this review will be limited to the addition of sp² hybridized carbons.

2. Intermolecular Coupling Reactions

The Heck reaction is limited to alkenyl halides (or triflates). But, it is a general process with regard to the alkene partner, which can be a simple olefin, or an olefin substituted by electron withdrawing, or donating groups. The reaction is sensitive to steric hindrance. Mono-subsituted alkenes are the most reactive olefins, and increasing substitution lowers the reactivity. With substituted alkenes, carbon-carbon bond formation usually takes place at the less hindered side of the double bond. Electronic factors, however, can override steric effects (see enol ethers). Selected examples of intermolecular Heck reactions are presented below to illustrate the scope of the coupling process.

To begin with, I would like to illustrate the mildness of the method. The Heck reaction represents an exceptionally mild, and often selective, method for the construction of carbon-carbon bonds between sp² centers. It has been employed with success in the derivatization of complex natural products. An example by Witty and co-workers dramatically illustrates the selectivity obtainable by the Heck reaction. These authors explored the structure-activity relationship of avermectin derivatives. The sensitivity of the avermectin molecule prevented the use of acidic or basic reagents. Selective substitution on the terminal alkene was achieved without any protection of the sensitive functionalities, using a neutral palladium reagent. The polyyene macrocyclic lactone containing a sensitive spiroketal moiety did not suffer any decomposition during the arylation reaction (Equation 1).
This section, dealing with intermolecular Heck reactions of alkenes with various halides and triflates, has been divided into two parts: reaction of unactivated olefins and reactions of activated olefins.

2.1 Unactivated Olefins

2.1.1 Terminal Alkenes

Numerous examples show that monosubstituted alkenes undergo Heck coupling reactions at the terminal carbon exclusively, to produce the thermodynamically more stable (E) olefin. During vinylation reaction, the geometry of the vinylic halide or triflate is generally retained.\(^4\) As shown in Scheme 2, the coupling product arises from syn elimination of palladium hydride. Two possible intermediates A and B are available. Intermediate B is higher in energy due to the steric repulsion between the eclipsed substituents. The E isomer arises from the collapse of intermediate A.

**Scheme 2: Intermediates in the Heck Reaction of Linear Alkenes**
Two inhibitors of the thromboxane synthase enzyme (5 and 8) were prepared by vinylation of 3-bromo-pyridine (Equation 2 and 3). Derivatives of 2,3-dihydro-7-iodoindole have been coupled to 2-methyl-3-buten-2-ol to afford an intermediate in the total synthesis of annodine A, an indole alkaloid isolated from a West African medicinal plant. Quinolinones and other derivatized heterocycles have also been prepared by coupling with 2-methyl-3-buten-2-ol. Some 3-indolyl halides and triflates have been reported to undergo Heck reaction with a variety of terminal alkenes in fair to good yields. Vinylation of haloazulenes and halotropolones with styrenes and 2-vinylpyridines represents a convenient method for the introduction of conjugated carbon side chains to these compounds. Mercuriated derivatives of quinolones have been reported to participate in the Heck transformation. A full equivalent of Pd(OAc)$_2$ is required in these reactions, because a palladium (II) complex is produced by transmetallation.

Unlike mercuriated compounds, vinyl silanes do not appear to participate in transmetallation reactions. Vinyl silanes have, however, been used as alkene partners in the Heck reaction. In 1985, Hallberg and co-workers reported that the treatment of aryl iodides with vinyltrimethylsilane under ordinary Heck arylation conditions resulted in the formation of
styrene derivatives (Equation 4a). \(^{20,21}\) They found that the desilylation could be suppressed by adding one equivalent of a silver(I) salt (Equation 4b), in which case the product 15 resulted from arylation at the less substituted carbon. In 1990, Tanaka\(^ {22}\) found that, even in the absence of a silver salt, the reaction proceeded without desilylation, provided that the starting vinylsilane had electronegative substituents attached to the silicon (Equation 4c).

\[
\text{Arl} + \begin{array}{c}
\text{SiMe}_3 \\
13
\end{array} \xrightarrow{\text{Pd(OAc)}_2, \text{PPh}_3, \text{Et}_3\text{N}} \begin{array}{c}
\text{Ar} \\
14
\end{array} \quad (\text{Eqn. 4a})^{20} \\
\text{Arl} + \begin{array}{c}
\text{SiMe}_3 \\
13
\end{array} \xrightarrow{\text{Pd(OAc)}_2, \text{PPh}_3, \text{Et}_3\text{N}, \text{AgNO}_3, 95\%} \begin{array}{c}
\text{Ar} \\
15
\end{array} \quad (\text{Eqn. 4b})^{20} \\
\text{Arl} + \begin{array}{c}
\text{SiMeCl}_2 \\
13
\end{array} \xrightarrow{\text{Pd(PPh}_3)_2\text{Cl}_2, \text{Et}_3\text{N}, 97\%} \begin{array}{c}
\text{Ar} \\
16
\end{array} \quad (\text{Eqn. 4c})^{22}
\]

The synthesis of non-proteinogenic α-amino acids, which are potential enzyme inhibitors, has recently attracted much attention. Crisp and co-workers reported the synthesis of various glycine derivatives, through the Heck coupling reactions of vinyl glycine and alkenyl halides or triflates.\(^ {23a}\) They observed no racemization during the coupling process (Equation 4d). Itaya has demonstrated the utility of the Heck reaction with optically active vinyl glycine derivatives in his synthesis of the fluorescent nucleoside, wybutosine, a component of the yeast phenylalanine tRNA.\(^ {23b}\)

\[
\begin{array}{c}
\text{9} \\
\text{OTf}
\end{array} + \begin{array}{c}
\text{10} \\
\text{COOH}
\end{array} \xrightarrow{\text{Pd(OAc)}_2, \text{P(o-toI)}_3, \text{K}_2\text{CO}_3, \text{nBu}_4\text{NCl, DMF, 60}^\circ\text{C, 77}\%} \begin{array}{c}
\text{11} \\
\text{COOH}
\end{array} \quad (\text{Eqn. 4d})^{23a}
\]

The Heck reaction of terminal dienes has been described.\(^ {24,25}\) However, low yields are obtained when the diene is not activated by a carbonyl or a phenyl group. Recently, Jeffery developed a procedure to couple unactivated terminal dienes to aryl iodides.\(^ {26}\) Good yields of (E,E) conjugated aromatic dienes were obtained upon treatment of benzyl iodide and linear
terminal dienes with palladium acetate, triphenylphosphine and silver carbonate, in DMF. This procedure has not been yet extended to the vinylation reaction.

2.1.2 Internal Alkenes

Symmetrical alkenes undergo the Heck coupling reaction with no regiochemical consequences. On the other hand, unsymmetrical alkenes do usually produce mixtures of regioisomers. The major product arises from coupling at the less hindered olefinic carbon.

2.2 Activated Olefins

2.2.1 Electron-Poor Alkenes

Electron deficient alkenes have been used extensively in Heck coupling reactions. Arylation and vinylation of $\alpha$-$\beta$-unsaturated esters, acids, amides, nitriles, ketones, and aldehydes occur regiospecifically at the $\beta$-carbon.

A series of substituted pyrazole mevalonolactones was synthesized by palladium catalyzed vinylation with ethyl acrylate (Equation 5). Transmetallation of mercurated pyrrole 5 with PdCl$_2$, followed by coupling with methyl acrylate, conveniently afforded the tetrasubstituted pyrrole 6, in 84% yield (Equation 6). Halogenochromones served as common precursors for the synthesis of chromones functionalized with unsaturated esters. The (E) isomer is often exclusively obtained.

![Chemical Structures](image-url)
As the above cases illustrate, the coupling of α,β-unsaturated esters to alkenes affords exclusively the E isomer. This observation reflects the preference for intermediate A (see Scheme 2), where the substituents are in a staggered arrangement. The same result is not always true for α,β-unsaturated nitriles, which can give rise to a mixture of isomers. This observation indicates that nitriles are not as sterically demanding as esters.

In contrast to acyclic cases, cyclic esters cannot adopt the conformation required for syn β-elimination of palladium hydride. According to Stokker, lactone 17 (Scheme 3) underwent a Michael arylation upon treatment with Pd(0) and triethylamine. In this transformation, triethylamine was the source of hydride. A proposed mechanism for this unusual reaction is depicted in Scheme 3.

Scheme 3: Michael arylation

Acrylamide derivatives show only moderate activity in standard Heck reactions. Strong chelation of the amide group to the catalyst generally prevents a good turn over. Two solutions to this problem have been developed. Zhuangyu and co-workers investigated a polymer-bound Pd(0) catalyst that efficiently promotes the arylation of acrylamide (Equation 7). Heck arylation of acrylamides and α-amidoacrylates has also been achieved using an excess of lithium chloride (Equation 8). The chloride anion is believed to chelate the catalyst. This chelation is likely to preclude a strong coordination of the amide nitrogen. The reaction is
regioselective, affording the (2) isomer only. Aromatic amino acids have been prepared by Heck arylation of α-amidoacrylates followed by catalytic hydrogenation.40

\[
\text{CONH}_2 + \text{PhI} \xrightarrow{\text{Polymer-Pd(0), DMF, H}_2\text{O, NaOAc, } 100^\circ\text{C}} \text{Ph} = \text{CHCONH}_2
\]

(Eqn.7)42

In a similar way, α-methoxyacrylates react stereospecifically with vinyl triflates and aryl iodides to give (2) enol ethers of pyruvate derivatives (Equation 9).38

\[
\text{F} \quad \text{I} \quad \text{CO}_2\text{Me} \xrightarrow{\text{K}_2\text{CO}_3, \text{Pd/C, DMF, LiCl, } 100^\circ\text{C, 77%}} \text{F} \quad \text{CO}_2\text{Me}
\]

(Eqn.8)39

2.2.2 Electron rich alkenes

The Heck arylations and vinylations of acyclic enol ethers often yield a mixture of regioisomers.6, 36,44-46 The arylation of n-butyl vinyl ether with iodosobenzene, for instance, affords a 2/3 mixture of β- and α- arylated enol ethers.44 Consequently, the Heck reaction of acyclic enol ethers has not been used in synthesis. The reason for this lack of selectivity is not well understood.6,44-46 On the other hand, cyclic enol ethers undergo regiospecific palladium promoted arylation and vinylation. Derivatives of 3,4-dihydropyran and 2,3-dihydrofuran both undergo coupling at the α-carbon, site of lower electron density.47-50 Hayashi and Ozawa
recently reported that high enantioselectivity (>90% ee) could be achieved in the arylation of 2,3-dihydropyran with aryl triflates when a chiral phosphorus ligand (BINAP) was employed.\textsuperscript{51}

The Heck reaction of cyclic enol ethers has been used extensively in carbohydrate chemistry for the synthesis of C-glycosides.\textsuperscript{6, 52-57} This chemistry was recently reviewed by Daves, and will not be discussed at length.\textsuperscript{52} The Pd alkenyl or aryl complex is delivered from the less hindered side of the carbohydrate unit. The resulting σ-alkyl complex decomposes via several competing modes\textsuperscript{52} (Scheme 4). Whenever possible, traditional syn β-elimination of HPdX is preferred \textsuperscript{(25)}. In a case where an axial acetate was present on the carbon α to the palladated center, elimination of palladium acetate has been observed \textsuperscript{(26)}. An unusually stable palladium σ complex \textsuperscript{(27a)} was isolated from the reaction mixture of \textsuperscript{(27} and \textsuperscript{(24} with Pd(OAc)\textsubscript{2}. In this example, an intramolecular chelation through a six-membered ring was responsible for the stability of \textsuperscript{(27a).} β-elimination did not occur, because chelate formation prevented proper alignment of the syn β-hydrogen and the carbon-palladium bond. The complex \textsuperscript{(27a} was isolated, and treated with hydrogen to afford the reduction product \textsuperscript{(28).}\textsuperscript{55}

\textbf{Scheme 4: Palladium Mediated C-Glycoside Formation}

\begin{center}
\includegraphics[width=\textwidth]{scheme.png}
\end{center}
The intermolecular coupling reactions of acyclic enamides, like enol ethers, give rise to mixtures of regioisomers. No application in synthesis has been reported. A number of cyclizations of enamides have been developed, and examples are discussed in part four.

3. Carbobcyclizations

In connection with the synthesis of natural products, there is increasing interest in the development of intramolecular variants of the Heck reaction that offer a general route to carbocycles. These transformations are similar to the radical cyclizations, and usually proceed predictably and in high yield. A variety of 5- and 6-membered carbocycles have been prepared very efficiently. In the recent years, the Heck methodology has also been extended to polycyclization processes.

3.1 5-membered Carbocycles

2-halo-1,6-dienes and 1-halo-1,5-dienes undergo smooth conversion to 5-membered ring upon treatment with a Pd(0) catalyst (Equation 10a and 10b). Like in radical chemistry, 5-exo cyclization is usually preferred over 6-endo cyclization. But, unlike radical processes, the cyclization step is not followed by a reduction, but by an elimination reaction that regenerates the alkene. Equation 10a and 10b illustrate the two possible 5-exo Heck cyclizations. The first reaction leads to a cisoid diene, and the second one affords the transoid isomer.

\[ \text{(Eqn. 10a)} \]

\[ \text{(Eqn. 10b)} \]

Grigg and co-workers investigated the chemistry of substituted 2-bromo-1,6-heptadienes (Equation 11). Although the cyclizations proceeded in good yields, the reactions were not specific, a minor amount of 6-membered rings (endo cyclization) being obtained.
A more sophisticated version of this chemistry has been reported by Gaudin, as part of his ongoing work on the construction of functionalized 5-membered carbocycles. A series of allylic alcohols possessing a suitable vinyl (or aryl) bromide appendage were submitted to the Heck cyclization conditions (equations 1 to 14). In the first example (Equation 1.2) the initial 5-exo cyclization yields a σ-palladium complex (32a), which collapses to afford the aldehyde 33 through an enolic tautomerization. In the case of a secondary allylic alcohol (34), a ketone is produced (Equation 1.3). The substituted bromobenzene 36 does not follow a similar reaction pathway (Equation 1.4). Elimination of palladium hydride cannot occur so as to generate an enol. In this case, a mixture of diastereomeric alcohols (37 and 38) is produced. Gaudin has also combined, in one operation, a Pd(0) catalyzed alkylation of a vinyl epoxide (39) and a Heck cyclization, to afford the bicycle 41 in 60% overall yield (Equation 1.5). The intermediate in this transformation is believed to be the allylic alcohol 39a.
Recently, vinyl\textsuperscript{63-65} and aryl\textsuperscript{63} triflates of elaborated systems have also been submitted to the intramolecular Heck reaction. Paquette\textsuperscript{63} investigated the regioselectivity of the β-hydride elimination step in systems related to diquinanes (Equation 16 and 17). In his studies, non-activated olefins (42) were converted to the less conjugated cyclization product (43), whereas activated olefins (44) afforded a mixture of conjugated (45) and non-conjugated (46) dienes. The major product was reported to be the conjugated isomer. Formation of 45 was not the result of Pd-mediated equilibration, as longer reaction times did not alter the ratio of products (kinetic control). Moreover, pure samples of isomers 45 and 46 were found to be stable to the reaction conditions.
Within the past few years, there has been increasing interest in the development of enantioselective transformations. Several examples of asymmetric Heck reactions have been reported. Asymmetric palladium promoted synthesis of cyclopentanoids have been achieved by Shibasaki. The cis-hydrindan derivative was obtained from vinyl iodide 47, in 78% yield and 82% ee using a catalytic amount of PdCl₂(R-BINAP) (Equation 18). Differentiation of the two enantiotopic endocyclic double bonds resulted from chelation with the chiral phosphorus ligand, R-BINAP.

In a related study, the author developed a catalytic asymmetric preparation of a key intermediate (50) in the synthesis of capnellenol sesquiterpenes. Treatment of the vinyl iodide 49 with [Pd(allyl)Cl₂]₂ (10mol%), (R,R)-Chiraphos (10mol%), and nBu₄NOAc in toluene provided the bicyclic allylic acetate 50 in fair yield, but low ee (20% ee). As shown in Scheme 5, complexation of the endocyclic alkene to the vinyl palladium moiety necessitated the dissociation of at least one chiral phosphorus ligand. This dissociation, obviously, decreased the possibility of asymmetric induction. In an effort to overcome this problem, Shibasaki and al. carried out the reaction in the presence of a silver (I) salt, which, by abstracting I⁻, was expected to liberate a coordination site. The starting iodide, unfortunately, suffered extensive decomposition in the presence of silver carbonate. Very good leaving groups, like triflate, do not usually require the
assistance of silver (I) salts. Indeed, the cyclization of vinyl triflate 51 proceeded efficiently in the absence of silver salt, with an enantiomeric excess of 80%.

**Scheme 5: An Asymmetric Heck Cyclization**

Gore has developed an interesting approach to cyclopentane derivatives. A cascade of reactions, leading to 5-membered carbocycles, was triggered by Heck additions of vinyl (or aryl) iodides (or bromides) to alkenes. This transformation is believed to involve a reductive cyclization with a malonate anion. An example of these new Pd(0) promoted cyclopentanellation reactions is depicted in Scheme 6.

**Scheme 6: Gore’s Cyclopentanellation Reaction**

3.2. 6-Membered Carbocycles

Some of the annulation procedures developed for 5-membered carbocycles have been extended to cyclohexyl homologues, albeit less successfully. The cyclizations of 2-bromo-
1,7-octadienes, reported by Griggs, gave rise to a mixture of the expected exo-cyclization product 53, along with the isomerized diene 54 (Equation 1). The cyclization of allylic alcohol 55 (Equation 2), described by Gaudin in 1991, yielded the aldehyde 56, through a mechanism similar to the one depicted in Equation 12. Shibasaki has demonstrated that the transformation of cyclohexadiene 57 to decalin 58 (Equation 21a) proceeded with high enatiomeric excess, when the chiral ligand R-BINAP was employed.

Ishibashi and Ikeda have taken advantage of the Heck carbocyclization in their studies directed toward the total synthesis of podophyllum lignans. The radical cyclization (nBu3SnH, AIBN) of aryl bromide 59 afforded a mixture of 5-exo and 6-endo adducts. On the other hand, the palladium promoted cyclization cleanly yielded the desired substituted cyclohexene 60 (Equation 21b).
Recent studies by Negishi\textsuperscript{77} have demonstrated that some 6-membered carbocycles, which are products of apparent endo cyclizations,\textsuperscript{62, 76} could be arising through a more complex mechanism. The palladium catalyzed cyclization of vinyl iodide \(61\), for example, afforded cyclohexene \(62\) exclusively. It is significant to note that the cyclization proceeded with complete inversion of the exocyclic olefin geometry (Equation 2.2).\textsuperscript{77} This reaction is not a traditional endo-cyclization.

The mechanism of this transformation has been investigated by Negishi\textsuperscript{76}. The first step involves the expected exo-cyclization, to give the neopentyl type \(\sigma\)-alkyl palladium complex \(61\text{a}\) (Scheme 7). As it is connected to a quaternary carbon, this complex cannot undergo \(\beta\)-elimination. It reacts intramolecularly with the alkene to yield the cyclopropane derivative \(61\text{b}\). After proper alignment of the \(\sigma\)-alkyl palladium bond with the internal cyclopropane carbon-carbon bond, ring cleavage occurs to produce a new \(\sigma\)-alkyl palladium complex (\(61\text{c}\)). During this step, the geometry of the exocyclic double bond is inverted. The complex \(61\text{c}\), which can undergo a fast \(\beta\)-elimination, collapses to provide the isolated diene \(62\). Cyclopropanations of alkylpalladium species have been reported.\textsuperscript{78-81}
An other intriguing type of palladium promoted annulation reaction has been reported by De Meijere and co-workers.\textsuperscript{82-84} Their process combines intermolecular and intramolecular Heck arylations (Equation 23). Although the mechanism of this reaction has not been thoroughly investigated, the participation of Pd(IV) intermediates has been speculated.\textsuperscript{85}

A new palladium catalyzed carbocyclization, developed by Trost, is based on the carbopalladation of 1,6 and 1,7-enynes.\textsuperscript{86-92} The discovery that enynes could be reductively isomerized to cyclic dienes\textsuperscript{90-92} (Equation 24) led to the investigation of alkylative cycloadditions, outlined in Equation 25.\textsuperscript{66-89} The potential of this transformation in the synthesis of complex structures has been demonstrated. Efficient strategies directed toward the vitamin D system\textsuperscript{87,88} (Equation 26), as well as other functionalized 6-membered carbocycles\textsuperscript{89} (Equation 27), have been published.
3.3 Polycyclizations

Since the original communication of Overman\textsuperscript{93} on the Heck-type polyene carbocyclizations, Pd(0) promoted multiannulations have been investigated by several different groups.\textsuperscript{94-100} The power of this chemistry for assembling complex polycycles is illustrated in equations 28 through 30. A remarkable transformation\textsuperscript{95} was observed upon heating the
cycloheptene derivative 77 with a catalytic amount of Pd(0) in acetic acid (Equation 30). Tetracycle 78 was obtained via an initial Pd-ene cyclization of a π-allyl palladium species, followed by two intramolecular Heck reactions. This synthesis of polyfused ring systems by intramolecular tandem palladium-ene/Heck reactions proceeded with high stereospecificity. The palladium-ene step afforded the thermodynamically more stable trans junction between rings A and B (77a), and the Heck cyclization occurred with retention of configuration at the metalated carbons.

\[
\begin{align*}
\text{72} & \xrightarrow{\text{Pd(OAc)}_2, \text{PPh}_3, \text{Ag}_2\text{CO}_3, \text{MeCN}, \text{rt}, 90\%} \text{73} + \text{74} \\
\text{75} & \xrightarrow{\text{Pd(OAc)}_2, \text{PPh}_3, \text{K}_2\text{CO}_3, \text{MeCN}, 75\%} \text{76}
\end{align*}
\]

(Eqn.28)93a

(Eqn.29)94

(Eqn.30)95

4. Heterocyclizations

The field of natural product synthesis provides a challenging arena to explore new preparations of heterocycles. Not surprisingly, the Heck cyclization methodology has been expanded to nitrogen containing heterocycles (alkaloids chemistry) and, to a lesser extent, to
oxygen containing heterocycles.

4.1 Oxygen Heterocycles

Some recent examples of Heck cyclizations leading to oxygenated heterocycles are presented below. To investigate the scope of their polycyclization procedure (see Equation 29), De Meijere et al. submitted oxo-analogues of 75 to the Pd(0) catalyzed cyclization reaction. They isolated the expected tricycles in comparable yields. Phenolic ethers have been successfully cyclized to dihydropyrans by action of Pd(OAc)$_2$, PPh$_3$, and triethylamine in acetonitrile. Bromo-propenyl allyl ethers (79), o-iodo benzyl allyl ethers (81), and propargyl allyl ethers (83) have also been converted to the corresponding oxocycles in good yield (Equations 31 to 33).

\[
\text{Pd(OAc)$_2$, P(o-tol)$_3$} \xrightarrow{\text{Et$_3$N, 100°C, 47%}} \text{80}
\]

(Eqn. 31)$^{102}$

\[
\text{Pd(OAc)$_2$, PPh$_3$, MeCN, 80°C} \xrightarrow{\text{Et$_3$N, 74%}} \text{82}
\]

(Eqn. 32)$^{62}$

\[
\text{Pd(dba)$_2$, HCO$_2$} \xrightarrow{\text{PPh$_3$, Et$_3$N, tol. 62%}} \text{84}
\]

(Eqn. 33)$^{89}$

The Heck cyclization has also been used for the synthesis of macrolides. Macrocyclic lactone 34, a model compound for the synthesis of carbonolide, was prepared by the intramolecular coupling reaction of a terminal iodide with a vinyl ketone, under high dilution conditions (Equation 34). The instability of the catalyst during slow addition of the substrate required the use of a stoichiometric amount of PdCl$_2$(MeCN)$_2$. Macrocyclic dienone 86, having the all trans geometry, was produced in 55% yield.
The construction of sterically demanding quaternary centers was recently achieved using Heck cyclizations. The central step in Overman's syntheses of (±)-Tazettine and (±)-6a-Epipretazettine was based on a palladium catalyzed construction of the benzopyran subunit (Equation 35). The cyclization was performed in the presence of a stoichiometric amount of Ag(I) salt to prevent olefin isomerization. A high degree of stereoselection (>20/1) was observed in the formation of the quaternary center. This outcome can be rationalized by considering the two transition states, A and B (Scheme 8). The major product is believed to arise through the lower energy boat transition state, in which non-bonding interactions are minimized.

Scheme 8: Overman's Tazettine Synthesis - Boat versus Chair
4.2 Nitrogen Heterocycles

The synthesis of a variety of plant metabolites and analogues thereof necessitates the construction of nitrogen containing heterocycles. Numerous azacycles can arise through a Heck cyclization of linear amines, amides, carbamates and tosylates. o-Halo allylic phenyl amines,¹⁰⁶-¹⁰⁸ amides,¹⁰⁶,¹⁰⁸ and carbamates¹¹⁰ afforded indoles,¹⁰⁶-¹⁰⁹ indolines,¹⁰⁶ and quinolines¹⁰⁶ in good yields. Similarly, a catalytic amount of Pd(0) in the presence of a base catalyzed the cyclization of halo-propenyl homoallylic sulfonamides to substituted piperidines.⁷³ Hegedus' original procedure¹⁰⁷ has been improved using Jeffery's palladium catalyst system (Equation 3.6 and 3.7).¹⁰⁶ The rate of the reaction at ambient temperature was greatly increased when a phase transfer catalyst, usually nBu₄NCl, was employed along with a base in the solid state, a carbonate or an acetate anion. It should be noted also that alkyl palladium complexes, generated by Heck carbopalladation of an olefin, have been trapped intramolecularly by nitrogen nucleophiles to afford pyrrolidines,⁷¹,⁸⁰ pyrrolizidines,¹⁰⁵ and quinolizidines.¹⁰⁵

\[
\begin{align*}
\text{H} & \quad \text{Pd(OAc)}_2, \text{Na}_2\text{CO}_3 \\
& \quad \text{nBu}_4\text{NCl}, \text{DMF}, \text{rt} \quad 97\% \\
& \quad \text{Pd(OAc)}_2, \text{NaO}_2\text{CH} \\
& \quad \text{nBu}_4\text{NCl}, \text{Et}_3\text{N}, \text{DMF} \quad 65\%
\end{align*}
\]

(Eq. 3.6)¹⁰⁶

An unusual combination of an intermolecular Heck olefination and an ortho-palladation of 1,2-diodobenzene yielded the heterocycle 96 (Equation 3.8). The formation of indole-2-carboxylic ester 96 indicated the intermediacy of an ortho-palladated complex (95), originating from a second oxidative addition of Pd(0).
Intramolecular cyclizations of N-allyl substituted 2-bromo-1,4-benzoquinones have been reported to give indoloquinones by Heck reactions. Rappoport described the synthesis of mitomycin analogues from 2,3-dibromo-1,4-benzoquinones (Equation 39). In this example, the carboxyla addition evidently occurs through an endocyclization.

Several biologically important antimitotic agents possess the phenanthridone skeleton. A palladium promoted annulation has been used as the key step in two syntheses of these alkaloids (Equation 40). The construction of the 6-lactam and the introduction of the conjugated alkene was achieved simultaneously. Analogues of the antineoplastic dimeric vinca alkaloids have also been prepared using palladium chemistry. Sunberg has shown that the Heck cyclization efficiently constructs 102, the 5,6-homologues of the iboga structure (Equation 41).
Cyclization of ortho halo benzyl amides affords isoindolenones\textsuperscript{60,61,106,114-117} and isoquinolones\textsuperscript{106,111,112,116} (Equation 4.2 to 4.4). Stereospecific construction of isoindolenone 106 is efficiently achieved with chiral induction (Equation 4.2).\textsuperscript{117} The chiral auxiliary is easily removed by reductive cleavage of the N-N bond, to afford one enantiomer of the corresponding isoindolenone. In cases where the \( \sigma \)-alkyl palladium species resulting from intramolecular cyclizations are not able to undergo \( \beta \)-elimination, trapping of the palladium complex by carbon monoxide, or carbon-carbon double bonds, are observed. For instance, aryl iodide 103 reacts with a catalytic amount of Pd(0) to afford, after Heck cyclization, the intermediate 103a, which does not possess a \( \beta \) hydrogen. Under an atmosphere of carbon monoxide, complex 103a undergoes insertion of CO, followed by methanolyisis, to produce ester 104 in 85% yield (Equation 4.3). The conversion of 107 to 108 doubly illustrates the same concept. Intramolecular carbopalladation of alkyne 107 affords an alkenyl palladium complex, which is trapped by a molecule of norbornene to yield \( \sigma \)-alkyl complex 107a. In a subsequent step, 107a reacts intramolecularly with the exo cyclic olefin to produce cyclopropane 108 as a single isomer (Equation 4.4).
Analogous reactions of acetamide derivatives have been reported to give oxindoles. The lack of regioselectivity in the β-elimination step, or double bond isomerization, have sometimes limited the value of these processes. Both Ti(I) and silver(I) salts have been used with success to improve the selectivity (equations 45 and 46). When treated with a catalytic amount of palladium diacetate, in the presence of triphenylphosphine and potassium carbonate, eneamide 109 was unselectively converted to a mixture of lactams (Equation 45). If 1.2 equivalents of thallium acetate were added to the reaction mixture, only one isomer (110) was produced. Similarly, silver nitrate greatly increased the selectivity in the conversion of α,β-unsaturated amide 113 to pyrrolidinone 114 (Equation 46).
Silver (I) was also found to alter the stereochemical outcome of an enatioselective Heck cyclization. In 1992, Overman reported that, in the presence of R-BINAP, aryl iodide 116 underwent an asymmetric Heck cyclization (Scheme 9). Surprisingly, depending upon the presence of silver (I), either enantiomer could be generated with good selectivity, using a single enantiomer of the chiral diphosphine ligand (Scheme 9). In the examples studied, the enantioselection observed with the amine base was always opposite to the one observed with the silver salt.

Scheme 9: Overman’s Asymmetric Heck Cyclization

Silver (I) was also found to alter the stereochemical outcome of an enatioselective Heck cyclization. In 1992, Overman reported that, in the presence of R-BINAP, aryl iodide 116 underwent an asymmetric Heck cyclization (Scheme 9). Surprisingly, depending upon the presence of silver (I), either enantiomer could be generated with good selectivity, using a single enantiomer of the chiral diphosphine ligand (Scheme 9). In the examples studied, the enantioselection observed with the amine base was always opposite to the one observed with the silver salt.
In his studies directed toward *gelsemium* alkaloids, Overman has also investigated the Heck cyclization of 2-bromoanilide 119. He established that an intramolecular chelation of the palladium aryl intermediate could control the stereochemistry of the coupling process (Equation 47). When the reaction was carried out in a "ligandless" medium, which was believed to favor the intramolecularly chelated intermediate 119a, spiropindolenone 120 was obtained selectively.

\[
\begin{align*}
&\text{MeO} \equiv C \quad \text{Pd(dba)}_3 \quad \text{SEM Br Ag}_2\text{PO}_4 \\
&\text{THF, 77%} \\
&\text{MeO} \equiv C \quad \text{SEM Br} \\
&\text{119} \quad \text{119a} \quad \text{120}
\end{align*}
\]

(Eqn. 47)

5. Conclusion

The palladium catalyzed vinylation and arylation of olefins provides a versatile and efficient method for the construction of a wide variety of complex structures. The Heck methodology is now often used in combination with other organometallic reactions. Many extensions involve sequential coupling and trapping reactions, which allow the formation of two or more carbon-carbon bonds in one pot. Conditions have also been developed so that the Heck reaction can be carried out at ambient temperature. Consequently, we can predict an increase in the use of palladium catalyzed transformations in organic synthesis.
Chapter II

Background and Synthetic Studies

Background

The indole alkaloids comprise one of the largest groups of natural products. So far, over 800 kinds of indole alkaloids have been isolated, and most of their structures elucidated. The Strychnos type, which forms a large subset of them, includes those containing the pentacyclic 3,5-ethano-3H-pyrrolo [2,3-d] carbazole substructure, also called the curan skeleton (Figure 1). Strychnos alkaloids are isolated from the plant species Apocynaceae and Loganiaceae, which grow in the rain forests of Southeast Asia and India.

Figure 1: Examples of Strychnos Alkaloids
Biogenetically, the *Strychnos* alkaloids derive from geissoschizine (128), the condensation product of tryptamine (126) and secologanin (127) (Scheme 10). Geissoschizine is recognized as an early intermediate in the syntheses of most of the indole alkaloids. Although several mechanisms have been postulated to convert tetracyclic amine 128 to strychnan 130, the details of this rearrangement is still unknown. Scheme 10 illustrates one possible pathway. An oxidative cyclization of 128 furnishes the spiro polycycle 129, which rearranges by means of two successive α-bond migrations, as described in scheme 10. The conversion of 128 to 130 has not been accomplished in vitro.

Scheme 10: Biosynthesis of *Strychnos* Alkaloids

Strychnine (121), the most famous member of the *Strychnos* family, was first isolated in a pure form from the beans of *Strychnos ignatti* in 1818 by Pelletier and Caventou. This isolation provided the first convincing evidence that complex nitrogenous bases can be elaborated in the vegetable kingdom. The structure of strychnine remained unknown for more than one hundred years, until the publication of the colossal work of Sir Robinson, who wrote 250 papers on the subject. At the same time, Leuchs and collaborators published more than 100 papers reporting their structural investigations of strychnine. These studies, completed before the time of NMR spectroscopy, surely represent the apogee of organic chemistry as a tool
to elucidate chemical structures. In 1954, Woodward reported his landmark total synthesis of "the tangled skein of atoms" which constitutes strychnine. This small assembly of atoms contains seven rings, and six contiguous chiral centers. It is remarkable—and a testimony to the complexity of its structure—that in the forty years since that feat, only one other (relay) synthesis of strychnine has been reported, despite numerous efforts.

The Strychnos alkaloids exhibit powerful biological activities. Akuammicine (122) shows antitumor activity in vitro (Figure 1). C-toxiferine I (125), a dimeric alkaloid arising from the condensation of two molecules of Wieland-Gumlich aldehyde methachloride, induces muscular relaxation. Toxiferine-I has been found to be important in the treatment of tetanus, and in surgery requiring light anesthesia. In recent years, there has been a resurgence of interest in the biological properties of strychnine. Strychnine, which is well absorbed by mouth, is a powerful CNS stimulant, exerting its effect primarily as a potent antagonist of the hyperpolarizing effect of glycine on spinal neurons. Small doses of strychnine sulfate (2 mg) were prescribed, at one time, as respiratory stimulant. Higher doses produce tonic convulsions leading to death. Strychnine shows also anticholinesterase action in vitro, but this property is not believed to be the basis of its action in vivo. In modern medicine, Strychnine has become obsolete, because of its toxicity. The fatal dose for human is approximately 60 to 90 mg, although death has been reported with doses as small as 15 mg. Nowadays, some of strychnine's actions are duplicated by less potent drugs such as morphine, thebaine, codeine, or brucine.

Synthetic Studies

The early works on the chemistry of Strychnos alkaloids has been reviewed by Smith. More recent reviews have summarized later accomplishments in the field. This section reviews several representative strategies for the synthesis of strychnine, and this general class of alkaloids.
To illustrate the nature of the problems that synthetic chemists are facing with the *Strychnos* family, I would like to start by analyzing the architecture of strychnine. Although a relatively small assembly of atoms (25 atoms), strychnine possesses an intricate architecture (Figure 1). It contains seven intertwined rings, among which are several different heterocycles. At the center of the molecule, in ring C, are five contiguous chiral centers. In addition, ring C is connected to ring E through a [3,3,1] bridged-bicycle arrangement, arguably the most challenging structural feature of the *Strychnos* alkaloids. Another distinguishing structural feature is the \( \text{C}_{19} - \text{C}_{20} \) double bond exocyclic to ring E, which has an \( E \) geometry. The geometry of this alkene has been proven to be difficult to control in synthesis. Indeed, Woodward as well as Magnus introduced this component by low yielding and non-stereoselective processes (vide infra). Since Robinson\(^{131a}\) has converted 124 into strychnine by treatment with \( \text{CH}_2(\text{CO}_2\text{H})_2, \text{NaOAc} \) and \( \text{Ac}_2\text{O} \) (equation 48), the construction of rings F and G does not represent a synthetic challenge. Most of the synthetic efforts have therefore been directed toward the elaboration of the ABCDE ring system, which is present in all the members of the *Strychnos* family. In this survey of the literature, emphasis will be given on the elaboration of this pentacyclic unit.

![Structural diagram for strychnine](image)

**1- Woodward's Synthesis of Strychnine**

The first and for a long time only total synthesis of strychnine was reported by Woodward and collaborators.\(^{126}\) After confirmation of Robinson's structure by two separate X-ray crystallographic investigations, Woodward decided to undertake a total synthesis of the molecule which was considered, at that time, as "the most complex substance known". Woodward's
achievement remains today a major victory of organic synthesis. His starting material, 2-veratrylindole (131) (available in one step from phenylhydrazine and acetoveratrone), was converted to the spirocyclic muconic ester 132 in 9 steps (Scheme 1). A Mannich procedure was used to elaborate the tryptamine derivative of 131, which was converted to a Schiff base by condensation with ethyl glyoxalate. A novel iminium ion induced cyclization, constructing the pyrrolidine ring, was promoted by the action of tosyl chloride. Finally, ozonolysis of the dimethoxy benzene provided the muconic ester 132 in a selective transformation, albeit in modest yield (29%). The dimethoxy phenyl substituent in 131 served two purposes. First, it blocked the α position of the indole nucleus toward electrophilic substitution. Elaboration of the spiro-fused pyrrolidine unit required disubstitution on the β site. Secondly, the veratryl group was selectively ozonolyzed to give the unsaturated diester 132, a good precursor for ring G of strychnine.

Upon acidic treatment (HCl, MeOH), 132 was converted to a six-membered lactam, which isomerized to the aromatic tautomer 133. The formation of an alternative five-membered lactam would have necessitated the cyclization of the trans ester in 132. Vigorous hydrolysis of the sulfonamide (H, red P), followed by acetylation (Ac₂O, Py) led to a diester which possessed a doubly activated methylene, suitable for Dieckman condensation (MeONa, MeOH). The conversion of 132 to the pentacyclic keto-ester 134 was thus accomplished efficiently in only four steps.

Generation of the benzyl thioether (TsCl in pyridine, then PhSNa in methanol), followed by reduction (RaNi, then H₂/Pd/C) and hydrolysis (aqueous KOH in methanol) yielded the trans acid 135. With the preparation of 135, the authors had reached their first relay point. Indeed, trans acid 135 was prepared on large scales from strychnine, by chemical degradation. When this acid was treated with acetic anhydride in pyridine, it was converted to an enol acetate which, after hydrolysis to the ketone and oxidation by selenium dioxide, provided the hexacycle 136 (second relay point). This sequence of transformations installed the bridged cycle E in a very elegant way.
The synthesis was carried on by addition of sodium acetylide, hydrogenation over Lindlar catalyst, reduction with LiAlH₄, and acid promoted isomerization (HBr, AcOH) of the tertiary alcohol 137. Unfortunately, the geometry of the exo-cyclic olefin in 138 could not be controlled. When the hydrochloride salt of carbinol 137 was heated to 120 °C, in a sealed tube, with 30% HBr, a complex mixture of tertiary amines was obtained. Careful purification by chromatography on neutral alumina, followed by recrystallization from methanol afforded isostrychnine (138) in 12% yield. The side products were not fully characterized. Finally, isostrychnine was converted to strychnine by treatment with ethanolic KOH. Woodward's exceptional synthesis required 29 steps with two relay points, and proceeded in about 10⁻⁵% yield. Each ring of strychnine (beside the indole nucleus) was constructed successively, using transformations that illustrate the best in the art of organic synthesis.

Scheme 11: Woodward's Synthesis of Strychnine

![Scheme 11: Woodward's Synthesis of Strychnine](image_url)

- **a)** HCHO, Me₂NH, AcOH, dioxane; then Me; **b)** NaCN, DMF; **c)** LiAlH₄, THF; **d)** ethyl glyoxylate, PhH; **e)** TsCl, Py; **f)** NaBH₄, EtOH
- **g)** Ac₂O, Py; **h)** O₂, AcOH; **i)** HCl, MeOH; **j)** HCl, MeOH; then Ac₂O; **k)** MeONa, MeOH; **l)** TsCl, Py; **m)** Ph₃PA, MeOH
- **n)** RanH, EIOH; then H₂, Pd/C; **o)** KOH, MeOH; **p)** Ac₂O, Py; then HCl, H₂O; **q)** SeO₂, EtOH; **r)** NaCCH, THF; **s)** NaCNH, THF; **t)** H₂, Pd/C, quinoline; **u)** LiAlH₄, Et₂O; **v)** HBr, AcOH; **w)** KOH, EIOH.
2. Magnus' Synthesis of Strychnine

In 1992, Magnus reported the second total synthesis of strychnine (Scheme 1). His starting point, amine 139, is obtained by condensation of tryptamine with 5-chloro-4-ketomethyl pentanoate. In the first step, 139 is treated with α,α,α-trichloroethyl chloroformate to give a ring-expanded compound, carbamate 140. A ten-step standard procedure converts carbamate 140 to tetracyclic lactam 141, which yields strychnan 142, upon treatment with Hg(OAc)$_2$ in acetic acid. This biomimetic cyclization is surprisingly selective. Oxidation of the tertiary amine in 141 could possibly give rise to three iminium cations. Fortunately, the desired cation appears to be the least strained of the three; it is endocyclic to both the six and the nine membered ring. Formation of the iminium cation leading to strychnan 142 is thus favored. In addition, this cyclization is stereospecific with regard to the C-D ring junction (thermodynamic product).

Scheme 12: Magnus' Synthesis of Strychnine

![Scheme 12](image)

---

a) TrocClCH$_2$Cl; b) NaOMe/MeOH; c) ClCO$_2$Me, NaOH, PTC, CH$_2$Cl$_2$; d) Zn, THF, AcOH; e) PhSCH$_2$CO$_2$H, BOPCI, Et$_3$N; f) MCPBA, CH$_2$Cl$_2$; g) NaH, THF; h) TFAA, DBMP; i) HgO, THF; j) BrCH$_2$CH$_2$OH, DBU, toluene; k) BH$_3$THF; l) Na$_2$CO$_3$, MeOH; m) Hg(OAc)$_2$, AcOH; n) Zn, H$_2$SO$_4$, MeOH; o) NaOMe, MeOH; p) TsCl, ENIP$_2$, CH$_2$Cl$_2$; q) LiBH$_4$, THF, H$_2$(CH$_2$CH$_2$OH)$_2$; r) HClO$_4$; s) (EtO)$_2$P(O)CH$_2$CN, KHMD$_5$, THF; t) Dibal, CH$_2$Cl$_2$; then NaBH$_4$, MeOH; u) HCl, MeOH; v) TBDMSOTf, DBU, CH$_2$Cl$_2$; w) SO$_3$PY, DMSO, Et$_3$N; x) HF, Py; y) Na, anthracenoid, DMF; z) CH$_2$(CO$_2$)$_2$Na, NaOAc, Ac$_2$O.
Six subsequent chemical manipulations provide the cyclic ketone 143, set up for the step intended to introduce the key exocyclic olefin. When ketone 143 is treated with \((\text{EtO})_2\text{POCH}_2\text{CN}\) and base, the wittig adduct 144 is obtained in good yield (72%), but low selectivity (3:2 mixture of \(E,Z\) isomers). This step can be considered as the main drawback in Magnus' otherwise elegant strategy. Separation of the stereoisomers, followed by reduction of the nitrile (DIBAL-H, NaBH\(_4\)), and deprotection (H\(_3\)O\(^+\)), yields diol 145, which can be converted to strychnine in 6 steps via the Wieland Gumlich aldehyde (146). This synthesis involves 29 steps and proceeds in about \(10^{-4}\) % overall yield. Magnus' approach to strychnine does not address the critical issue of the selective introduction of the exocyclic double bond.

### 3- Synthetic Approaches Based on the Biomimetic Cyclization of a Stemmadenine Intermediate

In scheme 10, is described the biochemical pathway by which the alkaloids of the *Strychnos* family are synthesized in the plant kingdom. As mentioned earlier, in vitro experiments have, so far, failed to imitate this pathway. Yet, Magnus\(^\text{127}\) and others\(^\text{132-134}\) are describing their approaches as biomimetic syntheses. They are referring to an alternative biochemical pathway, which allows the conversion of *stemmadenine* alkaloids to *Strychnos* (Scheme 13).

The stemmadenine (151) group of alkaloids are distinguished from the *Strychnos* group by the absence of the C\(_7\)-C\(_3\) bond\(^\text{123}\). Biochemical transformation of medium-sized ring 148 to akuammicine (122), or condylocarpine (147), occurs by enzymatic oxidation, via iminium compounds 150, or 149.

#### Scheme 13: Biochemical Conversion *Stemmadenine*–*Strychnos*

![Diagram showing biochemical conversion of stemmadenine to strychnine](attachment:image.png)
Magnus' synthesis of strychnine evidently includes a biomimetic step, the transannular cyclization of amine 141 to pentacyle 142 (vide supra). This transannular ring formation was used earlier by other groups.132-134

Harley-Masson, first, investigated this chemistry and developed a general strategy toward the pentacyclic Strychnos alkaloids (Scheme 14).132 His total syntheses of dehydrotubifoline and condyfoline are summarized here. Lithium aluminum hydride reduction of lactam 152, obtained from the condensation of tryptamine and α-ketoglutaric acid, afforded the rearranged base 153. A ring expansion induced by 2,2'-dichlorobutyric anhydride yielded the versatile nine membered ring 154. Selective hydrolysis of the ester (cold NaOH), followed by oxidation (MnO₂), afforded the corresponding ketone, which was treated with sodium t-amylxide in benzene to give, after Wolff-Kichner reduction, lactam 155 as a single isomer (thermodynamic control). A mixture of tubifoline (156) and condyfoline (157) was then generated by aerial oxidation over platinum oxide.

Scheme 14: Harley-Mason’s Syntheses of Tubifoline and Condyfoline
Both Ban\textsuperscript{133} and Takano\textsuperscript{134} have developed their own methodology to elaborate the nine-membered ring. Ban took advantage of a novel photoisomerization of 1-acylindoles. When a solution of amide 158 in methanol was irradiated for a day, lactam 159, a possible precursor in the synthesis of stemmadenine, was obtained in good yield. The mechanism of this unusual transformation is depicted in scheme 15. Keto-indolenine 158a, the first intermediate, arises through the anticipated 1,3 carbonyl shift. In a second step, intramolecular addition of the primary amine to the ketone affords mixed-hemiketal 158b, which collapses by retro-aldol condensation to give product 159. The regeneration of the indole nucleus drives this isomerization reaction toward product formation.

**Scheme 15: Ban's Approach to Stemmadenine**

Takano’s biomimetic approach\textsuperscript{134} to dehydrotubifoline (123) illustrates two key transformations: a reductive ring cleavage that constructs the nine-membered heterocycle 165, and a thioclaisen rearrangement that selectively introduces the 19-20(\textit{E}) exocyclic double bond (Scheme 16). The synthesis begins with thiolactam 160 which reacts with methyl-$$\gamma$$-bromocrotonate to give iminium salt 161. Sodium methoxide promotes transformation to the thioaminoketene, and subsequent [3,3] sigmatropic shift, affords the (\textit{E}) $$\alpha$$,\(\beta\)-unsaturated ester 162 in good yield. Bischler-Napieralski cyclization yields a quaternary iminium salt which is reduced to amine 163 with NaBH\textsubscript{4}. Ammonium salt 164 is obtained by intramolecular displacement of an allylic tosylate. The key ring cleavage (164$$\rightarrow$$165) is then achieved using sodium metal in liquid ammonia. Oxidation of 165 with mCPBA yields an N-oxide which, when

\[38\]

\[158\]

\[159\]
submitted to the Polonovsky-Potier reaction, furnishes dehydrotubifoline in a selective manner. The formation of the alternative isomer 166 is not observed.

**Scheme 16: Takano's Synthesis of Dehydrotubifoline**

5. Kim's Approach to Strychnine

Kim's synthetic approach\(^{135}\) involves a series of inter- and intramolecular conjugate additions (Scheme 17). The stereoselective construction of the tricyclic ester 172 started from N-phenacyl amide (167). Robinson annulation directly afforded the cyclohexenone 168 which, after amide hydrolysis and carboethoxycetylation under Schotten-Baumann condition provided enone 169. The intramolecular Michael adduct was generated upon treatment with NaH in refluxing THF, and converted to the lactam 170 by saponification and decarboxylation. Reduction of the amide, alkylation with propargyl bromide, carbomethoxylation and deprotection gave the keto ester 171, ready to undergo another intramolecular Michael addition. When conjugated alkyne 171 was treated with Triton B in DME at -20°C, tricycle 172 was isolated.
None of the desired exo-cyclic olefin isomer was produced, because complete isomerization of the double bond occurred after ring closure.

Scheme 17: Kim's Approach to Strychnine

6- Vollhardt's Approach to Strychnine

A cobalt mediated [2+2+2] cycloaddition is the basis for Vollhardt's strategy\textsuperscript{136} (Scheme 18). The reaction of the substituted tryptamine 173 with trimethylsilyl-methoxyacetylene in the presence of cyclopentadienylcobalt dicarbonyl efficiently generated the tetracycle 174. This tetracycle was cleanly converted to the propellane derivative 175 upon treatment with ferricinium ion (Cp\textsubscript{2}Fe\textsuperscript{4+}PF\textsubscript{6}). Upon investigating conditions for the décomplexation of propellane diene 175, Vollhardt and co-workers made a striking discovery. The standard oxidative demetalation [CuCl\textsubscript{2}, Et\textsubscript{3}N, DME-H\textsubscript{2}O] of 175 provided, not only the expected "ligand-free diene" 176 (4% yield), but also the pentacycle 177 (82% yield), an advanced intermediate toward strychnine. CuCl\textsubscript{2} also promoted direct conversion of 174 to 177, but in an unspecified yield.
Scheme 18: Vollhardt's Approach to Strychnine

7- Overman's Total Synthesis of Dehydrotubifoline

Overman and co-workers\textsuperscript{137} accomplished a total synthesis of dehydrotubifoline\textsuperscript{137a} (123), a potential intermediate in the synthesis of other members of the Strychnos family. The strychnan skeleton was constructed by an "aza-Cope-Mannich" rearrangement of the 2-azabicyclo[3.2.1]octane 179 (Scheme 19). The required piperidine moiety was introduced by aminolysis of chloro-epoxide 178, obtained from 2-cyclopentenone in nine steps. Although direct aminolysis of 178 with ammonia was not clean, the sodium salt of trifluoroacetamide efficiently displaced the allylic chloride and ring-opened the epoxide, in one step, to provide piperidine 179 in fair yield. The cis stereochemical relationship, between the styrene substituent and the amine, resulted from trans opening of the epoxide. This stereochemistry was required in order to put the styrene double bond and the nitrogen atom in close proximity. The key rearrangement, whose mechanism is depicted in scheme 19, was triggered by condensation with formaldehyde. Hydrolysis of amide 180, then, provided dehydrotubifoline in 70% yield. The synthesis of dehydrotubifoline was accomplished in 12 steps from 2-cyclopentenone with a 6% overall yield.
8- Kraus' Approach to Strychnine

The original approach of Kraus\(^{138}\) relies upon an intramolecular Diels-Alder reaction of 3-alkenylindole 182. His analysis is illustrated in scheme 20. The tetracyclic silyl enol ether 181 underwent a Lewis acid promoted alkylation, followed by ozonolysis of the terminal alkene, to afford keto aldehyde 183, which served as a key intermediate for subsequent elaboration. The sequence that converted 183 to 184 features a Sakurai reaction. Keto iodide 184 was condensed with ammonia to afford a cyclic imine, which was reduced to a pyrrolidine unit with sodium cyanoborohydride. Conversion to the \textit{Strychnos} skeleton (186) was then achieved by ozonolysis of the double bond, followed by intramolecular condensation of the aldehyde with the pyrrolidine nitrogen. Hexacycle 186 contains functional groups that may allow Kraus and co-workers to complete a total synthesis of strychnine. Implementation of the last ring will require further manipulation of the enamine double bond. It is worth noting that structural constraints in molecule 186 prevent a good overlap between the amine lone pair and the carbon-carbon double bond (not a true enamine). The construction of ring F of strychnine may not be therefore easily achieved by taking advantage of enamine chemistry.
Scheme 20: Kraus' Approach to Strychnine

9- Bosch's Syntheses of tubifolidine

During the last ten years, Bosch and al. have intensively explored new strategies for the synthesis of pentacyclic *Strychnos* alkaloids. A series of papers summarizes their accomplishment in this field.\(^{139}\) They have reported two total syntheses of tubifolidine (194).\(^{139a,b}\) Their first strategy is based upon the introduction of the pyrrolidine moiety at the end of the synthesis.\(^{139b}\) I have chosen, here, to present their second approach,\(^{139a}\) which differs significantly from the first one. The crucial step of this synthesis involves the closure of the piperidine ring by an intramolecular Michael addition (Scheme 21). Bosch's starting material, \(\beta\)-diketone 187 (available in one step from 1,3-cyclohexadiene and o-fluoro-nitrobenzene), is treated with allyl bromide, to afford an allyl vinyl ether which undergoes a claisen rearrangement, followed by ozonolysis of the double bond, to yield dicarbonyl compound 188. Double reductive amination of 188 (MeNH\(_2\)Cl, MeOH, then NaBH\(_3\)CN) provides octahydro-indolone 189 as a single stereoisomer. Conversion to the chloroethyl carbamate, followed by selenium promoted oxidation, gives enone 190 in 50% yield. At this stage, the author decided to introduce the piperidine ring. Standard deprotection of the pyrrolidine nitrogen, and
condensation with vinyl methyl ketone efficiently generate diketone 191, the anticipated precursor for the Michael addition. The base catalyzed cyclization is promoted by (R)-α-methylbenzylamine and molecular sieves. The tricycle 192 is isolated as a 4:1 mixture of the natural isomer (shown in scheme 21), and its epimer at the newly constructed chiral center. In order to complete their synthesis, the author needed to selectively reduce the exo-cyclic carbonyl. At ambient temperature, only one ketone reacts with ethanedithiol to give 193, which is directly reduced to tubifolidine (194) upon treatment with tributyltin hydride. This elegant step involves simultaneous desulfurization of the thioketal, reduction of the aryl nitro compound, and indoline ring closure.

Scheme 21: Bosch's Second Synthesis of Tubifolidine

187 \[\xrightarrow{\text{a-c}}\] 188 \[\xrightarrow{\text{d}}\] 189 \[\xrightarrow{\text{e-i}}\] 190 \[\xrightarrow{\text{k}}\] 191 \[\xrightarrow{\text{j}}\] 192 \[\xrightarrow{\text{l}}\] 193 \[\xrightarrow{\text{m}}\] 194: tubifolidine

a) BrCH₂CH₂=CH₂, K₂CO₃, acetone; b) toluene, 180°C; c) O₃, CH₂Cl₂; d) MeNH₂Cl, NaBH₃CN, MeOH;

193 \[\text{reduction with tributyltin hydride}\]

194: tubifolidine

187 \[\xrightarrow{\text{a-c}}\] 188 \[\xrightarrow{\text{d}}\] 189 \[\xrightarrow{\text{e-i}}\] 190 \[\xrightarrow{\text{k}}\] 191 \[\xrightarrow{\text{j}}\] 192 \[\xrightarrow{\text{l}}\] 193 \[\xrightarrow{\text{m}}\] 194: tubifolidine

a) BrCH₂CH₂=CH₂, K₂CO₃, acetone; b) toluene, 180°C; c) O₃, CH₂Cl₂; d) MeNH₂Cl, NaBH₃CN, MeOH;

e) CICO₂CH₂Cl, CH₂Cl₂; f) TMSI, HMDS, CH₂Cl₂; g) PhSeCl, (PhSe)₂, THF; h) O₃, iPr₂NH, CH₂Cl₂; i) MeOH, reflux; j) MVK, Et₃N, MeOH; k) (R)-α-methylbenzylamine, 3-Å MS, THF; l) (HSCCH₃)₂, AcOH; m) nBu₂SnH, AlBN, PhH.
9- Syntheses of Tubotaiwine and 19-hydroxytubotaiwine

Tubotaiwine (195), as well as condylocarpine (structure 147 in scheme 13), belongs to a second type of Strychnos alkaloids. In the strychnan type (strychnine), a two-carbon side chain is connected to C\textsubscript{20}, whereas in the condylocarpine type, it is connected to C\textsubscript{14}. The two types are, however, closely related, because they embody the same pentacyclic framework. To complete this survey of the literature, I would like to discuss two syntheses of condylocarpine like structures: kuehne's synthesis of Tubotaiwine, and Vercauteren's synthesis of 19-hydroxytubotaiwine.

Scheme 22: Kuehne's Synthesis of Tubotaiwine

Indoloazepine 196 (Scheme 22), the starting point of Kuehne's synthesis\textsuperscript{140} is condensed with acetaldehyde to afford amine 197 as one diastereoisomer. In the next step, the tetracyclic amine 199 is obtained through a novel intramolecular cycloaddition. Triene 198, generated in situ from 197 (PhCH\textsubscript{2}Br, Et\textsubscript{3}N), cyclizes spontaneously and stereospecifically at
room temperature to afford tetracycle 199. Then, reductive cleavage of the benzylic carbon-
carbon bond (sodium borohydride, acetic acid) cleanly provides nine-membered ring 200, which
is elaborated by familiar methods to the unsaturated ester 201. Condensation with
butyraldehyde gives 202, which spontaneously and stereospecifically isomerizes to 195 by
means of an inverse-electron-demand Diels–Alder reaction.

Scheme 23: Vercauteren’s Synthesis of 19-Hydroxytubotaiwine

Vercauteren and co-workers\textsuperscript{141} undertook the synthesis of 19-hydroxytubotaiwine\textsuperscript{141a}
(210), with the aim of establishing the stereochemistry of the naturally occurring isomer. Their
key step involved a “Kuehene type” intramolecular Diels–Alder cycloaddition of enamine 204,
generated in situ from ester 203 (Scheme 23). Deprotection of the ketone function (HgO/BF\textsubscript{3})
and reduction (NaBH\textsubscript{4}) afforded two diastereoisomeric alcohols (206), which were separated by
crystallization from ethanol. The structures of the two epimeric alcohols were determined by X-ray
crystallographic analysis. After deprotection of the pyrrolidine nitrogen (H₂, Pd/C), the pentacyclic lactam 207 was obtained by treatment with sodium methoxide in methanol. Conversion to the methyl ketone (MeLi), followed by selenium dioxide oxidation, led directly to the formation of the bridging ring (208). Excess Lawesson reagent afforded the bis-thiocarbonyl compound 209, which was desulfurized by Raney nickel to yield 19-hydroxytubotaiwine (210).

11. Conclusion

Having analyzed the synthetic efforts described above, one can recognize the complex and challenging features present in the Strychnos alkaloids:

a) a spiro-fused pyrrolidine moiety,
b) a 2-aza-bicyclo[3.3.1]nonane subunit,
c) an exocyclic double bond of defined geometry (E), and
d) a cyclohexyl ring, almost fully substituted, bearing 3 to 6 contiguous chiral centers.

The following chapters of this dissertation will expose our synthetic strategy toward the Strychnos alkaloids. Chapter III will report our retrosynthetic analysis of strychnine as well as preliminary studies. Chapter IV will describe our total synthesis of dehydrotubifoline, a pentacyclic Strychnos alkaloid, potential intermediate toward other strychnans.
Chapter III:  
Retrosynthetic Analysis and Model Studies

I Synthetic Strategy

In 1989, we initiated a research program directed toward the synthesis of strychnine. Despite numerous efforts (chapter II), the total synthesis of strychnine had been completed only twice in almost fifty years.\textsuperscript{126,127} Such a compact molecule represents a target of choice for those who wish to develop new routes to complex carbo- and heterocycles. The strategy that we are investigating differs significantly from those explored previously or under study. Our route has been designed with two goals: to complete the target in very few steps, and to control the stereocenters. The route described in our retrosynthetic analysis nicely supports these two goals.

This retrosynthetic analysis is depicted in Scheme 24 and shows, first, that the two bottom rings of strychnine do not represent a real problem. Ring F of strychnine should be obtained by an intramolecular Michael addition of the alcohol derivative 211. Indeed, it has already been established that the action of a base (KOH, EtOH) on isostrychnine (138) promotes the closure of the seven-membered cyclic ether, via intermediate 211 (Equation 49a).\textsuperscript{126b} This transformation generates stereospecifically the two asymmetric centers at C\textsubscript{16} and C\textsubscript{17}, as the other configurations would be impossibly strained. Thus, because C\textsubscript{16} in 211 is an epimerizable center, thermodynamic control will drive the formation of the natural stereoisomer (121).

\begin{center}
\textbf{Scheme 24}
\end{center}

\begin{center}
\textbf{Equation 49a} \textsuperscript{126b}
\end{center}
Scheme 24: Retrosynthetic Analysis of Strychnine

121: strychnine

route A

212

route B

211

214

213

215

216

217
The second disconnection \((C_{22} - C_{17})\) illustrates that ring \(G\) could be constructed by an intramolecular aldol condensation between the aldehyde and the acetamide moity. Robinson et al. have already realized that transformation.\(^{131a}\) They have demonstrated that epimerization of the aldehyde is not an issue, since only one epimer can afford the cyclic vinyl amide (Equation 49b).

\[
\begin{align*}
\text{CH}_2\text{OR} & \quad \text{CH}_2\text{OR} \\
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O}
\end{align*}
\]

\((\text{Eqn.} \ 49\text{b})^{131a}\)

Our efforts were thus directed toward the construction of the \text{ABCDE} ring system (212), which is common to all the members of the \text{strychnos} family. The first key disconnection is the cleavage of the axially oriented \(C_{20} - C_{15}\) bond to give the vinylic precursors 213 (route B) or 216 (route A). Various nucleophilic organometallic species can be considered to construct this bond. We examined the use of the Heck reaction to accomplish this bond formation, since this process has been employed with success in synthesis (see chapter I). The transformation can be described as a 6-exo-trig cyclization, a process which is allowed by Baldwin's rules.\(^{142a}\) This strategy addresses the delicate problem of the \(C_{19} - C_{20}\) double bond geometry, because the Heck cyclization is expected to take place with retention of the double bond configuration. Indeed, isomer \(E\) and \(Z\) should be obtainable, at will, by a Heck coupling process. One will need to prepare the corresponding vinyl halide isomer. It is an important issue, since a new type of \text{strychnos} alkaloids, possessing a \((Z)\) exocyclic olefin, was recently isolated from the leaves of \text{Rhaya stricta}.\(^{142b}\) In addition, the intramolecular Heck reaction will allow us to control the stereochemistry at \(C_{15}\).

Two routes to pentacycle 212 were envisioned (Scheme 24). Route A would involve the intramolecular Heck cyclization onto a simple bicyclic precursor (216). We felt that, in a subsequent step, an intramolecular Michael addition of the aniline nitrogen in 214 would allow us
to close the indoline ring. Route B involves the formation of the key C20–C15 bond from a tetracyclic precursor (213), in which the indole nucleus is already incorporated. Conveniently, both 213 and 216 could be obtained from the same starting material, β-aryl pyrrole 217, by Diels-Alder cycloadditions.

II Model Studies Directed Toward the Construction of Rings C and E

1- Nature of the Problem

In order to confirm the viability of our strategy, we carried out extensive model studies. The key step in our strategy involves the formation of the bridged bicyclic C-E ring system by an intramolecular Heck reaction, a process which has been used with much success in organic synthesis (chapter I). In the present case, the strategic carbon-carbon bond formation was expected to be facilitated by the axial orientation of N4 (see the three dimensional structure in Scheme 2.4). To test this hypothesis, we prepared model compound 218, which embodies the characteristic trans arrangement between the nitrogen side chain and the aryl substituent.

![Model Compound 218](image)

Although the formation of fused bicycles by Heck cyclization has been extensively studied (chapter I), the construction of bridged polycycles has not received much attention. Our first objective was thus to investigate the Heck cyclization capability of model compound 218. The Heck reaction of 218 can, in principal, proceed in two ways (Scheme 2.5). Coupling at the α carbon (endo process) should produce the desired bicycle, 224, while coupling at the β carbon (exo process) should afford the bicyclo[3.2.2]nonane isomer, 225. Inspection of molecular
models does not suggest any obvious preference for one path over the other. A further potential complication is also illustrated in Scheme 25. The palladium promoted cyclization involves the formation of an intramolecular chelate (223), a process which requires a conformational isomerization (diequatorial $\rightarrow$ diaxial) prior to carbon–carbon bond formation. In systems where coordination of the olefinic partner is slow\(^4\) reduction of the $\sigma$-alkyl palladium complex is a competing side reaction. Therefore, the success of this approach depends on the relative rates of chelate formation (conformational interconversion) and of $\sigma$-palladium complex reduction.

**Scheme 25: Regiochemistry of the Coupling Process: Endo vs Exo**

We also examined the cyclization of several related vinyl halides (Figure 2). The stereoisomeric vinyl iodides 219 and 220 were prepared in order to investigate the stereochemical outcome of the reaction. We have also studied the effect of substitution on the endocyclic olefin (221), and the effect of an amino substituent in the ortho position of the phenyl ring (222), because this substitution pattern is required for strychnine synthesis.
2: Results and Discussion

The required vinyl bromide 218 was prepared as outlined in Scheme 2.6. Diels-Alder cycloaddition of β-nitrostyrene (226) with 1,3-butadiene (toluene, 140°C) afforded the trans-nitro cyclohexene 227.\textsuperscript{142c} We considered several conditions for the reduction of the aliphatic nitro group,\textsuperscript{143} and found that this transformation could be effected under mild conditions using aluminum amalgam in THF/H\textsubscript{2}O.\textsuperscript{143e} Under these conditions, the carbon-carbon double bond was not reduced. The reaction was very reproducible and was not sensitive to the exact details of the preparation of the amalgam. In a typical experiment, Al(Hg) was prepared by successive treatment of aluminum foil with aqueous potassium hydroxide, 0.5% aqueous HgCl\textsubscript{2}, water and THF, and was added fresh to a THF/H\textsubscript{2}O solution of nitro cyclohexene 227. The reduction took place cleanly, and the polar primary amine 228 was obtained chromatographically homogeneous, simply after filtration and concentration. Primary amine 228 was converted directly to the sulfonamide 229, upon treatment with TsCl, triethylamine and a catalytic amount of the acylating catalyst DMAP. Attempted alkylation with 2,3-dibromopropene using standard conditions (NaH or KH, THF) met failure (low yields). On the other hand, the desired alkylation was efficiently achieved by phase transfer catalysis.\textsuperscript{144} When a benzene solution of sulfonamide 229 was treated with 50% sodium hydroxide, 2,3-dibromopropene, and tetrabutylammonium bisulfate, vinyl bromide 218 was obtained in 92% yield.
With 218 in hand, we were ready to test our first intramolecular Heck coupling reaction. The traditional Heck reaction calls for the use of a Pd(II) species [Pd(OAc)_2], PdCl_2(RCN)_2 or PdCl_2(PPh_3)_2, a triarylphosphine (or phosphite) and a tertiary amine base. The active Pd(0) catalyst is generated in situ; the detailed mechanism of the initial reduction of Pd(II) to Pd(0) has not been established. Although a number of pathways are conceivable, one possibility for generating the Pd(0) is depicted in Equation 50. It involves a 1,2-addition of palladium diacetate onto the vinyl halide double bond, followed by β-elimination of HPd(OAc). Other possibilities include oxidation of the base and/or the ligand. Recently, some evidence suggests that formation of zerovalent palladium from a mixture of Pd(OAc)_2 and triphenylphosphine takes place with concomitant generation of triphenylphosphine oxide (Scheme 27).
Scheme 27: Reduction of Pd(OAc)$_2$ by PPh$_3$

\[
Pd(OAc)_2 \xrightarrow{2 \text{ PPh}_3, \text{fast}} Ph_3P\xrightarrow{\text{slow}} Pd(0)
\]

\[
Ph_3P^+\xrightarrow{AcO^-} \xrightarrow{\text{slow}} Ph_3+\xrightarrow{AcO^-} Ph_3P
\]

In the actual cyclization, treatment of vinyl bromide 218 with 15 mol% of palladium diacetate, 45 mol% of triphenylphosphine, and two equivalents of triethylamine, in acetonitrile at reflux for 3 h, afforded a single bicycle in 85% yield (Scheme 28). The structure of the cyclization product was determined to be the 2-aza-bicyclo[3.3.1]nonane 230 through extensive spectroscopic studies. In particular, $^1$H NMR decoupling experiments (Figure 3) confirmed the structure: the methyne proton positioned $\alpha$ to the sulfonamide (H$_4$), which resonates at 4.10 ppm, was shown to be coupled to protons at 1.40 and 1.70 ppm, and not to an ethylenic proton. This observation ruled out structure 231. Other correlations also were consistent with our assignment (Figure 3). In addition, it should be noted that the Heck cyclization proceeded to afford bicycle 230, and none of the isomeric product where the double bond had moved into conjugation with the aromatic ring.

Scheme 28: Heck Cyclization of Vinyl Bromide 218
Having demonstrated that the Heck cyclization was proceeding with the desired regiochemistry, we next investigated the stereochemical outcome of this transformation. We prepared the two stereoisomeric vinyl iodides 219 and 220 by phase transfer alkylation of sulfonamide 229 (Scheme 29). The necessary alkylation agents, tosylates 238 and 239 were generated under standard conditions from the corresponding alcohols and were used without purification.

**Scheme 29: Syntheses of Vinyl Iodides 219 and 220**

<table>
<thead>
<tr>
<th>proton</th>
<th>( \delta ) (ppm)</th>
<th>coupled to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>( H_1 + H_2 )</td>
<td>1.40 + 1.77</td>
<td>( H_3 ) and ( H_4 )</td>
</tr>
<tr>
<td>( H_3 )</td>
<td>2.96</td>
<td>( H_7 ), ( H_1 ) and ( H_2 )</td>
</tr>
<tr>
<td>( H_4 )</td>
<td>4.10</td>
<td>( H_6 ), ( H_1 ) and ( H_2 )</td>
</tr>
<tr>
<td>( H_5 )</td>
<td>3.61</td>
<td>( H_4 ) and ( H_6 )</td>
</tr>
<tr>
<td>( H_6 )</td>
<td>5.88</td>
<td>( H_7 ) and ( H_5 )</td>
</tr>
<tr>
<td>( H_7 )</td>
<td>5.98</td>
<td>( H_6 ) and ( H_3 )</td>
</tr>
</tbody>
</table>

**Figure 3: 6-Exo versus 7-Endo Cyclization**
The known alcohols 234 and 237 were prepared by hydrostannylation of 2-butyn-1-ol as depicted in Scheme 30. Radical promoted anti-addition of tributyltinhydride to the carbon-carbon triple bond afforded the vinyltin compound 233, which was not isolated but converted to the vinyl iodide 234, by treatment with iodine in carbon tetrachloride. The addition of the tin is presumably directed by the hydroxyl group. Only one isomer was obtained provided that an excess of the starting alcohol was used. The cis-hydrostannylation of 2-butyn-1-ol could be achieved under mild conditions with a palladium zero catalyst, Pd(PPh3)4. Under these conditions the directing effect of the hydroxyl group was modest: a 5 to 1 mixture of regioisomers 235 and 236 was obtained. The isomers were easily separated by flash chromatography on silica gel. Cleavage of the tin carbon bond and formation of the desired vinyl iodide 237 occurred upon treatment of the major isomer with I2 in carbon tetrachloride.

Scheme 30: Preparation of Vinyl Iodides 234 and 237

The Heck cyclizations of vinyl iodides 219 and 220 (Scheme 31) were significantly more rapid than that of vinyl bromide 218. The reactions were over in less than an hour and did proceed stereospecifically. That the reactions had occurred with retention of configuration was confirmed through nOe studies. This technique was ideally suited for this problem, since we...
had obtained both stereoisomers of the bridged bicycle. Significant nOe's (13% and 18%) were recorded between the bridge-head hydrogen $H_3$ and the ethylenic quartet in isomer 241 (Figure 4). In isomer 240, on the other hand, a large nOe was detected between $H_3$ and the allylic methyl. The observed nOes were in total agreement with the assigned stereochemistry, and established with certainty the stereochemical profile of our intramolecular Heck reaction.

Scheme 31: Heck Cyclization of Vinyl Iodides 219 and 220

![Scheme 31: Heck Cyclization of Vinyl Iodides 219 and 220](image)

Figure 4: NOE Experiments on Bicycles 240 and 241

We then examined the cyclization of a system with substituents on both the endocyclic olefin and the side chain alkene, to better model the *strychnos* skeleton. The necessary precursor 245 was prepared by two alternative sequences. Our first pathway (Scheme 32)
involves a Diels-Alder cycloaddition of cinnamoyl chloride with isoprene (toluene, 190°C). The Diels-Alder adduct was not isolated, but treated, in the same pot, with an aqueous solution of sodium azide and tetrabutylammonium bisulfate, to yield two isomeric acyl azides. After extraction with toluene, the crude azides were directly submitted to a Curtius rearrangement to afford isomeric carbamates 243 and 244 in 80% overall yield. This high yielding sequence of three steps in one pot provided a 3:1 mixture of 244 and 243, indicating the Diels-Alder cycloaddition had proceeded with only modest selectivity. Fortunately, one crystallization from ether/hexane afforded pure 244 as a white crystalline solid. The Curtius rearrangement, a versatile method to convert carboxylic acids to derivatives of amines, preserves the stereochemical integrity of the migrating carbon. The trans relationship of the phenyl group and the nitrogen substituent in 245 was thus secured. Base-promoted hydrolysis of carbamate 244 (NaOH, EtOH) afforded a primary amine which was converted to the sulfonamide 245 by action of TsCl, triethylamine and DMAP in dichloromethane.

Scheme 32: Preparation of 245, First Route

Another option for the preparation of 245 is outlined in Scheme 33. Initially we carried out the thermal Diels-Alder reaction between β-nitrostyrene and isoprene, and obtained an unseparable mixture (3:1) of regioisomers. We found, however, that the selectivity can be enhanced significantly using the highly polar LiClO₄–Et₂O medium that Grieco and
others have investigated. Indeed, the ratio of isomers was increased up to 25, when the Diels-Alder reaction was performed at 70°C, in an ether solution saturated with LiClO₄. Reduction of the nitro group with aluminum amalgam, followed by sulfonamide formation, provided 245 in excellent yield.

**Scheme 33: Preparation of 245, Second Route**

![Chemical diagram](image)

Alkylation of sulfonamide 245 with iodo tosylate 238, under phase-transfer conditions, afforded vinyl iodide 247, precursor to the Heck reaction. Cyclization of 247 (Scheme 34) should proceed via the σ-alkyl palladium complex 248, which could collapse by β-elimination to generate either endocyclic olefin 249, or exocyclic olefin 250.

**Scheme 34: Regiochemistry of the β-Elimination Step**

![Chemical diagram](image)
Cyclization of compound 247, under the standard conditions [Pd(OAc)$_2$, El$_3$N, PPh$_3$ in acetonitrile] gave cleanly the endocyclic olefin 249 (90% yield). On the other hand, cyclization under Jeffery's conditions $^{35}$ [Pd(OAc)$_2$, K$_2$CO$_3$, nBu$_4$NCl, in DMF] afforded a 2:1 mixture of 249 and 250. It is possible that the first set of conditions are promoting isomerization to the more stable olefin (249). This experiment confirmed that the Heck cyclization was not prevented by the presence of substituents on the cyclohexene double bond, in spite of the development of non-bonding interactions between the two methyl groups.

This set of model studies demonstrated that the C-E ring system of the strychnos alkaloids could be conveniently assembled by a Heck cyclization. The difficult problem of controlling the geometry of the exocyclic double bond was specifically addressed. We then turned our attention to the preparation of more advanced intermediates toward strychnine. Part III of this chapter will deal with our initial studies directed toward the elaboration of the indoline unit (ring B) of the strychnos alkaloids.

III. Model Studies Directed Toward the Introduction of the Indoline Nucleus

Having investigated the scope of the Heck cyclization, we next directed our efforts on the preparation of systems in which an ortho-amino substituent on the phenyl ring will give us the opportunity to assemble the indoline unit. As depicted in Equation 51, we planned to close the indoline ring, after formation of the C-E bicyclic array, by a process involving an intramolecular amination of an alkene.

(Eqn. 51)
Since this proposed ring closure necessitated a nucleophilic addition of the aniline moiety onto the endocyclic olefin, activation of the olefin by an electrophile was required. Common electrophiles such as bromonium or iodonium cations were not suitable, because they were expected to react with the electron rich aromatic ring. On the other hand, more selective electrophiles, such as Pd(II) salts, appeared to offer a good solution. Indeed, Wacker like processes have been used with success in the synthesis of heterocycles from alkenyl precursors.

Hegedus has reported several examples of palladium (II) assisted amination of olefins. In particular, he has shown that o-allylanilines can be converted to 2-methyl-indoles by treatment with stoichiometric or catalytic amount of Pd(II). The course of this reaction is outlined in Scheme 35. The Initial step involves the formation of chelate 252 by complexation of both the aniline nitrogen and the double bond. At this stage, the amine is coordinated to the palladium, and it cannot attack the olefin. Addition of triethylamine induces the displacement of the weakly basic aniline nitrogen (253), which can then achieve the trans stereochemistry needed for amination of the olefin (254). Finally, elimination of HCl and HPdCl provides the metal-free intermediate 255, which quickly rearranges to the aromatic indole (256) by hydrogen shift, a process that may be catalyzed by the palladium.

Scheme 35: Palladium Assisted Synthesis of 2-Methyl-Indole
Our first objective was to investigate the palladium assisted amination procedure for model compound 257 (Scheme 36), in which R is a two-carbon side chain, possible precursor of the pyrrolidine ring.

Scheme 36: Model Studies–Construction of the Indole Nucleus

![Reaction Scheme]

The tertiary amine 258, our projected precursor for 257, was prepared as described in Scheme 37. Commercially available ortho-nitro cinnamic acid was converted to its acyl chloride by action of thionyl chloride in benzene at reflux. The crude acyl chloride underwent a Diels-Alder reaction with 1,3-butadiene (toluene, 140°C, 18 h) to afford a cyclohexyl acyl chloride, which was directly converted to the corresponding acyl azide, by action of an aqueous solution of sodium azide and tetrabutylammonium bisulfate. This unstable azide was not purified, but was treated with concentrated HCl in toluene at reflux to yield the cyclohexenyl amine 260, as its hydrochloride salt. This convenient one pot procedure provided, after basic work-up, amine 260 in 64% yield from ortho-nitro cinnamic acid. Michael addition of vinyl phenyl sulfone provided a two-carbon side chain in quantitative yield (261). Alkylation of the hindered secondary amine 261 with 2,3-dibromopropene proved to be surprisingly difficult: some representative examples of reaction conditions are given in Table 1. Alkylation could be achieved in very good yield with an excess of alkylation agent in DMF at 90°C.
Scheme 37: Synthesis of Aniline Derivative 258

Table 1: N-alkylation of 261 with 2,3-dibromopropene:

<table>
<thead>
<tr>
<th>base</th>
<th>solvent</th>
<th>additive</th>
<th>temp. (°C)</th>
<th>time (h)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IP6NET</td>
<td>MeCN</td>
<td>NaI</td>
<td>82</td>
<td>8</td>
<td>35(^a)</td>
</tr>
<tr>
<td>K(_2)CO(_3)</td>
<td>MeOH</td>
<td>NaI</td>
<td>64</td>
<td>8</td>
<td>31(^a)</td>
</tr>
<tr>
<td>K(_2)CO(_3)</td>
<td>benzene</td>
<td>NaI</td>
<td>80</td>
<td>7</td>
<td>30(^b)</td>
</tr>
<tr>
<td>K(_2)CO(_3)</td>
<td>toluene</td>
<td>NaI</td>
<td>110</td>
<td>20</td>
<td>52(^b)</td>
</tr>
<tr>
<td>K(_2)CO(_3)</td>
<td>DMF</td>
<td>/</td>
<td>90</td>
<td>6</td>
<td>94(^c)</td>
</tr>
</tbody>
</table>

\(^a\) 2.5 equivalents of 2,3 dibromopropene. \(^b\) 3 equivalents of 2,3 dibromopropene. \(^c\) 5.0 equivalents of 2,3 dibromopropene.

The conversion of 262 to the desired aniline derivative 258 necessitated the selective reduction of the nitro group. Although Al(Hg)\(^{143e}\) is an efficient reducing agent of aliphatic nitro derivatives (vide supra), nitro aromatics are usually converted to mixtures of anilines and hydroxylamines. Thus, we did not apply this procedure for the reduction of 262. The standard transfer hydrogenation, using ammonium formate as hydrogen source and 10% Pd on charcoal as catalyst,\(^{143c}\) failed to afford any reduction product (starting material was recovered). However,
selective reduction of the nitro group in 262 could be achieved using Cowan's procedure (NaBH₄, Cu(OAc)₂ in methanol).¹⁴³b As expected, sodium borohydride alone was not able to reduce 262. The mode of action of this combination of reagents is not well understood. It appears that the nitro group is activated toward hydride delivery, by means of coordination with the copper.

With an access to the vinyl bromide 258 secured, we concentrated our efforts on cyclization procedures. We had projected that a Heck cyclization would afford bicycle 257. When an acetonitrile solution of 258 was treated at reflux with 15 mol% of Pd(OAc)₂, triphenylphosphine and triethylamine, the mixture turned homogeneous. Thin layer chromatography indicated the slow disappearance of the starting material, with concomitant formation of two products of very similar polarity. After 4 h at reflux, three additional portions of catalyst (20 mol.% each) were added over a period of 3 h to push the reaction forward. Eventually, all the starting material was converted to the slower moving spot, as indicated by TLC. The mixture was concentrated, and the residue was purified by flash chromatography on silica gel to afford a single compound in 53% yield. Spectroscopic data were not in agreement with the expected structure 257. In particular,¹H NMR showed only two singlets in the ethylenic region, and the ¹³C DEPT revealed the presence of 5 triplets below 70 ppm. These data revealed that the reaction afforded directly the indolic tetracycle 263 (Scheme 38). Evidently, the cyclization proceeded in the normal way to give 257. Then, under the reaction conditions, aniline 257 underwent a palladium (II) mediated intramolecular amination onto the endocyclic double bond. The resulting tetracyclic intermediate rearranged, through what is formally a 1,3-hydrogen shift, to indole 263. It is important to note that the second cyclization was catalyzed by a palladium (II) species—and not a palladium (0) species. The extra catalyst that was added during the reaction was essential, since palladium (II) was converted to palladium (0) during the second cyclization. In that regard, a catalytic version of the palladium assisted amination of olefins has been developed by Hegedus and co-workers.¹⁵¹d In this modification, the palladium zero which is formed during
the reaction, is reoxidized to palladium (II) by various oxidants, such as benzoquinone or Cu(OAc)$_2$. However, attempted double cyclization under these conditions [15 mol.% Pd(OAc)$_2$, 1 equivalent benzoquinone, PPh$_3$, Et$_3$N, acetonitrile] proved to be unsuccessful; a low yield of tetracycle 263 being obtained (10%).

Scheme 38: Double Cyclization

Finally, it should be noted that, whereas 258 gives the double cyclization, the related compound 259 gives only the monocyclization product, under comparable conditions. The difference in the reactivity of these substrates can be rationalized by taking into account the basic nitrogen in 258, which may favor the chelation of a palladium (II) species from the most hindered face (the top face) of bicycle 257. Such chelation is required, in order to achieve the trans arrangement between the aniline nitrogen and the electrophilic palladium species.
IV. Conclusion

In this chapter, approaches to the BCE ring system of the *strychnos* skeleton were described. In the first section, we demonstrated that the C-E ring sub-unit can be easily elaborated by an intramolecular Heck reaction, and that the critical *E*-exocyclic olefin is generated with specificity. In the second section, we reported an interesting methodology for the construction of the indole nucleus, that involves a palladium catalyzed double cyclization. An application of this strategy to the synthesis of a member of the *strychnos* family is presented in the following chapter, which describes a stereoselective total synthesis of the pentacyclic strychnan, dehydrorubifoline.
Chapter IV:
Total Synthesis of Dehydrotubifoline

I. Introduction

As the model studies described in chapter III augured well for the success of our approach, we next undertook the synthesis of the strychnan skeleton. This chapter reports the successful implementation of our overall strategy to the synthesis of dehydrotubifoline, a typical pentacyclic *strychnos* alkaloid. Our retrosynthetic analysis is depicted in Scheme 39. The imine form of dehydrotubifoline is in equilibrium with its enamine tautomer. As expected, the tautomeric equilibrium lies far toward the side of the imine. By considering the enamine tautomer, we could envision the cleavage of the C_{15}-C_{20} bond as key disconnection. Encouraged by our model studies, we anticipated that this strategic bond could be formed by an intramolecular Heck reaction. Two possible precursors were considered: the tetracyclic vinyl iodide 264 and the aniline derivative 265. We projected that 265 could be converted to dehydrotubifoline by the double cyclization methodology we had developed during the model studies. Elaboration of 264 and 265 should be accomplished by, respectively, intra- and intermolecular cycloaddition of 3-aryl-δ2-pyrroline derivatives. Our initial objective was, therefore, to develop an effective route to the 3-aryl-δ2-pyrroline unit.
II. Preparation of the Pyrroline Unit

Since numerous alkaloids contain the pyrrolidine subunit, there is a need for methods that rapidly construct substituted pyroles, pyrrolines or pyrrolidines. At the beginning of our studies, we considered assembling pyrroline 266 through a transition-metal mediated coupling reaction of 3-bromo-$\delta_2$-pyrrolines with substituted benzenes (Scheme 39). However, we were not able to brominate the desired position of the pyrroline. In addition, we carried out different palladium mediated coupling reactions of $\delta_3$-pyrrolines with ortho-iodo-nitrobenzene, and found that a mixture of mono- and disubstituted pyrrolines was obtained. Since this chemistry proved to be problematic, and since our primary goal was not to develop new syntheses of substituted
pyrrolines, we searched for a literature procedure to prepare our starting material 266.

A unique transformation allows the conversion of cyclopropyl-imines into \( \delta_2 \)-pyrroline.\(^{152,153} \) Although, the reaction was discovered by Cloke in 1928,\(^{153} \) most of the synthetic work in the area was initiated by R. V. Stevens.\(^{152} \) Upon careful investigation of the cyclopropyl-imine rearrangement, Stevens and co-workers established that this transformation is not purely thermal, but that it requires an acid catalyst with a nucleophilic gegenion. The course of this reaction is depicted in Scheme 40.

Scheme 40: Cyclopropyl-Iminium Ion Rearrangement

The mechanism of this reaction is believed to involve the activation of the cyclopropyl-imine through protonation of the nitrogen. Then, the activated cyclopropane is ring-opened by nucleophilic attack of the gegenion to afford enamine 269. In the last step, 269 undergoes an intramolecular substitution reaction to yield the five-membered heterocycle 270. Ammonium chloride has been extensively employed to promote this rearrangement. It is a mild acid which does not induce decomposition of the resulting enamine.

Stevens and collaborators successfully explored this new methodology in the synthesis of complex alkaloids. For example, the cyclopropyl-imine rearrangement served as a key step in their formal synthesis of aspidospermine (Scheme 41).\(^{152a} \) Condensation of aldehyde 271
with the protected keto amine 272 led to aldimine 273. This imine rearranged in 82% yield to δ2-pyrroline 274, upon treatment with a catalytic amount of ammonium chloride at 160°C. Successive deprotection of the ketone and intramolecular aldol type condensation afforded bicycle 275, which was converted to 276 in 5 steps. This compound had been previously converted to aspidospermine 277.152a

**Scheme 41: Stevens' Formal Synthesis of Aspidospermine**

We wanted to follow a strategy similar to the one developed by Stevens to prepare pyrroline 282 (Equation 52). The nitro group served two purposes: it masked the aniline function, and it enhanced the acidity of the methylene protons in 278. Although starting material 278 was commercially available (Aldrich), it was readily prepared on large scale from ortho-nitrotoluene.154

(Eqn. 52)
The desired cyclopropyl moiety was assembled by double alkylation with dibromoethane (Scheme 4.2). On a small scale, deprotonation of 278 with tBuOK in DMSO, followed by addition of dibromoethane (10 equivalents) afforded the expected cyclopropyl nitrile 279 in good yields. Unfortunately, the yields declined appreciably upon scaling up this procedure (Table 2). After examining numerous conditions, we discovered that the double alkylation can be carried out on large scale and in good yield using a phase transfer catalyst.

Scheme 4.2: Synthesis of Cyclopropyl-imine 281

Table 2: Alkylation of Ortho–Nitrophenylacetonitrile

<table>
<thead>
<tr>
<th>base</th>
<th>solvent</th>
<th>additive</th>
<th>scale (mmol)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>tBuOK</td>
<td>DMF</td>
<td>/</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>tBuOK</td>
<td>DMSO</td>
<td>/</td>
<td>1</td>
<td>76</td>
</tr>
<tr>
<td>tBuOK</td>
<td>DMSO</td>
<td>/</td>
<td>5</td>
<td>48</td>
</tr>
<tr>
<td>tBuOK</td>
<td>DMSO</td>
<td>/</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>50% NaOH</td>
<td>CH₂Cl₂</td>
<td>nBu₄NBr (0.1 eq)</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>50% NaOH</td>
<td>CH₂Cl₂</td>
<td>nBu₄NBr (1.2 eq)</td>
<td>1</td>
<td>60</td>
</tr>
<tr>
<td>50% NaOH</td>
<td>MeCN</td>
<td>nBu₄NBr (1.2 eq)</td>
<td>1</td>
<td>97</td>
</tr>
<tr>
<td>50% NaOH</td>
<td>MeCN</td>
<td>nBu₄NBr (1.2 eq)</td>
<td>50</td>
<td>96</td>
</tr>
</tbody>
</table>

a) with 10 equivalents of dibromoethane
A useful approach to aldehydes consists in the partial reduction of nitriles to imines. The imines are then hydrolyzed to aldehydes. Diisobutylaluminum hydride (DIBAL-H) seems to be the reagent of choice for this purpose. Indeed, reduction of cyclopropyl nitrile 279 with DIBAL-H, at -78°C in toluene, afforded the expected aldehyde (280) after acidic work-up (Scheme 42). Condensation with benzyl amine led to the imine 281, substrate for the cyclopropyl-imine rearrangement.

The imine 281 was not isolated, but directly submitted to the rearrangement conditions. Stevens' original procedure (neat imine, NH₄Cl, 120°C) failed to give the desired δ₂-pyrroline 282, but afforded the aromatized derivative 283 in 77% yield (Equation 53a). On the other hand, when the reaction was carried out in acetonitrile, 282 was obtained in 90% from aldehyde 280 (Equation 53b).

\[
\begin{align*}
  \begin{array}{c}
  \text{CHO} \\
  \text{PhCH₂NH₂}
  \end{array} & \xrightarrow{\text{PhCH₂NH₂}} & \begin{array}{c}
  \text{N₄} \\
  \text{Ph}
  \end{array} & \xrightarrow{\text{NH₄Cl, 120°C, 4h}} & \begin{array}{c}
  \text{N₄} \\
  \text{Ph}
  \end{array} & 77\%
\end{align*}
\]

(Eqn.53a)

\[
\begin{align*}
  \begin{array}{c}
  \text{CHO} \\
  \text{1-PhCH₂NH₂}
  \end{array} & \xrightarrow{\text{2- NH₄Cl, MeCN, 120°C, 4h}} & \begin{array}{c}
  \text{N₄} \\
  \text{Ph}
  \end{array} & 90\%
\end{align*}
\]

(Eqn.53b)

Since this rearrangement was performed in a sealed tube, our procedure was not very practical on large scales. Therefore, we investigated further the reaction, and first examined the use of a higher boiling solvents. Indeed, the reaction can be promoted with ammonium chloride in DMF at 120°C, but the yields are modest (60%) and the reaction is not as clean. The finding by Stevens that the cyclopropyl-imine rearrangement does not proceed without a proton source, emphasizes the importance of the initial step, the iminium ion formation. Stevens suggested that the rate determining step in the rearrangement is the protonation of the imine by ammonium chloride. Consequently, it is expected that a stronger more soluble acid would speed up the
reaction. A potential problem with using strong, or mildly strong, acids is the acid sensitivity of the enamine product. To confirm that supposition, we reacted imine 281 with catalytic benzoic acid (15 mol%) and sodium iodide (15 mol%) in acetonitrile at reflux for 12 h. The reaction proceeded cleanly, and after 12 h, the starting material had disappeared. Unfortunately, the yield of isolated product remained low (30%).

Faced with this complication, we decided to examine new methods to effect this rearrangement. We realized that a good electrophile-nucleophile reagent pair should promote the reaction. Iodotrimethylsilane (TMSI)\textsuperscript{156}, which has been used as a substitute for Bronsted acids over the last decade, appeared quite promising. The silyl part of TMSI serves as a hard Lewis acid, and the iodide as a soft Lewis base. Therefore, it reacts very readily with compounds containing hard bases, to form a bond between the silicon and the base. The iodide acts as a strong nucleophile in a subsequent step. For example, N-trimethylsilylaziridine (284)\textsuperscript{157} has been reacted with iodotrimethylsilane to afford a ring opened product (285), arising from the collapse of the Lewis acid-Lewis base adduct (Equation 5.4).

\[
\text{SIM eq} \quad \text{TMSI} \quad \text{SIMe} \quad \text{SN} \quad \text{SiMe}_2 (\text{Eqn.54})
\]

Strained carbocycles have also been opened by TMSI. Relevant to our studies was the opening of the α-keto cyclopropane 286\textsuperscript{158} to afford the linear alkyl iodide 287, as outlined in Equation 5.5. We anticipated that the ring cleavage of our cyclopropyl imine would be achieved by TMSI in a similar way.

\[
\text{H} \quad \text{286} \quad \text{TMSI} \quad \text{H} \quad \text{287} (\text{Eqn.55})
\]
The series of events depicted in Scheme 43, indeed occurred, upon treatment of 281 with a catalytic amount of TMSI in DMF at 60°C. TMSI could also be generated in situ from TMSCI and ammonium iodide. We believe that 288, the adduct of DMF and TMSI (Equation 56) is the true catalyst in this reaction, since TMSI has been shown to react readily with amides.\(^\text{156}\)

\[\text{Scheme 43: TMSI Promoted Cyclopropyl-iminium Ion Rearrangement}\]

III. Attempted Intermolecular Cycloadditions with Enamine 282

With the synthesis of pyrroline 282, a route to the D ring of the strychnan skeleton was developed. In addition, the enamine function was positioned so as to allow the introduction of the cyclohexyl moiety (ring C). In fact, a possible precursor to dehydrotubifoline, bicycle 265 (Scheme 39) could, in principal, arise from a Diels-Alder cycloaddition of enamine 282 with
butadiene. Although enamides have served successfully as dienophiles in many inter and intramolecular cycloadditions,\textsuperscript{159} enamines has not been widely used. Reports of enamines reacting as dienophiles are limited to Diels-Alder cycloadditions with strongly electron deficient dienes.\textsuperscript{160} In a published approach to hasubanan alkaloids, for example, the reaction of sulfoxide 289 with enamine 290 gave cycloadduct 291 in good yield (Equation 57).\textsuperscript{160a} Backvall and co-workers\textsuperscript{160b} described the Diels-Alder reaction of 2-(phenylsulfonyl)-1,3-butadiene (292) with enamine 293 (Equation 58). The addition proceeded in 70\% yield to afford a single product, 294. Formally cycloadditions, these reactions may actually involve a conjugate addition of the enamine to the activated diene, followed by ring closure. It is worth mentioning that 2-(phenyl sulfonyl)-1,3-dienes are showing an unusual dual reactivity, since they react with both electron rich and electron poor dienophiles.

As a test reaction, we first investigated the Diels-Alder cycloaddition of 3-aryl-δ2-pyrroline 282 with 1,3-butadiene. Under the reaction conditions, 140°C in toluene, we observed a slow decomposition of the starting material and none of the desired cycloadduct. After 5 h at 140°C, we recovered 50\% of enamine 282. Next, we investigated the cycloaddition of 282 with electron deficient dienes. The phenylsulfonyl substituted 1,3-butadiene 292 was prepared...
according to the procedure published by Backvall. This diene was kept in a dichloromethane solution (0.02M) in order to avoid dimerization, and was rapidly added to alkene 282. The mixture was stirred at ambient temperature for 2 h, during which time the diene was consumed. However, the enamine 282 did not react and was recovered intact in 87% yield. Similarly, we did not meet with any success with 2-carboxethoxy-1,3-butadiene (296), generated in situ from the corresponding sulfone 295, which was prepared according to a literature procedure. Scheme 44 summarizes our attempted intermolecular Diels-Alder cycloadditions. We believe that pyrroline 282 does not easily undergo cycloaddition reactions, since it is not a typical enamine: the electron density of the double bond is greatly diminished by the presence of the ortho-nitro substituent on the benzene ring (push-pull effect).

Scheme 44: Attempted Intermolecular Cycloadditions

IV. Intramolecular Diels-Alder Cycloaddition

Since pyrroline 282 did not undergo intermolecular Diels–Alder reactions, we decided to investigate intramolecular transformations to construct the cyclohexyl moiety of dehydrotubifoline. In preparation for the intramolecular cycloaddition, we needed to introduce the diene appendage. We projected to unmask the aniline nitrogen by chemoselective reduction of the nitro group in 282. However, insurmountable problems were encountered. The NaBH4/Cu(OAc)2/MeOH procedure (vide supra) afforded a complex mixture of uncharacterized materials. We also examined transfer hydrogenation conditions, which have been shown to be effective for the reduction of various aliphatic and aromatic nitro compounds. Unfortunately, under these conditions (NH4HCO3, Pd/C, MeOH), the desired
aniline derivative could not be isolated in any appreciable yield. We suspected that the electron rich enamine was complicating the reduction, and we investigated the possibility of deactivating the enamine. A common procedure for the conversion of tertiary benzyl amines to carbamates, involved alkylchloroformates. For example, Hanessian and co-workers reported that the conversion of the benzyl amine 297 to the carbamate 298 (Equation 59) was achieved by upon treatment with ethylchloroformate in benzene at reflux.162

\[
\begin{align*}
\text{Ph} & \quad \text{CO}_2\text{Me} \\
\text{H} & \quad \text{H} \\
\text{N} & \quad \text{N} \\
\text{297} & \quad \text{ClCO}_2\text{Et, PhH} \quad \text{reflux} \\
& \quad \text{H} \\
& \quad \text{H} \\
& \quad \text{N} \\
\text{298} & \\
\end{align*}
\]

(Eqn. 59)

In a similar way, enamine 282 was conveniently converted to the corresponding methyl carbamate 299 in quantitative yield (Scheme 45). To our knowledge, this transformation represents the first example of an alkylchloroformate promoted dealkylation of an enamine. Chemoselective reduction of the nitro group in 299 was then efficiently achieved by catalytic hydrogenation over Pd/C (HCOONH₄, MeOH, rt)¹⁴³c to yield aniline derivative 300, our precursor of amino-diene 307.

**Scheme 45: Preparation of Carbamate 299**

\[
\begin{align*}
\text{Ph} & \quad \text{CO}_2\text{Me} \\
\text{282} & \quad \text{ClCO}_2\text{Me, acetone, rt} \\
\text{5\% Pd/C, HCOONH}_4 & \quad \text{MeOH, rt} \quad 86\% \text{ overall} \\
& \quad \text{H} \\
\text{300} & \\
\text{307: E=CO}_2\text{Me} \\
\end{align*}
\]
In connection with alkaloid synthesis, N-acyl-1-amino-1,3-dienes (302) have become popular substrates for Diels-Alder cycloadditions. There are principally two versatile and complementary methods for their preparation. The first method is based on the Curtius rearrangement of dienoic acid azides. The second method, which is depicted in Scheme 46, involves the condensation of α,β-unsaturated aldehydes with primary amines to afford vinylimines (301), which are trapped by an acylating agent.

Scheme 46: Preparation of Dienamides from α,β-unsaturated Aldehydes

In recent years, there has been an increased utilization of dienamides such as 302 in Diels-Alder cycloadditions. For example, in an approach toward the galanthane ring system common to many amaryllidacea alkaloids, dienamide 303 (Equation 60) afforded a single adduct (304) upon cycloaddition in refluxing chlorobenzene. The key step in Oppotzer total synthesis of (-)-pumiliotoxin involved the intramolecular Diels-Alder reaction of dieneamide 305 (Equation 61). The chiral center in 305 derived from (S)-norvalin, and controlled the stereochemistry of the three new asymmetric centers, through a boat-like transition state in which the non-bonding interactions were minimized.
In the actual synthesis of 307, the diene moiety was introduced by condensation with crotonaldehyde, followed by trapping with methyl chloroformate (Scheme 47). Five equivalents of crotonaldehyde were added to the starting aniline, and the mixture was stirred at room temperature for 1 h. The mixture was diluted with toluene and concentrated to remove the water. The crude imine was then reacted with methyl chloroformate, under different sets of conditions. Table 3 summarizes some of the most representative trials.

**Scheme 47: Preparation of Dienamide 307**

**Table 3: Preparation of 307, Reaction Conditions**

<table>
<thead>
<tr>
<th>base</th>
<th>solvent</th>
<th>additive</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>diisopropylethylamine</td>
<td>CH₂Cl₂</td>
<td>DMAP</td>
<td>43</td>
</tr>
<tr>
<td>diisopropylethylamine</td>
<td>MeCN</td>
<td>DMAP</td>
<td>40</td>
</tr>
<tr>
<td>diethylamine</td>
<td>toluene</td>
<td>/</td>
<td>57</td>
</tr>
<tr>
<td>proton sponge</td>
<td>toluene</td>
<td>DMAP</td>
<td>70</td>
</tr>
<tr>
<td>proton sponge</td>
<td>MeCN</td>
<td>DMAP</td>
<td>50</td>
</tr>
<tr>
<td>proton sponge</td>
<td>Et₂O</td>
<td>DMAP</td>
<td>60</td>
</tr>
</tbody>
</table>

a) N,N,N',N' tetramethyl-1,8-diamino-naphthalene
The following generalizations can be made about this conversion. Higher yields were obtained when the reaction was carried out in a non-polar solvent, such as toluene, using a non-nucleophilic base. Oppolzer's procedure calls for the use of diethylaminoline, but we found the reaction to proceed more cleanly, and in higher yields, with N,N,N',N'-tetramethyl-1,8-diamino-naphtalene (proton sponge). Under our conditions, the ammonium salt precipitated cleanly and rapidly. Any acid-catalyzed side reaction was thus avoided.

Many different conditions were examined for the key intramolecular Diels-Alder reaction. Early attempts to promote cycloaddition of dienamide under thermal conditions proved unsuccessful. Lewis acid catalysis, the traditional way to accelerate a Diels-Alder reaction was not expected to be useful, as the dienophile and the diene were electronically very similar. Indeed, diethylaluminum chloride in dichloromethane did not induce any chemical transformation.

The nature of substrate, in which both the diene and the dienophile are electron rich, prompted us to also investigate the possibility of catalyzing the cyclization using cation radical salts. The scope and the utility of the cation radical Diels-Alder cycloadditions has been enhanced by the discovery of efficient and stable chemical initiators, the triarylammonium salts, such as 312. The capacity of these salts to promote the cycloaddition of electron rich diene-dienophile systems is beautifully demonstrated by Equation 6.2. The stereospecific cyclization of 313 occurred at -78°C in 83% yield. A potential complication in the reaction of these salts is the formation of cyclobutane derivatives. Bauld and co-workers investigated the cation radical Diels–Alder reaction of N-vinyl-N-methyl-acetamide (316) with cyclohexadiene, and observed the exclusive formation of cyclobutane derivative 317 (Equation 6.3).
According to Bauld's procedure, our triene 307 was exposed to a catalytic amount of $(\text{pBrPh})_3\text{N}^+\text{SbCl}_6^-$ in dichloromethane at $0^\circ\text{C}$. An intractable mixture of decomposition products was obtained, and none of the cycloadduct could be detected. It was not possible to promote the transformation below $0^\circ\text{C}$, since the aminium salt was found to be too insoluble in dichloromethane.

During the course of this work, Livinghouse and co-workers\textsuperscript{169} described the use of rhodium complexes, such as $\text{(PPh}_3)_3\text{RhCl}$, to catalyze Diels-Alder reactions between electron rich dienes and electron rich dienophiles. However, even under Livinghouse's conditions $\{\text{(PPh}_3)_3\text{RhCl}, \text{trifluoroethanol}\}$, bis-carbamate 307 failed to undergo the desired cycloaddition.

At this point, we decided to reinvestigate the thermal Diels-Alder reaction under more forcing conditions. We were pleasantly surprised to find that not only did the cyclization take place at higher temperature ($220^\circ\text{C}$, toluene, steel bomb, 4h), but that it produced the desired adduct, 318, in high yield, as a single diastereomer (Scheme 4\textsuperscript{8}). The cycloaddition evidently takes place through the exo transition state in which non-bonding interactions are minimized (Scheme 4\textsuperscript{8}). The endo transition state is not stabilized by any secondary orbital overlap, and is disfavored by non-bonding interactions between the ethylenic protons of the diene moiety and the methylenes of the pyrroline ring. Tetracycle 318 should prove to be quite versatile, since it can serve as an intermediate in the synthesis of both strychnos and aspidosperma alkaloids (Figure 5).
Scheme 48: Diels-Alder Cycloaddition of Dlenamide 307

$$\begin{array}{c}
\text{Scheme 48: Diels-Alder Cycloaddition of Dlenamide 307} \\
\text{307} \xrightarrow{\text{220°C, toluene, 4 h}} \text{318} \\
\end{array}$$

307

CO₂Me

$\xrightarrow{\text{220°C, toluene, 4 h}}$

MeO₂C

steel bomb, 95%

318

CO₂Me

EXO

versus

ENDO

Figure 5: Aspidosperma and Strychnos Skeletons

The spectroscopic data observed for adduct 318 were consistent with the assigned structure. The $^1$H and $^{13}$C NMRs of tetracycle 318 were recorded respectively, in toluene-$d_8$ and DMSO-$d_6$, at 100°C. This temperature was required in order to overcome the rotational barrier of the carbamate carbon-nitrogen bonds, and resulted in simplified spectra.

aspidosperma skeleton

strychnos skeleton
The data from the $^1$H and $^{13}$C NMR's are summarized in Figure 6. The stereochemistry of the tetracycle, in particular the orientation of $H_8$, was confirmed by nOe's experiments.

$^1$H NMR in toluene $d_8$ at 370K

<table>
<thead>
<tr>
<th>proton</th>
<th>$\delta$ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1+2</td>
<td>1.60</td>
</tr>
<tr>
<td>3</td>
<td>2.15</td>
</tr>
<tr>
<td>4</td>
<td>2.37</td>
</tr>
<tr>
<td>5</td>
<td>3.26</td>
</tr>
<tr>
<td>6</td>
<td>3.51</td>
</tr>
<tr>
<td>7</td>
<td>3.79</td>
</tr>
<tr>
<td>8</td>
<td>4.40</td>
</tr>
<tr>
<td>9</td>
<td>5.53</td>
</tr>
<tr>
<td>10</td>
<td>6.00</td>
</tr>
<tr>
<td>11</td>
<td>6.71</td>
</tr>
<tr>
<td>12</td>
<td>6.83</td>
</tr>
<tr>
<td>13</td>
<td>7.00</td>
</tr>
<tr>
<td>14</td>
<td>7.86</td>
</tr>
</tbody>
</table>

characteristic nOes

$^{13}$C NMR in DMSO-$d_6$ at 370K

<table>
<thead>
<tr>
<th>carbon</th>
<th>$\delta$ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>62.76</td>
</tr>
<tr>
<td>3</td>
<td>59.45</td>
</tr>
<tr>
<td>5</td>
<td>44.05</td>
</tr>
<tr>
<td>6</td>
<td>25.49</td>
</tr>
<tr>
<td>7</td>
<td>51.30</td>
</tr>
<tr>
<td>8</td>
<td>140.13</td>
</tr>
<tr>
<td>9</td>
<td>122.22</td>
</tr>
<tr>
<td>10</td>
<td>127.79</td>
</tr>
<tr>
<td>11</td>
<td>122.65</td>
</tr>
<tr>
<td>12</td>
<td>114.23</td>
</tr>
<tr>
<td>13</td>
<td>135.25</td>
</tr>
<tr>
<td>14</td>
<td>37.00</td>
</tr>
<tr>
<td>15+16</td>
<td>126.23+126.99</td>
</tr>
<tr>
<td>2xC=O</td>
<td>154.59+152.40</td>
</tr>
<tr>
<td>2xOMe</td>
<td>51.30+51.52</td>
</tr>
</tbody>
</table>

Figure 6: Spectroscopic Data of Tetracycle 318
IV. Elaboration of Ring E - Heck Cyclization

To complete our total synthesis of dehydrotubifoline (1 2 3), we projected to assemble ring E by intramolecular Heck reaction. The introduction of a suitable appendage to tetracycle 318 necessitated first the hydrolysis of the carbamate functions. Again, at this stage, we took advantage of the high reactivity of iodo(trimethyl)silane. The hydrolysis of simple alkyl carbamates usually requires very acidic or basic reagents. Reactions are typically slow and yields are modest at best. In the last decade, TMSI has been used successfully as a substitute for acids in the hydrolysis of esters, amides, and carbamates. Because of the presence of the lone pair on the nitrogen, the carbonyl groups in carbamates are more polarized than in esters. For this reason, carbamates react more readily with iodo(trimethyl)silane. The first step in the TMSI promoted hydrolysis of carbamates (Scheme 49) is a transesterification reaction that generates a trimethylsilyl carbamate (320). Upon methanolic work-up, the silyl carbamate yields a carbamic acid (321), which collapses with spontaneous loss of carbon dioxide to release the free amine as its hydroiodide salt (322).

Scheme 49: TMSI-Promoted Hydrolysis of Carbamates-Mechanism

We did not expect any selectivity in the TMSI-induced hydrolysis of bis-carbamate 318. However, we discovered that the reactivity of TMSI could be tuned by varying the solvent and the
number of equivalents of the reagent (Table 4). The more reactive carbamate could be preferentially hydrolyzed, by running the reaction in dichloromethane at reflux for 1 h with 2.2 equivalents of TMSI. Under forcing conditions, however, the fully deprotected diamine 3 2 4 was isolated in 94% yield.

Table 4: Hydrolysis of BIs-carbamate 318

<table>
<thead>
<tr>
<th>TMSI (equivalent)</th>
<th>solvent (reflux)</th>
<th>time (h)</th>
<th>ratio (323/324)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2</td>
<td>CH₂Cl₂</td>
<td>1</td>
<td>10/1.0</td>
<td>95</td>
</tr>
<tr>
<td>2.2</td>
<td>CH₂Cl₂</td>
<td>4</td>
<td>3.5/1.0</td>
<td>81</td>
</tr>
<tr>
<td>3.0</td>
<td>CH₂Cl₂</td>
<td>1</td>
<td>2.5/1.0</td>
<td>85</td>
</tr>
<tr>
<td>5.0</td>
<td>CH₂Cl₂</td>
<td>3</td>
<td>1.0/1.0</td>
<td>90</td>
</tr>
<tr>
<td>10</td>
<td>CHCl₃</td>
<td>4</td>
<td>1.0/99</td>
<td>94</td>
</tr>
</tbody>
</table>

We chose first to investigate the chemistry of indoline carbamate 3 2 3. N-alkylation was accomplished efficiently upon treatment with tosylate 2 3 8 in acetone containing potassium carbonate. The Heck cyclization of vinyl iodide 3 2 5 was expected to give strychnan 3 2 6, a versatile pentacyclic intermediate (Scheme 5 0). Carbamate 3 2 6 would have been one step away from both dehydrotubifoline (mild hydrolysis) and Akuammicine. The conversion of 3 2 6 to Akuammicine would have required transposition of the carbomethoxy group from the nitrogen to the β-carbon. It has already been shown that, under photochemical conditions, enamides predominantly undergo a [1,3]-acyl shift to produce vinylogous amides.⁸⁵⁹b,170
Unfortunately, when compound 325 was submitted to the Heck reaction (Pd(OAc)$_2$, K$_2$CO$_3$, DMF, 60°C), an unexpected pentacycle was obtained. The proton NMR spectrum clearly indicated the presence of three ethylenic hydrogens, two as triplets, and one as a quartet (Figure 7). Only a quartet and a doublet would be expected from structure 326. The $^{13}$C NMR spectrum unequivocally revealed the presence of two ethylenic doublets. A careful analysis of the spectroscopic data ($^1$H-$^1$H correlation and nOes) confirmed that the cyclization had occurred to afford product 327 (Scheme 51). This unexpected cyclization, giving rise to the azabicyclo[3.2.2]nonane subunit, was in sharp contrast to the results from the many model systems (chapter III).
A more careful analysis of the spectroscopic data indicated that the cyclization had not simply taken place at the other end of the endocyclic olefin. NOe's experiment confirmed that the cyclization had occurred with inversion of the double bond geometry. This observation ruled out a direct 7-endo type mechanism for the coupling reaction. Negishi and co-workers have also observed inversion of configuration during the Heck cyclization of vinyl iodide 328 (Scheme 52). Their proposed mechanism involves the standard exo-type cyclization to afford the neopentyl type α-alkyl palladium complex 329. Unlike typical Heck reaction intermediates, this palladium complex has no β-hydrogen to allow a reductive elimination, and undergoes a closure to cyclopropyl carbinyl palladium species 330. The cleavage of the internal carbon-carbon bond of the cyclopropane which occurs in the next step necessitates proper alignment of
the carbon-palladium $\sigma$ bond. Thus, formation of intermediate 331 was accompanied by inversion of the exo-cyclic olefin geometry.

**Scheme 52: Inversion of Alkene Geometry via an Exo-mode Cyclization**

By analogy with Negishi's work, we propose the following mechanism for the conversion of vinyl iodide 325 to the pentacyclic carbamate 327 (Scheme 53).

**Scheme 53: Formation of 327-Mechanism**
The initial step involves the expected exo-mode carbopalladation to produce a \( \sigma \)-alkyl palladium species stabilized by intramolecular chelation (333). The \( \beta \)-elimination does not occur, presumably because chelate formation prevents proper alignment between the \( \beta \)-hydrogen and the carbon-palladium bond. In situ trapping of the reactive carbon-palladium bond by the exocyclic olefin affords cyclopropane 334. Cleavage of the cyclopropane "back bond" yields 335, a \( \sigma \)-alkyl palladium complex which is not stabilized by any intramolecular chelation. This unstable complex undergoes a fast elimination of HPdI to provide the observed product (327). This proposed mechanism is consistent with other observations. There is literature precedents for the formation of cyclopropane by double Heck cyclization (Scheme 54).\(^{171}\) The palladium promoted cyclopropylcarbinyl-homoallyl rearrangement is also well documented.\(^{172}\) In addition, there is at least one example in the literature of a stable \( \sigma \)-alkyl palladium species possessing a syn \( \beta \) hydrogen. Daves and collaborators described the isolation and the characterization of 342, a \( \sigma \)-palladium complex stabilized by intramolecular chelation.\(^{52,56,57}\)

**Scheme 54: Heck Cyclopropanation**
We realized that the removal of the carbamate function should prevent the "abnormal" cyclization from occurring. As mentioned before (Table 4), the two carbomethoxy group in 318 could be removed cleanly, using an excess of iodotrimethylsilane in chloroform, to give 324 in 94% yield. The vinylic iodide appendage was then introduced by chemoselective alkylation of diamine 324 (Scheme 55). The alkylation was performed at -5°C, since above 0°C dialkylation was a competing reaction. It is worth mentioning that in the absence of tetrabutyl ammonium chloride the reaction was unselective, even at low temperature. It is possible that the allylic bromide 343 was converted in situ to the corresponding chloride, which might be a more selective alkylating agent. When iodide 344 was treated with a catalytic amount of Pd(OAc)$_2$ in DMF, in the presence of triphenylphosphine and potassium carbonate (Scheme 55), the anticipated Heck 6-exo cyclization was observed. The α-alkyl palladium intermediate 345 was not stabilized by any intramolecular chelation. Therefore, it underwent a fast elimination of palladium hydride to afford enamine 346, which rapidly tautomerized to 123. After chromatographic purification on silica gel (elution with 5% diethyl amine in ether) the pentacyclic strychnos alkaloid dehydrotubifoline (123) was isolated as a clear beige solid. The $^1$H NMR and $^{13}$C NMR (Table 5) spectra of our synthetic sample correlated well with those provided by Professor L.E. Overman from the University of California at Irvine. For comparison purposes, the reduced spectra of Overman's samples are presented in appendices, along with the spectra of our synthetic samples.
Scheme 55: Final Steps In the Synthesis of Dehydrotubifoline

\[
\begin{align*}
\text{324} \quad \text{Br} - \text{343, K}_2\text{CO}_3 \\
\text{nBu}_4\text{NCl, DMF, -5°C, 68%} \\
\end{align*}
\]

\[
\begin{align*}
\text{344} \quad \text{Pd(OAc)}_2, \text{DMF} \\
\text{nBu}_4\text{NCl, K}_2\text{CO}_3 \\
\text{79%} \\
\end{align*}
\]

\[
\begin{align*}
\text{346} \quad \text{β-elimination} \\
\text{345} \quad \text{PdL}_2 \\
\end{align*}
\]

123: dehydrotubifoline

Table 5: $^1$H NMR of dehydrotubifoline, recorded in chloroform at rt

<table>
<thead>
<tr>
<th>carbon</th>
<th>$\delta$ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>12.85</td>
</tr>
<tr>
<td>6</td>
<td>25.39</td>
</tr>
<tr>
<td>15</td>
<td>30.25</td>
</tr>
<tr>
<td>14,16</td>
<td>35.10</td>
</tr>
<tr>
<td>5</td>
<td>35.95</td>
</tr>
<tr>
<td>20</td>
<td>55.53</td>
</tr>
<tr>
<td>7</td>
<td>65.40</td>
</tr>
<tr>
<td>3</td>
<td>66.67</td>
</tr>
<tr>
<td>12,18</td>
<td>119.55</td>
</tr>
<tr>
<td>10</td>
<td>121.23</td>
</tr>
<tr>
<td>9,11</td>
<td>125.27</td>
</tr>
<tr>
<td>19</td>
<td>127.73</td>
</tr>
<tr>
<td>8</td>
<td>142.03</td>
</tr>
<tr>
<td>13</td>
<td>154.43</td>
</tr>
<tr>
<td>2</td>
<td>189.02</td>
</tr>
</tbody>
</table>
V. Conclusion

This chapter presented our stereoselective total synthesis of (±) dehydrotubifoline (123). This synthesis, which required the formation of 4 rings and 5 carbon-carbon bonds, was executed in 11 steps and proceeded in 26% overall yield. Our approach, which uses an intramolecular Heck reaction to assemble the bridged bicyclic subunit, addresses also the critical problem of introducing the exocyclic double bond of defined geometry. Besides the Heck cyclization, two other key steps are worth mentioning: the iodotrimethylsilane promoted cyclopropylimine-pyrroline rearrangement, and the intramolecular Diels-Alder cycloaddition, which provided the tetracyclic core common to the *strychnos* and *aspidosperma* alkaloids. This overall strategy is currently being expanded to the synthesis of more complex members of the *strychnos* family.
EXPERIMENTAL

General Aspects: The melting points were taken with Thomas Hoover capillary melting point apparatus and are uncorrected. Proton nuclear magnetic resonance spectra ($^1$H NMR) were obtained on Brucker AC-200, Bruker AM-250, Bruker AC-300, or Bruker AM-500 spectrometers and recorded in parts per million from an internal standard (tetramethylsilane). The $^1$H NMR are reported as follow: chemical shift [multiplicity (b=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constant (Hertz), integration, and interpretation]. $^{13}$C nuclear magnetic resonance spectra ($^{13}$C NMR) were obtained on Brucker AC-200, Bruker AM-250, Bruker AC-300 or Bruker AM-500, and are reported as follow: chemical shift (multiplicity). Infrared spectra (IR) were taken with Perkin-Elmer 283b or 1600 infrared spectrophotometer. Mass spectra were obtained on Kratos MS-30 or Kratos VG70-250s instruments at an ionization energy of 70eV. Combustion analysis were performed by M.H.W. laboratories, Phoenix, Arizona.

Column chromatography was performed over EM Science Laboratories silica gel (230-400 mesh). Medium pressure liquid chromatography (MPLC) was performed using Merck Lobar Fertigsäule prepacked silica gel columns (40-63 mm). Analytical thin layer chromatography was conducted on Merck glass plates precoated with 0.25mm mm of silica gel 60F254. TLC plates were revealed using solutions of phosphomolybdic acid, anisaldehyde or potassium permanganate. All reactions were carried out under an argon atmosphere with use of standard techniques to exclude moisture. Solvents and reagents were purchased from Aldrich (reagent
grade) and were dried and purified prior to use when considered necessary. Tetrahydrofuran (THF) was purified by distillation from potassium-benzophenone ketyl. Benzene and toluene were distilled from sodium hydride. Dimethylformamide was distilled from calcium hydride.

\[
\begin{align*}
\text{1,3-butadiene} & \quad \text{toluene, } 140^\circ C \\
\end{align*}
\]

(±)-trans-(6-Nitro-3-cyclohexen-1-yl)-benzene (227): A suspension of β-nitrostyrene (5.00 g, 33.5 mmol) in toluene was introduced in a preweighted sealed tube, and cooled to -78°C. A stream of 1,3-butadiene was bubbled into the mixture until 5 g of 1,3-butadiene had been added. The tube was sealed and heated to 140°C for 18 h. The mixture was then cooled to room temperature and concentrated under reduced pressure. The crude material was crystallized in methanol to afford the desired product (5.8 g, 85% yield) as a white powder: mp. 102°C; \(^1\)H NMR (250 MHz, CDCl\(_3\)) \(\delta\) 2.38 (m, 2H, \(=CHCH_2\)), 2.74 (m, 2H, \(=CHCH_2\)), 3.39 (m, 1H, PhCH), 4.93 (m, 1H, CHNO\(_2\)), 5.71 (m, 2H, CH\(_2\)=CH\(_2\)), 7.22 (m, 5H, ArH); \(^1\)C NMR (63 MHz, CDCl\(_3\)) \(\delta\) 31.21 (t), 33.14 (t), 44.19 (d), 87.29 (d), 122.65 (d), 126.57 (d), 127.36 (d), 127.55 (d), 128.80 (d), 140.13 (s); IR (CH\(_2\)Cl\(_2\)) 3054, 1550, 1494, 1455, 1436, 1373, 1269, 895 cm\(^{-1}\); MS (El) \(m/e\) calc’d for C\(_{12}\)H\(_{13}\)NO\(_2\): 203.0946, found 203.0949; 156 (61), 141 (14), 128 (15), 115 (23), 91 (100), 77 (19); Analysis calc’d for C\(_{12}\)H\(_{13}\)NO\(_2\): C, 70.92; H, 6.45; found: C, 71.11; H, 6.40.
(±)-trans-4-Methyl-N-(6-phenyl-3-cyclohexen-1-yl)-benzenesulfonamide (229):

Aluminum amalgam was prepared by sequential treatment of aluminum foil (Reynolds) with warm 1N KOH (100 mL/g of Al, 30 s), distilled water (2X100 mL/g of Al), warm 0.5% aqueous HgCl$_2$ (100 mL/g of Al, 45 s), distilled water (100 mL/g of Al) and THF (100 mL/g of Al).

To a THF/H$_2$O (150:15 mL) solution of nitrocyclohexene 227 (2.00 g, 10 mmol) was added, at room temperature, freshly prepared Al(Hg) (2.7 g). The mixture was stirred for 2 h at room temperature and then poured in 300 mL of THF. The resulting mixture was filtered through a cake of Celite, dried over anhydrous magnesium sulfate, and concentrated to afford the crude amine (1.60 g) as a yellow oil. To a dichloromethane solution (60 mL) of this crude amine was added triethylamine (2.0 mL, 13 mmol), a catalytic amount of DMAP, and TsCl (2.30 g, 12 mmol). The reaction mixture was stirred at room temperature for 16 h and then quenched with water (15 mL). The organic phase was separated. The aqueous layer was extracted twice with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Purification by flash chromatography over silica gel (elution with 40% hexane in dichloromethane) yielded a yellow brown powder. One crystallization from ether/hexane afforded the desired sulfonamide (2.03 g, 64% yield) as a white powder: mp. 104°C; $^1$HNMR (250 MHz, CDCl$_3$) δ 2.30 (m, 2H, =CHCH$_2$), 2.40 (s, 3H, CH$_3$Ar), 2.65 (m, 2H, =CHCH$_2$), 2.80 (m, 1H, TsNH), 4.80 (m, 1H, CHN), 5.60 (m, 2H, CH=CH), 6.90 (d, J=11 Hz, 2H, ArH), 7.18 (m, 5H, ArH), 7.48 (d, J=8.2 Hz, 2H, ArH); $^{13}$C NMR (63 MHz, CDCl$_3$) δ 21.27 (q),
32.53 (t), 32.89 (t), 44.84 (d), 53.29 (d), 124.44 (d), 125.99 (d), 126.63 (d), 126.85 (d), 127.41 (d), 128.52 (d), 129.32 (d), 137.17 (s), 141.64 (s), 142.75 (s); IR (KBr) 3240, 3020, 2910, 1650, 1590, 1485, 1435, 1320, 1155, 1080, 890 cm⁻¹; MS (El) m/e calc'd for C₁₉H₂₁NSO₂: 327.1292, found 327.1269; 327 (12), 273 (39), 236 (100), 155 (61), 118 (60), 91 (90); Analysis calc'd for C₁₉H₂₁NSO₂: C, 69.69; H, 6.46; found: C, 69.70; H, 6.56.

(±)-trans-N-(2-Bromo-2-propenyl)-4-methyl-N-(6-phenyl-3-cyclohexen-1-yl)-benzenesulfonamide (218): To a mixture of sulfonamide 229 (239 mg, 0.73 mmol) and 2,3-dibromopropene (175 mg, 0.87 mmol) in benzene (7.5 mL) were added nBu₄HSO₄ (292 mg, 0.87 mmol) and 50% aqueous NaOH (1 mL). The mixture was stirred vigorously at room temperature for 40 min, then quenched with aqueous ammonium chloride. The organic phase was separated. The aqueous layer was extracted twice with ether. The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude material was purified by flash chromatography over silica gel (elution with 50% hexane in dichloromethane) to give the desired product (300 mg, 92% yield) as a pale yellow powder: mp. 111°C; ¹H NMR (250 MHz, CDCl₃) δ 2.35 (m, 4H, CH₂CH=CHCH₂), 2.41 (s, 3H, ArCH₃), 3.05 (m, 2H, PhCH), 3.79 (d, J=17.8 Hz, 1H, CH=CHBr=), 3.81 (d, J=17.8 Hz, 1H, CH=CHBr=), 4.28 (m, 1H, CHN), 5.37 (s, 1H, =CHH), 5.47 (s, 1H, =CHH), 5.60 (m, CH=CH), 7.25 (m, 7H, ArH), 7.55 (d, J=7.3 Hz, 2H, ArH); ¹³C NMR (63 MHz, CDCl₃) δ 21.34 (q), 31.52 (t), 36.64 (t), 44.55 (d), 52.63 (t), 58.67 (d), 119.55 (t), 125.22 (d), 125.88 (d), 126.36 (d), 127.47 (d), 127.85 (d), 128.22
(d). 128.81 (s), 129.32 (d), 137.83 (s), 142.46 (s), 143.04 (s); IR (CHCl3) 3020, 2900, 1595, 1485, 1330, 1150, 1085, 895 cm⁻¹; MS (El) m/e calc'd for C22H24NSO2Br: 445.0712, found 445.0723; 447 (11), 445 (11), 393 (7), 391 (7), 356 (43), 354 (42), 312 (21), 155 (42), 91 (82).

(Z)-2-Iodo-2-buten-1-ol (234): To a mixture of 2-butyn-1-ol (1.40 g, 20.0 mmol) and nBu3SnH (1.96 mL, 7.25 mmol) was added AIBN (164 mg, 1.00 mmol) at room temperature in one portion. The mixture was stirred at 85°C for 2 h. The solution was cooled to room temperature and diluted with CCl4 (50 mL). An excess of iodine (1.90 g, 7.50 mmol) was added at 0°C. The mixture was warmed up to room temperature, stirred for 1 h, and quenched with 5% aqueous sodium bisulfite. The phases were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography over silica gel (30% hexane in dichloromethane) to afford the desired alcohol (1.24 g, 86% yield based on nBu3SnH) as a pale yellow oil: ¹H NMR (250 MHz, CDCl3) δ 1.70 (d, J=7 Hz, 3H, CHCH3), 2.92 (bs, 1H, OH), 4.21 (s, 2H, CH2), 5.98 (q, J=7 Hz, 1H, =CH); ¹³C NMR (63 MHz, CDCl3) δ 21.4 (q), 71.4 (t), 109.6 (s), 131.0 (d); IR (neat) 3300, 1650 cm⁻¹.
(±)-[α(Z),6β]-N-(2-iodo-2-butenyl)-4-methyln-(6-phenyl-3-cyclohexene-1-yl)-benzensulfonamide (219): A solution of alcohol 234 (1.1 g, 5.5 mmol), Et₃N (836 mL, 6.0 mmol) and DMAP (61 mg, 0.5 mmol) in dichloromethane (10 mL) was treated with TsCl (1.05 g, 5.5 mmol) at 0°C. The mixture was stirred at room temperature for 3 h and quenched with water. The organic phase was separated. The aqueous layer was extracted with dichloromethane. The organic layers were combined, dried over anhydrous sodium sulfate and concentrated to afford the crude tosylate as a yellow oil which was used without further purification. ¹H NMR (250 MHz, CDCl₃) δ 1.70 (d, J=6.5 Hz, 3H, O=CH=), 2.44 (s, 2H, ArOHg), 4.72 (s, 2H, OHgOTs), 6.02 (q, J=6.5 Hz, 1H, O=H=), 7.33 (d, J=7.8 Hz, 2H, ArH), 7.50 (d, J=7.8 Hz, 2H, ArH).

To a mixture of sulfonamide 229 (100 mg, 0.3 mmol) and tosylate 238 (144 mg, 0.40 mmol) in benzene (3 mL) were added nBu₄HSO₄ (134 mg, 0.40 mmol) and 50% aqueous NaOH (0.4 mL). The mixture was stirred vigorously at room temperature for 3 h, then quenched with 1N HCl (1 mL) and distilled water (5 mL). The organic phase was separated. The aqueous layer was extracted twice with ether. The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography over silica gel (elution with 50% dichloromethane in hexane) afforded the desired product (110 mg, 72% yield) as a pale yellow solid (crystallized from ether): mp. 77°C; ¹H NMR (250 MHz, CDCl₃) δ 1.49 (d, J=6 Hz, 3H, CH₃CH=), 2.30 (m, 4H, CH₂CH=CHCH₂), 2.38 (s, 3H, CH₃Ar), 3.05 (m, 1H, PhCH), 3.80 (d, J=17.8 Hz, 1H, NCH=HBr=), 3.95 (d, J=17.8 Hz, 1H, NCH=HBr=).
4.30 (m, 1H, CHN), 5.41 (q, J=6 Hz, 1H, =CHCH₃), 5.61 (m, 2H, CHC=CH), 7.10 (m, 7H, ArH), 7.52 (d, J=7 Hz, 2H, ArH); ¹³C NMR (75 MHz, CDCl₃) δ 21.33 (q), 21.86 (q), 31.44 (t), 36.84 (t), 44.65 (d), 56.68 (t), 58.59 (d), 104.19 (s), 125.21 (d), 125.86 (d), 126.27 (d), 127.53 (d), 127.92 (d), 128.14 (d), 129.21 (d), 133.41 (d), 138.12 (s), 142.73 (s), 142.85 (s); IR (CHCl₃) 3010, 2900, 1592, 1485, 1330, 1150, 1085, 748 cm⁻¹; MS (EI) m/e calc'd for C₂₉H₂₆NSO₂I: 507.0730, found 507.0691; 507 (18), 416 (55), 236 (43), 169 (60), 155 (50), 91 (100).

(E)-2-Iodo-2-buten-1-ol (237): To a mixture of 2-butyne-1-ol (215 mg, 3.0 mmol) and nBu₄SnH (0.9 mL, 3.3 mmol) in benzene (6 mL) was added a catalytic amount of Pd(PPh₃)₄ (69 mg, 0.06 mmol) at 0°C. The reaction mixture was stirred at room temperature for 8 h. The solution was washed with 10% aqueous KF. The organic phase was separated. The aqueous layer was extracted twice with ether. The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by flash chromatography over silica gel (elution with 50% hexane in dichloromethane) to give two separable regioisomers 235 and 236 in a 5:1 ratio. Regioisomer 236 was further treated with iodine (0.95 g, 3.75 mmol) in CCl₄ (50 mL) at 0°C. The mixture was warmed up to room temperature, stirred for 1 h, and quenched with 5% aqueous sodium bisulfite. The phases were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over anhydrous
magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography over silica gel (30% hexane in dichloromethane) to afford the desired alcohol (237) (420 mg, 70% yield) as a pale yellow oil: $^1H$ NMR (300 MHz, CDCl$_3$) $\delta$ 1.62 (d, $J=7$ Hz, 3H, =$CHCH_3$), 3.48 (bs, 1H, OH), 4.11 (bs, 2H, CH$_2$), 6.21 (q, $J=7$ Hz, 1H, =$CHMe$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 16.36 (q), 63.81 (t), 102.23 (s), 137.37 (d); IR (neat) 3300, 1650 cm$^{-1}$.

\[
\begin{align*}
\text{H} & \begin{array}{c}
\text{N} \\
\text{Ts}
\end{array} & \text{OTs} & \text{H} & \begin{array}{c}
\text{N} \\
\text{Ts}
\end{array} & \text{I} & \text{OTs}
\end{align*}
\]

(±)-[1α(E),6β]-N-(2-io-do-2- but enyl)-4-methyl-N-(6-phenyl-3-cyclohex en-1-yl)-benzensulfonamide (220). To a solution of alcohol 237 (222 mg, 1.1 mmol), Et$_3$N (167 mL, 1.2 mmol) and DMAP (13 mg, 0.1 mmol) in dichloromethane (2 mL) was added TsCl (210 mg, 1.1 mmol) in one portion at 0°C. The mixture was stirred at room temperature for 3 h and quenched with water. The organic phase was separated. The aqueous layer was extracted with dichloromethane. The organic layers were combined, dried over anhydrous sodium sulfate and concentrated to afford the crude tosylate as a yellow oil which was used without further purification. To a mixture of sulfonamide 229 (248 mg, 0.758 mmol) and allylic tosylate 239 (217 mg, 0.834 mmol) in benzene (5 mL) were added nBu$_4$HSO$_4$ (175 mg, 0.5 mmol) and 50% aqueous NaOH (0.5 mL). The mixture was stirred vigorously at room temperature for 30 min, then quenched with aqueous ammonium chloride. The organic phase was separated. The aqueous layer was extracted twice with ether. The organic layers were combined, dried over anhydrous
sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography over silica gel (elution with 50% dichloromethane in hexane) afforded the desired product (321 mg, 84% yield) as a white solid: mp. 83°C; $^1$H NMR (300 MHz, CDCl$_3$) δ 1.57 (d, J=7 Hz, 3H, CH$_3$CH=), 2.30 (m, 2H, CH$_2$CH=CHCH$_2$), 2.37 (s, 3H, CH$_3$Ar), 2.57 (m, 1H, CH$_2$CH=CHCH=H), 2.78 (m, 1H, CH$_2$CH=CHCH=H), 3.30 (m, 1H, PhCH), 3.60 (d, J=15.6 Hz, 1H, CH=H), 3.85 (d, J=15.6 Hz, 1H, NCH=H), 4.18 (m, 1H, CHN), 5.68 (m, 2H, CH=CH), 6.30 (q, J=7 Hz, 3H, =CHCH$_3$), 7.12 (d, J=8 Hz, 2H, ArH), 7.28 (m, 5H, ArH), 7.51 (d, J=8 Hz, 2H, ArH); $^{13}$C NMR (63 MHz, CDCl$_3$) δ 16.85 (q), 21.39 (q), 32.09 (t), 36.75 (t), 45.29 (d), 51.92 (t), 60.35 (d), 96.94 (s), 125.49 (d), 126.08 (d), 126.49 (d), 128.26 (d), 128.53 (d), 129.05 (d), 138.61 (s), 141.90 (d), 142.63 (s), 142.79 (s); IR (KBr) 3027, 2918, 1494, 1453, 1434, 1338, 1155, 1092 cm$^{-1}$; MS (EI) m/e calc'd for C$_{23}$H$_{26}$NOSO$_2$: 507.0730, found 507.0726; 507 (5), 416 (76), 326 (37), 236 (74), 170 (46), 91 (100); Analysis calc'd for C$_{23}$H$_{26}$NOSO$_2$: C, 54.44; H, 5.16; found: C, 54.50; H, 5.24.

(±)-exo-4-Methylene-2-[4-methylphenylsulfonyl]-8-phenyl-2-azabicyclo[3.3.1]non-6-ene (230): To a solution of vinyl bromide 218 (177 mg, 0.397 mmol) in acetonitrile (8 mL) were added sequentially at room temperature triethylamine (120 µL, 0.794 mmol), triphenylphosphine (53.1 mg, 0.202 mmol) and palladium acetate (15.1 mg, 0.068 mmol). The mixture was stirred at room temperature for 10 min, then at reflux for 3 h. The reaction
was monitored by TLC (elution with 10% ethyl acetate in hexane). The solution was concentrated and the brown residue was purified by flash chromatography over silica gel (elution with 50% hexane in dichloromethane) to afford the product (126 mg, 85% yield) as a white powder: mp. 102°C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 1.40 (d, J=12.5 Hz, 1H, CH-HCH(CH=)(CH=)), 1.77 (d, J=12.5 Hz, 1H, CH(HHCH(CH=)(CH=))), 2.38 (s, 3H, CH\(_3\)Ar), 2.96 (t, J=2.8 Hz, 1H, =C=CH=), 3.61 (bs, 1H, PhCH), 4.05 (d, J=14.1 Hz, 1H, CH(HHNTs)), 4.18 (d, J=14.1 Hz, 1H, CH(HHNTs)), 4.10 (bs, 1H, CHNTs), 4.82 (s, 1H, =CH=H), 4.84 (s, 1H, =CH=H), 5.88 (dd, J=9.8, 3.7 Hz, 1H, CH=CH), 5.98 (dd, J=9.8, 6.2 Hz, 1H, CH=CH), 7.25 (m, 7H, ArH), 7.72 (d, J=8.1 Hz, 2H, ArH); \(^13\)C NMR (63 MHz, CDCl\(_3\)) \(\delta\) 21.38 (q), 26.25 (t), 36.80 (d), 45.36 (t), 46.30 (d), 54.53 (d), 109.71 (t), 126.62 (d), 126.98 (d), 128.27 (d), 128.40 (d), 129.27 (d), 129.54 (d), 130.09 (d), 137.70 (s), 142.02 (s), 142.39 (s), 143.06 (s); IR (KBr) 3010, 2905, 1595, 1485, 1435, 1335, 1150, 930 cm\(^{-1}\); MS (El) m/e calc'd for C\(_{22}\)H\(_{23}\)NSO\(_2\): 365.1449, found 365.1486; 365 (16), 210 (100), 167 (23), 155 (17), 91 (49).

(\(\pm\)-(1\(\alpha\), 4\(E\), 5\(\alpha\), 8\(\alpha\))-4-Ethylidene-2-[(4-methylphenyl)sulfonyl]-8-phenyl-2-azabicyclo[3.3.1]non-6-ene (240): To a solution of vinyl iodide 219 (268 mg, 0.520 mmol) in acetonitrile (10 mL) were added sequentially, at room temperature, triethylamine (158 \(\mu\)L, 1.04 mmol), triphenylphosphine (70 mg, 0.265 mmol), and palladium acetate (20 mg, 0.088 mmol). The mixture was stirred at room temperature for 10 min, then at reflux for 45 min. The reaction
was monitored by TLC (elution with 10% ethyl acetate in hexane). The solution was concentrated
and the brown residue was purified by flash chromatography over silica gel (elution with 50%
hexane in dichloromethane) to afford the product (176 mg, 90% yield) as a white powder: mp.
103°C; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 1.30 (d, J=12.5 Hz, 1H, CH$_2$HCH(CH=)(C=)), 1.63 (d, J=6.5
Hz, 3H, CH$_3$CH=), 1.75 (d, J=12.5 Hz, 1H, CH$_2$HCH(CH=)(C=)), 2.39 (bs, 3H, CH$_3$Ph), 3.32 (bs,
1H, PhCH), 3.62 (s, 1H, =CCH=), 4.05 (m, 3H, CH$_3$NCH$_2$), 5.38 (q, J=6.5 Hz, 1H, =CH$_2$CH$_3$), 5.82
(m, 2H, CH=CH), 7.23 (m, 7H, ArH), 7.71 (d, J=8.0 Hz, 2H, ArH); $^{13}$C NMR (63 MHz, CDCl$_3$) $\delta$
12.44 (q), 21.46 (q), 25.66 (t), 29.81 (d), 46.30 (d), 46.95 (t), 55.21 (d), 119.30 (d), 126.64 (d),
127.18 (d), 128.44 (d), 129.18 (d), 129.55 (d), 133.27 (s), 137.71 (s), 142.29 (s), 143.02 (s); IR
(KBr) 3010, 2920, 1595, 1490, 1440, 1335, 1150 cm$^{-1}$; MS (El) $m/e$ calc'd for C$_{23}$H$_{25}$NSO$_2$: 379.1606, found 379.1624; 379 (12), 224 (100), 169 (18), 117 (12), 91 (39); Analysis calc'd for
C$_{23}$H$_{25}$NSO$_2$: C, 72.79; H, 6.64; found: C, 72.64; H, 6.64.

(±)-(1α,4Z,5α,8α)-4-Ethyllide ne-2-[(4-methylphenyl)sulfonyl]-8-phenyl-2-
azabicyclo[3.3.1]non-6-ene (241): To a solution of vinyl iodide 220 (191 mg, 0.378 mmol)
in acetonitrile (8 mL) were added sequentially, at room temperature triethylamine (116 µL, 0.757
mmol), triphenylphosphine (51 mg, 0.193 mmol), and palladium acetate (14.5 mg, 0.0643 mmol).
The mixture was stirred at room temperature for 10 min, then at reflux for 90 min. The reaction
was monitored by TLC (elution with 10% ethyl acetate in hexane). The solution was concentrated
and the brown residue was purified by flash chromatography over silica gel (elution with 50%
hexane in dichloromethane) to afford the product (132 mg, 90% yield) as a white powder:
mp. 105°C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.30 (d, $J=12.5$ Hz, 1H, CH$_3$CH(CH=)(C=)), 1.61 (d,
$J=6.8$ Hz, 3H, CH$_3$CH=), 1.73 (d, $J=12.5$ Hz, 1H, CH$_3$CH(CH=)(C=)), 2.39 (bs, CH$_3$Ar), 2.83 (t,
2.6H, PhCH), 3.60 (s, 1H, =CCH=), 3.83 (d, 14.4H, CH$_2$HN), 4.13 (s, 1H, CHN), 4.52 (d, 14.4H,
CH$_2$HN), 5.30 (q, 6.8H, =CHCH$_3$), 5.86 (2H, CH=CH), 7.25 (m, 7H, ArH), 7.70 (d, $J=8.2$ Hz, 2H,
ArH); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 13.06 (q), 21.44 (q), 26.29 (t), 38.00 (d), 40.02 (t), 46.69 (d),
55.12 (d), 119.02 (d), 126.63 (d), 126.95 (d), 128.39 (d), 128.42 (d), 128.63 (d), 129.54 (d),
130.71 (d), 133.17 (s), 138.04 (s), 142.24 (s), 142.98 (s); IR (KBr) 3025, 2923, 1598, 1493,
1450, 1338, 1158 cm$^{-1}$; MS (El) m/e calc'd for C$_{23}$H$_{25}$NSO$_2$: 379.1606, found 379.1603; 379
(3), 224 (49), 169 (15), 117 (19), 91 (100); Analysis calc'd for C$_{23}$H$_{25}$NSO$_2$: C, 72.79; H, 6.64;
found: C, 72.19; H, 6.80.

(±)-trans-[(N-Carbomethoxy-6-amino)-3-cyclohexen-1-yl]-benzene (244):
A toluene solution (10 ml) of isoprene (3 mL, 30 mmol) and cinnamoyl chloride (2.5 g, 15 mmol)
was heated in a sealed tube to 190°C for one day. After cooling to room temperature, an aqueous
solution (5 mL) of sodium azide (1.17 g, 18 mmol) and nBu$_4$NHSO$_4$ (1 g, 3 mmol) was added.
The reaction mixture was stirred vigorously at room temperature for 15 min. The phases were
separated and the aqueous layer was extracted twice with toluene. The combined organic layers were dried over magnesium sulfate, and then heated to reflux for 4 h. Methanol (10 mL) was added to quench the isocyanate. The reaction mixture was kept at reflux for three hours. After cooling, the solvent was evaporated and the crude product was purified by flash chromatography over silica gel (elution with 50% hexane in dichloromethane) to afford a 3 to 1 mixture of regioisomers 243 and 244 (80% yield). One crystallization in ether/hexane yielded a single isomer (244) as a white powder: mp. 91°C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.70 (s, 3H, CH$_3$C=), 1.95 (m, 1H, CH$_3$HMe=), 2.25 (m, 2H, CH$_2$CMe=CHCH$_2$), 2.50 (bd, J=12.5 Hz, 1H, CH$_3$HMe=), 2.90 (q, J=8.4 Hz, 1H, PhCH), 3.55 (s, 3H, OCH$_3$), 3.98 (bs, 1H, CHN), 4.50 (bs, 1H, NH), 5.37 (bs, 1H, =CH), 7.20 (m, 5H, ArH); $^{13}$C NMR (63 MHz, CDCl$_3$) $\delta$ 22.96 (q), 31.92 (t), 37.64 (t), 45.34 (d), 50.61 (q), 51.80 (d), 118.97 (d), 126.56 (d), 127.57 (d), 128.48 (d), 133.64 (s), 142.90 (s), 156.45 (s); IR (KBr) 3300, 3025, 2940, 1680, 1535, 1430, 1245, 1165 cm$^{-1}$; MS (El) m/e calc’d for C$_{15}$H$_{19}$NO$_2$: 245.1415, found 245.1406; 245 (3), 177 (46), 170 (100), 155 (32), 91 (32); Analysis calc’d for C$_{15}$H$_{19}$NO$_2$: C, 73.44; H, 7.81; found: C, 73.58; H, 7.60.

(±)-trans-4-Methyl-N-(4-methyl-6-phenyl-3-cyclohexen-1-yl)-benzenesulfonamide (245): Method A: To a solution of carbamate 244 (272 mg, 1.11 mmol) in 95% ethanol (8 mL) was added 50% aqueous NaOH (2 mL). The solution was stirred at reflux for 16h. The mixture was concentrated to half its volume, washed with aqueous ammonium chloride, and
extracted with ether. The combined ether layers were dried over magnesium sulfate and concentrated. The crude amine was then dissolved in dichloromethane (15 mL). Triethylamine (222 μL, 1.44 mmol), TsCl (330 mg, 1.7 mmol), and a catalytic amount of DMAP were successively added at room temperature. The mixture was stirred at room temperature overnight. The reaction was quenched with aqueous ammonium chloride. The layers were separated. The aqueous layer was extracted twice with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated. Purification by flash chromatography over silica gel (elution with 40% hexane in dichloromethane) yielded the expected sulfonamide 245 (301 mg, 80%) as a pale yellow powder: mp. 112°C; 1H NMR (300 MHz, CDCl₃) δ 1.66 (s, 3H, CH₃C=), 2.25 (m, 4H, CH₂C=CHCH₂CH₂), 2.43 (s, 3H, CH₃Ar), 2.82 (m, 1H, PhCH), 3.35 (m, 1H, CHN), 4.40 (bd, J=5.1 Hz, 1H, NH), 5.31 (bs, 1H, =CH), 6.90 (m, 2H, ArH), 7.19 (m, 5H, ArH), 7.50 (d, J=8.0 Hz, 2H, ArH); 13C NMR (63 MHz, CDCl₃) δ 21.50 (q), 22.89 (q), 32.57 (t), 37.16 (t), 45.33 (d), 53.39 (d), 118.71 (d), 126.97 (d), 127.16 (d), 127.52 (d), 128.81 (d), 129.52 (d), 133.44 (s), 137.05 (s), 141.70 (s), 143.07 (s); IR (neat) 3260, 3020, 2905, 1700, 1595, 1490, 1435, 1320, 1150 cm⁻¹; MS (El) m/e calc'd for C₂₀H₂₃NO₂: 341.1449, found 341.1438; 341 (3), 273 (18), 191 (35), 170 (100), 155 (64), 118 (36), 91 (86).

(±)-**trans**-(4-Methyl-6-phenyl-3-cyclohexen-1-yl)-benzene (246): A mixture of β-nitrostyrene (5.0 g, 33.5 mmol), isoprene (10 mL, 100.5 mmol), and anhydrous lithium perchlorate (16 g, 150 mmol) in ether (35 mL) was heated in a sealed tube to 70°C for two days.
The mixture was diluted with ether (200 mL), and washed with water (2x100 mL). The ether layer was dried over anhydrous sodium sulfate and concentrated to afford the desired compound (6.50 g, 90% yield) as a pale yellow solid: mp. 97°C; \( ^1 \)H NMR (250 MHz, CDCl\(_3\)) \( \delta \) 1.68 (s, 3H, \(-\text{CCH}_3\)), 2.30 (m, 2H, \(-\text{CHCH}_2\)), 2.70 (m, 2H, \(-\text{CHCH}_2\)), 3.42 (m, 1H, PhCH), 4.90 (m, 1H, CHNO\(_2\)), 5.38 (s, 1H, -CH), 7.20 (m, 5H, ArH); \( ^{13} \)C NMR (63 MHz, CDCl\(_3\)) \( \delta \) 22.7 (q), 31.20 (t), 37.91 (t), 44.51 (d), 87.38 (d), 116.81 (d), 127.34 (d), 127.51 (d), 128.81 (d), 134.07 (s), 140.20 (s); IR (KBr) 3020, 2840, 1580, 1380, 690 cm\(^{-1}\); MS (El) \( m/e \) 170 (80), 155 (76), 91 (100), 77 (22).

(\pm\)-trans-4-Methyl-N-(4-methyl-6-phenyl-3-cyclohexen-1-yl)-benzenesulfonamide (245): Method B: To a solution of nitro compound 246 (1.1 g, 5 mmol) in THF (75 mL) and water (7.5 mL), was added freshly prepared aluminum amalgam (2.7 g) in one portion at room temperature. The heterogeneous mixture was stirred at room temperature for 24 h, and then poured into 300 mL of THF. The mixture was filtered through a cake of Celite and the filtrate was dried over anhydrous sodium sulfate. Concentration under reduced pressure gave the crude primary amine, which was not further purified. The amine was dissolved in dichloromethane (30 mL). Triethylamine (1.0 mL, 6.5 mmol), TsCl (1.2 g, 6.0 mmol) and DMAP (50 mg, 0.40 mmol) were successively added at room temperature. The solution was stirred at room temperature for 16 h. The reaction was quenched with aqueous ammonium chloride. The layers were separated. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried
over anhydrous magnesium sulfate and concentrated. Purification by flash chromatography over silica gel (elution with 10% ethyl acetate in hexane) yielded the desired sulfonamide 245 (1.2 g, 70% yield) as a pale yellow powder.

(±)-[1 α(E), 6 β]-N-(2-iodo-2-butanyl)-4-methyl-N-(4-methyl-6-phenyl-3-cyclohexen-1-yl)-benzensulfonamide (247): To a mixture of sulfonamide 245 (407 mg, 1.20 mmol) and tosylate 238 (540 mg, 1.50 mmol) in benzene (10 mL) were added nBu₄HSO₄ (441 mg, 1.30 mmol), and 50% aqueous NaOH (2 mL). The mixture was stirred vigorously at room temperature for 2 h, then quenched with 1N HCl (1 mL) and distilled water (5 mL). The organic phase was separated. The aqueous layer was extracted twice with ether. The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude material was purified by flash chromatography over silica gel (elution with 10% ethyl acetate in hexane) to give the desired product (432 mg, 70% yield) as a pale yellow viscous oil: 

$^1$H NMR (300 MHz, CDCl₃) δ 1.48 (d, J=6.0 Hz, 3H, CH₂=CH), 1.60 (s, 3H, CH₃C=), 2.20 (m, 4H, CH₂C=CH), 2.39 (s, 3H, CH₃Ar), 3.05 (m, 1H, PhCH), 3.82 (d, J=17.0 Hz, 1H, CHJdN), 3.90 (d, J=17.0 Hz, 1H, CHJdN), 4.26 (m, 1H, CHN), 5.29 (bs, 1H, =CH₂CH₂), 5.42 (q, J=6.0 Hz, 1H, =CHCH₃), 7.12 (m, 7H, ArH), 7.54 (d, J=8.0 Hz, 2H, ArH); $^{13}$C NMR (63 MHz, CDCl₃) δ 21.46 (q), 21.96 (q), 22.60 (q), 31.07 (t), 41.67 (t), 44.86 (d), 56.67 (t), 58.70 (d), 104.29 (s), 119.46 (d), 125.34 (s), 126.37 (d), 127.67 (d), 128.00 (d), 128.29 (d), 129.34 (d), 133.29 (s), 133.38 (d),
(±)-(1 α, 4E,5 α, 8 α)-4-Ethylidene-6-methyl-2-[(4-methylphenyl)sulfonyl]-8-phenyl-2-azabicyclo[3.3.1]non-6-ene (249): To a solution of vinyl iodide 247 (157 mg, 0.300 mmol) in acetonitrile (6 mL) were added sequentially, at room temperature, triethylamine (92 µl, 0.600 mmol), triphenylphosphine (39 mg, 0.150 mmol), and palladium acetate (12 mg, 0.050 mmol). The mixture was stirred at room temperature for 10 min, then at reflux for 45 min. The reaction was monitored by TLC (elution with 10% ethyl acetate in hexane). The solution was quenched with water (3 mL). The organic phase was separated. The aqueous layer was extracted twice with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The brown residue was purified by flash chromatography over silica gel (elution with 50% hexane in dichloromethane) to afford the product (106 mg, 90% yield) as a white powder: mp. 113°C; 1H NMR (250 MHz, CDCl3) δ 1.30 (m, 1H, C(HCH(C=)2), 1.65 (m, 1H, C(HCH(C=)2), 1.68 (d, J=6.7 Hz, 3H, CH3C=), 1.75 (s, 3H, CH3C=), 2.41 (s, 3H, CH3Ar), 3.15 (bs, =CCHC=), 3.53 (bs, PhCH), 4.00 (m, 3H, CHNCH2), 5.47 (q, J=6.7 Hz, 1H, =CH(CH2), 5.56 (bs, 1H, =CHCH), 7.20 (m, 7H, ArH), 7.73 (d, 8.0H, ArH); 13C NMR (63 MHz, CDCl3) δ 12.56 (q), 21.50 (q), 22.27 (q), 26.31 (t), 34.73 (d),
46.28 (d), 47.10 (t), 54.53 (d), 119.85 (d), 123.36 (d), 126.55 (d), 127.17 (d), 128.41 (d), 129.58 (d), 133.06 (s), 137.08 (s), 138.08 (s), 143.01 (s), 143.03 (s); IR (KBr) 3020, 2920, 1592, 1485, 1438, 1325, 1150, 1090 cm⁻¹; MS (El) m/e calc'd for C_{24}H_{27}NSO_2: 393.1762, found 393.1753; 393 (24), 238 (60), 183 (23), 155 (23), 91 (100); Analysis calc'd for C_{24}H_{27}NSO_2: C, 73.25; H, 6.92; found: C, 73.28; H, 6.99.

(±)-trans-(1α,4E,5α,8α)-4-Ethylidene-6-methenyl-2-[(4-methylphenyl)sulfonyl]-8-phenyl-2-azabicyclo[3.3.1]non-6-ene (250): To a solution of vinyl iodide 247 (45 mg, 0.086 mmol) in DMF (1 mL) were added sequentially, at room temperature, K₂CO₃ (60 mg, 0.432 mmol), nBu₄NCl (37 mg, 0.129 mmol), and palladium acetate (1.0 mg, 0.004 mmol). The mixture was stirred at 80°C for 3h. The reaction was monitored by TLC (elution with 10% ethyl acetate in hexane). The solution was quenched with water (3 mL), and diluted with ether. The organic phase was separated. The aqueous layer was extracted twice with ether. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The brown residue was purified, first by flash chromatography over silica gel (elution with 50% hexane in dichloromethane), then by MPLC (same eluent) to afford two fractions. The first fraction contained the exocyclic alkene 250 (8.5 mg, 25% yield), and the second, the endocyclic isomer 249 (17 mg, 50% yield). Bicycle 250: mp. 109°C; ¹H NMR (300 MHz, CDCl₃) δ 1.40 (dt, J=13.7, 2.6 Hz, 1H, CHCH=CH(C=)₂), 1.60 (d, J=6.9 Hz, 3H, CH₃CH=),
1.70 (dt, J=13.7, 2.6 Hz, 1H, CH\(\text{Ph}CH(C=)\)), 2.39 (s, 3H, CH\(_3\text{Ar}\)), 2.52 (d, J=15 Hz, 1H, CH\(\text{Ph}H\)), 2.96 (dd, J=15, 7 Hz, 1H, CH\(\text{Ph}C\)), 3.37 (bs, 1H, CH\(\text{Ph}C\)), 3.50 (bd, J=7 Hz, 1H, PhCH), 3.61 (d, J=13.4 Hz, 1H, NCH\(_{3}\)), 5.00 (s, 1H, =CH\text{H}), 5.54 (q, 6.9H, =CH\text{CH}_3), 7.22 (m, 5H, ArH), 7.53 (d, J=7.2 Hz, 2H, ArH), 7.70 (d, J=8.3 Hz, 2H, ArH); \(^{13}\text{C} \text{NMR} \text{ (63 MHz, CDCl}_3\)) \(\delta\) 13.15 (q), 21.48 (q), 25.33 (t), 30.88 (t), 38.47 (d), 45.69 (d), 48.88 (t), 55.90 (d), 110.54 (t), 123.40 (d), 126.17 (d), 127.43 (d), 128.21 (d), 128.39 (d), 129.68 (d), 133.69 (s), 134.79 (s), 143.32 (s), 144.32 (s), 147.32 (s); IR (CH\(_2\text{Cl}_2\)) 3040, 2920, 1595, 1490, 1450, 1345, 1160, 1090 cm\(^{-1}\); MS (El) \text{m/e calc'd for C}_{24}\text{H}_{27}\text{NSO}_2: 393.1762, found 393.1753; 393 (4), 302 (10), 262 (29), 238 (36), 146 (13), 106 (16), 91 (100).

\(\pm\)-\text{trans}-2-(6-Amino-3-cyclohexen-1-yl)-1-nitro-benzene (260): A mixture of ortho nitro cinnamic acid (800 mg, 4 mmol), thionyl chloride (8 mL) and benzene (8 mL) was stirred at reflux for 35 min. The solution was then cooled to room temperature and concentrated to afford a quantitative yield of ortho nitro cinnamoyl chloride, a beige solid which was used in the next step without further purification. A suspension of ortho nitro cinnamoyl chloride (846 mg, 4 mmol) in toluene (4 mL) was cooled to -78°C (dry ice acetone bath), and a stream of butadiene was bubbled into the preweighted sealed tube (2.6 g,48 mmol of butadiene were added). The tube was sealed and heated to 140°C (oil bath) for 18 h. After cooling to room temperature, a solution of nBu\(_4\text{NHSO}_4\) (330 mg,1 mmol) and sodium azide (667 mg,10 mmol) in water (2 mL) was added.
The mixture was stirred vigorously at room temperature for 20 min. The phases were separated and the aqueous layer was extracted with toluene. The combined organic layers were dried over magnesium sulfate and filtered. Concentrated HCl (0.5 mL) was added to the toluene solution, which was then heated to reflux for 1 h. The heterogeneous mixture was cooled to 0°C (ice water bath) and the ammonium salt (651 mg) was collected by suction filtration. The free amine was obtained upon basification with aqueous sodium hydroxide, followed by extraction with ether (558 mg, 64% yield): mp. 96°C; \(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\) 1.12 (bs, 2H, NH\(_2\)), 1.95 (m, 1H, \(-CCH\)), 2.22 (m, 1H, \(-CCH\)), 2.50 (m, 2H, \(-CH\)), 3.27 (m, 2H, CHN and ArCH), 5.31 (m, 2H, CH=CH), 7.37 (t, \(J=8.1\) Hz, 1H, ArH), 7.46 (d, \(J=8.1\) Hz, 1H, ArH), 7.61 (t, \(J=8.1\) Hz, 1H, ArH), 7.71 (d, \(J=8.1\) Hz, 1H, ArH); \(^1^3\)C NMR (63 MHz, CDCl\(_3\)) \(\delta\) 34.07 (t), 35.44 (t), 43.67 (d), 50.85 (d), 123.74 (d), 125.57 (d), 125.91 (d), 126.96 (d), 128.09 (d), 132.58 (d), 138.07 (s), 151.61 (s); IR (CH\(_2\)Cl\(_2\)) 3408, 3029, 2923, 1644, 1608, 1520, 1435, 1351 cm\(^{-1}\); MS (El) \(m/e\) calc'd for C\(_{12}\)H\(_{14}\)N\(_2\)O\(_2\): 218.1055, found 218.1131; 219 (11), 184 (12), 172 (15), 147 (12), 115 (13), 82 (100), 77 (15), 51 (8); Analysis calc'd for C\(_{12}\)H\(_{14}\)N\(_2\)O\(_2\): C, 66.04; H, 6.47; found: C, 66.07; H, 6.31.

\(\pm\)-trans-2-\([N-(2-\text{Phenylsulfonyl})\text{ethyl}-6-amino-3-cyclohexen-1-yl]-1-nitrobenzene\) (261): A mixture of amine 260 (863 mg, 3.959 mmol) and vinyl phenyl sulfone (673 mg, 3.959 mmol) in methanol (8 mL) was stirred at reflux for 2 h. The solution was cooled to room
temperature and concentrated. One recrystallization in ether / hexane afforded the product (1.5 g, 98% yield) as a pure yellow solid: mp. 95°C (dec); \(^1H\) NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.80 (m, 1H, =CCH), 2.20 (m, 1H, =CCH), 2.42 (m, 2H, =CCH x2), 3.00 (m, 5H, NCH\(_2\)CH\(_2\)SO\(_2\)Ph and CHN), 3.32 (m, 1H, ArCH), 5.70 (m, 2H, CH=CH), 7.50 (m, 9H, ArH); \(^{13}\)C NMR (63 MHz, CDCl\(_3\)) \(\delta\) 31.58 (t), 32.84 (t), 40.01 (d), 40.14 (t), 55.95 (d), 56.12 (t), 124.03 (d), 124.86 (d), 126.05 (d), 127.17 (d), 127.82 (d), 128.37 (d), 129.24 (d), 132.70 (d), 133.70 (d), 137.75 (s), 139.25 (s), 151.06 (s); IR (CH\(_2\)Cl\(_2\)) 3395, 3028, 2928, 1666, 1524, 1306, 1148 cm\(^{-1}\); MS (El) m/e calc'd for C\(_{20}\)H\(_{22}\)N\(_2\)SO\(_4\): 386.1300, found 386.1291; 386 (12), 369 (21), 341 (21), 315 (41), 250 (100), 137 (49), 77 (94); Analysis calc'd for C\(_{20}\)H\(_{22}\)N\(_2\)SO\(_4\): C, 62.16; H, 5.74; found: C, 62.30; H, 5.71.

(±)-trans-2-[N-(2-Phenylsulfonyl)ethyl-N-(2-bromo-2-propenyl)-6-amino-3-cyclohexen-1-yl]-1-nitro-benzene (262): A mixture of secondary amine 261 (405 mg, 1.117 mmol), 2,3-dibromopropene (577 mL, 5.587 mmol) and K\(_2\)CO\(_3\) (772 mg, 5.587 mmol) in DMF (2 mL) was stirred at 90°C for 6 h. The mixture was diluted with dichloromethane and washed with water. The phases were separated, and the organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by flash chromatography over silica gel (elution with 17% ethyl acetate in hexane) to give the tertiary amine 262 (531 mg, 94% yield) as a pale yellow solid: mp. 122°C (dec); \(^1H\) NMR (250 MHz, CDCl\(_3\)) \(\delta\) 2.15 (m, 3H, =CCH x3), 2.50 (m,
1H, =CCH), 2.72 (m, 2H, CH₂SO₂Ph), 2.85 (m, 1H, CHN), 3.10 (m, 4H, CHN x4), 3.45 (m, 1H, ArH), 5.22 (two s, 2H, =CH₂), 5.68 (m, 2H, CH=CH), 7.35 (m, 2H, ArH), 7.60 (m, 3H, ArH), 7.85 (d, J=8.0 Hz, 2H, ArH); ¹³C NMR (63 MHz, CDCl₃) δ 25.52 (t), 36.28 (t), 38.50 (d), 44.25 (t), 55.08 (t), 59.10 (t), 59.97 (d), 118.33 (t), 123.76 (d), 125.13 (d), 126.10 (d), 126.77 (d), 127.81 (d), 129.29 (d), 129.88 (d), 131.65 (s), 132.18 (d), 133.73 (d), 137.76 (s), 139.02 (s), 150.64 (s); IR (CH₂Cl₂) 3026, 2917, 1607, 1520, 1480, 1446, 1352, 1306, 1148 cm⁻¹; MS (El) m/e calc'd for C₂₃H₂₅N₂O₄SBr: 504.0719, found 504.0736; 504 (8), 425 (10), 370 (100), 290 (15), 250 (13), 167 (16), 141 (12), 77 (44).

(±)-trans-2-[N-(2-Phenylsulfonyl)ethyl-N-(2-bromo-2-propenyl)-6-amino-3-cyclohexen-1-yl]-aniline (258): Compound 262 was dissolved in methanol saturated with copper acetate (9 mL). Sodium borohydride (212 mg, 5.54 mmol) was added in five portions at room temperature, over a period of 30 min. The reaction was monitored by TLC (elution with 30% ethyl acetate in hexane). After disappearance of the starting material (about 45 min), the black mixture was filtered through a cake of Celite. The filtrate was diluted with ether and washed with 2N aqueous sodium hydroxide. The organic phase was separated and dried over anhydrous sodium sulfate and concentrated to afford the desired product (261 mg, 99% yield) as a beige solid: mp. 109°C (dec.); ¹H NMR (300 MHz, CDCl₃) δ 2.18 (m, 4H, =CHCH₂), 2.70 (m, 5H, ArCH, CH₂CH₂SO₂Ph), 3.12 (d, J=15.4 Hz, 1H, =CCl₃H₂N), 3.20 (m, 1H, CHN), 3.27 (d, J=15.4 Hz, 1H,
\(-\text{CCHHN})\), 3.55 (bs, 2H, NHg), 5.26 (s, 1H, \(-\text{CCH})\), 5.40 (s, 1H, \(-\text{CHH})\), 5.70 (m, 2H, CH=CH), 6.62 (d, J=6.5 Hz, 1H, ArH), 6.70 (t, J=6.5 Hz, 1H, ArH), 6.95 (m, 2H, ArH), 7.58 (m, 3H, ArH), 7.81 (m, 2H, ArH); \(^{13}\text{C} \text{NMR}\) (63 MHz, CDCl\(_3\)) \(\delta 27.13, 34.58, 38.32, 43.81, 55.47, 60.98, 61.13, 116.71, 118.07, 119.28, 125.64, 126.74, 126.94, 127.95, 128.22, 129.23, 129.29, 132.49, 133.67, 139.59, 143.83; IR (CH\(_2\)Cl\(_2\)) 3300, 3020, 2920, 1520, 1450, 1300, 1150, 1080, 730 cm\(^{-1}\); MS (El) m/e 370 (100), 290 (11), 170 (20), 106 (49), 77 (58).

\[\begin{array}{c}
\text{PhO}_2\text{S} \quad \text{N} \quad \text{Ph} \\
\text{H} \quad \text{Br} \quad \text{N} \quad \text{PhO}_2\text{S} \\
\end{array}\]

\([\pm]-1\alpha,3,4,5\alpha,6,7\text{-Hexahydro-4-methylene-2-[2-(phenylsulfonyl)ethyl]-1,5-methano-2H-azocino[4,3-b]Indole}\) (263): A mixture of vinyl bromide 258 (69 mg, 0.145 mmol), triethylamine (40 \(\mu\)l, 0.290 mmol), triphenylphosphine (19 mg, 0.74 mmol) and Pd(OAc)\(_2\) (5.5 mg, 0.025 mmol) in acetonitrile (3 mL) was stirred at room temperature for 10 min, then at reflux for 4h. The mixture was cooled to room temperature and additional palladium acetate (32 mg, 0.145 mmol) was added. The mixture was refluxed for 2 h, cooled to room temperature and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel (elution with 50\% ethyl acetate in hexane) to afford tetracycle 263 (30 mg, 53\% yield) as a pale yellow solid: mp. 190°C (dec.); \(^1\text{H} \text{NMR}\) (250 MHz, CDCl\(_3\)) \(\delta 1.76\) (bd, J=12.1 Hz, 1H, NCHCHHN), 1.90 (bd, J=12.1 Hz, 1H, NCHCHH), 2.51 (m, 1H, CH=CHCH\(_2\)SO\(_2\)Ph), 2.53 (d, J=17.2 Hz, 1H, \(-\text{CCHHN})\), 2.57 (d, J=12.7 Hz, 1H, N(C=)CHH), 2.78 (d, J=12.7 Hz, 1H,
N(C=CHH), 2.82 (bs, 1H, CHC=), 3.00 (d, J=17.2 Hz, 1H, CH=CHN), 3.12 (m, 1H, CH\_\_\_\_SO\_\_Ph), 3.43 (m, 2H, CH\_\_\_\_SO\_\_Ph), 4.03 (bs, 1H, CHN); \(^{13}\)C NMR (63 MHz, CDCl\_3) δ 33.24 (t), 35.27 (d), 50.07 (t), 106.38 (s), 109.02 (t), 110.55 (d), 118.02 (d), 119.94 (d), 121.22 (d), 127.82 (s), 128.40 (d), 129.07 (d), 131.92 (s), 132.17 (d), 135.80 (s), 139.75 (s), 147.99 (s); IR (CH\_2Cl\_2) 3360, 3040, 2920, 1660, 1445, 1300, 1140, 730 cm\(^{-1}\); MS (EI) m/e calc'd for C\_23H\_24N\_2SO\_2: 392.1558, found 392.1564; 392 (23), 354 (18), 288 (35), 262 (21), 208 (63), 169 (81), 168 (100), 130 (68), 125 (47), 77 (62).

\[
\begin{align*}
\text{278} & \xrightarrow{1,2\text{-dibromoethane}} \text{279} \\
& \quad \quad 50\% \text{ NaOH in H\_2O} \\
& \quad \quad MeCN, nBu\_4\text{NBr}
\end{align*}
\]

1-(2-Nitrophenyl)-cyclopranecarbonitrile (279). To a solution of 2-nitrophenyl-acetonitrile (2.65 g, 16 mmol), dibromoethane (13.6 mL, 160 mL) and nBu\_4\text{NBr} (5.21 g, 16 mmol) in acetonitrile (40 mL) was added 50% aqueous NaOH (8.0 mL), in one portion, at room temperature. The dark purple solution was stirred at room temperature for 12 h. The reaction mixture was then quenched with 2N HCl (64 mL), and the layers were separated. The aqueous layer was extracted twice with ether. The combined organic layers were washed with saturated aqueous NaHCO\_3 and brine, then dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The brown residue was purified by flash chromatography over silica gel (elution with 30% hexane in dichloromethane) to afford the desired product (2.92 g, 96% yield) as a pale yellow solid: mp. 78°C; \(^1\)H NMR (200 MHz, CDCl\_3) δ 1.26 (dd, J=7, 5 Hz, 2H, CH\_\_\_H), 1.74 (dd, J=7, 5 Hz, 2H, CH\_\_\_H), 7.55 (m, 3H, ArH), 7.98 (d, J=6.5 Hz, 1H, ArH); \(^{13}\)C NMR (63
MHz, CDCl$_3$ $\delta$ 12.8 (s), 16.2 (t), 121.4 (s), 125.0 (d), 130.0 (d), 130.5 (s), 132.8 (d), 133.6 (d), 150.0 (s); IR (KBr) 3032, 2234, 1750, 1738, 1675, 1444, 1256, 1173 cm$^{-1}$; MS (El) m/e calc'd for C$_{10}$H$_8$N$_2$O$_2$: 188.0586, found 188.0506; 160 (27), 140 (22), 116 (98), 102 (100), 89 (17), 77 (22), 63 (23), 51 (28); Analysis calc'd for C$_{10}$H$_8$N$_2$O$_2$: C, 63.83; H, 4.28; found: C, 63.72; H, 4.49.

![Chemical Structure](image)

1-((2-Nitrophenyl)cyclopropanecarboxaldehyde (280). A 1.0 M hexane solution of DIBAL-H (1.46 mL, 1.46 mmol) was added to a chilled solution (-78°C) of cyclopropanenitrile 279 (154 mg, 0.81 mmol) in toluene (4.5 mL). After 5 min at -78°C, water was added (1 mL), and the reaction mixture was allowed to warm up to room temperature. The mixture was poured into 1N HCl (9 mL) and stirred at room temperature for 5 min. The phases were separated, and the aqueous layer was extracted six times with ether. The combined organic layers were washed with saturated aqueous bicarbonate and brine, then dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield the expected aldehyde (160 mg, 97% yield) as a yellow oil which was not further purified (aldehyde 280 was unstable over silica gel): $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 1.34 (dd, J=7.7, 4.6 Hz, 2H, CH=CHCH$_3$), 1.69 (dd, J=7.7, 4.6 Hz, 2H, CH=CHCH$_3$), 7.55 (m, 3H, ArH), 7.98 (dd, J=7.9, 1.4 Hz, 1H, ArH), 9.10 (s, 1H, CHO); $^{13}$C NMR (63 MHz, CDCl$_3$) $\delta$ 15.64 (t), 35.32 (s), 124.69 (d), 129.02 (d), 132.61 (s), 133.22 (d), 133.36 (d), 151.01 (s), 198.08 (d); IR (neat) 3086, 2830, 1713, 1610, 1575, 1520, 1489, 1249, 903 cm$^{-1}$. 

MS (El) m/e calc'd for C_{10}H_{9}NO_{3}: 191.0582, found 191.0556; 191 (1), 134 (90), 115 (64), 104 (100), 91 (45), 79 (63), 63 (44), 51 (47).

\[
\begin{align*}
&\text{280} \\
&\text{1-PhNH}_{2}\text{, ether} \\
&\text{2-} \text{method A or B} \\
&\text{282}
\end{align*}
\]

2,3-Dihydro-3-(2-nitrophenyl)-1-phenylmethyl-1H-pyrrole (282): A mixture of cyclopropylaldehyde 280 (580 mg, 3.0 mmol) and benzylamine (345 mL, 3.2 mmol) in ether (5 mL) was stirred at room temperature for 4 h. The solution was diluted with toluene (10 mL) and concentrated under reduced pressure to afford the crude imine (831 mg, 99% yield) as a brown oil, which was used as such in the next step.

Method A: To a solution of the crude imine in acetonitrile (25 mL) was added solid ammonium chloride (53 mg, 1 mmol). The mixture was placed in a sealed tube and heated to 125°C for 4 h. The resulting dark red solution was cooled to room temperature and washed with water. The phases were separated and the aqueous layer was extracted with ether. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by flash chromatography over silica gel (elution with 50% hexane in dichloromethane) afforded the product (750 mg, 91% yield) as a dark red solid.

Method B: To a solution of the crude imine (1.70 g, 6.34 mmol) in DMF (22 mL) was added, at room temperature, nBu_{4}NI (867 mg, 2.35 mmol), and TMSCl (406 mL, 3.14 mmol). The mixture was stirred at 60°C for 3 h, cooled to room temperature, and washed with 2 N NaOH (5 mL) and water (50 mL). The mixture was extracted with ether/hexane (1:1). The combined organic
layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude oil was purified by flash chromatography over silica gel (elution with 50% hexane in dichloromethane) to yield the product (1.53 g, 90% yield) as a red solid: mp. 50°C (dec.); $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 2.70 (t, $J$=9.5 Hz, 2H, CH$_2$CH$_2$N), 3.17 (t, $J$=9.5 Hz, 2H, CH$_2$CH$_2$N), 4.06 (s, 2H, PhCH$_2$), 6.57 (t, $J$=1.3 Hz, 1H, CHN), 7.03 (t, $J$=7.2 Hz, 1H, ArH), 7.18 (d, $J$=9.4 Hz, 1H, ArH), 7.30 (m, 6H, ArH), 7.46 (d, $J$=8.0 Hz, 1H, ArH); $^{13}$C NMR (63 MHz, CDCl$_3$) $\delta$ 31.0 (t), 51.8 (t), 56.2 (t), 107.6 (s), 123.7 (d), 123.8 (d), 127.4 (d), 127.7 (d), 128.2 (d), 128.5 (d), 130.6 (s), 131.3 (d), 137.3 (s), 141.8 (d), 147.1 (s); IR (neat) 3020, 2980, 1588, 1515, 1357, 1158 cm$^{-1}$; MS (El) m/e calc'd for C$_{17}$H$_{16}$N$_2$O$_2$: 280.1212. found 280.1211; 280 (12), 145 (11), 115 (12), 91 (100), 65 (20); Analysis calc'd for C$_{17}$H$_{16}$N$_2$O$_2$: C, 72.84; H, 5.75; found: C, 72.84; H, 5.85.

![Reactions](image.png)

3-(2-nitrophenyl)-1-phenylmethyl-1H-pyrrole (283): An heterogeneous mixture of the crude imine 281 (323 mg, 1.24 mmol) and ammonium chloride (14 mg, 0.264 mmol) was heated to 120°C under an Argon atmosphere for 12 h. The crude mixture was directly purified by flash chromatography over silica gel (elution with 10% ethyl acetate in hexane) to afford the product (265 mg, 77%) as a yellow oil. $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 5.06 (s, 2H, CH$_2$N), 6.30 (t, $J$=4 Hz, ArH pyrrole), 6.71 (t, $J$=4Hz, ArH pyrrole), 6.88 (t, $J$=4 Hz, ArH pyrrole), 7.40 (m, 9H, ArH); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 53.59 (t), 108.61 (d), 119.12 (s), 120.07 (d), 122.14 (d), 123.23 (d),
126.11 (d), 127.10 (d), 127.86 (d), 128.81 (d), 129.68 (s), 130.69 (d), 131.37 (d), 137.34 (s),
149.04 (s); IR (neat) 3020, 2980, 1585, 1515, 1357 cm⁻¹; MS (El) m/e calc'd for C₁₇H₁₆N₂O₂:
278.1053, found 278.1089; 278 (14), 91 (100), 65 (34).

![Chemical Structure](image)

1-Carbomethoxy-2,3-dihydro-3-(2-nitrophenyl)-1-H-pyrrole (299). To an acetone
solution (8 mL) of the pyrrole 282 (470 mg, 1.68 mmol) was added at room temperature
methylchloroformate (1.3 mL, 16.8 mmol). The mixture was stirred at room temperature for 16 h,
then diluted with dichloromethane, and washed with aqueous ammonium chloride. The phases
were separated and the aqueous layer was extracted with dichloromethane. The combined
organic layers were dried over anhydrous sodium sulfate and concentrated under reduced
pressure. The crude product was purified by flash chromatography over silica gel (elution with
20% ethyl acetate in hexane) to give 375 mg (90% yield) of the desired product as a yellow solid:
mp. 80°C; ¹H NMR (300 MHz, CDCl₃) δ 2.90 (t, J=9.0 Hz, 2H, CH₂CH₂N), 3.77 (s, 3H, OMe),
3.91 (m, 2H, CH₂CH₂N), 6.78 (bs, 1H, =CHN), 6.91 (bs, 1H, =CHN other amide rotamer), 7.35 (m,
2H, ArH), 7.48 (t, J=6.4 Hz, 1H, ArH), 7.70 (d, J=9.0 Hz, 1H, ArH); ¹³C NMR (75 MHz, CDCl₃) δ
30.3 (t), 31.2 (t), 45.8 (t), 52.7 (q), 117.4 (s), 117.7 (s), 123.9 (d), 127.3 (d), 128.2 (d), 129.1 (d),
129.5 (s), 129.8 (d), 130.0 (d), 132.0 (d), 148.3 (s), 152.4 (s), 153.1 (s); IR (CHCl₃) 3000, 2960,
1710, 1630, 1530, 1450, 1410, 1260, 1130, 980 cm⁻¹; MS (El) m/e calc'd for C₁₂H₁₂N₂O₄:
248.0797, found 278.0789; 248 (22), 145 (100), 115 (76), 90 (39), 77 (30), 59 (56); Analysis
1-Carboxy-2,3-dihydro-3-(2-aminophenyl)-1H-pyrrole (300): To a mixture of the starting nitro aromatic 299 (424 mg, 1.70 mmol) and 5% Pd/C (170 mg) in methanol (8.4 mL) was added ammonium formate (1.11 g, 17.0 mmol) at 20°C (water bath), over a period of 1 h. The reaction mixture was filtered through a cake of Celite and concentrated under reduced pressure. The crude residue was triturated with water and the insoluble product (349 mg, 95% yield, yellow solid) was isolated by suction filtration: mp. 106°C; 1H NMR (250 MHz, CDCl3) δ 3.01 (m, 2H, CH₂CH₂N), 3.65 (s, 3H, OMe), 3.88 (m, 2H, CH₂CH₂N), 6.70 (m, 2H, ArH and =CHN), 7.00 (m, 3H, ArH and =CHN). 13C NMR (75 MHz, CDCl3) δ 31.4 (t), 32.6 (t), 44.4 (t), 44.6 (t), 52.5 (q), 116.2 (d), 118.5 (d), 118.7 (d), 119.4 (s), 119.6 (s), 120.6 (s), 120.8 (s), 125.7 (d), 126.2 (d), 127.2 (d), 143.8 (s); IR (CH₂Cl₂) 3430, 3350, 3050, 2980, 1700, 1615, 1495, 1460, 1405, 1265, 1120 cm⁻¹; MS (EI) m/e calc'd for C₂H₁₄N₂O₂: 218.1055, found 218.1053; 218 (31), 143 (13), 130 (100), 117 (9), 77 (10), 59 (7); Analysis calc'd for C₂H₁₄N₂O₂: C, 66.04; H, 6.47; found: C, 65.93; H, 6.49.
1-Carboxymethoxy-2,3-dihydro-3-[N'-{(1,3-butadine-1-yl)}-N'-carboxymethoxy-2-aminophenyl]-1H-pyrrole (307): To the aniline derivative 300 (750 mg, 3.438 mmol) was added crotonaldehyde at room temperature (1.54 mL, 17.20 mmol). The mixture was stirred at room temperature for 1 h, and then diluted with toluene (100 mL). After concentration under reduced pressure, the crude imine was dissolved in toluene (17.0 mL). DMAP (84 mg, 0.688 mmol), N,N,N',N'-tetramethyl-1,8-diaminonaphtalene (proton sponge) (960 mg, 4.470 mmol) and methylchloroformate (320 mL, 4.126 mmol) were sequentially added at 0°C (ice water bath). The mixture was allowed to warm up to room temperature, stirred for 8 h, and quenched with aqueous ammonium chloride. The organic phase was separated, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude material was purified by flash chromatography over silica gel (elution with 50% ethyl acetate in hexane) to afford the expected product (750 mg, 70% yield) as a yellow solid: mp. 118°C (dec.); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.90 (t, $J$=7 Hz, 2H, CH$_2$CH$_2$N), 3.71 (m, 6H, 2x OMe), 3.82 (m, 2H, CH$_2$CH$_2$N), 4.83 (m, 2H, CH=CH$_2$), 5.02 (dd, $J$=12.7, 7.5 Hz, 1H, CH=CH$_2$), 6.32 (m, 1H, N(CO$_2$Me)CH=CH$_2$), 6.86 (two bs, 1H, ArC=CHN), 7.12 (d, $J$=7.1 Hz, 1H, N(CO$_2$Me)CH=CH$_2$), 7.32 (m, 4H, ArH); $^{13}$C NMR (63 MHz, CDCl$_3$) $\delta$ 30.67 (t), 31.66 (t), 45.35 (l), 52.80 (q), 53.66 (q), 113.36 (d), 113.92 (l), 117.91 (s), 127.32 (s), 127.58 (d), 128.10 (d), 128.71 (d), 129.18 (s), 130.12 (d), 131.86 (d), 133.59 (s), 134.19 (s), 134.69 (d); IR (KBr)
3040, 2950, 1700, 1485, 1445, 1380 cm\(^{-1}\); MS (El) m/e calc'd for \(\text{C}_{18}\text{H}_{20}\text{N}_{2}\text{O}_{4}\): 328.1423, found 328.1429; 328 (11), 227 (14), 201 (76), 167 (32), 140 (100), 115 (29), 85 (22), 59 (42); Analysis calc'd for \(\text{C}_{18}\text{H}_{20}\text{N}_{2}\text{O}_{4}\): C, 65.84; H, 6.14; found: C, 65.86; H, 6.15.

\(
\begin{align*}
\text{N} &\quad \text{OMe} \\
\text{toluene} &\quad 220°C \\
307 &\quad \rightarrow \\
&\quad \text{OMe}
\end{align*}
\)

\((\pm)-3\alpha,6\alpha\beta\)-3,7-Dicarbomethoxy-2,3,3a,4,6a,7-hexahydro-1H-pyrrolo[2,3-d]carbazole (318): A toluene solution (300 mL) of the starting bis-carbamate 307 (1.0 g, 3.1 mmol) was introduced in a 1 L steel bomb. The air was removed and the mixture placed under an argon atmosphere. The bomb was heated to 220°C for 4 h, then cooled to room temperature. The mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography over silica gel (elution with 20% ethyl acetate in hexane) to afford the desired tetracycle 318 (940 mg, 94% yield) as a pale yellow solid: mp. 121°C; \(^1\text{H}\) NMR (250 MHz, toluene-d\(_8\) at 370K) \(\delta\) 1.60 (m, 2H, CH\(_2\)CH\(_2\)N), 2.15 (m, 1H, CH\(_2\)HCH=), 2.37 (dt, J=16.6, 5.3 Hz, 1H, CH\(_2\)HCH=), 3.26 (m, 1H, CH\(_2\)CH\(_2\)HN), 3.51 (m, 1H, CH\(_2\)CH\(_2\)HN), 3.52 (s, 3H, OMe), 3.55 (s, 3H, OMe), 3.79 (dd, J=5.3, 5.2 Hz, 1H, CHN), 4.40 (bs, 1H, NCHC=), 5.53 (m, 1H, NCHCH=CH), 6.00 (d, J=10.1 Hz, 1H, NCHCH=CH), 6.75 (m, 2H, ArH), 7.00 (m, 1H, ArH), 7.86 (d, J=8.1 Hz, 1H, ArH); \(^1\text{C}\) NMR (63 MHz, DMSO-d\(_6\) at 370K) \(\delta\) 25.5 (t), 32.0 (t), 44.0 (t), 51.3 (s), 51.5 (q), 52.1 (q), 59.4 (d), 62.8 (d), 114.2 (d), 122.2 (d), 122.8 (d), 126.2 (d), 127.0 (d),
(±)-(3α, 6αβ)-2, 3, 3a, 4, 6a, 7-hexahydro-1H-pyrrolo[2, 3-d]carbazole (324): To a solution of bis carbamate 318 (1.097 g, 3.342 mmol) in methanol-free chloroform (20 mL) was added at room temperature in one portion TMSI (4.9 mL, 33.42 mmol). The mixture was stirred at reflux for 4 h, cooled to room temperature, and quenched with methanol (evolution of CO₂). The solution was concentrated under reduced pressure and the residue was partitioned between ether and 1N HCl. The organic phase was separated. The aqueous layer was basified with 50% aqueous NaOH (pH=12) and extracted with dichloromethane. The dichloromethane solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the desired product (677 mg, 95%) as a yellow solid: mp. 119°C; ¹H NMR (300 MHz, DMSO-d₆) δ 1.85 (m, 1H, CHHCH₂N), 2.25 (m, 3H, CH₂CH= and CHHCH₂N), 3.29 (m, 2H, CH₂CH₂N), 3.88 (bs, 1H, CHN), 3.98 (bs, 1H, C=NHar), 5.62 (m, 2H, CH=CH₂), 5.90 (bs, 1H, NH), 6.48 (d, J=6.0 Hz, 1H, ArH), 6.53 (t, J=6.0 Hz, 1H, ArH), 6.91 (t, J=6.0 Hz, 1H, ArH), 7.71 (d, J=6.0 Hz, 1H, ArH);
$^{13}$C NMR (63 MHz, DMSO-$d_6$) $\delta$ 22.86 (t), 37.32 (t), 41.68 (t), 51.27 (s), 56.76 (d), 58.87 (d), 109.09 (d), 117.39 (d), 122.16 (d), 122.43 (d), 128.35 (s), 128.39 (d), 128.97 (d), 150.95 (s); IR (CH$_2$Cl$_2$) 3340, 3020, 2870, 1600, 1480, 1460, 1020 cm$^{-1}$; MS (El) $m/e$ calc'd for C$_{14}$H$_{16}$N$_2$: 212.1313, found 212.1314; 212 (100), 182 (52), 168 (78), 131 (89), 82 (79).

(Z)-1-Bromo-2-iodo-2-butene (343): To a mixture of $trans$ 2-iodo-2-butene-1-ol (234) (631 mg, 3.188 mmol) and triphenylphosphine (1.26 g, 4.781 mmol) in dichloromethane (30 mL) was added at 0°C N-bromosuccinimide (851 mg, 4.781 mmol). The mixture was stirred at 0°C for 10 min, then concentrated. The crude residue was purified by flash chromatography over silica gel (elution with hexane) to afford the desired allylic bromide 343 (682 mg, 82% yield) as a colorless oil. $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 1.78 (d, $J$=6.5 Hz, 3H, $=CHCH_3$), 4.34 (s, 2H, $-CH_2Br$), 6.03 (q, $J$=6.5 Hz, 1H, $=CHMe$); $^{13}$C NMR (63 MHz, CDCl$_3$) $\delta$ 22.22 (q), 43.33 (t), 103.36 (s), 135.96 (d).

$\pm$-[3α(Z),6αβ]-2,3,3α,4,6α,7-hexahydro-3-(2-iodo-2-butene-1-yl)-1H-pyrrolo[2,3-d]carbazole (344): To a mixture of bis-amine 324 (675 mg, 3.182 mmol), K$_2$CO$_3$ (1.32 g, 9.546 mmol) and nBu$_4$NCl (1.35 g, 4.773 mmol) in DMF (30 mL) was added
allylic bromide 3 4 3 (785 mg, 3.023 mmol) at -8°C (NaCl / ice water bath). The mixture was stirred at -5°C for 2 h 40 min, then diluted with ether, and washed with 0.2N aqueous NaOH (400 mL). The layers were separated. The ether layer was extracted with 1N HCl. The acidic water solution was separated, basified with 50% aqueous NaOH (pH=12), and extracted with ether. The ether layers were combined, dried over anhydrous sodium sulfate and concentrated. The residue was purified by flash chromatography over silica gel (elution with 20% ethyl acetate in hexane) to give the product (815 mg, 68% yield) as a pale yellow solid: mp. 148°C; 1 H NMR (300 MHz, CDCl3) δ 1.77 (d, J=6.4 Hz, 3H, CH3CH=), 1.90 (m, 1H, CH=CH2), 2.11 (m, 2H, CH2CH=), 2.68 (m, 1H, CH=CH2), 3.10 (m, 2H, CH2N), 3.34 (d, J=14.4 Hz, 1H, CH2CH2N), 3.63 (d, J=14.4 Hz, 1H, CH2CH2N), 3.98 (bs, 1H, CHNHAr), 5.63 (m, 2H, CH=CH2), 5.90 (q, J=6.4 Hz, 1H, CHMe), 6.61 (d, J=7.4 Hz, 1H, ArH), 6.73 (t, J=7.4 Hz, 1H, ArH), 7.03 (t, J=7.4 Hz, 1H, ArH), 7.13 (d, J=7.4 Hz, 1H, ArH); 13C NMR (63 MHz, CDCl3) δ 21.71 (q), 24.41 (t), 37.96 (t), 50.37 (t), 53.19 (s), 62.17 (d), 62.93 (d), 65.57 (t), 109.59 (s), 109.94 (d), 119.03 (d), 123.44 (d), 125.64 (d), 127.84 (d), 130.52 (d), 134.02 (s), 150.04 (s); IR (CHCl3) 3364, 3022, 2912, 1649, 1605, 1483, 1346, 812 cm⁻¹; MS (El) m/e calc’d for C38H31N2: 392.0749, found 392.0726; 392 (46), 262 (100), 211 (300), 168 (67), 130 (37), 82 (26), 53 (49).

(±)-[3aα(Z),6aβ]-7-Carbomethoxy-2,3,3a,4,6a,7-hexahydro-3-(2-iodo-2-buten-1-yl)-1H-pyrrolo[2,3-d]carbazole (325): To a solution of bis carbamate 318 (200
mg, 0.60 mmol) in dichloromethane (10 mL) was added at room temperature in one portion TMSI (200 μL, 1.32 mmol). The mixture was stirred at reflux for 1 h, cooled to room temperature and quenched with methanol (evolution of CO₂). The solution was concentrated under reduced pressure and the residue was partitioned between ether and 1N HCl. The organic phase was separated. The aqueous layer was basified with 50% aqueous NaOH (pH=12) and extracted with dichloromethane. The dichloromethane solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford monocarbamate 323 (160 mg), contaminated with about 10 % of diamine 324. The monocarbamate could not be further purified and was directly submitted to the alkylation reaction.

To a mixture of the crude monocarbamate 323 (90 mg, < 0.33 mmol) and K₂CO₃ (460 mg, 3.3 mmol) in acetone (3 mL) was added at room temperature the allylic tosylate 238 (150 mg, 0.43 mmol). The mixture was stirred at room temperature for 2 h, then filtered and concentrated. The residue was partitioned between ether and 1N HCl. The organic phase was separated. The aqueous layer was basified with 50% aqueous NaOH (pH=12) and extracted with dichloromethane. The dichloromethane solution was concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (elution with 10 % ethyl acetate in hexane) to afford the desired vinyl iodide 325 (117 mg, 79% yield from 318) as a yellow viscous oil: ¹H NMR (250 MHz, DMSO-d₆ at 40°C) δ 1.72 (d, J=7 Hz, 3H, =CHCH₂), 2.05 (m, 3H, CH₂CH₂N and =CHCHH), 2.54 (m, 1H, =CHCHH), 3.08 (m, 1H, CHN), 3.28 (m, 3H, CHNₓ3), 3.65 (d, J=12 Hz, 1H, =CCHH₂), 3.79 (s, 3H, OMe), 4.50 (bs, 1H, MeO₂CCH), 5.67 (m, 2H, CH=CH), 6.00 (q, J=7 Hz, 1H, =CHCH₂), 6.99 (t, J=8 Hz, 1H, ArH), 7.21 (m, 2H, ArH), 7.60 (m, 1H, ArH); ¹³C NMR (63 MHz, DMSO-d₆ at 40°C) δ 21.19 (q), 23.64 (t), 38.62 (t), 49.60 (t), 50.88 (s), 52.28 (q), 61.50 (d), 63.25 (d), 65.03 (t), 110.04 (s), 114.44 (d), 122.70 (d), 122.83 (d), 124.51 (d), 126.09 (d), 127.67 (d), 130.19 (d), 134.98 (s), 140.82 (s), 152.69 (s); IR (CH₂Cl₂) 3031, 2951,
1714, 1651, 1601, 1486, 1462, 1443, 1385, 751 cm\(^{-1}\); MS (El) \(m/e\) calc'd for \(\text{C}_{20}\text{H}_{23}\text{N}_{2}\text{O}_{2}\): 450.0804, found 450.0806; 450 (10), 323 (33), 262 (100), 202 (13), 167 (25), 128 (18), 82 (34), 53 (22).

\[
\text{Pd(OAc)}_2, \text{K}_2\text{CO}_3, \text{nBu}_4\text{NCl, DMF}
\]

(±)-[3α, 6α, 6aβ, 13(Z)]-7-Carbomethoxy-13-ethylen-1, 2, 3a, 6, 6a, 7-hexahydro-3,6-ethano-3H-pyrrolo[2,3-d]carbazole (327). A catalytic amount of \(\text{Pd(OAc)}_2\) (3 mg, 0.013 mmol) was added at room temperature to a mixture of the vinyi iodide 325 (60 mg, 0.133 mmol), \(\text{K}_2\text{CO}_3\) (92 mg, 0.666 mmol), and \(\text{nBu}_4\text{NCl}\) (40 mg, 0.266 mmol) in DMF (1.2 mL). The heterogeneous mixture was heated to 65°C and stirred for 2 h. The dark solution was filtered, diluted with water and extracted with ether. The organic layers were combined and extracted with 2N HCl. The aqueous layer was basified with 50% aqueous NaOH (pH=12), and extracted with dichloromethane. The dichloromethane solution was dried over anhydrous sodium sulfate and concentrated. The residue was purified by flash chromatography over silica gel (elution with 5% diethyl amine in ether) to yield the carbamate 327 (36 mg, 84%) as a viscous yellow oil: \(^1\text{H NMR}\) (300 MHz, DMSO-\(d_6\) at 343 K) δ 1.64 (d, \(J=6.8\) Hz, 3H, \(\text{CH}_3\)), 2.12 (m, 2H, \(\text{CH}_2\text{CH}_2\text{N}\)), 2.65 (m, 1H, \(\text{CH}_2\text{CH}_2\text{HN}\)), 3.14 (d, \(J=15.4\) Hz, 1H, \(=\text{CHHN}\)), 3.33 (d, \(J=15.4\) Hz, 1H, \(=\text{CHHN}\)), 3.40 (m, 1H, \(\text{CH}_2\text{CH}_2\text{HN}\)), 3.65 (d, \(J=6.6\) Hz, 1H, \(=\text{CHHN}\)), 3.80 (m, 1H, \(=\text{CHHN}\)), 3.81 (s, 3H, OMe), 3.95 (d, \(J=2\) Hz, 1H, CHNCO), 5.70 (q, \(J=6.8\) Hz, 1H, \(=\text{CHMe}\)).
5.89 (dd, J=7, 6.6 Hz, 1H, CH=CHN), 6.17 (t, J=7 Hz, 1H, CH=CHN), 6.98 (t, J=7.0 Hz, 1H, ArH), 7.08 (d, J=7.0 Hz, 1H, ArH), 7.28 (d, J=7.0 Hz, 1H, ArH), 7.70 (m, 1H, ArH); NMR (75 MHz, DMSO-d$_6$ at 343 K) δ 12.57 (q), 39.39 (t), 46.25 (d), 48.52 (t), 49.96 (t), 52.03 (q), 56.13 (s), 66.27 (d), 73.58 (d), 113.60 (d), 122.22 (d), 122.25 (d), 123.57 (d), 126.92 (d), 127.09 (d), 132.70 (d), 133.46 (s), 133.79 (s), 142.99 (s), 152.94 (s); IR (neat) 3045, 2924, 1713, 1599, 1486, 1462, 1441, 1385, 1074 cm$^{-1}$; MS (EI) m/e calc’d for C$_{20}$H$_{22}$N$_2$O$_2$: 322.1681, found 322.1683; 322 (49), 251 (6), 201 (6), 134 (100), 105 (8), 91 (9), 84 (16), 66 (17).

(±)-(19E)-1,2,19,20-Tetrahydro-17-norcuran (dehydrotubifoline) (123). A catalytic amount of Pd(OAc)$_2$ (7.3 mg, 0.032 mmol) was added at room temperature to a mixture of the vinyl iodide 344 (255 mg, 0.650 mmol), K$_2$CO$_3$ (449 mg, 3.25 mmol) and nBu$_4$NCl (277 mg, 0.975 mmol) in DMF (6.5 mL). The mixture was stirred at 75°C for 1h. The dark brown solution was cooled to room temperature, washed with 0.2N NaOH (70 mL) and extracted four times with ether. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (elution with 3% diethyl amine in ether) to afford dehydrotubifoline, 123, (137 mg, 79% yield) as a beige solid: mp. 75°C (dec); $^1$H NMR (300 MHz, CDCl$_3$) δ 1.10 (d, J=14.2 Hz, 1H, CH=CHN), 1.66 (d, J=6.6 Hz, 3H, CHCH$_3$), 1.80 (d, J=14.2 Hz, 1H, CHCH$_3$N), 2.17 (m, 2H, CH$_2$CH$_2$N), 2.70 (d, J=15.2 Hz, 1H, =CH$_2$N), 3.16 (d, J=15.2 Hz, 1H, =CH$_2$N), 3.22 (bs, 1H, CHC=), 3.32
(m, 3H, CH₂CH₂N and CH=HC=), 3.77 (d, J=15.4 Hz, 1H, CH=HC=N), 4.00 (s, 1H, CHN), 5.40 (t, J=6.6 Hz, 1H, =CHCH₃), 7.21 (m, 3H, ArH), 7.53 (d, J=7.5 Hz, 1H, ArH); ¹³C NMR (63 MHz, CDCl₃) δ 12.85 (q), 25.39 (t), 30.25 (d), 35.10 (t), 35.95 (t), 53.68 (t), 55.53 (t), 65.40 (s), 66.67 (d), 119.55 (d), 119.87 (d), 121.23 (d), 125.27 (d), 127.73 (d), 142.03 (s), 144.10 (s), 154.43 (s), 189.02 (s); IR (CH₂Cl₂) 3040, 2920, 1570, 1480, 1450, 1110 cm⁻¹; MS (El) m/e calc'd for C₁₈H₂₀N₂: 264.1626, found 264.1619; 264 (18), 245 (15), 158 (47), 121 (38), 93 (37), 83 (14), 71 (64), 57 (100); Analysis calc'd for C₁₈H₂₀N₂: C, 81.78; H, 7.63; found: C, 81.66; H, 7.57.
LIST OF REFERENCES

133


135


<table>
<thead>
<tr>
<th>Reference</th>
<th>Authors</th>
<th>Title and Details</th>
</tr>
</thead>
</table>


d) ref. 81.

APPENDICES
Figure 8: $^1$H NMR spectrum of 227 (250 MHz, CDCl$_3$)
Figure 9: $^{13}$C NMR spectrum of 227 (63 MHz, CDCl$_3$)
Figure 10: $^1$H NMR spectrum of 229 (250 MHz, CDCl$_3$)
Figure 12: $^1$H NMR spectrum of 218 (250 MHz, CDCl$_3$)
Figure 13: $^1$H NMR spectrum of 218 (63 MHz, CDCl$_3$)
Figure 14: $^1$H NMR spectrum of 230 (250 MHz, CDCl$_3$)
Figure 15: $^{13}$C NMR spectrum of 230 (63 MHz, CDCl$_3$)
Figure 16: $^1$H NMR spectrum of 219 (250 MHz, CDCl$_3$)
Figure 17: $^{13}$C NMR spectrum of 219 (75 MHz, CDCl$_3$)
Figure 18: $^1$H NMR spectrum of 220 (300 MHz, CDCl$_3$)
Figure 19: $^{13}$C NMR spectrum of 220 (63 MHz, CDCl$_3$)
Figure 20: $^1$H NMR spectrum of 240 (300 MHz, CDCl$_3$)
Figure 21: $^1$H NMR spectrum of 240 (63 MHz, CDCl$_3$)
Figure 22: $^1$H NMR spectrum of 241 (300 MHz, CDCl$_3$)
Figure 23: $^{13}$C NMR spectrum of 241 (75 MHz, CDCl$_3$)
Figure 24: $^1$H NMR spectrum of 244 (300 MHz, CDCl$_3$)
Figure 25: $^{13}$C NMR spectrum of 244 (63 MHz, CDCl$_3$)
Figure 26: $^1$H NMR spectrum of 246 (250 MHz, CDCl$_3$)
Figure 27: $^{13}$C NMR spectrum of 246 (63 MHz, CDCl$_3$)
Figure 28: $^1$H NMR spectrum of 245 (300 MHz, CDCl$_3$)
Figure 29: $^{13}$C NMR spectrum of 245 (63 MHz, CDCl$_3$)
Figure 30: $^1$H NMR spectrum of 247 (300 MHz, CDCl$_3$)
Figure 31: $^{13}$C NMR spectrum of 247 (63 MHz, CDCl$_3$)
Figure 32: $^1$H NMR spectrum of 249 (250 MHz, CDCl$_3$)
Figure 33: $^{13}$C NMR spectrum of 249 (63 MHz, CDCl$_3$)
Figure 34: $^1$H NMR spectrum of 250 (300 MHz, CDCl$_3$)
Figure 35: $^{13}$C NMR spectrum of 250 (63 MHz, CDCl$_3$)
Figure 36: $^1$H NMR spectrum of 260 (200 MHz, CDCl$_3$)
Figure 37: $^{13}$C NMR spectrum of 260 (63 MHz, CDCl$_3$)
Figure 38: $^1$H NMR spectrum of 261 (300 MHz, CDCl$_3$)
Figure 39: $^{13}$C NMR spectrum of 261 (63 MHz, CDCl$_3$)
Figure 40: $^1$H NMR spectrum of 262 (250 MHz, CDCl$_3$)
Figure 41: $^{13}$C NMR spectrum of 262 (63 MHz, CDCl$_3$)
Figure 42: $^1$H NMR spectrum of 258 (300 MHz, CDCl$_3$)
Figure 43: $^{13}$C NMR spectrum of 258 (63 MHz, CDCl₃)
Figure 44: $^1$H NMR spectrum of 263 (300 MHz, CDCl$_3$)
Figure 45: $^{13}$C NMR spectrum of 263 (63 MHz, CDCl$_3$)
Figure 46: $^1$H NMR spectrum of 279 (300 MHz, CDCl$_3$)
Figure 47: $^{13}$C NMR spectrum of 279 (63 MHz, CDCl$_3$)
Figure 48: $^1$H NMR spectrum of 280 (250 MHz, CDCl$_3$)
Figure 49: $^{13}$C NMR spectrum of 280 (63 MHz, CDCl$_3$)
Figure 50: $^1$H NMR spectrum of 282 (300 MHz, CDCl$_3$)
Figure 51: $^1$H NMR spectrum of 282 (63 MHz, CDCl$_3$)
Figure 52: $^1$H NMR spectrum of 299 (300 MHz, CDCl$_3$)
Figure 53: $^1{\text{H}}$ NMR spectrum of 299 (75 MHz, CDCl$_3$)
Figure 54: $^1$H NMR spectrum of 300 (250 MHz, CDCl$_3$)
Figure 55: $^{13}$C NMR spectrum of 300 (75 MHz, CDCl$_3$)
Figure 56: $^1$H NMR spectrum of 307 (250 MHz, CDCl$_3$)
Figure 57: $^{13}$C NMR spectrum of 307 (63 MHz, CDCl$_3$)
Figure 58: $^1$H NMR spectrum of 318 at 370 K (250 MHz, toluene-d$_8$)
Figure 59: $^{13}$C NMR spectrum of 318 at 370 K (63 MHz, DMSO-d$_6$)
Figure 60: $^1$H NMR spectrum of 324 (300 MHz, DMSO-$d_6$)
Figure 61: $^{13}$C NMR spectrum of 324 (63 MHz, DMSO-d$_6$)
Figure 62: $^1$H NMR spectrum of 325 at 313 K (250 MHz, DMSO-d$_6$)
Figure 63: $^{13}$C NMR spectrum of 325 at 313 K (63 MHz, DMSO-d$_6$)
Figure 64: $^1$H NMR spectrum of 327 at 343 K (300 MHz, DMSO-d$_6$)
Figure 65: $^1$H NMR COSY spectrum of 327 at 343 K (300 MHz, DMSO-$d_6$)
Figure 66: $^{13}$C NMR spectrum of 327 at 343 K (75 MHz, DMSO-d$_6$)
Figure 67: $^1\text{H}$ NMR spectrum of 344 (300 MHz, CDCl$_3$)
Figure 68: $^{13}$C NMR spectrum of 344 (63 MHz, CDCl$_3$)
Figure 69: $^1$H NMR spectrum of 123 (300 MHz, CDCl$_3$)
Figure 70: $^1$C NMR spectrum of 123 (63 MHz, CDCl$_3$)
$^1$H NMR spectrum of Dehydrotubifoline, provided by Dr. L. E. Overman
<table>
<thead>
<tr>
<th>LINE#</th>
<th>HEIGHT</th>
<th>HEIGHT(L)</th>
<th>FREQ(HZ)</th>
<th>PPM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>82.21</td>
<td>82.64</td>
<td>23781.64</td>
<td>189.083</td>
</tr>
<tr>
<td>2</td>
<td>81.63</td>
<td>81.11</td>
<td>19423.37</td>
<td>154.431</td>
</tr>
<tr>
<td>3</td>
<td>62.14</td>
<td>63.90</td>
<td>18122.67</td>
<td>144.090</td>
</tr>
<tr>
<td>4</td>
<td>80.15</td>
<td>90.22</td>
<td>17842.22</td>
<td>141.860</td>
</tr>
<tr>
<td>5</td>
<td>223.04</td>
<td>304.53</td>
<td>16086.60</td>
<td>127.897</td>
</tr>
<tr>
<td>6</td>
<td>245.76</td>
<td>260.12</td>
<td>15777.39</td>
<td>125.443</td>
</tr>
<tr>
<td>7</td>
<td>206.16</td>
<td>249.16</td>
<td>15270.32</td>
<td>121.411</td>
</tr>
<tr>
<td>8</td>
<td>362.79</td>
<td>408.22</td>
<td>15091.03</td>
<td>119.986</td>
</tr>
<tr>
<td>9</td>
<td>57.23</td>
<td>57.28</td>
<td>9727.66</td>
<td>77.343</td>
</tr>
<tr>
<td>10</td>
<td>3053.74</td>
<td>3102.24</td>
<td>9716.44</td>
<td>77.253</td>
</tr>
<tr>
<td>11</td>
<td>318.79</td>
<td>119.05</td>
<td>9703.97</td>
<td>77.154</td>
</tr>
<tr>
<td>12</td>
<td>93.54</td>
<td>93.59</td>
<td>9636.38</td>
<td>77.094</td>
</tr>
<tr>
<td>13</td>
<td>3113.05</td>
<td>3183.47</td>
<td>9664.52</td>
<td>77.000</td>
</tr>
<tr>
<td>14</td>
<td>94.11</td>
<td>94.34</td>
<td>9667.44</td>
<td>76.864</td>
</tr>
<tr>
<td>15</td>
<td>101.41</td>
<td>104.38</td>
<td>9663.49</td>
<td>76.832</td>
</tr>
<tr>
<td>16</td>
<td>3046.17</td>
<td>3139.58</td>
<td>9652.56</td>
<td>76.745</td>
</tr>
<tr>
<td>17</td>
<td>77.54</td>
<td>79.35</td>
<td>9637.53</td>
<td>76.626</td>
</tr>
<tr>
<td>18</td>
<td>209.27</td>
<td>241.16</td>
<td>8380.77</td>
<td>66.634</td>
</tr>
<tr>
<td>19</td>
<td>84.26</td>
<td>85.56</td>
<td>8229.45</td>
<td>65.431</td>
</tr>
<tr>
<td>20</td>
<td>222.03</td>
<td>225.44</td>
<td>6982.86</td>
<td>55.519</td>
</tr>
<tr>
<td>21</td>
<td>238.25</td>
<td>252.77</td>
<td>6756.15</td>
<td>53.717</td>
</tr>
<tr>
<td>22</td>
<td>225.43</td>
<td>269.65</td>
<td>4541.07</td>
<td>36.105</td>
</tr>
<tr>
<td>23</td>
<td>205.88</td>
<td>211.52</td>
<td>4423.06</td>
<td>35.167</td>
</tr>
<tr>
<td>24</td>
<td>245.31</td>
<td>246.87</td>
<td>3810.95</td>
<td>30.300</td>
</tr>
<tr>
<td>25</td>
<td>186.32</td>
<td>191.36</td>
<td>3734.04</td>
<td>29.688</td>
</tr>
<tr>
<td>26</td>
<td>230.41</td>
<td>231.00</td>
<td>3200.73</td>
<td>25.448</td>
</tr>
<tr>
<td>27</td>
<td>171.80</td>
<td>173.60</td>
<td>1635.96</td>
<td>13.007</td>
</tr>
</tbody>
</table>

$^{13}$C NMR spectrum of Dehydrotubifolone, provided by Dr. L. E. Overman