I. AN AZABORAPYRIDINE NUCLEOSIDE AS A THYMIDINE ANALOGUE

II. FUSED RING SYSTEMS VIA THE DEMETHOXYCARBONYLATION-MICHAEL OR REDUCTION-MICHAEL SEQUENCE

By

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PREFACE

The work presented over the course of the following chapters covers research done in two different areas of organic chemistry. Chapters 1 and 2 center around the compound 2'-deoxy-2,3-azaborapyridine. Chapter 1 discusses the development of 2'-deoxy-2,3-azaborapyridine and its potential use as an antiviral/anticancer agent. Chapter 2 details the work done toward the synthesis of 2'-deoxy-2,3-azaborapyridine.

The second half of the thesis - chapters 3 and 4 - discusses the use of tandem reactions in synthesis. Chapter 3 provides a brief overview of the anionic-anionic sequence and its use in synthesizing molecules with specific regio-, chemo-, diastereo-, and enantioselectivity. Chapter 4 covers the application of the anionic-anionic and reduction-Michael sequences toward the synthesis of fused-ring systems.

I would like to extend thanks to Sarah Pope for her generous donation of the pentenylriboside. I would also like to thank Dr. Steven M. Graham and Dr. Richard A. Bunce for giving me the opportunity to work in their groups.

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CHAPTER 1

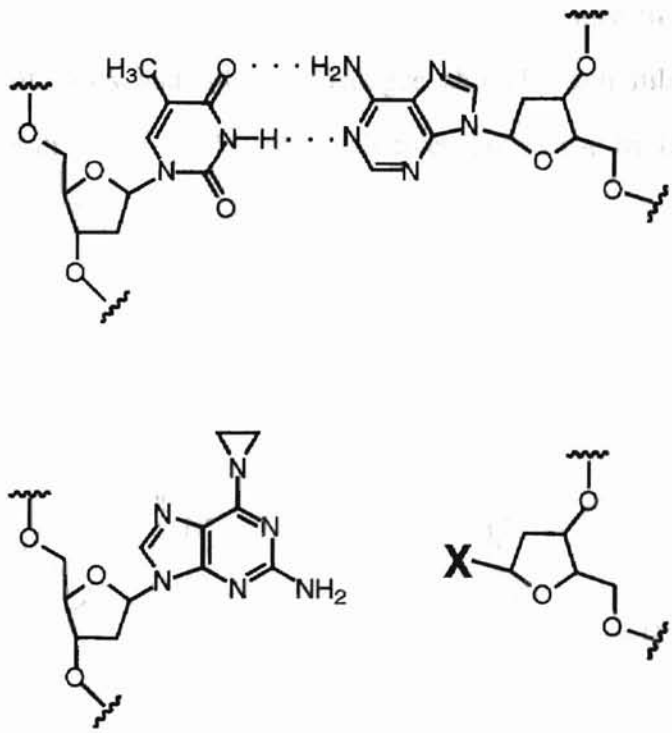
2'-DEOXY-2,3-AZABORAPYRIDINE AS A POTENTIAL ANTIVIRAL/ANTICANCER AGENT

Background

The goal of many antiviral/anticancer agents is the disruption of DNA replication. A common method, especially in the treatment of cancer,[1-4] is alkylation-induced DNA damage. Anticancer DNA alkylating drugs (*e.g.*, mitomycin C, nitrogen mustards, nitrosoureas), however, suffer from several drawbacks. These include an inability to distinguish replicating from non-replicating DNA and a reaction with other non-DNA cellular nucleophiles with the end result being the drug's deactivation. Although damage by such agents to diseased cells may demonstrate therapeutic cytotoxicity, healthy cells are not immune to the action of an alkylating drug. Mutagenesis[2,4-6] has been implicated to damage the DNA of healthy cells primarily through mismatched-induced mutations and deletions [*i.e.* the drug alkylates the DNA such that the normal base-pairing pattern is disrupted resulting in one of the following: (1) the substitution of one base pair for another; (2) the deletion of one or more base pairs or; (3) the insertion of one or more base pairs]. There are two principle ways to avoid mismatched-induced mutagenesis. First, an alkylation event that results in an interstrand cross-link can obstruct mutations by providing a barrier to separation of the DNA strands and subsequent replication. Such DNA adducts are resistant toward denaturation and *in vivo* repair and are unable to undergo transcription.[1,3,7] Second, alkylations that maintain the normal Watson-Crick (WC)

hydrogen bonding pattern will be less mutagenic in the event that the alkylation does not lead to an interstrand cross-link.[3,8]

Cowart and Benkovic[9,10] synthesized an aziridine-containing guanosine-based triphosphate analogue 6edDTP (Figure 1) which was shown to be a substrate for several DNA polymerases. The Klenow fragment of DNA polymerase I showed little selective incorporation as it placed 6edDTP opposite any of the natural nucleotides [Note: the Klenow fragment is a 67-kd fragment of DNA polymerase I composed of a polymerase and 3' —> 5' exonuclease; the Klenow fragment's responsibilities are to incorporate nucleotides into a growing chain of DNA as well as "proofread" and correct mistakes in the DNA]. Significant cross-linking occurred, however, only when the complimentary nucleotide was deoxycytidylate or deoxyadenylate. Also, polymerization past the cross-



6edDTP

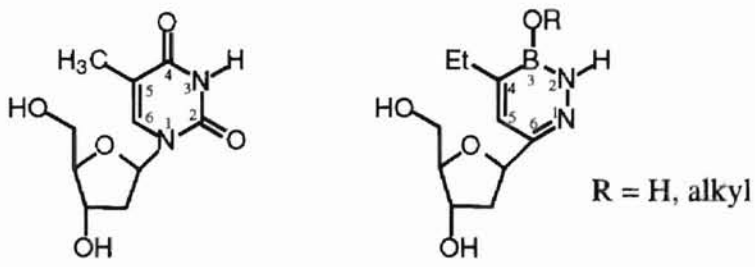
X = A, C, G, or T
Cross-link forms only when
X = A or C

Figure 1. Normal WC Hydrogen Bonding in the Thymidine-Adenosine Base Pair (top) and the Cross-linking Analogue, 6edDTP (bottom).

link continued relatively unimpeded indicating minimal disruption of the DNA structure. This appears to be the only example where a nucleoside analogue capable of forming an interstrand cross-link was successfully incorporated by a polymerase into DNA. Our objective was to develop a nucleoside analogue which would exhibit qualities similar to that of 6edDTP but be more selective in its incorporation and enhance the potential that a cross-linking event would occur.

Based upon the work of Cowart and Benkovic, the interstrand cross-linking reagent should possess the following characteristics: (1) it should be a nucleoside analogue, capable of *in vivo* 5'-triphosphorylation, and be a substrate for DNA polymerases; (2) the alkylating functionality/interstrand cross-link should be small (in order to meet the requirements of (1), *i.e.* to be a substrate) and, to avoid repair enzymes, the interstrand cross-link should not disturb the structure of the DNA duplex to any great extent; (3) the analogue should place the alkylating group in close proximity to a nucleophile on the opposite strand of DNA and; (4) the analogue should retain fully the WC hydrogen bonding pattern of the parent nucleoside, again to ensure its use by DNA polymerases, but also to avoid mismatched-induced mutations.

The Thymidine Analogue



Thymidine BCNA **1**

Figure 2. Structures for Thymidine and BCNA **1**.

To this end, Figure 2 presents thymidine and its boron containing nucleoside analogue 2'-deoxy-2,3-azaborapyridine (BCNA **1**). BCNA **1** features a novel replacement of the normal thymidine C-4 carbonyl with a boron-oxygen single bond. This substitution should maintain the normal WC hydrogen bonding pattern of thymidine while at the same time allow the introduction of alkyl groups. In conventional WC hydrogen bonding involving thymidine, both the O-4 and the N-3 imino proton make contacts to the complimentary base. In contrast, alkylation of thymidine O-4 requires the loss of the N-3 imino proton, the resultant O-4 alkyl thymidine now has the WC hydrogen bonding pattern characteristic of the enol form of thymidine (Figure 3). In previous studies of O-4 alkyl

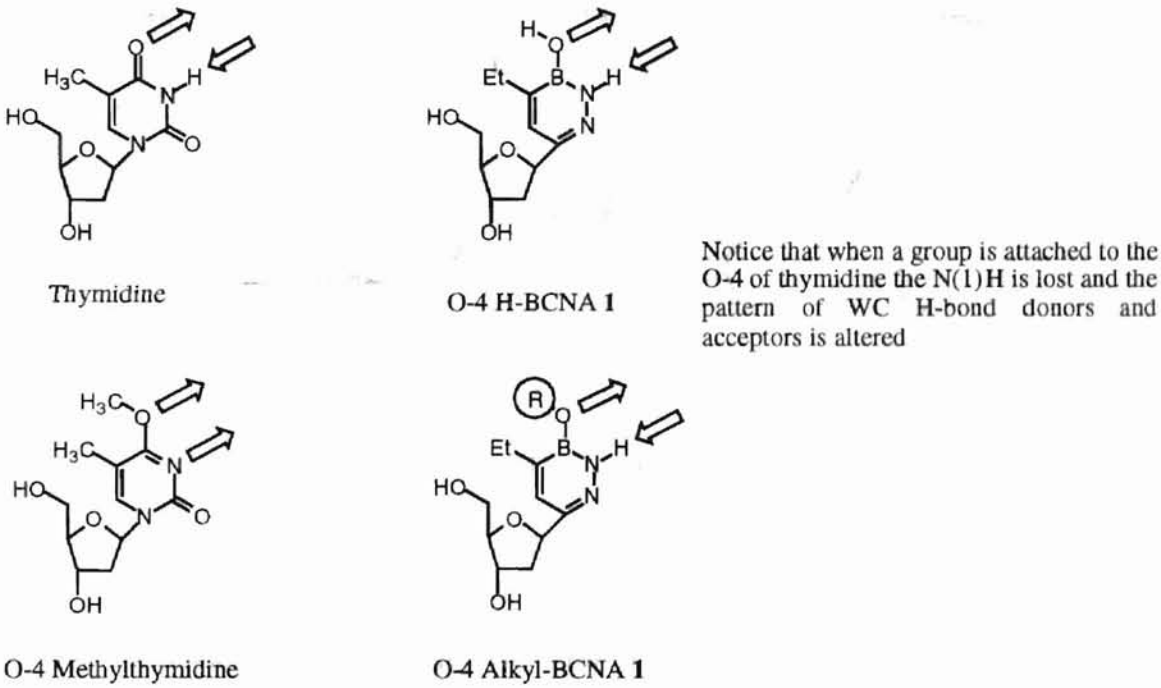


Figure 3. Effect of Alkyl Substitution in Thymidine and BCNA **1**.

donors and acceptors, (1) the 5'-triphosphates were not incorporated into replicating DNA, and (2) oligomers containing O-4 alkylthymidine analogues were destabilized relative to duplex DNA.[5,11] In principle, alkyl groups can be incorporated into **1** without altering the

WC hydrogen bonding pattern. Upon incorporation into the target DNA, **1** would hydrogen bond with its complimentary base (in this instance adenine).

Figure 4 presents a proposed alkylation event that could occur upon incorporation of **1** into DNA. As mentioned above, **1** allows for the introduction of alkyl groups. Specifically, the alkyl functionality would be electrophilic in nature (*i.e.* B-OR-X, where X is a leaving group). In theory, rotation about the B-O bond gives an orientation favorable for nucleophilic attack resulting in the desired interstrand cross-link.

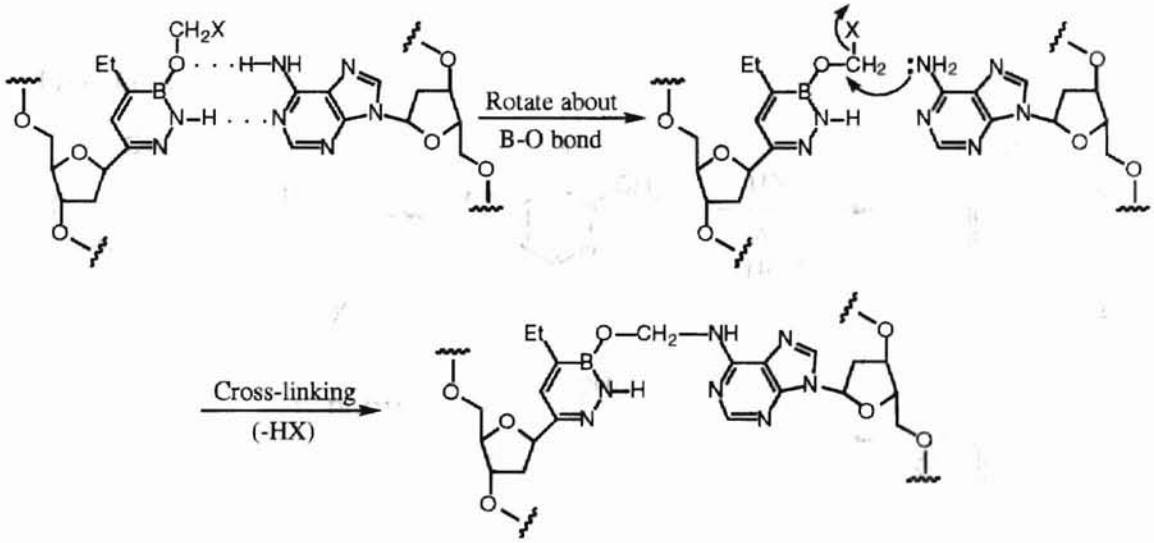


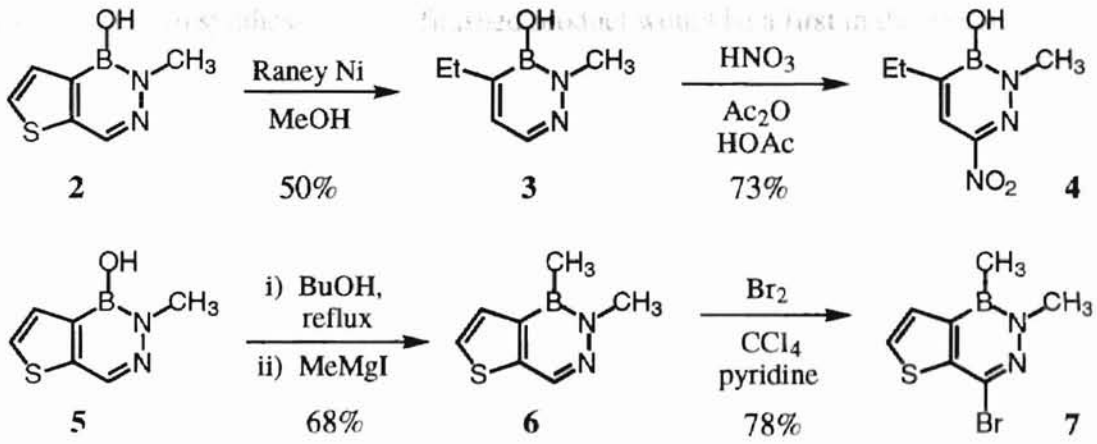
Figure 4. Proposed Alkylation of DNA by BCNA **1**.

In the event that an interstrand cross-link does not form, there is still a potential use for **1**. A second anticancer strategy is boron neutron capture therapy,[12,13] currently in Phase III clinical trials. In this therapy, boron-rich tumor cells are selectively destroyed by the high-energy disintegration products $^{4}He^{2+}$ and $^{7}Li^{+}$ emitted when ^{10}B captures a thermal (slow) neutron. Tumor cells require higher levels of deoxynucleoside triphosphates in order to support their enhanced level of DNA synthesis. Thus, tumor cells may sequester **1** in quantities sufficient to provide an alternative to the current spectrum of boron-based drugs.[12-16]

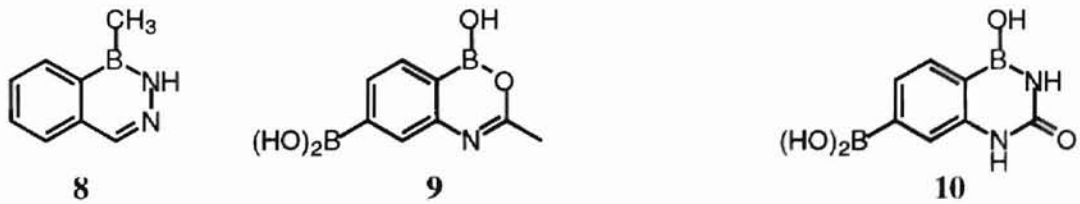
Literature Precedence for Stable Boron Heterocycles

Considering **1**, the question of stability of the boron heterocycle moiety arises. Fortunately, ample evidence exits in the literature to show that boron heterocycles are stable to various conditions and reactions (Figure 5). Gronowitz and co-workers have shown boron heterocycles to be stable to nitration,[17] reduction,[17,18] halogenation,[19] and Grignard conditions.[18] Boron heterocycles have also been shown[20,21] to be stable to acidic and basic reagents as well as aqueous media.

From Gronowitz *et al.*:



From Dewar *et al.* and Yale *et al.*:



8 **9** **10**

Stable to boiling 15% KOH or conc. HCl > 2 h

Recrystallized from water

Figure 5. Examples of Boraheteroaromatic Compounds from the Literature.

Conclusions

Gronowitz[17,18,19] and others[20,21] have shown that heterocycles containing boron can be synthesized and have shown these boron heterocycles to be stable toward a variety of conditions. Likewise, biologically relevant boron-containing compounds are being used for boron neutron capture therapy.[12,13] To date, however, no one has synthesized a boron analogue of a purine or pyrimidine nucleoside. In the known boron-containing nucleosides,[15,16,22,23] the boron was a ring substituent rather than a ring atom (bora-heteroaromatic). Of particular interest is that syntheses of heterocycles with boron as a ring atom peaked in the late 1960's to mid 1970's. After that point, the literature leaves the subject. Thus, to synthesize **1** as a finished product would be a first in the literature.

CHAPTER 2

TOWARD THE SYNTHESIS OF 2'-DEOXY-2,3-AZABORAPYRIDINE

Introduction

Retrosynthesis of BCNA **1** shows that this compound can be assembled through coupling of the boraheteroaromatic ring, as in **2** and **3** with either 5-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-D-ribono-1,4-lactone (**4**, ribonolactone) or with pent-4-enyl 2',3',5'-*O*-acetyl-β-D-*erythro*-pentofuranoside (**5**, pentenylriboside, Figure 6). The 2,3-*O*-protected ribonolactone can be purchased from Sigma; the unprotected

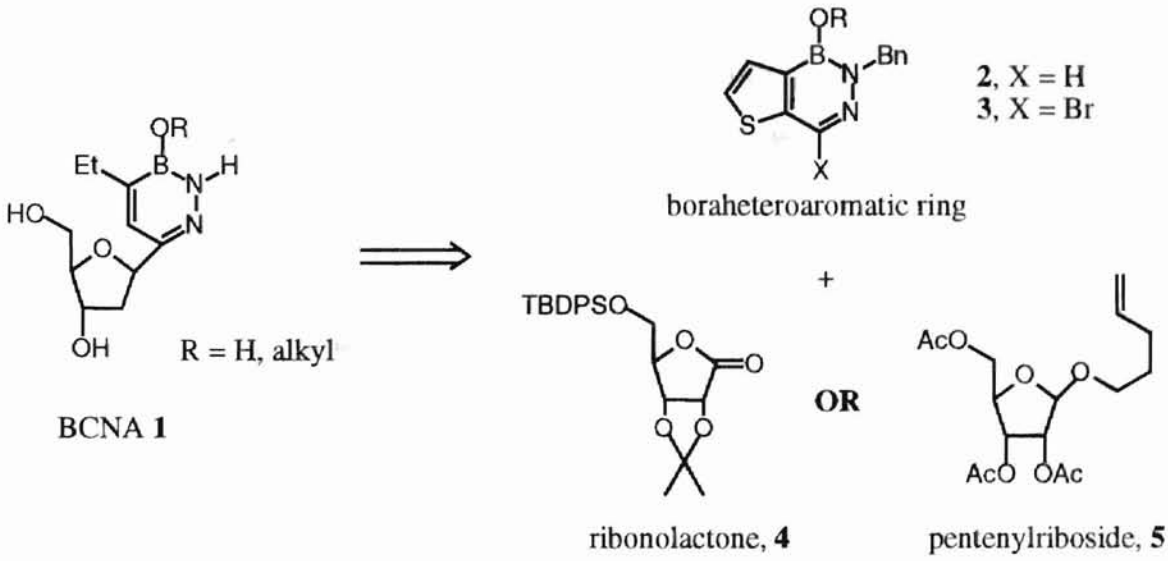


Figure 6. Retrosynthesis of BCNA **1**.

pentenylriboside was diverted from another project. Thus, the methodology presented below concentrates on the synthesis of the boraheteroaromatic ring and the attempted coupling of the latter with the ribonolactone or the pentenylriboside.

Results

Synthesis of the Boraheteroaromatic Ring. Figure 7 presents a synthetic scheme to obtain the boraheteroaromatic ring. Treatment of **6** with *n*-BuLi followed by addition of DMF and acidic work-up gave aldehyde **7**.[24,25] After protection of the aldehyde functionality as its cyclic acetal, **8** was reacted with *n*-BuLi followed by tributylborate to give the thiopheneboronic acid **9** in 66% yield.[24,25] Initially, the first three steps (2,3-

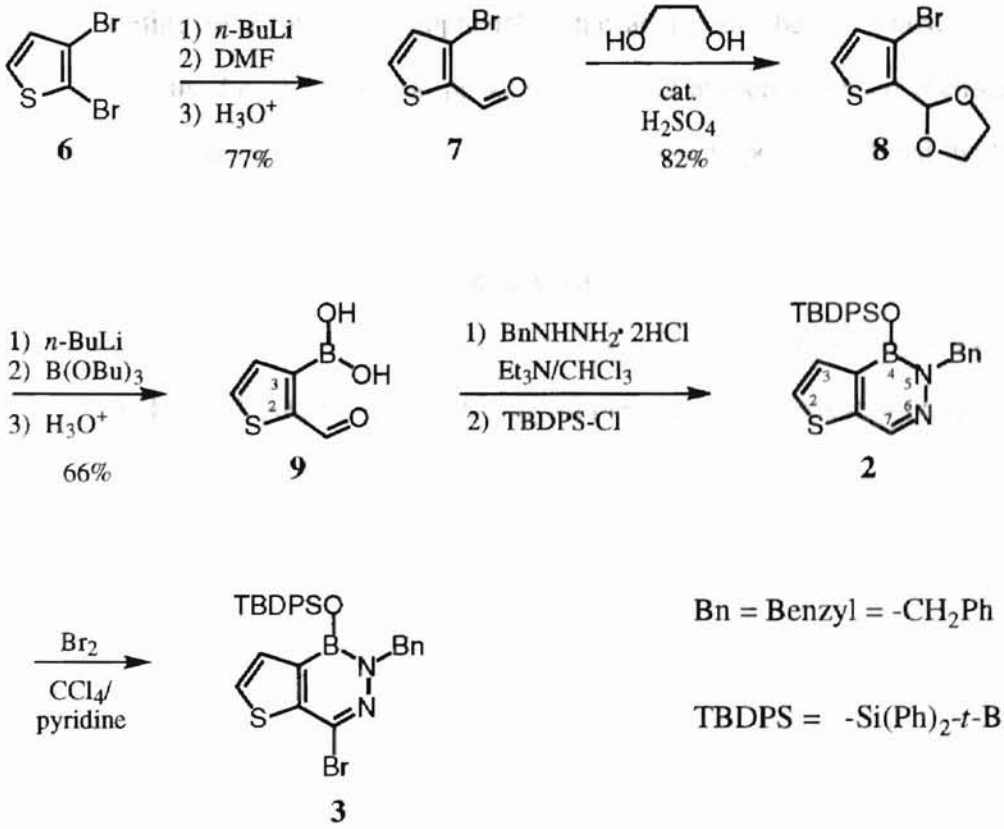


Figure 7. Synthesis of the Boraheteroaromatic Ring.

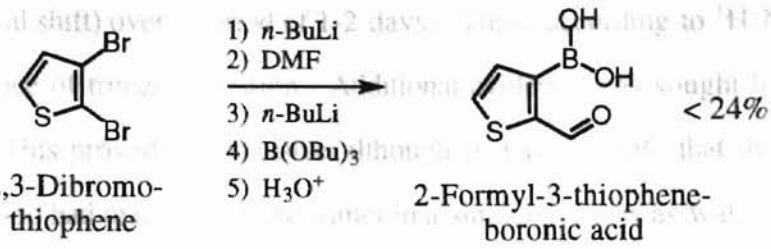


Figure 8. One-pot Synthesis of 2-Formyl-3-thiopheneboronic Acid.

dibromothiophene (**6**) to 2-formyl-3-thiopheneboronic acid (**9**), were attempted as a one-pot synthesis (Figure 8). Due to consistently low yields (< 24%), however, it was decided to break this procedure up into three steps. Isolation of **9** initially proved problematic, but ultimately interesting. At first, yields of **9** were low averaging 23%. It was found (by observation) that upon slow evaporation of the post work-up organic layer crystal formation occurred. Proton NMR analysis of these crystals showed that all of the proton peaks corresponding to 2-formyl-3-thiopheneboronic acid could be accounted for except the hydroxyl protons, *i.e.* those proton peaks were absent at their expected chemical shift nor were such visible anywhere else in the spectrum. It was hypothesized that the boronic acid was forming a trimer (Figure 9) thus accounting for the loss of the hydroxyl protons. To test the hypothesis an NMR sample of the crystals was prepared which contained water. If the boronic acid had formed a trimer, addition of water should hydrolyze the trimer to the boronic acid. Indeed ^{1}H NMR showed the appearance of the hydroxyl protons (at their

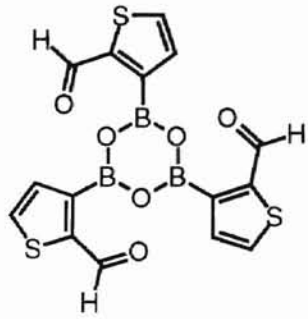
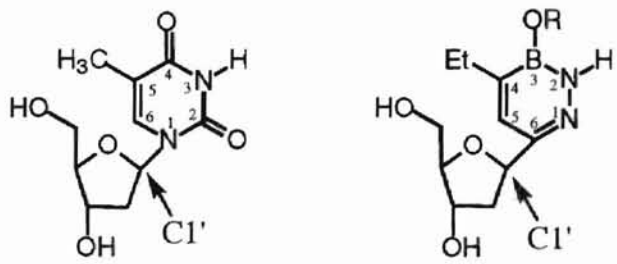


Figure 9. Proposed Structure for the Cyclic Anhydride Trimer.

expected chemical shift) over a period of 1-2 days. Thus, according to ^{1}H NMR analysis, there was evidence of trimer formation. Additional evidence was sought by conducting a FAB analysis. This proved inconclusive although it was possible that the 3-nitrobenzyl alcohol matrix used had reacted with the trimer in a similar manner as water. Further FAB experiments were not conducted, in part because either the thiopheneboronic acid **9** or the "cyclic anhydride trimer" could be used to provide **2**.

Compound **9** was cyclized by reaction with benzylhydrazine dihydrochloride[24] and the resultant hydroxyl was protected[26] with *tert*-butyldiphenylsilyl chloride (TBDPS-Cl) yielding the azaborapyridine **2**. Bromination[19] of **2** gave the bromo azaborapyridine **3**. For the synthesis of **2**, it was necessary to isolate this compound as its TBDPS derivative. Attempted isolation/purification of **2** without hydroxyl protection proved impossible. Gronowitz[24] was able to isolate the *N*5-phenyl boron heterocycle (*i.e.* a derivative of **2** with a phenyl substituent replacing the benzyl group) with its free hydroxyl group, consequently it was thought that the additional methylene group of the *N*5-benzyl analogue would not prove problematic. Since the coupling reaction was two steps away, hydroxyl protection would be necessary.

Attempted Coupling of the Boraheteroaromatic Ring with the Ribonolactone. Literature precedent for the synthesis of *C*-nucleosides is sparse. Using BCNA **1** as an example (Figure 10), a *C*-nucleoside is a nucleoside that has a C-C linkage



Thymidine BCNA **1**

Figure 10. Normal Nucleoside and *C*-Nucleoside Linkages.

between C1' of the sugar and C6 of the attached ring system. A normal nucleoside linkage - as seen in thymidine - is between C1' of the sugar and a N of the attached thymine ring. The three examples presented here served as the basis for our coupling strategy. First, Matulic-Adamic and co-workers[27] successfully synthesized *C*-ribonucleoside 1'-deoxy-1'-phenyl-β-D-ribofuranose (Figure 11) in an overall yield of 72%. The key feature for this reaction was the addition of phenyllithium to the ribonolactone **4**.

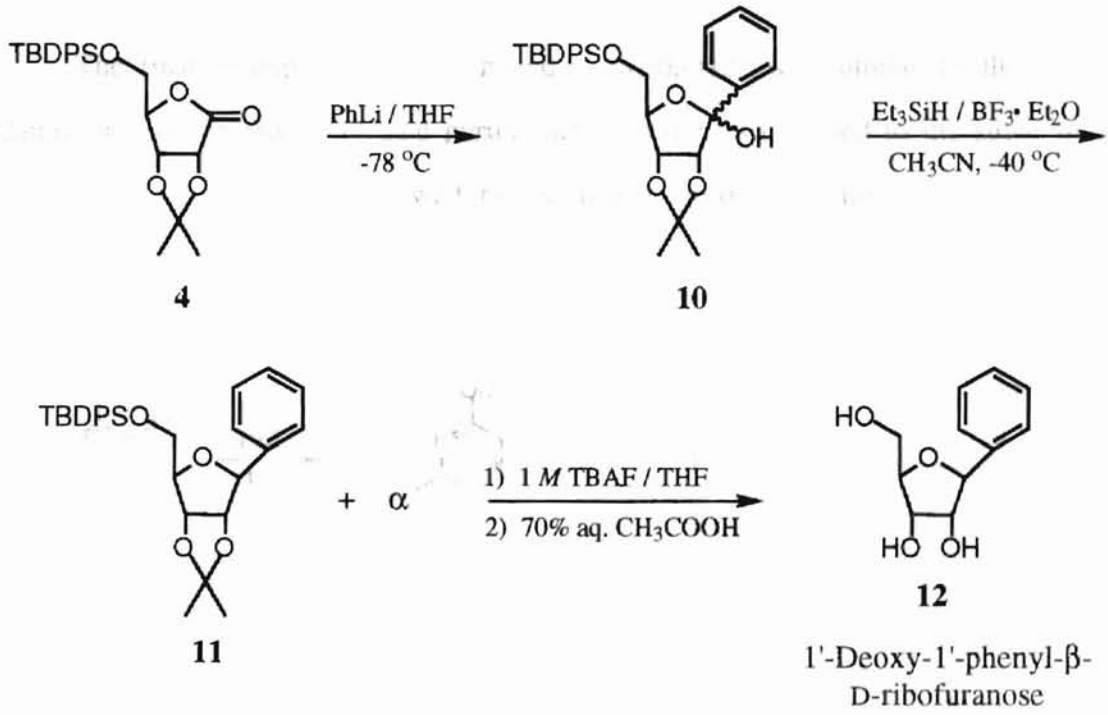
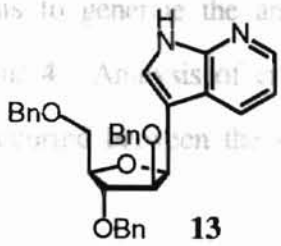


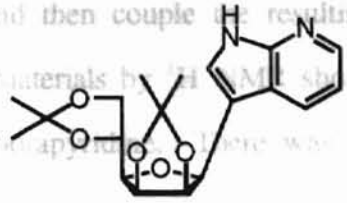
Figure 11. Synthesis of 1'-Deoxy-1'-phenyl-β-D-ribofuranose.

Second, Cornia and co-workers[28] synthesized 3-(2,3,5-tri-*O*-benzyl-β-D-arabino-furanosyl)-7-azaindole and 3-(2,3:5,6-di-O-isopropylidene-β-D-mannofuranosyl)indole (Figure 12). Though the yields were low (12% and 10%, respectively), Cornia was able to show that a carbon nucleoside could be made.



13

3-(2,3,5-tri-*O*-benzyl-β-D-arabino-furanosyl)-7-azaindole



14

3-(2,3:5,6-di-*O*-isopropylidene-β-D-mannofuranosyl)indole

Figure 12. *C*-Nucleosides.

The final example, from Lerch and co-workers,[29] was similar to the Matulic-Adamic protocol in that a lithiated pyrimidine derivative was added to the sugar moiety (Figure 13). Deprotection followed by cyclization produced a mixture of the desired products.

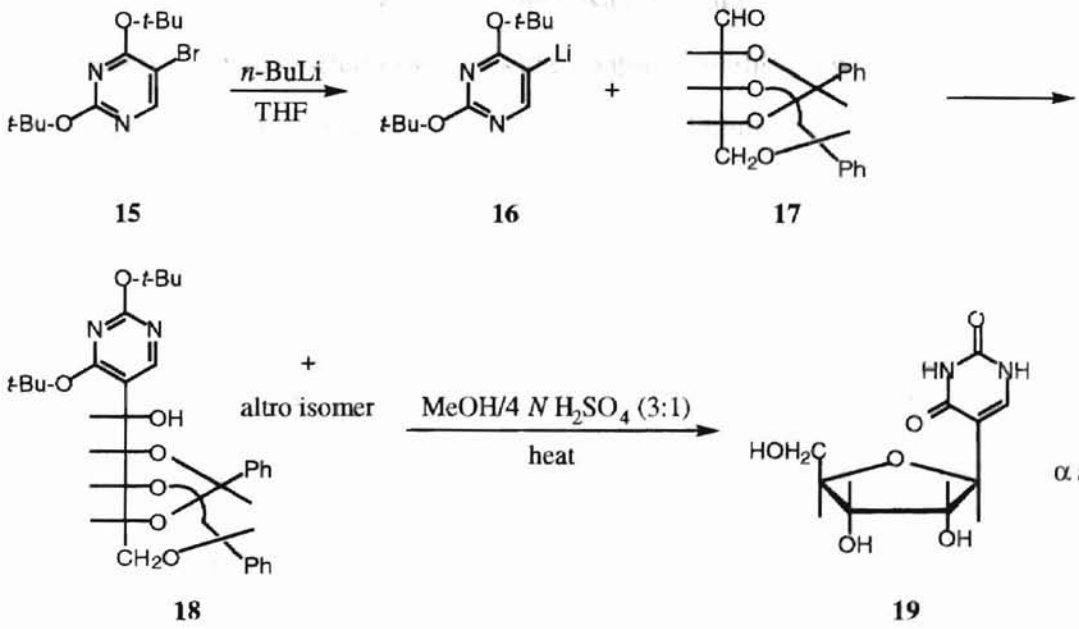


Figure 13. Synthesis of *C*-Nucleosides.

With this knowledge in hand, several coupling reactions were attempted with azaborapyridine **2** or bromo azaborapyridine **3** and ribonolactone **4** (Figure 14). Our

strategy was to generate the anion of **2** or **3** and then couple the resulting anion to ribonolactone **4**. Analysis of crude and purified materials by ^{1}H NMR showed that no coupling occurred between the sugar and the azaborapyridine. There was doubt as to

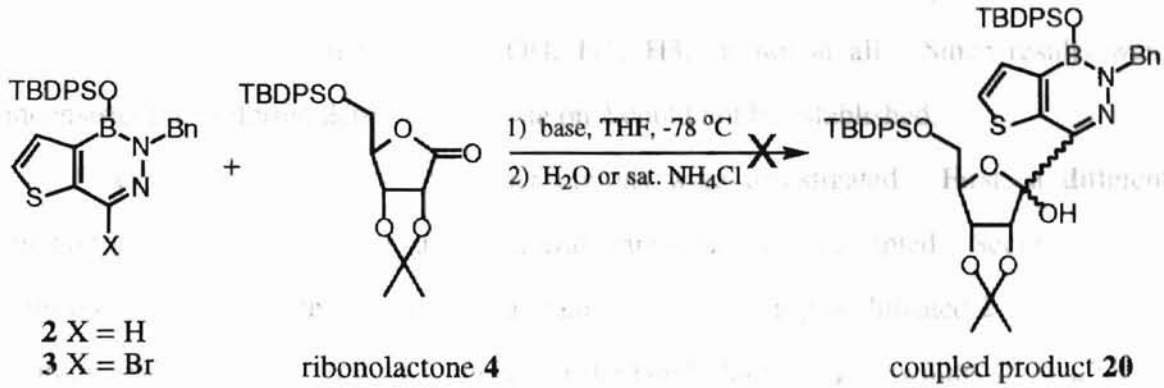


Figure 14. Expected Coupling Between Azaborapyridine **2** or Bromo Azaborapyridine **3** and the Ribonolactone **4**.

whether the anion of the azaborapyridine was forming. To verify anion formation, experiments were conducted using the same coupling conditions with the exception that the ribonolactone **4** was replaced with D_2O or H_2O (Figure 15). Analysis of D_2O/H_2O

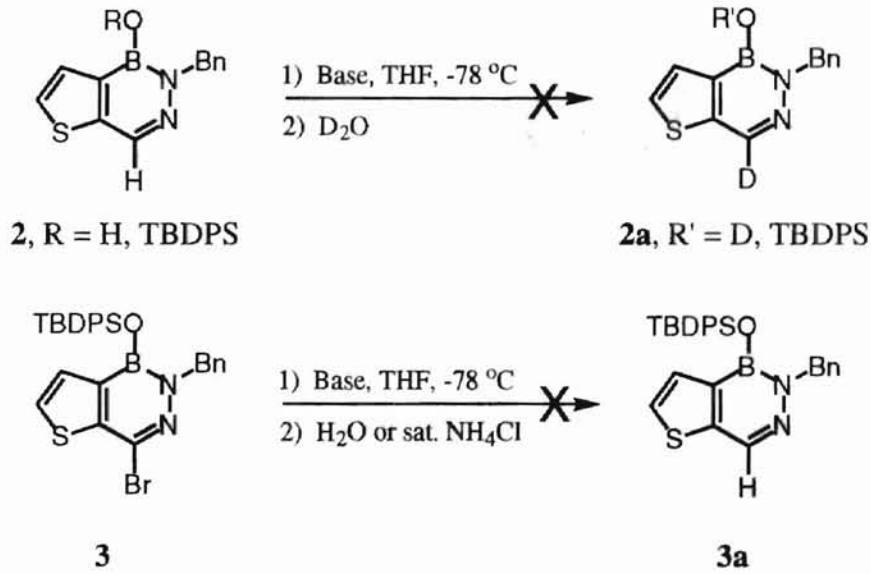
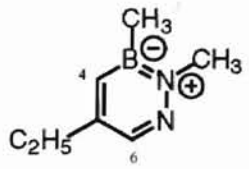


Figure 15. Test Reactions to Verify Anion Formation in **2** and **3**.

reactions by ^{1}H NMR provided no evidence that anion formation was occurring, *i.e.* **2a** and **3a** were not observed by ^{1}H NMR analysis. While ^{1}H NMR analysis of **3** was straightforward, analysis of **2** was complicated. In the instance when R = TBDPS, no deprotonation was observed. When R = H, though, ^{1}H NMR analysis indicated that deprotonation had occurred at either OH, H2, H3, or not at all. Since results were inconsistent, a preferred deprotonation site on **2** could not be established.

At this point in time, two other options were investigated. First, a different methodology for coupling the sugar and azaborapyridine was attempted. Second, it was believed that the butyllithium reagent was faulty thus providing no lithiated **2** or **3** to react with the ribonolactone. Storage and use[30] of the butyllithium reagent would allow a return to the above synthesis (see Figure 14).

Attempted Coupling of the Boraheteroaromatic Ring with the Pentenylriboside. The methodology for this reaction sequence was developed by examining previous Gronowitz reactions and recent work done by Chapeau and Marnett.[31] Gronowitz had investigated bromination, iodination and nitration of 3,2-borazaropyridine **21** and bromination of the thieno-fused 3,2-borazaropyridine **22**.[19] From his study,



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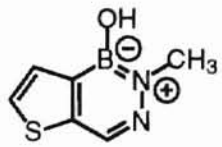

22

Figure 16. 3,2-Borazaropyridine **21** and Thieno-fused 3,2-Borazaropyridine **22**.

Gronowitz found that under strongly acidic conditions **21** did not react. Under slightly acidic or non-acidic conditions, **21** readily underwent substitution with the substitution pattern dependent upon the electrophile present. Nitration predominantly resulted in substitution at the 6-position, iodination at the 4-position, and bromination provided a

mixture of 4- and 6-substituted 3,2-borazaropyridines. Bromination of **22** was perplexing as well. Under strongly acidic conditions substitution occurred in the thiophene ring while with slightly acidic or non-acidic conditions bromination occurred in the boron-nitrogen containing ring.

Based upon these results, it could not be said that a "normal" electrophilic aromatic substitution mechanism was occurring through a Wheland intermediate. Gronowitz and others[32] have proposed two possible mechanisms (Figure 17) to account for the observed

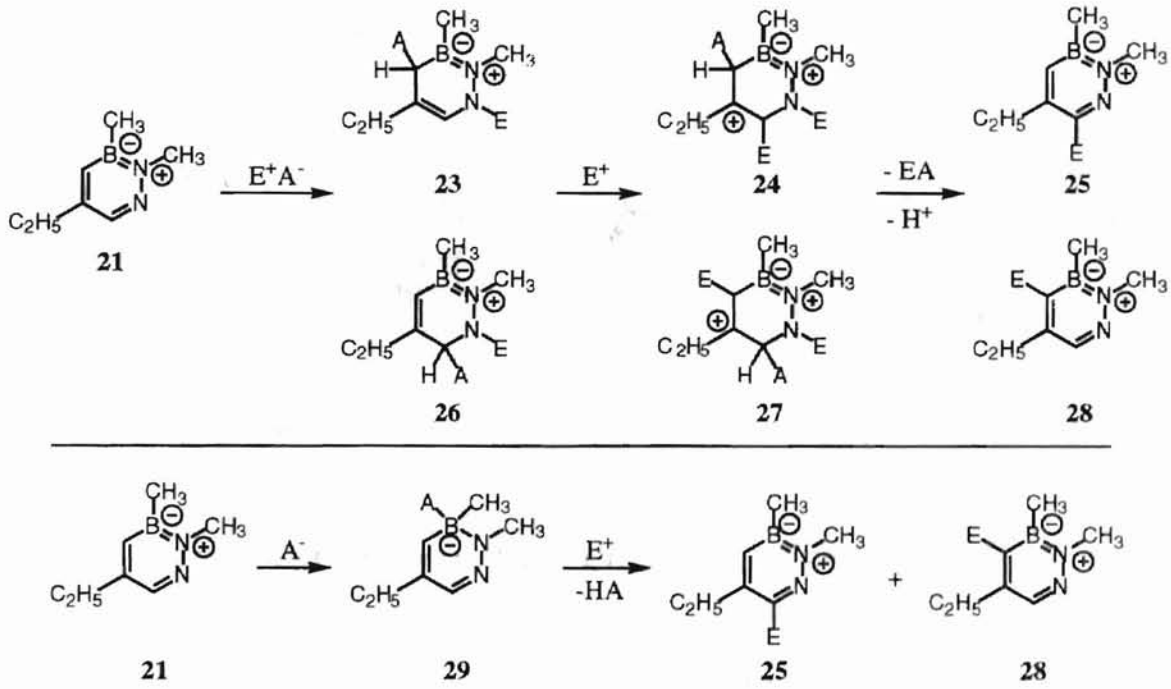

Figure 17. Proposed Mechanisms for the Addition of an Electrophile to **21**.

substitution patterns. The first mechanism involves a three step process: (1) addition of the species E^+A^- to **21**; (2) substitution at the 4- or 6-position by E^+ and; (3) elimination of EA and H^+ from **24** or **27** to provide the final product. The second mechanism takes into account the characteristic properties of boron. The boron atom of **21** is attacked by a nucleophile followed by addition of the electrophile to the 4- or 6-position. Subsequent

loss of HA then gives the substituted product. Although the mechanism was never definitively proven, to Gronowitz and others it was apparent that there was the addition of an electrophilic species to either **21** or **22**. How to affect the substitution pattern was dependent upon the reaction conditions employed.

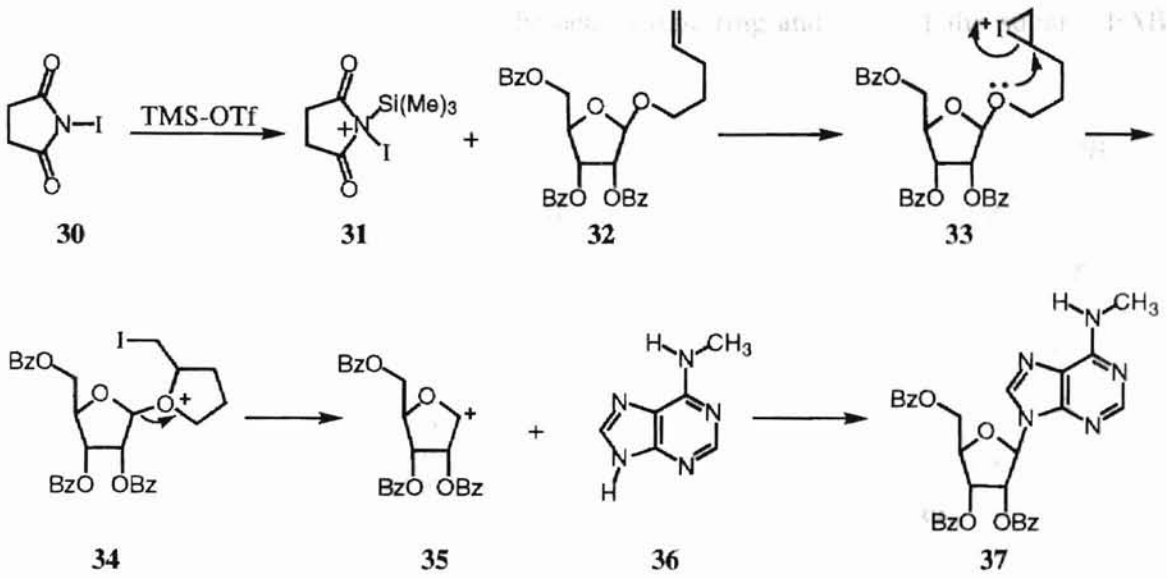

Figure 18. Proposed Mechanism for the Coupling of the Pentenylriboside with a Purine Base.

Chapeau's paper[31] deals with the coupling of the pentenylriboside **5** with various purine base derivatives. Figure 18 presents a proposed mechanism for the coupling of the pentenylriboside with a purine base. Taking into consideration Gronowitz' study of the electrophilic substitution mechanism, our plan was to use Chapeau's reaction conditions and to replace the purine base with our own azaborapyridine **2** or other azaborapyridine derivative (Figure 19). Also of interest was whether a different functional group could be incorporated into the O-4 position of the azaborapyridine molecule. The reasons for this were long term. Referring back to BCNA **1** and Figure 4, it would ultimately be necessary to incorporate a leaving group into the O-4 position of BCNA **1**. Following the protocol outlined by Gronowitz *et al.*,[24,33] the synthesis of 4-*tert*-butoxyazaborapyridine (**38**) was carried out in a yield of 79%. Based upon the results of this reaction, it should be possible

to run a similar synthesis with an alcohol of the general form HO-CH_2CH_2-X (recall from Chapter 1 that BCNA **1** ultimately will need to incorporate a leaving group at the O-4 position).

Three coupling reactions were attempted with different results. The first experiment was a run with **5** and **38** (Figure 19). Proton NMR indicated that coupling may have occurred, albeit between *N*6 or *N*5 of the heterocyclic ring and C-1' of the sugar. FAB

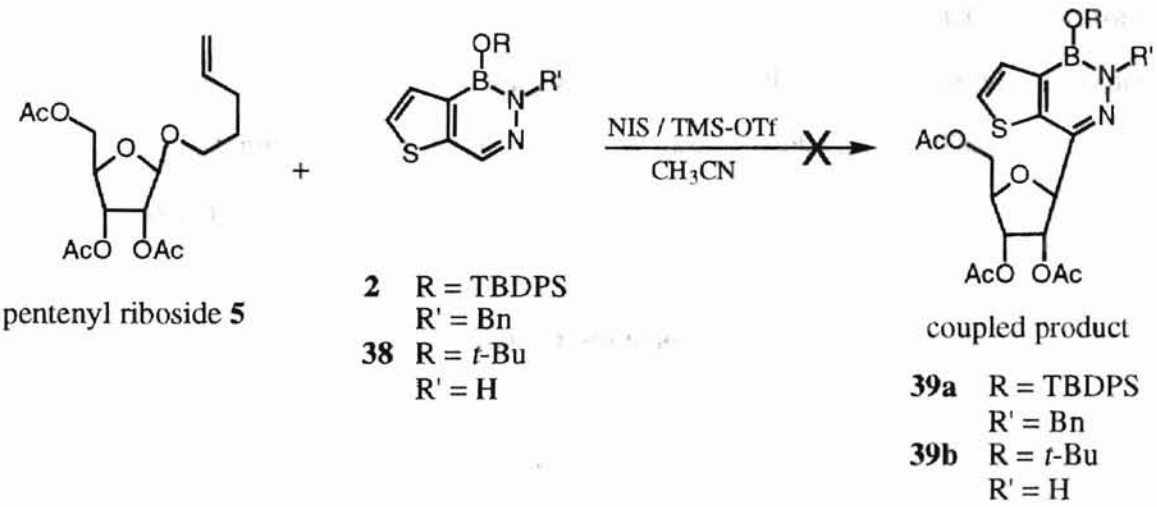

Figure 19. Expected Coupling Between Azaborapyridine **2** or 4-*tert*-Butoxyazaborapyridine **38** and the Pentenylriboside **5**.

analysis could not confirm the presence of **39**. Additionally, with the low yield of "coupled" product **39** (13%) in conjunction with a 71% recovery of starting materials, the reaction conditions need to be optimized or modified.

The second and third coupling attempts were with **5** and **2**. Unlike the first run, ^{1}H NMR analysis indicated no coupling had taken place between the base and sugar in either reaction. Again, experimental conditions require modification.

Conclusions

The above encompasses the research done toward the synthesis of 2'-deoxy-2,3-azaborapyridine, BCNA **1**. While the synthesis of the boraheteroaromatic base was relatively successful the coupling reaction proved difficult. This, however, was expected since the literature for such a reaction is sparse. There are several additional options to be examined. First, as mentioned above, the pentenylriboside couplings need further investigation. Second, a return to the synthesis of coupled product **20** warrants investigation. Finally, a third methodology is available in the event the previous avenues do not work. Essentially this protocol involves working "backwards." That is, synthesis of **1** would begin with the sugar moiety and the boraheterocycle would be built on to this.

Experimental

General. All reactions were done under a nitrogen atmosphere. Pyridine was distilled from KOH. CCl_4 was distilled from P_2O_5. DMF was dried over 4-Å molecular sieves. Titration[34] of butyllithium reagents was done before each reaction in which they were used. ^{1}H NMR (400 MHz) were taken in DMSO-d_6 unless otherwise stated. ^{13}C NMR (100 MHz) were taken in $CDCl_3$ unless otherwise stated.

2-Formyl-3-bromothiophene (7).[17,25] To a stirred solution of 10.9 g (5.00 mL, 45.1 mmol) of 2,3-dibromothiophene in 250 mL of ether at -75 °C was added 5.30 mL (45.1 mmol) of 8.5 M *n*-BuLi in a dropwise fashion over a period of 5-6 min. The mixture was stirred for 1 h and a solution of 5.00 mL (4.71 g, 64.5 mmol) of DMF in 90 mL of ether was added dropwise with stirring at -75 °C. After 1 h the solution was warmed to rt, cooled in an ice bath, acidified by dropwise addition of 33 mL of 4 M HCl, and stirred for 1 h. The aqueous layer was washed with ether (2 x 25 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (1 x 25 mL),

saturated NaCl (1 x 25 mL), and dried ($MgSO_4$). The organic layer was filtered, concentrated and the resulting oil was distilled under reduced pressure to give 6.64 g (34.8 mmol, 77%) of **7** as a yellow liquid, bp 60-61 °C (0.5 mm Hg). ^{1}H NMR δ 7.42 (d, J = 5.1 Hz, 1 H), 8.24 (dd, J = 5.1, 1.3 Hz, 1 H), 9.90 (d, J = 1.3 Hz, 1 H).

2-(3-Bromo-2-thienyl)-1,3-dioxolane (8).[24] In a 500-mL one-necked round-bottomed flask equipped with a Dean-Stark trap was placed 13.0 g (68.0 mmol) of **7**, 4.64 g (74.8 mmol) of ethylene glycol, 200 mL of benzene, and two drops of concentrated H_2SO_4. After stirring at reflux for 3 h, the reaction was cooled to rt, washed with saturated aqueous $NaHCO_3$ (2 x 25 mL) and saturated NaCl (1 x 25 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give 15.5 g of a yellow liquid. The crude product was distilled under reduced pressure to give 13.1 g (55.7 mmol, 82%) of **8** as a colorless liquid, bp 90-95 °C (0.9 mm Hg). ^{1}H NMR δ 3.94-4.08 (m, 4 H), 6.00 (d, J = 0.6 Hz, 1 H), 7.11 (d, J = 5.3 Hz, 1 H), 7.72 (dd, J = 5.2, 0.5 Hz, 1 H).

2-Formyl-3-thiopheneboronic acid (9).[17,25] To a stirred solution of 14.0 g (59.5 mmol) of **8** in 40 mL of ether at -75 °C was added 6.50 mL (63.7 mmol) of 9.8 M *n*-BuLi in a dropwise fashion over a period of 15 min. After 10 min, a solution of 16.7 g (19.6 mL, 72.6 mmol) of tributyl borate in 65 mL of ether was added and the resulting mixture was stirred for 1 h. The mixture was warmed to rt, then cooled to 0 °C and quenched by dropwise addition of 20 mL of 4 M HCl. The reaction was stirred for 1 h at which time the layers were separated and the aqueous layer extracted with ether (3 x 20 mL). The combined ether layers were extracted with 2 M Na_2CO_3 (7 x 15 mL). The combined aqueous carbonate layers were cooled to 0 °C, acidified to pH 2-3 (ca. 130 mL of 4 M HCl), and the resultant precipitate collected to give 4.40 g (28.2 mmol, 47%) of a yellow solid. Further extraction of the ether layers with 2 M Na_2CO_3 (3 x 10 mL) and acidification to pH 2-3 (ca. 34 mL of 4 M HCl) gave an additional 1.90 g (12.2 mmol, 19%) of **9** (total yield 66%). This material was used without further purification in the next

reaction. ^{1}H NMR δ 7.51 (d, J = 4.8 Hz, 1 H), 8.03 (dd, J = 4.8, 1.2 Hz, 1 H), 8.64 (bs, 2 H), 10.24 (d, J = 1.2 Hz, 1 H).

***N*5-Benzyl-4-(*tert*-butyldiphenylsilyloxy)-5,4-azaborathieno [3,2-*d*] pyridine (2).**[33] To a suspension of 1.25 g (6.40 mmol) of benzylhydrazine dihydrochloride in 18.0 mL of ethanol was added 1.30 g (1.80 mL, 12.8 mmol) of triethylamine dropwise with stirring. The resulting solution was stirred for 5 min after which it was added to a solution of 1.00 g (6.40 mmol) of **9** in 32.0 mL of ethanol. After stirring for 30 min at rt, the ethanol was evaporated and the remaining solid was dissolved in 20 mL of CH_2Cl_2. The organic layer was washed with water (3 x 10 mL), dried ($MgSO_4$), filtered, and concentrated to give a brown oil. The brown oil was dissolved in 4.50 mL of DMF and to the resulting solution was added 1.10 g (16.0 mmol) of imidazole followed by dropwise addition of 2.12 g (2.00 mL, 7.70 mmol) of TBDPS-Cl with stirring. The resulting solution was stirred for 24 h and then diluted with 15 mL of CH_2Cl_2. The organic layer was washed with water (4 x 8 mL), dried ($MgSO_4$), filtered, and concentrated to give a brown oil. The oil was chromatographed (hexane-$CHCl_3$, 70/30 to 50/50) on silica gel to yield 905 mg (1.90 mmol, 30%) of **2** as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 1.03 (s, 9 H), 5.39 (s, 2 H), 6.41 (d, J = 5.1 Hz, 1 H), 7.16 (d, J = 4.8 Hz, 1 H), 7.24-7.39 (m, 11 H), 7.67 (dd, J = 8.1, 1.5 Hz, 4 H), 8.27 (s, 1 H); ^{13}C NMR δ 20.6, 27.7, 56.2, 128.0, 128.3, 128.9, 129.4, 129.5, 130.9, 131.5, 134.3, 135.3, 136.1, 141.1, 147.6; FAB MS (*m/z*) 481 (MH^+).

***N*5-Benzyl-7-bromo-4-(*tert*-butyldiphenylsilyloxy)-5,4-azaborathieno [3,2-*d*] pyridine (3).**[19] To a stirred solution of 0.20 mL of pyridine, 0.30 mL of CCl_4, and 99 mg (0.21 mmol) of **2** was added a solution of bromine (37 mg, 0.23 mmol) in 0.45 mL of anhydrous CCl_4. A brown precipitate formed and the resulting mixture was stirred for 24 h. The mixture was diluted with 5 mL of $CHCl_3$ and the brown precipitate filtered and washed with $CHCl_3$ (2 x 2 mL). The combined organic layers were washed with water (3 x 15 mL), dried ($MgSO_4$), filtered, and concentrated to give 113 mg of a crude

yellow-brown oil. Chromatography on silica gel (hexane-$CHCl_3$, 70/30 to 40/60) yielded 47 mg (0.08 mmol, 38%) of **3** as a yellow syrup. ^{1}H NMR ($CDCl_3$) δ 1.00 (s, 9 H), 6.47 (d, J = 5.1 Hz, 1 H), 5.38 (s, 2 H), 7.10 (d, J = 5.1 Hz, 1 H), 7.21-7.39 (m, 11 H), 7.64 (dd, J = 6.6, 1.5 Hz, 4 H).

5-*O*-(*tert*-Butyldiphenylsilyl)-2,3-*O*-isopropylidene-D-ribono-1,4-lactone (4). To a stirred solution of 1.00 g (5.31 mmol) of 2,3-*O*-isopropylidene-D-ribono-1,4-lactone and 1.07 g (15.7 mmol) of imidazole in 10.0 mL of DMF was added a solution of 1.64 g (5.97 mmol) of TBDPS-Cl in 2.00 mL of DMF. The solution was stirred for 20 min, then diluted with 20 mL of ether and washed with water (2 x 10 mL), and saturated NaCl (1 x 10 mL). The organic layer was dried ($NaSO_4$), filtered, and concentrated to give 1.93 g of crude product. Chromatography on silica gel (hexane-$CHCl_3$, 50/50 to 0/100) yielded 1.37 g (3.21 mmol, 60%) of **4** as a colorless syrup. ^{1}H NMR δ 0.93 (s, 9 H), 1.35 (s, 3 H), 1.38 (s, 3 H), 3.76 (dd, J = 11.4, 2.6 Hz, 1 H), 3.88 (dd, J = 11.6, 1.7 Hz, 1 H), 4.72 (s, 1 H), 4.78 (d, J = 5.5 Hz, 1 H), 4.94 (d, J = 5.5 Hz, 1 H), 7.54 (m, 10 H).

Pent-4-enyl 2',3',5'-*O*-Acetyl-β-D-*erythro*-pentafuranoside (5). To a stirred solution of 1.12 g (5.13 mmol) of pent-4-enyl-β-D-*erythro*-pentafuranoside in 13.0 mL of pyridine was added 2.14 g (1.95 mL, 27.4 mmol) of acetyl chloride. After 2.5 h of stirring, the reaction was diluted with 35 mL of ether. The organic layer was washed with water (1 x 50 mL), 1 M HCl (1 x 50 mL), and 1 M Na_2CO_3 (1 x 50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give a yellow oil. The crude material was purified by silica gel chromatography (hexanes-ethyl acetate, 90/10 to 80/20) to yield 1.30 g (3.77 mmol, 73%) of **5** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.65 (quintet, J = 6.9 Hz, 2 H), 2.05 (s, 3 H), 2.09 (s, 3 H), 2.11 (s, 3 H), 2.21 (m, 2 H), 3.39 (dt, J = 9.5, 6.6 Hz, 1 H), 3.72 (dt, J = 9.5, 6.6 Hz, 1 H), 4.11 (m, 1 H), 4.29 (m, 1 H), 4.34 (d, J = 3.8 Hz, 1 H), 4.97 (m, 1 H), 5.02 (m, 1 H), 4.98 (d, J = 0.8 Hz, 1 H), (dd, J = 4.9, 0.9 Hz, 1 H), 5.34 (m, 1 H), 5.79 (ddt, J = 17.0, 10.2, 6.7 Hz, 1 H).

4-*O*-*tert*-Butyl-5,4-azaborathieno [3,2-*d*] pyridine (38).[33] To a stirred solution of 998 mg (6.40 mmol) of **9** in 4 mL of ethanol and 11 mL of ether was added a solution of 780 mg (760 μL, 24.3 mmol) of hydrazine in 4 mL of ethanol and 1 mL of ether. The resulting yellow solution was stirred for 15 min and the solvent was removed under reduced pressure to give a bright yellow solid. Subsequent recrystallization from ethanol-water (1:2) gave 721 mg (4.74 mmol, 73%) of 4-hydroxy-5,4-azaborathieno [3,2-*d*] pyridine as a yellow powder. ^{1}H NMR δ 7.61 (dd, J = 5.0, 0.8 Hz, 1 H), 7.76 (d, J = 5.0 Hz, 1 H), 8.17 (bs, 1 H), 8.17 (d, J = 0.7 Hz, 1 H), 10.2 (bs, 1 H); ^{13}C NMR (DMSO-d_6) δ 124.1, 125.1, 128.2, 141.5.

In a 250 mL three-necked round-bottomed flask was placed 100 mL of *t*-BuOH and 25 mL of benzene. The solution was distilled until an internal temperature of 74 °C was reached and maintained for 10 min. After this time, 361 mg (2.38 mmol) of 4-hydroxy-5,4-azaborathieno[3,2-*d*] pyridine was added. Distillation was continued until almost dry. The remaining solvent was removed under vacuum to give 392 mg (1.88 mmol, 79%) of **38** as a yellow solid. ^{1}H NMR δ 1.27 (s, 9 H), 7.28 (dd, J = 5.1, 0.7 Hz, 1 H), 7.51 (d, J = 5.1 Hz, 1 H), 8.32 (d, J = 0.7 Hz, 1 H), 8.96 (bs, 1 H).

Attempted Synthesis of *N*5-Benzyl-4-(*tert*-butyldiphenylsilyloxy)-7-[5-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-D-ribono-1,4-lactone]-5,4-azaborathieno [3,2-*d*] pyridine (20). General. Five attempts were made to couple the ribonolactone **4** with either **2** or **3**.

Run 1. To a stirred solution of 153 mg (0.32 mmol) of **2** in 0.30 mL of THF at -75 °C was slowly added 38 μL (0.32 mmol) of 8.4 M *n*-BuLi. After 20 min, a solution of 130 mg (0.30 mmol) of **4** in 0.80 mL of THF was added dropwise over a period of 15 min. The resulting solution was stirred for 3 h at -75 °C, then warmed to rt and quenched with 3 mL of water. The aqueous layer was separated and washed with ether (3 x 3 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated to give 205

mg of a crude brown oil. Analysis of the crude product by ^{1}H NMR showed no coupling had occurred.

Run 2. To a stirred solution of 162 mg (0.29 mmol) of **3** in 0.40 mL of THF at -78 °C was added 170 μL (0.29 mmol) of 1.7 M *t*-BuLi over a period of 3 min. After 20 min, a solution of 113 mg (0.27 mmol) of **4** in 0.80 mL of THF was added in a slow, dropwise manner. The resulting solution was stirred for 4 h at -78 °C, then warmed to rt and quenched with cold water. The aqueous layer was separated and washed with ether (3 x 1.5 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated to give 216 mg of a crude brown oil. Column chromatography (hexanes-ethyl acetate, 98/2 to 5/95) returned only starting materials.

Run 3. To a stirred solution of 41 mg (0.07 mmol) of **3** in 0.30 mL of THF at -75 °C was slowly added 44 μL (0.07 mmol) of 1.6 M *n*-BuLi. After 15 min, a solution of 28 mg (0.07 mmol) of **4** in 0.30 mL of THF was added over a period of 15 min. The resulting solution was stirred for 3.25 h at -75 °C, then warmed to rt and quenched with cold saturated NH_4Cl. The layers were separated and the aqueous layer was washed with ether (3 x 1.5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give 46 mg of a crude yellow oil. Analysis of the crude oil by ^{1}H NMR showed no coupling had occurred.

Run 4. To a stirred solution of 79 mg (0.13 mmol) of **2** in 0.20 mL of THF at -75 °C was added 320 μL (0.14 mmol) of 0.44 M *n*-BuLi in a slow, dropwise fashion. After 1 h, a solution of 56 mg (0.13 mmol) of **4** in 0.40 mL THF was added slowly. The resulting solution was stirred for 2 h, then warmed to rt and quenched with saturated NH_4Cl. The layers were separated and the aqueous layer was washed with ether (3 x 1.5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give 96 mg of a crude yellow oil. Analysis of the material by ^{1}H NMR showed no coupling had occurred.

Run 5. To a stirred solution of 49 mg (0.10 mmol) of **2** in 0.20 mL of THF at -75 °C was slowly added 90 µL (0.14 mmol) of 1.5 M *t*-BuLi. After 15 min, a solution of 44 mg (0.10 mmol) of **4** in 0.4 mL of THF was added dropwise. The resulting solution was stirred for 3 h, then warmed to rt and quenched with cold saturated NH_4Cl. The layers were separated and the aqueous layer was washed with ether (3 x 1.5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give 57 mg of a crude brown oil. Analysis of the crude oil by ^1H NMR showed no coupling had occurred.

Attempted Synthesis of 4-*O*-*tert*-Butyl-7-(2',3',5'-*O*-acetyl-β-D-*erythro*-pentafuranosyl)-5,4-azaborathieno [3,2-*d*] pyridine (39). General. Three attempts were made to couple the pentenylriboside **5** with either **38** or **2**.

Run 1. To a stirred solution of 50.0 mg (0.24 mmol) of **38** in 24 mL of CH_3CN was added 248 mg (0.72 mmol) of **5** and 162 mg (0.72 mmol) of *N*-iodosuccinimide (**30**). After 10 min, 160 mg (120 µL, 0.72 mmol) of TMS-OTf was added dropwise. The resulting orange-brown solution was stirred for 2 h, then quenched with 6 mL of 10% $Na_2S_2O_3$ and 6 mL of saturated $NaHCO_3$, and extracted with 25 mL of ether. The organic layer was separated and the aqueous layer was washed with ether (3 x 10 mL). The combined organic layers were washed with 10 mL of saturated NaCl, dried (Na_2SO_4), and concentrated to give a crude brown oil. Subsequent chromatography on silica gel (chloroform-ethanol, 98.5/1.5 to 97/3) gave two sets of collected fractions. ^1H NMR analysis of the fractions showed an undesired coupling had occurred between the *N*5 or *N*6 of the base and C-1' of the sugar.

Run 2. To a stirred solution of 49 mg (0.14 mmol) of **5** in 10 mL of CH_3CN was added 38 mg (0.17 mmol) of *N*-iodosuccinimide (**30**) and 51 mg (0.11 mmol) of **2**. The reaction was chilled in an ice bath and 11 mg (9.0 µL, 0.05 mmol) of TMS-OTf was added. The resulting solution was stirred for 4.5 h, then quenched with 5 mL of 10% $Na_2S_2O_3$ and 5 mL of saturated $NaHCO_3$, and extracted with 20 mL of ether. The organic layer was separated and the aqueous layer was washed with ether (3 x 15 mL). The

combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give a crude yellow oil. Subsequent chromatography on silica gel (hexanes-chloroform, 75/25 to chloroform-ethanol, 98.5/1.5) yielded three fractions. ^1H NMR analysis of fractions showed no coupling had occurred.

Run 3. To a stirred solution of 49 mg (0.14 mmol) of **5** in 4 mL of CH_3CN was added 63 mg (0.28 mmol) of *N*-iodosuccinimide (**30**) and 62 mg (51 µL, 0.28 mmol) of TMS-OTf. After stirring for 5 min, a solution of 208 mg (0.43 mmol) of **2** in 7 mL of CH_3CN and 2 mL of CCl_4 was added dropwise. The resulting solution was stirred for 5.25 h, then quenched with 5 mL of 10% $Na_2S_2O_3$ and 5 mL of saturated $NaHCO_3$, and extracted with 20 mL of ether. The organic layer was separated and the aqueous layer was washed with ether (3 x 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give a crude yellow oil. Silica gel chromatography (hexanes-chloroform, 50/50 to chloroform-ethanol, 97/3) yielded three fractions. Analysis of the fractions by ^1H NMR showed no coupling had occurred.

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CHAPTER 3

TANDEM ANIONIC-ANIONIC REACTIONS IN ORGANIC SYNTHESIS

Introduction

Tandem reactions have been known and used for many years. Only recently has a focused effort been undertaken to expand their use in organic synthesis. Of major importance is the use of tandem reactions for the synthesis of complex ring systems found in natural products. Organic chemists are continually looking for methodologies which generate complex structures in a minimum number of steps. Tandem reactions, also known as domino, sequential, cascade, consecutive, iterative, zipper, and one-pot (one-flask) reactions, provide such an avenue. They allow the organic chemist to combine two or more reactions into one synthetic operation. This effectively cuts down on labor involved, the quantities of chemicals/solvents used, and the amount of waste produced.

An overview of the literature shows a wide range of reactions which could conceivably be classified as tandem reactions. Thus, before beginning, an adequate definition of a tandem reaction needs to be made. Tietze[35] defines a tandem reaction as "...a process involving two or more bond-forming transformations (usually C-C bonds) which take place under the same reaction conditions without adding additional reagents [or] catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step." Furthermore, the literature shows that those reactions which do qualify as tandem reactions require further classification. Tietze provides a system

(Table 1) which allows for the categorization of tandem reactions based upon the mechanisms of the steps involved. Those most frequently seen in the literature are the cationic-cationic (**1a/2a**), anionic-anionic (**1b/2b**), radical-radical (**1c/2c**), pericyclic-pericyclic (**1d/2d**), and sequential transition metal-catalyzed reactions (**1g/2g**). The anionic-pericyclic (**1b/2d**) and anionic-pericyclic-pericyclic (**1b/2d/3d**) are not as prevalent but are just as powerful.

Table 1. Classification of Tandem Reactions According to the Mechanism of the Different Steps.

	1st step		2nd step		3rd step
1a	cationic	**2a**	cationic	**3a**	cationic
1b	anionic	**2b**	anionic	**3b**	anionic
1c	radical	**2c**	radical	**3c**	radical
1d	pericyclic	**2d**	pericyclic	**3d**	pericyclic
1e	photochemical	**2e**	photochemical	**3e**	photochemical
1f	carbinoid	**2f**	carbinoid	**3f**	carbinoid
1g	transition metal-catalyzed	**2g**	transition metal-catalyzed	**3g**	transition metal-catalyzed
1h	oxidation/reduction	**2h**	oxidation/reduction	**3h**	oxidation/reduction

Since the project presented in this thesis is based on an anionic sequence, the rest of this chapter will be focused toward this end. The reader may refer to reviews[35-37] to gain a better understanding of the diversity and richness of these intriguing reactions.

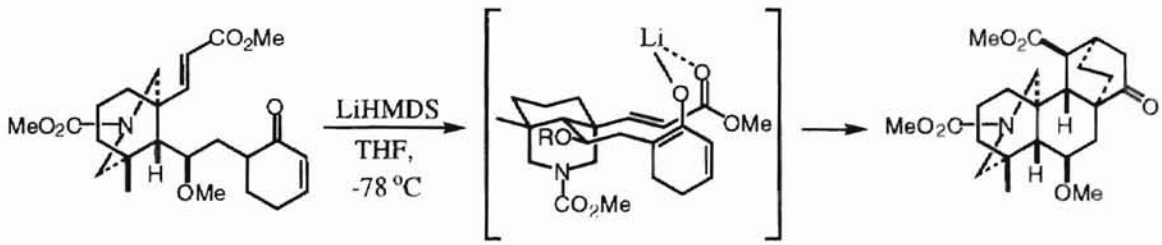
Anionic Sequences

Of all the sequences present in tandem reactions, the anionic sequences are the most prevalent. Bunce[37] has broken the anionic sequence down into four sub-categories – anionic-radical and anionic-carbene, anionic-pericyclic, and anionic-anionic sequences, the latter being the largest of the four. Anionic-radical and anionic-carbene reactions are relatively new and have been added only recently to the growing list of tandem reactions. Anionic-pericyclic sequences have been fairly well documented in the literature.[38-47] This

reaction involves an initial addition or elimination which leads to a reactive intermediate capable of further pericyclic reactions with inter- or intramolecular functionality. Anionic reactions have been coupled with the Diels-Alder and [3+2] cycloadditions, Claisen rearrangements, electrocyclizations, and [2,3]-sigmatropic shifts. Anionic-anionic sequences involve either a Michael-initiation or a Michael-termination step with the final result being a cyclic structure. This tandem process proves very useful for the synthesis of ring structures commonly found in natural products. In this sequence, a nucleophilic species adds to an activated alkene to produce a stabilized anion, which then adds to a second activated alkene positioned so as to close a five- or six-membered ring. The sequence is terminated by reaction with an electrophile, most often a proton, an alkylating agent, or yet another alkene.

Anionic-anionic reactions abound in the literature. Due to the vast array and utility of these reactions, it is virtually impossible to present a complete and comprehensive overview. Thus, a few prime examples are presented below to show how this reaction introduces regio-, chemo-, diastereo-, and enantioselectivity into ring systems.

Fukumoto and co-workers[48] described the use of an intramolecular double Michael addition (Figure 20) in their synthesis of oxygenated derivatives of the diterpene alkaloid atisine. Chiral cyclization substrate **1**, synthesized in six steps by adaptation of previously



1 **2** **3** (62%)

Figure 20. Synthesis of Tricyclic Intermediate **3**.

reported methods, was treated with lithium hexamethyldisilazide (LiHMDS) to give tricyclic intermediate **3** as a single stereoisomer in 62% yield. The observed stereochemistry presumably arises from the lithium chelated intermediate **2**.

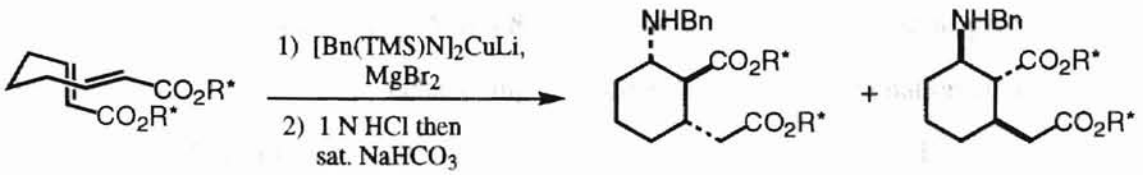


Figure 21. Synthesis of Cyclohexyl Diester **5**.

High diastereo- and enantioselectivity was exhibited in the synthesis of cyclohexyl diester **5** (Figure 21). In the treatment of di-(-)-menthyl (2*E*,7*E*)-2,7-nonadienedioate (**4**) with lithium *N*-benzyl-*N*-(trimethylsilyl)amide "cuprate" in the presence of $MgBr_2$,[49] a high preference was shown for the all equatorial product **5a**. It was believed that chelation of the $MgBr_2$ with the nonadienedioate in the indicated conformation led to the observed selectivity.

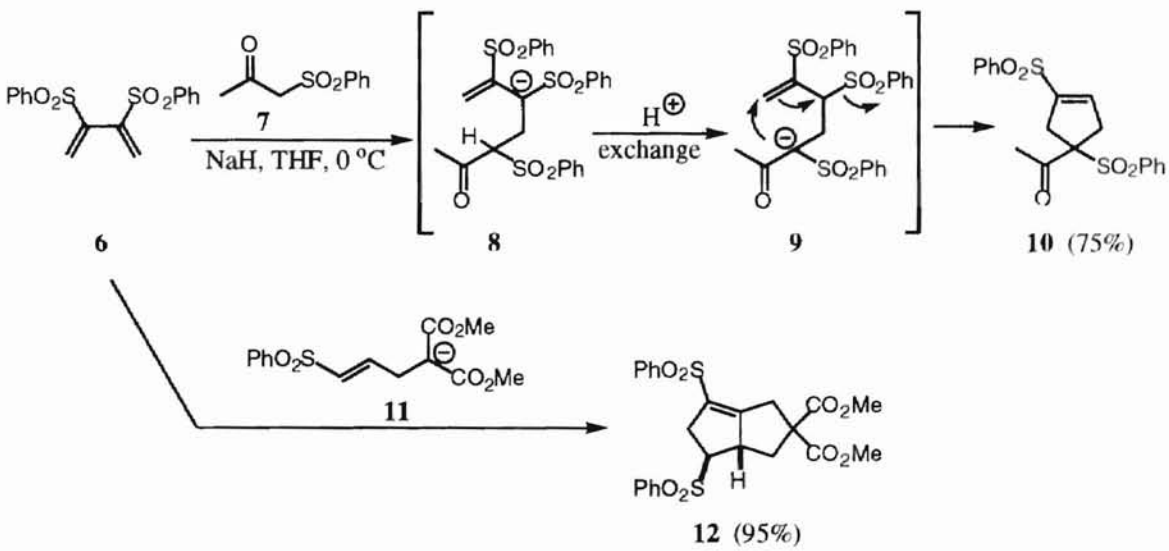
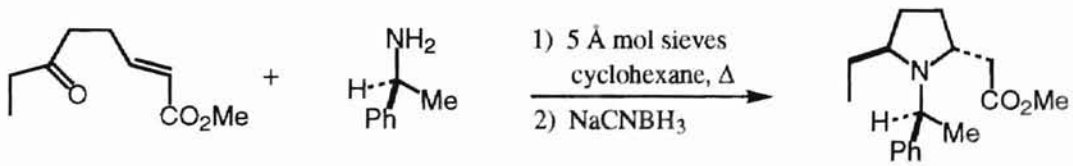


Figure 22. Synthesis of Diphenylsulfonyl Cyclopentene **10** and Bicyclo[3.3.0]octene **12**.

Padwa and co-workers have developed an interesting Michael-Michael-elimination sequence as an approach to the synthesis of cyclopentenes from 2,3-bis(phenylsulfonyl)-1,3-butadiene (**6**).[50] Treatment of phenylsulfonylacetone (**7**) with a slight excess of NaH in the presence of **6** gave the intermediate anion **8** via Michael addition of **7** to the unsaturated sulfone (Figure 22). Anion **8** underwent a proton exchange to give the more stable anion **9**. Subsequent Michael ring closure followed by elimination of the allylic sulfone provided the diphenylsulfonyl cyclopentene **10** in 75% yield. Extension of this protocol gave the bicyclo[3.3.0]octene **12**.[51] Michael addition of diester anion **11** to **6** followed by consecutive anion exchange, Michael, Michael, and elimination reactions afforded 95% of **12**.

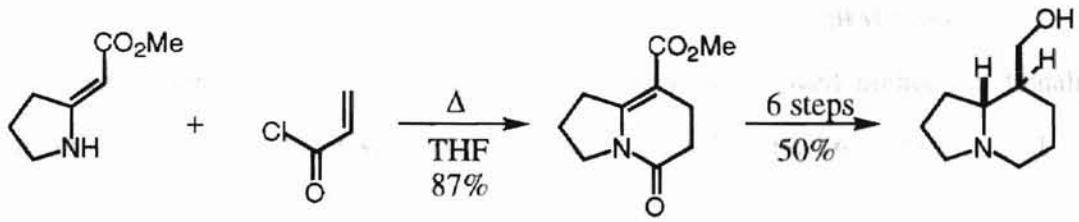
Nitrogen heterocycles are also possible via tandem reaction methodology. Dumas and d'Angelo have made pyrrolidine derivatives by using a novel reductive amination/Michael addition sequence.[52] Condensation of keto acrylate **13** with (*S*)-1-phenylethylamine (**14**) followed by imine reduction with $NaCNBH_3$ provided 67% of the racemic *trans*-2,5-disubstituted pyrrolidine **15** along with 8% of the cis isomer (Figure 23). Interestingly, the observed selectivity was dictated by the steric bulk rather than the chirality of the amine. For example, reaction with benzylamine produced a 2.6:1 ratio of trans:cis pyrrolidines while the use of α-isopropylbenzylamine gave essentially 100% of the trans-disubstituted product.



13 **14** **15** (67%)

Figure 23. Synthesis of a *trans*-2,5-Disubstituted Pyrrolidine.

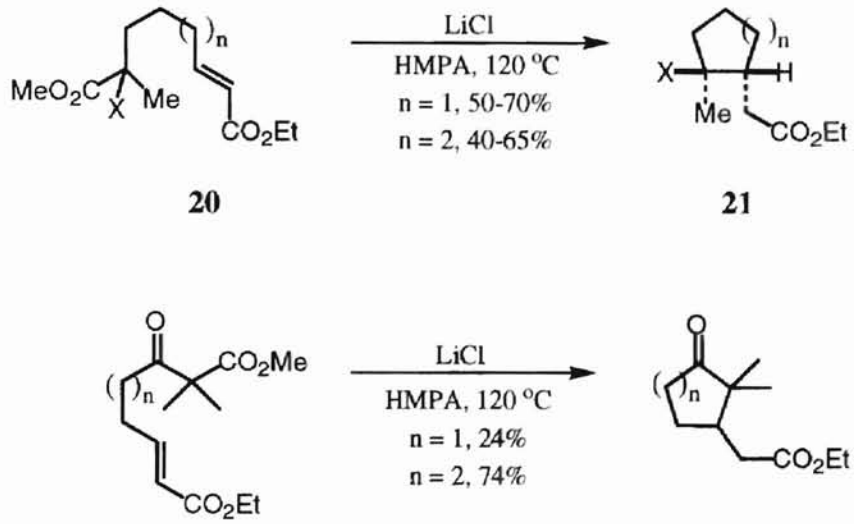
Paulvannan and Stille employed a unique acylation-Michael reaction (Figure 24) in their synthesis of tashiromine (**19**).[53] Treatment of β-enamino ester **16** with acryloyl chloride (**17**) yielded 87% of indolizidine **18**. Conversion to tashiromine was then accomplished in six steps with an overall yield of 50%.



16 **17** **18** **19**

Figure 24. Use of an Acylation-Michael Reaction in the Synthesis of Tashiromine (**19**).

Bunce and co-workers have developed a demethoxycarbonylation-Michael addition sequence to generate highly functionalized carbocycles.[54,55] Figure 25 presents two examples of this methodology. Substrates were designed to be activated toward



20 **21**

22 **23**

Figure 25. Synthesis of Funtionalized Carbocycles.

decarboxylation once the methyl ester was cleaved (i.e. X = EWG for **20**). Chemoselective nucleophilic attack on the methyl ester (by chloride) initiated demethoxycarbonylation to produce a stabilized anion which then cyclized by Michael addition to the tethered acrylate ester. Ring closure resulted in a majority of the product having the X group (e.g. CO_2Et, COMe, COPh) and the acetate side chain oriented trans as in **21**, even when the donor moiety was further substituted with an alkyl group.

Using a similar protocol Bunce and co-workers synthesized highly functionalized fused ring oxygen heterocycles.[56] Cyclization substrates **24** and **26** were prepared using standard literature methods. Treatment of **24** or **26** with lithium chloride (Figure 26) produced the stabilized anion which then underwent Michael addition to the acrylate ester to give chroman **25** or benzofuran **27**, respectively. The observed trans preference of the ester functionalities was speculated to result from electronic rather than steric factors.[56,57]

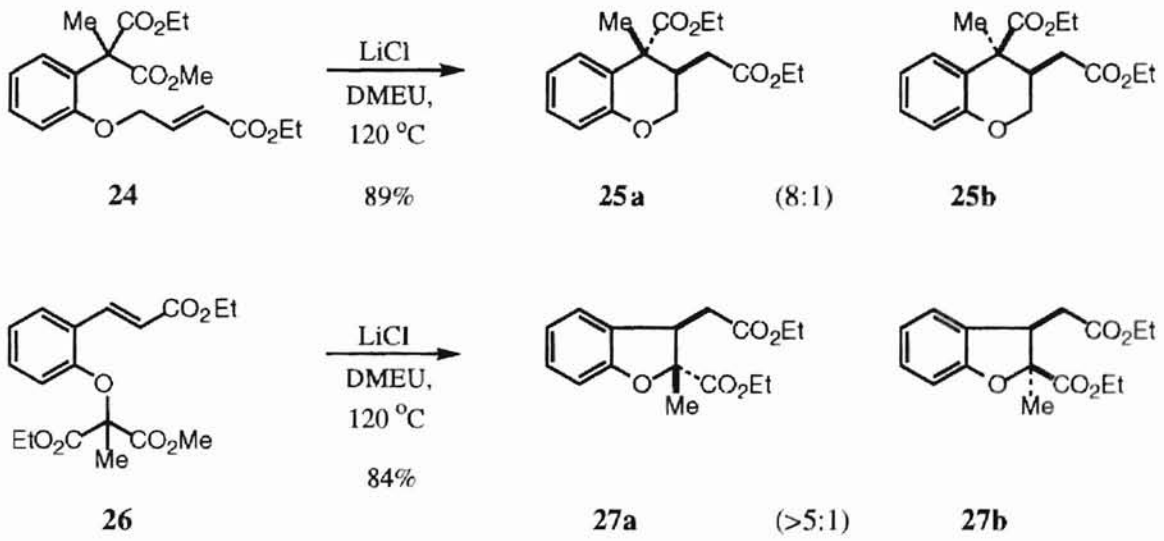


Figure 26. Synthesis of Fused Ring Oxygen Heterocycles.

Conclusions

The above discussion provides just a few examples of how tandem anionic-anionic sequences can be used to synthesize ring systems with specific regio-, chemo-, diastereo-, and enantioselectivity. This field continues to expand and receive more attention as organic chemists turn toward tandem methods to aid them in synthesizing natural products that bear complex and unusual substitution patterns. Tandem reactions also serve as an approach to the development of reaction schemes that minimize cost and waste but provide high efficiency.

CHAPTER 4

TOWARD THE SYNTHESIS OF RING SYSTEMS VIA TANDEM SEQUENCES

Introduction

This chapter details the use of two types of tandem sequences – the anionic-anionic and reduction-Michael addition sequences – which have been used to synthesize highly functionalized ring systems. A survey of natural products shows a diverse collection of complex ring systems. To synthesize such compounds in the most efficient manner (the ability to combine two or more reactions into one synthetic step with minimal labor, quantities of chemicals/solvents, and waste) can be accomplished by the tandem sequence. The compounds presented in this chapter – namely indans **1** and **2**, indanone **3**, cyclopentenes **4** and **5**, quinoxaline **6**, and benzoxazine **7** – can have a two-fold impact in the area of natural product synthesis: (1) the compounds themselves could serve as building blocks for other ring systems or; (2) the methodologies could be applied to synthesis of other compounds.

While **1**, **2**, **4**, and **5** were unattainable, **3**, **6**, and **7** were readily prepared, the one appealing factor being the ease of synthesis of **3**, **6**, and **7**. Specifically, all three compounds are easily made from readily available starting materials and require four steps or less to prepare. Thus, the methodologies presented below provide a useful addition to the field of tandem reactions.

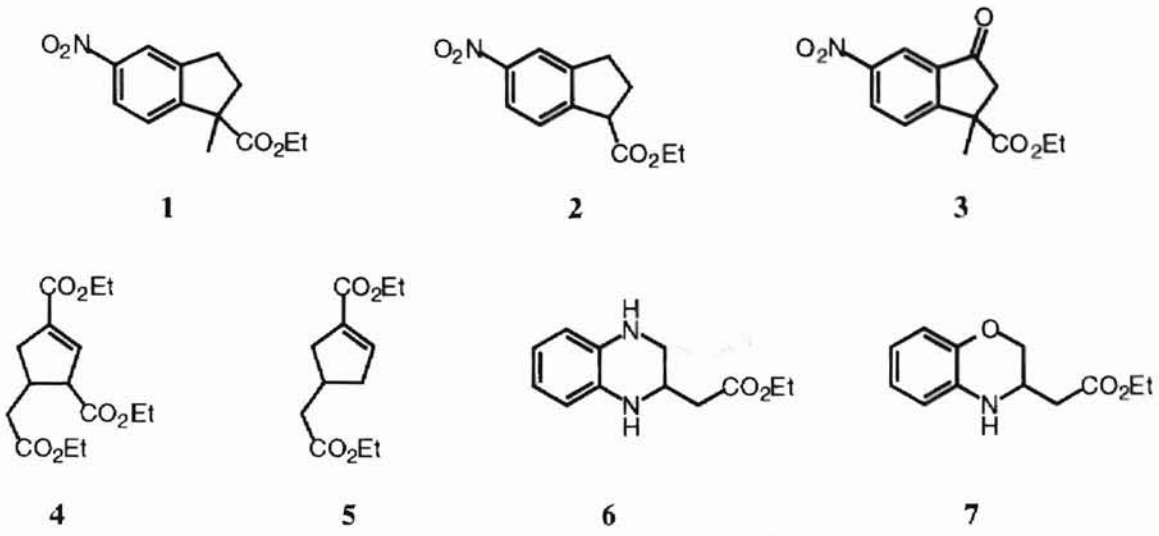


Figure 27. Indans **1** and **2**, Indanone **3**, Cyclopentenes **4** and **5**, Quinoxaline **6**, and Benzoxazine **7**.

Results

Anionic-anionic Reactions. Initial attempts were made to synthesize indan derivatives **1** and **2**. To set up the tandem sequence which was to provide **1** or **2**, it was necessary to synthesize the initial cyclization substrates **8** and **9** (Figures 28 and 29, respectively). To this end, (2-chlorophenyl)acetic acid (**10**) was treated[58] with lithium aluminum hydride to provide alcohol **11**. Treatment[59] of **11** with methanesulfonyl (mesyl) chloride gave mesylate **12** which was converted to iodide **13** in an overall 63% yield. Addition of iodide **13** to the anion of ethyl methyl methylmalonate **14** afforded chlorophenyl diester **15**. Nitration[60] of **15** yielded the 2-chloro-5-nitrophenyl diester **8**. In the next step, **8** was treated with LiCl in DMEU to initiate a demethoxycarbonylation nucleophilic aromatic substitution sequence to give cyclized product **1**.[61] Indan derivative **1**, however, was not observed. While the anion had formed (^{1}H and ^{13}C NMR spectra showed loss of the methoxycarbonyl group), **8** did not undergo the subsequent ring closure to form **1**. It was hypothesized that the anion was too sterically hindered to react at the aromatic ring. Therefore, a similar synthesis was conducted (Figure 29) to give

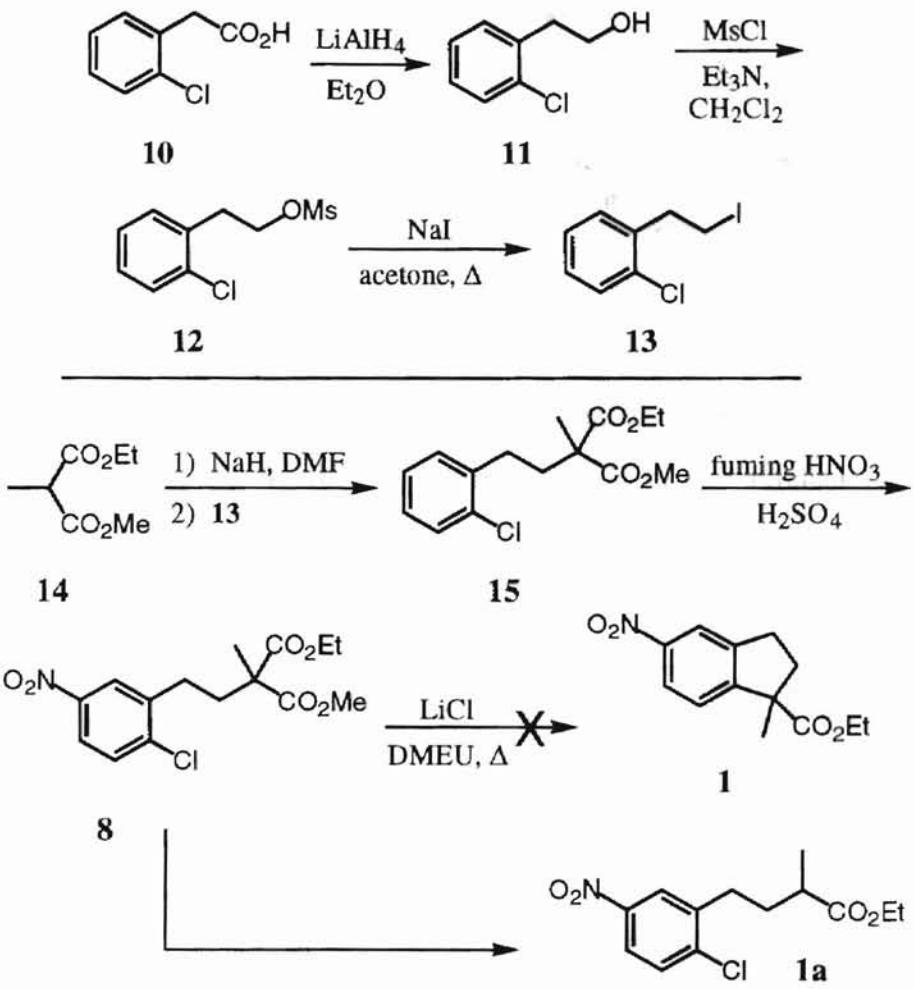


Figure 28. Synthesis of Iodide **11** (top) and Attempted Synthesis of Cyclized Product **1** (bottom).

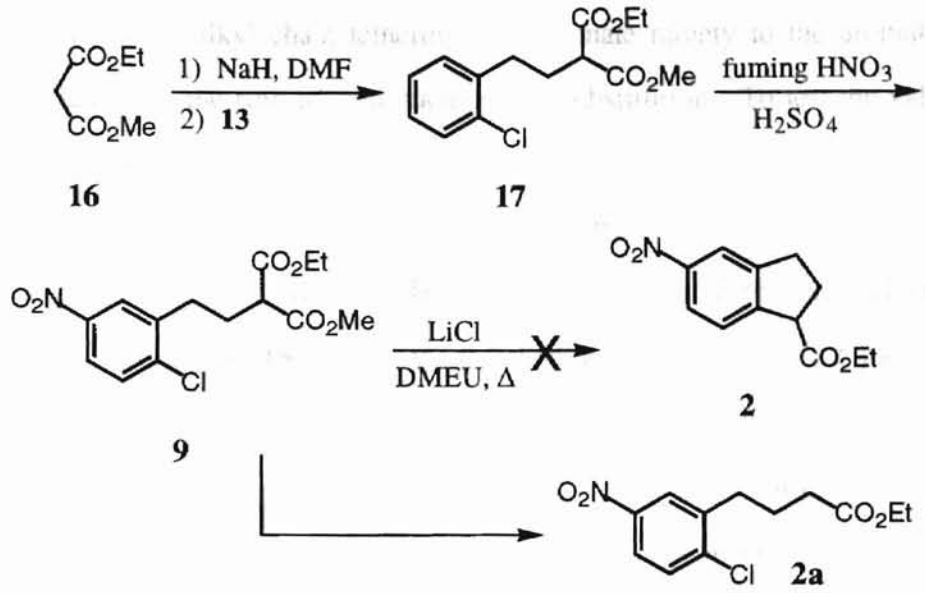


Figure 29. Attempted Synthesis of Cyclized Product **2**.

chloronitrophenyl diester **9**, the main difference being the omission of the side chain methyl group. Attempts to cyclize **9** also resulted in a decarboxylated product (**2a**). It was

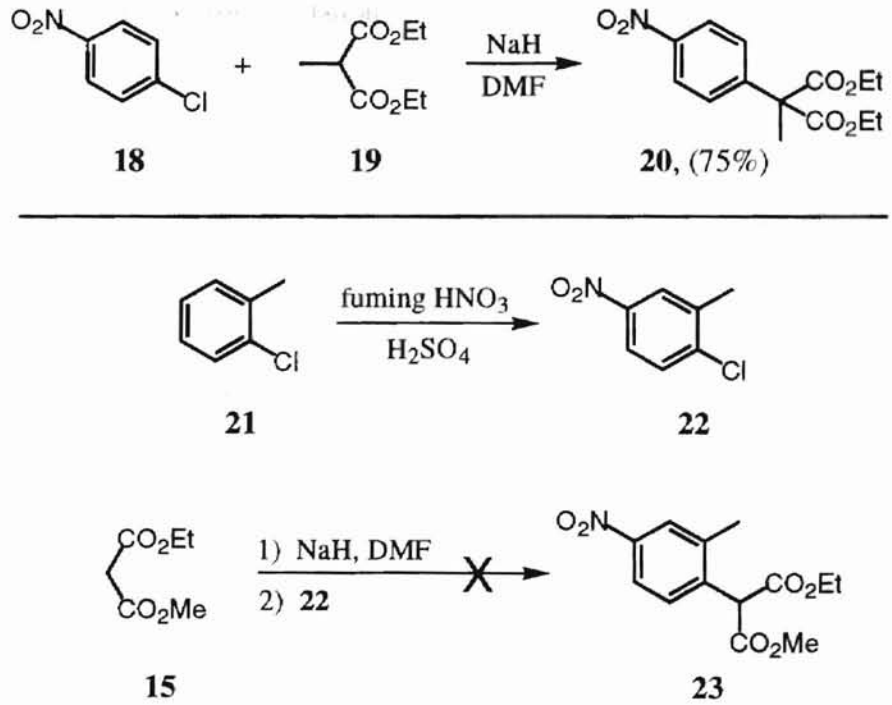
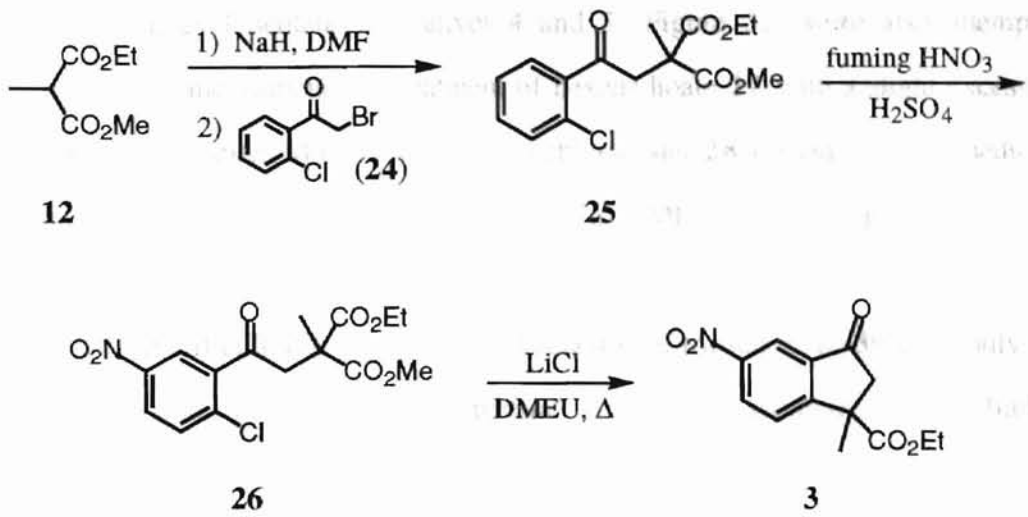


Figure 30. Synthesis of Diethyl (4-Nitrophenyl)methylmalonate (**20**, top) and Test Reaction for Alkylation of 2-Chloro-5-nitrotoluene (**23**, bottom).

hypothesized that the alkyl chain tethering the malonate moiety to the aromatic ring was possibly deactivating the ring toward nucleophilic substitution. To test the validity of this hypothesis a test reaction was conducted (Figure 30) on **22** using protocol outlined by Guerrato and co-workers.[62] In their work, Guerrato and co-workers were able to synthesize diethyl methyl(4-nitrophenyl)malonate (**20**) from diethyl methylmalonate (**19**) and *p*-chloronitrobenzene (**18**) in 75% yield. A similar reaction with **22** gave none of the addition-elimination product **23**. Since nitrophenyl diester **23** was not observed (starting material was recovered), it was concluded that the alkyl substituent was indeed deactivating the ring. To alleviate this problem, it was decided to incorporate another electron withdrawing group (specifically a carbonyl functionality) into the system at the benzylic position of the alkyl chain to further activate the ring toward substitution.

Initial attempts were made to oxidize the benzylic position of **8** with the Jones reagent. Eisenbraun[63] had shown that tetralin derivatives were readily oxidized by the Jones reagent at the benzylic methylene position but it was not known to us if such a procedure would allow for oxidation of the benzylic methylene in an acyclic alkyl substituent. Attempts to oxidize the benzylic position using Jones reagent were unsuccessful. A second attempt was made using the procedure of Schmidt and Schäfer.[64] These authors were able to oxidize the benzylic methylene of isobutylbenzene and *n*-butylbenzene to the respective ketones using benzyltriethylammonium permaganate. Use of this reagent on **8**, however, did not afford the desired ketone.

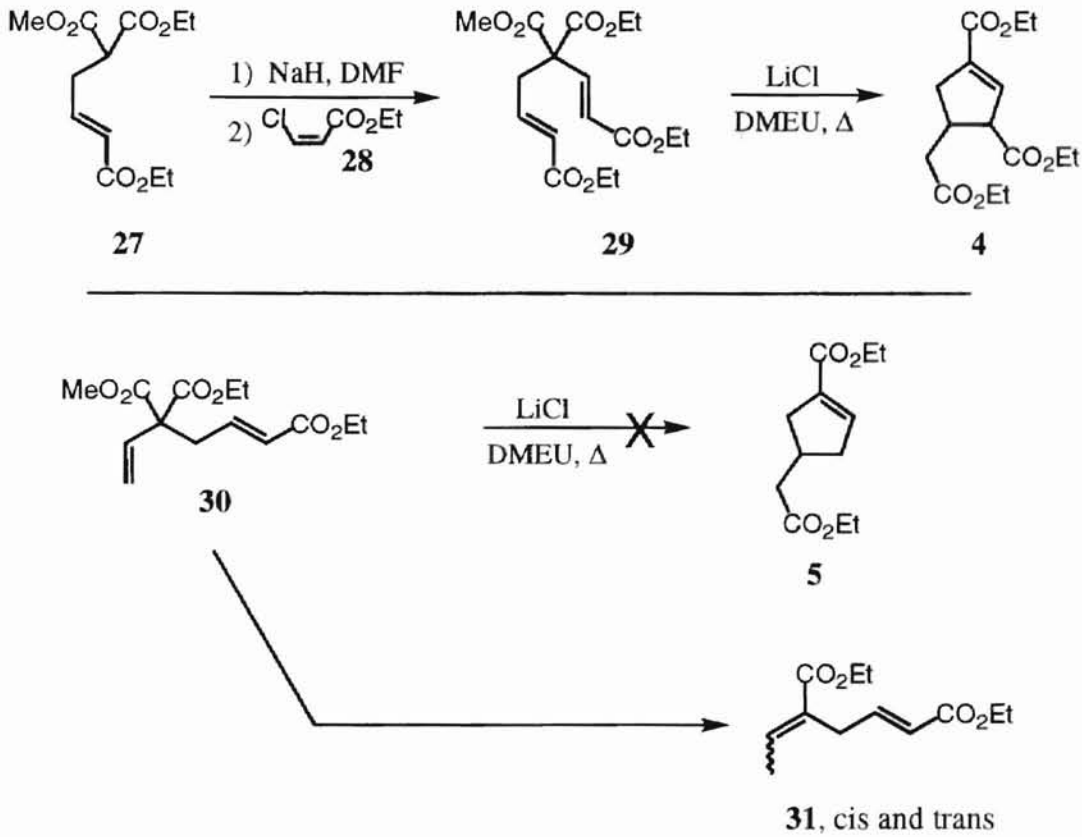
Rather than investigate oxidation of **14** further, the synthesis was redesigned to build the substrate with a carbonyl functionality already present at the benzylic position (Figure 31). Thus, the anion of ethyl methyl methylmalonate (**14**) was treated with 2-bromo-1-(2-chlorophenyl)ethanone (**24**) to afford keto diester **25**. Nitration[60] of **25** provided the 5-nitro adduct in 67% yield. Treatment of the nitro compound with LiCl in DMEU at 120 °C gave the desired cyclized product **3** in low yield (13%). The cyclization reaction was attempted only once. Possible avenues available to improve the yield include



12 **25** **26** **3**

Figure 31. Synthesis of Cyclized Product **3**.

adjustment of reaction conditions, replacement of the ethyl methyl methylmalonate with ethyl methyl malonate and/or use of the less sterically hindered fluoroaromatic.



27 **29** **4**

30 **5**

31, cis and trans

Figure 32. Attempted Synthesis of Cyclopentene Derivatives **4** and **5**.

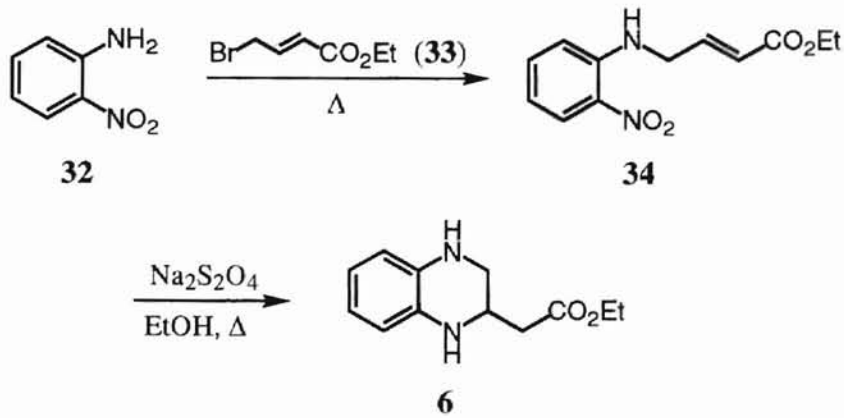
Synthesis of cyclopentene derivatives **4** and **5** (Figure 32) were also attempted using the anionic-anionic sequence. Treatment of hexenedioate **27** with a slight excess of NaH followed by subsequent Michael addition to chloro ester **28** provided octadienedioate **29**. Reaction[61] of **29** with five equivalents of LiCl in DMEU at 120 °C gave a complex mixture. Analysis of the crude mixture by ^{1}H NMR suggested that **4** might be present, but the products proved difficult to separate. Similar reaction of triester diene **30** gave only the demethoxycarbonylation product **31** as a mixture of *E* and *Z* isomers. Thus, further investigations should focus on substrates having structures similar to **29**.

Reduction-Michael Addition Reactions. The reduction-Michael addition sequence was used to synthesize quinoxaline derivative **6** and benzoxazine derivative **7**.

6 **7**

Figure 33. Quinoxaline Derivative **6** and Benzoxazine Derivative **7**.

The synthesis of **6** was accomplished by alkylation[65] of *o*-nitroaniline (**32**) with ethyl 4-bromocrotonate (**33**) to give anilinobutenoate **34**. Reduction of the nitro functionality in



32 **34**

6

Figure 34. Synthesis of Quinoxaline Derivative **6**.

34 with sodium hydrosulfite ($Na_2S_2O_4$) followed by subsequent intramolecular Michael addition of the intermediate amine to the α,β-unsaturated ester provided tetrahydroquinoxaline **6** in 44% yield.

The synthesis of **7** required a more indirect route (Figure 35). Alkylation of *o*-nitrophenol (**35**) with allyl bromide (**36**) provided phenoxyalkene **37**. Ozonolysis of the side chain double bond in **37** followed by Wittig olefination[54,61] then gave the phenoxy-substituted 2-butenoate ester **39**. Nitro reduction and subsequent ring closure of **39** yielded dihydrobenzoxazine **31** in 10% yield.

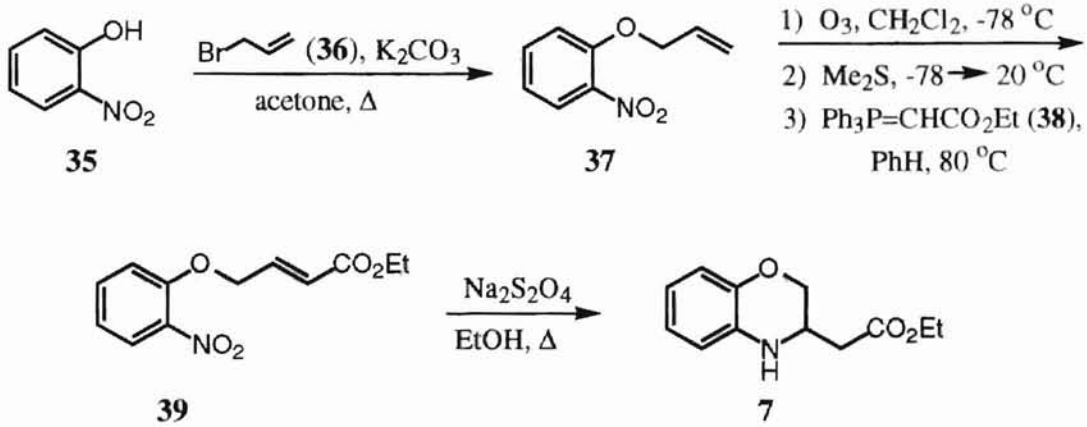


Figure 35. Synthesis of Benzoxazine Derivative **7**.

The synthesis of **6** resulted in a relatively modest yield of 44%. This, coupled with the fact **6** does not require purification, allows for improvement of yield to focus on the reaction conditions. Potential avenues are reaction time and/or temperature. Although the synthesis of **7** resulted in a poor yield, this can be remedied through reaction time and the amount of heat applied to the reaction. For example, the reduction of the nitro group to the amine readily occurs at room temperature over a 10-15 min period. Application of heat to the reaction for an equivalent amount of time should allow for cyclization to go to completion. Adjustment of stir times as well as the amount of heat applied to the reaction should lead to increased yield.

In conclusion, with the successful syntheses of **3**, **6**, and **7** and upon optimization of the yields, valuable additions have been made to the field of tandem sequences. The compounds, while simple in their construction, have incorporated a high degree of functionality. Their potential use in natural product synthesis or the application of the methodologies to other reaction schemes should prove useful in the future.

Experimental

General. All reactions were carried out under a nitrogen atmosphere. DMF was stored over 4-Å molecular sieves. DMEU was distilled from CaH_2 (0.5 mm Hg) and stored over 4-Å molecular sieves. THF was distilled from $LiAlH_4$ under nitrogen. Reactions were followed by either: (1) TLC on hard layer silica gel GF plates (Analtech) using UV detection or (2) capillary GC with FI detection (SE-30 column, 6 m x 0.25 mm i.d., 0.25 μm film thickness). Preparative separations were performed using one of the following methods: (1) PTLC on 20-cm x 20-cm silica gel GF plates (Analtech) or (2) column chromatography on silica gel (60-200 mesh) mixed with Sylvania no. 2282 UV-active phosphor. Band elution, where appropriate, was monitored using a hand-held UV lamp. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were taken in $CDCl_3$.

2-(2-Chlorophenyl)ethanol (11). To a stirred suspension of 1.10 g (29.0 mmol) of $LiAlH_4$ in 50 mL of THF at 0 °C was added a solution of 5.00 g (29.3 mmol) of 2-chlorophenylacetic acid in 125 mL of THF. The resulting solution was stirred at rt for 0.5 h and then refluxed for 2.5 h. The reaction was cooled to 0 °C and quenched by alternating addition of 10% NaOH and H_2O until a fine ppt had formed. The mixture was filtered through Celite and the filtrate was concentrated to give a yellow oil. Vacuum distillation of the crude product afforded 3.43 g (22.0 mmol, 76%) of **11** as a colorless oil, bp 88-89 °C (0.6 mm Hg). IR (thin film) 3345, 3061, 3025, 1573, 1481, 1445, 755 cm^{-1};

^{1}H NMR δ 1.45 (bs, 1 H), 3.03 (t, J = 6.7 Hz, 2 H), 3.89 (q, J = 6.3 Hz, 2 H), 7.17-7.39 (m, 4 H); ^{13}C NMR δ 36.6, 61.6, 126.7, 127.8, 129.5, 131.3, 134.2, 136.1.

2-(2-Chlorophenyl)ethyl mesylate (12). To a stirred solution of 3.43 g (22.0 mmol) of **4** and 3.34 g (4.60 mL, 33.0 mmol) of triethylamine in 100 mL of CH_2Cl_2 at 0 °C was added 2.75 g (1.85 mL, 24.0 mmol) of methanesulfonyl (mesyl) chloride over a 4 min period. The resulting mixture was stirred for 30 min at 0 °C, then washed with cold water (1x), cold 1 M HCl (1x), saturated $NaHCO_3$ (1x), and saturated NaCl. The organic layer was dried ($MgSO_4$), filtered, and concentrated to give a quantitative yield of **12** as a pale yellow oil. IR (thin film) 3068, 3026, 1573, 1510, 1353, 1175, 754 cm^{-1}; ^{1}H NMR δ 2.88 (s, 3H), 3.21 (t, J = 6.9 Hz, 2 H), 4.46 (t, J = 6.8 Hz, 2 H), 7.21-7.39 (m, 4 H); ^{13}C NMR δ 33.5, 37.2, 68.4, 126.1, 127.2, 128.8, 129.8, 131.6, 134.0.

2-(2-Chlorophenyl)-1-iodoethane (13). In a 250-mL round-bottomed flask was placed 3.21 g (13.7 mmol) of **12**, 8.60 g (57.4 mmol) of NaI and 100 mL of acetone. The resulting mixture was refluxed for 4 h, then cooled to rt and concentrated. The solid was transferred to a separatory funnel with the aid of water and ether. The aqueous layer was washed with ether (3x) and the combined organic layers were washed with water (1x), sodium thiosulfate (1x), saturated NaCl (1x), dried (Na_2SO_4), filtered, and concentrated to give 3.38 g (12.7 mmol, 93%) of **13** as a yellow-orange oil. The iodide was used without further purification in the next reaction. IR (thin film) 3068, 3018, 1573, 1474, 755 cm^{-1}; ^{1}H NMR δ 3.27-3.41 (m, 4 H), 7.20-7.38 (m, 4 H); ^{13}C NMR δ 3.0, 38.1, 127.1, 128.5, 129.9, 130.8, 133.9, 138.2.

Ethyl Methyl (2-(2-Chlorophenyl)ethyl)methylpropanedioate (15). To a stirred suspension of 0.46 g (19.0 mmol) of oil-free NaH in 15 mL of DMF was slowly added a solution of 2.90 g (18.0 mmol) of ethyl methyl methylmalonate in 15 mL of DMF. The resulting mixture was stirred for 30 min after which a solution of 5.10 g (19.0 mmol) of **6** in 15 mL of DMF was added dropwise. The reaction was stirred until complete (GC), then transferred to a separatory funnel containing saturated NaCl. The aqueous layer was

washed with ether (3x) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a yellow oil. The crude product was chromatographed on silica gel (hexanes-ether, 95/5) to provide 3.27 g (11.0 mmol, 61%) of **15** as a colorless oil. IR (thin film) 1737, 762 cm^{-1}; ^1H NMR δ 1.27 (t, J = 7.1 Hz, 3 H), 1.54 (s, 3 H), 2.12-2.17 (m, 2 H), 2.67-2.73 (m, 2 H), 3.74 (s, 3 H), 4.21 (q, J = 7.1 Hz, 2 H), 7.13-7.37 (m, 4 H); ^{13}C NMR δ 13.9, 19.8, 28.6, 35.7, 52.4, 53.6, 61.3, 127.0, 127.7, 129.6, 130.5, 133.9, 139.1, 172.2, 172.8.

Ethyl Methyl (2-(2-Chloro-5-nitrophenyl)ethyl)methylpropanedioate (8). To a stirred solution of 2.51 g (8.40 mmol) of **15** in 4 mL of H_2SO_4 at -5 °C was added a solution of 0.40 mL of fuming HNO_3 in 0.85 mL of H_2SO_4 at a rate of 1-2 drops every 10 min. The reaction was stirred for 2.75 h and then poured into ice water. The aqueous layer was washed with ether (3x) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a viscous yellow oil. Chromatography on silica gel (hexanes-ether, 95/5 to 88/12) afforded 2.18 g (6.34 mmol, 75%) of **8** as a yellow oil. IR (thin film) 3106, 1744, 1527, 1348, 749 cm^{-1}; ^1H NMR δ 1.28 (t, J = 7.1 Hz, 3 H), 1.55 (s, 3 H), 2.13-2.19 (m, 2 H), 2.78-2.82 (m, 2 H), 3.77 (s, 3 H), 4.22 (q, J = 7.1 Hz, 2 H), 7.51 (d, J = 8.7 Hz, 1 H), 8.03 (dd, J = 8.8, 2.7 Hz, 1 H), 8.13 (d, J = 2.7 Hz, 1 H); ^{13}C NMR δ 13.5, 19.3, 28.3, 34.8, 52.1, 52.9, 61.1, 122.2, 124.8, 130.1, 140.4, 140.7, 146.4, 171.3, 172.0.

Attempted Synthesis of Ethyl-1-methyl-5-nitroindancarboxylate (1). In a 25-mL round-bottomed flask was placed 210 mg (0.61 mmol) of **8**, 110 mg (2.44 mmol) of LiCl, and 10 mL of DMEU. The resulting solution was heated at 120 °C until the reaction was complete (GC), then poured into a separatory funnel containing 25 mL of ether. The organic layer was washed with water (3x) and saturated NaCl (1x). The aqueous layer was washed with ether (2x) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give an orange-brown oil. Preparative TLC (hexanes-ether, 95/5 to 85/15) produced three bands, the major band being decarboxylated

product (**1a**). IR (thin film) 3100, 1736, 1527, 1354, 1174, 749 cm^{-1}; ^1H NMR δ 1.25 (d, J = 7.0 Hz, 3 H), 1.30 (t, J = 7.1 Hz, 3 H), 1.67-1.83 (m, 2 H), 1.96-2.09 (m, 2 H), 2.48-2.55 (m, 1 H), 4.18 (q, J = 7.1 Hz, 2 H), 7.52 (d, J = 8.8 Hz, 1 H), 8.01 (dd, J = 8.8, 2.7 Hz, 1 H), 8.13 (d, J = 2.7 Hz, 1H); ^{13}C NMR δ 14.1, 17.1, 31.2, 32.9, 39.0, 60.4, 120.0, 122.4, 125.1, 130.4, 141.1, 141.3, 176.1.

Ethyl Methyl (2-(2-Chlorophenyl)ethyl)propanedioate (17). To a stirred suspension of 0.30 g (12.3 mmol) of oil-free NaH in 10 mL of DMF was added a solution of 1.77 g (12.1 mmol) of ethyl methyl malonate in 10 mL of DMF dropwise. The resulting mixture was stirred for 30 min and a solution of 3.38 g (12.7 mmol) of **13** in 10 mL of DMF was added dropwise. The resulting solution was stirred for 5.25 h, then poured into 50 mL of saturated NaCl and extracted with ether (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a yellow oil. Column chromatography (hexanes-ether, 95/5) provided 2.64 g (9.3 mmol, 77%) of **17** as a colorless oil. IR (thin film) 3070, 1736, 1484, 1441, 1152, 756 cm^{-1}; ^1H NMR δ 1.28 (t, J = 7.0 Hz, 3 H), 2.19-2.27 (m, 2 H), 2.76-2.82 (m, 2 H), 3.40 (t, J = 7.4 Hz, 1 H), 3.75 (s, 3 H), 4.21 (q, J = 7.1 Hz, 2 H), 7.15-7.36 (m, 4 H); ^{13}C NMR δ 14.0, 28.5, 31.0, 51.2, 52.4, 61.5, 126.9, 127.8, 129.7, 130.6, 134.1, 138.3, 169.3, 169.9.

Ethyl Methyl (2-(2-Chloro-5-nitrophenyl)ethyl)propanedioate (9). To a stirred solution of 2.60 g (9.30 mmol) of **17** in 5 mL of H_2SO_4 at -5 °C was added a solution of 0.45 mL of fuming HNO_3 in 1.0 mL of H_2SO_4 at a rate of 2 drops every 10 min. The reaction was stirred for 3 h, then poured into ice water. The aqueous layer was washed with ether (3x) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a viscous yellow oil. Column chromatography on silica gel (hexanes-ether, 93/7) gave 1.80 g (5.5 mmol, 59%) of **9** as a yellow oil. IR (thin film) 3106, 1744, 1614, 1578, 1527, 1347, 749 cm^{-1}; ^1H NMR δ 1.30 (t, J = 7.1 Hz, 3 H), 2.23-2.30 (m, 2 H), 2.87-2.92 (m, 2 H), 3.41 (t, J = 7.4 Hz, 1 H), 3.77 (s, 3 H), 4.24 (q, J = 7.1 Hz, 2 H), 7.53 (d, J = 8.8 Hz, 1 H), 8.05 (dd, J = 8.7, 2.6 Hz, 1 H), 8.14 (d, J = 2.6 Hz, 1 H);

^{13}C NMR δ 13.9, 28.0, 31.1, 51.0, 52.6, 61.7, 122.8, 125.3, 130.6, 140.3, 141.1, 146.0, 168.9, 169.5.

Attempted Synthesis of Ethyl-5-nitroindancarboxylate (2). In a 25-mL round-bottomed flask was placed 340 mg (1.00 mmol) of **9**, 180 mg (4.20 mmol) of LiCl, and 5 mL of DMEU. The resulting solution was heated at 135 °C for 4 h, then poured into 20 mL of ether. The organic layer was washed with water (3x) and the combined aqueous layers were washed with ether (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a brown oil. Preparative TLC (hexanes-ether, 90/10) produced four bands, the major band being decarboxylated product (**2a**). IR (thin film) 3106, 1736, 1614, 1578, 1520, 1347, 1189, 749 cm^{-1}; ^{1}H NMR δ 1.29 (t, J = 7.1 Hz, 3 H), 2.01 (quintet, J = 7.3 Hz, 2 H), 2.40 (t, J = 7.3 Hz, 2 H), 2.88 (t, J = 7.7 Hz, 2 H), 4.16 (q, J = 7.1 Hz, 2 H), 7.53 (d, J = 8.8 Hz, 1H), 8.03 (dd, J = 8.8, 2.7 Hz, 1H), 8.13 (d, J = 2.7 Hz, 1 H); ^{13}C NMR δ 14.1, 24.2, 32.6, 33.3, 60.4, 119.8, 122.2, 122.5, 125.1, 130.4, 141.0, 173.0.

2-Chloro-5-nitrotoluene (22). To a stirred solution of 1.00 g (0.90 mL, 7.90 mmol) of 2-chloro-1-methylbenzene in 4 mL of H_2SO_4 at -5 °C was added a solution of 0.40 mL of fuming HNO_3 in 0.80 mL of H_2SO_4 at a rate of 2 drops every 10 min. The resulting solution was stirred for 3 h, then poured into ice water. The aqueous layer was washed with ether (3x) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a brown oil. Column chromatography on silica gel (hexanes-ether, 95/5) afforded 1.20 g (7.0 mmol, 89%) of **22** as a yellow oil. IR (thin film) 3113, 1614, 1585, 1527, 1354, 922, 806, 749 cm^{-1}; ^{1}H NMR δ 2.49 (s, 3 H), 7.54 (d, J = 8.4 Hz, 1 H), 8.01 (dd, J = 8.8, 2.2 Hz, 1 H), 8.13 (d, J = 2.1 Hz, 1 H); ^{13}C NMR δ 20.2, 121.7, 122.2, 125.7, 130.0, 138.0, 141.5.

Attempted Synthesis of Ethyl Methyl (2-Methyl-4-nitrophenyl)propanedioate (23). To a stirred suspension of 70 mg (3.10 mmol) of oil-free NaH in 2 mL of DMF was slowly added a solution of 0.40 g (3.42 mmol) of ethyl methyl malonate

in 2 mL of DMF. The resulting mixture was stirred for 30 min after which a solution of 0.50 g (2.90 mmol) of **23** in 2 mL of DMF was added dropwise. The reaction was heated for 12 h at 55 °C and 24 h at 80 °C. GC indicated only a small amount of starting material (ca. 7%) had been converted to product.

Ethyl Methyl (2-(2-Chlorophenyl)-2-oxoethyl)methylpropanedioate (25). The synthesis of 2-bromo-1-(2-chlorophenyl)ethanone (**24**) was carried out using the method of Cowper and Davidson.[66] To a stirred solution of 6.00 g (39.0 mmol) of 2'-chloroacetophenone in 10 mL of anhydrous ether at 0 °C was added 0.050 g (0.35 mmol) of aluminum chloride. To the resulting solution was added 6.20 g (2.00 mL, 39.0 mmol) of bromine dropwise with stirring. After addition of bromine the solvent was removed by rotary evaporation and the resulting yellow oil was washed with water, saturated NaCl, dried ($MgSO_4$), filtered and concentrated to give 8.20 g (35.0 mmol, 90%) of **24** as a yellow oil. IR (thin film) 3029, 1695, 1595, 760, 720 cm^{-1}; ^1H NMR δ 4.53 (s, 2H), 7.36-7.59 (m, 4H); ^{13}C NMR δ 34.4, 127.2, 129.5, 130.3, 130.6, 131.2, 132.8, 194.2.

To a stirred suspension of 0.20 g (8.40 mmol) of oil-free NaH in 10 mL of DMF was slowly added a solution of 1.30 g (8.20 mmol) of ethyl methyl methylmalonate in 10 mL of DMF dropwise. The resulting mixture was stirred for 30 min after which a solution of 2.00 g (8.6 mmol) of **24** in 10 mL of DMF was added dropwise. The resulting solution was stirred for 9.5 h, then poured into a separatory funnel containing 30 mL of water. The aqueous layer was washed with ether (3x) and the combined ether layers were dried ($MgSO_4$), filtered, and concentrated to provide a yellow oil. Column chromatography on silica gel (hexanes-ether, 95/5 to 85/15) gave 1.37 g (4.4 mmol, 54%) of **25** as yellow oil. IR (thin film) 3068, 1736, 1583, 1478, 1241, 1110, 761 cm^{-1}; ^1H NMR δ 1.23 (t, J = 7.3 Hz, 3 H), 1.64 (s, 3 H), 3.63 (s, 2 H), 3.76 (s, 3 H), 4.22 (q, J = 7.3 Hz, 2 H), 7.27-7.52 (m, 4 H); ^{13}C NMR δ 13.8, 20.5, 48.4, 51.8, 52.8, 61.7, 127.0, 129.1, 130.7, 132.0, 133.0, 138.9, 171.4, 172.1, 199.8.

Ethyl Methyl (2-(2-Chloro-5-nitrophenyl)-2-oxoethyl)methylpropanedioate (26). To a stirred solution of 3.50 g (11.2 mmol) of **25** in 20 mL of H_2SO_4 at -5 °C was added a solution of 0.65 mL of fuming HNO_3 in 1.3 mL of H_2SO_4 over a period of 5 min. The resulting solution was stirred for 3 h, then poured into 40 mL of ice water. The aqueous layer was washed with ether (3x) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a red-orange oil. Column chromatography on silica gel (hexanes-ether, 93/7) yielded 2.66 g (7.50 mmol, 67%) of **26** as a yellow oil. Subsequent recrystallization from absolute ethanol provided 2.66 g (7.50 mmol, 100%) of **26** as a yellow powder, mp 66-68 °C. IR (thin film) 3105, 1736, 1605, 1532, 1320, 1249, 1023, 746 cm^{-1}; ^1H NMR δ 1.28 (t, J = 7.1 Hz, 3 H), 1.66 (s, 3 H), 3.60 (s, 2 H), 3.79 (s, 3 H), 4.24 (q, J = 7.1 Hz, 2 H), 7.62 (d, J = 8.8 Hz, 1 H), 8.26 (dd, J = 8.8, 2.7 Hz, 1 H), 8.39 (d, J = 8.7 Hz, 1 H); ^{13}C NMR δ 13.8, 20.7, 48.3, 52.1, 52.9, 62.0, 124.4, 126.3, 131.9, 137.6, 139.9, 155.9, 171.1, 171.8, 197.6.

3-Ethoxycarbonyl-3-methyl-6-nitro-1-indanone (3). In a 25-mL round-bottomed flask was placed 0.75 g (2.1 mmol) of **26**, 0.45 g (10.5 mmol) of LiCl, and 10 mL of DMEU. The resulting mixture was stirred at rt until dissolution of the LiCl was complete and the reaction was heated at 120 °C for 5 h. The mixture was poured into a separatory funnel containing water and extracted with ether (3x). The combined ether layers were washed with water (2x), saturated NaCl (1x), dried ($MgSO_4$), filtered, and concentrated to give a brown oil. Column chromatography on silica gel (hexanes-ether, 95/5) gave 150 mg of **3** which required further purification by preparative TLC (hexanes-ether, 90/10) to provide 70 mg (0.27 mmol, 13%) of **3** as a brown oil. IR (thin film) 3110, 1730, 1609, 1538, 1353, 1196, 1097, 748 cm^{-1}; ^1H NMR δ 1.24 (t, J = 7.1 Hz, 3 H), 1.75 (s, 3 H), 2.68 (d, J = 19.2 Hz, 1 H), 3.52 (d, J = 19.2 Hz, 1 H), 4.19 (q, J = 7.1 Hz, 2 H), 7.87 (d, J = 8.5 Hz, 1 H), 8.50 (dd, J = 8.4, 2.2 Hz, 1 H), 8.56 (d, J = 1.8 Hz, 1 H); ^{13}C NMR δ 13.9, 25.8, 48.8, 49.1, 62.2, 119.1, 126.6, 129.3, 136.9, 148.7, 162.0, 173.0, 201.7.

Ethyl *cis*-3-Chloroacrylate (28). To a stirred solution of 0.42 g (2.2 mmol) of copper(I) iodide in 7.2 mL of conc. HCl was added 3.00 g (2.60 mL, 43.0 mmol) of propiolic acid over a period of 7-8 min while maintaining a temperature <10 °C. The resulting mixture was stirred for 10 h at 0 °C, then stored overnight in a freezer. The reaction mixture was washed with $CHCl_3$ (6 x 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a peach colored product. Recrystallization from hexanes provided 3.00 g (28.0 mmol, 65%) of *cis*-3-chloroacrylic acid as pale, yellow needles, mp 61-62 °C. IR (thin film) 3450-2450, 1716, 1616 cm^{-1}; ^1H NMR δ 6.25 (d, J = 8.4 Hz, 1 H), 6.86 (d, J = 8.4 Hz, 1 H); ^{13}C NMR δ 120.8, 135.5, 168.5.

In a 100-mL round-bottomed flask was placed 1.53 g (14.4 mmol) of *cis*-3-chloroacrylic acid, 50 mL of ethanol, and 2.5 mL of conc. H_2SO_4. The resulting solution was refluxed for 3 h, then poured into a separatory funnel containing water. The aqueous layer was washed with ether (3x) and the combined ether layers were washed with saturated $NaHCO_3$ (until the aqueous layer was basic), dried ($MgSO_4$), and concentrated to give 1.48 g (11.0 mmol, 76%) of **28** as a pale, yellow oil. IR (thin film) 3075, 1730, 1616 cm^{-1}; ^1H NMR δ 1.31 (t, J = 7.1 Hz, 3 H), 4.24 (q, J = 7.1 Hz, 2 H), 6.19 (d, J = 8.2 Hz, 1 H), 6.70 (d, J = 8.2 Hz, 1 H); ^{13}C NMR δ 14.0, 60.6, 121.6, 132.5, 158.0.

Ethyl Ethyl (*E*,*E*)-4-Ethoxycarbonyl-4-methoxycarbonyl-2,6-octadienedioate (29). To a stirred suspension of 0.05 g (1.94 mmol) of oil-free NaH in 2 mL of DMF was slowly added a solution of 0.50 g (1.90 mmol) of ethyl ethyl (*E*)-5-methoxycarbonyl-2-hexenedioate (**27**) in 2 mL of DMF. The resulting mixture was stirred for 30 min, then cooled to 0 °C and a solution of 0.27 g (2.00 mmol) in 2 mL of DMF was added dropwise. The resulting solution was warmed to rt and stirred for 12 h. The reaction was poured into 30 mL of saturated NaCl and the aqueous layer was extracted with ether (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a red-orange oil. Preparative TLC (hexanes-ether 95/5 to 90/10) afforded 0.29 g

(0.80 mmol, 42%) of **29** as a pale, yellow oil. IR (thin film) 1737, 1659, 1274, 1196, 1033 cm^{-1}; ^1H NMR δ 1.22-1.43 (m, 9 H), 3.16-3.20 (m, 2 H), 3.74 (s, 3 H), 4.12-4.26 (m, 6 H), 5.81 (dt, J = 15.5, 1.5 Hz, 1 H), 6.05 (d, J = 12.2 Hz, 1 H), 6.78 (dt, J = 15.5, 7.8 Hz, 1 H), 6.82 (d, J = 12.2 Hz, 1 H); ^{13}C NMR δ 13.6, 13.8, 13.9, 37.9, 52.8, 58.7, 60.1, 60.4, 62.0, 122.2, 124.9, 142.4, 143.0, 165.2, 165.7, 168.5, 169.1.

Attempted Synthesis of 1,3-Bis(ethoxycarbonyl)-1-cyclopentene-4-acetate (4). In a 25-mL round-bottomed flask was placed 140 mg (0.40 mmol) of **27**, 80 mg (1.90 mmol) of LiCl, and 5 mL of DMEU. The resulting mixture was stirred at rt until dissolution of LiCl was complete and the reaction was heated at 120 °C for 2.25 h. The mixture was cooled, poured into water and extracted with ether (3x). The combined organic layers were washed with water (3x), saturated NaCl (1x), dried ($MgSO_4$), filtered, and concentrated to provide a crude yellow oil. Preparative TLC (hexanes-ether, 90/10) gave two bands, neither of which could be identified as the desired product **4**.

Attempted Synthesis of 1-Ethoxycarbonyl-1-cyclopentene-4-acetate (5). To a stirred suspension of 0.37 g (15.3 mmol) of oil-free NaH in 10 mL of DMF was added a solution of 3.87 g (15.0 mmol) of ethyl ethyl (*E*)-methoxycarbonyl-2-hexenedioate[67] in 4 mL of DMF. The mixture was stirred for 10-15 min, then cooled to 0 °C, and 2.97 g (1.40 mL, 15.8 mmol) of 1,2-dibromoethane was added dropwise. The reaction was stirred at 0 °C for 3 h and at 25 °C for 1 h. The reaction was quenched with 25 mL of saturated NH_4Cl and the mixture was extracted with ether (3x). The combined organic layers were washed with saturated NaCl (1x), then dried ($MgSO_4$), and concentrated under vacuum. Chromatography on silica gel (increasing concentrations of ether in hexanes) gave 3.62 g (9.92 mmol, 66%) of ethyl ethyl (*E*)-5-(2-bromoethyl)-5-methoxycarbonyl-2-hexenedioate as a light yellow oil. IR (thin film) 1729, 1656, 1368, 984 cm^{-1}; ^1H NMR δ 1.27 (t, J = 7.1 Hz, 3 H), 1.29 (t, J = 7.1 Hz, 3H), 2.46 (m, 2 H), 2.80 (dq, J = 7.6, 0.8 Hz, 2 H), 3.36 (m, 2 H), 3.77 (s, 3 H), 4.20 (dq, J = 7.1 Hz, 2 H), 4.23 (q, J = 7.1 Hz, 2 H), 5.90 (dt, J = 15.5, 1.4 Hz, 1 H), 6.76 (dt, J = 15.5, 7.6

Hz, 1 H); ^{13}C NMR δ 13.8, 14.0, 26.5, 36.1, 36.4, 52.7, 57.2, 60.4, 61.9, 125.6, 141.6, 165.7, 169.6, 170.3.

A solution of 3.57 g (9.78 mmol) of ethyl ethyl (*E*)-5-(2-bromoethyl)-5-methoxycarbonylhexenedioate and 1.86 g (12.23 mmol) of DBU was heated at 75-80 °C until GC indicated complete consumption of the bromo diester. The reaction was cooled to rt, 50 mL of NH_4Cl was added, and the mixture was agitated until the viscous residue dissolved. The solution was extracted with ether (2x) and the combined organic layers were washed with 0.5 M HCl, saturated $NaHCO_3$, and saturated NaCl, then dried ($MgSO_4$), and concentrated under vacuum. Preparative TLC (increasing concentration of ether in hexanes) provided 1.14 g (4.01 mmol, 41%) of ethyl ethyl (*E*)-5-ethenyl-5-methoxycarbonyl-2-hexenedioate (**30**) as a colorless oil. IR (thin film) 1736, 1657, 1368, 986 cm^{-1}; ^{1}H NMR δ 1.25 (t, *J* = 7.1 Hz, 3 H), 1.27 (t, *J* = 7.1 Hz, 3 H), 2.94 (dd, *J* = 7.6 1.4 Hz, 2 H), 3.76 (s, 3 H), 4.17 (q, *J* = 7.1 Hz, 2 H), 4.22 (q, *J* = 7.1 Hz, 2 H), 5.23 (d, *J* = 17.7 Hz, 1 H), 5.37 (d, *J* = 10.9 Hz, 1 H), 5.87 (dt, *J* = 15.7, 1.4 Hz, 1 H), 6.29 (dd, *J* = 17.7, 10,9 Hz, 1 H), 6.80 (dt, *J* = 15.7, 7.5 Hz, 1 H); ^{13}C NMR δ 13.8, 14.0, 37.3, 52.7, 59.5, 60.2, 61.8, 117.7, 125.0, 133.9, 142.4, 165.9, 169.4, 170.1.

In a 25-mL round-bottomed flask was placed 110 mg (0.39 mmol) of **30**, 70 mg (1.70 mmol) of LiCl, and 4 mL of DMEU. The resulting mixture was stirred at rt until dissolution of the LiCl was complete and the reaction was heated at 120 °C for 6.5 h. The reaction was poured into water and extracted with ether (3x). The organic layer was washed with water (3x) and the combined aqueous layers were washed with ether (2x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a yellow oil. Preparative TLC (hexanes-ether, 98/2 to 90/10) did not provide the desired **5** but rather an inseparable mixture of *E* and *Z* ethyl ethyl 5-ethylidene-2-hexenedioate (**31**). ^{1}H NMR δ 1.28-1.37 (m, 12 H), 1.81 (d, *J* = 7.1 Hz, 3 H), 1.92 (d, *J* = 7.4 Hz, 2 H), 3.22 (t, *J* = 7.3 Hz, 2 H), 4.11-4.25 (m, 8 H), 5.79 (dt, *J* = 15.7, 1.5 Hz, 1 H), 6.26 (d, *J* = 16.0 Hz, 1 H), 6.86 (q, *J* = 7.3 Hz, 1 H); ^{13}C NMR δ 14.1, 14.2, 14.6, 23.3, 24.8,

27.8, 28.9, 38.9, 60.2, 60.3, 60.5, 60.6, 121.8, 125.5, 127.3, 137.3, 138.3, 139.9, 145.6, 166.7, 167.0, 167.1, 171.7, 175.3.

Ethyl (*E*)-4-(*N*-(2-Nitrophenyl)amino)-2-butenoate (34). In a 100-mL round-bottomed flask was placed 7.00 g (50.0 mmol) of *o*-nitroaniline and 9.70 g (50.0 mmol) of ethyl 4-bromocrotonate. The resulting mixture was heated at 95 °C for 17.5 h, then transferred to a separatory funnel with the aid of ether. The ether layer was washed with saturated $NaHCO_3$ (4x), dried ($MgSO_4$), filtered, and concentrated to give a brown oil. Column chromatography on silica gel (hexanes-ether, 95/5 to 90/10) provided 4.80 g (19.2 mmol, 38%) of **34** as an orange solid. mp 50-51 °C; IR (thin film) 3395, 3096, 1716, 1666, 1623, 1517, 1313, 1275, 1246, 1040, 741 cm^{-1}; ^1H NMR δ 1.29 (t, J = 7.0 Hz, 3 H), 4.18 (m, 2 H), 4.20 (q, J = 7.2 Hz, 2 H), 6.01 (dt, J = 15.6, 2.1 Hz, 1 H), 6.72 (m, 2 H), 7.03 (dt, J = 15.8, 4.5 Hz, 1 H), 7.45 (m, 1 H), 8.21 (dd, J = 8.5, 1.6 Hz, 1 H), 8.26 (bs, 1 H); ^{13}C NMR δ 14.1, 43.6, 60.6, 113.8, 116.2, 122.6, 127.0, 133.0, 136.4, 143.1, 144.8, 166.0.

2,3-Dihydro-1*H*,4*H*-quinoxaline-2-acetate (6). To a stirred solution of 0.13 g (0.52 mmol) of **34** in 10 mL of 95% ethanol was slowly added a suspension of 0.56 g (3.22 mmol) of sodium hydrosulfite and 0.84 g (10.0 mmol) of $NaHCO_3$ in 4 mL of water. The resulting mixture was heated at 58 °C for 35 min, then cooled, filtered, and diluted with water. The aqueous layer was saturated with NaCl, extracted with ether (3x), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated to afford 50 mg (0.23 mmol, 44%) of **6** as a yellow oil which did not require further purification. IR (thin film) 3385, 3054, 1728, 1603, 1520, 747 cm^{-1}; ^1H NMR δ 1.27 (t, J = 7.1 Hz, 3 H), 2.54 (m, 2 H), 3.13 (dd, J = 10.9, 6.3 Hz, 1 H), 3.39 (dd, J = 10.9, 3.0 Hz, 1 H), 3.81-3.87 (m, 1 H), 3.90 (bs, 2H), 4.17 (q, J = 7.1 Hz, 2 H), 6.48-6.63 (m, 4 H); ^{13}C NMR δ 14.1, 38.7, 45.7, 46.6, 60.7, 114.6, 114.9, 118.8, 119.1, 132.8, 133.0, 172.3.

3-(2-Nitrophenoxy)-1-propene (37). In a 500-mL round-bottomed flask was placed 14.0 g (101 mmol) of 2-nitrophenol, 13.4 g (9.60 mL, 111 mmol) of allyl

bromide, 14.0 g (101 mmol) of K_2CO_3, and 125 mL of acetone. The resulting mixture was refluxed for 6 h, the solvent was evaporated and water was added to the solid. The aqueous layer was washed with ether (3x) and the combined organic layers were washed with saturated $NaHCO_3$ (2x), dried ($MgSO_4$), filtered, and concentrated to give a yellow oil. Vacuum distillation provided 12.7 g (70.9 mmol, 70%) of **37** as a yellow oil. bp 93-94 °C (0.30 mm Hg); IR (thin film) 3096, 1616, 1538, 1360, 1275, 862, 748 cm^{-1}; ^1H NMR δ 4.69 (dt, J = 4.9, 1.6 Hz, 2H), 5.33 (dq, J = 10.6, 1.2 Hz, 1 H), 5.49 (dq, J = 17.3, 1.5 Hz, 1 H), 6.04 (ddt, J = 17.2, 10.5, 4.9 Hz, 1 H), 7.00-7.1 (m, 2 H), 7.49-7.54 (m, 1 H), 7.83 (dd, J = 8.1, 1.6 Hz, 1 H); ^{13}C NMR δ 69.8, 114.8, 118.3, 120.5, 125.6, 131.7, 134.1, 151.9.

Ethyl (*E*)-4-(2-Nitrophenoxy)-2-butenoate (39). A solution of 2.51 g (14.0 mmol) of **37** in 75 mL of CH_2Cl_2 was cooled to -78 °C and treated with O_3 until the solution turned a light blue color. The reaction was quenched at -78 °C with 2.18 g (2.58 mL, 35 mmol) of Me_2S, warmed to 20 °C, stirred for 3 h, and concentrated under vacuum. To the resulting oil was added 65 mL of benzene and 7.32 g (21.0 mmol) of ethyl (triphenylphosphoranylidene)acetate.[68] The solution was refluxed for 12 h, then cooled and concentrated under vacuum to afford a semisolid mass. The residue was layered on top of a 8 cm x 6 cm plug of silica gel in a sintered glass frit, and 2 L of 15% ether in hexanes was poured through under aspirator vacuum. Concentration of the filtrate gave the crude product as a yellow oil. Column chromatography on silica gel (increasing concentrations of ether in hexanes) provided 2.00 g (8.00 mmol, 57%) of **39** as a light yellow solid, mp 32-34 °C. IR (thin film) 3082, 3053, 1716, 1659, 1616, 1587, 1530, 1388, 1352, 748 cm^{-1}; ^1H NMR δ 1.33 (t, J = 7.1 Hz, 3 H), 4.22 (q, J = 7.1 Hz, 2 H), 5.31 (dd, J = 4.7, 2.5 Hz, 2 H), 5.96 (dt, J = 11.5, 2.5 Hz, 1 H), 6.54 (dt, J = 11.5, 4.5 Hz, 1 H), 7.03-7.13 (m, 2 H), 7.50-7.56 (m, 1 H), 7.85 (dd, J = 8.1, 1.6 Hz, 1 H); ^{13}C NMR δ 14.1, 60.6, 67.7, 114.7, 120.7, 120.8, 125.8, 134.2, 140.1, 145.1, 151.7, 166.1.

3,4-Dihydro-4*H*-1,4-benzoxazine-3-acetate (7). To a stirred solution of 250 mg (1.0 mmol) of **39** in 20 mL of ethanol was slowly added a mixture of 1.11 g (6.40 mmol) of sodium hydrosulfite and 1.68 g (20.0 mmol) of $NaHCO_3$ in 8 mL of water. The resulting mixture was stirred at rt until complete (TLC), the reaction was filtered and the ethanol was removed by rotary evaporation. The crude solid was transferred to a separatory funnel with the aid of water and ether and the aqueous layer was saturated with NaCl. The layers were separated and the aqueous layer was extracted with ether (2x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to provide a yellow oil. Preparative TLC (hexanes-ether, 95/5 to 85/15) afforded 20 mg (0.10 mmol, 10%) of **7** as a yellow oil. IR (thin film) 3381, 3061, 3039, 1729, 1605, 1503, 746 cm^{-1}; ^1H NMR δ 1.28 (t, J = 7.1 Hz, 3 H), 2.54 (m, 2 H), 3.84 (m, 1 H), 3.95 (dd, J = 10.6, 6.0 Hz, 1 H), 4.18 (q, J = 7.1 Hz, 2 H), 4.20 (dd, J = 10.6, 2.6 Hz, 1 H), 4.44 (bs, 1H), 6.58-6.80 (m, 4 H); ^{13}C NMR δ 14.0, 36.6, 46.1, 60.8, 68.4, 115.7, 116.6, 118.8, 121.7, 132.8, 143.6, 171.8.

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