I. SYNTHESIS OF VARIOUS HETEROCYCLES USING DISSOLVING METAL REDUCTION PROCESS. II. SYNTHESIS OF HETERO-AROTINOID SCAFFOLDS FOR ANTICANCER AGENTS

By

BASKAR NAMMALWAR

Master of Science
Anna University
Chennai, India
2003

Master of Philosophy
Bharthidasan University
Tiruchy, India
2005

Submitted to the Faculty of the
Graduate College of the
Oklahoma State University
in partial fulfillment of
the requirements for
the Degree of
DOCTOR OF PHILOSOPHY
May, 2010

I. SYNTHESIS OF VARIOUS HETEROCYCLES USING DISSOLVING METAL REDUCTION PROCESS. II. SYNTHESIS OF HETERO-AROTINOID SCAFFOLDS FOR ANTICANCER AGENTS

Dissertation Approved:

Dr. Richard A. Bunce

Dissertation Adviser

Dr. Kenneth Darrell Berlin

Dr. Ziad El Rassi

Dr. Legrande M Slaughter

Dr. Ramanjulu Sunkar

Dr. A. Gordon Emslie

Dean of the Graduate College

ACKNOWLEDGMENTS

I owe my deepest gratitude to Dr. R. A. Bunce, for being a wonderful advisor throughout my studies at Oklahoma State University. I thank you Dr. Bunce for your advice, invaluable guidance, wise counsel, encouragement and friendly support through my time in graduate school. I also thank you for your patience with me as I have learned over these past few years. One simply could not wish for a better or friendlier supervisor than you.

I would like to thank Drs. K. D. Berlin, L. M. Slaughter, Z. EL. Rassi, and Ramanjulu Sunkar for agreeing to be on my graduate committee. I especially thank you Dr. Berlin for your valuable guidance throughout my research and helping me to write and complete my dissertation on time. I would also thank Dr. O. C. Dermer for awarding me with a scholarship for the year 2009-2010.

I also thank James Schammerhorn, a fellow graduate student in Dr. Bunce's research group, for his assistance and valuable suggestions on some of my experiments. Thanks to Takahiro Nago, Brian White and Eric Lee for making the laboratory a more pleasant place to work.

I would like to thank the Department of Chemistry for providing a teaching assistantship to me during my studies at OSU. I would like Dr. K. D. Berlin and Dr. Richard A. Bunce for giving me research assistantship. Many thanks to all my friends and my departmental colleagues who helped me all along to complete my PhD in time. I also thank all the secretaries and staff of the Chemistry Department for their help and support. I would like to thank my family members especially my wife Subhashini

Selvaraju and our lovely son Haresh Baskar. Thank you so much Subhashini for your valuable suggestions and ideas throughout my research which helped me to complete my projects on time. Without your love and support for all these years I would not have finished my PhD.

Finally, I would like to thank my mom and dad, Jeevarathnam Megavarnam and Nammalwar Kuppusamy for there inseparable support, love and prayer. I would also thank my brother Murali Krishnan for his endless encouragement, support and patience with me for all these years. I also appreciate my in-laws Mr. and Mrs. Selvaraju for there timely help and support during my son's birth. .

TABLE OF CONTENTS

Chapter Page

LIST OF FIGURES

Figure Page

Figure Page

CHAPTER I

REDUCTION OF AROMATIC AND ALIPHATIC NITRO COMPOUNDS USING DISSOLVED METAL REDUCTION PROCESSES

Introduction

Tandem reactions are often referred as 'multistep one-pot syntheses'.[1] The term tandem reaction involves breaking and forming of several bonds in a single step sequence to generate complex molecules with a high degree of stereoselectivity.[2] The terms 'tandem', 'cascade', 'one-pot', 'zipper', 'iterative', one-flask', 'sequential' and 'domino' are used as synonyms for this class of reactions.

The advantages of tandem reactions include: (1) all the transformation occur in the same flask in a single laboratory operations; (2) economically less waste and fewer byproducts are generated by the use of a tandem reaction sequence; and (3) the process of purification becomes much simpler by avoiding the isolation of intermediates.

The use of tandem reactions initiated by the reduction of nitroaromatics has provided an efficient route to a variety of heterocyclic systems. The synthesis involves the reduction of the nitro group which reacts *in situ* with other reactive functional groups present in the substrate to give the heterocyclic ring system.

The tandem reduction of a nitroaromatic substrate can be done by two methods, catalytic hydrogenation or dissolving metal reduction. In the case of dissolving metal reductions,the nitro group undergoes reduction in the presence of metals such a Fe or Zn

under different acid conditions such as with acetic acid, hydrochloric acid or sulphuric acid. The nitro groups undergo reduction, followed by reaction with other functional groups present in the molecule to provide various nitrogen heterocycles. The product of the cyclization depends on the functional group that reacts with the reduced nitro and can include aldehydes, ketones and esters as well as α,β-unsaturated carbonyl group.

In the present work, the reduction of an aromatic nitro group, followed by cyclization of the resulting aromatic nitrogen with an aldehydes, ketones, esters or α,β-unsaturated carbonyl groups (Michael acceptors) present in the molecule, resulted in cyclization to a nitrogen heterocycle.[3]

Dissolving Metal Reduction of Nitro Compounds

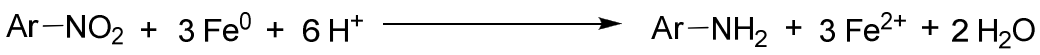
Dissolving metal reductions, discovered nearly 140 years ago, were among the first reductions performed on organic compounds. The reduction of nitro to amine was first discovered by Bechamp[4] in 1854 using iron and acetic acid. After three years, Perkin[5] applied this technique in the commercial production of aniline and also found that hydrochloric acid can be used instead of acetic acid in this reduction process.

These metal reduction processes are most widely used in the reduction of polar compounds and in selective reduction of specific types of bonds. The reduction of nitro compounds by iron under acidic conditions is one such reaction that is still important today. In addition to being an inexpensive reagent, iron is very mild and selective for the nitro group. Other functional groups in the compound are seldom affected when reduction is carried out using iron.

Mechanism of Reduction

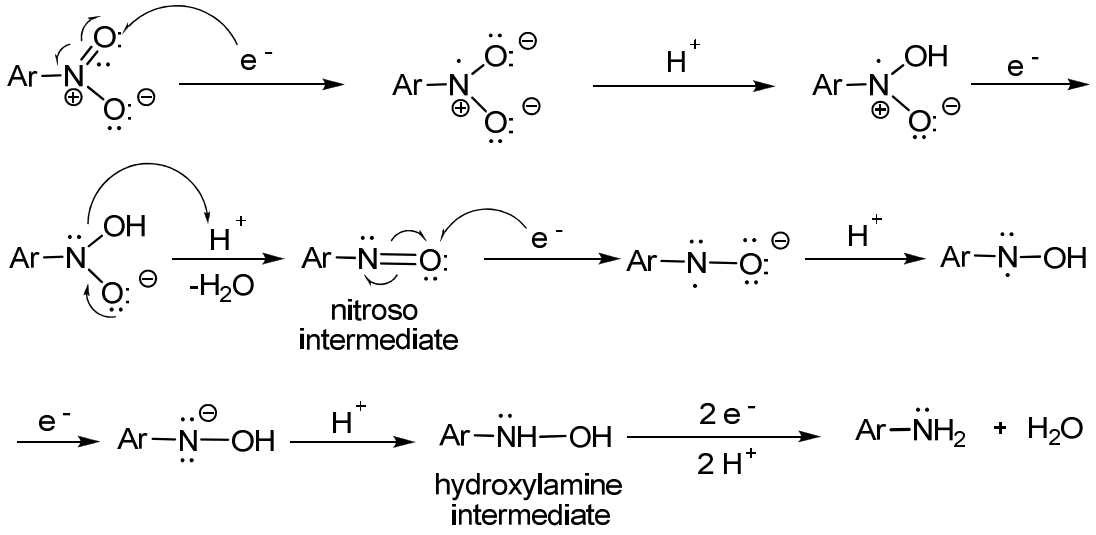
Reduction is defined as the acceptance of electrons. In dissolving metal reductions, electrons are transferred from the surface of the metal to the organic molecule being reduced. The radical ion that is produced is then rapidly protonated under the (normally) acidic conditions. The process is repeated one more time until the reduction is complete. The hydrogen gas emitted during the course of reaction of the metal with the acid does not contribute to the reduction process but sometimes leads to side reactions. The coupling of radicals will result if acidic conditions or a protic solvent is not used in the reaction.

Balanced Equation



A balanced equation and the mechanism for the reduction of nitro benzene by iron in acid are shown above. The mechanism starts with the transfer of an electron to the double bonded nitrogen of the nitro group from iron. This results in the formation of a radical anion, which is protonated by the acidic medium. Once the protonation occurs, a second electron is transferred from the iron to the nitrogen. Further addition of another proton, followed by elimination of water, gives the nitroso intermediate. The same sequence is repeated again to get the hydroxylamine. Finally, two more electrons are added to break the N-O bond to give anions of the two products, which are protonated in the acidic medium to give aniline and water. This whole process consumes 3 atoms of iron (2 e^- from each, 6 e^- total) and 6 protons for each nitro group. Generally, a large excess of iron and acid is used in this process.

Mechanism



Early Examples of Ring Closures using Dissolved Metal Reduction Process

Bunce and coworkers[6] prepared 1,2,3,4-tetrahydroquinolines by using a tandem reduction-Michael addition process. In this process, the ethyl(*E*)-3-methyl-4-((2-nitrophenyl)amino)-2-butenoate (**1)** was reacted with iron and acetic acid over a period of 30 minutes to give ethyl (±)-2-methyl-1,2,3,4-tetrahydroquinoxaline-2-acetate (**2)**. The mechanism involves the reduction of nitro group to an amine, which then undergoes Michael addition to the pendent acrylate in a favorable pathway to give the tetrahydroquinoline.

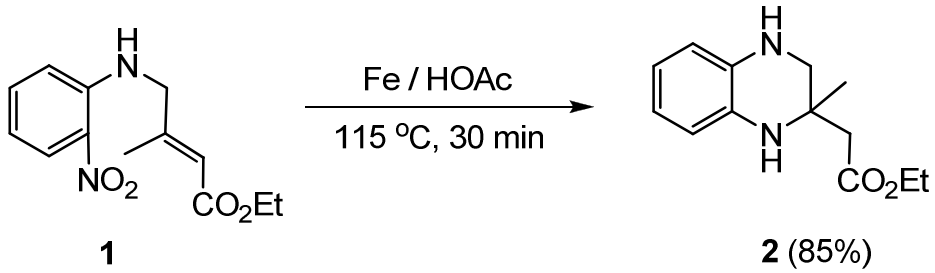
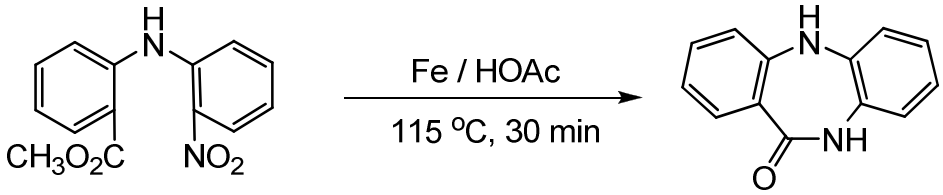


Figure 1.1. Dissolved metal reduction followed by Michael cyclization

The second example involved the formation of dibenzo-fused nitrogen heterocycles by a tandem reduction-lactamization process.[7] These dibenzodiazepinone compounds are found to have potent antiarrhythmic defibrillatory activity.[8] In this process methyl-2-[(2-nitrophenyl)amino]benzoate **(3)** reacted to give 5,10-dihydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one **(4)** using Fe and acetic acid. The same reaction using catalytic condition such as 5% Pd/C in ethanol gave a reduced amine but could not generate the cyclized product.



3 **4** (92%)

Figure 1.2. Tandem reduction-lactamization reduction using iron and acetic acid

The tandem reaction process was extended to include a reduction-addition-elimination sequence for the preparation of 2-alkyl-1*H*-indole-3-carboxylate esters (**6**).[9] These indole-3-carboxylic acid derivatives are known to have significant biological activity[10] and are valuable building blocks in the synthesis of various drugs.[11]

In one example, ethyl (2*Z*)-3-hydroxy-2-(2-nitrophenyl)-2-butenoate (**5)** underwent ring closure by direct treatment with 6 equivalents of iron powder in glacial acetic acid at 115 ºC to give **6** in 82% yield. This treatment resulted in the reduction of the nitroarene to the aniline followed by Michael addition to the unsaturated ester to yield the final compound via elimination of water. Another mechanistic possibility could involve the addition of the aniline nitrogen to the carbonyl (keto form) under acidic

conditions, followed by a loss of water molecule. The final cyclization in this reaction is very mild and permits substitution that would not be tolerated by more vigorous reduction conditions.

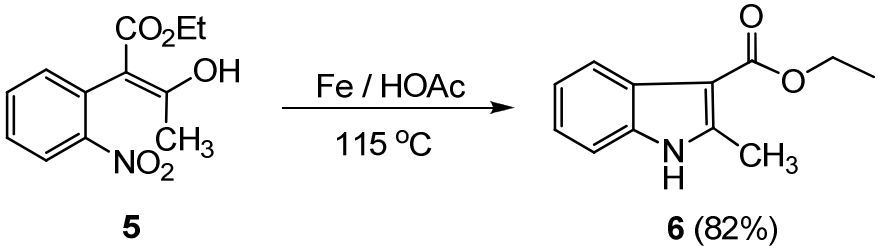
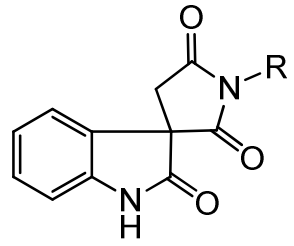


Figure 1.3. Dissolved metal lactamization process to form indole rings

A recent use of tandem reduction-cyclization sequence is used in the preparation of spirooxindoles,[12] such as **7** using iron and acetic acid. Spirooxindoles are known to be anti-inflammatory agents.[13] These compound can be prepared using spiroimides as a source of starting material. Spiroimides are one such compounds which contains the spirooxindole core ring systems and attributes to the presence of pentacyclic spiro-oxindole scaffold in their architecture.

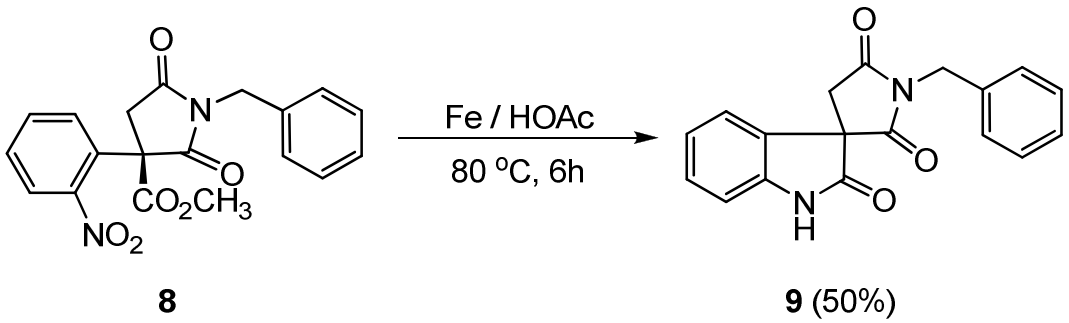


R = alkyl or aryl

7

Figure 1.4. Structure of spirooxindole ring

In an example, nitro imide **8** was converted to the spiro compound **9** using iron and acetic acid at 80 ºC over a period of 6 hours. The yield for this reaction was about 50%.

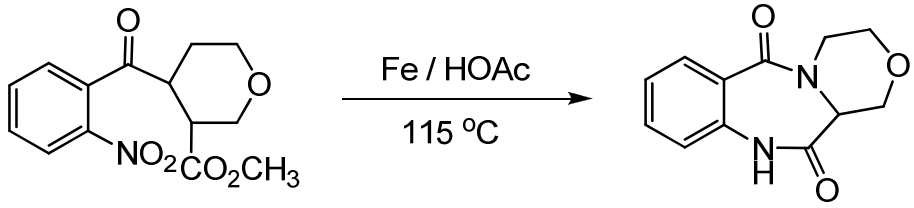


8 **9** (50%)

Figure 1.5. Formation of spiroimide

In this tandem reduction sequence, the nitro was first reduced to an amine which then reacted with the ester moiety to close the spiroimide compound.

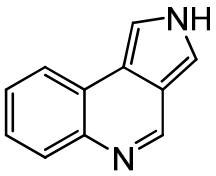
A new improved scaleable process to prepare 1,3,4,12*a*-tetrahydro-11*H*-[1,4]-oxanio[3,4-*c*][1,4]benzodiazepine-6,12-dione (**11**) using iron and acetic acid was developed by Stefanick and coworkers.[14] In this application, the target compound was obtained in a pure form in 85% yield without the need for chromatographic purification. These compounds are used as psychoactive drugs.[15]



10 **11** (85%)

Figure 1.6. Synthesis of 1,3,4,12*a*-tetrahydro-11*H*-[1,4]-oxanio[3,4-*c*][1,4]benzo diazepine-6,12-dione

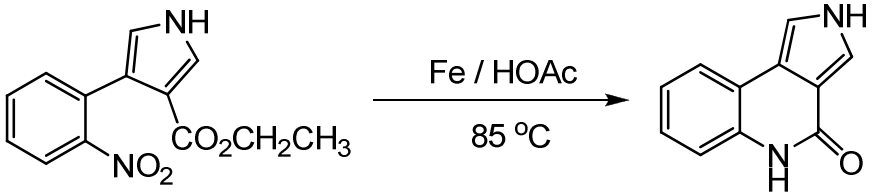
Di Santo and coworkers[16] developed a new synthetic procedure to obtain 2*H*-pyrrolo[3,4-*c*]quinolines (**12**). These ring systems are used as lead structures for developing chemotherapeutic agents and also for drugs to treat central nervous system disorders.[17]



12

Figure 1.7. Structure of 2*H*-pyrrolo[3,4-*c*]quinolines

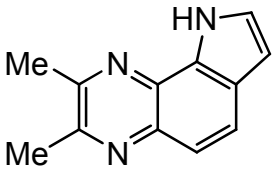
In the process of preparing target **14**, one of the steps involved the tandem reduction of a nitro group, from **13** using iron and acetic acid. The product was obtained in 75% yield and was highly pure.



13 **14** (75%)

Figure 1.8. Synthesis of 2*H*-pyrrolo[3,4-*c*]quinoline-4(5*H*)-one

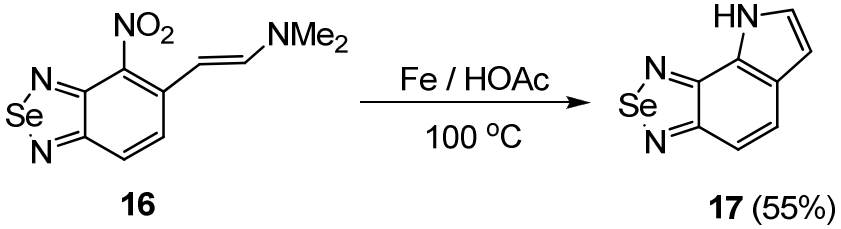
Pyrroloquinoxaline **15** represents an important class of compounds in a wide variety of biological activity including as food carcinogens.[17,18]



15

Figure 1.9. Structure of pyrroloquinoxaline

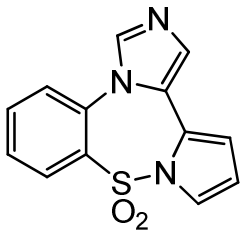
Grivas and Edin[19] discovered a new method to synthesize pyrroloquinoxalines using a selenadiazoloindole **17** as an intermediate. This intermediate was the first of its kind to be discovered. In the presence of iron and acetic acid at 100 ºC enamine **16** underwent ring closure to give selenadiazoloindole **17** in 55% yield. Initially, the nitro group was converted to amine which then underwent ring closure by displacing the dimethylamino group.



16 **17** (55%)

Figure 1.10. Synthesis of selenadiazoloindole

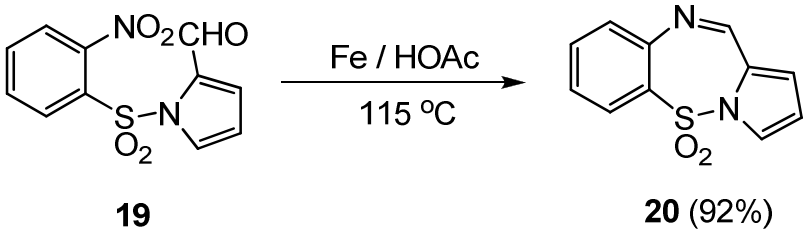
Another interesting reaction that used iron and acetic acid was the preparation of imidazo[5,1-*d*]pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine-9,9-dioxide (**18**), developed by Artico and coworkers.[20] These novel sulfur containing tetracyclic benzodiazepines have a received great attention as pscychotropic agents. [21]



18

Figure 1.11. Structure of imidazo[5,1-*d*] pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine-9,9-dioxide

In the course of preparing this drug, one of the intermediates involved a tandem intramolecular ring closure to form imine **20** from intramolecular condensation of aromatic nitro aldehyde **19**. This ring closure was achieved by the use of iron and acetic acid in the presence of THF.

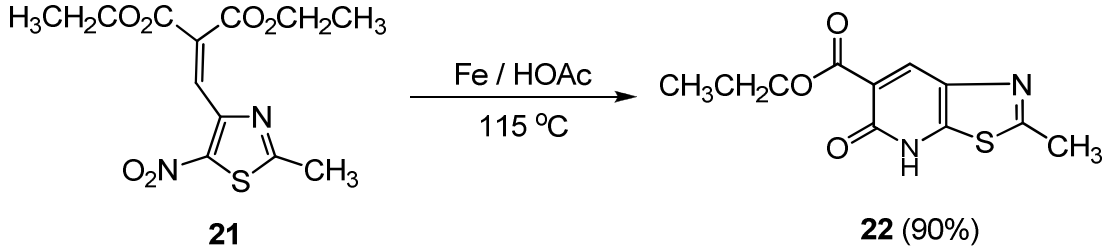


19 **20** (92%)

Figure 1.12. Tandem reduction-cyclization of a nitro with an aldehyde

Vanelle and coworkers[22] discovered bioactive family of bicyclic 2-pyridones for the treatment of central nervous system disorders. Thiazolopyridine **22** is one such bicyclic 2-pyridone which is biologically very active. In this case, nitrothiazole **21** was treated with iron and acetic acid at 115 ºC over a period of 30 minutes to give thiazolopyridone **22**. The same reaction was tried under different hydrogenation

conditions but resulted in a very poor yield. These conditions resulted in a 90% yield of the lactam is highly pure form.

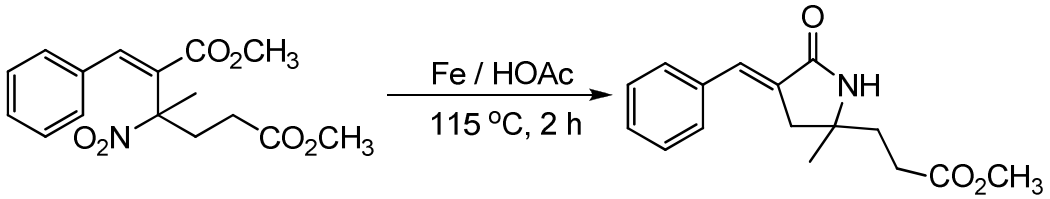


21 **22** (90%)

Figure 1.13. Synthesis of thiazolopyridone ring

Syntheses of various heterocyclic compounds were accomplished in the past by the use of iron and acetic acid on various Baylis-Hillman adducts. Baylis-Hillman is an organic reaction in which aldehydes react with variety of activated alkenes in the presence of tertiary bicyclic amines to give multifunctional products. These heterocycles are present as a framework in numerous structures which are precursors to natural products or pharmaceutical agents.

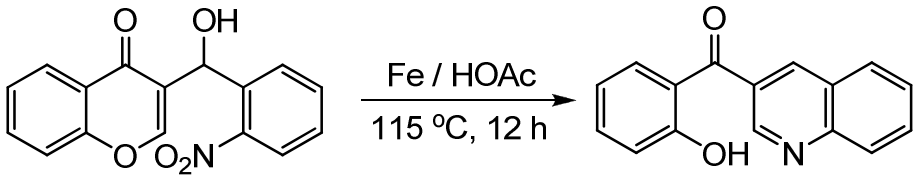
Basavaish and coworkers[23] reported the synthesis of substituted γ-lactam **24** which was obtained from the acetate derivative of a Baylis-Hillman adduct e.g. (**23**). In this reaction, the adduct acetate underwent reductive cyclization in the presence of iron and acetic acid to give the γ-lactam in a moderate yield of 54%.



23 **24** (54%)

Figure 1.14. Synthesis of γ-lactams using iron and acetic acid

Another interesting, one-pot sequence was developed by Basvaish and coworkers[24] for the synthesis of 3-benzoquinoline **26** using Baylis-Hillman alcohol **25** along with iron and acetic acid. The reaction mechanism involves the easy transformation of an acyclic nitrogen and a cyclic oxygen into another important



25 **26** (61%)

Figure 1.15. Formation of a 3-benzoylquinoline

structural framework containing cyclic nitrogen along with acyclic oxygen by a reduction-addition-elimination process.

Batra and coworkers[25] developed a convenient, practical approach to the synthesis of imidazo[2,1-*b*]quinazolin-2-ones (**28**) using a Baylis-Hillman derivative **27** along with iron powder and acetic acid. The method involves a sequential reduction of the nitro group and addition of the resulting amine to the cyano group to give the heterocyclic ring system.

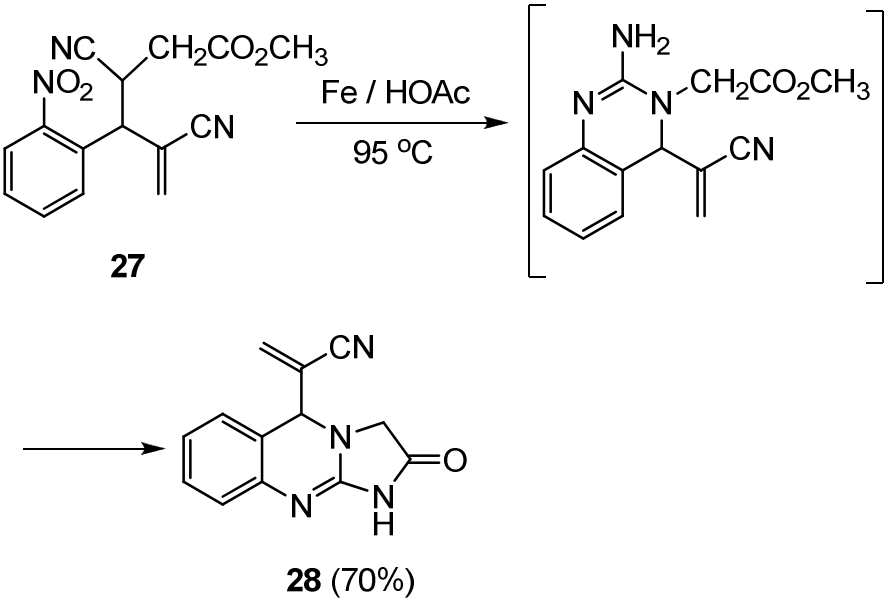


Figure 1.16. Formation of imidazo[2,1-*b*]quinazolin-2-ones

Bathadoss[26] recently reported the synthesis of (*E*)-3-arylidene-2,3 dihydrobenzo[*b*][1,4]-oxazepin-4(*5H*)-one **29** using a modified Baylis-Hillman adduct **28**. Iron and acetic acid promoted the key step by *in situ* reduction of the nitro group to an amino group, followed by cyclization to give the target molecule.

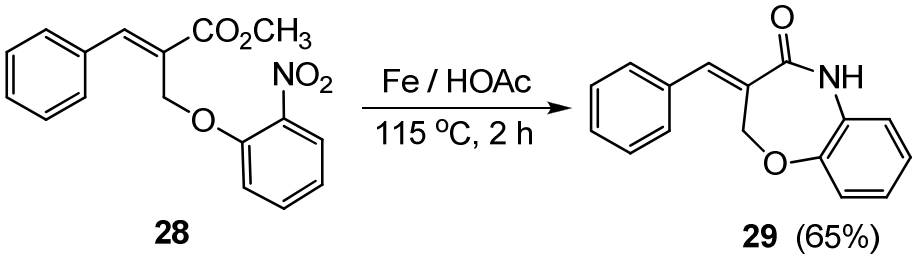
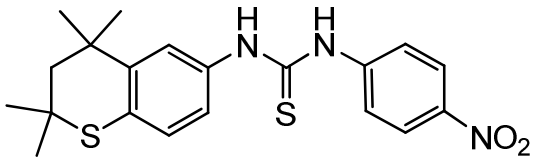


Figure 1.17. Synthesis of dihydrobenzooxazepin derivative using metal reduction

Use of Iron and Acetic Acid without Ring Closures

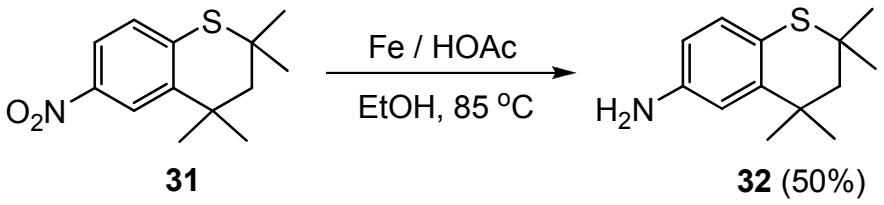
The use of iron and acetic acid in the preparation of a drug candidate has been reported by Berlin and coworkers[27] in the synthesis of heteroarotinoids. Heteroarotinoids are a class of modified synthetic retinoids. They are structural arotinoids which contain one aryl moiety in the molecular framework. These heteroarotinoids demonstrate promising inhibitory activities towards various cancer cells. *N*-(3,4-Dihydro-2,2,4,4-tetramethyl-2H-1-benzothiopyran-6-yl)-*N'*-(4-nitrophenyl)thiourea (**30**) is one such heteroarotinoid and which is scheduled for human clinical studies for the treatment of kidney cancer cells in 2010.



30

Figure 1.18. *N*-(3,4-Dihydro-2,2,4,4-tetramethyl-2H-1-benzothiopyran-6-yl)-*N'*-(4-nitrophenyl)thiourea

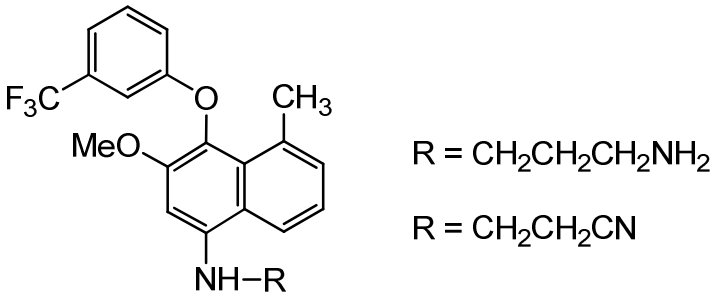
The key step in the synthesis of this drug is the conversion of 2,2,4,4-tetramethyl-6-nitrothiochroman (**31**) to 2,2,4,4-tetramethylthiochroman-6-amine (**32**). In this example, the nitro derivative **31** was heated at 85 ºC in the presence of iron and acetic acid in ethanol to give **3** in a yield of 50% with minimum side reactions. Other methods to synthesize the same target resulted in much lower yields with more side reactions.



31 **32** (50%)

Figure 1.19. Reduction of a nitrothiochroman to an aminothiochroman

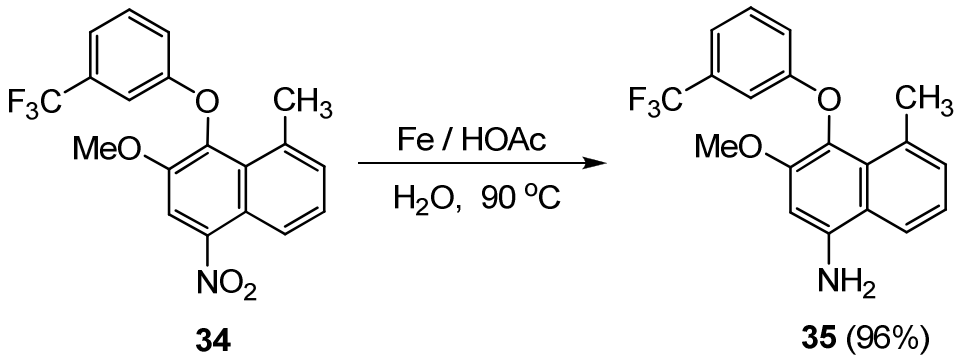
An effective way to synthesize amino-substituted naphthalene **33** for the treatment of breast cancer was developed by Shi and coworkers.[28] Quinolines are known for their diverse biological activity, especially their antimalarial and anticancer properties.[29] Based on the available literature, the novel derivative **33** was synthesized.



33

Figure 1.20. Structure of an amino substituted napthalene

In this synthesis, one of the intermediate steps was the conversion of an 1-nitro naphthalene compound **34** to amine **35**. For this conversion, iron and acetic acid was used along with water to yield 35 (96%) in a very high purity without cleaving any of the

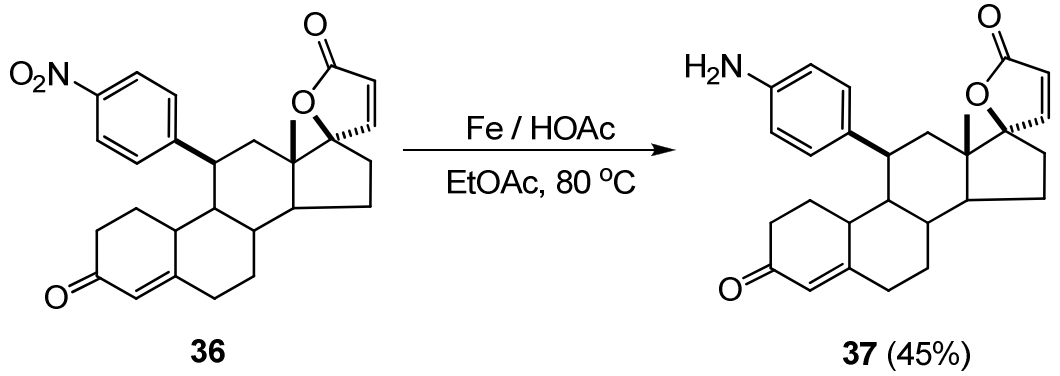


34 **35** (96%)

Figure 1.21. Conversion of an aromatic nitro compound to an amine using iron and acetic acid

ether functions or damaging the benzylic C-F bonds of the trifluoromethyl group

Geisler and coworkers[29] developed an efficient synthesis of 11β-(4-aminophenyl) spiro[estr-4-ene-17β,2'(5'H)-furan]3,5'-dione which is an 19-nor steroid exhibiting progesterone antagonistic activity. In this procedure, the precursor nitroaromatic **36** was converted to the target amine **37** in 45% yield via the use of iron and acetic acid with ethyl acetate as a co-solvent at 80 °C.



36 **37** (45%)

Figure 1.22. Use of iron and acetic acid in the synthesis of 19-nor steroid **37**

References and Notes

1. (a) Ho, T. L. Tandem Organic Reactions; Wiley: New York, 1992. (b). Posner, G. H. *Chem. Rev.* **1986**, *86*, 831-844. (c). Tietze, L.; Beifuss, U. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131.

2. (a) Ihara, M.; Fukumoto, K. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1010-1022. (b). Bunce, R. A. *Tetrahedron*, **1995**, *51*, 13103-13159. (c). Tietze, L. *Chem. Rev.* **1996**, *96*, 115.

3. [a] Bunce, R. A.; Herron, D. M.; Johnson, L. B.; Kotturi, S. V. *J. Org. Chem.* **2001**, *66*, 2822; [b] Bunce, R. A.; Herron, D. M.; Lewis, J. R.; Kotturi, S. V.; Holt, E. M. *J. Heterocyclic Chem.* **2003**, *40*, 101; [c] Bunce, R. A.; Herron, D. M.; Lewis, J. R.; Kotturi, S. V. *J. Heterocyclic Chem.* **2003**, *40*, 113; [d] Bunce, R. A.; Herron, D. M.; Hale, L. Y. *J. Heterocyclic Chem.* **2003**, *40*, 1031; [e] Bunce, R. A.; Johnson, L. B.; Holt, E. M. *J. Heterocyclic Chem.* **2004**, *41*, 563; [f] Bunce, R. A.; Smith, C. L.; Lewis, J. R. *J. Heterocyclic Chem.* **2004**, ***41***, 963.

4. Bechamp. A. *Ann.*, **1854**, *92*, 402.

5. Meldola, R.; J. *Chem. Soc.* **1908**, *93*, 2214.

6. Bunce, R. A.; Herron, D. M.; Ackerman, M. L. *J. Org. Chem.* **2000**, *65*, 2847.

7. Bunce, R. A.; Schammerhorn, J. E. *J. Heterocyclic. Chem.* **2006**, *43*, 1031.

8. Levy, O.; Erez, M.; Varon, D.; Keinan, E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2921.

9. Bunce, R. A.; Randall, M. H.; Applegate, K. G. *Org. Prep. Proceed. Intl.* **2002**, *34*, 493.

10. (a) Richardson, B. P.; Engel, G.; Donatsch, P.; Stadler, P. A. *Nature* **1985**, *316*, 126. (b) Romanelli, M. N.; Ghelardini, C.; Dei, S.; Matucci, R.; Mori, F.; Scapecchi, S.; Teodori, E.; Bartolini, A.; Galli, A. *et. al., Arzneim.-Forsch.*, **1993**, *43*, 913. (c) Wyman, P. A.; Gaster, L. M.; King, F. D.; Sutton, J. M.; Ellis, E. S.; Wardle, K. A.; Young, T. J. *Bioorg. Med. Chem.* **1996**, *4*, 255.

11. Macor, J. E.; Ryan, K.; Newman, M. E. *J. Org. Chem.* **1989**, *54*, 4785.

12. Allous, I.; Comesse, S.; Berkes, D.; Alkyat, A.; Daich, A. *Tetrahedron Lett.* **2009**, *50*, 4411.

13. (a). Piscoya, J.; Rodriguez, Z.; Bustamante, S. A.; Okuhama, N. N.; Miller, M. J. S.; Sandavol, M. *Inflamm. Res.* **2001**, *51*, 442. (b). Aguilar, J. L.; Rojas, R.; Marcelo, A.; Plaza, A.; Bauer, R.; Reninger, E.; Klaas, C. A.; Merfort, I. *J. Ethnopharmacol.* **2002**, *81*, 271-276.

14. Grimm, J.; Liu, F.; Stefanick, S.; Sorgi, K. L.; Maryanoff, C. A. *Org. Prep. Res. Dev.* **2003**, *7*, 1067.

15. Hoekstra, W. J.; Dyatkin, A. B.; Maryanoff, B. E.; Mathews, J. M. International Patent WO 2000043398, 71 pp. *Chem. Abst.* **2000**, *133*, 120350

16. Santo, R. D.; Costi, R.; Forte, M.; Galeffi, C. *ARKIVOC* **2004**, (*v*), 181.

17. Knize, M. G.; Salmon, C. P.; Pais, P.; Felton, J. S. *Adv. Exp. Med. Biol.* **1999**, *459*, 179.

18. Grivas, S.; Tian, W.; Ronne, E.; Lindstron, S.; Olsson, K. *Acta Chem. Scand.* **1993**, *47*, 521.

19. Edin, M.; Grivas, S. *ARKIVOC* **2000**, (*i*), 1.

20. Silverstri, R.; Artico, M.; Pagnozzi, E. *J. Heterocyclic. Chem.* **1994**, *31*, 1033.

21. Original monograph., *Drugs Fut.* **1983**, 759; update; *ibid.* **1984**, 695; update *ibid.* **1985**, 776.

22. Crozet, M. D.; George, P.; Crozet, M. P.; Vanelle, P. *Molecules* **2005**, *10*, 1318.

23. Basavaiah, D.; Rao, J. S. *Tetrahedron Lett.* **2004**, *45*, 1621.

24. Basavaiah, D.; Reddy, R. J.; Rao, J. S. *Tetrahedron* **2006**, *62*, 8740.

25. Nag, S.; Mishra, S.; Batra, S. *Tetrahedron* **2008**, *64*, 10162.

26. Bathadoss, M.; Murugan, G. *Synth. Commun.* **2009**, *39*, 1290.

27. Brown, C. W.; Liu, S.; Klucik, J.; Berlin, K. D.; Brennan, P. J.; Kaur, D.; Benbrook, D. M. *J. Med. Chem.* **2004**, *47*, 1008.

28. Shi, A.; Nguyen, T. A.; Battina, S. K.; Rana, S.; Takemoto, D. J.; Chiang, P. K.; Hua, D. H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3364.

29. Geisler, J.; Cleve, A.; Harre, M. *Tetrahedron* **2000**, *56*, 6489.

CHAPTER II

1,2,3,9-TETRAHYDRO-4*H*-CARBAZOL-4-ONE AND 8,9-DIPYRIDO-[1,2-*a*]INDOL-6(7*H*)-ONE FROM 1*H*-INDOLE-2-BUTANOIC ACID

Introduction

Earlier studies from this laboratory[1] and by others[2] described the synthesis of substituted indoles from 2-nitrobenzyl ketone derivatives by a tandem reduction-cycloaromatization reaction. The current project sought to assemble more complex rings using this strategy. In particular, we have developed a route to 1,2,3,9-tetrahydro-4*H*-carbazol-4-one and 8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one through a common intermediate 1*H*-indole-2-butanoic acid. We have further found that the tetrahydro-4*H*-carbazol-4-one can be prepared in one step by a tandem reduction-cycloaromatization-acylation sequence. The 1,2,3,9-tetrahydro-4*H*-carbazol-4-one is a building block for the synthesis of alkaloids[3] as well as the core ring system in current drugs used for the treatment of cancer,[4] HIV,[5] congestive heart failure[6] and emesis brought on by chemotherapy[7]; the 8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one system has been studied for the treatment of ischemic disorders[8] and vomiting resulting from cancer treatment.[9]

Several other approaches have been reported for this ring system. The Fischer indole synthesis, by far the simplest, uses phenyhydrazine but provides at most a 50% yield.[10] Other routes include C4 oxidation of tetrahydrocarbazole,[11] base promoted cyclization of 2-(2-trifluoroacetamidophenyl)-2-cyclohexene-1-one,[12] copper(I)

mediated[13] or photochemical[14] arylation of *N*-substituted enaminones and several different palladium catalyzed coupling reactions.[15] Our synthesis requires several steps, but permits reasonable structural variation and does not require excessively hazardous reagents or expensive catalysts. We have also found that other saturated ring homologues of the tetrahydro-4*H*-carbazol-4-one system are accessible using this strategy.

Results and Discussion

Our cyclization studies required the preparation of a series of 1*H*-indole-2-alkanecarboxylic acids. Our synthesis began with Meldrum's acid[16] and commercially available methyl (ω-chlorocarbonyl)alkane carboxylate derivatives **1a-c** (Figure 2.1). Acylation of Meldrum's acid in the presence of pyridine, followed by refluxing in *tert*-butyl alcohol, gave the *tert*-butyl methyl 3-oxoalkanedicarboxylic esters **2a-c** in 68-76% yields.[17] Deprotonation of **2a-c** with sodium hydride in anhydrous *N,N*-dimethyl-formamide and reaction with 2-fluoro-1-nitrobenzene at 55-60 ºC afforded the nucleophilic aromatic substitution products **3a-c** in yields ranging from 60-70%.[1,2] Subsequent exposure of **3a-c** to trifluoroacetic acid in the presence of triethylsilane[18] resulted in *tert*-butyl ester cleavage and decarboxylation to provide nitro keto ester **4a-c** in 92-94% yields.

Treatment of 4a-c with iron powder in acetic acid then intitated a tandem reduction-cycloaromatization reaction ot furnish 1*H*-indole-2-alkanecarboxylic esters **5a-c** in 90-95%.[1] Finally, basic hydrolysis of **5a-c** provided acids 6a-c in 90-96% yields. Treatment of **6a-c** with 2.0-6.0 equivalents of *p*-toluenesulfonic acid in refluxing toluene resulted in a Friedel-Crafts like ring closure of the acid to C3 of the indole moiety to

yield **7a-c** in 67-80% yields (Figure 2.2). Refluxing **6b** in toluene without the added *p*-toluenesulfonic acid resulted in closure to the lactam **8b** (90%), but no reaction occurred

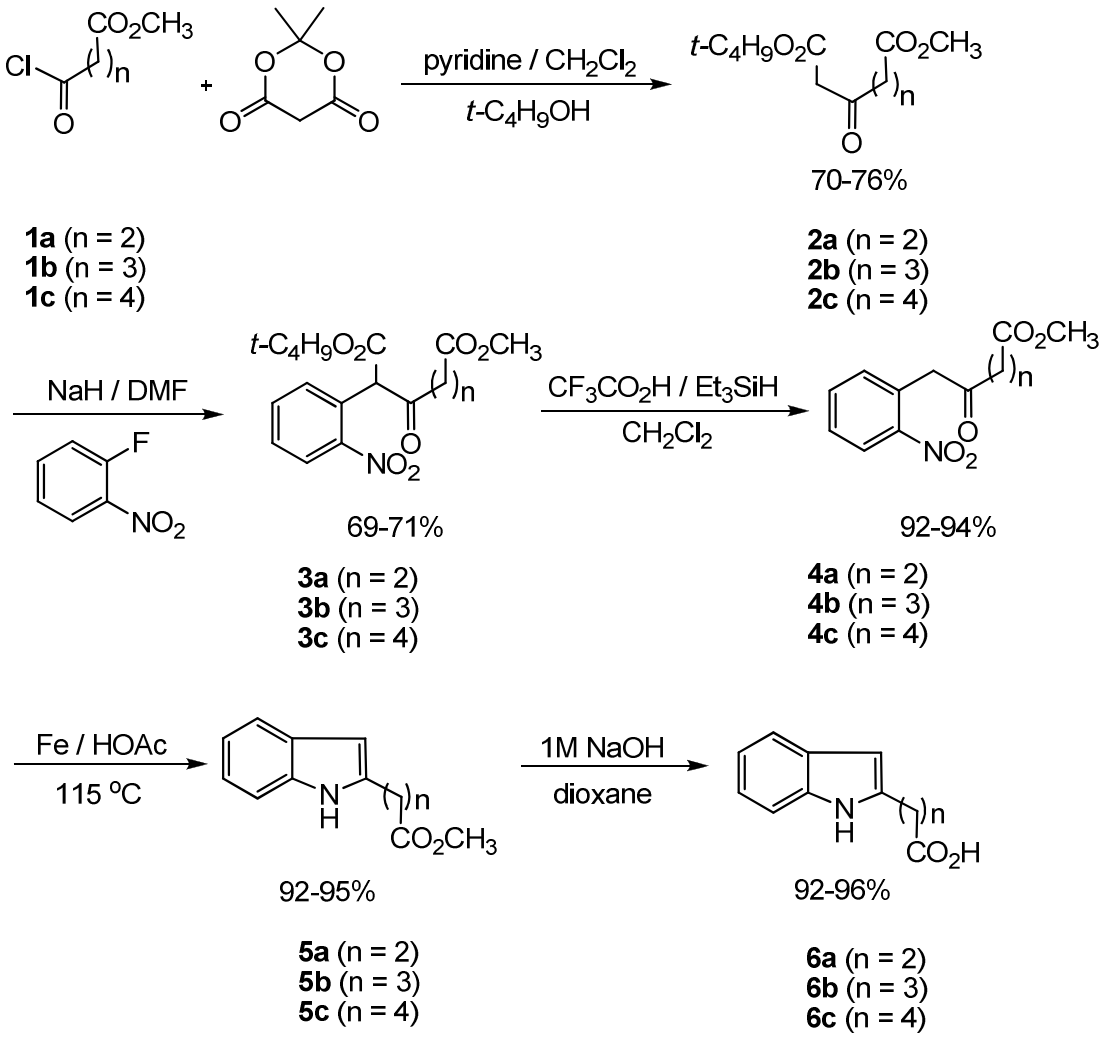


Figure 2.1. Syntheis of indole carboxylic acid derivatives

with **6a** or **6c**, reflecting the additional strain and entropy effects involved in closing a five- or a seven membered rings. Acids **6a** and **6c** could be lactamized, however, using *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride[19] in the presence of

excess 4-dimethylaminopyridine.[20] Numerous other conditions[21] failed to give the desired lactams. This appears to be the first report to use *N*-(3-dimethylaminopropyl)-*N*'-ethyl carbodiimide with 4-dimethylaminopyridine for lactam closure. The function of the base in this reaction appears to be two fold. First it neutralizes the hydrochloride salt of the carbodiimide and, secondly, it scavenges the proton from the cyclized amide. The results of our cyclization studies are summarized in Figure 2.2.

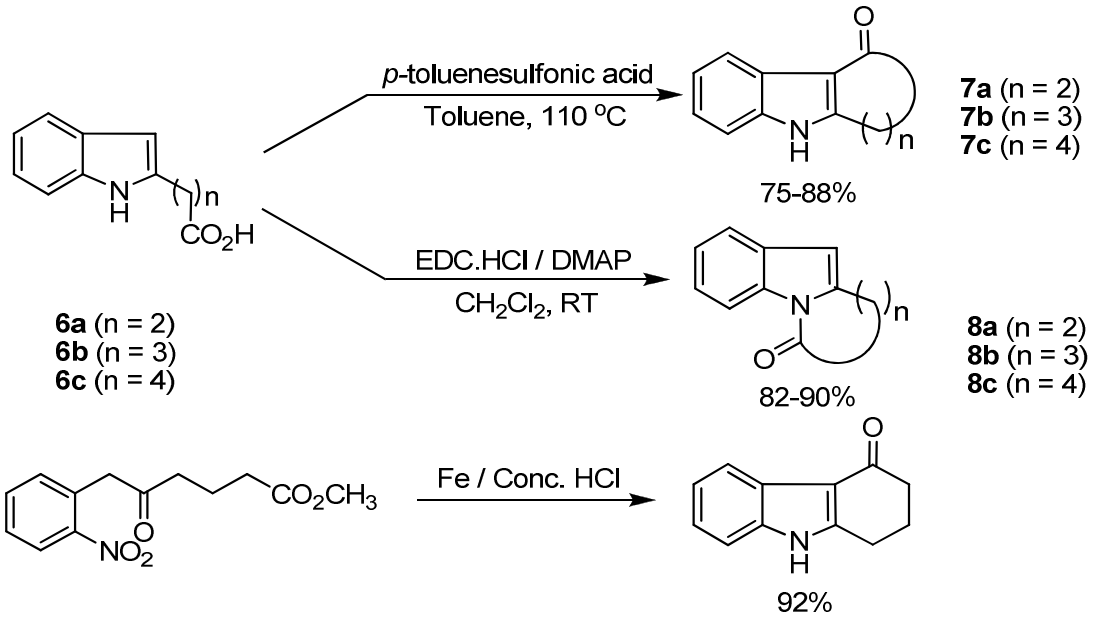


Figure 2.2. Cyclization methods to give carbazole and lactam rings

Remarkably, it was found that treatment of **4b** with iron in concentrated hydrochloric acid yielded **7b** in 92% yield by a tandem process involving a reduction-cycloaromatization-acylation sequence. Attempts to cyclize **6a** and **6c** under the same conditions afforded significantly lower yields, and the product mixtures were more complex. The one-step conversion of **4b** to **7b** represents a new tandem reaction sequence.

Mechanistically, reduction of the aromatic nitro group is followed by cycloaromatization to the indole system as previously observed.[1,2] Under strong acid conditions, however, the methyl ester is cyclized onto the C3 position of the indole. This most likely occurs by protonation of the ester carbonyl, attack by the electron-rich indole double bond to the carbonyl carbon, followed by methanol elimination and rearomatization (see Figure 2.3). The closure of acids **6a** to **6c**-**7a** and **7c** should be

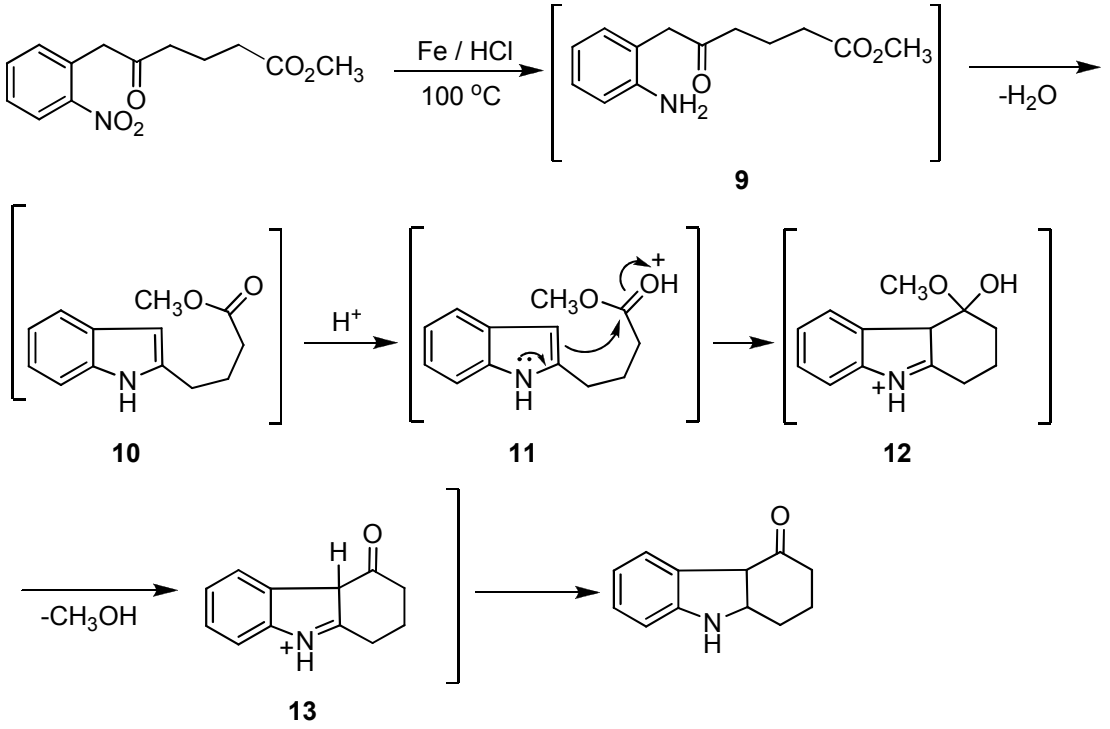


Figure 2.3. Mechanism for tetrahydrocarbazole ring system

analogous to the conversion of **10** to **7b** with loss of water in the penultimate step. Finally, the lactamization reactions proceed *via* the expected cyclocondensation mechanisms, with and without added carbodiimide.

CONCLUSION

We have developed an alternative approach to the synthesis of the title compounds from 1*H*-indole-2-butanoic acid (**6b**) prepared by a tandem reduction cycloaromatization process using iron in acetic acid. Heating this acid **6b** in the presence of *p*-toluenesulfonic acid in refluxing toluene affords 1,2,3,9-tetrahydro-4*H*-carbazol-4-on (**7b**), while heating in toluene with no added acid afforded 8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one (**8b**). Interestingly, a high yield of **7b** can be achieved directly from **4b** via a reduction-cycloaromatization acylation reaction promoted by iron in concentrated hydrochloric acid. Analogous systems incorporating five- and seven-membered fused cycloalkanones can be prepared by treatment of **6a** and **6c** with *p*-toluenesulfonic acid in refluxing toluene. However, direct conversion of **4a** and **4c** with iron in concentrated hydrochloric acid gives complex mixtures containing only small amounts of **7a** and **7c**. Cyclization of **6a** and **6c** to the lactams requires treatment with *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride in the presence of excess 4-dimethylaminopyridine. The reaction permits reasonable structural variation and furnished the products in high yield without toxic reagents or expensive catalysts.

Experimental Section

N,*N*-Dimethylformamide, from a freshly opened bottle, was dried over 4 Å molecular sieves under nitrogen and transferred by syringe into reactions where it was used. The acid chlorides were used as received. The HCl (2 M and 6 M), $NaHCO_3$ (saturated), and NaCl (saturated) employed in various procedures refer to aqueous solutions. All reactions were run under N_2 in oven-dried glassware.

Evaporation of solvents was accomplished *in vacuo* via the use of a Buchi Rotovapor RE-111® and a Brinkman B-169 water aspirator unless otherwise specified. For those intermediates that were liquids and required distillation for purification, vacuum distillation was employed using a Welch® Chemstar™ 1402N vacuum pump. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech 21521). Preparative separations were performed using flash column chromatography[22] on silica gel (grade 62, 60-200 mesh) mixed with ultraviolet-active phosphor (Sorbent Technologies UV-5) or thin layer chromatography on 20-cm × 20-cm silica gel GF plates (Analtech 02015). Band elution, for both methods, was monitored using a hand held ultraviolet lamp. Hexanes used in chromatography had a boiling range of 65-70 ºC. Melting points of all solids were uncorrected and taken on a MelTemp purchased from Laboratory Devices, Cambridge, MA 02139. Infrared spectra were taken on a Varian 800 FT-IR (Scimitar series) run as thin films on sodium chloride disks and were referenced to polystyrene. Unless otherwise indicated, ^{1}H and ^{13}C nuclear magnetic resonance spectra were measured in deuteriochloroform at 300 MHz and 75 MHz, respectively, on a Varian 300 MHz unit and were referenced to internal tetramethylsilane; coupling constants (J) are reported in Hertz

Representative Procedure for the Preparation of *tert*-Butyl Methyl 3-Oxoalkyldicarboxylic Esters: *tert*-Butyl Methyl 3-Oxohexanediate (2a).

The procedure of Yonemitsu and co-workers was used.[18] A 250-mL, two-necked, round-bottomed flask equipped with a magnetic stirrer, a condenser and a nitrogen inlet, was charged with 7.00 g (48.6 mmoles) of Meldrum's acid along with 7.68 g (97.2 mmoles) of pyridine in 50 mL of dichloromethane. A solution of 7.68 g (51.0 mmoles)

of **1a** in 10 mL of dichloromethane was added after 5 minutes and the solution was stirred at 0 ºC. Stirring was continued at 0 ºC for 30 minutes and at 22 ºC for 1 hour. The crude reaction mixture was washed with 2 *N* hydrochloric acid (3 × 150 mL) to remove the excess pyridine, and the solution was dried (magnesium sulfate) and concentrated under vacuum. The resulting oil was dissolved in 50 mL of *tert*-butyl alcohol and refluxed for 3 hours. The crude reaction mixture was concentrated under vacuum, and the compound was distilled under high vacuum to give 8.20 g (78%, containing some enol) of the keto diester as a colorless oil, bp 85-110 ºC (0.5 mm Hg). IR: 1737, 1717 cm^{-1}; ^{1}H NMR: δ 3.68 (s, 3H), 3.41 (s, 2H), 2.87 (t, 2H, J = 6.6), 2.62 (t, 2H, J = 6.6), 1.47 (s, 9H); ^{13}C NMR: δ 201.4, 172.8, 166.2, 81.9, 51.7, 50.4, 37.2, 27.8 (3C), 27.5.

***tert*-Butyl Methyl 3-oxoheptanedioate (2b).** This compound (9.00 g, 81% containing some enol) was isolated as a colorless oil, bp 110-130 ºC (0.5 mm Hg). IR: 1738, 1716 cm^{-1}; ^{1}H NMR: δ 3.67 (s, 3H), 3.35 (s, 2H), 2.62 (t, 2H, J = 7.0), 2.36 (t, 2H, J = 7.2), 1.92 (quintet, 2H, J = 7.1), 1.47 (s, 9H); ^{13}C NMR: δ 202.5, 173.5, 166.4, 82.0, 51.5, 50.5, 41.6, 32.7, 27.9 (3C), 18.5.

***tert*-Butyl Methyl 3-Oxooctanedioate (2c).** This compound (8.50 g, 68% containing some enol) was isolated as a colorless oil, bp 125-140 ºC (0.5 mm Hg). IR: 1735, 1716 cm^{-1}; ^{1}H NMR: δ 3.67 (s, 3H), 3.35 (s, 2H), 2.56 (distorted t, 2H, J = 6.7), 2.33 (distorted t, 2H, J = 6.7), 1.63 (m, 4H), 1.47 (s, 9H); ^{13}C NMR: δ 202.8, 173.7, 166.4, 81.9, 51.5, 50.5, 42.3, 33.7, 27.9 (3C), 24.2, 22.7.

Representative Procedre for the Nucleophilic Aromatic Substitutions: *tert*- Butyl Methyl 2-(2-Nitrophenyl)-3-oxohexanedioate (3a):

A modification of the procedure described by Bunce and co-workers was used.[1] A 250-mL, three-necked, round-bottomed flask, equipped with magnetic stirring, a reflux condenser and a nitrogen inlet, was charged with 1.9 g of NaH in a 60% mineral oil suspension. The solid was washed with hexane (3 × 25 mL) to remove the mineral oil, and the remaining 1.36 g (56.7 mmol) of NaH was suspended in 20 mL of dry *N*,*N*-dimethyl formamide. Stirring was initated and a solution of 4.00 g (28.4 mmoles) of 2-fluoro-1-nitrobenzene in 25 mL of dimethylformamide was added, followed by a solution of 6.35 g (29.7 mmoles) of **2a** in 5 mL of dimethylformamide. The reaction mixture was heated to 60 ºC and stirred for 48 hours, then added to 50 mL of saturated ammonium chloride and the mixture was extracted with ether (3 × 150 mL). The combined organic extracts were washed with saturated sodium chloride (1 × 100 mL), dried (magnesium sulfate) and concentrated under vacuum. The crude product was purified by flash chromatography on a 50-cm × 2-cm silica gel column eluted with 10% ether in hexanes to give 6.65 g (18.9 mmoles 66% containing some enol) of **3a** as a yellow oil. IR: 1736, 1640, 1613, 1520, 1351 cm^{-1}; ^{1}H NMR: δ 7.98 (dd, 1H, J = 8.0, 1.2), 7.58 (td, 1H, J = 7.6, 1.4), 7.46 (td, 1H, J = 7.9, 1.6), 7.33 (dd, 1H, J = 7.6, 1.4), 5.28 (s, 1H), 3.64 (s, 3H), 2.50 (m, 4H), 1.32 (s, 9H); ^{13}C NMR: δ 200.4, 172.7, 170.6, 149.7, 133.7, 132.6, 130.1, 128.3, 124.5, 82.6, 61.3, 51.7, 37.4, 29.8, 27.8 (3C).

***tert*-Butyl Methyl 2-(2-Nitrophenyl)-3-oxoheptanedioate (3b)**. This compound (6.00 g, 72%, containing some enol) was isolated as a yellow oil. IR: 1738, 1645, 1526, 1394, 1352 cm^{-1}; ^{1}H NMR: δ 7.98 (dd, 1H, J = 8.0, 1.2), 7.57 (td, 1H, J = 7.6, 1.4), 7.45 (td, 1H,

J = 7.9, 1.4), 7.25 (dd, 1H, J = 7.6, 1.4), 5.25 (s, 1H), 3.57 (s, 3H), 2.25 (m, 4H), 1.88 (m, 2H), 1.33 (s, 9H); ^{13}C NMR: δ 200.8, 172.7, 170.7, 149.7, 133.7, 132.8, 130.1, 128.4, 124.3, 82.6, 61.3, 51.8, 37.4, 29.9, 28.0, 27.8 (3C).

***tert*-Butyl Methyl 2-(2-Nitrophenyl)-3-oxooctanedioate (3c).** The compound (4.20 g, 62%, containing some enol) was isolated as a yellow oil. IR: 1735, 1643, 1615, 1524, 1352 cm^{-1}; ^{1}H NMR: δ 7.98 (dd, 1H, J = 8.0, 1.3), 7.56 (td, 1H, J = 7.5, 1.4), 7.45 (td, 1H, J = 7.9, 1.6), 7.25 (dd, 1H, J = 7.7, 1.4), 5.26 (s, 1H), 3.63 (s, 3H), 2.21 (m, 2H), 2.12 (m, 2H), 1.57 (m, 4H), 1.24 (s, 9H); ^{13}C NMR: δ 201.8, 173.7, 170.7, 149.7, 133.7, 132.5, 130.5, 128.8, 124.3, 82.4, 61.0, 51.5, 33.6, 32.5, 27.8 (3C), 25.7, 24.3.

Representative Procedure for *tert*-Butyl Ester Cleavage and Decarboxylation: Methyl 5-(2-Nitrophenyl)-4-oxopentanoate (4a).

The procedure of Mehta and co-workers was used.[17] A 250-mL three-necked round-bottomed flask, equipped with magnetic stirring, a reflux condenser and a nitrogen inlet, was charged with a solution of 5.20 g (14.8 mmoles) of **3a** in 50 mL of dichloromethane to which were added 27.6 g (18.0 mL, 242 mmoles) of trifluoroacetic acid and 4.88 g (6.70 mL, 421 mmoles) of triethylsilane. The mixture was stirred for 1 hour and then concentrated under high vacuum to give 3.50 g (94%) of **4a** as light yellow oil which was used without further purification. IR: 1735, 1722, 1525, 1351 cm^{-1}; ^{1}H NMR: δ 8.11 (dd, 1H, J = 8.0, 1.1), 7.60 (td, 1H, J = 7.7, 1.3), 7.46 (td, 1H, J = 7.9, 1.5), 7.31 (dd, 1H, J = 7.7, 1.1), 4.16 (s, 2H), 3.67 (s, 3H), 2.93 (t, 2H, J = 6.5), 2.65 (t, 2H, J = 6.5); ^{13}C NMR: δ 204.0, 173.1, 148.5, 133.7, 133.6, 130.1, 128.5, 125.2, 51.8, 47.8, 37.1, 27.8.

Methyl 6-(2-Nitrophenyl)-5-oxohexanoate (4b). This compound (3.46 g, 92%) was isolated as a light yellow oil and was used without further purification. IR: 1729, 1525, 1346 cm^{-1}; ^{1}H NMR: δ 8.11 (dd, 1H, J = 8.0, 1,1), 7.59 (td, 1H, J = 7.7, 1.5), 7.46 (td, 1H, J = 7.9, 1.5), 7.28 (dd, 1H, J = 7.7, 1.1), 4.09 (s, 2H), 3.68 (s, 3H), 2.70 (t, 2H, J = 7.1), 2.38 (t, 2H, J = 7.1), 1.96 (quintet, 2H, J = 7.1); ^{13}C NMR: δ 204.9, 173.6, 148.6, 133.6 (2C), 130.2, 128.4, 125.2, 51.6, 47.9, 41.4, 32.9, 18.7.

Methyl 7-(2-Nitrophenyl)-6-oxoheptanoate (4c). This compound (1.45 g, 92%) was isolated as a light yellow oil and used without further purification. IR: 1727, 1528, 1352 cm^{-1}; ^{1}H NMR: δ 8.10 (dd, 1H, J = 8.2, 1.3), 7.59 (td, 1H, J = 7.5, 1.3), 7.46 (td, 1H, J = 8.1, 1.5), 7.27 (dd, 1H, J = 7.6, 1.1), 4.10 (s, 2H), 3.67 (s, 3H), 2.62 (distorted, t, 2H, J = 6.8), 2.34 (distorted, t, 2H, J = 6.8), 1.67 (m, 4H); ^{13}C NMR: δ 205.2, 173.8, 148.6, 133.5 (2C), 130.3, 128.3, 125.2, 51.5, 47.8, 42.2, 33.7, 24.3, 22.9.

Representative Procedure for Reductive Cyclization to the 1*H*-Indoles: Methyl 1*H*-Indole-2-propanate (5a). The procedure of Bunce and coworkers[1] was used. Into a 25-mL three-necked round-bottomed flask, equipped with magnetic stirring, a reflux condenser and a nitrogen inlet, was placed a mixture of 1.50 g (5.98 mmoles) of **4a**, 25 mL of acetic acid and 2.00 g (6.00 eq, 35.9 mmoles) of iron powder (>100 mesh). The mixture was heated with stirring at 115 ºC (oil bath) until thin layer chromatography indicated complete consumption of the starting material (ca 30 minutes). The crude reaction mixture was cooled, transferred to a separatory funnel containing 50 mL of water and extracted with ether (3 × 100 mL). The combined ether layers were washed with water (1 × 100 mL), saturated sodium bicarbonate (3 × 150 mL), saturated sodium chloride (1 × 100 mL), then dried (magnesium sulfate) and concentrated under vacuum to

give a brown solid. Recrystallization from hexanes gave 1.10 g (91%) of **5a** as a tan solid, mp 97-98 ºC (lit[23] mp 97-98 ºC). IR: 3357, 1720 cm^{-1}; ^{1}H NMR: δ 8.47 (br s, 1H), 7.52 (dd, 1H, J = 7.9, 0.6), 7.31 (dq, 1H. J = 8.0, 0.9), 7.12 (td, 1H, J = 7.9, 1.3), 7.06 (td, 1H, J = 7.9, 1.1), 6.24 (dd, 1H, J = 2.0, 0.9), 3.72 (s, 3H), 3.08 (t, 2H, J = 6.7), 2.73 (t, 2H, J = 6.7); ^{13}C NMR: δ 174.3, 138.1, 136.0, 128.4, 121.3, 119.9, 119.6, 110.5, 99.8, 51.9, 33.9, 23.1.

Methyl 1*H*-Indole-2-butanoate (5b). This compound (1.15 g, 95%) was isolated as a tan solid, mp 69-71 ºC. IR: 3392, 1718 cm^{-1}; ^{1}H NMR: δ 8.06 (br s, 1H), 7.52 (d, 1H, J = 7.6), 7.30 (d, 1H, J = 6.0), 7.08 (m, 2H), 6.25 (s, 1H), 3.66 (s, 3H), 2.81 (t, 2H, J = 7.2), 2.40 (t, 2H, J = 7.2), 2.04 (m, 2H); ^{13}C NMR: δ 173.9, 138.4, 128.8, 121.1, 119.8, 119.6, 110.3, 100.0, 51.6, 33.1, 30.0, 27.3, 24.5.

Methyl 1*H*-Indole-2-pentanoate (5c). This compound (1.10 g, 90%) was isolated as a tan solid, mp. 121-124 ºC. IR: 3353, 1719 cm^{-1}; ^{1}H NMR: δ 7.98 (br, s, 1H), 7.52 (d, 1H, J = 6.8), 7.28 (d, 1H, J = 8.0), 7.08 (m, 2H), 6.24 (s, 1H), 3.67 (s, 3H), 2.76 (t, 2H, J = 7.2), 2.37 (t, 2H, J = 3.6), 1.76 (m, 4H); ^{13}C NMR: δ 174.2, 139.3, 136.0, 128.9, 121.2, 119.6, 119.8, 110.5, 99.8, 51.7, 33.9, 28.7, 28.0, 24.6.

Representative Procedure for the Ester Hydrolysis: 1*H*-Indole-2-propanic Acid (6a).

A 25-mL three-necked round-bottomed flask, equipped with magnetic stirring, a reflux condenser and a nitrogen inlet, was charged with a mixture of 1.00 g (4.93 mmoles) of **5a** in 2 mL of dioxane along with 15.0 mL of a 1.0 *M* aqueous solution of sodium hydroxide. The mixture was stirred for 1 hour. The solution was then concentrated to one-half volume under vacuum, acidified with 3 *M* hydrochloric acid and extracted with ether (3 × 100 mL). The combined ether layers were washed with

saturated sodium chloride (1 × 150 mL), then dried (magnesium sulfate) and concentrated under vacuum. The crude product was purified by flash chromatography on a 15-cm × 2-cm silica gel column eluted with 50% ether in hexanes to give 0.85 g (91%) of **6a** as white solid, mp 165-167 ºC (lit[24] mp 167 ºC). IR: 3462-2300, 3392, 1701 cm^{-1}. ^{1}H NMR: δ 9.87 (br, s, 1H), 8.26 (br s, 1H), 7.52 (dd, 1H, J = 7.7, 1.3), 7.30 (dd, 1H, J = 8.0, 0.9), 7.13 (td, 1H, J = 7.7, 1.3), 7.07 (td, 1H, J = 7.9, 1.1), 6.26 (dd, 1H, J = 1.9, 0.8), 3.08 (t, 1H, J = 6.8), 2.81 (t, 2H, J = 6.8); ^{13}C NMR: δ 178.4, 137.6, 135.5, 128.4, 121.4, 119.9, 119.7, 110.5, 99.9, 33.6, 22.9.

1*H*-Indole-2-butanoic Acid (6b). This compound (0.31 g, 85%) was isolated as a white solid, mp 114-115 ºC. IR: 3252-2348, 3386, 1700 cm^{-1}. ^{1}H NMR: δ 10.85 (br s, 1H), 7.95 (br s, 1H), 7.52 (dd, 1H, J = 7.7, 0.7), 7.29 (dd, 1H, J = 8.0, 0.9), 7.12 (td, 1H, J = 7.9, 1.3), 7.07 (td, 1H, J = 7.7, 1.1), 6.27 (dd, 1H, J = 2.0, 0.8), 2.83 (t, 2H, J = 7.3), 2.45 (t, 2H, J = 7.3), 2.06 (quintet, 2H, J = 7.3); ^{13}C NMR: δ 179.2, 138.1, 135.9, 128.7, 121.2, 119.9, 119.7, 110.4, 100.1, 33.0, 27.3, 24.2.

1*H*-Indole-2-pentanoic Acid (6c). This compound (0.90 g, 96%) was isolated as a white solid, mp 145-147 ºC. IR: 3425-2350, 3384, 1700 cm^{-1}. ^{1}H NMR: δ 10.50 (s, 1H), 7.92 (br s, 1H), 7.52 (d, 1H, J = 6.8), 7.30 (d, 1H, J = 8.0), 7.10 (m, 2H), 6.24 (s, 1H), 2.80 (t, 2H, J = 6.8), 2.42 (t, 2H, J = 7.2), 1.76 (m, 4H); ^{13}C NMR: δ 178.4, 138.9, 135.7, 128.7, 121.0, 119.7, 119.6, 110.2, 99.7, 33.4, 28.4, 27.8, 24.1.

Representative Procedure for the Acylation Reactions: 3,4-Dihydrocyclo-pent[*b*]indol-1(2*H*)-one (7a).

A 500-mL, one-necked, round-bottomed flask, equipped with magnetic stirring, a reflux condenser and a nitrogen inlet, was charged with a solution of 200 mg (1.06

mmoles) of **6a** in 10 mL of toluene. The mixture was heated to reflux and 200 mg of *p*-toluenesulfonic acid was slowly added through the top of the condenser. After 1 hour at reflux, a second 200-mg portion of *p*-toluenesulfonic acid monohydrate (total 400 mg, 2.00 eq, 2.10 mmoles) was added, and refluxing was continued for a total of 12 hours. The resulting solution was cooled, added to water (50 mL) and extracted with ether (3 × 100 mL). The ether layer was washed with saturated sodium bicarbonate (3 × 150 mL) and sodium chloride (1 × 100 mL), then dried (magnesium sulfate) and concentrated under vacuum. The crude product was purified by flash chromatography on a 20-cm × 2-cm silica gel column eluted with 10% ether in hexanes to give 136 mg (75%) of pure **7a.** IR: 3371, 1648 cm^{-1}; ^{1}H NMR (dimethyl sulfoxide-d_6): δ 12.0 (br, s, 1H), 7.67 (d, 1H, J = 7.5), 7.45 (d, 1H, J = 8.0), 7.22 (td, 1H, J = 7.7, 1.3), 7.16 (td, 1H, J = 7.7, 1.3), 3.08 (m, 2H), 2.82 (m, 2H); ^{13}C NMR: δ 194.7, 167.7, 142.2, 129.8, 127.6, 122.9, 121.5, 119.4, 112.6, 40.6, 21.0.

1,2,3,9-Tetrahydro-4*H*-carbazol-4-one (7b). This compound was prepared from 150 mg (0.74 moles) of **6b** using a modified procedure. In this case, 844 mg (4.44 mmoles, 6.0 eq) of *p*-toluenesulfonic acid monohydrate was required, and this acid was added in 2.0-eq portions at one hour intervals during the first three hours of the twelve hour reflux period. Product **7b** (120 mg, 88%) was isolated as an off-white solid, mp 225-228 ºC (dec) (lit[11] mp 219-221 ºC). IR: 3368, 1588, 1566 cm^{-1}; ^{1}H NMR (dimethyl sulphoxide-d_6): δ 11.7 (br, s, 1H), 7.99 (d, 1H, J = 7.5), 7.46 (dd, 1H, J = 7.8, 1.1), 7.25 (td, 1H, J = 7.7, 1.2), 7.19 (td, 1H, J = 7.7, 1.2), 2.99 (t, 2H, J = 6.3), 2.42 (t, 2H), J = 6.4), 2.13 (quintet, 2H, J = 6.4); ^{13}C NMR (dimethyl sulfoxide-d_6): 192.1, 148.4, 134.1, 122.7, 122.2, 120.5, 120.2, 108.8, 106.5, 37.7, 22.9, 20.4.

6**,7,8,9-Tetrahydrocyclohept[*b*]indol-10(5*H*)-one (7c).** This compound was prepared as described for **7b** using 203 mg (0.93 mmoles) of **6c** to give 133 mg (72%) of **7c** as a tan solid, mp 217-218 ºC. (lit[11] mp 220-221 ºC). IR: 3365, 1718 cm^{-1}; ^1H NMR (dimethyl sulfoxide-d_6): δ 11.7 (br s, 1H), 8.14 (dd, 1H, J = 7.4, 1.4), 7.34 (dd, 1H, J = 7.9, 1.3), 7.12 (m, 2H), 3.10 (t, 2H, J = 6.3), 2.64 (m, 2H), 1.93 (quintet, 2H, J = 6.4), 1.83 (m, 2H); ^{13}C NMR (dimethyl sulfoxide-d_6): δ 196.4, 149.0, 135.0, 127.3, 122.2, 121.2, 120.9, 113.7, 110.9, 42.7, 27.0, 24.3, 21.8.

Direct Preparation of 7b from 4b. A 100-mL single-necked round-bottomed flask, equipped with a reflux condenser (N_2 inlet) and a magnetic stirrer, was charged with 200 mg (0.75 mmoles) of **4b** and 8 mL of concentrated hydrochloric acid. The mixture was heated to 80 ºC (oil bath), and 126 mg (3.00 eq, 2.25 mmoles) of Fe powder (>100 mesh) was added. The reaction was refluxed at 110 ºC until thin layer chromatography indicated complete consumption of starting material (ca 20 minutes). The mixture was cooled, added to 15 mL of water and extracted with ether (3 × 50 mL). The combined ether layers were washed with saturated sodium chloride (1 × 50 mL), dried (magnesium sulfate) and concentrated under vacuum. The resulting solid was flash chromatographed on a 20-cm × 2-cm silica gel column eluted with increasing concentrations of ether in hexanes to give 128 mg (92%) of **7b**. The physical properties and spectral data matched those reported above.

Representative Procedure for Five- and Seven-Membered Lactam Formation: 1,2-Dihydro-3*H*-pyrrolo[1,2-*a*]indol-3-one (8a). A 100-mL one-necked round-bottomed flask, equipped with magnetic stirring, a reflux condenser and a nitrogen inlet, was charged with 100 mg (0.53 mmoles) of **6a** in 5 mL of dichloromethane along with 103

mg (0.85 mmoles, 1.6 eq) of 4-dimethylaminopyridine. The mixture was stirred for 10 minutes to give a clear light brown solution. To this solution was added 101 mg (0.53 mmoles, 1.0 eq) of *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride and the reaction mixture was stirred at room temperature for 24 hours. The crude reaction mixture was washed with water (1 × 20 mL), 1 *M* hydrochloric acid (1 × 25 mL), saturated sodium bicarbonate (1 × 25 mL) and saturated sodium chloride (1 × 25 mL), then dried (magnesium sulfate) and concentrated under vacuum. The resulting semisolid was purified by preparative thin layer chromatography eluted with 60% ether in hexanes to give 72 mg (80%) of the lactam as a light tan solid, mp 148-151 ºC (lit[25] mp 151-153 ºC). IR: 1731 cm^{-1}; ^{1}H NMR: δ 8.07 (m, 1H), 7.48 (m, 1H), 7.25 (m, 2H), 6.27 (s, 1H), 3.14 (A of ABm, 2H), 3.08 (B of ABm, 2H); ^{13}C NMR: δ 171.6, 143.6, 135.3, 130.4, 124.0, 123.2, 120.5, 113.5, 100.3, 34.9, 19.6.

8,9-Dihydropyrido[1,2-*a*]indol-6(7*H*)-one (8b). This compound was prepared by dissolving 100 mg (0.493 mmoles) of **6b** in 15 mL of dry toluene and refluxing the mixture for 36 hours. The solvent was evaporated to dryness under vacuum. The crude product was purified by preparative thin layer chromatography on a 20-cm × 20-cm silica gel GF plate using 50% ether in hexanes to give 82 mg (90%) of a **8b** as a white solid, mp 78-79 ºC (lit[24] mp 79-81 ºC). IR: 1690 cm^{-1}; ^{1}H NMR: δ 8.44 (dd, 1H, J = 8.1, 0.9), 7.45 (dd, 1H, J = 6.8, 1.6), 7.25 (m, 2H), 6.31 (s, 1H), 2.97 (td, 2H, J = 6.8, 1.2), 2.78 (t, 2H, J = 6.4), 2.07 (quintet, 2H, J = 6.4); ^{13}C NMR: δ 169.4, 138.1, 134.8, 129.7, 124.0, 123.9, 119.6, 116.3, 104.8, 34.4, 23.8, 21.4.

7,8,9,10-Tetrahydro-6*H*-azepino[1,2-*a*]indol-6-one (8c). This compound was prepared as described for **8a** on an 80 mg (0.37 mmole) scale to give 60 mg (81%) of the lactam as

a white solid, mp 172-175 ºC. IR: 1692 cm^{-1}; ^{1}H NMR: δ 8.42 (dm, 1H, J = 7.9), 7.46 (dm, 1H, J = 7.3), 7.32-7.20 (complex, 2H), 6.36 (s, 1H), 3.06 (t, 2H, J = 5.9), 2.94 (distorted, t, 2H, J = 5.8), 1.94 (m, 4H); ^{13}C NMR: δ 173.8, 139.5, 136.9, 129.6, 124.1, 123.5, 119.5, 116.3, 107.9, 35.9, 25.8, 23.7, 20.8.

References and Notes

1. Bunce, R. A.; Randall, M. H.; Applegate, K. G. *Org. Prep. Proceed. Int.* **2002**, *34*, 493.
2. Augustine, R.; Gustavsen, A. J.; Wanat, S. F.; Pattison, I. C.; Houghton, K. S.; Koletat, G. *J. Org. Chem.* **1973**, *38*, 2004.
3. Scott, T. L.; Soderberg, B. C. G. *Tetrahedron* **2003**, *59*, 6323.
4. Sissoumma, D.; Maingot, L.; Collet, S.; Guigant, A. *J. Org. Chem.* **2006**, *22*, 8384.
5. Li, X.; Vince, R. *Bioorg & Med. Chem.* **2006**, *14*, 2942.
6. [a] Kohno, T.; Yoshikawa, T.; Yoshizawa, A.; Nakamura, I.; Anzai, T.; Satoh, T.; Ogawa, S. Cardiovascular Drugs and Therapy **2005**, *19*, 347. [b] Romeo, G.; Materia, L.; Pittala, V.; Modica, M.; Salerno, L.; Siracusa, M.; Russo, F.l Minneman, K. P. *Bioorg. & Med. Chem.* **2006**, *14*, 5211.
7. [a] Elz, S.; Heil, W. L. *Bioorg & Med. Chem. Lett.* **1995**, *5*, 667. [b] Scott, T. L.; Soderberg, B. C. G. *Tetrahedron Lett*. **2002**, *43*, 1621.
8. Kato, M.; Ito, K.; Takasugi, H. European Patent EP 451538 1991; *Chem Abstr.* **1992**, *116*, 207822.

9. [a] Kato, M.; Ito, K.; Nishino, S.; Yamakuni, H.; Takasugi, H. *Chem. Pharm. Bull.* **1994**, *42*, 2546. [b] Kato, M.; Nishino, S.; Ito, K.; Takasugi, H. *Chem. Pharm. Bull.* **1995**, *43*, 1346.

10. [a] Czeski, B. A.; Wheeler, W. J. *J. Label Compd. Radiopharm.* **2005**, *48*, 407. [b] Clemo, G, R.; Felton, D. G. I. *J. Chem. Soc.* **1951**, 700.

11. Oikawa, Y.; Yonemitsu, O. *J. Org. Chem.* **1977**, *42*, 1213.

12. [a] Wender, P. A.; White, A. W. *Tetrahedron* **1983**, *39*, 3767. [b] For a related approach, see Kudzma, L. V. *Synthesis* **2003**, 1661.

13. [a] Osuka, A.; Mori, Y.; Suzuki, H. *Chem Lett.* **1982**, 2031. [b] Yan, S.; Wu, H.; Wu, N.; Jiang, Y. *Synlett* **2007**, 2699.

14. Iida, H.; Yuasa, Y.; Kibayashi, C. *J. Org. Chem.* **1979**, *44*, 123.

15. [a] Scott, T. L.; Burke, N.; Carrero-Martinez, G.; Soderberg, B. C. G. *Tetrahedron* **2007**, *63*, 1183. [b] Soresen, U. S.; Pombo-Villar, E. *Helv. Chim. Acta* **2004**, *87*, 82. [c] Wang, H.-M.; Chou, H.-L; Chen, L-C. *J. Chin. Chem. Soc.* (Taipei) **1995**, *42*, 593. [d] Mori, M.; Uozumi, Y.; Sibasaki, M. *Heterocycles* **1992**, *33*, 819. [e] Sakamoto, S.; Nagano, T.; Kondo, Y.; Yamanaka, H. *Synthesis* **1990**, 215.

16. Davidson, D.; Bernhard, S. A. *J. Am. Chem. Soc.* **1948**, *70*, 3426.

17. Mehta, A.; Jaouhari, R.; Benson, T. J.; Douglas, K. T. *Tetrahedron Lett.* **1992**, *33*, 5441.

18. [a] Oikawa, Y.; Sugano, K.; Yonemitsu, O. *J. Org. Chem.* **1978**, *43*, 2087. [b] Oikawa, Y.; Sugano, K.; Yonemitsu, O. *Organic Syntheses;* Wiley-Interscience, New York, NY; Coll. Vol. VII, pp 359-361.

19. [a] Sheehan, J. C.; Cruickshank, P. A.; Boshart, G. L. *J. Org. Chem*. **1961**, *26*, 2525. [b] Kopple, K. D.; Nitecki, D. E. *J. Am. Chem. Soc.* **1962**, *84*, 4457.

20. The use of a larger excess of 4-(dimethylamino)pyridine promotes side reactions that generate more complex product mixtures.

21. Several other reagent combinations were explored for the lactamization reaction. [a] *N*-(3-Dimethylaminopropyl)-*N*'-ethyl carbodiimide alone: ref 18b. [b] N-(3-Dimethylaminopropyl)-N'-ethyl carbodiimide with 1-hydroxybenzotriazole: Harigawa, D.; Neya, M.; Miyazaki, Y.; Hemmi, K.; Hashimoto, M. *J. Chem. Soc.*, *Chem Commun*. **1984**, 1676. [c] Polymer-bound *N*-benzyl-*N*'-Cyclohexylcarbodiimide: LeBas, M.-D. H.; McKinley, N. F.; Hogan, A. –M. L.; O'Shea, D. F. *J. Comb. Chem.* **2005**, *7*, 503. *N,N'*-Dicyclohexylcarbodiimide appeared to promote lactam formation, but *N,N'*-dicyclohexylurea and excess carbodiimide but could not be removed from the products. All reactions were run in dichloromethane; each was tried with added triethylamine and 4-dimethylaminopyridine.

22. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

23. Mohri, K.; Oikawa, Y.; Hirao, K.; Yonemitsu, O. *Heterocycles* **1982**, *19*, 515.

24. Julia, M.; Bagot, J. *Bull Soc Chim Fr.* **1964**, 1924.

25. Crenshaw, M. D.; Zimmer, H. *J. Heterocyclic Chem.* **1984**, *21*, 623.

.

CHAPTER III

DIVERGENT REACTIVITY IN TANDEM REDUCTION-MICHAEL RING CLOSURES OF FIVE AND SIX-MEMBERED CYCLIC ENONES

Introduction

The reductive cyclization of 2-nitrobenzyl ketones under dissolving metal conditions is a well established route to indoles.[1,2] Earlier work from our laboratory reported a tandem reduction-Michael addition variant of this reaction as a route to 1,2,3,4-tetrahydroquinoline-2-acetic esters,[3] and we have recently utilized this reaction to synthesize 1,2,3,9-tetrahydro-4*H*-carbazole-4-one.[4] In the current investigation, we sought to expand the scope of the tandem reduction-Michael sequence to access functionalized, linear-fused tricyclic systems. For this study, we prepared six- and five-membered cyclic enones, substituted at C4 by a methyl ester and a 2-nitrobenzyl group, and subjected each to mild reduction using iron in acetic acid. To our surprise, divergent reactivity was observed from the cyclohexenone and cyclopentenone substrates resulting in two relatively uncommon ring systems. In addition, a mechanistically novel competitive ester reduction process was observed. Thus, we wish to report our findings in this area.

Results and Discussion

The syntheses of the cyclization substates are summarized in Figure 3.1. Ketoester **3** was prepared from 1,3-cyclohexanedione (**1**) by Lewis acid-catalyzed enol

ether formation to give **2,**[5] followed by kinetic deprotonation[6] and subsequent reaction with methyl cyanoformate[7]. In this case methyl cyanoformate gave better yields of the ketoester than methyl chloroformate with easier purification of the product. Ketoester **6** was prepared as previously described.[8]

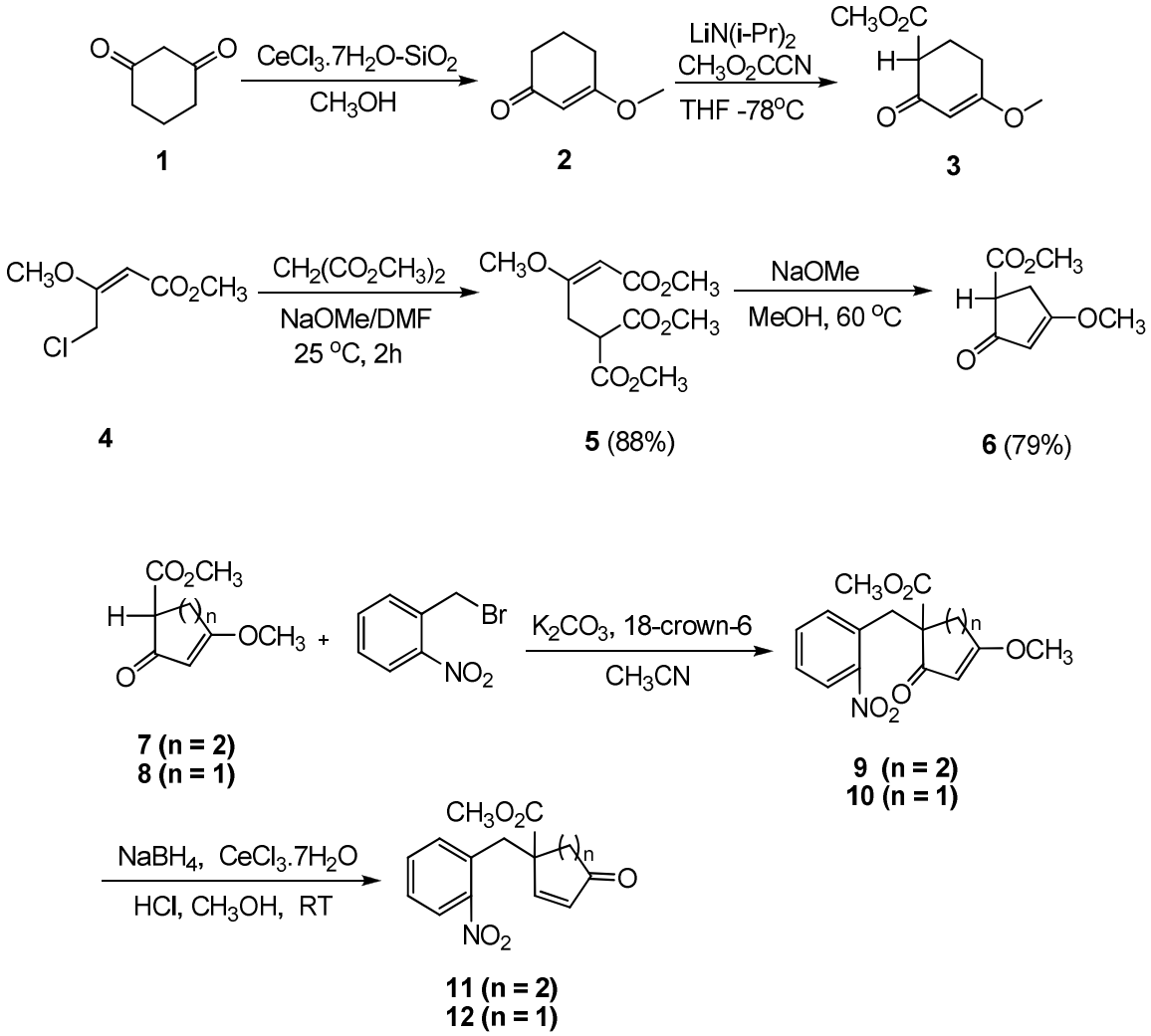


Figure 3.1. Synthesis of Cyclization Substrates

Alkylation of **5** and **6** with 2-nitrobenzyl bromide[9] using potassium carbonate and catalytic 18-crown-6 in acetonitrile under anhydrous conditions[10] gave products **7** and **8**,

respectively. Reduction of the enone carbonyls in **7** and **8** with sodium borohydride in the presence of cerium(III) chloride,[11] followed by treatment with aqueous acid, resulted in 1,3-carbonyl transposition to give substrates **9** and **10**.

The results of this reduction-cyclization study are outlined in Figure 3.2. In each case, the reaction was complete in 30 minutes and led predominantly to a single product.

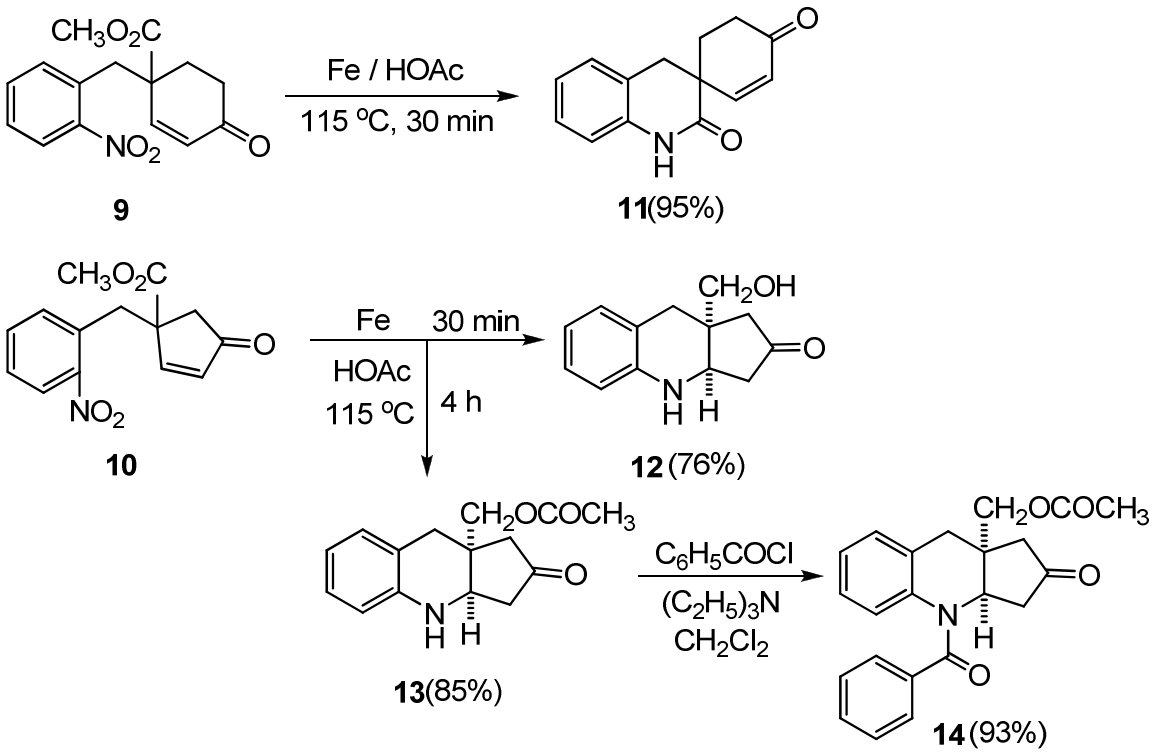


Figure 3.2. Ring cyclization and its derivatization

For cyclohexenone **9**, the expected reduction-Michael addition was not observed, but instead, reduction of the nitro group was followed by addition of the aniline nitrogen to the ester to give the spiro-fused 3,4-dihydro-2(1*H*)-quinolinone derivative **11** (95%) yield. For cyclopentenone **10**, the reduction-Michael sequence proceeded as planned but

was accompanied by reduction of the ester to afford alcohol **12** in 76% yield. Extended reaction times (4 hours) led to further acylation of the primary alcohol in **12** to give **13**.

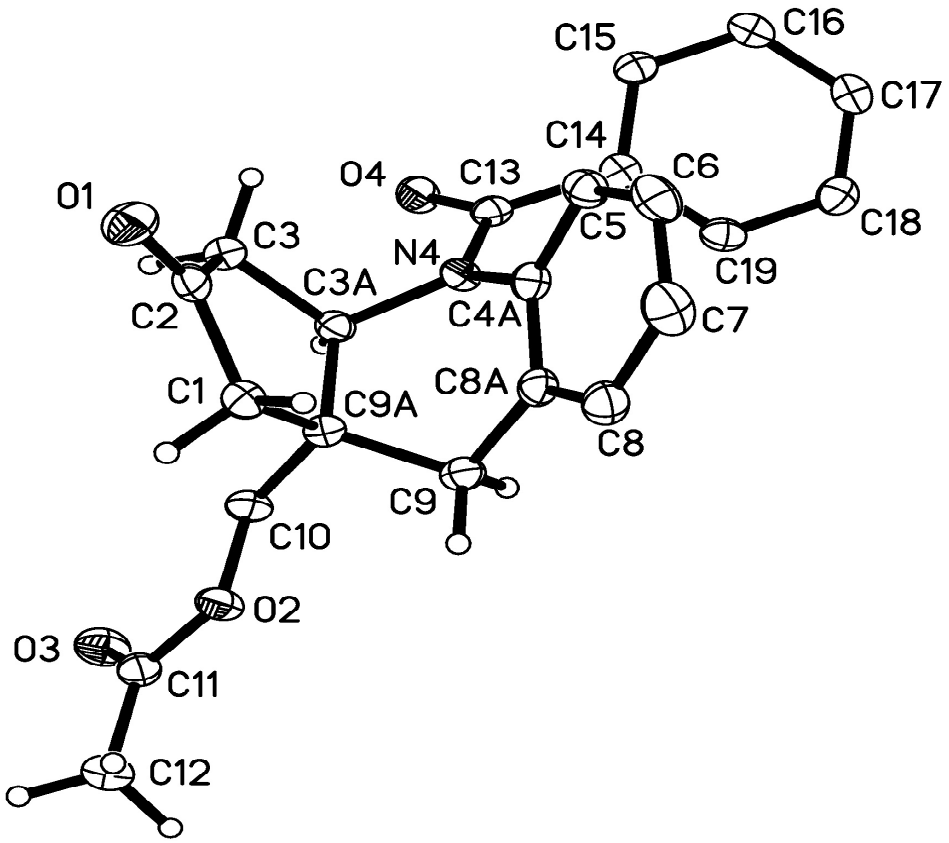


Figure 3.3. Molecular structure of compound **14**, with thermal ellipsoids drawn at the 50% probability level. Hydrogen atoms on C10 and on the aromatic rings have been removed for clarity.

The *cis* stereochemistry of the ring junction was confirmed by single crystal X-ray analysis of the *N*-benzoyl derivative **14** derived from 13 (Figure 3.3).

Examination of molecular models provides some insight into the observed difference in reactivity. Following reduction of the nitro function in **9**, alignment of the amino group for addition to the enone would result in steric repulsion between the C5 methylene of the cyclohexenone ring and the aromatic ring as in **A** (Figure 3.4). Rotation

about the benzylic bond to minimize this interaction would then lead to conformation **B**, which is more prone to react at the ester carbonyl. By comparison, similar steric interference is not present in cyclopentenone **10**. Furthermore, the five-membered cyclic enone should be more reactive due to strain. Eclipsing interactions that develop in the five-membered ring of **12** during addition should not significantly deter cyclization since the starting enone also possesses considerable torsional strain. The eclipsing in the cyclized product is clearly visible in the X-ray structure of **14** (Figure 3.3).

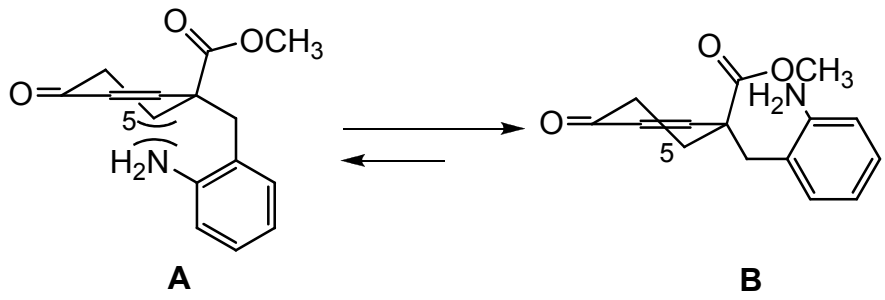


Figure 3.4. Steric repulsion of the six membered cyclohexenone ring

The preference for the *cis* stereochemistry of the ring junction in **12** is in accord with both strain and stereoelectronic considerations. The *cis*-fused stereochemistry would be expected based on strain arguments, with the *cis*-fused ring junction preferred over the more strained *trans.*[12] Stereoelectronically, it is well established the *cis*-fused isomer is strongly favored in nucleophilic ring closures on pre-existing rings via an axial attack that permits a chair-like transition state.[13] Although, a true chair transition state is not possible due to the aromatic sp^2 carbons, pseudoaxial attack would still be expected to afford a *cis* product.

The reduction of the ester group in **10** is also an interesting observation. The reduction is analogous to the classical Bouveault-Blanc reaction[14] but would not be expected to occur with iron as the electron source.[15] In our substrates, the α,β-unsaturated ketone is the functional group most susceptible to reduction under dissolving metal conditions,[16] and it is reasonable that this moiety is the key to reducing the ester.

To explore this process without interference from the amino group, methyl (±)-1-benzyl-4-oxo-2-cyclohexene-1-carboxylate (**15**) and methyl (±)-1-benzyl-4-oxo-2-cyclopentene-1-carboxylate (**16**) were prepared using the same method described for the nitro-bearing substrates above. Treatment of **15** with iron in acetic acid for 24 hours yielded a 33:67 mixture (by NMR) of starting material **15** and the double bond reduction product **17**. This ratio varied little with longer reaction times or increased amounts of iron. A similar reaction of **16** gave more interesting results, and the reaction was considerably faster. Exposure of **16** to iron in refluxing acetic acid gave nearly complete conversion to alcohol **20** in 15 minutes. Prolonged treatment (2 hours) under the same conditions gave a 67:33 mixture (by NMR) of **20:22**, as the acetates, in 95% yield. These results are summarized in Figure 3.5.

Mechanistically, reduction of **15** and **16** is initiated by protonation of the enone carbonyls followed by addition of two electrons to each conjugated system[16] to give of anions **23** and **24**, respectively (Figure 3.6). In **23**, the six-membered ring is conformationally flexible making the ester at C4 less accessible to attack by the anionic center at C3. Thus, protonation and tautomerization occur to give **17**. In the more rigid

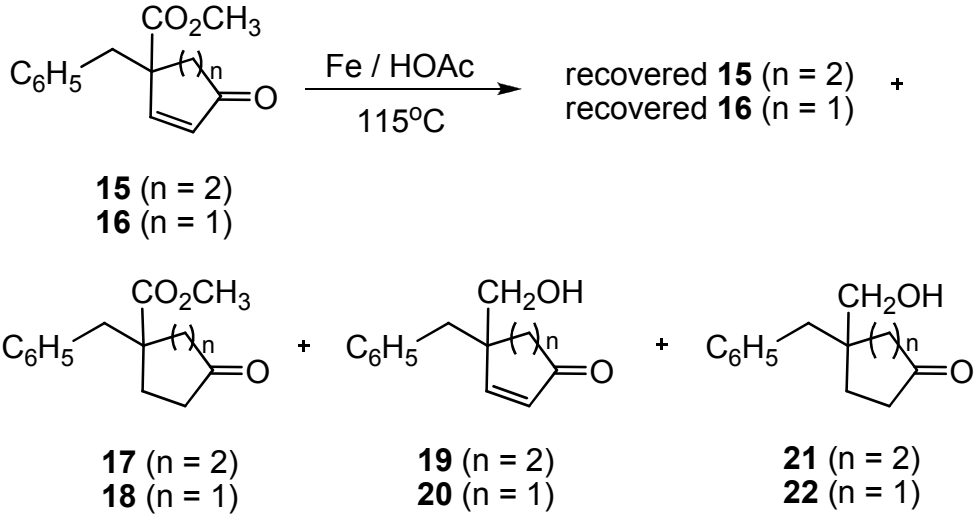


Figure 3.5. Cyclization of the substrate in the absence of nitro group

Substrate	time (hours)	**15**	**17**	**19**	**21**
15(n = 2)	24	33	67	0	0
		16	**18**	**20**	**22**
16(n = 1)	0.25	10[b]	0	72 [b]	trace
	2	0	0	67 [c]	33 [c]

[a] Percentage listed are from the ^{1}H NMR. [b] Isolated yields. [c] Products detected were the acetates of the indicated alcohols.

structure **24**, the C3 anion is closer to the C4 ester, and cyclization occurs to afford the strained cyclopropanone hemiketal **25**. Under the acidic conditions of the reaction, **25** would undergo rapid proton and enol assisted three-ring opening,[17] as in **26**, followed by loss of methanol to give aldehyde **27**. Further reduction of **27** would then afford alcohol **20** and, eventually, **22**.

The systems resulting from these ring closures have minimal precedent in the literature. The 3,3-dialkyl-3,4-dihydro-2(1*H*)-quinolinone scaffold of **11** is found in

some antidepressants,[18] but spiro-fused compounds have not been extensively investigated.[19] The 2,3,3a,4,9,9a-hexahydro-1*H*-cyclopenta[*b*] quinoline system has been reported[20] and is known to exhibit some antipsychotic activity,[21] but structures with the functional group arrangement of **12** are unknown.

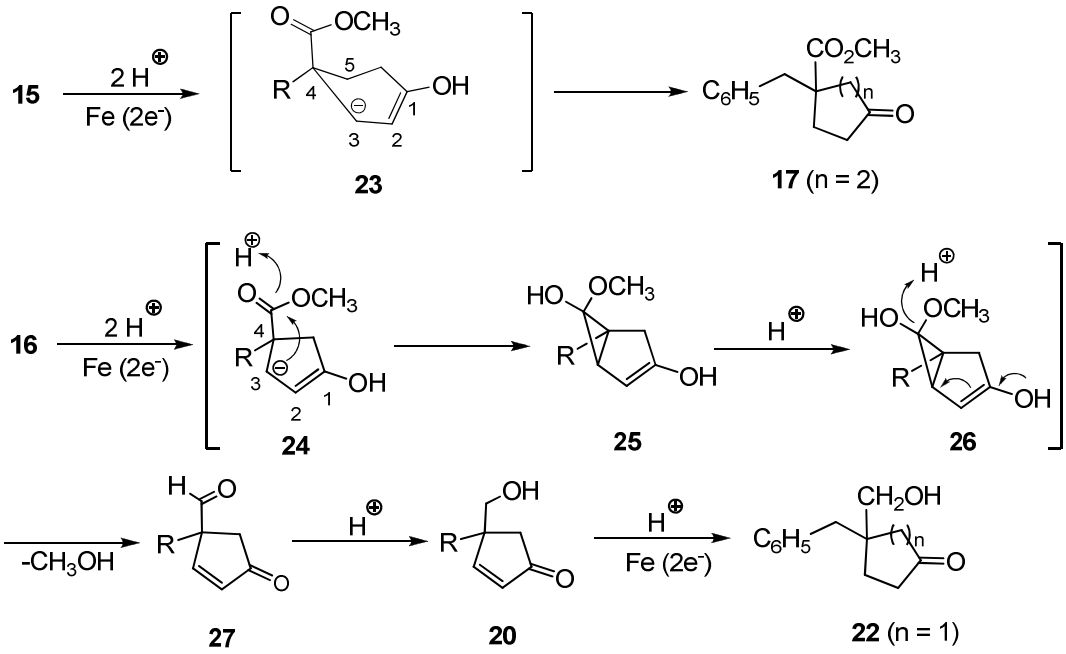


Figure 3.6. Mechanism of the benzylic substrate

Conclusion

Divergent behavior has been observed in the dissolving metal reduction-Michael reaction of two substrated differing only in the size of the ring incorporating the Michael acceptor. The disparate reaction pathways can be attributed to differences in stain and steric environment of the enone acceptor as well as the alignment of the reacting functionality in the two systems. The reaction is clean and offers an efficient route to a relatively rare ring skeleton from each substrate. The reduction of the ester functionality

in the five-membered ring substrate is novel and likely involved participation of the enone moiety.

Experimental Section

Commercial reagents and solvents were used as received. Tetrahydrofuran was dried over potassium hydroxide pellets and distilled from lithium aluminium hydride prior to use. The hydrochloric acid (3 *M*), ammonium chloride (saturated), sodium bicarbonate (saturated) and sodium chloride (saturated) used in workup procedures refer to aqueous solutions. All reactions were run under dry nitrogen in oven-dried glassware. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech 21521). Preparative separations were performed using flash column chromatography[22] on silica gel (grade 62, 60-200 mesh) mixed with ultraviolet-active phosphor (Sorbent Technologies 5) or thin layer chromatography on 20-cm × 20-cm silica gel GF plates (Analtech 02015); band elution was monitored using a hand held ultraviolet lamp. Hexanes used in chromatography had a boiling range of 65-70 ºC. Melting points of all solids were uncorrected and taken on a MelTemp purchased from Laboratory Devices, Cambridge, MA 02139. Infrared spectra were run as thin films on sodium chloride disks. ^{1}H and ^{13}C Nuclear magnetic resonance spectra were measured in deuteriochloroform at 300 MHz and 75 MHz, respectively, on a Varian 300 MHz unit and were referenced to internal tetramethylsilane; coupling constants (J) are reported in Hertz.

3-Methoxy-2-cyclohexen-1-one (2). The procedure of Sabitha and coworkers[5] was modified. A mixture of 20.0 g of silica gel (Alfa-Aesar, 220-440 mesh) and 3.60 g (9.60 mmoles) of cerium(III) chloride heptahydrate in 60 mL of dry acetonitrile was stirred for

12 hours at 22 ºC. The acetonitirle was removed under vacuum, and a solution of 5.00 g (44.6 mmoles) of **1** in 20 mL of methanol was added. The mixture was stirred for 72 hours at 22 ºC and filtered with ethyl acetate. The filtrate was concentrated under reduced pressure and the crude product was purified by flash chromatography on a 30-cm × 2.5-cm silica gel column eluted with 50% ethyl acetate in hexanes to give 3.70 g (90%) of **2** as a colorless oil. IR: 1671, 1645, 1605 cm^{-1}; ^{1}H NMR: δ 5.37 (s, 1H), 3.70 (s, 3H), 2.42 (t, 2H, J = 6.4), 2.35 (t, 2H, J = 6.9), 1.98 (quintet, 2H, J = 6.6); ^{13}C NMR: δ 199.4, 178.4, 102.1, 55.4, 36.5, 28.6, 21.0.

Methyl (±)-4-Methoxy-2-oxo-3-cyclohexene-1-carboxylate (3). To a stirred solution of 2.88 g (4.00 mL, 28.6 mmoles) of diisopropylamine in 30.0 mL of tetrahydrofuran at -78 ºC, was slowly added 17.0 mL of 1.75 *M n*-butyllithium in hexanes (30.0 mmoles). After 30 minutes, a solution of 3.00 g (23.8 mmoles) of **2** in 20.0 mL of tetrahydrofuran was added dropwise and stirring was continued at -78 ºC for 30 minutes. A solution of 3.40 g (40.0 mmoles) of methyl cyanoformate in 10 mL of tetrahydrofuran was then added dropwise and the reaction was stirred for 1 hour at -78 ºC. The reaction mixture was slowly warmed to 22 ºC, stirred for 30 minutes, cautiously added to saturated ammonium chloride (50 mL) and extracted with ether (3 × 100 mL). The ether extracts were washed with saturated sodium bicarbonate (1 × 100 mL), water (1 × 100 mL) and saturated sodium chloride (1 × 100 mL), then dried (magnesium sulfate) and concentrated under vacuum. The crude product was purified by flash chromatography on a 100-cm × 2.5-cm silica gel column eluted with 30% ethyl acetate in hexanes to give 0.60 g (20%) of **2** and 3.20 g (73%) of **3**. The yield of **3** was 91% based on recovered starting material. IR: 1740, 1656, 1606 cm^{-1}; ^{1}H NMR: δ 5.41 (s, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.35 (dd, 1H,

J = 9.2, 5.3), 2.57 (m, 1H), 2.46 (m, 1H), 2.36 (m, 1H), 2.17 (m, 1H); ^{13}C NMR: δ 193.5, 178.4, 170.6, 101.6, 55.8, 52.2, 52.0, 27.0, 24.0.

Trimethyl (*E*)-3-Methoxy-3-butene-1,1,4-tricarboxylate (**5**): This compound was prepared by the method of Fuchs and McGarrity.[8] To a stirred solution of 6.60 g (50.0 mmol) of dimethyl malonate in 25 mL of dry *N*,*N*-dimethyl formamide was added 2.78 g (50.0 mmol) of sodium methoxide, and the solution was stirred at room temperature for 10 minutes. After 10 minutes, 4.16 g (25.0 mmol) of methyl (*E*)-4-chloro-3-methoxy-2-butenoate (**4**) was added and stirring was continued for 2 hours. The solvent was distilled off at 45 ºC/15 mm, and the residue was mixed with in 25 mL of dichloromethane and 25 mL of water. The aqueous layer was acidified with 15 mL of 30% HCl. The combined aqueous and organic layer was transferred into a separatory funnel, and the dichloromethane layer was separated. The organic layer was further washed with water (1 × 25 mL), saturated sodium chloride (1 × 25 mL), dried over magnesium sulfate and concentrated under vacuum to give a colorless liquid. The liquid was further distilled at 180 ºC /15 mm to give **5** (78%). The spectral data matched with those reported.

Methyl (±)-4-Methoxy-2-oxo-3-cyclopentene-1-carboxylate (6). Exactly 1.4 g (61.3 mmol) of sodium was added into a 100-mL, three necked round-bottomed flask, equipped with an additional funnel, a reflux condenser and a magnetic stir bar, containing 70 mL of dry methanol. The reaction mixture was heated at 60 ºC under nitrogen atmosphere for 30 minutes and 8.0 g (30.0 mmol) of trimethyl (*E*)-methoxy-3-butene-1,1,4-tricarboxylate (**5**) was added dropwise to the reaction mixture under hot conditions. After stirring for 4 hours at reflux, the reaction mixture was cooled to room temperature, and 4.0 mL of acetic acid was added. The methanol layer was concentrated under vacuum.

The crude residue was dissolved in 50 mL of dichloromethane and washed with water (1 × 50 mL), and saturated sodium chloride (1 × 50 mL), then dried (magnesium sulfate) and concentrated under vacuum to give a colorless liquid. The liquid was purified by distilling at 116-117 ºC/5 mm to give a colorless liquid **6** (82 %). The physical and spectral data matched those reported.

Representative Procedure for Alkylation of 3 with 2-Nitrobenzyl Bromide: Methyl (±)-4-Methoxy-1-(2-nitrobenzyl)-2-oxo-3-cyclohexene-1-carboxylate (7): The general procedure of Makosza and Tyrala[10] was used. A 100-mL three-necked round-bottomed flask, equipped with an addition funnel, a reflux condenser and a magnetic stir bar, was charged with a 35 mL of dry acetonitrile, 4.87 g (35.2 mmoles) of anhydrous potassium carbonate and 10 mg of 18-crown-6. Stirring was initiated, and a solution of 2.16 g (11.7 mmoles) of **3** in 10 mL of acetonitrile was added dropwise at 22 ºC. The resulting blue solution was stirred for 10 minutes, and a solution of 2.80 g (13.0 mmoles) of 2-nitrobenzyl bromide[9] in 10 mL of acetonitrile was added dropwise. The reaction was refluxed for 18 hours at which time thin layer chromatography indicated complete consumption of **3**. The crude reaction mixture was cooled, diluted with ether, vacuum filtered and concentrated under vacuum. The resulting dark yellow oil was purified by flash chromatography on a 100-cm × 2.5-cm silica gel column eluted with 20-30% ether in hexanes to give 3.30 g (88%) of **7** as a light yellow oil. IR: 1729, 1660, 1609, 1526, 1384, 1350 cm^{-1}; ^{1}H NMR: δ 7.82 (dd, 1H, J = 8.2, 6.6), 7.47 (td, 1H, J = 7.5, 1.5), 7.36 (td, 1H, J = 7.9, 1.6), 7.35 (d, 1H, J = 7.0), 5.41 (d, 1H, J = 1.5), 3.87 (d, 1H, J = 14.1), 3.68 (s, 3H), 3.67 (s, 3H), 1.77 (m, 1H); ^{13}C NMR: δ 193.9, 177.7, 171.1, 150.9, 133.4, 133.3, 131.5, 127.9, 124.7, 101.9, 57.0, 55.8, 52.7, 34.7, 28.3, 26.3.

Methyl (±)-4-Methoxy-1-(2-Nitrobenzyl)-2-oxo-3-cyclopentene-1-carboxylate (8). This compound (3.00 g, 84%) was obtained as a light yellow oil. IR: 1740, 1699, 1596, 1526, 1359 cm^{-1}; ^{1}H NMR: δ 7.86 (dd, 1H, J = 8.1, 1.5), 7.47 (td, 1H, J = 7.5, 1.5), 7.38 (td, 1H, J = 7.9, 1.6), 7.35 (dd, 1H, J = 7.7, 1.5), 5.26 (t, 1H, J = 1.1), 3.80 (s, 3H), 3.75 (d, 1H, J = 14.6), 3.75 (s, 3H), 3.52 (d, 1H, J = 14.6), 3.17 (dd, 1H, J = 17.9, 1.1), 2.48 (dd, 1H, J = 17.9, 1.1); ^{13}C NMR: δ 200.3, 191.0, 170.8, 150.5, 132.7, 132.2, 131.4, 128.0, 124.7, 102.0, 59.8, 59.1, 53.1, 37.0, 33.7.

Representative Procedure for 1,3-Carbonyl Transposition: Methyl (±)-1-(2-Nitrobenzyl)-4-oxo-2-cyclohexene-1-carboxylate (9). The procedure of Luche was modified.[11] A 250-mL three-necked round-bottomed flask, equipped with a reflux condenser and a magnetic stir bar, was charged with 20 mL of methanol followed by 4.60 g (12.4 mmoles) of cerium(III) chloride heptahydrate. The mixture was stirred for 10 minutes, and a solution of 2.50 g (7.84 mmoles) of **5** in 10 mL of methanol was added dropwise. After 5 minutes, 1.25 g (32.9 mmoles) of sodium borohydride was added in small portions over a period of 20 minutes. [**Caution!** Frothing is a problem if the added portions of sodium borohydride are too large.]. The reaction mixture was stirred for 15 minutes at which time 12 mL of 3 *M* hydrochloric acid was added. After 20 minutes, the mixture was concentrated under vacuum to one-third its volume and extracted with ether (3 × 75 mL). The combined ether extracts were washed with water (3 × 50 mL) and saturated sodium chloride (1 × 50 mL), then dried (magnesium sulfate) and concentrated under vacuum. The resulting dark brown liquid was purified by flash chromatography on a 50-cm × 2.5-cm silica gel column eluted with 20-30% ether in hexanes to give 1.78 g (79%) of **9** as thick yellow oil. IR: 1732, 1685, 1609, 1528, 1351 cm^{-1}; ^{1}H NMR: δ 7.92

(dd, 1H, J = 8.1, 1.5), 7.55 (td, 1H, J = 7.5, 1.3), 7.43 (td, 1H, J = 8.1, 1.5), 7.27 (dd, 1H, J = 7.7, 1.5), 6.82 (d, 1H, J = 10.4), 6.02 (d, 1H, J = 10.4), 3.70 (s, 3H), 3.66 (d, 1H, J = 13.8), 3.50 (d, 1H, J = 13.8), 2.45 (m, 2H), 2.36 (m, 1H), 2.06 (m, 1H); ^{13}C NMR: δ 197.8, 172.8, 50.2, 149.0, 133.0, 132.7, 130.3, 129.7, 128.5, 125.2, 52.8, 48.6, 39.5, 34.4, 30.9.

Methyl (±)-1-(2-Nitrobenzyl)-4-oxo-2-cyclopentene-1-carboxylate (10). This compound (1.65 g, 73%) was obtained as yellow crystals, mp 103-105 ºC. IR: 1712, 1679, 1608, 1526, 1352 cm^{-1}; ^{1}H NMR: δ 7.86 (dd, 1H, J = 8.2, 1.3), 7.52 (td, 1H, J = 7.5, 1.3), 7.47 (d, 1H, J = 5.7), 7.39 (td, 1H, J = 8.1, 1.5), 7.29 (dd, 1H, J = 13.7), 3.17 (d, 1H, J = 13.7), 2.36 (d, 1H, J = 18.7), 2.18 (d, 1H, J = 18.7); ^{13}C NMR: δ 208.7, 167.3 (2C), 150.1, 134.9, 133.4, 132.6, 131.2, 128.1, 125.0, 67.7, 52.3, 42.6, 36.5.

(±)1',4'-Dihydrospiro[2-cyclohexene-1'-3(2'*H*)-quinoline]-2',4-dione (11). The procedure of Bunce and co-workers was used.[1] A 50-mL three necked round-bottomed flask, equipped with a reflux condenser and a magnetic stir bar, was charged with a mixture of 500 mg (1.73 mmoles) of **9**, 7.25 mL of acetic acid and 773 mg (13.8 mmoles, 8.0 eq) of iron powder (>100 mesh). The reaction mixture was heated with stirring at 115 ºC (oil bath) until thin layer chromatography indicated complete consumption of the starting material (ca 30 minutes). The reaction mixture was cooled, diluted with 50 mL of water and extracted with ether (3 × 50 mL). The combined ether layers were washed with water (1 × 50 mL), saturated sodium bicarbonate (3 × 50 mL), saturated sodium chloride (1 × 50 mL), then dried (magnesium sulfate) and concentrated under vacuum to give 373 mg (95%) of **11** as a pale white solid, mp 212-215 ºC. IR: 3195, 1667 cm^{-1}; ^{1}H NMR: δ 8.69 (br, s, 1H), 7.21 (complex, 2H), 7.05 (td, 1H, J = 7.5, 1.3), 6.82 (obscured,

1H), 6.81 (d, 1H, J = 10.3), 6.14 (d, 1H, J = 10.3), 3.13 (d, 1H, J = 15.9), 2.99 (d, 1H, J = 15.9), 2.73 (ddd, 1H, J = 17.1, 8.4, 4.9), 2.49 (ddd, 1H, J = 17.1, 8.4, 4.9), 2.34 (ddd, 1H, J = 13.4, 8.4, 4.9), 1.98 (ddd, 1H, J = 13.4, 8.4, 4.9); ^{13}C NMR: δ 198.2, 172.1, 148.9, 136.1, 130.7, 128.6, 128.2, 123.7, 121.1, 115.1, 42.6, 36.6, 33.6, 29.4.

(±)-(3aR*,9aR*)-9a-Hydroxymethyl-1,3,3a,4,9,9a-hexahydro-2*H*-cyclopenta[*b*]-quinoline-2-one (12). The procedure used to prepare **11** was followed using 200 mg (0.73 mmoles) of **10** and 325 mg (5.84 mmoles) of iron powder in 12 mL of acetic acid. After 30 minutes at 115 ºC, workup and preparative thin layer chromatography using 40% ether in hexanes gave 120 mg (76%) of **12** as a light yellow oil. IR: 3395, 1733 cm^{-1}; ^{1}H NMR: δ 7.01 (td, 1H, J = 7.3, 1.2), 6.98 (dd, 1H, J = 7.5, 0.8), 6.64 (td, 1H, J = 7.3, 1.2), 6.48 (dd, 1H, J = 7.9, 0.8), 3.92 (br s, 1H), 3.94 (t, 1H, J = 6.4), 3.59 (d, 1H, J = 10.9), 3.55 (d, 1H, J = 16.7), 2.37 (d, 1H, J = 18.7), 2.17 (dd, 1H, J = 18.7, 1.6), 2.20 (m, 1H); ^{13}C NMR: δ 216.6, 141.7, 129.6, 127.4, 117.5, 117.4, 113.4, 66.6, 52.0, 46.4, 45.9, 41.3, 31.3. This reaction also gave 26 mg (14%) of compound **13**.

(±)-(3aR*,9aR*)-9a-Acetoxymethyl-1,3,3a,4,9,9a-hexahydro-2*H*-cyclopenta[b]-quinolin-2-one (13). The procedure used to prepare **9** was followed using 500 mg (1.82 mmoles) of **10** and 812 mg (14.6 mmoles) of iron powder in 30 mL of acetic acid. After 4 hours at 115 ^{o}C, workup and flash chromatography on a 25-cm × 2-cm silica gel column eluted with 15% ether in hexanes gave 400 mg (85%) of **14** as a tan oil. IR: 3394, 1740 cm^{-1}; ^{1}H NMR: δ 7.05 (m, 2H), 6.66 (td, 1H, J = 7.5, 1.3), 6.50 (dd, 1H, J = 7.8, 0.8), 4.10 (br s, 1H), 4.08 (d, 1H, J = 11.4), 4.02 (d, 1H, J = 11.4), 3.92 (t, 1H, J = 6.4), 2.80 (d, 1H, J = 16.5), 2.70 (d, 1H, J = 16.5), 2.70 (m, 1H), 2.27 (m, 2H), 2.21 (dd,

1H, J = 5.4, 1.1), 2.06 (s, 3H); ^{13}C NMR: δ 214.9, 170.8, 141.4, 129.7, 127.6, 117.7, 116.8, 113.5, 67.6, 52.4, 46.3, 46.0, 39.6, 31.5, 20.8.

(±)-(3aR*,9aR*)-9a-Acetoxymethyl-4-benzoyl-1,3,3a,4,9,9a-hexahydro-2*H*-cyclopenta[*b*]quinolin-2-one (14). To a stirred solution of 200 mg (0,77 mmoles) of **13** and 85.6 mg (0.85 mmoles) of triethylamine in 20 mL of dichloromethane was slowly added a solution of 120 mg (0.85 mmoles) of benzoyl chloride in 1 mL of dichloromethane over a period of 5 minutes. The reaction mixture was stirred at 22 ºC for 2 hours at which time thin layer chromatography confirmed the absence of starting material. The reaction mixture was poured into cold water, and the dichloromethane layer was separated. The organic phase was washed with cold water (2 × 20 mL), dried (magnesium sulfate) and concentrated under vacuum. The resulting residue was passed through a small plug of silica gel with 30% ether in hexanes to give 260 mg (93%) of **14** as a light yellow solid, mp 108-110 ºC. IR: 1744, 1643 cm^{-1}; ^{1}H NMR: δ 7.38-7.21 (complex, 6H), 7.07 (td, 1H, J = 7.5, 1.1), 6.93 (t, 1H, J = 7.5), 6.49 (d, 1H, J = 7.9), 5.19 (dd, 1H, J = 9.0, 4.4), 4.28 (d, 1H, J = 10.9), 4.20 (d, 1H, J = 10.9), 3.04 (ddd, 1H, J = 19.4, 9.0, 1.8), 2.94 (d, 1H, J = 14.1), 2.73 (d, 1H, J = 14.1), 2.29 (ddd, 1H, J = 19.4, 4.4, 1.8), 2.20 (dd, 1H, J = 18.5, 1.8), 2.10 (s, 3H), 2.06 (dd, 1H, J = 18.5, 1.8); ^{13}C NMR: δ 214.1, 170.7, 169.8, 138.1, 134.8, 130.8, 130.6, 129.1, 129.0, 128.1, 127.4, 126.9, 126.1, 171.1, 57.4, 48.0, 45.6, 45.2, 34.6, 20.7.

X-Ray Crystallographic Analysis of 14. Flat, elongated rods of **14** were obtained by slow diffusion of pentane into an ether solution of the compound. A sample measuring 0.4 × 0.4 × 0.1 mm, which was cut from a longer rod, was immersed in polyisobutylene and placed in a nylon loop under a nitrogen cold stream. The X-ray intensity data were

measured at 115(2) K on a Bruker SMART Apex II diffractometer. Graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å, fine-focus sealed tube) was used with the CCD detector placed 6.0 cm from the sample. Data frames were collected in a series of φ and ω scans with 0.5 º scan widths and 30 second exposure times. Data integration employed the Bruker SAINT software package.[23] Data were corrected for absorption effects using the multi-scan technique (SADABS).[24] The structure was solved by direct methods and refined by full-matrix least-squares of F^2 using the Bruker SHELXTL software suite.[25] Non-hydrogen atoms were assigned anisotropic temperature factors. Hydrogen atoms were placed in calculated positions based on the geometry at carbon (riding model). Refined formula: $C_{22}H_{21}NO_4$, M = 363.40, monoclinic, space group $P2_1/n$, a = 11.1983(2) Å, b = 8.18310(10) Å, c = 19.7453(3) Å, β = 101.7010(10)º, U = 1771.80(5) Å^3, Z = 4, D_c = 1.362 g cm^{-1}, μ = 0.094 mm^{-1}, T = 115(2) K, $2\theta_{max}$ = 50.6 º, completeness to $2\theta_{max}$ = 100.0%, 13372 total reflections, 3227 independent (R_{int} = 0.0248), 2619 observed [I>2σ(I)]. Final R1 [I>2σ(I)] = 0.0336, wR2 (all data) = 0.0833, largest difference peak and hole 0.225 and -0.194 eÅ^{-3}. CCDC 692896 contains the supplementary crystallographic data for compound **14.** These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Methyl (±)-1-Benzyl-4-oxo- 2-cyclohexene-1-carboxylate (15). The procedure used to prepare **7** was followed using 1.08 g (5.85 mmoles) of **3** and 1.11 g (6.5 mmoles) of benzyl bromide. Following flash chromatography, 1.52 g (95%) of methyl (±)-1-benzyl-4-methoxy-2-oxo-3-cyclohexene-1-carboxylate was isolated as a white solid, mp 68-70 ºC. IR: 1729, 1660, 1610 cm^{-1}; ^{1}H NMR: δ 7.28-7.17 (complex, 3H), 7.14 (m, 2H), 5.41

(d, 1H, J = 1.2), 3.71 (s, 3H), 3.66 (s, 3H), 3.32 (d, 1H, J = 13.7), 3.23 (d, 1H, J = 13.7), 2.63 (m, 1H), 2.29 (m, 2H), 1.80 (m, 1H); ^{13}C NMR: δ 194.4, 177.8, 171.5, 136.5, 130.4, 128.1, 126.7, 101.9, 56.9, 55.7, 52.4, 40.0, 28.1, 26.3.

Reduction and carbonyl transposition was carried out as described for the preparation of **9** was followed using 1.52 g (5.56 mmoles) of the benzylated product from above. Following flash chromatography, 1.22 g (90%) of **15** was isolated as a colorless oil. IR: 1732, 1681 cm^{-1}; ^{1}H NMR: δ 7.32-7.22 (complex, 3H), 7.09 (dd, 1H, J = 7.8, 1.8), 6.95 (d, 1H, J = 10.3), 6.02 (d, 1H, J = 10.3), 3.69 (s, 3H), 3.08 (s, 2H), 2.47 (m, 2H), 2.40 (m, 1H), 2.07 (m, 1H); ^{13}C NMR: δ 198.3, 173.2, 150.3, 135.4, 129.8, 129.2, 128.4, 127.2, 52.3, 49.0, 44.5, 34.5, 30.5.

Methyl (±)-1-Benzyl-4-oxo-2-cyclopentene-1-carboxylate (16). The procedure used to prepare **7** was followed using 0.99 g (5.85 mmoles) of **6** and 1.11 g (6.50 mmoles of benzyl bromide. Following flash chromatography, 1.46 g (96%) of methyl (±)-1-benzyl-4-methoxy-2-oxo-3-cyclopentene-1-carboxylate was isolated as white solid, mp 96-98 $^{\circ}$C. IR: 1741, 1699, 1597 cm^{-1}; ^{1}H NMR: δ 7.27-7.17 (complex, 3H), 7.13 (m, 2H), 5.18 (s, 1H), 3.76 (2s, 6H), 3.30 (d, 1H, J = 14.1), 3.25 (d, 1H, J = 14.1), 3.11 (dd, 1H, J = 17.7, 1.0), 2.61 (dd, 1H, J = 17.7, 1.0); ^{13}C NMR: δ 200.6, 190.3, 171.0, 136.2. 130.0, 128.2, 126.9, 102.3, 60.1, 59.0, 52.9, 39.1, 36.5.

Reduction and carbonyl transposition was carried out as described for the preparation of **9** was followed using 1.46 g (5.62 mmoles) of the benzylated product from above. Following flash chromatography, 1.16 g (90%) of **16** was isolated as colorless oil. IR: 1710, 1677 cm^{-1}; ^{1}H NMR: δ 7.54 (d, 1H, J = 5.7), 7.32-7.20 (complex, 3H), 7.13 (m, 2H), 6.14 (d, 1H, J = 5.7), 3.62 (s, 3H), 2.97 (d, 1H, J = 13.3), 2.84 (d, 1H, J = 13.3),

2.29 (s, 2H); ^{13}C NMR: δ 209.0, 168.2, (2C)., 136.4, 130.2, 128.3, 126.8, 67.3, 51.7, 43.0, 41.5.

Reduction of 15 with Iron and Acetic Acid. Methyl 1-Benzyl-4-oxocylohexane-1-carboxylate (17). The procedure used to prepare **11** was followed using 500 mg (2.05 mmoles) of **15** and 915 mg (16.4 mmoles) of iron powder in 35 mL of acetic acid. After 24 hours, workup gave 450 mg of an inseparable 33:67 mixture of **15:17**. The spectral data for **17** were: IR: 1727, 1702 cm^{-1}; ^{1}H NMR: δ 7.36-7.27 (complex, 3H), 7.12 (m, 2H), 3.77 (s, 3H), 2.96 (s, 2H), 2.56-2.33 (complex, 6H), 1.78 (m, 2H); ^{13}C NMR: δ 210.4, 174.8, 129.4, 128.1, 127.9, 126.6, 51.6, 47.5, 45.6, 38.1, 33.1. The use of more iron and longer reation times failed to significantly alter this product ratio.

Reduction of 16 with Iron and Acetic Acid: (±)-4-Benzyl-4-hydroxymethyl-2-cyclopenten-1-one (20). The procedure used to prepare **11** was followed using 500 mg (2.17 mmoles) of **16** 969 mg (17.3 mmoles) of iron powder in 35 mL of acetic acid. After 15 minutes, workup and preparative thin layer chromatography gave 320 mg (72%) of **20** as a colorless oil. IR: 3416, 1711, 1677 cm^{-1}; ^{1}H NMR: δ 7.53 (d, 1H, J = 5.7), 7.30-7.21 (d, 1H, J = 10.7), 7.10 (d, 2H, J = 6.8), 6.11 (d, 1H, J = 5.7), 3.60 (d, 1H, J = 10.7), 3.58 (d, 1H, J = 10.7), 2.96 (d, 1H, J = 13.5), 2.81 (d, 1H, J = 13.5), 2.62 (br s, 1H), 2.29 (d, 1H, J = 18.6), 2.26 (d, 1H, J = 18.6); ^{13}C NMR: δ 209.5, 168.7, 136.3, 134.4, 130.1, 128.2, 126.7, 67.0, 51.8, 42.9, 41.3.

Upon prolonged heating for 2 hours, the reaction gave 450 mg of an inseparable 67:33 mixture of **20:22** as the acetates. The spectral data for **20** (acetate) were: IR: 1743, 1715 cm^{-1}. ^{1}H NMR: δ 7.46 (d, 1H, J = 5.7), 7.33-7.17 (complex, 3H), 7.09 (m, 2H), 6.13 (d, 1H, J = 5.7), 4.17 (d, 1H, J = 10.9), 4.00 (d, 1H, J = 10.9), 2.96 (d, 1H, J = 13.7),

2.84 (d, 1H, J = 13.6), 2.31 (s, 2H), 2.06 (s, 3H); ^{13}C NMR: δ 207.6, 170.6, 166.7, 135.5, 134.6, 130.0, 128.4, 127.0, 67.7, 49.4, 43.0, 42.0, 20.7; The spectra data for **22** (acetate) were IR: 1743 cm^{-1}; ^{1}H NMR: δ 7.34-7.18 (complex, 3H), 7.10 (m, 2H), 3.98 (d, 1H, J = 11.1), 3.89 (d, 1H, J = 11.1), 2.79 (s, 2H), 2.39-2.21 (complex, 2H), 2.33 (s, 2H), 2.10 (s, 3H), 1.93 (m, 2H); ^{13}C NMR: δ 217.5, 170.7, 136.6, 130.0, 128.3, 126.7, 68.4, 47.0, 43.6, 42.3, 36.3, 30.2, 20.8.

References and Notes

1. Bunce, R. A.; Randall, M. H.; Applegate, K. G. *Org. Prep. Proced. Int.* **2002**, *34*, 493.
2. Augustine, R. L.; Gustavsen, A. J.; Wanat, S. F.; Pattison, I. C.; Houghton, K. S.; Koletar, G. *J. Org. Chem.* **1973**, *38*, 3004.
3. Bunce, R. A.; Herron, D. M.; Ackerman, M. L. *J. Org. Chem.* **2000**, *65*, 2847.
4. Bunce, R. A.; Nammalwar, B. *J. Heterocyclic Chem.* **2009**, *46*, 172.
5. Sabitha, G.; Reddy, M.; Sudhakar, K.; Yadav, J. S. *Lett, in Org. Chem.* **2005**, *2*, 763.
6. Lee, R. A.; McAndrews, C.; Patel, K. M.; Reusch, W. *Tetrahedron Lett.* **1973**, 965.
7. [a] Crabtree, S. R.; Mander, L. N.;Sethi, S. P. *Organic Syntheses*; Wiley: New York, NY, 1988; Coll. Vol. 9. p.619. [b] Mandler, L. N.; Sethi, S. P, *Tetrahedron Lett.* **1983**, *24*, 5425.
8. Fuchs, R.; McGarrity, J. F. *Synthesis* **1992**, 373.
9. Collins, D. J.; Drygala, P. F.; Swan, J. M. *Aust. J. Chem.* **1983**, *36*, 209.
10. Makosza, M.; Tyrala, A. *Synth. Commun.* **1986**, *16*, 419.

11. Luche, J,-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

12. Eliel, E.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds;* Wiley-Interscience, New York, 1994; pp 774-776.

13. Oare, D. A.; Heathcock. C. A. in Eliel, E.; Wilen, S. H. (Eds.) *Topics in Stereochemistry;* Wiley-Interscience: New York, 1989, Vol. 19, p 227. See, particular, pp 372-374.

14. Hudlicky, M. *Reduction in Organic Chemistry;* 2nd Ed., American Chemical Society: Washington, D. C.; 1996; ACS Monograph 188; p 213.

15. Iron in acetic acid spiked with nickel chloride hexahydrate has been used to reduce aldehydes, but not esters, see Clarket, H. T.; Dreger, E. E. *Organic Syntheses;* J. Wiley and Sons: New York, 1932; Coll. Vol. I, pp 304-306. A control experiment run by treating methyl 1-methyl-1-cyclopentanecarboxylate (prepared according to Fadel, A.; Salaun, J. *Tetrahedron* **1985**, *41*, 1267) with iron in refluxing acetic acid for 60 minutes resulted in >96% recovery of the starting material.

16. [a] House, H. O.; Huber, L. E.; Umen, M. J. *J. Am. Chem. Soc.* **1972**, *94*, 8471. [b] Mann, C. K.; Barnes, K. K. *Electrochemical Reactions in Nonaqueous Systems*; Marcel Dekker: New York, 1970; pp 179-189.

17. [a] Wilberg, K. B.; Kass, S. R. *J. Am. Chem. Soc.* **1985**, *107*, 988. [b] Dewar, M. J. S.; Healy, E. F.; Ruiz, J. M. *Chem. Commun.* **1987**, 943. [c] Koch, W.; Liu, B.; von Rague Schleyer, P. *J. Am. Chem. Soc.*, **1989**, *111*, 3479.

18. [a] Beadle, C. D.; Boot, J.; Camp, N. P.; Dezutter, N.; Findaly, J.; Hayhurst, L.; Masters, J. J; Penariol, R.; Walter, M. W. *Bioorg. Med. Chem. Lett.* **2005**, *15*,

4432. [b] Cho, S. S. Y.; Gregory, T. F.; Guzzo, P. R.; Howard, H. R., Jr.; Nikkam, S. S.; Surman, M. D.; Walters, M. A. International Patent WO 2005066165, **2005**, 144 pp; Chem Abstr. **2005**, *143*, 153404. [c] Andreana, T. L.; Cho, S. S. Y.; Graham, J. M.; Gregory, T. F.; Howard, H. R., Jr.; Kornberg, B. E.; Nikam, S. S.; Pflum, D. A. International Patent WO 2004026864, **2004**, 158 pp; *Chem. Abstr.* **2004**, *140*, 287412.

19. Conley, R. T.; Frainier, L. J. *J. Org. Chem.* **1962**, *27*, 3844.

20. Bunce, R. A.; Herron, D. M.; Lewis, J. R.; Kotturi, S. V.; Holt, E. M. *J. Heterocyclic Chem.* **2003**, *40*, 101.

21. Ramamoorthy, P. S.; McDevitt, R. E. International Patent WO200309125, **2003**, 39 pp; *Chem. Abstr.* **2003**, *139*, 364966.

22. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

23. SAINT, Version 7.23 A, Bruker AXS Madison, WI, USA, **2006**.

24. Sheldrick, G. M. *SADABS*, Version 2.10, Bruker AXS Inc., Madison, WI, USA, **2000**.

25. Sheldrick, G. M. *SHELXTL*, Version 6.14, Bruker AXS Inc., Madison, WI, USA, **2000**.

CHAPTER IV

SYNTHESIS OF (±)-2-ARYL- AND 2-ALKYL-SUBSTITUTED 2,3-DIHYDRO-4(1*H*)-QUINAZOLINONES FROM 2-NITRO- AND 2-AMINOBENZAMIDE

Introduction

Dihydroquinazolinones are an important class of heterocycles that have expressed a broad range of biological activities.[1] This ring system is found as the core structure in compounds investigated as anticancer,[2] anti-inflammatory,[3] anticonvulsant,[4] anti-bacterial,[5] antifungal,[6] anti-osteoporosis[7] and diuretic[8] drug candidates. Additionally, several dihydroquinazolinone derivatives have been found to be potent plant growth regulators and herbicidal agents.[9]

We have previously utilized tandem reactions initiated by dissolving metal reduction of nitroarenes to prepare indole-3-carboxylic esters[10] and benzo-fused oxepinones, diazepinones,[11] and carbazoles[12] as well as various linear-fused ring systems.[13] In the current project, we have employed a tandem reduction-condensative cyclization strategy involving 2-nitrobenzamide (**1**) and an aldehyde or ketone **2** for the formation of 2-aryl- or 2-alkyldihydroquinazolinones **3**. This method has been further extended to include sequences involving additional reactions following the heterocyclic ring closure. Finally, we have also found that heating 2-aminobenzamide (**4**) with aldehydes and ketones in glacial acetic acid provides the target heterocycles cleanly and

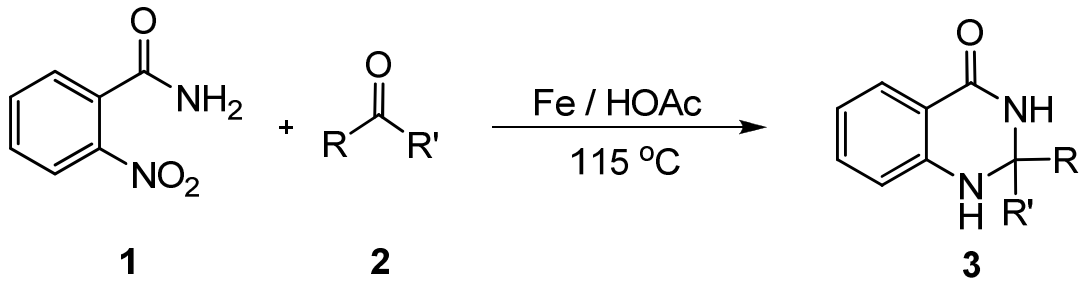
in high yields.

Earlier methods reported to prepare dihydroquinazolinones utilized **1** with aldehydes and ketones in the presence of titanium(IV) chloride and zinc,[14] samarium iodide[15] and samarium in the presence of iodine.[16] The target compounds have also been prepared by condensation of **4** with aldehydes or ketones in the presence of catalysts such as gallium(III) triflate,[17] scandium(III) triflate[18] or by heating in solvents such as trifluoroethanol.[19] Most of these reagents and catalysts are expensive and require dry box conditions; additionally, the reaction workup procedures are often tedious. Alternative methods are available using isatoic anhydride with amines and carbonyl compounds in the presence of montmorillonite K-10,[20] *p*-toluenesulfonic acid[21] or Amberlyst-15 under microwave conditions.[22] The yields reported for these methods are slightly lower and have been evaluated on only a limited selection of aldehydes and ketones. To overcome these shortcomings, we report a method which uses inexpensive, readily available reagents and mild conditions that hydroquinazolinones from a wide variety of aldehydes and ketones. The only general procedure that compares well with our approach involves the cyclization of **4** with aldehydes and ketones promoted by catalytic ammonium chloride in ethanol.[23]

Results and Discussion

The results of our tandem synthesis of dihydroquinazolinones from reductive cyclization of **1** with aldehydes and ketones are summarized in Figure 4.1. The reaction is performed by reacting a 1:1 mole ratio of 2-nitrobenzamide (**1**) and the carbonyl compound **2** with 5 equivalents of iron powder in acetic acid at 115 ^{o}C for 30 minutes.

After quenching with water, extractive workup and recrystallization, dihydroquinazolinones **3** are isolated in nearly pure form. Only rarely is chromatography



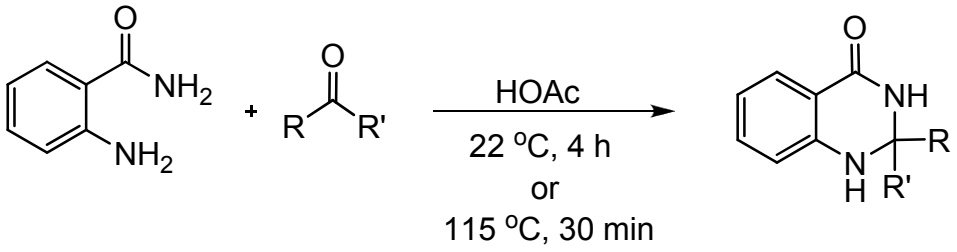
1 **2** **3**

R	R'	Yield of **3** (%)
Aldehydes		
a. C_6H_5-	H	90
b. 4-$CH_3OC_6H_4$-	H	90
c. 4-CF_3-C_6H_4-	H	89
d. 2-ClC_6H_4	H	93
e. $CH_3CH_2CH_2CH_2$-	H	94
f. (*E*)-C_6H_4-CH=CH-	H	89
g. $CH_3CH_2O_2C(CH_2)_3$-	H	78
h. $CH_3CH_2O_2C(CH_2)_4$-	H	73
Ketones		
i. CH_3-	CH_3-	95
j. $CH_3CH_2CH_2$-	CH_3-	90
k. C_6H_5-	CH_3-	86
l. $C_6H_5CH_2$-	CH_3-	91
m.	-$(CH_2)_4$-	93
n.	-$(CH_2)_5$-	92

Figure 4.1. Cyclization of aldehydes and ketones with **1**

required. Finally, the target heterocycles can also be prepared in comparable yields by reacting 2-aminobenzamide (**4**) with an aldehyde or ketone (1:1) in acetic acid for 30 minutes at 115 ^{o}C or 4 hours at room temperature (see Figure 4.2).

In the current project, we have prepared 2-aryl and 2 alkyl-substituted dihydroquinazolinone derivatives from both 2-nitrobenzamide (**1**) and 2-aminobenzamide



4 **2** **3**

Carbonyl substrates	Yield of **3** (%)
Aldehydes	
2a	90
2b	90
2d	92
2g	76
Ketones	
2i	92
2j	90
2l	88
2n	90

Figure 4.2. Cyclization of aldehydes and ketones with **4**

(**4**) in acetic acid. Starting from **1** under dissolving metal conditions, the process is initiated by reduction of the nitro group to give **4** (Figure 4.3). The aniline amino group then reacts with the aldehyde or ketone **2** to form an iminium intermediate **5**, which adds

the amide nitrogen to close the heterocyclic portion of the structure. Reactions starting with **4** do not require added iron and proceed rapidly at reflux or more slowly at room temperature (see Figure 4.2).

We have also used modified carbonyl substrates to generate more complex structures such as **6-9** (see Figure 4.4). This involved reacting **1** with aldehydes and ketones bearing reactive functionality γ to the carbonyl function. Cyclization of these substrates would yield dihydroquinazolinones with functionality δ to the aniline nitrogen

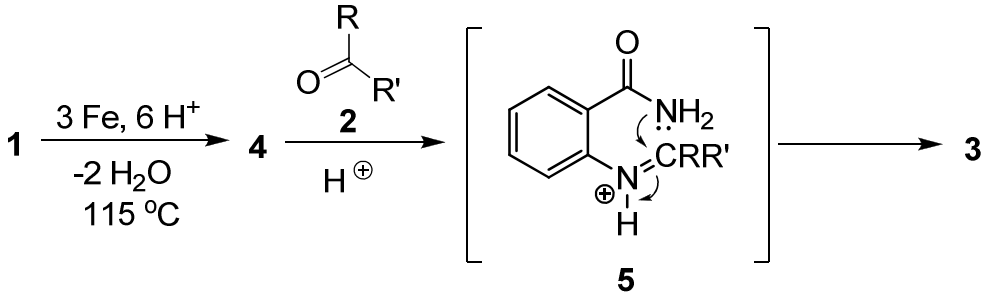
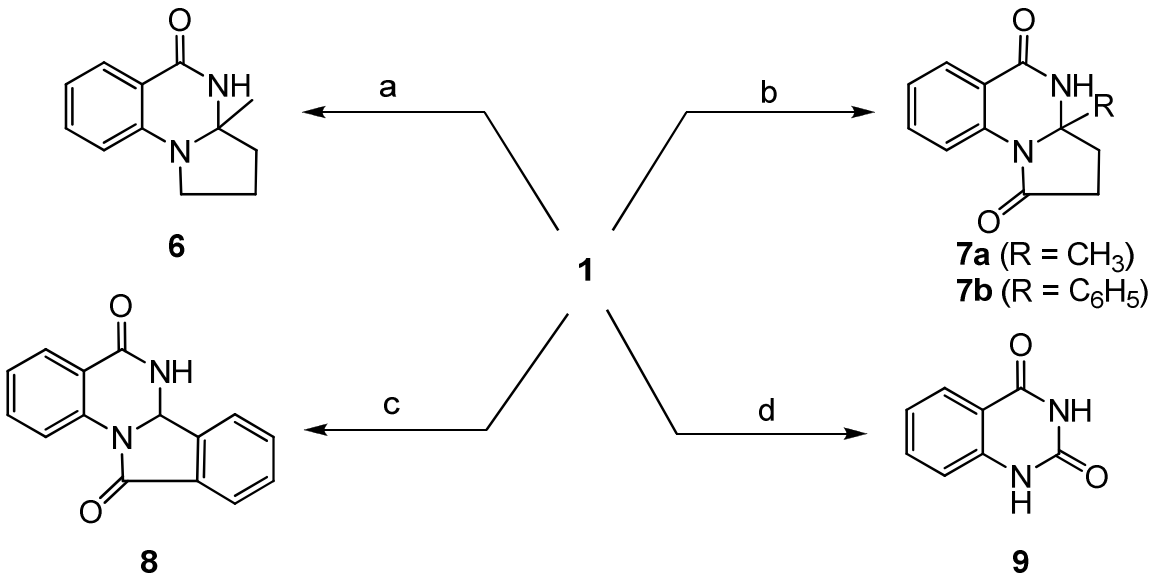


Figure 4.3. Mechanism for dihydroquinazolinone formation

such that a subsequent reaction would close to a five-membered ring. This was the only ring size that successfully formed in these extended tandem sequences. For example, the reaction of **1** with 5-chloro-2-pentanone (**10**) under dissolving metal conditions furnished tetrahydropyrrolo[1,2-*a*]quinazolinone (**6**) in 73% yield. This reaction involved reduction of the nitro function and ring closure to generate the dihydroquinazolinone ring with a chloride leaving group δ to the aniline nitrogen. Further reaction then occurred by S_N2 displacement of chloride by the more reactive aniline nitrogen[24] to deliver the final product. The extremely mild nature of the reduction conditions was evidenced by the



[a] Key: Fe, CH_3CO_2H in the presence of (a) 5-chloro-2-pentanone (**10**); (b) **7a**: methyl levulinate (**11**); **7b**: methyl 3-benzoyl propionate (**12**); (c) methyl 2-formyl benzoate (**13**); (d) diphosgene (**14**)

Figure 4.4. Preparation of more complex systems from **1**

fact that no hydrogenolysis of the aliphatic chloride was observed.[25] Another extended sequence resulted when **1** was reacted with γ-keto esters such as methyl levulinate (**11**) and methyl 3-benzoylpropionate (**12**). These reactions proceeded to give reduction, condensative ring closure and cyclization by addition-elimination of the aniline nitrogen with the δ ester groups to give tetrahydropyrrolo[1,2-*a*]quinazolin-1,5-diones **7a** and **7b** in 74% and 77% yields, respectively.[26] Oxoesters with greater separation between the carbonyl moieties (e.g. **2g** and **2h**) failed to undergo the final cyclization even after extended refluxing for 24 hours. In a related transformation, **1** was reduced in the presence of methyl 2-formylbenzoate (**13**)[27] to produce 6,6a-dihydroisoindolo[2,1-

a]quinazolin-5,11-dione (**8**) in 72% yield. Finally, **1** was also reacted with diphosgene (**14**) to afford 2,4(1*H*,3*H*)-quinazolinedione (**9**) in 86% yield.

One extended reaction was investigated using **4** as the starting material (see Figure 4.4). Treatment of **4** with **11** in acetic acid with no iron at room temperature for 24 h gave (±)-methyl 3-(2-methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)propanoate **(15**) in 70% yield. Further heating of **15** in acetic acid at 115 ^{o}C for 8 hours then effected quantitative ring closure to **7a**. This two-step synthesis was simplified to a one-step process by running the reaction at 115 ^{o}C.

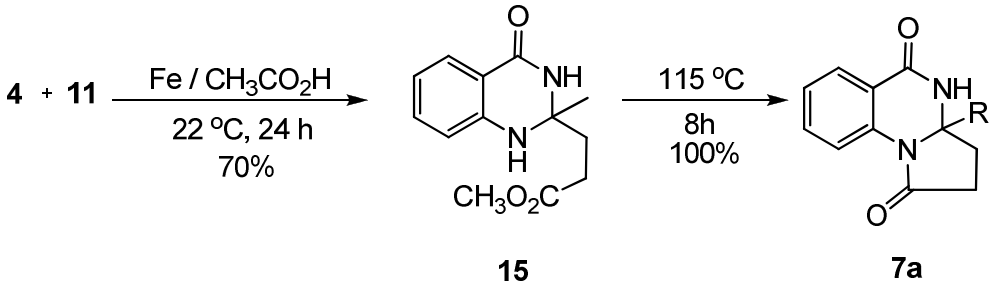


Figure 4.5. Preparation of complex system from **4**

Conclusion

We have developed an efficient one-pot syntheses for the preparation of (±)-2-aryl- and 2-alkyl-substituted 2,3-dihydro-4(1*H*)-quinazolinones from 2-nitro- and 2-aminobenzamide. The procedures utilize inexpensive reagents, mild conditions and simple laboratory procedures. The method furnishes high yields of the title compounds from a wide range of aldehydes and ketones without the need for extensive purification. This method can be extended to the synthesis of more complex structures by positioning additional functionality γ to the carbonyl of the aldehyde or ketone (δ to the aniline

nitrogen in the initially-formed dihydroquinazolinone), which allows subsequent reactions to occur.

Experimental Section

All reactions were run under dry nitrogen in oven-dried glassware. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech 21521). Commercial reagents and solvents were used as received. Preparative separations were performed using flash column chromatography[28] on silica gel (Grade 62, 60-200 mesh) mixed with ultraviolet-active phosphor (Sorbent Technologies UV-5); band elution was monitored using a hand held UV lamp. Melting points were taken on a MelTemp purchased from Laboratory Devices, Cambridge, MA 02139 and were uncorrected. Infrared spectra were taken on a Varian 800 FT-IR (Scimitar series) run as thin films on sodium chloride disks. Unless otherwise indicated, ^{1}H and ^{13}C NMR spectra were measured in dimethyl sulfoxide-d_6 using a broadband Gemini 2000 High-Resolution NMR spectrometer operating at 300 MHz and 75 MHz respectively. All the NMR signals were referenced to internal tetramethylsilane; coupling constants (J) are reported in Hz. Low-resolution mass spectra (electron impact/direct probe) were run at 70 eV or 30 eV as indicated. Elemental analysis were performed by Altlantic Microlab Inc., Norcross, GA.

Representative Procedure from 2-Nitrobenzamide: (±)-2-Phenyl-2,3-dihydro-4(1*H*)-quinazolinone (3a). A 100-mL three-necked round-bottomed flask, equipped with magnetic stirring and a reflux condenser, was charged with 7 mL of acetic acid, 498 mg (3.00 mmoles) of **1** and 318 mg (3.00 mmoles) of benzaldehyde (**2a**). The flask was placed in an oil bath preheated to 115 ^{o}C, 840 mg (5.0 eq, 15.0 mmoles) of iron powder

(>100 mesh) was added, and the reaction was refluxed for 30 minutes. The reaction was cooled and poured into saturated aqueous sodium chloride and extracted with ether (1 × 50 mL) and ethyl acetate (1 × 50 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (two times) and saturated aqueous sodium chloride (one time), then dried (magnesium sulfate) and concentrated under vacuum to give 610 mg (90%) of **3a** as a white solid, mp 220-221 ^{o}C (lit[23] mp 218-220 ^{o}C). IR: 3302, 3185, 1652, 1611 cm^{-1}; ^{1}H NMR: δ 8.29 (br s, 1H), 7.61 (d, 1H, J = 7.8), 7.49 (d, 2H, J = 7.0), 7.42-7.32 (complex, 3H), 7.24 (td, 1H, J = 7.6, 1.6), 7.11 (br s, 1H), 6.75 (d, 1H, J = 8.0), 6.67 (t, 1H, J = 7.6), 5.75 (s, 1H); ^{13}C NMR: δ 163.6, 147.9, 141.6, 133.3, 128.4, 128.3, 127.3, 126.8, 117.1, 114.9, 114.4, 66.5; ms (30 eV): *m/z* 224 (M^{+}).

(±)-2-(4-Methoxyphenyl)-2,3-dihydro-4(1*H*)-quinazolinone (3b). This compound (686 mg, 90%) was prepared from 498 mg (3.00 mmoles) of **1** and 408 mg (3.00 mmoles) of 4-methoxybenzaldehyde (**2b**), and isolated as a white solid, mp 192-193 ^{o}C (lit[23] mp 193-195 ^{o}C). IR: 3300, 3188, 1655, 1609 cm^{-1}; ^{1}H NMR: δ 8.17 (br s, 1H), 7.61 (d, 1H, J = 6.6), 7.41 (d, 2H, J = 8.6), 7.23 (td, 1H, J = 7.6, 1.4), 6.99 (br s, 1H), 6.94 (d, 2H, J = 8.6), 6.72 (d, 1H, J = 8.2), 6.67 (t, 1H, J = 7.7), 5.70 (s, 1H), 3.74 (s, 3H); ^{13}C NMR: δ 163.4, 159.4, 148.0, 133.4, 133.2, 128.2, 127.3, 117.0, 115.0, 114.4, 113.6, 66.3, 55.1; ms (30 eV): *m/z* 254 (M^{+}).

(±)-2-[4-(Trifluoromethyl)phenyl]-2,3-dihydro-4(1*H*)-quinazolinone (3c). This compound (779 mg, 89%) was prepared from 498 mg (3.00 mmoles) of **1** and 522 mg (3.00 mmoles) of 2-(trifluoromethyl)benzaldehyde (**2c**), and isolated as a white solid, mp 194-196 ^{o}C. IR: 3285, 3187, 1648, 1618 cm^{-1}; ^{1}H NMR: δ 8.46 (d, 1H, J = 1.3), 7.78 (d, 2H, J = 8.2), 7.72 (d, 2H, J = 8.2), 7.63 (dd, 1H, J = 7.7, 1.1), 7.26 (overlapping td, 1H, J

= 7.1, 1.1 and br s, 1H), 6.77 (d, 1 H, J = 7.7), 6.69 (t, 1H, J = 7.7), 5.88 (d, 1H, J = 1.3); ^{13}C NMR: δ 163.4, 147.5, 146.4, 133.5, 129.0, 128.9 (q, J = 31.7), 127.7 (2C), 127.4, 125.3 (q, J = 3.7), 124.2 (q, J = 271.6), 117.4, 114.9, 114.5, 65.7; ms (30 eV): *m/z* 292 (M^+). *Anal*. Calcd. for $C_{15}H_{11}F_3N_2O$: C, 61.64; H, 3.79; N, 9.59. Found: C, 61.58; H, 3.81; N, 9.56.

(±)-2-(2-Chlorophenyl)-2,3-dihydro-4(1*H*)-quinazolinone (3d). This compound (721 mg, 93%) was prepared from 498 mg (3.00 mmoles) of **1** and 421 mg (3.00 mmoles) of 2-chlorobenzaldehyde (**2d**), and isolated as an off-white solid, mp 205-206 ^{o}C. IR: 3286, 3192, 1645, 1614 cm^{-1}; ^{1}H NMR: δ 8.20 (s, 1 H), 7.65 (d, 1H, J = 6.6), 7.50 (m, 1H), 7.40 (m, 2H), 7.26 (t, 2H, J = 7.1), 7.00 (s, 1H), 6.74 (m, 2H); ^{13}C NMR: δ 163.6, 147.6, 137.8, 133.4, 131.8, 130.2, 129.5, 128.7, 127.4, 127.3, 117.4, 114.6, 114.5, 63.6; ms (30 eV): *m/z* 258, 260 (M^+:M^++2, 3:1). *Anal*. Calcd. for $C_{14}H_{11}ClN_2O$: C, 64.99; H, 4.29; N, 10.83. Found: C, 65.03; H, 4.28; N, 10.79.

(±)-2-Butyl-2,3-dihydro-4(1*H*)-quinazolinone (3e). This compound (383 mg, 94%) was prepared from 332 mg (2.00 mmoles) of **1** and 172 mg (2.00 mmoles) of pentanal (**2e**) and isolated as a white solid, mp 143-144 ^{o}C (lit[15] mp 144-146 ^{o}C). IR: 3293, 1651, 1614 cm^{-1}; ^{1}H NMR: δ 7.90 (br s, 1H), 7.58 (d, 1H, J = 7.7), 7.23 (t, 1H, J = 7.7), 6.73 (d, 1H, J = 7.7), 6.65 (t, 1H, J = 7.7), 6.58 (br s, 1H), 4.69 (s, 1H), 1.62 (m, 2H), 1.40 (m, 2H), 1.30 (m, 2H), 0.88 (t, 3H, J = 6.8); ^{13}C NMR: δ 163.9, 148.5, 133.0, 127.3, 116.8, 115.0, 114.3, 64.4, 34.7, 25.4, 22.1, 13.9; ms (70 eV): *m/z* 147 (M^+-C_4H_9).

(±)-2-[(1*E*)-2-Phenylethenyl]-2,3-dihydro-4(1*H*)-quinazolinone (3f). This compound (445 mg, 89%) was prepared from 332 mg (2.00 mmoles) of **1** and 264 mg (2.00 mmoles) of *trans*-cinnamaldehyde (**2f**), and isolated as a yellow solid, mp 170-173 ^{o}C

[lit[7] mp 168-172 °C). IR: 3276, 1651, 1611 cm^{-1}; ^1H NMR: δ 8.16 (br s, 1H), 7.63 (d, 1H, J = 7.7), 7.46 (d, 2H, J = 8.2), 7.35 (t, 2H, J = 7.7), 7.26 (m, 2H), 6.90 (s, 1H), 6.76 (d, 1H, J = 8.2), 6.68 (d, 1H, J = 15.9), 6.67 (d, 1H, J = 7.7,), 6.38 (dd, 1H, J = 15.9, 6.6), 5.31 (d, 1H, J = 6.6); ^{13}C NMR: δ 163.3, 147.8, 135.7, 133.2, 131.6, 128.7, 128.3, 128.1, 127.4, 126.6, 117.1, 114.8, 114.5, 65.8; ms (30 eV): *m/z* 250 (M^+).

(±)-Ethyl 4-(4-Oxo-1,2,3,4-tetrahydroquinazolin-2-yl)butanoate (3g). This compound (408 mg, 78%) was prepared from 332 mg (2.00 mmoles) of **1** and 288 mg (2.00 mmoles) of ethyl 5-oxopentanoate (**2g**),[29] and isolated a pale pink solid, mp 105-108 °C. IR: 3302, 3204, 1731, 1661, 1614 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.87 (d. 1 H, J = 7.7), 7.30 (t, 1H, J = 7.7), 7.04 (br s, 1H), 6.84 (t, 1H, J = 7.7), 6.69 (d, 1 H, J = 8.2), 4.91 (s, 1 H), 4.49 (br s, 1H), 4.14 (q, 2 H, J = 7.1), 2.39 (m, 2H), 1.82 (m, 4H), 1.26 (t, 3H, J = 7.1); ^{13}C NMR ($CDCl_3$): δ 173.2, 165.5, 147.3, 133.8, 128.4, 119.2, 115.8, 114.8, 64.9, 60.6, 34.7, 33.5, 19.1; ms (30 eV): *m/z* 262 (M^+). *Anal*. Calcd. for $C_{14}H_{18}N_2O_3$: C, 64.12; H, 6.87; N, 10.69. Found: C, 64.16; H, 6.91; N, 10.63. Extended heating of this reaction for 24 h failed to induce cyclization.

(±)-Ethyl 5-(4-Oxo-1,2,3,4-tetrahydroquinazolin-2-yl)pentanoate (3h). This compound (402 mg, 73%) was prepared from 332 mg (2.00 mmoles) of **1** and 316 mg (2.00 mmoles) of ethyl 6-oxohexanoate (**2h**),[30] and isolated as a white solid following flash chromatography eluted with 50% ether in hexanes containing 1% methanol, mp 110-113 °C. IR: 3307, 3203, 1736, 1643, 1614 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.88 (d, 1H, J = 7.7), 7.31 (t, 1H, J = 7.7), 6.86 (t, 1H, J = 7.7), 6.69 (d, 1H, J = 8.2), 6.24 (br s, 2H), 4.91 (t, 1H, J = 5.8), 4.14 (q, 2H, J = 7.1), 2.35 (t, 2H, J = 7.1), 1.80 (q, 2H, J = 7.1), 1.69 (quintet, 2H, J = 7.1), 1.51 (m, 2H), 1.26 (t, 3H, J = 7.1); ^{13}C NMR ($CDCl_3$): δ 173.4,

165.4, 147.4, 133.7, 128.4, 119.2, 115.8, 114.7, 65.0, 60.4, 35.0, 33.8, 24.3, 23.4, 14.2; ms (30 eV): *m/z* 276 (M^+). *Anal*. Calcd. for $C_{15}H_{20}N_2O_3$: C, 65.22; H, 7.24; N, 10.14. Found: C, 65.29; H, 7.27; N, 10.09. Extended heating of this reaction for 24 h failed to induce cyclization.

2,2-Dimethyl-2,3-dihydro-4(1*H*)-quinazolinone (3i). This compound (334 mg, 95%) was prepared from 332 mg (2.00 mmoles) of **1** and 116 mg (2.00 mmoles) of acetone (**2i**) and isolated as a white solid, mp 182-183 ^oC (lit[31] mp 183-184 ^oC). IR: 3260, 3172, 1640, 1614 cm^{-1}; ^1H NMR: δ 7.94 (br s, 1H), 7.57 (d, 1H, J = 8.2), 7.20 (t, 1H, J = 7.7), 6.63 (br s, 1H), 6.62 (d, 1H, J = 8.2), 6.61 (t, 1H, J = 7.7), 1.36 (s, 6H); ^{13}C NMR: δ 163.1, 147.1, 133.2, 127.2, 116.4, 114.2, 113.8, 66.8, 29.0; ms (70 eV): *m/z* 161 (M^+-CH_3).

(±)-2-Methyl-2-propyl-2,3-dihydro-4(1*H*)-quinazolinone (3j). This compound (367 mg, 90%) was prepared from 332 mg (2.00 mmoles) of **1** and 172 mg (2.00 mmoles) of 2-pentanone (**2j**), and isolated as a white solid, mp 192-195 ^oC. IR: 3272, 3184, 1645, 1613 cm^{-1}; ^1H NMR: δ 7.90 (br s, 1H), 7.56 (d, 1H, J = 7.7), 7.20 (td, 1H, J = 8.2, 1.6), 6.64 (d, 1H, J = 8.2), 6.59 (br s, 1H), 6.59 (t, 1H, J = 7.7), 1.60 (m, 2H), 1.35 (m, 2H), 1.34 (s, 3H), 0.84 (t, 3H, J = 7.1); ^{13}C NMR: δ 163.1, 147.2, 133.1, 127.1, 116.0, 113.9, 113.5, 69.0, 43.7, 27.9, 16.7, 14.1; ms (70 eV): *m/z* 161 (M^+-C_3H_7). *Anal*. Calcd. for $C_{12}H_{16}N_2O$: C, 70.59; H, 7.84; N, 13.73. Found: C, 70.64; H, 7.86; N, 13.70.

(±)-2-Methyl-2-phenyl-2,3-dihydro-4(1*H*)-quinazolinone (3k). This compound (409 mg, 86%) was prepared from 332 mg (2.00 mmoles) of **1** and 240 mg (2.00 mmoles) of acetophenone (**2k**), and isolated as a white solid, mp 222-224 ^oC. IR: 3297, 3182, 1651, 1611 cm^{-1}; ^1H NMR: δ 8.76 (br s, 1H), 7.63 (br s, 1H), 7.48 (m, 3H), 7.28 (d, 2H, J = 7.4), 7.19 (m, 2H), 6.77 (d, 1H, J = 8.0), 6.57 (t, 1H, J = 7.1), 1.64 (s, 3H); ^{13}C NMR: δ

163.8, 147.7, 147.2, 133.3, 127.9, 127.2, 127.0, 125.1, 116.8, 115.0, 114.3, 70.1, 30.7; ms (70 eV): *m/z* 223 (M^+-CH_3). *Anal*. Calcd. for $C_{15}H_{14}N_2O$: C, 75.63; H, 5.88; N, 11.76. Found: C, 75.61; H, 5.89; N, 11.73.

(±)-2-Benzyl-2-methyl-2,3-dihydro-4(1*H*)-quinazolinone (3l). This compound (458 mg, 91%) was prepared from 332 mg (2.00 mmoles) of **1** and 268 mg (2.00 mmoles) of phenyl acetone (**2l**), and isolated as a white solid, mp 162-165 ^oC. IR: 3292, 1655, 1615 cm^{-1}; ^1H NMR: δ 7.96 (br s, 1H), 7.50 (d, 1H, J = 7.7), 7.22 (m, 3H), 7.15 (d, 2H, J = 7.1), 6.71 (br s, 1H), 6.65 (d, 1H, J = 8.2), 6.57 (t, 1H, J = 7.7), 2.93 (d, 1H, J = 13.2), 2.83 (d, 1H, J = 13.2), 1.37 (s, 3H); ^{13}C NMR: δ 163.0, 146.8, 136.5, 133.2, 130.7, 127.7, 127.0, 126.2, 116.1, 114.0, 113.6, 69.3, 46.5, 27.5; ms (70 eV): *m/z* 161 (M^+-C_7H_7). *Anal*. Calcd. for $C_{16}H_{16}N_2O$: C, 76.19; H, 6.35; H, 11.11. Found: C, 76.24; H, 6.36; N, 11.05.

Spiro[cyclopentane-1,2'(1'*H*)-quinazolin]-4'(3'*H*)-one (3m). This compound (374 mg, 93%) was prepared from 332 mg (2.00 mmoles) of **1** and 168 mg (2.00 mmoles) of cyclopentanone (**2m**), and isolated as an off-white solid, mp 258-259 ^oC (lit[23] mp 257-260 ^oC). IR: 3289, 3162, 1638, 1613 cm^{-1}; ^1H NMR: δ 8.10 (br s, 1H), 7.59 (d, 1H, J = 7.7), 7.22 (t, 1H, J = 7.7), 6.75 (br s, 1H), 6.70 (d, 1H, J = 8.2), 6.63 (t, 1H, J = 7.7), 1.80 (s, 4H), 1.67 (s, 4H); ^{13}C NMR: δ 163.4, 147.5, 133.0, 127.2, 116.5, 114.6, 114.3, 77.1, 39.3, 22.0; ms (30 eV): *m/z* 202 (M^+).

Spiro[cyclohexane-1,2'(1'*H*)-quinazolin]-4'(3'*H*)-one (3n). This compound (396 mg, 92%) was prepared from 332 mg (2.00 mmoles) of **1** and 196 mg (2.00 mmoles) of cyclohexanone (**2n**), and isolated as an off-white solid, mp 216-218 ^oC (lit[23] mp 217-219 ^oC). IR: 3287, 1651, 1613 cm^{-1}; ^1H NMR: δ 7.94 (br s, 1H), 7.57 (d, 1H, J = 7.7), 7.22 (td, 1H, J = 8.2, 1.1), 6,82 (d, 1H, J = 8.2), 6.62 (t, 1H, J = 7.1), 6.62 (br s, 1H), 1.74 (m,

2H), 1.61 (m, 2H), 1.58 (m, 4H), 1.42 (m, 1H), 1.25 (m, 1H); ^{13}C NMR: δ 163.2, 146.8, 133.1, 127.1, 116.5, 114.6, 114.4, 67.8, 37.2, 24.7, 20.9; ms (30 eV): *m/z* 216 (M^+).

(±)-3a-Methyl-2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (6). The reaction to prepare this compound required refluxing for 8 hours under the conditions described for the preparation of **3a** from 415 mg (2.50 mmoles) of **1** and 301 mg (2.50 mmoles) of 5-chloro-2-pentanone (**10**). The compound (368 mg, 73%) was isolated directly from the reaction as a white solid, mp 143-145 ^{o}C. IR: 3190, 1660, 1609 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.92 (dd, 1H, J = 7.7, 1.1), 7.36 (td, 1H, J = 7.7, 1.6), 7.04 (br s, 1H), 6.78 (t, 1H, J = 7.1), 6.59 (d, 1H, J = 8.2), 3.50 (m, 2H), 2.17 (m, 2H), 2.04 (m, 1H), 1.39 (s, 3H); ^{13}CNMR ($CDCl_3$): δ 164.9, 145.3, 134.0, 128.6, 117.3, 114.9, 113.8, 74.9, 47.1, 39.6, 25.6, 21.8; ms (30 eV): *m/z* 202 (M^+). *Anal*. Calcd. for $C_{11}H_{14}N_2O$: C, 71.29; H, 6.93; N, 13.86. Found: 71.33; H, 6.94; N, 13.83.

(±)-3a-Methyl-2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-dione (7a). This compound was prepared as described for **6** from 415 mg (2.50 mmoles) of **1** and 325 mg (2.50 mmoles) of methyl levulinate (**11**). Flash chromatography on a 30 cm x 2 cm silica gel column eluted with 50% ether in hexanes containing 2% methanol gave 400 mg (74%) of **7a** as a pale yellow solid, mp 175-177 ^{o}C (lit[26] mp 179-180 ^{o}C). IR: cm^{-1}; ^{1}H NMR: δ 8.25 (br s, 1H), 8.16 (d, 1H, J = 8.2), 8.06 (dd, 1H, J = 7.8, 1.4), 7.59 (td, 1H, J = 7.8, 1,4), 7.29 (t, 1H, J = 8.2), 2.71 (m, 2H), 2.40 (m, 2H), 1.58 s, 3H); ^{13}C: δ 171.7, 163.5, 135.8, 133.8, 128.2, 125.0, 120.7, 119.5, 74.5, 32.9, 30.0, 26.9; ms (30 eV): *m/z* 216 (M^+).

(±)-3a-Phenyl-2,3,3a,4-tetrahydropyrrolo[1,2-*a*]quinazoline-1,5-dione (7b). This compound was prepared as described for **6** from 415 mg (2.50 mmoles) of **1** and 480 mg

(2.50 mmoles) of methyl 3-benzoylpropionate (**12**). Flash chromatography on a 30-cm × 2-cm silica gel column eluted with 50% ether in hexanes containing 2% methanol gave 536 mg (77%) of **7b** as a pale yellow solid, mp 290 ^{o}C (decomposition) (lit[26] mp >290 ^{o}C). IR: 3203, 1716, 1668, 1604 cm^{-1}; ^{1}H NMR: δ 9.82 (br s, 1H), 8.09 (d, 1H, J = 8.2), 7.77(dd, 1H, J = 7.7, 1.1), 7.60 (td, 1H, J = 7.7, 1.6), 7.34 (m, 4H), 7.26 (m, 2H), 2.68 (m, 3H), 2.26 (m, 1H); ^{13}C: δ 173.0, 161.9, 144.0, 136.3, 133.3,128.7, 128.0, 127.6, 124.9, 124.8, 120.8, 120.7, 77.2, 34.7, 29.3; ms (30 eV): *m/z* 278 (M^{+}).

(±)-6,6a-Dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione (8). This compound was prepared as described for **6** from 415 mg (2.50 mmoles) of **1** and 415 mg (2.50 mmoles) of methyl 2-formylbenzoate (**13**).[27] Flash chromatography eluted with 50% ether in hexanes containing 5% methanol gave 450 mg (72%) of **8** as an off-white solid, mp 255-258 ^{o}C. IR: 3154, 1715, 1681, 1605 cm^{-1}; ^{1}H NMR: δ 9.43 (br s, 1H), 8.30-7.55 (complex, 7H), 7.36 (br s, 1H), 6.25 (br s, 1H); ^{13}C: δ 164.1, 163.6, 140.7, 137.1, 133.5, 133.2, 131.1, 130.1, 128.1, 124.7, 124.1, 123.8, 119.9, 119.5, 67.0; ms (30 eV): *m/z* 250 (M^{+}). *Anal*. Calcd. for $C_{15}H_{10}N_2O_2$: C, 72.00; H, 4.00; N, 11.20. Found: C, 72.03; H, 3.99; N, 11.15.

2,4(1*H*,3*H*)-Quinazolinedione (9). This compound was prepared as described for **6** from 415 mg (2.50 mmoles) of **1** and 495 mg (2.50 mmoles) of diphosgene (**14**). The product (348 mg, 86%) was isolated as a gray solid, mp 343-345 ^{o}C (lit [32] mp >300 ^{o}C). The spectral data matched those reported previously.[32]

Representative Procedure from 2-Aminobenzamide: (±)-2-Phenyl-2,3-dihydro-4(1*H*)-quinazolinone (3a). A 100-mL three-necked round-bottomed flask, equipped with magnetic stirring and a reflux condenser, was charged with 7 mL of acetic acid, 250 mg

(1.84 mmoles) of **4** and 195 mg (1.84 mmoles) of benzaldehyde (**2a**). The resulting solution was stirred at room temperature for 4 hours or, alternatively, at 115 ^{o}C for 30 minutes. The crude reaction mixture was cooled and poured into saturated aqueous sodium chloride and extracted with ether (1 × 50 mL) and ethyl acetate (1 × 50 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (2 × 50 mL) and saturated aqueous sodium chloride (1 × 50 mL), then dried (magnesium sulfate) and concentrated under vacuum to give 370 mg (90%) of **3a** as a white solid. The mp and spectral data matched those reported above.

(±)-2-(4-Methoxyphenyl)-2,3-dihydro-4(1*H*)-quinazolinone (3b). This compound (420 mg, 90%) was prepared from 250 mg (1.84 mmoles) of **4** and 250 mg (1.84 mmoles) of **2b**. The mp and spectral data matched those reported above.

(±)-2-(2-Chlorophenyl)-2,3-dihydro-4(1*H*)-quinazolinone (3d). This compound (437 mg, 92%) was prepared from 250 mg (1.84 mmoles) of **4** and 258 mg (1.84 mmoles) of **2d**. The mp and spectral data matched those reported above.

(±)- Ethyl 4-(4-Oxo-1,2,3,4-tetrahydroquinazolin-2-yl)butanoate (3g). This compound (366 mg, 76%) was prepared from 250 mg (1.84 mmoles) of **4** and 265 mg (1.84 mmoles) of **2g**. The mp and spectral data matched those reported above.

2,2-Dimethyl-2,3-dihydro-4(1*H*)-quinazolinone (3i). This compound (297 mg, 92%) was prepared from 250 mg (1.84 mmoles) of **4** and 107 mg (1.84 mmoles) of **2i**. The mp and spectral data matched those reported above.

(±)-2-Methyl-2-propyl-2,3-dihydroquinazolin-4(1*H*)-one (3j). This compound (335 mg, 90%) was prepared from 250 mg (1.84 mmoles) of **4** and 158 mg (1.84 mmoles) of **2j**. The mp and spectral data matched those reported above.

(±)-2-Methyl-2-(phenylmethyl)-2,3-dihydro-4(1*H*)-quinazolinone (3l). This compound (408 mg, 88%) was prepared from 250 mg (1.84 mmoles) of **4** and 247 mg (1.84 mmoles) of **2l**. The mp and spectral data matched those reported above.

Spiro[cyclohexane-1,2'(1'*H*)-quinazolin]-4'(3'*H*)-one (3n). This compound (357 mg, 90%) was prepared from 250 mg (1.84 mmoles) of **4** and 180 mg (1.84 mmoles) of **2n**. The mp and spectral data matched those reported above.

(±)-Methyl 3-(2-Methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)propanoate (15). This compound (192 mg, 70%) was prepared from 150 mg (1.10 mmoles) of **4** and 143 mg (1.10 mmoles) of **11** by stirring in acetic acid at room temperature for 24 h, mp 141-142 ^{o}C. IR: 3287, 1722, 1655, 1615 cm^{-1}; ^{1}H NMR: δ 7.85 (dd, 1H, J = 7.7, 1.6), 7.28 (ddd, 1 H, J = 8.2, 7.7, 1.6), 6.80 (t, 1H, J = 7.7), 6.62 (br s, 1H), 6.59 (d, 1H, J = 8.2), 4.22, (br s, 1H), 3.65 (s, 3H), 2.64 (dt, 1H, J = 17.0, 7.1), 2.52 (dt, 1H, J = 17.0, 7.1), 2.15 (dt, 1H, J = 14.0, 7.1), 2.06 (dt, 1H, J = 14.0, 7.1), 1.55, 2, 3H); ^{13}C NMR δ 174.2, 164.5, 145.8, 134.0, 128.3, 118.6, 114.5, 114.0, 69.8, 51.9, 36.4, 29.0, 28.7; ms (30 eV): *m/z* 248 (M^{+}). *Anal*. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.90; H, 6.45; N, 11.29. Found: C, 62.96; H, 6.46; N, 11.21. Treatment of equimolar amounts of **4** and **11** in acetic acid at 115 ^{o}C for 8 hours gave **7a** in 75% yield. Additionally, heating **15** in acetic acid at 115 ^{o}C for 8 hours resulted in quantitative conversion to **7a**. The mp and spectral data for **7a** matched those reported above.

References and Notes

1. [a] Wolfe, J. F.; Rathman, T. L.; Sleevi, M. C.; Campbell, J. A.; Greenwood, T. D. *J. Med. Chem.* 1990, *33*, 161. [b] Padia, J. K.; Field, M.; Hinton, J.; Meecham,

K.; Pablo, J.; Pinnock, R.; Roth, B. D.; Singh, L.; Suman-Chauhan, N.; Trivedi, B. K.; Webdale, L. *J. Med. Chem* **1998**, *41*, 1042.

2. Xia, Y.; Yang, Y.; Hour, M. J.; Kuo, S. C.; Xia, P.; Bastow, K. F.; Nakanishi, Y.; Nampoorthri, P.; Hackl, T.; Hamel, E.; Lee, K. H. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1193.

3. Kenichi, O.; Yoshihisa, Y.; Toyonari, O.; Toru, I.; Yoshio, I. *J. Med. Chem.* **1985**, *28*, 568.

4. Buchanan, J. G.; Sable, H. Z. in *Selective Organic Transformations*; Thyagarajan, B. S. (Ed); Wiley-Interscience: New York; **1972**, Vol 2, pp 1-95.

5. Farbewerke Hoechst A.-G. Dutch Patent 6,609,924 (**1967**); *Chem. Abstr.* **1968**, *68*, 59609.

6. Gupta, R. C.; Nath, R.; Shanker, K.; Bhargava, K. P.; Kishore, K. *J. Ind. Chem Soc.* **1979**, *56*, 219.

7. [a] Orme, M. W.; Baindur, N.; Robbins, K. G., *et. al.* Intenational Patent WO 9817267, **1998**; *Chem. Abstr*. **1998**, *128*, 321662. [b] Petrie, C.; Orme, M. W.; Baindur, N.; Robbins, K. G.; Harris, S. M.; Kontoyianni, M.; Hurley, L. H.; Kervin, S. M.; Mundy, G. R. International Patent WO 9715308, **1998**; *Chem. Abstr*. **1997**, *127*, 17703.

8. Biressi, M. G.; Cantrelli, G.; Carissimi, M.; Cattaneo, A.; Ravenna, F. *Farmaco Ed. Sci.* 1969, 24, 199; *Chem. Abstr.* **1969**, *71*, 61357.

9. Bhalla, P. R.; Walworth, B. L., U.S. Patent 4,431,440; *Chem. Abstr.* **1984**, *100*, 174857.

10. Bunce, R. A.; Randall, M. H.; Applegate, K. G. *Org. Prep. Proced. Int.* **2002**, *34*, 493.

11. Bunce, R. A.; Schammerhorn, J. E. *J. Heterocycl. Chem.* **2006**, *43*, 1031.

12. Bunce, R. A.; Nammalwar, B. *J. Heterocycl. Chem.* **2009**, *46*, 172.

13. Bunce, R. A.; Nammalwar, B. *J. Heterocycl. Chem.* **2009**, *46*, 854.

14. Shi, D.-Q.; Rong, L.-C.; Wang, J.-X.; Wang, X.-S.; Tu., S.-J.; Hu, H.-W. *Gaodeng Xuexiao Huaxue Xuebao* **2004**, *25*, 2051; *Chem. Abstr*. **2005**, *153*, 266896.

15. Su, W.; Yang, B. *Aust. J. Chem.* **2002**, *55*, 695.

16. Cai, G.; Xu, X.; Li, Z.; Weber, W. P.; Lu, P. *J. Heterocycl. Chem.* **2002**, *39*, 1271.

17. Chen, J.; Wu, D.; He, F.; Liu, M.; Wu, H.; Ding, J.; Su, W. *Tetrahedron Lett.* **2008**, *49*, 3814.

18. Chen, J. X.; Wu, H. Y.; Su, W. K. *Chin. Chem. Lett.* **2007**, *18*, 536; *Chem. Abstr*. **2008**, *148*, 517663.

19. Qiao, R. Z.; Xu, B.-L.; Wang, Y. H. *Chin. Chem. Lett*. **2007**, *18*, 656; *Chem. Abstr*. **2008**, *148*, 517638.

20. Salehi, P.; Dabiri, M.; Baghbanzadeh, M.; Bahramnejad, M. *Synth. Commun.* **2006**, *36*, 2287.

21. Baghbanzedeh, M.; Salehi, P.; Dabiri, M.; Kozehgary, G. *Synthesis* **2006**, 344.

22. Surpur, M. P.; Singh, P. R.; Patil, S. B.; Samant, S. D. *Synth. Commun.* **2007**, *37*, 1965.

23. Shaababi, A.; Maleki, A.; Mofakham, H. *Synth. Commun.* **2008**, *38*, 3751.

24. Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456. The larger pKa of the aniline protons (30.6) *vs* benzamide (23.4) protons indicates that the aniline nitrogen is more basic and, therefore, more nucleophilic.

25. It was well known that these conditions do not hydrogenolyze aromatic halides, see Mosley, W. L. *J. Org. Chem.* **1959**, *24*, 421 and ref. 10, but less is known about aliphatic halides such as **11**.

26. Aeberli, P.; Houlihan, W. *J. Org. Chem.* **1968**, *33*, 2402.

27. Osuka, A.; Nakajima, S.; Maruyama, K. *J. Org. Chem.* **1992**, *57*, 7355.

28. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

29. Xu, G.; Micklacher, M.; Silvestri, M. A.; Hartman, T. L.; Burrier, J.; Osterling, M. C.; Wargo, H.; Turpin, J. A.; Buckheit, Jr. R. W.; Cushman, M. *J. Med. Chem.* **2001**, *44*, 4092.

30. Wilson, J. E.; Casarez, A. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 11332.

31. Larsen, S. D.; Connell, M. A.; Cudahy, M. M.; Evans, B. R.; May, P. D.; Meglasson, M. D.; O'Sullivan, T. J.; Schostarez, H. J. ; Sih, J. C.; Stevens, F. C.; Tanis, S. P.; Tegley, C. M.; Tucker, J. A.; Vaillancourt, V. A.; Vidmar, T. J.; Watt, W.; Yu, J. H. *J. Med. Chem.* **2001**, *44*, 1217.

32. Jiarong, L.; Xian, C.; Daxin, S.; Shuling, M.; Qing, L.; Qi, Z.; Jianhong, T. *Org. Lett*. **2009**, *11*, 1193.

CHAPTER V

4(1*H*)-QUINOLINONES BY A TANDEM REDUCTION-ADDITION-ELIMINATION REACTION

Introduction

Compounds incorporating the 4(*1H*)-quinolinone ring system are commonly encountered in drug chemistry and express a broad spectrum of biological activities.[1-13] Thus, they have become attractive targets for synthesis. In this project, we wish to report an efficient and simple synthesis of 4(1*H*)-quinolinone (**3**), 2,4(1*H*,3*H*)-quinolinedione (**8**) and ethyl 4-oxo-1,4-dihydroquinoline-3-carboxylate (**10**) using an adaptation of the Batcho-Leimgruber reaction.[14-17]

Numerous methods have been devised for the synthesis of **3**. In the most practical sequence, aniline was reacted with Meldrum's acid[18,19] or methyl propiolate[20] to form an adduct that underwent thermal cyclization to give the target heterocycle. Another useful approach involved the condensation of 2-nitroacetophenone with *N*,*N*-dimethylformamide dimethyl acetal to give an enaminone, followed by cyclization in the presence of cyclohexene and 10% Pd/C.[21] Though this reaction is similar to our procedure, we were not able to achieve the yield reported for the preparation of **3**. Finally, the palladium-catalyzed coupling 2-bromoacetophenone with formamide, followed by intramolecular cyclization using sodium *tert*-butoxide, also provided access to this ring system.[22] A disadvantage of this procedure is the expensive catalyst required.

for the initial coupling reaction

There are also many reported syntheses of 2,4(1*H*,3*H*)-quinolinedione (**8**). In the classical synthesis, 2-aminobenzoic acid was condensed with urea in a high boiling solvent.[23-27] This method appears to be the most viable approach since it is simple, inexpensive and scalable. Other preparations have been reported from 2-aminobenzamide,[28] 2-aminobenzonitrile,[29,30] methyl 2-bromobenzoate[31] and 1*H*-indole-2,3-dione.[32] While elegant, most of these approaches use expensive or hazardous reagents that would not be practical on a large scale.

The approaches to the synthesis of ethyl 4-oxo-1,4-dihydroquinoline-3-carboxylate (**10**) are more limited. All of the methods were based on the addition of aniline to diethyl 2-(ethoxymethylene)propandioate[7,9,33-35] and closure under high temperature conditions. The drawback of these processes was the high temperature conditions and the requirement of removing a high-boiling solvent from the product.

Results and Discussion

The syntheses of 4(1*H*)-quinolinone (**3**), 2,4(1*H*,3*H*)-quinolinedione (**8**) and ethyl 4-oxo-1,4-dihydroquinoline-3-carboxylate (**10**) are outlined in Figures 5.1 and 5.2. The strategy is an adaptation of the Batcho-Leimgruber reaction, which is normally used to prepare indoles.[14-17] The synthesis of **3** was achieved in an overall yield of 80% in a two step sequence. The first step involved the addition of *N*,*N*-dimethylformamide dimethyl acetal to 2-nitroacetophenone (**1**) in DMF under hot conditions (100 ºC) to give the 3-(dimethylamino)-1-(2-nitrophenyl)prop-2-en-1-one (**2**) in 95% yield. Enaminone **2** then underwent ring closure via treatment with hydrazine hydrate and 10% Pd/C in ethanol at reflux to give 4(1*H)*-quinolinone (**3**) in 75% yield.

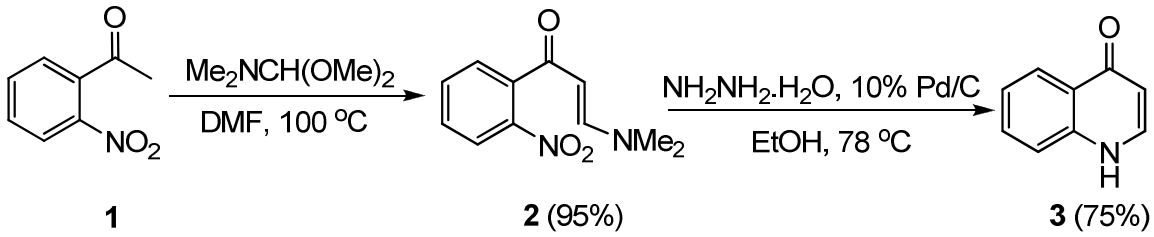


Figure 5.1. Synthesis of 4(1*H*)-quinolinone (**3**)

The preparations of **8** and **10** were readily achieved from 3-(2-nitrophenyl)-3-oxopropanoate (**7**). To prepare **7**,[23] ethyl hydrogen malonate (**6**) was converted to its dianion using 2 equivalents of *n*-BuLi in THF which was reacted with 1 equivalent of 2-nitrobenzoyl chloride **5**, prepared from 2- nitrobenzoic acid using oxalyl chloride. This procedure gave the ketoester **7** in 87% yield. Treatment of **7** with 85% hydrazine hydrate and 10% Pd/C in refluxing ethanol for 20 minutes led to dione **8** in 86% yield. The conversion of **7** to **10** was analogous to the procedure used to prepare **3**. Ketoester **7** was converted to enaminone **9** in DMF in 98% yield by addition of *N*,*N*-dimethylformamide dimethyl acetal at 100 ^{o}C and continued heating for 4 hours. Treatment of enaminone **9** with hydrazine hydrate and 10% Pd/C in refluxing ethanol for 30 minutes then initiated a one-pot sequence involving the reduction of the nitro function, addition of the resulting amino group to the enaminone double bond, and loss of dimethylamine. Both **8** and **10** were easily purified by crystallization.

An alternative synthesis was also tried for the preparation of **10** using ethyl 3-ethoxy-2-(2'-nitrobenzoyl)acrylate (**11**). Treatment of **7** with triethyl orthoformate in acetic anhydride at reflux gave **11** in 90% yield.[36] Various attempts were made for the

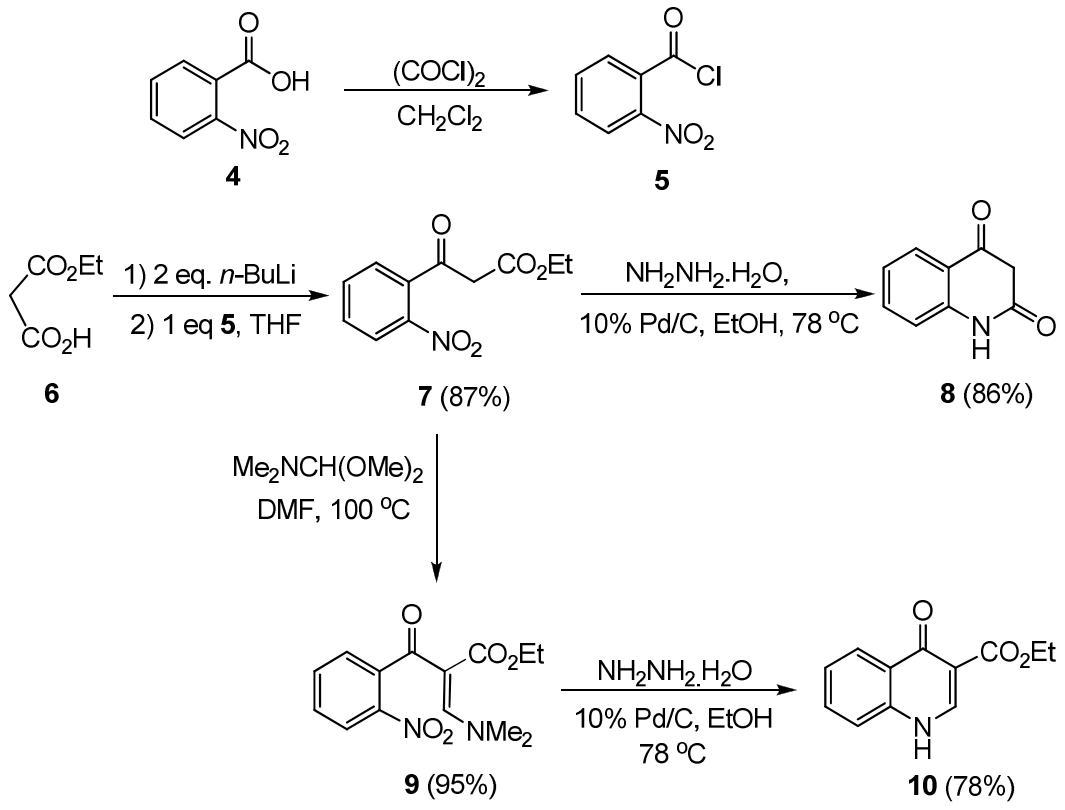


Figure 5.2. Preparation of 2,4(1*H*,3*H*)-quinolinedione (**8**) and ethyl 4-oxo-1,4-dihydroquinoline-3-carboxylate (**10**)

conversion of **11** to **10** through the use of Fe/HCl, Fe/HOAc and hydrazine hydrate and 10% Pd/C in ethanol, but these all resulted the formation of an intractable materials.

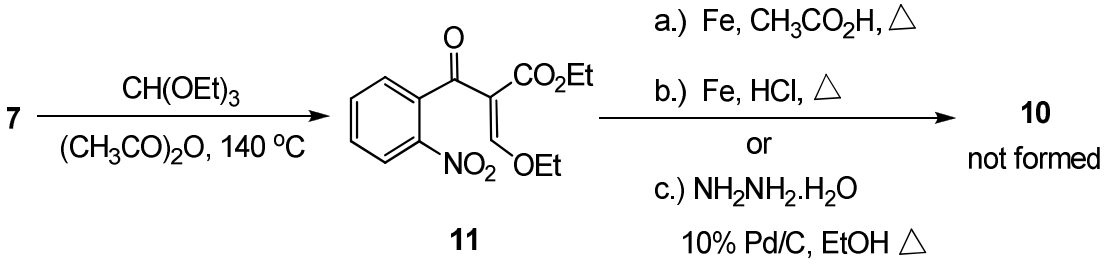


Figure 5.3. Attempted preparation of **10** from **11**

Conclusion

We have developed a relatively simple and efficient method for the syntheses of two quinolinones (**3** and **10)** and a quinolinedione (**8**) using commercially available starting materials. The yields are comparatively higher than previous methods used by Kosinen *et. al*.[21] These ring systems can serve as building blocks for the syntheses of a number of pharmaceutically active drug compounds.

Experimental Section

All reactions were run under dry nitrogen in oven-dried glassware. Reactions were monitored by thin layer chromatography on silica gel GF plates. Preparative separations were performed using flash column chromatography[37] on silica gel (Grade 62, 60-200 mesh) mixed with ultraviolet-active phosphor (Sorbent Technologies UV-5) or thin layer chromatography on 20-cm × 20-cm silica gel GF plates (Analtech 02015). Band elution for both separation methods was monitored using a hand held UV lamp. Melting points were taken on a MelTemp purchased from Laboratory Devices, Cambridge, MA 02139 and were uncorrected. Infrared spectra were taken on a Varian 800 FT-IR (Scimitar series) run as thin films on sodium chloride disks. Unless otherwise indicated, ^{1}H and ^{13}C NMR spectra were measured in deuteriochloroform using a broadband Gemini 2000 High-Resolution NMR spectrometer operating at 300 MHz and 75 MHz respectively. All the NMR signals were referenced to internal tetramethylsilane; coupling constants (J) are reported in Hz. Low-resolution mass spectra (electron impact/direct probe) were run at 70 eV. Elemental analysis were performed by Altlantic Microlab Inc., Norcross, GA.

N,N-Dimethylformamide, from a freshly opened bottle, was dried over 4 Å molecular sieves under nitrogen and was transferred by syringe into reactions where it was used.

Tetrahydrofuran was dried over potassium hydroxide pellets and distilled from lithium aluminium hydride. Commercial reagents and solvents were used as received. The NaCl, $NaHCO_3$ and HCl used in various workup procedures refer to saturated aqueous solutions.

(*E*)-3-(Dimethylamino)-1-(2-nitrophenyl)-2-propen-1-one (2). The procedure of Kosinen and coworkers[21] was modified. In a one-necked round-bottomed flask, equipped with a magnetic stir bar and a nitrogen atmosphere, was placed 5.0 g (30.2 mmol) of 2-nitroacetophenone (**1**) dissolved in 25 mL of dry DMF. To this was added 3.60 g (30.2 mmoles) of dimethylformamide dimethyl acetal, and the mixture was heated for 45 minutes at 90 ^{o}C (oil bath). The crude reaction mixture was quenched with ice water, stirred for 5 minutes, and then extracted with ether (2 × 300 mL). The aqueous layer was saturated with NaCl and extracted one final time with ether (1 × 150 mL). The ether layers were combined and washed with saturated sodium chloride solution (2 × 200 mL), then dried ($MgSO_4$) and concentrated under vacuum. Concentration under vacuum for 30 minutes gave 6.30 g (95%) of **2** as a yellow solid, which was used directly in the next step, mp 119-121 ºC. IR: 1645, 1556, 1527, 1355 cm^{-1}; ^{1}H NMR: δ 7.96 (d, 1H, J = 7.0), 7.62 (apparent t, 2H, J ≈ 7.5), 7.49 (m, 2H), 5.27(d, 1H, J = 12.5), 3.10 (s, 3H), 2.87 (s, 3H); ^{13}C NMR: δ 154.8, 147.1, 138.3, 133.0, 129.2 (2C), 128.7, 123.9, 85.3, 45.0, 37.0; ms (30 eV): *m/z* 220 (M^{+}). *Anal.* Calcd. for $C_{11}H_{12}N_2O_3$: C, 60.00; H, 5.45; N, 12.72. Found: C, 59.93; H, 5.40; N, 12.81.

4(1*H*)-Quinolinone (3). A solution of 2.00 g (9.10 mmoles) of **2** was dissolved in ethanol, and 0.27 g (0.26 mL, 5.44 mmoles, 0.6 equivalents) of 85% hydrazine monohydrate was added to a three-necked round-bottomed flask, fitted with a condenser

and a nitrogen inlet, and stirred for about 5 minutes. To this solution under nitrogen was carefully added 15 mg of 10% palladium-on-charcoal and stirring was continued until thin layer chromatography indicated complete consumption of the starting material (*ca* 60 minutes). The crude product was refluxed at 80 ºC over a period of 60 minutes. The resulting hot solution was filtered through a Celite® bed and concentrated under vacuum. The resulting mixture was flash chromatographed on a 20-cm × 2-cm silica gel column using increasing concentrations of ether in hexanes to give 99 mg (75%) of **3** as a white solid, mp 208-210 ^{o}C [lit[20] mp 209-211 ^{o}C]. IR: 3600-2410, 1613, 1587, 1507 cm^{-1}; ^{1}H NMR: δ 11.81 (br s, 1H), 8.12 (d, 1H, J = 8.2), 7.93 (t, 1H, J = 6.3), 7.65 (td, 1H, J = 8.2, 1.3), 7.57 (d, 1H, J = 8.4), 7.33 (td, 1H, J = 6.8, 1.3), 6.07 (d, 1H, J = 7.4); ^{13}C NMR: δ 176.9, 140.0, 139.4, 131.6, 125.8, 124.9, 123.1, 118.3, 108.7.

Ethyl 3-(2-nitrophenyl)-3-oxopropanoate (7). The procedure of Domagala and coworkers was modified.[36] A 250-mL one-necked round-bottomed flask, equipped with a magnetic stir bar, a condenser and a nitrogen inlet, was charged with 3.00 g (18.0 mmoles) of 2-nitrobenzoic acid (**4**) and 100 mL of dichloromethane. The resulting solution was stirred for 5 minutes and 2.76 g (1.84 mL, 21.7 mmoles) of oxalyl chloride was added drop-wise over a period of 20 minutes, followed by 5 drops of *N*,*N*-dimethylformamide. The reaction was stirred for 12 hours during which time gas evolution subsided and the acid completely dissolved in the dichloromethane. The crude mixture was then concentrated under vacuum to give 2-nitrobenzoyl chloride (**5**).

In a three-necked round-bottomed flask, equipped with a strong magnetic stirrer, was placed a solution of 4.17 g (31.6 mmoles) of ethyl hydrogen malonate (**6**) dissolved in 200 mL of tetrahydrofuran along and 10 mg of bipyridyl was adeed as an internal

indicator. The mixture was cooled to –30 ^{o}C and 16.0 mL of 2.0 *M n*-butyllithium (32.0 mmoles) was added drop-wise over 20 minutes. The reaction mixture was then warmed to –5 ^{o}C, and another portion of 16.0 mL of 2.0 *M n*-butyllithium (32.0 mmoles) was added until a red color persisted for about 5-10 minutes. The mixture was cooled to –78 ^{o}C, and a solution of 2-nitrobenzoyl chloride (from above) in 15 mL of tetrahydrofuran was added drop-wise over 25 minutes. [**Note**: The solution became a thick yellow liquid and stirring was a problem with a weak magnetic stirrer]. The solution was kept at –78 ºC for 30 minutes and then was slowly warmed to –30 ºC and stirred for 30 minutes. The reaction mixture was the poured into ice water containing 20 mL (3 equivalents) of concentrated HCl and the resulting mixture was extracted with dichloromethane (3 × 200 mL). The combined organic extracts were washed with water (1 × 200 mL), 5% $NaHCO_3$ solution (1 × 150 mL) and 1 *N* HCl (1 × 150 mL). The dichloromethane layer was finally washed with saturated NaCl solution (1 × 150 mL), dried ($MgSO_4$), and then concentrated under vacuum to give 3.70 g (87%) of **3** as thick yellow oil. The keto ester was mostly in its keto form (with 8-10% enol) estimated from ^{1}H NMR and was used directly in the next reaction. IR: 1740, 1708, 1531, 1348 cm^{-1}; ^{1}H NMR (keto form): δ 8.16 (d, 1H, J = 8.4), 7.77 (t, 1H, J = 7.6), 7.65 (td, 1H, J = 7.6, 1.2), 7.53 (dd, 1H, J = 7.6, 1.3), 4.16 (q, 2H, J = 7.1), 3.83 (s, 2H), 1.23 (t, 3H, J = 7.1); ^{13}C NMR: δ 194.6, 166.5, 144.5, 134.5, 132.6, 130.9, 128.1, 124.2, 61.6, 49.0, 13.9; ms (30 eV): 237 (M^{+}). *Anal*. Calcd. for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.64; N, 5.91. Found: C, 55.96; H, 4.66; N, 5.83.

2,4(1*H*,3*H*)-Quinolinedione (8). To a solution of 1.00 g (4.20 mmoles) of **7** in 10 mL of ethanol was added 0.1 g (0.1 mL, 0.6 equivalents, 2.52 mmoles) of 85% hydrazine

monohydrate, and the reaction was stirred for 10 minutes. To this solution under nitrogen was carefully added 15 mg of 10% palladium-on-carbon and stirring was continued until thin layer chromatography indicated complete consumption of the starting material (*ca* 20 minutes). The compound was filtered through Celite® and concentrated under vacuum to give a viscous oil. To the crude product was added 10 mL of ether to give a solid precipitate. The solid was filtered and washed with ether and chloroform to give 0.58 g (86%) of **10** as a white solid, mp 315-317 ^{o}C (dec) [lit[29] mp 320 ^{o}C (dec)]. IR: 3620-2360, 1657, 1630, 1508 cm^{-1}. The ^{1}H and ^{13}C NMR data matched those reported previously.[29]

Attempted Preparation of 2,4(1*H*,3*H*)-Quinolinedione under Dissolving Metal Conditions. A 25-mL three-necked round-bottomed flask, equipped with a reflux condenser and a magnetic stir bar, was charged with 50 mg (0.21 mmoles) of **7** and 5 mL of acetic acid (or concentrated hydrochloric acid). The flask was suspended in a bath preheated to 115 ^{o}C (for acetic acid) or 100 ^{o}C (for concentrated hydrochloric acid) for 5 minutes prior to addition of the iron. Heating was briefly intempted and 59 mg (1.05 mmoles, 5 eq) of iron powder was added, and heating was resumed for 30 minutes. The mixture was cooled, added to ice water and extracted with ethyl acetate (3 × 25 mL). The combined extracts were washed with saturated sodium bicarbonate (three times), saturated sodium chloride (one time), and then was dried and concentrated under vacuum to give a dark brown oil. ^{1}H NMR analysis indicated that none of the desired quinolindione was present.

(*Z*)-Ethyl 3-(Dimethylamino)-2-(2-nitrobenzoyl)acrylate (9). A 100-mL single-necked, round-bottomed flask, equipped with a reflux condenser and a magnetic stirrer,

was charged with 1.00 g (4.20 moles) of **7** dissolved in 5 mL of *N*,*N*-dimethylformamide. To this solution was added 0.50 g (0.56 mL, 4.20 mmoles) of dimethylformamide dimethylacetal, and the mixture was heated at 100 ºC for 4 hours. The crude reaction mixture was quenched with ice water, stirred for 5 minutes and extracted with ether (2 × 100 mL). The aqueous solution was saturated with sodium chloride (1 × 100 mL) and extracted one final time with ether (1 × 150 mL). The combined ether layers were washed with saturated sodium chloride (1 × 100 mL), dried ($MgSO_4$) and concentrated under vacuum. The resulting oil solidified to give 1.10 g (89%) of **8** as a yellow solid, mp 122-124 ^{o}C. IR: 1682, 1633, 1570, 1526, 1377, 1349 cm^{-1}; ^{1}H NMR: δ 8.05 (d, 1H, J = 8.2), 8.00 (s, 1H), 7.62 (t, 1H, J = 7.6), 7.48 (td, 1H, J = 7.4, 0.8), 7.36 (d, 1H, J = 7.6), 3.83 (q, 2H, J = 7.1), 3.38 (s, 3H), 3.09 (s, 3H), 0.82 (t, 3H, J = 7.1); ^{13}C NMR: δ 166.7, 160.0, 146.3, 140.2, 133.3, 128.6, 127.8, 123.6, 59.7, 48.2, 42.7, 13.6; ms (30 eV): *m/z* 292 (M^{+}). Several signals in the ^{13}C NMR spectrum were quite broad. However, even with a high sample concentration, long delay time (3 seconds) and up to 5000 transients, it was not possible resolve all of the carbons.

Ethyl 4-Oxo-1,4-dihydroquinoline-3-carboxylate (10). The procedure used to prepare **3** was followed to convert 1.00 g (3.42 mmoles) of **9** to **10**. The reaction was complete in 30 minutes. Workup and crystallization using ether and chloroform and yielded 0.58 g (78%) of **10** as an off-white solid, mp 268-269 ºC [lit[1] mp 270-272 ^{o}C]. IR: 3424, 1642 cm^{-1}; ^{1}H NMR: δ 12.33 (br s, 1H), 8.56 (s, 1H), 8.16 (dd, 1H, J = 8.2, 1.0), 7.71 (td, 2H, J = 7.5, 1.4), 7.63 (d,1H, J = 8.2), 7.42 (td, 1H, J = 7.5, 1.0), 4.22 (q, 2H, J = 7.1), 1.29 (t, 3H, J = 7.1); ^{13}CNMR: δ 173.4, 164.8, 144.9, 138.9, 132.4, 127.2, 125.6, 124.7, 118.8,

109.7, 59.5, 14.3; ms (30 eV): *m/z* 217 (M^+). *Anal*. Calcd. for $C_{12}H_{11}NO_3$: C, 66.34; H, 5.08; N, 6.40. Found: C, 66.36; H, 5.07; N, 6.45.

Attempts to convert **9** to **10** using the conventional procedures with iron in acetic acid and iron in concentrated hydrochloric acid, as above, failed and resulted in the isolation of an intractable tar.

(*E*)- and (*Z*)-Ethyl 3-Ethoxy-2-(2-nitrobenzoyl)acrylate (11). The procedure of Domagala and coworkers was modified.[36] To a stirred solution of 0.50 g (2.11 mmoles) of **7** in 0.34 g (2.32 mmoles) of triethyl orthoformate was added 8 mL of acetic anhydride and the mixture was refluxed for 1 hour. The mixture was concentrated under vacuum, added to water and extracted with ether (2 × 75 mL). The combined ether extracts were washed with water (2 × 50 mL) and saturated NaCl (2 × 50 mL), then dried ($MgSO_4$), and concentrated under vacuum to give 0.56 g (90%) of product as a viscous yellow oil. This product was a mixture of *E* and *Z* isomers and was used directly in subsequent reactions. IR: 1717, 1617, 1529, 1349 cm^{-1}; ^1H NMR: δ 8.15 (d, 1H, J = 8.2), 8.06 (d, 1H, J = 8.2), 7.98 (s, 1H), 7.92 (s, 1H), 7.68 (m, 2H), 7.56 (m, 2H), 7.41 (dd, 1H, J = 7.4, 1.0), 7.33 (dd, 1H, J = 7.6, 1.0), 4.36 (q, 2H, J = 7.2), 4.21 (q, 2H, J = 7.0), 4.11 (q, 2H, J = 7.0), 4.01 (q, 2H, J = 7.2), 1.45 (t, 3H, J = 7.2), 1.27 (t, 3H, J = 7.0), 1.13 (t, 3H, J = 7.2), 1.01 (t, 3H, J = 7.0); ^{13}C NMR: δ 190.6, 188.3, 169.3, 168.7, 166.3, 165.0, 146.0, 145.9, 138.7, 138.1, 133.8, 133.6, 129.6, 129.5, 128.1, 127.2, 123.8, 123.5, 111.8, 110.4, 74.0, 73.9, 60.6, 60.3. 15.2, 14.9, 13.9, 13.6; ms (30 eV): *m/z* 293 (M^+).

Attempts to convert **11** to **10** using iron powder in acetic acid, iron powder in concentrated hydrochloric acid, or hydrazine hydrate and 10% Pd/C in ethanol, as above, all failed and resulted in the isolation of an intractable tar.

References and Notes

1. Lager, E.; Andersson, P.; Nilsson, J.; Pettersson, I.; Nielsen, E. O.; Nielson, M.; Sterner, O.; and Liljefors, T. *J. Med. Chem.* **2006**, *49*, 2526.
2. Seman, M.; Belicova, A.; Milata, V.; Ilavsky, D. *Ceska a Slovenska Farmacie* **1997**, *46*, 128; *Chem. Abstr*. **1998**, *128*, 88842.
3. Boteva, A. A.; Krasnykh, O. P.; Tomilov, M. Y.; Vakhrin, M. I.; Babushkina, E. B.; Odegova, T. F. *Bashkirskii Khimicheskii Zhurnal* **2007**, *14*, 32; *Chem. Abstr*. **2008**, *149*, 409166.
4. Yang, Y.; Zhao, S.; Dai, S.; Chen, K. *Yaoxue Xuebao* **1998**, *33*, 157; *Chem. Abstr*. **1998**, *129*, 254155.
5. Cecchetti, V.; Parolin, C.; Moro, S.; Pecere, T.; Filipponi, E.; Calistri, A.; Tabarrini, O.; Gatto, B.; Palumbo, M.; Fravolini, A.; Palu, G. *J. Med. Chem.* **2000**, *43*, 3799.
6. Nakahira, H.; Hochigai, H.; Takamura, M.; Ikuma, Y. International Patent WO 2009005002 **2009**; *Chem. Abstr*. **2009**, *150*, 98174.
7. Crespo, M. I.; Gracia, J.; Puig, C.; Vega, A.; Bou, J.; Beleta, J.; Domenech, T.; Ryder, H.; Segarra, V.; Palacios, J. M. *Bioorg. & Med. Chem. Lett.* **2000**, *10*, 2661.
8. Hall, C. M.; Johnson, H. G.; Wright, J. B. *J. Med. Chem.* **1974**, *17*, 685.
9. Suen, Y. -F.; Robins, L.; Yang, B.; Verkman, A. S.; Nantz, M. H.; Kurth, M. J. *Bioorg. & Med. Chem.* Lett. **2006**, *16*, 537.

10. Liang, J.; Wang, S.; Wang, X.; Xu, T.; Pu, X.; Shang, R.; Guo, W.; Guo, Z.; Liu, Y.; Guo, Y.; Hua, L. Chinese Patent CN 101554380, **2009**; *Chem. Abstr*. **2009**, *151*, 440623.

11. Meisel, G. M.; Ciociola, A. A. U.S. Patent 2004013741, **2004**; *Chem Abstr*. **2004**, *140*, 105290.

12. Cutler, N. R. U.S. Patent **2001**, 6303135; *Chem. Abstr*. **2001**, *135*, 308886.

13. Davies, R. V.; Yates, D. B. *Progress Med. Chem.* **1995**, *32*, 115.

14. A. Batcho and W. Leimgruber, German Patent DE 2057840, **1971**; *Chem. Abstr*., **1971**, *75*, 63605.

15. Maehr, H.; Smallheer, J. M. *J. Org. Chem*. **1981**, *46*, 1752.

16. Batcho, A. D.; Leimgruber, W. *Org. Synth*. **1984**, *63*, 214.

17. For a review, see Clark, R. D.; Repke, D. B. *Heterocycles* **1984**, *22*, 195.

18. Cassis, R.; Tapia, R.; Valderrama, J. A. *Synth. Commun.* **1985**, *15*, 125.

19. Huang, X.; Liu, Z. *J. Org. Chem.* **2002**, *67*, 6731.

20. Heindel, N. D.; Kennewell, P. D.; Fish, V. B. *J. Heterocycl. Chem.* **1969**, *6*, 77.

21. Tois, J.; Vahermo, M.; Koskinen, A. *Tetrahedron. Lett.* **2005**, *46*, 735.

22. Huang, J.; Chen, Y.; King, A. O.; Dilmeghani, M.; Larsen, R. D.; Faul, M. M. *Org. Lett.* **2008**, *10*, 2609.

23. Smits, R. A.; de Esch, I. J. P.; Zuiderveld, O. P.; Broeker, J.; Sansuk, K.; Guaita, E.; Coruzzi, G.; Adami, M.; Haaksma, E.; Leurs, R. *J. Med. Chem.* **2008**, *51*, 7855.

24. Kumar, S.; Shakya, N.; Gupta, S.; Sarkar, J.; Sahu, D. P. *Bioorg. & Med. Chem. Lett*. **2009**, *19*, 2542.

25. Roopan, S. M.; Maiyalagan, T.; Khan, F. N. *Can. J. Chem*. **2008**, *86*, 1019.

26. Nikpour, F.; Paibast, T. *Chem. Lett*. **2005**, *34*, 1438.

27. Smith, A. L.; Thomson, C. G.; Leeson, P. D. *Bioorg. & Med. Chem. Lett*. **1986**, *6*, 1483.

28. Petrov, J. S.; Andreev, G. N. *Org. Prep. Proced. Int*. **2005**, *37*, 560.

29. Jiarong, L.; Xian, C.; Daxin, S.; Shuling, M.; Qing, L.; Qi, Z.; Jianhong, T. *Org. Lett.* **2009**, *11*, 1193.

30. Mizuno, T.; Mihara, M.; Nakai, T.; Iwai, T.; Ito, T. *Synthesis* **2007**, 2524.

31. Willis, M. C.; Snell, R. H.; Fletcher, A. J.; Woodward, R. L. *Org. Lett.* **2006**, *8*, 5089.

32. Yadav, J. S.; Subba Reddy, B. V.; Subba Reddy, U. V.; Praneeth, K. *Tetrahedron Lett*. **2008**, *49*, 4742.

33. Goldsworthy, J.; Ross, W. J.; Verge, J. P. European Patent EP55068, **1982**; *Chem. Abstr*. **1982**, *97*, 162848.

34. Nicholson, J. R.; Singh, G.; McCullough, K. J.; Wightman, R. H. *Tetrahedron* **1989**, *45*, 889.

35. Banerji, B.; Conejo-Garcia, A.; McNeill, L. A.; McDonough, M. A.; Buck, M. R. G.; Hewitson, K. S.; Oldham, N. J.; Schofield, C. J. *Chem. Commun.* **2005**, 5438.

36. Domagala, J. M.; Bridges, A. J.; Culbertson, T. P.; Gambino, L.; Hagen, S. E.; Karrick, G.; Porter, K.; Sanchez, J. P.; Sesnie, J. A.; Spense, F. G.; Szotek, D.; Wemple, J. *J. Med. Chem*. **1991**, *34*, 1142.

37. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

CHAPTER VI

(±)-3-ARYL-2,3-DIHYDRO-4(1*H*)-QUINOLINONES BY A TANDEM REDUCTION-MICHAEL ADDITION REACTION

Introduction

Over the past several years, we have described a number of tandem reaction approaches to nitrogen heterocycles whose syntheses were initiated by dissolving metal reduction of nitroarenes.[1] In the current project, we sought to extend this strategy to the synthesis of 2,3-dihydro-4(1*H*)-quinolinone as well as several (±)-3-aryl-2,3-dihydro-4(1*H*)-quinolinones, which have demonstrated antimalarial[2] and anticancer activity.[3] Our approach involves the reductive cyclization of 1-(2-nitrophenyl)prop-2-en-1-one derivatives.

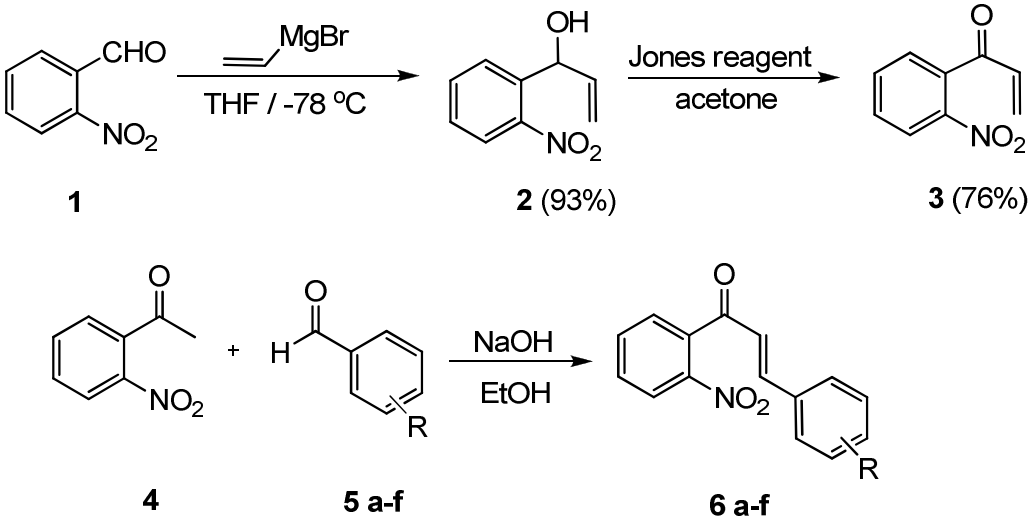
The value of the title compounds has made them common targets for synthesis and numerous approaches using both basic and acidic reagents have been reported. The original synthesis involved treatment of 2'-aminochalcone[4] with a base, and the yields were modest. Work by others described the cyclization of more acidic *N*-acylated 2'-aminochalcones,[5] and yields improved to 50-60%. Subsequent studies focused on cyclizations of 2'-aminochalcone using mixtures of acetic acid and phosphoric acid,[6] which gave the 3-arylquinolinones in 50-70% yields. More recently, montmorillonite K-10 with microwave irradiation[7] and Lewis acids on silica or alumina[8] have been used to promote the cyclization in 60-90% yields. Additionally, the ring closure of 2'-

aminochalcone has been reported to occur in PEG-400 solvent at 130 ^{o}C with no additives in 80-90% yield.[9] In another recent approach, metathesis of 2-alkynylanilines with aldehdyes in the presence of an antimony pentafluoride-methanol catalyst gave (±)-2,3-disubstituted-2,3-dihydro-4(1*H*)-quinolinones[10] as *cis-trans* mixtures in 25-95% yields. Finally, condensation of 2-aminoacetophenone with various benzaldehydes in the presence of L-proline has been reported as a potential route to chiral 3-aryldihydroquinolinones[11] and, while yields were high (79-93%), asymmetric induction was low (< 10% ee). To date, there have been no reports on the synthesis of 3-aryldihydroquinolinones from 2-'nitrochalcones.

Results and Discussion

The synthesis of the cyclization substrates is shown in Figure 6.1. To prepare the precursor to 2,3-dihydro-4(1*H*)-quinolinone, vinylmagnesium bromide was added to 2-nitrobenzaldehyde (**1**) in tetrahydrofuran to give alcohol **2**, and the latter further oxidized to deliver 1-(2-nitrophenyl)prop-2-en-1-one (**3**) in 71% overall yield.[12] The 2'-nitrochalcones **6a-f** used for the preparation of the (±)-3-aryl-2,3-dihydro-4(1*H*)-quinolinones were prepared in 92-97% from 2-nitroacetophenone (**4**) and a series of benzaldehyde derivatives (**5a-f**) using standard conditions of sodium hydroxide in ethanol (Figure 6.1).

The cyclization of **3** to the parent 2,3-dihydro-4(1*H*)-quinolinone (**7**) was initially attempted in 1:1 v/v acetic acid/phosphoric acid, and the product was isolated in 72% yield via chromatography. During the course of the reaction, a heavy precipitate formed, which caused problems with stirring and isolation of the product. The same transformation proved to be faster and easier using iron powder in concentrated



5		Yield of **6** (%)
a	H	95
b	4-CH_3	97
c	4-CH_3O	93
d	3,4-$(CH_3O)_2$	95
e	3,4-OCH_2O	95
f	2-Cl	92

Figure 6.1. Synthesis of cyclization substrates

hydrochloric acid at 100 °C for 30 minutes. Critical to the success of the reaction was the addition of the iron to the hot solution. This minimized the formation of side products and afforded the target heterocycle in 83% yield after chromatography (Figure 6.2).

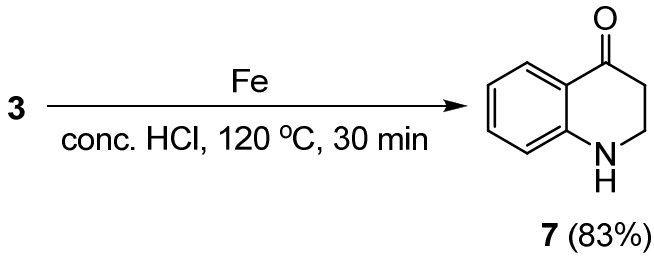


Figure 6.2. Reductive cyclization of **3** with iron in concentrated hydrochloric acid

We began our study on the conversion of 2'-nitrochalcone (**6a**) to (±)-3-phenyl-2,3-dihydro-4(1*H*)-quinolinone by attempting to effect the cyclization using iron powder in acetic acid since these conditions have proven successful in many of our other reactions. Unfortunately, this protocol yielded only mixtures of 2'-aminochalcone (**8a**) and its double bond reduction product **9a** (Figure 6.3). None of the 2,3-dihydro-3-phenyl-

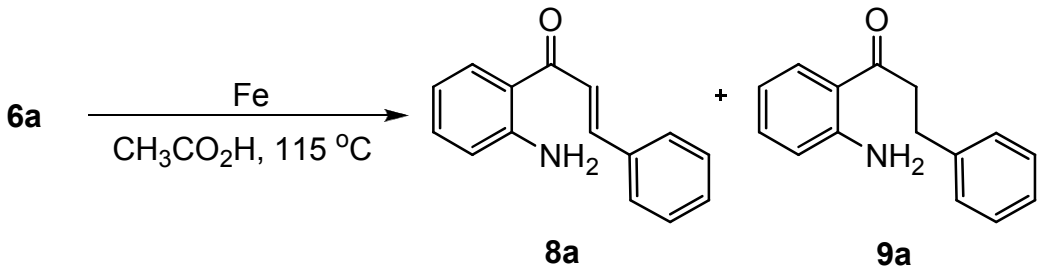
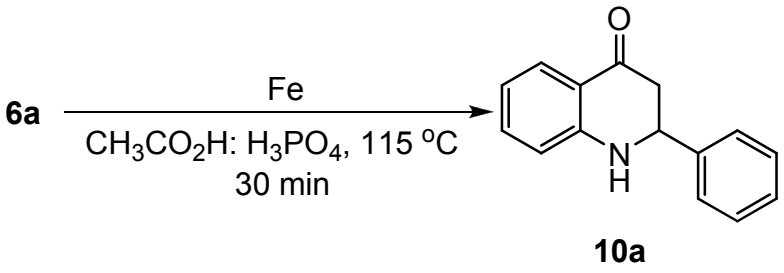


Figure 6.3. Reduction of **6a** with iron in acetic acid

quinolinone was observed. Similar results were obtained with substrates **6e** and **6f**.

We also explored the use of iron powdered in various mixtures of acetic acid and phosphoric acid since our work with **3** suggested that this might be successful. Under these conditions, the cyclization proceeded smoothly (Figure 6.4) with maximum yields in the 60-78% range. Best results were achieved using a 70:30 ratio of CH_3CO_2H:H_3PO_4. With higher percentages of phosphoric acid, the reaction became very thick due to reaction between iron and phosphoric acid. This impaired stirring, made extraction of the product difficult and decreased the isolated yields significantly (see Figure 6.4).

Based on the improvement in yield noted by using stronger acid, we decided to explore the use of iron powder in concentrated hydrochloric acid. Under these conditions, we found that yields improved to 70-90% for all cases. Surprisingly, no significant degradation of any of the ether groups was observed. It should be noted that



10a

CH_3CO_2H:H_3PO_4	Yield of **10a** (%)
100:0	3 [a]
90:10	24
80:20	50
70:30	78

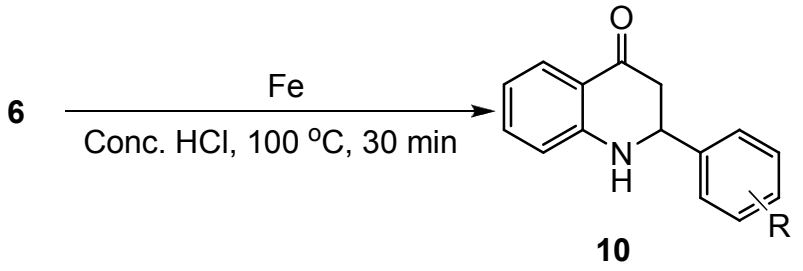
[a] Yield estimated from ^{1}H NMR

Figure 6.4. Reductive cyclization of **6a** with various mixtures of acetic acid and phosphoric acid

only substrates derived from benzaldehydes bearing resonance electron-donating substituents were explored. This was due to the fact that many electron-withdrawing groups, such as ester and cyano, are unstable to the basic conditions used to prepare the chalcones and others, such as nitro, are reduced in the cyclization reaction.

The optimized conditions involved treating 1.00 eq (*ca* 500 mg) of the 2'-nitrochalcone derivative **6** with four equivalents of iron powder in 10 mL of concentrated hydrochloric acid at 100 ^{o}C for 30 minutes. Again, it was important to add the iron to the hot mixture to achieve optimum yields with a minimum of side products. After quenching with ice water, extractive workup and recrystallization, the 3-

aryldihydroquinazolinones **10** were isolated in nearly pure form. Chromatography was generally not necessary since all reactions went to completion and gave highly crystalline products. Our results are summarized in Figure 6.5.



	R	Yield of **10** (%)
a	H	88
b	4-CH_3	85
c	4-CH_3O	82
d	3,4-$(CH_3O)_2$	73
e	3,4-OCH_2O	83
f	2-Cl	80

Figure 6.5. Reductive cyclization of **6** with iron in concentrated HCl

Following reduction of the nitro group in **6a**, two mechanistic pathways can be envisoned for the ring closure of aminochalcone **8a**. Iron does not appear to play a significant role in the cyclization since **8a** has been successfully cyclized to **10a** using 1:1 acetic acid/phosphoric acid[6] or concentrated hydrochloric acid (this study) without iron present. In the first mechanistic scenario, strong acid would protonate the carbonyl oxygen of **8a** to give **11**, which would be activated toward conjugate addition by the amino group. Since the amino function in **8a** is part of a vinylogous amide, it is not as basic as typical aniline nitrogen and, thus, some of the amino form should be present to

add to the activated enone system **10a**. Alternatively, strong acid conditions could also protonate the enone double bond to give the benzylic carbocation **12**, which would then be attacked by the nucleophilic aniline nitrogen. These mechanistic possibilities for the cyclization of **8a** to **10a** are outlined in Figure 6.6.

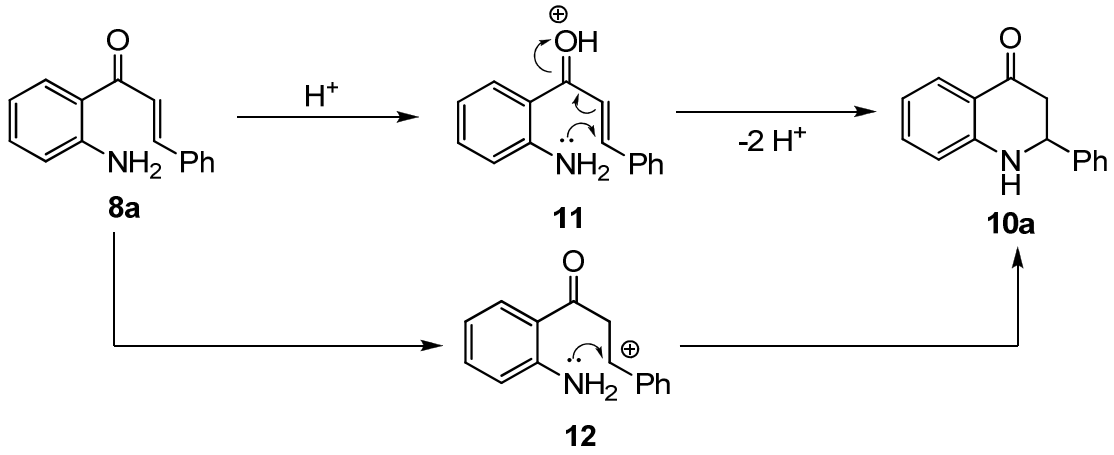


Figure 6.6. Mechanisitic possibilities of ring closure of 2'-aminochalcone

Conclusion

We have successfully developed a synthesis of 2,3-dihydro-4(1*H*)-quinolinone from 1-(2-nitrophenyl)prop-2-en-1-one and a series of (±)-3-aryl-2,3-dihydro-4(1*H*)-quinolinones from 2'-nitrochalcones. Reductive cyclization of these derivatives using iron powder in concentrated hydrochloric acid gave the best results, affording the target heterocycles in 72-88% yields. Products were obtained in good yields without the need for extensive purification. This synthetic approach is limited to chalcone substrates bearing electron-donating groups on the C3 aromatic ring carbon since these groups are most stable to the base used in the preparation and the reductive conditions in their final cyclization.

Experimental Section

All reactions were run under dry nitrogen in oven-dried glassware. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech No 21521) using ultraviolet or iodine vapor detection. Preparative separations were performed using flash chromatography[13] on silica gel (grade 62, 60-200 mesh) mixed with ultraviolet-active phosphor (Sorbent Technologies UV-5), or thin layer chromatography on 20-cm × 20-cm silica gel GF plates (Analtech 02015) band elution was monitored using a hand-held ultraviolet lamp. Melting points were taken on a MelTemp purchased from Laboratory Devices, Cambridge, MA 02139 and were uncorrected. Infrared spectra were taken on a Varian 800 FT-IR (Scimitar series) run as thin films on sodium chloride disks and were referenced to polystyrene. ^{1}H NMR and ^{13}C spectra were obtained using a UNITY INOVA 400 BB NMR spectrometer operating at 400 and 100 MHz respectively; In addition some ^{1}H and ^{13}C spectra were recorded using a broadband Gemini 2000 High-Resolution NMR (300 MHz) spectrometer operating at 300 MHz and 75 MHz, respectively. All NMR signals were referenced to internal tetramethylsilane; coupling constants (J) are reported in Hz. Low resolution mass spectra (direct probe/electron impact) were obtained at 70 electron volts or 30 electron volts as indicated. Elemental analysis were obtained at Atlantic Microlabs Inc., Norcross, GA 30091.

Tetrahydrofuran was dried over potassium hydroxide pellets and distilled from lithium aluminum hydride. All other commercial reagents and solvents were used as received. The ammonium chloride, sodium bicarbonate and sodium chloride used in various workup procedures refer to saturated aqueous solution.

1-(2-Nitrophenyl)prop-2-en-1-ol (2). The general procedure of Danishefsky and coworkers[12] was used. A 250-mL three-necked round-bottomed flask, equipped with magnetic stirring, a rubber septum and a reflux condenser (nitrogen inlet), was charged with 50 mL of dry tetrahydrofuran, followed by 3.00 g (19.9 mmoles) of 2-nitrobenzaldehyde (**1**). The reaction mixture was then cooled to −78 ºC, and 29.5 mL of 1.0 *M* vinylmagnesium bromide (29.5 mmoles) was added dropwise via syringe over a period of 20 minutes. The reaction was stirred for 2 hours at −78 ^{o}C at which time thin layer chromatography indicated the reaction was complete. The reaction mixture was then poured into 50 mL of 3 *M* HCl solution, stirred for 10 minutes and extracted with 50 mL of ether. The aqueous layer was then saturated with sodium chloride and extracted with ether (2 × 50 mL). The combined ether layers were washed with saturated sodium chloride solution, dried (magnesium sulfate) and concentrated under vacuum to yield 3.32 g (93%) of **2** as a viscous yellow liquid. This product was spectroscopically pure and was used in the next step without any further purification. IR: 3415, 1639, 1609, 1524, 1349 cm^{-1}; ^{1}H NMR (400 MHz): δ 7.90 (d, 1H, J = 7.7), 7.76 (d, 1H, J = 7.7), 7.64 (t, 1H, J = 7.9), 7.44 (t, 1H, J = 7.9), 6.07 (ddd, 1H, J = 17.2, 10.4, 5.3), 5.79 (d, 1H, J = 5.3), 5.41 (d, 1H, J = 17.2), 5.25 (d, 1H, J = 10.4), 2.82 (br s, 1H); ^{13}C NMR (100 MHz): δ 148.2, 138.0, 137.6, 133.5, 128.8, 128.4, 124.5, 116.1, 69.9; ms (30 eV): *m/z* 179 (M^{+}). *Anal*. Calcd. for $C_9H_9NO_3$: C, 60.34; H, 5.03; N, 7.82. Found: C, 60.51; H, 5.07; N, 7.69.

1-(2-Nitrophenyl)prop-2-en-1-one (3). A 100-mL three-necked round-bottomed flask, fitted with magnetic stirring, an addition funnel and a reflux condenser (nitrogen inlet), was charged with 3.00 g (16.7 mmoles) of **2** and 20 mL of acetone. To the resulting

solution was slowly added 8.5 mL of 2.97 *M* Jones reagent (25.5 mmoles) over a period of 25 minutes at room temperature. [***Note*:** The addition was done very slowly. Fast addition led to significant heating, loss of solvent and a reduced yield.] After 1 hour at room temperature, thin layer chromatography indicated that the reaction was complete. Excess Jones reagent was quenched with saturated sodium bisulfite solution (ca 3 mL), and the crude reaction mixture was extracted with 50 mL of ether. The aqueous layer was then saturated with sodium chloride solution and extracted again with ether (2 × 50 mL). The combined ether layers were washed with saturated sodium chloride, then dried (magnesium sulfate) and concentrated under vacuum. The crude product was purified by flash chromatography on a 20-cm × 2-cm silica gel column using increasing concentrations of ether in hexanes to give 2.26 g (76%) of **3** as a yellow oil. IR: 1672, 1613, 1527, 1347 cm^{-1}; ^{1}H NMR (300 MHz): δ 8.16 (dd, 1H, J = 8.2, 1.3), 7.75 (td, 1H, J = 7.5, 1.3), 7.65 (ddd, 1H, J = 8.2, 7.5, 1.5), 7.45 (dd, 1H, J = 7.5, 1.5), 6.65 (dd, 1H, J = 17.6, 10.6), 6.05 (d, 1H, J = 10.6), 5.85 (d, 1H, J = 17.6); ^{13}C NMR (75 MHz): δ 193.4, 146.8, 136.5, 135.4, 134.1, 131.2, 130.7, 128.8, 124.4; ms: *m/z* 177 (M^{+}). *Anal*. Calcd. for $C_9H_7NO_3$: C, 61.01; H, 3.95; N, 7.91. Found: C, 61.12; H, 3.98; N, 7.83.

Representative Aldol Condensation: (2*E*)-1-(2-Nitrophenyl)-3-phenylprop-2-en-1-one (6a). A 100-mL three-necked round-bottomed flask, equipped with magnetic stirring, an addition funnel and a nitrogen inlet, was charged with 800 mg (4.84 mmoles) of 2'-nitroacetophenone (**4**) and 15 mL of ethanol. The resulting solution was cooled to 0 ºC, stirring was begun, and 232 mg (5.80 mmoles, 1.2 eq) of sodium hydroxide powder was added and allowed to dissolve. To was added on a solution of 539 mg (5.08 mmoles, 1.05 eq) of benzaldehyde (**5a**) in 5 mL of ethanol dropwise with continued stirring. The

reaction was stirred for 3 hours at 0 ºC to give a white precipitate. The product was filtered, and the crystals which formed were washed thoroughly with ice-cold ethanol to give 1.16 g (95%) of **4a** as a white solid, mp 125-127 ºC (lit[14] mp 128 ºC). IR: 1652, 1608, 1527, 1347 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.18 (dd, 1H, J = 8.2, 1.1), 7.77 (td, 1H, J = 7.6, 1.1), 7.66 (td, 1H, J = 7.6, 1.1), 7.53-7.46 (complex, 3H), 7.42-7.34 (complex, 3H), 7.24 (d, 1H, J = 16.2), 7.01 (d, 1H, J = 16.2); ^{13}C NMR (100 MHz): δ 192.9, 146.7, 146.3, 136.3, 134.0, 133.9, 131.0, 130.5, 129.0, 128.8, 128.5, 126.2, 124.5; ms: *m/z* 253 (M^{+}).

(2*E*)-3-(4-Methylphenyl)-1-(2-nitrophenyl)prop-2-en-1-one (6b). This compound (1.25 g, 97%) was prepared from 800 mg (4.84 mmoles) of **4** and 610 mg (5.08 mmoles, 1.05 eq) of 4-methylbenzaldehyde (**5b**), and isolated as a pale yellow solid, mp 133-135 ºC (lit[14] mp 134-135 ºC) IR: 1652, 1599, 1528, 1348 cm^{-1}; ^{1}H NMR (300 MHz): δ 8.16 (dd, 1H, J = 7.7, 1.1), 7.76 (td, 1H, J = 7.7, 1.1), 7.65 (td, 1H, J = 7.7, 1.1), 7.50 (dd, 1H, J = 7.7, 1.1), 7.39 (d, 2H, J = 8.2), 7.21 (d, 1H, J = 15.9), 7.18 (d, 2H, J = 8.2), 6.97 (d, 1H, J = 15.9), 2.37 (s, 3H); ^{13}C NMR (75 MHz): δ 193.0, 146.52, 146.49, 141.7, 136.4, 133.9, 131.2, 130.4, 129.7, 128.8, 128.6, 125.3, 124.5, 21.5; ms: *m/z* 267 (M^{+}).

(2*E*)-3-(4-Methoxyphenyl)-1-(2-nitrophenyl)prop-2-en-1-one (6c). This compound (1.27 g, 93%) was prepared from 800 mg (4.84 mmoles) of **4** and 762 mg (5.08 mmoles, 1.05 eq) of 4-methoxybenzaldehyde (**5c**), and isolated as an off-white solid, mp 96-98 ºC. IR: 2840, 1645, 1600, 1528, 1348 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.16 (dd, 1H, J = 8.2, 1.2), 7.75 (dt, 1H, J = 7.5, 1.2), 7.64 (ddd, 1H, J = 8.2, 7.5, 1.4), 7.50 (dd, 1H, J = 7.5, 1.4), 7.45 (d, 2H, J = 8.8), 7.24 (d, 1H, J = 16.2), 6.90 (d, 1H, J = 16.2), 6.87 (d, 2H, J = 8.8), 3.83 (s, 3H); ^{13}C NMR (100 MHz): δ 192.9, 162.0, 146.6, 146.3, 136.5, 133.9,

130.40, 130.38, 128.8, 126.6, 124.5, 123.9, 114.4, 55.4; ms: *m/z* 283 (M^+). *Anal*. Calcd. for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.59; N, 4.95. Found: C, 67.88; H, 4.62; N, 4.87.

(2*E*)-3-(3,4-Dimethoxyphenyl)-1-(2-nitrophenyl)-prop-2-en-1-one (6d). This compound (1.44 g, 95%) was prepared from 800 mg (4.84 mmoles) of **4** and 914 mg (5.08 mmoles, 1.05 eq) of 3,4-dimethoxybenzaldehyde (**5d**), and isolated as a yellow solid, mp 116-117 ºC. IR: 2839, 1645, 1594, 1512, 1347 cm^{-1}; ^1H NMR (300 MHz): δ 8.18 (d, 1H, J = 7.7), 7.76 (td, 1H, J = 7.7, 1.1), 7.65 (td, 1H, J = 7.7, 1.6), 7.51 (dd, 1H, J = 7.7, 1.1), 7.19 (d, 1H, J = 15.9), 7.10-7.01 (complex, 2H), 6.89 (d, 1H, J = 15.9), 6.85 (d, 1H, J = 7.7), 3.91 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (75 MHz): δ 192.8, 151.8, 149.3, 146.6, 146.5, 136.5, 133.9, 130.4, 128.8, 126.7, 124.5, 124.2, 123.6, 111.0, 109.8, 56.0, 55.9; ms: *m/z* 313 (M^+). *Anal*. Calcd. for $C_{17}H_{15}NO_5$: 65.18; H, 4.79; N, 4.47. Found: C, 65.23; H, 4.78; N, 4.44.

(2*E*)-3-(1,3-Benzodioxol-5-yl)-1-(2-nitrophenyl)prop-2-en-1-one (6e). This compound (1.36 g, 95%) was prepared from 800 mg (4.84 mmoles) of **4** and 762 mg (5.08 mmoles) of piperonal (**5e**), and isolated as a pale yellow solid, mp 128-130 ºC. IR: 1650, 1599, 1528, 1384 cm^{-1}; ^1H NMR (300 MHz): δ 8.17 (d, 1H, J = 8.2), 7.76 (td, 1H, J = 7.7, 1.1), 7.64 (td, 1H, J = 8.2, 1.1), 7.51 (dd, 1H, J = 7.7, 1.6), 7.17 (d, 1H, J = 15.9), 7.03 (d, 1H, J = 1.6), 6.96 (dd, 1H, J = 7.7, 1.1), 6.84 (d, 1H, J = 15.9), 6.79 (d, 1H, J = 8.2), 6.02 (s, 2H); ^{13}C NMR (75 MHz): δ 192.7, 150.3, 148.5, 146.7, 146.1, 136.5, 133.9, 130.4, 128.8, 128.4, 125.5, 124.5, 124.2, 108.6, 106.7, 101.7; ms: *m/z* 297 (M^+). *Anal*. Calcd. for $C_{16}H_{11}NO_5$: C, 64.65; H, 3.70; N, 4.71. Found: C, 64.71; H, 3.73; N, 4.66.

(2*E*)-3-(2-Chlorophenyl)-1-(2-nitrophenyl)prop-2-en-1-one (6f). This compound (1.28 g, 92%) was prepared from 800 mg (4.84 mmoles) of **4** and 714 mg (5.08 mmoles,

1.05 eq) of 2-chlorobenzaldehyde (**5f**), and isolated as a pale yellow solid, mp 87-88 ºC (lit[14] mp 88-89 ºC). IR: 1657, 1605, 1527, 1347 cm^{-1}; ^{1}H NMR (300 MHz): δ 8.20 (d, 1H, J = 7.7), 7.79 (t, 1H, J = 7.1), 7.75-7.60 (complex, 3H), 7.53 (d, 1H, J = 7.1), 7.42-7.23 (complex, 3H), 6.97 (d, 1H, J = 16.5); ^{13}C NMR (75 MHz): δ 192.8, 146.7, 141.8, 136.0, 135.2, 134.1, 132.2, 131.7, 130.7, 130.2, 128.9, 128.6, 127.8, 127.2, 124.5; ms: *m/z* 287, 289 (*ca* 3:1, M^{+}).

2,3-Dihydro-4(1*H*)-quinolinone (7). A 100-mL one-necked round-bottomed flask, equipped with magnetic stirring, and a reflux condenser (nitrogen inlet), was charged with 400 mg (2.26 mmoles) of **3** and 10 mL of concentrated hydrochloric acid and the mixture was brought to reflux in a pre-heated oil bath at 120 ºC. The heat was briefly removed, 630 mg (1.13 mmoles, 5 eq) of iron powder (>100 mesh) was added, and heating was resumed for 1 hour. The reaction mixture was cooled, poured into ice water, and extracted with 50 mL of ether. The aqueous layer was then saturated with sodium chloride and extracted again with ether (1 x 50 mL) and ethyl acetate (1 x 50 mL). The combined organic layers were washed with saturated sodium chloride solution, dried (magnesium sulfate) and concentrated under vacuum. The resulting mixture was flash chromatographed on 20-cm × 2-cm silica gel column eluted with increasing concentrations of ether in hexane to give 276 mg (83 %) of **7** as a yellow solid, mp 42-44 ºC (lit.[15] mp 43-44.5 ºC). IR: 3347, 1659, 1611 cm^{-1}; ^{1}H NMR (300 MHz): δ 7.84 (dd, 1H, J = 8.2, 1.1), 7.29 (td, 1H, J = 7.7, 1.1), 6.74 (t, 1H, J = 7.7), 6.67 (d, 1H, J = 8.2), 4.43 (br s, 1H), 3.58 (t, 2H, J = 6.6), 2.70 (t, 2H, J = 6.6); ^{13}C NMR (75 MHz): δ 193.7, 152.0, 135.1, 127.6, 119.4, 117.9, 115.8, 42.3, 38.1; ms: *m/z* 147 (M^{+}). *Anal*. Calcd. for C_9H_9NO: C, 73.47; H, 6.12; N, 9.52. Found: C, 73.51; H, 6.11; N, 9.47.

This same reaction was carried out using 5 eq of iron powder in 1:1 v/v acetic acid/phosphoric acid, but the product yield was only 72%. This reaction was more difficult to perform due to the formation of a heavy insoluble precipitate during the heating period.

Attempted Reductive Cyclization of 6a with Iron Powder in Acetic Acid: (2*E*)-1-(2-Aminophenyl)prop-2-en-1-one (8a) and 1-(2-aminophenyl)propan-1-one (9a). A 100-mL one-necked round-bottomed flask was charged with 500 mg (1.98 mmoles) of **6a** in 10 mL of acetic acid and the solution was brought to reflux in a preheated oil bath at 120 ºC. The heat was briefly removed, 440 mg (7.88 mmoles) of iron powder (>100 mesh) was added heating was resumed for 10 minutes. The reaction mixture was cooled, poured into ice-cold water and extracted with ether (3 × 25 mL). The combined ether layers were washed with saturated sodium bicarbonate (three times) and saturated sodium chloride (one time), then dried (magnesium sulfate) and concentrated under vacuum. The crude product was purified on a 40-cm × 2-cm silica gel column eluted with increasing concentrations of ether in hexanes to give 220 mg (50%) of **8a** as a yellow solid, mp 70-71 ºC (lit[4] mp 72 ºC) and 169 mg (38%) of **9a** as a yellow solid, mp 85-86 ºC. The spectral data for **8a** were: IR: 3471, 3334, 1645, 1614 cm^{-1}; ^{1}H NMR (400 MHz): δ 7.85 (dd, 1H, J = 8.4, 1.4), 7.74 (d, 1H, J = 15.6), 7.62 (d, 1H, J = 15.6). 7.60 (obscured, 1H), 7.43-7.33 (complex, 4H), 7.28 (ddd, 1H, J = 8.4, 7.2, 1.6), 6.69 (overlapping d and t, 2H, J ≈ 8.0) 6.34 (br s, 2H); ^{13}C NMR (100 MHz): δ 191.6, 150.9, 142.8, 135.2, 134.3, 130.9, 130.0, 128.8, 128.2, 123.0, 118.9, 117.2, 115.8; ms: *m/z* 223 (M^{+}).

The spectral data for **9a** were: IR: 3475, 3346, 1647, 1614 cm^{-1}; ^{1}H NMR (400 MHz): δ 7.73 (dd, 1H, J = 6.6, 8.2), 7.33-7.16 (complex, 6H), 6.65 (d, 1H, J = 7.2), 6.63

(td, 1H, J = 7.7, 1.0), 6.26 (br s, 2H), 3.28 (t, 2H, J = 7.4), 3.04 (t, 2H, J = 7.4); ^{13}C NMR (100 MHz): δ 201.5, 150.3, 141.5, 134.3, 131.0, 128.5, 128.4, 126.0, 117.8, 117.3, 115.8, 41.0, 30.6; ms: *m/z* 225 (M^+). *Anal*. Calcd. for $C_{15}H_{15}NO$: C, 80.00; H, 6.67; N, 6.22. Found: C, 79.93; H, 6.69; N, 6.17.

(2*E*)-1-(2-Aminophenyl)-3-(1,3-benzodioxol-5-yl)prop-2-en-1-one (8e) and 1-(2-aminophenyl)-3-(1,3-benzodioxol-5-yl)propan-1-one (9e). Reduction of 500 mg (1.68 mmoles) of **6e** using 375 mg (6.72 mmoles) of iron powder gave 207 mg (46%) of **8e** as a yellow solid, mp 110-112 ºC, and 171 mg (40%) of **9e** as a yellow solid, mp 85-87 ºC. The spectral data for **8e** were: IR: 3468, 3339, 1643, 1614 cm^{-1}; ^{1}H NMR (300 MHz): δ 7.85 (dd, 1H, J = 8.2, 1.1), 7.67 (d, 1H, J = 15.4), 7.45 (d, 1H, J = 15.4), 7.29 (dt, 1H, J = 8.2, 1.6), 7.16 (d, 1H, J = 1.6), 7.11 (dd, 1H, J = 8.2, 1.6), 6.84 (d, 1H, J = 8.2), 6.70 (m, 2H), 6.31 (br s, 2H), 6.02 (s, 2H); ^{13}C NMR (75 MHz): δ 191.6, 150.9, 149.5, 148.3, 142.8, 134.1, 130.9, 129.7, 124.7, 121.1, 119.2, 117.3, 115.8, 108.6, 106.6, 101.5; ms: *m/z* 267 (M^+). *Anal*. Calcd. for $C_{16}H_{13}NO_3$: C, 71.91; H, 4.87; N, 5.24. Found: C, 71.98; H, 4.89; N, 5.15.

The spectral data for **9e** were: IR: 3468, 3352, 1645, 1614 cm^{-1}; ^{1}H NMR (300 MHz): δ 7.72 (d, 1H, J = 7.7), 7.26 (t, 1H, J = 7.7), 6.78-6.59 (complex, 5H), 6.27 (br s, 2H), 5.92 (s, 2H), 3.23 (t, 2H, J = 7.6), 2.96 (t, 2H, J = 7.6); ^{13}C NMR (75 MHz): δ 201.4, 150.3, 147.6, 146.3 135.3, 134.2, 131.0, 121.1, 117.8, 117.3, 115.8, 108.9, 108.2, 100.8, 41.2, 30.3; ms: *m/z* 269 (M^+). *Anal*. Calcd. for $C_{16}H_{15}NO_3$: C, 71.38; H, 5.58; N, 5.20. Found: C, 71.44; H, 5.61; N, 5.14.

(2*E*)-1-(2-Aminophenyl)-3-(2-chlorophenyl)prop-2-en-1-one (8f) and 1-(2-aminophenyl)-3-(2-chlorophenyl)propan-1-one (9f). Reduction of 500 mg (1.74

mmoles) of **6f** using 389 mg (6.96 mmoles) of iron gave 235 mg (53%) of **8f** as a yellow solid, mp 87-89 ^{o}C, and 156 mg (34%) of **9f** as a yellow solid, mp 86-87 ^{o}C. The spectral data for **8f** were: IR: 3464, 3338, 1644, 1615 cm^{-1}; ^{1}H NMR (300 MHz): δ 8.11 (d, 1H, J = 15.4), 7.84 (d, 1H, J = 8.2), 7.73 (m, 1H), 7.59 (d, 1H, J = 15.4), 7.43 (m, 1H), 7.36-7.25 (complex, 3H), 6.70 (d, 1H, J = 7.7), 6.69 (t, 1H, J = 7.7), 6.37 (br s, 2H); ^{13}C NMR (75 MHz): δ 191.3, 151.1, 138.7, 135.2, 134.5, 133.6, 131.1, 130.7, 130.2, 127.7, 127.0, 125.8, 118.8, 117.3, 115.8; ms: *m/z* 257, 259 (*ca* 3:1, M^{+}). *Anal*. Calcd for $C_{15}H_{12}ClNO$: C, 69.90; H, 4.66; N, 5.44. Found: C, 69.97; H, 4.67; N, 5.39.

The spectral data for **9f** were: IR: 3478, 3348, 1647, 1615 cm^{-1}; ^{1}H NMR (300 MHz): δ 7.73 (d, 1H, J = 8.2), 7.38-7.12 (complex, 5H), 6.64 (d, 1H, J = 8.2), 6.62 (t, 1H, J = 7.7), 6.28 (br s, 2H), 3.27 (m, 2H), 3.14 (m, 2H); ^{13}C NMR (75 MHz): δ 201.2, 150.3, 139.0, 134.3, 133.9, 131.0, 130.6, 129.5, 127.6, 126.9, 117.7, 117.3, 115.8, 39.0, 28.7; ms: *m/z* 259, 261 (*ca* 3:1, M^{+}). *Anal*. Calcd. for $C_{15}H_{14}ClNO$: C, 69.36; H, 5.39; N, 5.39. Found: C, 69.45; H, 5.44; N, 5.30.

Attempted Reductive Ring Closure with Iron Powder in Acetic Acid/Phosphoric Acid Mixtures: **(±)-2-Phenyl-2,3-dihydro-4(1*H*)-quinolinone (10a)**. Using the procedure given for the preparation of **3** (with various ratios of acetic acid:phosphoric acid), 500 mg (1.97 mmoles) of **6a** and 440 mg (7.88 mmoles) of iron were reacted for 30 minutes at 120 ^{o}C. Product **10a** was formed, but the maximum yields were generally not as high as the procedure using iron and concentrated HCl. Yields for different acid mixtures are given in Figure 6.4.

Representative Reductive Ring Closure using Iron Powder in Concentrated Hydrochloric Acid: (±)-2-Phenyl-2,3-dihydro-4(1*H*)-quinolinone (10a). A 100-mL

one-necked round-bottomed flask, equipped with magnetic stirring and a reflux condenser (nitrogen inlet), was charged with 500 mg (1.97 mmoles) of **6a** and 10 mL of concentrated hydrochloric acid and heated to 80-85 ºC (oil bath). The heat was briefly removed, and 440 mg (7.88 mmoles, 4 eq) of iron powder (>100 mesh) was added. [*Caution!* The addition is sufficiently exothermic to boil the mixture. The reaction froths while adding the iron powder.] Heating was resumed at 100 ºC until thin layer chromatography indicated complete consumption of the starting material (*ca* 30 minutes). The reaction was cooled, added to 50 mL of water and extracted with ether (2 × 25 mL) and ethyl acetate (1 × 25 mL). The combined organic layers were washed with saturated sodium chloride, dried (magnesium sulfate) and concentrated under vacuum. The resulting mixture was flash chromatographed on 20-cm × 2-cm silica gel column eluted with increasing concentrations of ether in hexanes to give 386 mg (88%) of **10a** as a pale yellow solid, mp 149-151 ºC (lit[3] mp 149-150 ºC). IR: 3326, 1661, 1608, 1482 cm^{-1}; ^{1}H NMR (400 MHz): δ 7.87 (dd, 1H, J = 8.0, 1.5), 7.45 (dd, 2H, J = 7.6, 1.5), 7.42-7.31 (complex, 4H), 6.78 (t, 1H, J = 7.6), 6.71 (d, 1H, J = 8.2), 4.74 (dd, 1H, J = 13.8, 3.7), 4.55 (br s, 1H), 2.87 (dd, 1H, J = 16.2, 13.8), 2.77 (dm, 1H, J = 16.2); ^{13}C NMR (100 MHz): δ 193.3, 151.5, 141.0, 135.4, 128.9, 128.4, 127.6, 126.6, 119.0, 118.4, 115.9, 58.4, 46.4; ms: *m/z* 223 (M^{+}).

(±)-2-(4-Methylphenyl)-2,3-dihydro-4(1*H*)-quinolinone (10b). Reductive cyclization of 415 mg (1.87 mmoles) of **6b** with 417 mg (7.48 mmoles, 4 eq) of iron gave 378 mg (85%) of **10b** as an off-white solid, mp 147-149 ºC (lit[3] mp 148-149 ºC). IR: 3331, 1655, 1608 cm^{-1}; ^{1}H NMR (300 MHz): δ 7.87 (d, 1H, J = 7.7), 7.35 (d, 2H, J = 7.7), 7.34 (obscured signal, 1H), 7.21 (d, 2H, J = 7.7), 6.79 (t, 1H, J = 7.7), 6.70 (d, 1H, J = 8.2),

4.72 (dd, 1H, J = 13.7, 3.7), 4.47 (br s, 1H), 2.88 (dd, 1H, J = 16.2, 13.7), 2.75 (dd, 1H, J = 16.2, 3.7), 2.37 (s, 3H); ^{13}C NMR (75 MHz): δ 193.4, 151.6, 138.3, 138.0, 135.3, 129.6, 127.6, 126.5, 119.0, 118.4, 115.9, 58.2, 46.5, 21.1; ms: *m/z* 237 (M^+). *Anal*. Calcd. for $C_{16}H_{15}NO$: C, 81.01; H, 6.33; N, 5.91. Found: 80.94; H, 6.32; N, 5.85.

(±)-2-(4-Methoxyphenyl)-2,3-dihydro-4(1*H*)-quinolinone (10c). Reductive cyclization of 415 mg (1.76 mmoles) of **6c** with 393 mg (7.04 mmoles, 4 eq) of iron gave 365 mg (82%) of **10c** as a yellow solid, mp 147-148 ºC (lit[8c] mp 147 ºC). IR: 3329, 2836, 1660, 1608 cm^{-1}; ^{1}H NMR (400 MHz): δ 7.87 (dd, 1H, J = 8.0, 1.6), 7.37 (d, 2H, J = 8.6), 7.33 (td, 1H, J = 7.7, 1.2), 6.92 (d, 2H, J = 8.6), 6.78 (t, 1H, J = 7.7), 6.70 (d, 1H, J = 8.2), 4.69 (dd, 1H, J = 13.8, 3.7), 4.48 (br s, 1H), 3.82 (s, 3H), 2.87 (dd, 1H, J = 16.2, 13.8), 2.74 (dd, 1H, J = 16.2, 3.7); ^{13}C NMR (75 MHz): δ 193.5, 159.6, 151.6, 135.3, 133.0, 127.8, 127.6, 119.0, 118.3, 115.9, 114.2, 57.9, 55.3, 46.5; ms: *m/z* 253 (M^+). *Anal*. Calcd. for $C_{16}H_{15}NO_2$: C, 75.89; H, 5.93; N, 5.53. Found: C, 75.83; H, 5.94; N, 5.49.

(±)-2-(3,4-Dimethoxyphenyl)-2,3-dihydro-4(1*H*)-quinolinone (10d). Reductive cyclization of 426 mg (1.59 mmoles) of **6d** and 355 mg (6.36 mmoles, 4 eq) of iron gave 326 mg (72%) of **10d** as a white solid, mp 145-147 ºC. IR: 3348, 2836, 1660, 1611 cm^{-1}. ^{1}H NMR (300 MHz): δ 7.87 (d, 1H, J = 7.7), 7.35 (t, 1H, J = 7.1), 7.00 (s, 1H), 6.99 (d, 1H, J = 7.7), 6.87 (d, 1H, J = 8.2), 6.80 (t, 1H, J = 7.7), 6.72 (d, 1H, J = 8.2), 4.70 (dd, 1H, J = 13.7, 3.7), 4.51 (br s, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 2.88 (dd, 1H, J = 15.9, 13.7), 2.75 (dd, 1H, J = 15.9, 3.7); ^{13}C NMR (75 MHz): δ 193.4, 151.5, 149.3, 149.0, 135.3, 133.5, 127.6, 119.0, 118.9, 118.4, 115.9, 111.2, 109.4, 58.3, 55.97, 55.94, 46.7; ms: *m/z* 283 (M^+). *Anal*. Calcd. for $C_{17}H_{17}NO_3$: C, 72.08; H, 6.01; N, 4.95. Found: C, 72.11; H, 6.02; N, 4.91.

(±)-2-(1,3-Benzodioxol-5-yl)-2,3,dihydro-4(1*H*)-quinolinone (10e). Reductive cyclization of 423 mg (1.68 mmoles) of **6e** and 375 mg (6.72 mmoles, 4 eq) of iron gave 374 mg (83%) of **10e** as an off-white solid, mp 145-147 ºC. IR: 3328, 1663, 1610 cm^{-1}; ^1H NMR (300 MHz): δ 7.86 (d, 1H, J = 7.7), 7.34 (td, 1H, J = 7.7, 1.6), 6.97 (d, 1H, J = 1.1), 6.89 (dd, 1H, J = 8.0, 1.6), 6.79 (overlapping d and t, 2H, J ≈ 8.2), 6.71 (d, 1H, J = 8.2), 5.98 (s, 2H), 4.65 (dd,1H, J = 13.4, 3.7), 4.49 (br s, 1H), 2.83 (dd, 1H, J = 16.2, 13.4), 2.71 (dd, 1H, J = 16.2, 3.7); ^{13}C NMR (75 MHz): δ 193.3, 151.5, 148.0, 147.6, 135.4, 134.9, 127.6, 120.1, 119.0, 118.4, 115.9, 108.5, 106.9, 101.2, 58.3, 46.6; ms: *m/z* 267 (M^+). *Anal*. Calcd. for $C_{16}H_{13}NO_3$: C, 71.91; H, 4.87; N, 5.24. Found: C, 71.92; H, 4.89; N, 5.22.

(±)-2-(2-Chlorophenyl)-2,3-dihydro-4(1*H*)-quinolinone (10f). Reductive cyclization of 399 mg (1.73 mmoles) of **6f** and 386 mg (6.92 mmoles, 4 eq) of iron gave 357 mg (80%) of **10f** as a yellow solid, mp 126-128 ºC. IR: 3429, 1659, 1609 cm^{-1}. ^1H NMR (300 MHz): δ 7.88 (d, 1H, J = 7.7), 7.68 (dd, 1H, J = 7.1, 1.6), 7.44-7.23 (complex, 4H), 6.81 (t, 1H, J = 7.1), 6.74 (d, 1H, J = 8.2), 5.27 (dd, 1H, J = 12.1, 3.7), 4.52 (br s, 1H), 2.96 (ddd, 1H, J = 16.2, 3.7, 1.5), 2.78 (dd, 1H, J = 16.2, 12.1); ^{13}C NMR (75 MHz): δ 192.7, 151.5, 138.3, 135.4, 132.8, 130.0, 129.3, 127.6, 127.5, 127.4, 119.1, 118.7, 116.0, 54.2, 44.0; ms: *m/z* 257, 259 (*ca* 3:1, M^+). *Anal*. Calcd. for $C_{15}H_{12}ClNO$: C, 69.90; H, 4.66; N, 5.44. Found: C, 69.97; H, 4.69; N, 5.39.

Cyclization of 8a Using Concentrated Hydrochloric Acid: **(±)-2-Phenyl-2,3-dihydro-4(1*H*)-quinolinone (10a)**. Using the procedure for the reductive cyclization of **6a** to **10a** above, 150 mg (0.67 mmoles) of **8a** and 6 mL of concentrated hydrochloric acid were treated with 150 mg (2.69 mmoles, 4 eq) of iron powder at 100 ^oC for 3 hours. Workup

and purification on a 20 cm x 20 cm preparative thin layer chromatography plate, eluted with 30% ether in hexanes, yielded 128 mg (85%) of **10a** as a pale yellow solid. The physical properties and spectral data matched those reported above.

References and Notes

1. [a] Bunce, R. A.; Herron, D. M.; Ackerman, M. L. *J. Org. Chem.* **2000**, *65*, 2847. [b] Bunce, R. A.; Randall, M. H.; Applegate, K. G. *Org. Prep. Proced. Int.* **2002**, *34*, 493. [c] Bunce, R. A.; Nammalwar, B. *J. Heterocyclic. Chem.* **2009**, *46*, 172. [d] Bunce, R. A.; Nammalwar, B. *J. Heterocyclic. Chem.* **2009**, *46*, 854.
2. Ibrahim, E.-S.; Montgomerie, A. M.; Sneddon, A. H.; Proctor, G. R.; Green, B. *Eur. J. Med. Chem.* **1988**, *23*, 183.
3. [a] Xia, Y.; Yang, Z.-Y.; Bastow, K. F.; Tachibana, Y.; Kuo, S.-C.; Hamel, E.; Hackl, T.; Lee, K.-H. *J. Med. Chem.* **1998**, *41*, 1155. [b] Shintani, R.; Yamagami, T.; Kimura, T.; Hayashi, T. *Org. Lett.* **2005**, *7*, 5317. [c] Choi, S.; Jung, K.; Ryu, J. *Arch. Pharm. Res.* **2006**, *29*, 369.
4. [a] Mannich, C.; Dannehl, M. *Chem. Ber.* **1938**, *71B*, 1899; no yield reported. [b] Tokes, A. L.; Szilagyi, L. *Synth. Commun.* **1987**, *17*, 1235; a yield of 24% was reported.
5. Donnelly, J. A.; Farrell, D. F. *J. Org. Chem.* **1990**, *55*, 1757.
6. [a] Tokes, A. L.; Szilagyi, L. *Synth. Commun.* **1989**, *19*, 3159. [b] Kundu, N. G.; Mahanty, J. S.; Das, P.; Das, B. *Tetrahedron Lett*. **1993**, *34*, 1625. [c] See ref 5.
7. Varma, R. S. *J. Heterocycl. Chem.* **1999**, *36*, 1565.
8. [a] Kumar, K. H.; Muralidharan, D.; Perumal, P. T. *Synthesis* **2004**, 63. [b] Ahmed, N.; van Lier, J. E. *Tetrahedron Lett*. **2006**, *47*, 2725. [c] Kumar, K. H.;

Perumal, P. T. *Can. J. Chem*. **2006**, *84*, 1079. [d] Ahmed, N.; van Lier, J. E. *Tetrahedron Lett*. **2007**, *48*, 13. [e] Lee, J. I.; Youn, J. S. *Bull. Korean Chem. Soc*. **2008**, *29*, 1853.

9. Kumar, D.; Patel, G.; Mishra, B. G.; Varma, R. S. *Tetrahedron Lett.* **2008**, *49*, 6974.

10. Saito, A.; Kasai, J.; Fukaya, H.; Hanzawa, Y. *J. Org. Chem.* **2009**, *74*, 5644.

11. Chandrasekhar, S.; Vijeender, K.; Sridhar, Ch. *Tetrahedron Lett.* **2007**, *48*, 4935.

12. Shen, W.; Coburn, C. A.; Bornmann, W. G.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 611.

13. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

14. Barnes, R. P.; Graham, J. H.; Qureshi, M. A. S. *J. Org. Chem.* **1963**, *28*, 2890.

15. Johnson, W. S.; Woroch, E. L.; Buell, B. G. *J. Am. Chem. Soc.* **1949**, *71*, 1901.

CHAPTER VII

EFFICIENT SYNTHENTIC ROUTE FOR THE SYNTHESIS OF SHETA2 HETEROAROTINOID DRUG

Introduction

Kidney cancer is known to have a high mortality rate due to a lack of treatment options.[1] The incidence of renal cancer appears to have increased over the last 50

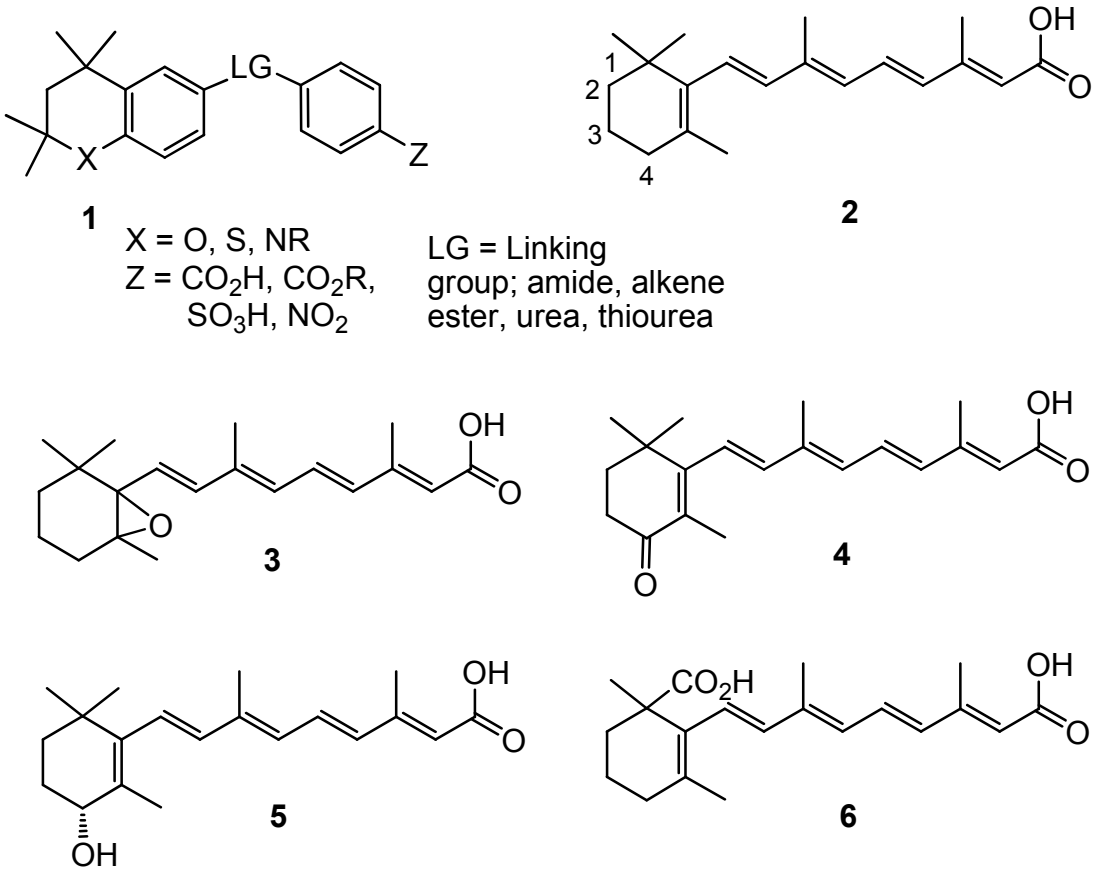


Figure 7.1. Structures of retinoic acid and heterarotinoid rings

years.[2] Preliminary evidence is available which demonstrates that certain heteroarotinoids can be effective in the treatment of such cancers.[3] Heteroarotinoids **1** have been known for more than a decade with much of the early chemistry being reviewed in 2002.[4]

The basic structural unit **1** was originally designed for heteroarotinoids as illustrated above and was based, in part, on a partial structural relationship with *trans*-retinoic acid (**2**) (see Figure 7.1). Studies of the biological activity of **2** and isomers thereof revealed them to possess high toxicity and therefore limited utility.[5] Pioneering work in which heteroatoms were inserted into strategic positions, as shown in **1**, within the molecular framework reduced the toxicity significantly.[4,6] Since an aryl ring was also present, the term heteroarotinoids was established to identify such systems.[4,6] The toxicity associated with acid **2** has been presumed to arise from metabolites the major members of which are shown as **3**-**6**.[7] An initial objective was to ascertain if heteroarotinoids with a heteroatom at C-4 had reduced toxicity and to avoid oxidation at the C-4 position which could lead to derivatives reminiscent of those from **2**, such as **4** and **5** which are toxic. The hypothesis that heteroatoms reduce toxicity has been validated.[4,6,8,9] Moreover, the addition of the benzene ring fused to the cyclohexyl unit in **1** would also prevent epoxidation as found in **3** derived from **2**. Variations in the linking group also produced marked changes in biological responses.[6,8-21] A second benzene ring with a functional group *Z* in **1** locked the double bonds into a *cis*-arrangement at the terminus which was deemed important for activity. Consequently, strong activity against cancers for the breast, head/neck, kidney, and lung has been observed.[8-23]

The long term objective of the current research is to provide the foundation *N*-(3,4-dihydro-2,2,4,4-tetramethyl-2*H*-1-benzothiopyran-6-yl)-*N'*-(4-nitrophenyl) thiourea **7** to be acceptable to the FDA as an agent to treat or prevent kidney cancer and possibly other cancers.[3,32-33] The identification and importance in meeting the MIST (human metabolites in safety testing) standards for metabolites of potential drugs are well documented.[36-39] The synthetic work outlined in this chapter was needed before biological evaluations of the metabolites could be made. However, as small samples of the metabolites become available, they will be sent to NCI as for preliminary screening.

The most recent discovery is that the thiourea derivative **7** has enhanced inhibitory properties with respect to cancers of the breast, head-neck, kidneys, lung and certain ovarian cancers.[3,12-15,17-23] The urea derivative **8** has also displayed strong activity against ovarian cancer cells[18] and especially against kidney cancers.[3] Of prime significance was the observation that no inhibitory activity against benign cells has been detected with **7** and related urea and thiourea analogs.[15,19] Preclinical pharmacokinetic studies have revealed that plasma protein binding by **7** is 99.3-99.5% at low micromolar concentrations which is a useful clinical range.[23] An interesting observation is that **8** forms co-crystals to a large extent in the solid state while **7** forms them to a lesser extent. The area of co-crystals, as correlated to drug discovery, has now been established and includes a number of substituted ureas and derivatives.[38]

A need to obtain metabolites from **7** is imperative to satisfy federal requirements prior to filing a request for FDA approval of the agent for human use. Although the metabolities are known,[2,39] an appraisal of biological activity and toxicity will be required in the near future. A determination of the major metabolites of **7** has been accomplished

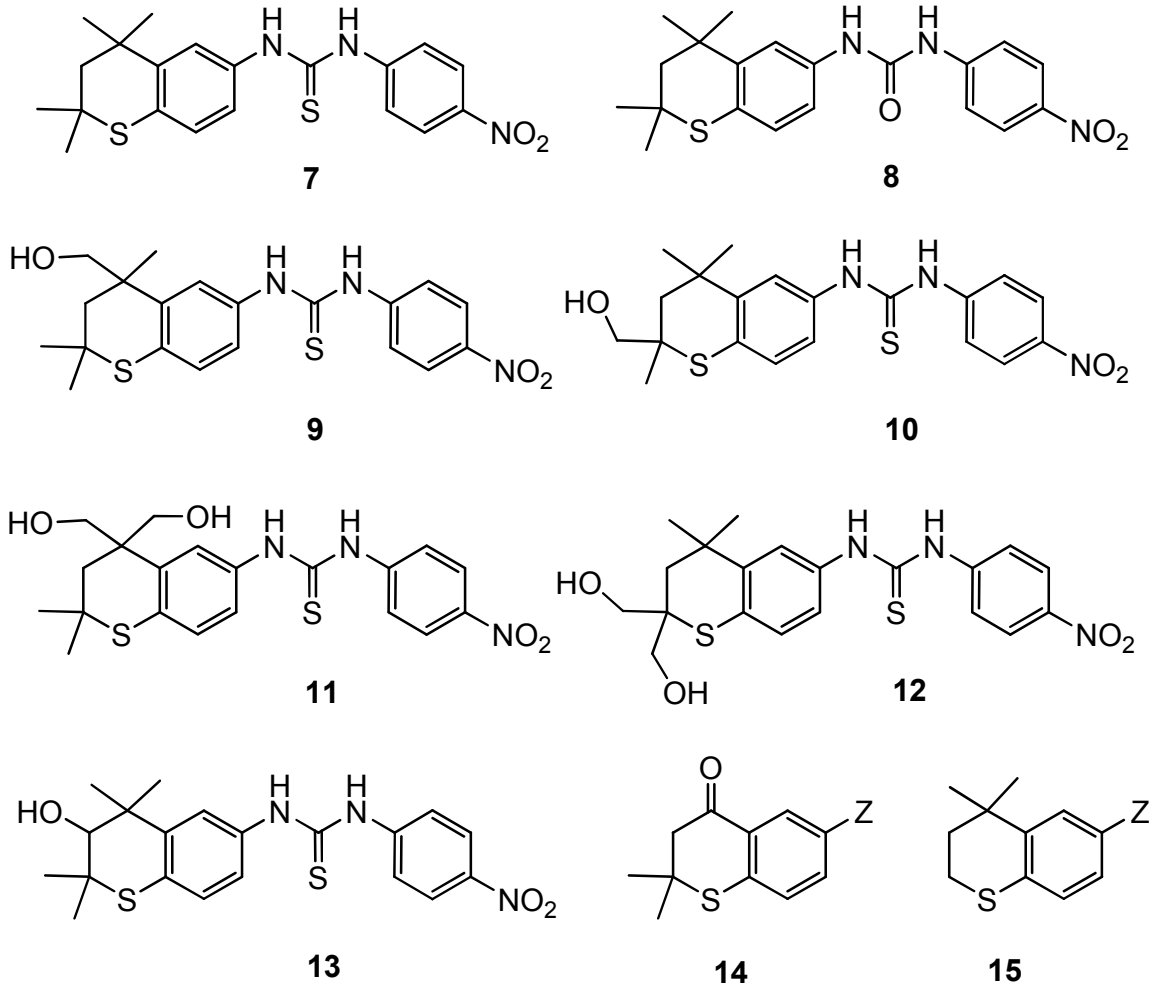


Figure 7.2. Various heteroarotinoid metabolites

with compound **9-13** being identified (see Figure 7.2).[41] The metabolites **9-13** from **7** are somewhat reminiscent of alcohol **5** which arose from **2**. Oxidation of the cyclohexyl unit to give a secondary alcohol **13** is surprising since the position is hindered by flanking methyl groups. Agent **7** regulates, growth, differentiation, and apotosis in cancer cells,[3] but it is not known if the metabolites are involved. Consequently, it is important to obtain such metabolites[36-39] for future evaluation of biological activity and for

comparison of activities with those of **7**. This work will aid in eventual identification of the location of hydroxymethyl groups which initiate the greatest apoptosis action.[13] It is important to recognize that **7** induces apoptosis in cancer cells and not benign cells.[15]

The need for an improved synthesis of **7** is apparent. Preclinical trials of **7** are nearly complete by the National Cancer Institute (NCI) of the National Institutes of Health (NIH). A second toxicity study is underway and will be complete by March, 2010, with human clinical trials to begin in the early summer of 2010. If **7** is to be approved by the FDA and brought to market, a high yielding synthetic procedure to obtain the compound must be available to minimize costs. Consequently, this part of the thesis has been directed to the development of a preparative methodology to obtain **7** in the highest yield possible.

Results and Discussion

The goal of this project was to develop improved methodology for the synthesis of SHetA2 (**7**) potentially applicable to a commercial scaleup with few steps and high yields for all intermediates and the final product. The synthetic pathways for the prepartion of SHetA2 are outlined in Figure 7.3**.** Methyl ketone **18** was prepared from acetamidothiophenol (1**6**) by a Michael addition with mesityl oxide (**17**) in chloroform with triethylamine at reflux to give **18** (89%). In this case, it was found that an addition of 0.6 equivalent excess of mesityl oxide and triethylamine at regular intervals (~ every 4 h) ensured completion of the reaction. In this manner a 5% increase in the yield of **18** (83%) was realized compared to that reported.[40]

Treatment of methyl ketone **18** with excess methyllithium (3 equivalents) gave alcohol **19**. The addition protocol and temperature played vital roles in the conversion of

ketone **18** to alcohol **19**. Initially the reaction was cooled to -50 ºC, and 1.5 equivalents of methyllithium was added quickly over a period of 20 minutes. The remaining 1.5 equivalents of methyllithium was added slowly and dropwise over a period of 1 hour. When the addition was complete, the reaction was stirred at -5 ºC for 1 hour and finally at room temperature for 1 hour. Stirring at room temperature ensured a high yield (82%) of **19**.

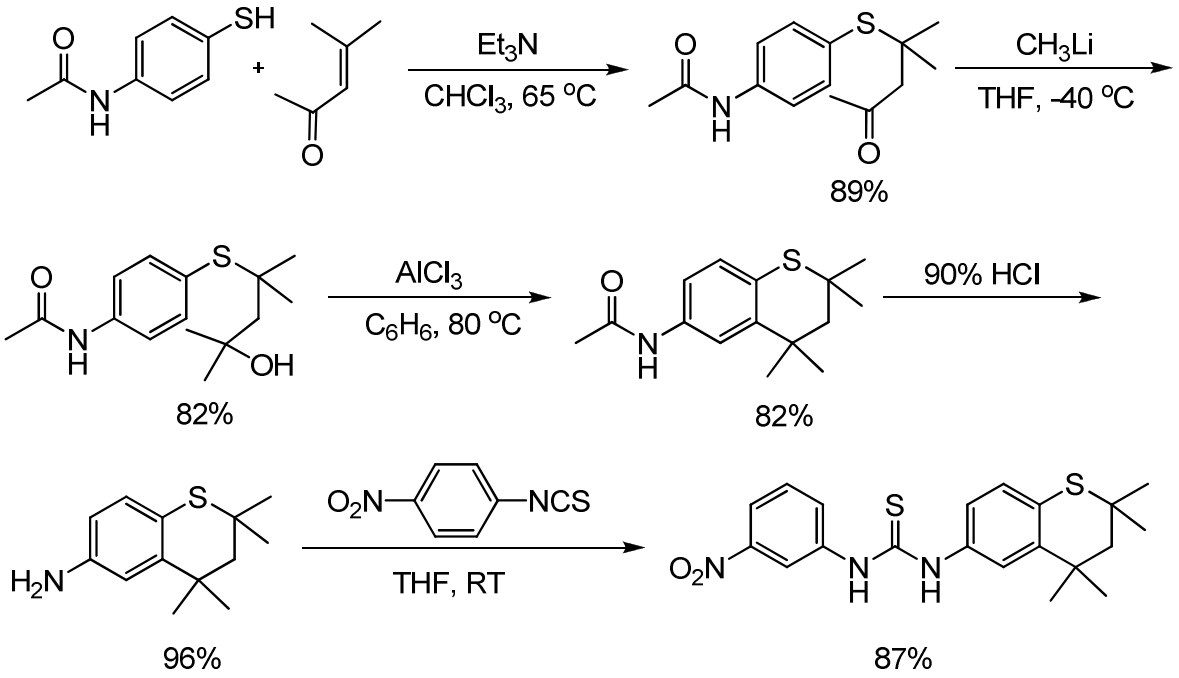


Figure 7.3. Synthetic scheme for the prepartion of SHetA2

Cyclodehydration of **19** was accomplished by the use of anhydrous $AlCl_3$ in benzene. changes in anhydrous $AlCl_3$ and the reaction solvent from chlorobenzene to benzene markedly improved the yield (82%) of the cyclization product **20**. This process had an advantage in that few impurities were formed which made for easy separation of the product **20** from the crude mixture by column chromatography. The ease of removal of

solvent from the reaction mixture becomes simpler due to the lower boiling point of benzene compared to chlorobenzene.

Final hydrolysis of the amide group in **20** was accomplished by refluxing the acetamidothiochroman (**20**) in 90% HCl for a period of 9 hours which gave pure 6-aminothiochroman (**21**) in a yield of 96%. The 6-aminothiochroman (**21**) was coupled by stirring with 4-nitrophenylisothiocyanate in dry THF. The crude product was recrystallized using chloroform:pentane (1:3) as solvent to provide the desired compound **7** in a yield of 87%. The overall yield obtained was about 75% compared to 50% by the previously developed method.[40]

Conclusion

An optimized synthesis of 7 has been accomplished, straightforward, efficient, and more cost effective than the methods currently available for the synthesis of this drug. This improved procedure should be feasible on an industrial scale for the bulk preparation of the thiourea heteroarotinoid **7**. The synthesis gives an overall increase of 25% higher yield compared to the original route[40] and also avoids the use of excesses of expensive solvents and reagents.

Experimental Section

All reactions were run under dry nitrogen in an oven-dried glassware. All reactions were carried out under argon unless otherwise noted. Commercial reagents and solvents were used as received. Tetrahydrofuran was dried over potassium hydroxide pellets and distilled from lithium aluminium hydride prior to use. The hydrochloric acid (1 M), ammonium chloride (saturated), sodium bicarbonate (saturated) and sodium chloride (saturated) used in workup procedures refer to aqueous solutions.

Evaporation of solvents was accomplished *in vacuo* via the use of a Buchi Rotovapor® RE-111 and a Brinkman B-169 water aspirator unless otherwise specified. For those intermediates that were liquids and required distillation for purification, vacuum distillation was employed using a Welch® Chemstar™ 1402N vacuum pump. Final compounds or intermediates that were solids were also dried using the same vacuum pump. Solid intermediates and compounds were purified by flash column chromatography on silica gel (Grade 62, 60-200 mesh). Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech 21521). Preparative separations were performed using flash chromatography on silica gel (grade 62, 60-200 mesh) mixed with ultraviolet-active phosphor (Sorbent Technologies UV-5); band elution was monitored using a hand held ultraviolet lamp. In addition to the synthesis and purification techniques, each product was analyzed for structure and purity using IR spectroscopy, ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy, and TLC. Melting points of all solids were uncorrected and taken on a MelTemp purchased from Laboratory Devices, Cambridge, MA 02139. Infrared spectroscopy were taken on a Varian 800 FT-IR (Scimitar series) run on a thin films on sodium chloride disks. ^{1}H and ^{13}C Nuclear magnetic resonance spectra were measured in deuteriochloroform at 300 MHz and 75 MHz, respectively, on a Varian Gemini 300 MHz unit and were referenced to internal tetramethylsilane; coupling constants (*J*) are reported in Hertz.

4-Methyl-4-(4-acetamidophenylthio)-2-pentanone (18). A 1-L three-necked round-bottomed flask, equipped with an addition funnel, a reflux condenser, a magnetic stir bar and an argon inlet was charged with 25.0 g (149.7 mmol) of acetamidothiophenol (**16**), 200 mL of dry chloroform and 7.0 mL of triethylamine. Stirring was initiated and 17.0

mL (50.3 mmol) of freshly distilled mesityl oxide (**17**) was added dropwise over a period of 15 min. The resulting grey slurry was heated to reflux in an oil bath preheated to 70 ºC. After refluxing for 3 h the grey slurry slowly changed into a dark brown solution. Following this initial period, two portions of triethylamine (1.1 g, 1.5 mL, 10.9 mmol) and mesityl oxide (2.6 g, 3.0 mL, 26.2 mmol) were added twice at regular intervals of 4 h and the solution was allowed to reflux for 24 h. A TLC analysis at this point indicated product formation with only a trace of starting material. The reaction mixture was cooled to room temperature, filtered through Celite® and concentrated under vacuum. The resulting crude product was purified by flash chromatography on a 55-cm × 5-cm silica gel column. Elution with 1.5 L of dichloromethane removed the unreacted mesityl oxide and this was followed by 3.5 L of dichloromethane:ethyl acetate (1:1) to elute the product. The solvent was evaporated, and the resulting residue was dried under high vacuum for 4 h to give ketone **18** as a viscous dark yellow liquid. The dark liquid was placed in the freezer at −20 °C where it slowly solidified into a pale yellow solid. The solid was crushed into a fine powder and dried under high vacuum (5 h) before being used in the next step. The final yield was 35.3 g (89%), mp 50-51 ºC [Lit[40] 46-49 °C]. IR: 3311, 1699, 1675 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.90 (br s, 1H), 7.53 (d, *J* = 8.8 Hz, 2 H), 7.45 (d, *J* = 8.8 Hz, 2 H), 2.65 (s, 2 H), 2.19 (s, 3 H), 2.15 (s, 3 H), 1.36 (s, 6 H); ^{13}C NMR: δ 206.9, 168.6, 139.0, 138.3, 126.2, 119.6, 54.3, 47.0, 32.1, 28.0, 24.5.

2,4-Dimethyl-4-(4-acetamidophenylthio)-2-pentanol (19). A 2-L three-necked round-bottomed flask, fitted with a mechanical stirrer, an addition funnel and an argon inlet, was charged with a solution of 20.0 g (75.5 mmol) of ketone **18** in 1 L of dry THF. As the solution was cooled to −50 °C (dry ice-acetone), 142 mL of 1.6 M methyllithium in

ether (227.2 mmol) was transferred by cannula into a 250-mL graduated addition funnel. Approximately 70 mL of the methyllithium solution was added dropwise to the solution of **3** over a period of 20 min. A white precipitate started to form after the addition. After 10 min, the remaining 72 mL of the methyllithium solution was added dropwise over a period of 1 h. The reaction mixture was allowed to warm slowly to –5 to –10 ºC during 1 h, and maintained at –5 ^{o}C (salt-ice bath) for a period of 3 h. Finally, the reaction mixture was stirred at room temperature for 1 h. The crude reaction mixture was cautiously quenched by slow dropwise addition of 25 mL of ice water. When the initial reaction subsided, an additional 175 mL of ice water was added portionwise to the mixture. The aqueous layer was adjusted to pH 7 using 1 *N* HCl and the crude mixture was transferred to a separatory funnel. The two phases were separated, and the aqueous phase was further extracted with ethyl acetate (2 × 300 mL). The combined organic layers were washed with saturated aqueous sodium chloride (1 × 200 mL) and dried (magnesium sulfate). Evaporation of the solvent yielded a crude, white solid which was purified by chromatography on a packed silica gel column (50 cm × 5 cm, grade 62, 60-120 mesh) via elution with 7:3 of ethyl acetate:hexanes. The solvent was evaporated to give 17.3 g (82%) of alcohol **19** as a white solid, mp 140-142 ºC [lit[40] yield 65%, mp 138-144 ºC]. IR: 3400, 3303, 1676 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.68 (br s 1 H), 7.52 (s, 4 H), 3.50 (br s, 1 H), 2.19 (s, 3 H), 1.77 (s, 2 H), 1.34 (s, 6 H), 1.33 (s, 6 H); ^{13}C NMR ($CDCl_3$): δ 168.4, 138.8, 138.1, 126.3, 119.6, 72.0, 52.0, 49.2, 32.2, 30.8, 24.6.

2,2,4,4-Tetramethyl-6-acetamidothiochroman (20). A 500-mL three-necked round-bottomed flask, fitted with a condenser, a magnetic stir bar and a nitrogen inlet, was charged with 150 mL of dry benzene and 15.0 g (53.4 mmol) of the dry alcohol **19**. The

mixture was stirred for 10 min to partially dissolve the alcohol. To this mixture as added 11.4 g (85.3 mmol) of dry aluminum chloride and the mixture was stirred for 5 min. The reaction was then placed in an oil bath preheated to 70 ºC and stirring was continued for 90 min at which time TLC analysis confirmed that the reaction was complete. The reaction mixture was cooled to room temperature and added to a 1-L Erlenmeyer flask containing 200 mL of ice-cold water. The resulting white, turbid mixture was transferred to a separatory funnel and extracted with ethyl acetate:ether (1:1, 2 × 200 mL). The combined organic layers were washed with saturated aqueous sodium chloride (1 × 400 mL), dried ($MgSO_4$) and concentrated under vacuum to give a yellow liquid. The crude product was purified by chromatography on a packed silica gel column (40 × 4 cm, grade 62, 60-200 mesh) and eluted with 7:3 hexanes:ethyl acetate to give 11.5 g (82%) of **20** as a white solid, mp 107-109 ºC [lit[40] mp 104-107 ºC]. IR: 3294, 1660 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.60 (br s, 1 H), 7.57 (d, *J* = 2.2 Hz, 1 H), 7.20 (dd, *J* = 8.2, 2.2 Hz, 1 H), 7.04 (d, *J* = 8.2 Hz, 1 H), 2.1 (s, 3 H), 1.92 (s, 2 H), 1.39 (s, 6 H), 1.35 (s, 6 H); ^{13}C NMR ($CDCl_3$): δ 168.3, 143.4, 135.1, 128.4, 128.2, 118.7, 118.2, 54.4, 42.0, 35.7, 32.4, 31.4, 24.4.

2,2,4,4-Tetramethyl-6-aminothiochroman (21). A 250-mL one-necked round-bottomed flask, equipped with a condenser, a magnetic stir bar, a condenser and a nitrogen inlet, was charged with 8.0 g (30.4 mmol) of amide **20** and 100 mL of 10:90 water/concentrated HCl at room temperature. The resulting slurry was stirred for 10 min and the flask was then suspended in an oil bath preheated to 100 ºC. The brown slurry became a clear solution after 2 h and on continued heating once again became a half white suspension. After 7 h, TLC analysis indicated the reaction was complete. The

reaction was cooled to room temperature and carefully poured into 200 mL of ice-cold water. The compound was then extracted with 1:1 ethyl acetate:ether (2 × 150 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (1 × 200 mL) and saturated aqueous sodium chloride (1 × 250 mL), then dried ($MgSO_4$) and concentrated under vacuum to give 6.4 g (96%) of amine **21** as a pale brown shiny solid, mp 57-59 ºC. [lit[40] mp 35-65 ºC; the HCl derivative of **21** has been prepared[42] in a yield of 91% with a mp of 165 ºC; the melt then re-solidified and melted at 275-290 ºC]; IR: 2863 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9-10 (br s, 2 H), 7.47 (s, 1 H), 7.16 (m, 2 H), 1.92 (s, 2 H), 1.39 (s, 6 H), 1.37 (s, 6 H); ^{13}C NMR ($CDCl_3$): δ 144.8, 133.7, 129.3, 127.8, 121.0, 120.2, 53.9, 42.3, 35.8, 32.2, 31.5.

***N*-(3,4-Dihydro-2,2,4,4-tetramethyl-2*H*-1-benzothiopyran-6-yl)-*N*'-(4-nitrophen-yl)thiourea (7)**. A one-necked round-bottomed flask, equipped with a magnetic stir bar and a nitrogen atmosphere was charged with 5.0 g (22.8 mmol) of amine **21** and dissolved in 100 mL of dry THF. To the stirred solution was added 4.1 g (22.8 mmol) of 4-nitrophenylisothiocyanate and stirring was continued for 24 h. The reaction mixture was then concentrated under vacuum to give a crude yellow solid. Chromatography of the solid on a 25-cm × 4 cm column of silica gel (grade 62, 60-200 mesh) eluted with 7:3 ethyl acetate:hexanes gave a yellow solid. The compound was further purified by recrystallization from 1:3 chloroform:pentane to give 7.9 g (95%) of **7** as a bright yellow solid, mp 154-155 ºC [lit[41] mp 153-155 ºC]. IR: 3307, 3192 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.37 (br s, 1 H), 8.19 (d, J = 8.8 Hz, 2 H), 7.91 (br s, 1 H), 7.74 (d, J = 9.3 Hz, 2 H), 7.33 (d, J = 2.2 Hz, 1 H), 7.20 (d, J = 8.2 Hz, 1 H), 7.02 (dd, J = 8.2, 2.2 Hz, 1 H), 1.97 (s, 2

H), 1.44 (s, 6 H), 1.39 (s, 6 H); ^{13}C NMR ($CDCl_3$): δ 178.8, 145.0, 144.4, 143.8, 133.9, 132.1, 129.5, 124.5, 124.1, 122.9, 122.8, 53.6, 42.4, 35.8, 32.4, 31.5.

References and Notes

1. Amtao, R. J. *Semin. Oncol.* **2000**, *27*, 177-186.
2. Pantuck, A. J.; Zisman, A.; Belldegrun, A. S. *J. Urol.* **2001**, *166*, 1611-1623.
3. Liu, T.; Masamha, C.; Chengedza, S.; Berlin, K. D.; Lightfoot, S.; He, F.; Benbrook D. M. *Mol. Can. Therapeutics.* **2009**, *8*, 1227-1238.
4. Benbrook, D. M. *Minireviews in Med. Chem.* **2002**, *2*, 271-272.
5. [a] Spron, M. B.; Roberts, A. B.; Goodman, D. S., Eds., The Retinoids, Vol. 1 and Vol. 2, Academic Press: Orlando, 1984. [b] Dawson, M. I.; Okamura, W. H., Eds., Chemistry and Biology of Synthentic Retinoids; CRC: Boca Raton, Florida, 1990. [c] Packer, L. *In Methods Enzymol.* **1990**, *189*, 1-536. [d] Packer, L. *In Methods Enzymol.* **1990**, *190*, 1-448. [e] Lindamood, III. C.; Giles H. D.; Hill, D. L. *Fundam. Appl. Toxicol.* **1987**, *8*, 517-530. [f] Sporn, M. B.; Roberts, A. B.; Goodman, D. S., Eds., The Retinoids Biology Chemistry and Medicine, 2nd Ed, Raven Press: New York, 1994. [g] Dawson, M, I. Retinoids, Ch 44 in Burger's Medicinal Chemistry and Drug Discovery, Fifth edition, Burger A. Eds., Wiley: New York, 1996. [h] Degos, L.; Parkinson, D. R., Eds., Retinoids in Oncology. Springer: Hidelberg 1995. [i] Mangeldorf, D. J.; Umensono, K.; Evans, R. M. The Retinoid Receptors. In Retinoids: Biology Chemistry and Medicine, 2nd Ed. [j] Evans, T. R.; Kaye, S. B. *Br. J. Cancer* **1999**, *80*, 1-8. (k) Kurie, J. M.; Hong, W. K. *Cancer J.* **1999**, *5*, 150-151.

6. Waugh, K. M.; Berlin, K. D.; Ford, W. T.; Holt, E. M.; Carroll, J. P.; Schomber, P. R.; Shiff, L. J. *J. Med. Chem.* **1985**, *27*, 116-124.
7. [a] Hanni, R.; Bigler, F.; Mister, W.; Englert, G. *Helv. Chim Acta* **1976**, *59*, 2221-2227. [b] Hanni, R.; Bigler, F. *Helv. Chim. Acta* **1977**, *60*, 881-887. [c] Frolik, C. A. Metabolism of Retinoids Ch 11 in, The Retinoids, Vol 2, Sporn, M. B.; Robets, A. B.; Goodman, D. S., Eds., Academic Press, Inc. Orlando, FL, 1984.
8. Spruce, L. W.; Gale, J. B.; Berlin, K. D.; Verma, A. K.; Breitman, T. R.; Ji, X.; Van der Helm, D. *J. Med. Chem.* **1991**, *34*, 430-439.
9. Benbrook, D. M.; Madler, M. M.; Spruce, L. W.; Birckbichler, P. J.; Nelson, E. C.; Subraminain, S.; Weerasekare, G. M.; Gale, J. B.; Patterson, Jr., M. K.; Wang, B.; Wang, W.; Lu, S.; Rowland, T. C.; DiSivestro, P.; Lindawood, C.; Hill, D. L., Berlin, K. D. *J. Med. Chem.* **1997**, *40*, 3567-3583.
10. Benbrook, D. M.; Subramanian, S.; Gale, J. B.; Liu, S.; Brown, C. W.; Boehm, M. F.; Berlin, K. D. *J. Med. Chem.* **1998**, *41*, 3753-3757.
11. Dhar, A.; Liu, S.; Klucik, J.; Berlin, K. D.; Madler, M. M.; Lu, S.; Ivey, R. T.; Zacheis, D.; Brown C. W.; Nelson, E. C.; Birckbichler, P. J.; Benbrook, D. M.; *J. Med. Chem.* **1999**, *42*, 3602-3614.
12. Zacheis, D.; Dhar, A.; Lu, S.; Madler, M. M.; Klucik, J.; Brown, C. W.; Liu, S.; Clement, F.; Subramanian, S.; Weerasekare G. M.; Berlin, K. D.; Gold, M. A.; Houch, Jr., J. R.; Fountain, K. R.; Benbrook, D. M. *J. Med. Chem.* **1999**, *42*, 4434-4445.
13. Chun, K-H.; Benbrook, D. M.; Berlin, K. D.; Hong, W. K.; Lotan, R. *Cancer Res.* **2003**, *63*, 3826-3832.

14. Guruswamy, S.; Lightfoot, S.; Gold, M. A.; Hassan, R.; Berlin, K. D.; Ivey, R. T.; Benbrook, D. M. *J. Natl. Cancer Inst.* **2001**, *93*, 516-525

15. Liu, S.; Brown, C. W.; Berlin, K. D.; Dhar, A.; Guruswamy, S.; Brown, C. W.; Benbrook, D. M. *J. Med. Chem.* **2004**, *47*, 999-1007.

16. Brown, C. W.; Liu, S.; Klucik, J.; Berlin, K. D.; Brennan, P. J.; Kaur, D.; Benbrook, D. M. *J. Med. Chem.* **2004**, *47*, 1008-1017.

17. Benbrook, D. M.; Kamelle, S. A.; Guruswamy, S.; Lightfoot, S. A.; Hannfon, B. N.; Rutledge, T. L.; Gould, N. S.; Dunn, S. T.; Berlin K. D. *Investigational New Drugs.* **2005**, *23*, 417-428.

18. Le, T. C.; Berlin, K. D.; Benson, S. D.; Nelson, A. C.; Benbrook, D. M.; Eastman, M.; Bell-Eunice, G. *Open Medicinal Chemistry*. **2007**, *1*, 11-23.

19. Liu, T.; Hannafon, B.; Gill, L.; Kelly, W.; Benbrook, D. M. *Mol. Cancer Ther.* **2007**, *6*, 1814-1822.

20. Lin, Yi-D.; Chen, S.; Yue, P.; Zou, W.; Benbrook, D. M.; Liu, S.; Le, T. C.; Berlin, K. D.; Khuri, F. R.; Sun, S.-Y. *Cancer Res.* **2008**, *68*, 5335-5344.

21. Lin, Yi-D.; Lui, X.; Yue, P.; Benbrook, D. M.; Berlin, K. D.; Khuri, F. R.; Sun, S. -Y. *Mol. Can. Therapeutics*. **2008**, *7*, 3556-3565.

22. Private communication from the National Cancer Institute of the National Institutes of Health plus information in references 5-21.

23. Zhang, Y.; Hua, Y.; Benbrook, D. M.; Cvey, J. M. Dai, G.; Liu, Z.; Chan, K. K. *Can. Chemother. Pharmacol.* **2006**, *58*, 567-569.

24. Samant, M. P.; Gulas, J.; Hong, D. J.; Croston, G.; Rivier, G.; Rivier, J. *J. Med. Chem.* **2005**, *48*, 4851-4860.

25. Jia, Z. J.; Wu, Y.; Huang, W. *et. al. Bioorg & Med. Chem. Letters*. **2004**, *14*, 1229-1234.

26. Riedl, B. *et. al. Clinical Cancer Res.* **2001**, 83a.

27. Smith, R. A.; *et. al. Bioorg. Med. Chem. Lett.* **2001**, *11*, 2775-2778.

28. Lowinger, T. B.; Riedel, B.; Dumas, J.; Smith, R. A. *Curr. Pharm. Des.* **2002**, *8*, 2269-2278.

29. Wilhelm, S. M. *Proc. Am. Assoc. Cancer Res.* **2001**, *42*, 923.

30. Wilhelm, S. M. *Cancer Res.* **2004**, *64*, 7099-7109.

31. Wan, P. T. *Cell.* **2004**, *116*, 855-867.

32. Escudier, B.; Eisen, T.; Stadler. W. M. *et. al. N. Engl. J. Med.* **2007**, *356*, 125-134. [erratum appeared in *N. Engl. J. Med.* **2007**, *357*, 203]

33. Bhojani, N.; Jeldres, C.; Patard, J. J. *et. al. Eur. Urol.* **2008**, *53*, 917-930.

34. Tozer, T. N.; Rowland, M. Introduction to pharmacokinetics and pharmacodynamics. Lippincott Williams & Wilkins: Baltimore, MD, 2006; p-50.

35. Berlin, K. D.; Bunce, R. A.; Benbrook D. M. Unpublished results, **2010**.

36. Anderson, S.; Liffer-Atlas, D. Knadler, M. P. *Chem. Res. Toxicol* **2009**, *22*, 243-256.

37. Baillie, T. A. *Chem. Res. Toxicol.* **2009**, *22*, 263-266.

38. Smith, D. A.; Obach, R. S. *Chem. Res. Toxicol.* **2009**, *22*, 267-279.

39. Leclercq, L.; Cuyckens, F.; Mannens, G. S. J.; de Vries, R.; Timmerman, P.; Evans, D. C. *Chem. Res. Toxicol.* **2009**, *22*, 280-293.

40. Tallent, C. R.; Twine, C. E., Jr.; Risbood, P.; Seltzman, H. H. *Org. Prep. Proced. Intl.* **2006**, *39*, 96-101.

41. Brown, C. W.; Liu, S.; Klucik, J.; Berlin, K. D.; Brennan, Patrick J.; Kaur, D.; Benbrook, D. M. *J. Med. Chem.* **2004**, *47*, 1008-1017.

CHAPTER VIII

SYNTHESIS OF METABOLITES OF SHetA2 HETEROAROTINOID

Introduction

The development of useful drugs has often required an improvement in hydrophilicity which increases aqueous solubility and frequently biological activity as well.[1] Noted Examples include certain diaryl urea multikinase inhibitors which inhibit tumor growth.[2] Indeed, Sorafenib (BAY 43-9006) **1** is a compound which was developed

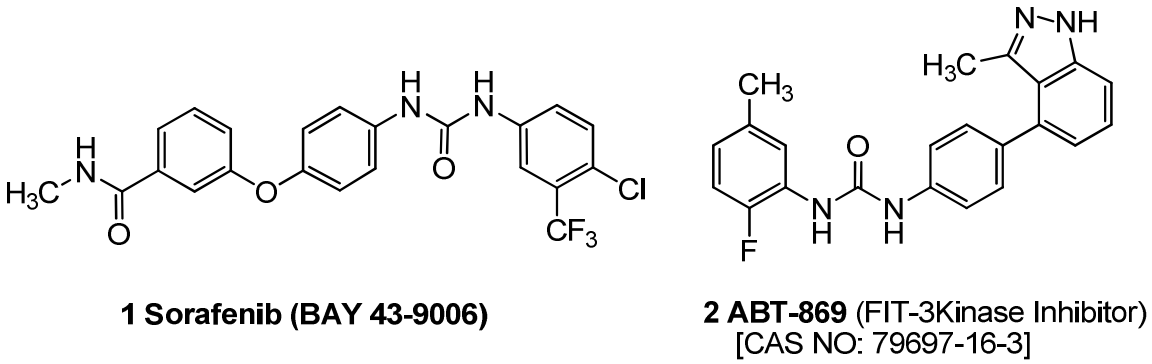


Figure 8.1. Structure of Sorafenib and ABT-86

by increasing the hydrophilicity of its precursor, which led to increased *in vivo* potency. The ability to prolong progression free survival in recurrent kidney cancer patients with manageable toxicity led to its FDA approval. However, the toxicity of Sorafenib remains a problem.[3] Since **3** has not shown any significant toxicity in the studies by NCI, it is predictable that the metabolites may not be toxic. The increased polarity of the metabolites could provide a number of pharmaceutical and pharmokinetic advantages

with increased aqueous solubility. Higher hydrophilicity correlates well with reduced lipid tissue uptake, typically resulting in higher blood or plasma concentrations available for delivery to target tumor cells. Compound **3** has shown interaction with the kinase KIT [Ambit Biosciences Corporation, 4215 Sorrento Valley Blvd, San Diego, CA] at 5 nM concentration. Recognition of the significance of ureas and derivatives for the inhibition of kinases is acknowledged by the American Custom Chemicals Corporation [P. O. Box 910574, San Diego, CA 92191-0574] who market such agents as ABT-869 (**2**) above.[4]

In view of the fact that *N*-(3,4-dihydro-2,2,4,4-tetramethyl-2*H*-1-benzothiopyran-6-yl)-*N*'-(4-nitrophenyl)thiourea (**3**) has not displayed any toxicity in animal studies and yet is active against breast, head-neck, kidney, ovarian and lung cancers, it is highly possible that a metabolite elicits the biological response and is not toxic.[5] Consequently, it is imperative that the metabolites be synthesized and screened for biological activity. The objective of this project was to obtain major metabolites such as **4** whose structure is illustrated below and its acetate derivative **5**. The second objective was to prepare a derivative of **4**, namely **6**, for eventual linking to a magnetic nanobead. The latter is to be done by scientists at SoluLink Biosciences, 9853 Pacific Heights Blvd, Suite H, San Diego, CA 92121 under the direction of Dr. David Schwartz, Chief Science Officer. The attached metabolite on the magnetic bead will be submitted to Dr. Doris M. Benbrook of the University of Oklahoma Health Sciences Center who will use it determine which proteins interact with the attached metabolite. The identified protein(s) will serve as targets for the development of agents to treat certain cancers.

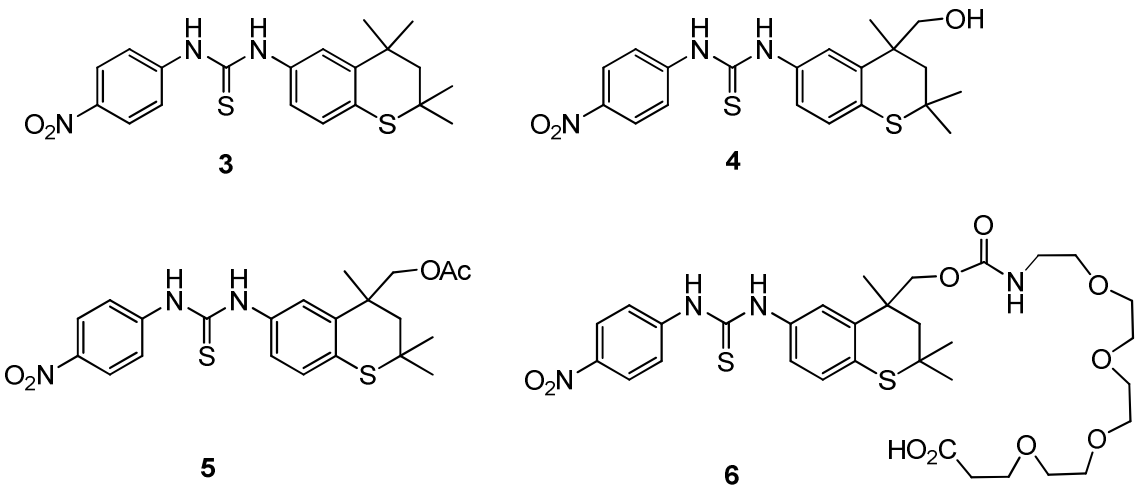


Figure 8.2. Structures of heteroarotinoid metabolites

Results and Dicussion

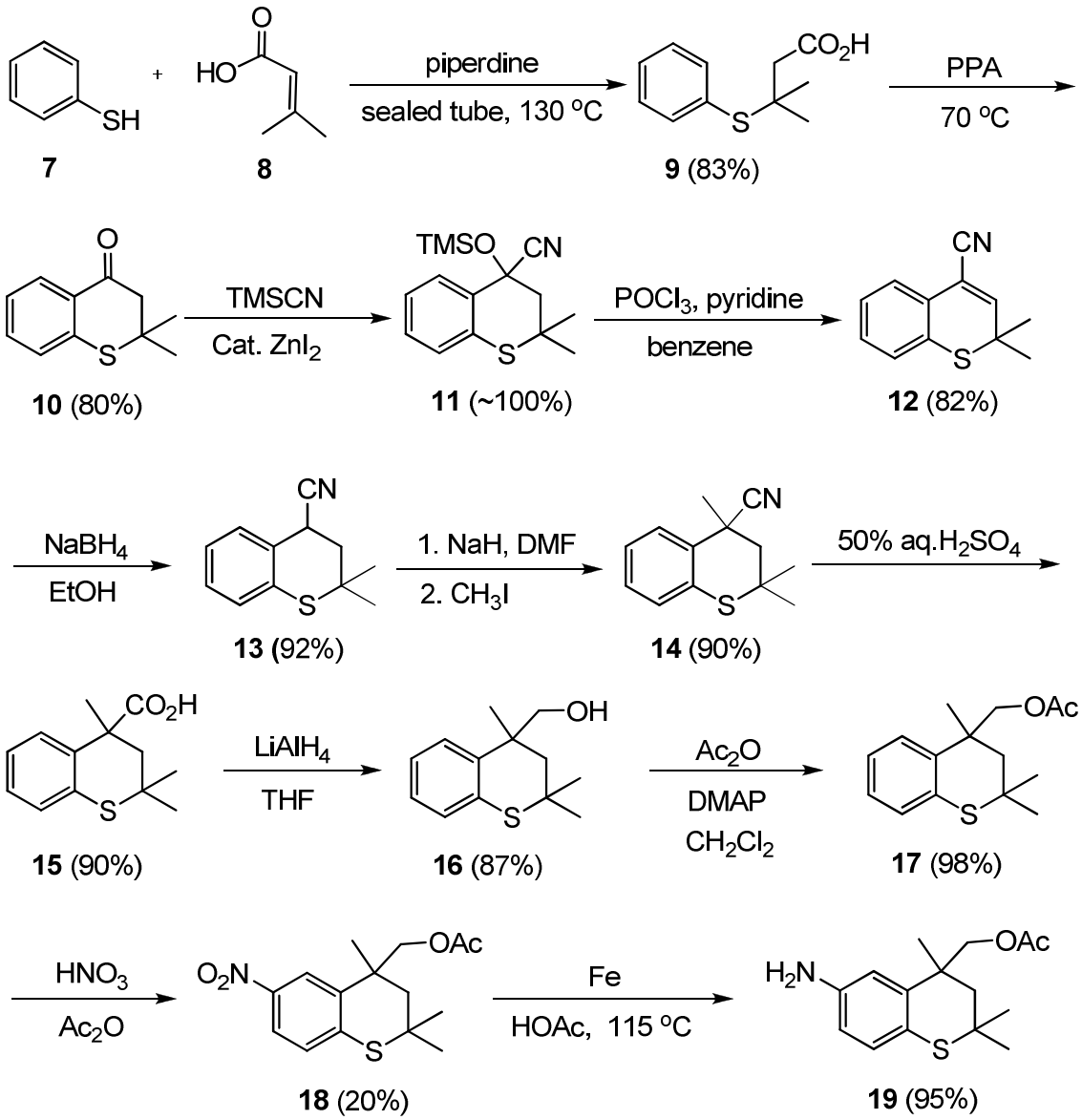
Due to the reduced toxicity reports available on SHetA2 (**3**) from the National Cancer Institute (NCI) and its ability to inhibit various cancer cells, we have developed methodology to obtain the sulfur-containing heteroarotinoid metabolites. The syntheses of the metabolites are outlined in Figure 8.3. Based on earlier work,[6] the core thiochroman **10** was built using benzenethiol (**7**) and methyl-2-butenoic acid (**8**) along with piperdine in sealed tube which was heated at 130 ºC for 24 hours to afford the acid **9** in a yield of 83%. Cyclodehydration of **9** was accomplished by stirring it in polyphosphoric acid at 70 ºC which afforded thiochroman **10**. Treatment of **10** with trimethylsilyl cyanide and a catalytic amount of ZnI_2 gave an unstable trimethylsilyl cyanohydrin **11**. Thus, **11** was converted immediately to **12** by dissolving it in benzene and refluxing the solution with triethylamine and $POCl_3$. The unsaturated nitrile **12** was converted to the saturated nitrile **13** by treatment with $NaBH_4$ in refluxing ethanol. Compound **13** was methylated at the position alpha to the cyanide group by

deprotonation using NaH in anhydrous *N*,*N*-dimethylformamide, followed by the addition of methyl iodide, to produced **14** (90%). Hydrolysis of nitrile **14** occurred with 50% H_2SO_4 at 90 ºC to yield **15** (90%). Reduction of acid **15** with $LiAlH_4$ gave alcohol **16** (87%). Acylation of **16** with acetic anhydride in the presence of DMAP in methylene chloride generated acetate **17** (98%).

The amine **19** was envisioned to be the key intermediate in the synthesis of these metabolites **20** and **22.** To accomplish the goal, nitration step of (**17**) was initiated. The nitration was effected by dissolving the compound in acetic anhydride, followed by addition of HNO_3/Ac_2O mixture at -5 ºC and stirring for 3.5 hours. The reaction mixtures afforded a mixture of isomers along with a variety of other products as evidenced by TLC analysis. However, a complete separation of the 6-isomer was done by flash chromatography to afford the nitrothiochroman acetate **18** in a modest yield of 20%. Earlier nitrations were performed on similar molecules in yields as high as 26%.[5] The acetate group in the thiochroman reduces the yield of the compound by about 7%.

A search for a clean, straightforward reduction procedure to accomplish the conversion of nitrothiochroman acetate **18** to aminothiochroman acetate **19** was initiated. A previous method[6] in the synthesis of the heteroarotinoid drug SHetA2 involved the use of Fe/AcOH/EtOH which afforded a yield of 45%. To overcome the problem, compound **18** was refluxed in glacial acetic acid, Fe powder (3 eq) was added under hot conditions and continued stirring at reflux for 30 minutes afforded **19** in a yield of 95%. By avoiding the use of EtOH and by avoiding overheating, the yield of the compound is increased by 50% over that reported 45%.[16] Furthemore, acetate **19** could be hydrolyzed with 10% NaOH to give the aminothiochroman alcohol **20** (94%). The advantage of the

procedure was that, after neutralization of the reaction mixture with 6 *M* HCl, **20** was obtained pure and was formed in high yield.



7 **8** **9** (83%) **10** (80%) **11** (~100%) **12** (82%) **13** (92%) **14** (90%) **15** (90%) **16** (87%) **17** (98%) **18** (20%) **19** (95%)

Figure 8.3. Synthentic scheme for SHetA2 arotinoid metabolites contd…

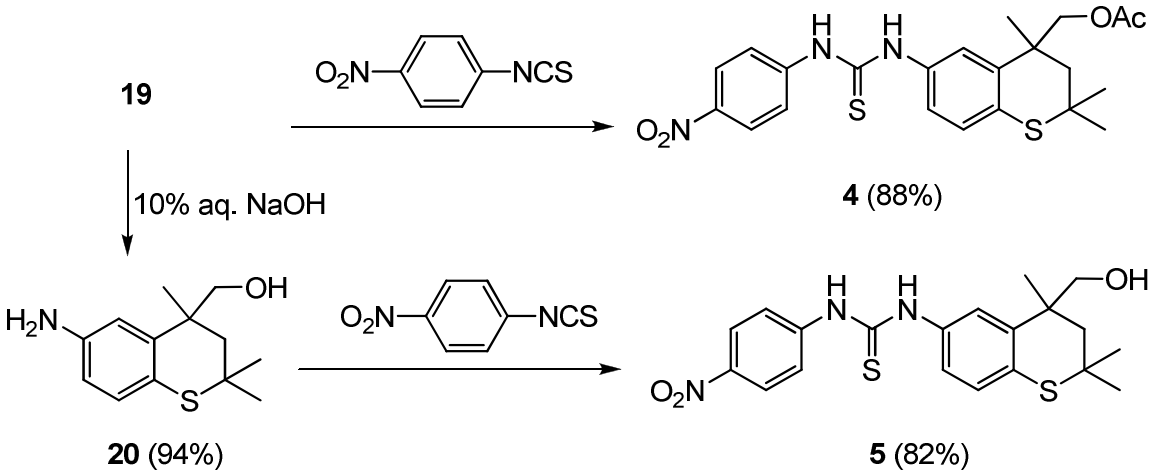


Figure 8.3. Synthentic scheme for SHetA2 arotinoid metabolites

Generation of the desired heteroarotinoid metabolite **4** and its acetate derivative **5**, was accomplished by coupling of 4-nitrophenylisothiocyanate with the respective amines **20** and **19** to give the corresponding thiourea derivatives **4** and **5** (Scheme 1). The crude products were crystallized from chloroform:pentane (1:3) to afford **4** (82%) and **5** (88%) in good yields.

Conclusion

We have developed a new route for the sytheses of the SHetA2 heteroarotinoid metabolites using a 15 step sequence. Except for the nitration step all other steps in this synthesis are high yielding. In view of the importance of the SHetA2 as a effective drug against kidney and ovarian cancer cells, the metabolites might also prove active against these cancer cells. Testing of these metabolites against various other cancer cells will also be carried out.

Experimental Section

All reactions were run under dry nitrogen (unless otherwise stated) in oven-dried glassware. Tetrahydrofuran (THF) was dried over potassium hydroxide pellets and distilled from lithium aluminium hydride. Anhydrous *N*,*N*-dimethylformamide (DMF) was purchased commercially and transferred by syringe into reactions where it was used. All other commercial reagents and solvents were used as received. Solutions of HCl, NaOH, NH_4Cl, $NaHCO_3$ and NaCl used in work-up procedures were all aqueous.

Evaporation of solvents was accomplished *in vacuo* via the use of a Buchi Rotovapor® R-3000 and a Brinkman B-169 water aspirator unless otherwise specified. For those intermediates and final compounds which required drying were dried using a Welch® Chemstar™ 1402N vacuum pump. For those intermediates and compounds that were solids and required purification, in addition to recrystallization, flash column chromatography was used. Chromatography was performed on silica gel packing (grade 62, 60-200 mesh). Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech No. 21521) using ultraviolet detection. Preparative separations were performed by flash column chromatography on silica gel (grade 62, 60-200 mesh) mixed with ultraviolet-active phosphor (Sorbent Technologies UV-5); band elution was monitored using a hand-held ultraviolet lamp. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA 30091.

Melting points were taken on a MelTemp purchased from Laboratory Devices, Cambridge, MA 02139 and were uncorrected. Infrared spectra were taken on a Varian 800 FT-IR (Scimitar series) run as thin films on sodium chloride disks. Unless otherwise indicated, ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ at 300 MHz and 75 MHz,

respectively, on a Varian Gemini 300 MHz unit and were referenced to internal tetramethylsilane; coupling constants (*J*) are reported in Hz.

3-(Phenylthio)-3-methylbutanoic Acid (9). The procedure of Comasseto and coworkers was modified[6]. A 200-mL pressure tube reactor was charged with 30.0g (0.30 mol) of 3-methyl-2-butenoic acid **8** along with 27.0 g (0.32 mol, 1.5 eq) of piperidine and 33.0 g (0.30 mol) of thiophenol **7**. The pressure tube was then sealed and heated at 130 ºC in a oil bath (silicone oil) for 24 h. The resulting mixture dark brown thick liquid was cooled to room temperature and diluted with 1 L of ether. The ether layer was washed with 1 *M* HCl (3 × 200 mL), water (1 × 200 mL) and saturated NaCl (1 × 200 mL), then dried (Na_2SO_4, 15 min) and concentrated under vacuum to give a pale yellow solid. The compound was further purified by recrystallization from benzene and petroleum ether (1:3) to give 52.3 g (83%) of acid **9** as an off-white solid, mp 70-72 ºC [lit[1] mp 69-71 ºC]. IR: 3700-2350, 1707 cm^{-1}; ^{1}H NMR: δ 10-11 (br s, 1 H), 7.57 (dd, *J* = 7.7, 1.6 Hz, 2 H), 7.36 (m, 3 H), 2.56 (s, 2 H), 1.41 (s, 6 H); ^{13}C NMR: δ 177.0, 137.7, 131.1, 129.2, 128.7, 46.7, 46.4, 28.4.

2,2-Dimethylthiochroman-4-one (10). A 1000-mL three-necked round-bottomed flask, fitted with a mechanical stirrer, a condenser and a nitrogen inlet, was charged with 400 mL of polyphosphoric acid and the acid was heated for 20 minutes to 70 ºC using an oil bath. To the stirred polyphosphoric acid was added 50 g (0.24 mol) of **9** over a period of 5 minutes, and the resulting dark mixture was stirred at 70 ^{o}C for 45 min. TLC analysis was performed after 45 minutes confirmed that the reaction was complete. [Note: Higher temperature or prolonged stirring in polyphosphoric acid led to an increased number of impurities]. The reaction mixture was cooled to 0 ^{o}C using an ice bath and

was carefully added into ice-cold water (1 L). [*Caution*! This process is extremely exothermic.]. The resulting solution was extracted with ether (3 × 600 mL), and the combined organic layers were washed with 1 *N* NaOH (1 × 200 mL) and saturated NaCl (1 × 200 mL), then dried ($MgSO_4$, 20 min) and concentrated under vacuum to afford a white solid. The compound was recrystallized from ethyl acetate and petroleum ether (1:3) to give 36.5 g (80%) of ketone **10** as a white solid, mp 67-68 ^oC [lit[1] mp 66-68 ^oC]. IR: 1686 cm^{-1}; ^1H NMR: δ 8.10 (dd, *J* = 7.7, 1.1 Hz, 1 H), 7.39 (td, *J* = 8.0, 1.6 Hz, 1 H), 7.22 (d, *J* = 7.7 Hz, 1 H), 7.16 (td, *J* = 7.7, 1.1 Hz, 1 H), 2.87 (s, 2 H), 1.47 (s, 6 H); ^{13}C NMR: δ 194.8, 141.3, 133.6, 129.6, 128.6, 127.5, 124.6, 53.8, 44.6, 28.5.

2,2-Dimethyl-2*H*-thiochromene-4-carbonitrile (12). The general procedure Johnson and coworkers[7] was used. A 250-mL one-necked round-bottomed flask, equipped with a magnetic stirrer, a condenser and a nitrogen inlet, was charged with 32.0 g (0.17 mol) of ketone **10**, along with 19.8 g (25 mL, 0.20 mol, 1.2 eq) of trimethylsilyl cyanide and 40 mg of anhydrous zinc iodide. The resulting reaction mixture was stirred at room temperature for 24 h under nitrogen at which time TLC analysis indicated the reaction was complete. Trimethylsilyl cyanohydrin **11** was unstable to purification and was used directly in the next step. Spectral data for the crude product were: IR: 2210 (weak) cm^{-1}; ^1H NMR: δ 7.70 (dd, J = 7.7, 1.6 Hz, 1 H), 7.28-7.10 (complex, 3 H), 2.53 (d, J = 14.0 Hz, 1 H), 2.47 (d, J = 14.0 Hz, 1 H), 1.54 (s, 3 H), 1.49 (s, 3 H), 0.22 (s, 9 H); ^{13}C NMR: 133.4, 132.0, 129.5, 129.3, 127.8, 125.3, 121.6, 69.9, 51.5, 41.4, 31.3, 31.0, 1.2.

In a 500-mL, three-necked, round-bottomed flask, fitted with a magnetic stirrer, a reflux condenser, an addition funnel and a drying tube was placed crude trimethylsilyl cyanohydrin **11** dissolved in 200 mL of benzene containing 10 mL of pyridine. Then

33.5 g (20 mL, 0.22 mol) of phosphorus oxychloride was cautiously added dropwise with stirring. The reaction mixture was refluxed for 4 h at which time TLC analysis indicated the reaction was complete. The reaction mixture was carefully poured into 500 g of ice and extracted with ether (3 × 300 mL). The organic layer was washed with water (1 × 200 mL) and saturated NaCl (1 × 150 mL), then dried ($MgSO_4$, 10 min) and concentrated under vacuum. The crude product was further purified by flash chromatography on a 55 × 5 cm silica gel column using increasing concentrations of ether [5%, 10%, 15%, 25%, 30%] in hexanes to give 27.5 g (82%) of unsaturated nitrile **12** as a white solid, mp 62-63 ^{o}C. IR: 2224 cm^{-1}; ^{1}H NMR: δ 7.59 (dd, J = 6.0, 2.7 Hz, 1 H), 7.36-7.18 (complex, 3 H), 6.56 (s, 1 H), 1.46 (s, 6 H); ^{13}C NMR: δ 146.8, 131.6, 129.7, 127.8, 126.9, 126.7, 126.0, 117.1, 113.5, 40.9, 28.2.

2,2-Dimethylthiochroman-4-carbonitrile (13). Exactly 24.0 g (0.12 mol) of unsaturated nitrile **12**, dissolved in dry ethanol (150 mL), was placed in a 500-mL three-necked round-bottomed flask, fitted with magnetic stirring, a reflux condenser and a nitrogen inlet. The reaction mixture was heated for 10 min to effect solution. To the warm solution 2.25 g (0.06 mol) of sodium borohydride was slowly added in small portions, and refluxing was continued for 45 min. The reaction mixture was evaporated under vacuum and purified by flash chromatography on a 25-cm × 4-cm silica gel column using ether:hexanes (1:1) to give 22.3 g (92%) of saturated nitrile **13** as a white solid, mp 62-63 ^{o}C. IR: 2243 cm^{-1}; ^{1}H NMR: δ 7.51 (d, *J* = 7.1 Hz, 1 H), 7.24-7.10 (complex, 3 H), 4.12 (dd, *J* = 11.0, 5.2 Hz, 1 H), 2.35 (dd, *J* = 13.7, 5.2 Hz, 1 H), 2.21 (dd, *J* = 13.7, 11.0 Hz, 1 H), 1.47 (s, 3 H), 1.44 (s, 3 H); ^{13}C NMR: δ 133.5, 128.6, 128.4, 127.7, 126.4, 125.1, 120.7, 41.9, 41.7, 30.9, 29.9, 29.4.

2,2,4-Trimethylthiochroman-4-carbonitrile (14). A 500-mL three-necked round-bottomed flask, equipped with magnetic stirring, a reflux condenser and a nitrogen inlet, was charged with 5.19 g of NaH (60% mineral oil suspension). The solid was washed with hexane (3 × 50 mL) to remove the mineral oil, and the remaining 3.11 g (0.13 mol) of NaH was suspended in 50 mL of dry DMF. The resulting suspension was chilled to 0 ºC (ice bath), and 22.0 g (0.11 mol) of nitrile **13**, in dry DMF (50 mL) was added dropwise (10 min). The ice bath was removed, and the resulting dark brown mixture was stirred at room temperature for 30 min. To the stirred solution was added dropwise 16.9 g (7.4 mL, 0.12 mol) of methyl iodide over a period of 15 min. The resulting pale white reaction mixture was stirred for an additional 30 min, and was then carefully quenched by addition of 25 mL of saturated NH_4Cl. The mixture was extracted with ether (3 × 200 mL). The combined organic layers were washed with saturated NaCl (1 × 200 mL), dried ($MgSO_4$, 10 min) and concentrated under vacuum to give 21.1 g (90%) of **13** as a pale yellow solid, mp 64-65 ^{o}C. IR: 2231 cm^{-1}; ^{1}H NMR: δ 7.56 (m, 1 H), 7.20-7.14 (complex, 3 H), 2.52 (d, *J* = 14.5 Hz, 1 H), 2.14 (d, *J* = 14.5 Hz, 1 H), 1.80 (s, 3 H), 1.59 (s, 3 H), 1.44 (s, 3 H); ^{13}C NMR: δ 132.8, 131.7, 128.7, 128.5, 128.2, 125.6, 124.5, 51.3, 41.4, 34.8, 30.8, 30.6, 28.2.

2,2,4-Trimethylthiochroman-4-carboxylic acid (15). A 500-mL one-necked round-bottomed flask, equipped with magnetic stirring, a reflux condenser and a nitrogen inlet, was charged with 20.0 g (0.09 mol) of nitrile **14**, along with 200 mL of 50% aqueous H_2SO_4. The solution was heated at 100 ºC and, after approximately 60 minutes, the reaction mixture turned from a turbid solution to a completely clear solution. Heating was continued for an additional 60 minutes during which time the reaction mixture once

again became a turbid suspension. TLC analysis indicates that the reaction was complete. The reaction mixture was then cooled to room temperature, slowly poured into a 600-mL beaker containing 250 g of ice and extracted with ether:ethyl acetate (1:1, 3 × 200 mL). The combined organic layers were washed with water (1 × 150 mL) and saturated NaCl (1 × 200 mL), then dried ($MgSO_4$, 10 min) and concentrated under vacuum to give 19.5 g (90%) of **15** as a pale yellow solid, mp 136-137 ºC. The solid was spectroscopically pure and was used in the next step without additional purification. IR: 3680-2360, 1699 cm^{-1}; ^1H NMR: δ 10.29 (br s, 1 H), 7.41 (m, 1 H), 7.22-7.14 (complex, 3 H), 2.82 (d, *J* = 14.3 Hz, 1 H), 1.81 (d, *J* = 14.3 Hz, 1 H), 1.66 (s, 3 H), 1.43 (s, 3 H), 1.31 (s, 3 H); ^{13}C NMR: δ 183.2, 136.6, 134.2, 128.7, 128.4, 127.3, 125.2, 50.5, 47.4, 42.6, 32.6, 29.4, 27.8.

(2,2,4-Trimethylthiochroman-4-yl)methanol (16). A 500-mL three-necked round-bottomed flask, fitted with magnetic stirring, a reflux condenser and a nitrogen inlet, was charged with 18.0 g (0.08 mol) of acid **15** along with 150 mL of dry THF and the mixture was stirred at room temperature to dissolve the acid. To the resulting solution, 5.78 g (0.15 mol, 2 eq) of lithium aluminium hydride was slowly added in small portions with stirring, and the reaction was allowed to stir for 4 h. [*Caution*! Frothing is a problem if the added portions of lithium aluminium hydride are too large]. The resulting gray suspension was slowly quenched with 20 mL of 10% sodium hydroxide solution. The reaction mixture turned into a turbid white solution, which slowly became a white precipitate. The solid was removed by filtration through Celite® and the filtrate was concentrated under vacuum. The crude product was purified by flash chromatography on a 20-cm × 4-cm silica gel column using 40% ethyl acetate in hexanes to give 14.7 g

(87%) of **16** as a pale yellow oil. IR: 3378 cm^{-1}; ^{1}H NMR: δ 7.36 (m, 1 H), 7.16-7.08 (complex, 3 H), 3.60 (d, *J* = 10.8 Hz, 1 H), 3.56 (d, J = 10.8 Hz, 1 H), 2.38 (d, *J* = 14.0 Hz, 1 H), 1.78 (d, *J* = 14.0 Hz, 1 H), 1.43 (s, 3 H), 1.41 (s, 3 H), 1.40 (s, 3 H), 1.40 (br s, 1 H); ^{13}C NMR: δ 138.2, 134.6, 128.6, 127.2, 126.5, 125.1, 72.0, 49.3, 41.8, 40.7, 31.3, 30.6, 27.2.

(2,2,4-Trimethylthiochroman-4-yl)methyl acetate (17). A 250-mL one-necked round-bottomed flask was charged with 14.0 g (0.06 mol) of alcohol **16**, along with 7.7 g (0.06 mol) of 4-dimethylaminopyridine dissolved in 100 mL of dichloromethane. Then 7.0 g (6.5 mL, 0.07 mol) of acetic anhydride dissolved in 5 mL of dichloromethane was added slowly to the solution over a period of 5 min at room temperature. The reaction mixture was stirred at room temperature for 3 h at which time TLC analysis confirmed that the reaction was completel. The reaction mixture was diluted with dichloromethane (1 × 100 mL) and washed with 2 *M* HCl (1 × 150 mL), water (1 × 200 mL) and saturated NaCl (1 × 175 mL) then dried ($MgSO_4$, 10 min) and concentrated under vacuum to give 16.3 g (98%) of **17** as a dark yellow oil. IR: 1742 cm^{-1}; ^{1}H NMR: δ 7.35 (m, 1 H), 7.17-7.07 (complex, 3 H), 4.18 (d, *J* = 11.0 Hz, 1 H), 4.14 (d, J = 11.0 Hz, 1 H), 2.23 (d, *J* = 14.3 Hz, 1 H), 2.03 (s, 3 H), 1.86 (d, *J* = 14.3 Hz, 1 H), 1.42 (2 s, 6 H), 1.41 (s, 3 H); ^{13}C NMR: δ 171.0, 138.0, 133.9, 128.5, 127.2, 126.7, 125.1, 71.9, 49.6, 41.6, 38.9, 31.3, 31.2, 27.3, 20.9.

(2,2,4-Trimethyl-6-nitrochroman-4-yl)methyl acetate (18). A 250-mL three-necked round-bottomed flask, equipped with magnetic stirring, an addition funnel and a nitrogen inlet was charged with 10.0 g (0.04 mol) of acetate **17** dissolved in 25 mL of freshly distilled acetic anhydride. The solution was cooled to −5 ºC (ice/salt bath) and a cold

solution of 3.4 mL of concentrated nitric acid in 8.1 mL of acetic anhydride was added drop-wise over 10 min. The reaction was stirred at –5 ºC for 90 min, then diluted with 250 mL of ether and washed with saturated $NaHCO_3$ (1 × 100 mL). The $NaHCO_3$ wash was back extracted with 50 mL of dichloromethane, and the combined organic layers were washed with water (1 × 150 mL) and saturated NaCl (1 × 100 mL) then dried ($MgSO_4$, 10 min) and concentrated under vacuum. The crude product was purified by flash chromatography on a 40-cm × 2-cm silica gel column using increasing concentrations of ethyl acetate [5%, 10%, 25%, 50%] in hexanes to give 2.3 g (20%) of **18** as a viscous yellow oil. IR: 1743, 1516, 1340 cm^{-1}; ^1H NMR: δ 8.29 (d, *J* = 2.2 Hz, 1 H), 7.95 (dd, *J* = 8.2, 2.2 Hz, 1 H), 7.28 (d, *J* = 8.2 Hz, 1 H), 4.20 (d, *J* = 11.0 Hz, 1 H), 4.11 (d, J = 11.0 Hz, 1 H), 2.23 (d, *J* = 14.3 Hz, 1 H), 2.05 (s, 3 H), 1.92 (d, *J* = 14.3 Hz, 1 H), 1.52 (s, 3 H), 1.47 (s, 3 H), 1.44 (s, 3 H); ^{13}C NMR: δ 170.7, 145.1, 144.1, 138.9, 128.6, 122.8, 121.6, 71.3, 48.9, 42.6, 39.1, 31.3, 31.2, 27.3, 20.8.

(6-Amino-2,2,4-trimethylthiochroman-4-yl)methyl acetate (19). The procedure of Bunce and co-workers was used.[8] In a 25-mL three-necked round-bottomed flask, equipped with magnetic stirring, a reflux condenser and a nitrogen inlet, was placed a mixture of 0.50 g (1.62 mmol) of nitro acetate **18**, 8 mL of acetic acid, acetic acid (8 mL) and 0.27 g (4.85 mmol, 3 eq) of iron powder (>100 mesh) which was added under reflux and stirred at 115 ºC (oil bath) until TLC analysis indicated complete consumption of starting material (*ca* 15 min). The crude reaction was cooled, transferred to a separatory funnel containing 50 mL of water and extracted with ether (3 × 25 mL). The combined ether layers were washed with water (1 × 50 mL), saturated $NaHCO_3$ (3 × 100 mL) and saturated NaCl (1 × 75 mL) then dried ($MgSO_4$) and concentrated under vacuum to give

0.43 g (95%) of **19** as pale brown liquid. IR: 3451, 3365, 3224, 1734 cm^{-1}; ^{1}H NMR: δ 6.97 (d, *J* = 8.2 Hz, 1 H), 6.73 (d, *J* = 2.2 Hz, 1 H), 6.51 (dd, *J* = 8.2, 2.2 Hz, 1 H), 4.19 (d, *J* = 11.0 Hz, 1 H), 4.14 (d, J = 11.0 Hz, 1 H), 3.61 (br s, 2 H), 2.19 (d, *J* = 14.3 Hz, 1 H), 2.06 (s, 3 H), 1.80 (d, *J* = 14.3 Hz, 1 H), 1.39 (s, 3 H), 1.38 (s, 3 H), 1.37 (s, 3 H); ^{13}C NMR: δ 171.1, 144.1, 139.4, 129.6, 122.2, 114.4, 114.2, 71.8, 49.8, 41.6, 39.1, 31.1, 29.6, 27.1, 20.9.

(6-Amino-2,2,4-trimethylthiochroman-4-yl)methanol (20). A 25-mL three-necked round-bottomed flask, equipped with magnetic stirring, a reflux condenser and a nitrogen inlet, was charged with 150 mg (0.54 mol) of amino acetate **19** along with 2 mL of 10% NaOH. The flask was suspended in an oil bath at 90 ºC for 30 min. After 30 minutes, TLC analysis indicated the reaction was complete. The reaction mixture was cooled to room temperature, adjusted to pH 9 with 1 *M* HCl and extracted with ether (2 × 25 mL). The combined ether layers were washed with water (1 × 25 mL) and saturated NaCl (1 × 25 mL), then dried ($MgSO_4$, 10 min) and concentrated under vacuum to give 120 mg (94%) of **20** as a viscous brown oil. IR: 3344 cm^{-1}; ^{1}H NMR: δ 6.96 (d, *J* = 8.2 Hz, 1 H), 6.73 (d, *J* = 2.2 Hz, 1 H), 6.49 (dd, *J* = 8.2, 2.2 Hz, 1 H), 3.60 (d, *J* = 11.0 Hz, 1 H), 3.55 (d, J = 11.0 Hz, 1 H), 2.90 (br s, 2 H), 2.30 (d, *J* = 14.3 Hz, 1 H), 1.72 (d, *J* = 14.3 Hz, 1 H), 1.39 (s, 3 H), 1.36 (s, 3 H), 1.34 (s, 3 H) 1.25 (br s, 1 H); ^{13}C NMR: δ 144.0, 139.7, 129.7, 123.1, 114.4, 114.3, 71.9, 49.9, 41.8, 41.0, 31.2, 30.4, 27.1.

General Procedure for Preparation of the Thiourea. *N*-[3,4-Dihydro-(4-methylacetate)2,2,4-trimethyl-2*H*-1-benzothiopyran-6-yl]-*N*'-(4-nitrophenyl) thiourea (4). The general procedure of Berlin and coworkers[5] was used. A 25-mL one-necked round-bottomed flask, equipped with magnetic stirring, an addition funnel

and a nitrogen inlet, was charged with a solution 79 mg (0.28 mmol) of amino acetate **19** in 3 mL of dry THF, and the flask was cooled to 0 ºC (ice bath). To this was added a solution of 54 mg (0.30 mmol) of 4-nitrophenylisothiocyanate in 3 mL of dry THF over 5 min. After the addition, the reaction mixture was allowed to warm to room temperature and stirring was continued for 24 h. The solvent was evaporated and the residue was purified using flash chromatography on a 10-cm × 2-cm silica gel column using 70% ether in hexanes to give **4** as pale yellow solid. The yellow solid was further recrystallized using dichloromethane:pentane (1:3) to give 114 mg (88%) of **4** as a yellow solid, mp 155-156 ºC. IR: 3291, 1727 cm^{-1}; ^{1}H NMR: δ 8.35 (br s, 1 H), 8.20 (d, *J* = 9.0 Hz, 2 H), 7.95 (br s, 1 H), 7.83 (d, *J* = 9.0 Hz, 2 H), 7.41 (d, *J* = 2.2 Hz, 1 H), 7.18 (d, *J* = 8.2 Hz, 1 H), 6.99 (dd, *J* = 8.2, 2.2 Hz, 1 H), 4.53 (d, *J* = 11.0 Hz, 1 H), 3.74 (d, *J* = 11.0 Hz, 1 H), 2.48 (d, *J* = 14.3 Hz, 1 H), 1.87 (s, 3 H), 1.86 (d, *J* = 14.3 Hz, 1 H), 1.45 (s, 6 H), 1.40 (s, 3 H); ^{13}C NMR: δ 179.6, 170.9, 144.6, 144.5, 139.3, 135.4, 132.2, 129.7, 126.0, 124.2, 124.1, 123.9, 72.6, 49.5, 42.1, 39.9, 30.9, 29.5, 27.3, 20.8. *Anal*. Calcd. for $C_{22}H_{25}N_3O_4S_2$: C, 57.49; H, 5.48; N, 9.14; S, 13.95. Found: C, 57.63; H, 5.48; N, 9.09; S, 13.83.

***N*-[3,4-Dihydro-(4-hydroxymethyl)2,2,4-trimethyl-2*H*-1-benzothiopyran-6-yl]-*N'*-(4-nitrophenyl)thiourea (5)**. This compound (97 mg, 82%) was prepared as above from 66 mg (0.28 mmol) of **20** and 54 mg (0.30 mmol) of 4-nitrophenylisothiocyanate. The product was purified by recrystallization from methanol, mp 154-155 ºC. IR: 3435 cm^{-1}; ^{1}H NMR (CD_3OD): δ 8.24 (d, *J* = 9.0 Hz, 2 H), 7.83 (d, *J* = 9.0 Hz, 2 H), 7.56 (d, *J* = 2.2 Hz, 1 H), 7.18 (dd, *J* = 8.2, 2.2 Hz, 1 H), 7.13 (d, *J* = 8.2 Hz, 1 H), 3.63 (d, *J* = 11.0 Hz, 1 H), 3.57 (d, J = 11.0 Hz, 1 H), 2.36 (d, *J* = 14.3 Hz, 1 H), 1.82 (d, *J* = 14.3 Hz, 1 H), 1.44

(s, 3 H), 1.40 (s, 6 H), the 2 NH and 1 OH were exchanged; ^{13}C NMR (CD_3OD): δ 181.5, 147.2, 144.9, 141.5, 136.8, 133.2, 129.7, 125.3, 125.2, 123.7, 123.6, 72.2, 50.2, 42.9, 42.0, 31.6, 31.1, 27.7. *Anal.* Calcd for $C_{20}H_{23}N_3O_3S_2$: C, 57.53; H, 5.55; N, 10.06; S, 15.36. Found C, 57.45; H, 5.52; N, 10.05; S, 15.23.

References and Notes

1. Escudier, B.; Eisen, T.; Stadler. W. M.; *et. al. N. Engl. J. Med.* **2007**, *356*, 125-134. [erratum appeared in *N Engl J. Med.* **2007**, *357*, 203].
2. Smith, R. A.; *et. al. Bioorg. Med. Chem. Lett.* **2001**, *11*, 2775-2778.
3. Bhojani, N.; Jeldres, C.; Patard, J. J.; *et. al. Eur. Urol.* **2008**, *53*, 917-930.
4. Dai, Y.; Hartandi, K.; Ji, Z.; Ahmed, A. A.; Albert, D. H.; *et. al. J. Med. Chem.* **2007**, *50*, 1584-1597.
5. Liu, S.; Brown, C. W.; Berlin, K. D.; Dhar, A.; Guruswamy, S.; Brown. D.; Gardner, G. J.; Birrer, M. J.; Benbrook, D. M. *J. Med. Chem.* **2004**, *47*, 999-1007.
6. Tercio, J.; Ferreria, B.; Catani, V.; Comasseto, J. V. *Synthesis* **1987**, *2*, 149-153.
7. Gregory, G. B.; Johnson, A. L.; Ripka, W. C. *J. Org. Chem.* **1990**, *55*, 1479-1483.
8. Bunce, R. A.; Randall, M. H.; Applegate, K. G. *Org. Prep. Proced. Int.* **2002**, *34*, 493-499.

VITA

Baskar Nammalwar

Candidate for the Degree of

Doctor of Philosophy

Dissertation: I. SYNTHESIS OF VARIOUS HETEROCYCLES USING DISSOLVING METAL REDUCTION PROCESS II. SYNTHESIS OF HETEROAROTINOID SCAFFOLDS FOR ANTICANCER AGENTS

Major Field: Chemistry

Biographical:

Personal Data: Born in Chennai, India to K.Nammalwar and M.Jeevarathanam; Citizenship: Indian

Education: Received Bachelor of Science in Chemisty (First Class) from Loyola College in May 1998; Received Master of Science (First Class with Distinction) from Anna University in May 2003. Received Master of Philosophy (First Class) in May 2005; completed requirements for Doctor of philosophy degree at Oklahoma State University at Stillwater in May 2010

Professional Experience: Graduate Research Assistant, OSU, 2009-2010. Graduate Teaching Assistant, Organic Chemistry Labs, OSU, 2007-2009. Research Scientist, Jubilant Biosys, Bangalore, 2006-2007. Research Scientsist, Aurigene Discovery Technologies, Bangalore 2004-2006. Officer R&D, Sanmar Speciality Chemicals, Chennai, 2003-2004.

Professional Memberships: Golden Key Member

Name: BASKAR NAMMALWAR Date of Degree: May, 2010

Institution: Oklahoma State University Location: Stillwater, Oklahoma

Title of Study: I. SYNTHESIS OF VARIOUS HETEROCYCLES USING DISSOLVING METAL REDUCTION PROCESS II. SYNTHESIS OF HETEROAROTINOID SCAFFOLDS FOR ANTICANCER AGENTS

Pages in Study: 149 Candidate for the Doctorate of Philosophy

Major Field: CHEMISTRY

Scope and Method of Study: Research

Findings and Conclusions: An efficient route to synthesize various heterocycles has been developed based on tandem reactions initiated by a dissolving metal reduction. New methods have been developed which involves either the use of a tandem reduction-reductive amination, reduction-cyclization or a reduction-lactamization sequence to achieve potentially valuable target molecules. The key steps involved in the procedure are (i) reduction of an aromatic nitro group using iron in presence of an acid followed by (ii) intramolecular cyclization with either an aldehyde, ketone, ester or α,β-unsaturated ketone. Different heterocycles such as carbazoles, pyridoindolones, spiro-fused 3,4-dihydro-2(1*H*)-quinolinone derivative, two tricyclic linear fused rings system, aryl and alkyl dihydro-4(1*H*)-quinazolinones, 4(1*H*)-quinolinones and dihydroquinolinones were successfully synthesized by this method. The use of these mild procedures allows reasonable structural variation and avoids the use of hazardous reagents or expensive catalysts. Some of the heterocyclic targets prepared by this method are currently used as drugs or are precursors to drugs in advanced clinical studies.

A commercial route for the sythesis of SHetA2 heteroarotinoid ring was developed. Syntheses of metabolites of SHetA2 were developed using a 17-step synthetic route.

ADVISER'S APPROVAL: RICHARD A. BUNCE