I. STERIC EFFECTS IN THE SYNTHESIS OF 2,3-DIHYDRO-4-(1*H*)-QUINOLINONES BY THE TANDEM MICHAEL-S_NAr REACTION

II. SYNTHESIS OF NITROGEN HETEROAROTINOIDS FOR ANTICANCER ACTIVITY

III. SYNTHETIC STUDY OF SUPRAMOLECULAR COMPOUNDS

BY

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Master of Science
National University Ireland Maynooth
Maynooth
2004

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
July, 2013

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ACKNOWLEDGEMENTS

I would like to thank and express my deep appreciation to my supervisor Dr. Richard A. Bunce for his supervision, friendly support, invaluable guidance, wise counsel and his patience throughout my dissertation writing. I am sure it would have not been possible without his help. My gratitude goes out as well to all my committee advisors, Dr. K. Darrell Berlin, Dr. Ziad El Rassi, Dr. Toby L. Nelson, and Dr. Andrew J. Mort.

A big thank you to Dr. K. Darrell Berlin, for his generosity, advice, kindness and unlimited help when I needed it. Thank you for helping me write my dissertation, especially the Dr. Laura Shirtcliff part. Thanks for the good times I had when grading exams.

I wish to thank my former supervisor Dr. Laura D. Shirtcliff for her supervision and guidance in the projects of Chapters IV and V, and I wish her a good future. Also I would like to thank Department of Chemistry for providing me with a teaching assistantship. Thank you to all the secretaries and staff of the chemistry department for their help and support. Thank you to all graduate students that I met in the department.

Finally, I would like to thank my family, especially my parents (Mohamed and Fatima), my husband (Abdalmajid) and my kids (Fatima and Ahmad). Thank you to my brothers and sisters for their encouragement and support.

SYMBOLS AND ABBREVIATIONS

Abbreviation	Name
AcOH	Acetic acid
Ar	Aryl
bp	Boiling point
br, s, d, t, m	Broad, singlet, doublet, triplet, multiplet
*m*CPBA	*meta*-Chloroperoxybenzoic acid
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMSO	Dimethylsulfoxide
DMF	*N,N*-Dimethylfomamide
Hz	Hertz
IR	Infra-red
LDA	Lithium diisopropylamide
MeI	Methyl iodide
MeOH	Methanol
MHz	MegaHertz
mp	Melting point
NMR	Nuclear magnetic resonance
PEG	Polyethylene glycol
PTLC	Preparative thin layer chromatography
rt	Room temperature
S_NAr	Nucleophilic aromatic substitution
TEA	Triethylamine
TES	Triethylsilane
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
p-TsOH	*para*-Toluenesulfonic acid
TTNPB	4-[(*E*)-2-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl) -1-propenyl]benzoic acid,
UV-VIS	Ultraviolet-Visible
$Zn(OAc)_2$	Zinc acetate

Name: SUAAD M. ABUSKHUNA

Date of Degree: JULY, 2013

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Major Field: CHEMISTRY

Abstract:

In the initial project, a one-pot tandem reaction sequence was developed for the preparation of 2,3-dihydro-4-(1*H*)-quinolinones by a Michael addition-S_NAr reaction sequence. The steric environment of the Michael terminus plays a vital role in controlling the outcome of the reaction. Larger groups at this site reverse the Michael-S_NAr reaction sequence and prevent the cyclization from occurring. Various amines were also examined to understand the steric control in this process. In the second project, we synthesized tetrahydrobenzo[*b*]azepine by tandem reduction Michael addition and reductive amination reaction. The third project focused on the development of a new synthetic route to prepare heteroarotinoids containing a nitrogen atom in the saturated heterocycle fused to the core aromatic ring. Heteroarotinoids exhibit significant anticancer activity with low toxicity toward normal cells. They regulate growth, differentiation, and apoptosis of cancer cells by interaction with nuclear proteins called retinoid receptors. By incorporating a nitrogen atom in the heteroarotinoid, the drug may exhibit increased activity, solubility and bioavailability. In Chapters IV and V, we aimed to synthesize supramolecular structures of porphyrins and phenyl acetylenes. Attempts were made to synthesize co-facial porphyrins and cyclized phenyl acetylenes that have central cavities capable of binding metals and small organic molecules. Neither of these studies was successful.

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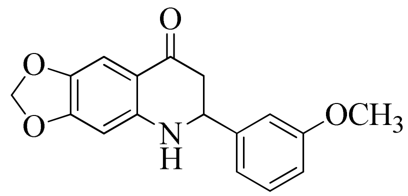
CHAPTER I

STERIC EFFECTS IN THE SYNTHESIS OF 2,3-DIHYDRO-4-(1*H*)-QUINOLINONES BY THE TANDEM MICHEAL-S_NAr REACTION

Introduction

Tandem, cascade, domino or multistep one-pot reactions involve a consecutive series of reactions in which several bonds are formed in sequence without isolating intermediates, changing reaction conditions, or adding reagents. Tandem reactions are important in organic synthesis for forming complex molecules with high selectivity from a single acyclic precursor in a few steps. Moreover, the development of this type of synthetic method can lead to a reduction in the number of undesired by-products and the quantity of solvents required in isolation and purification of intermediates using stepwise synthetic processes.[1]

The use of the tandem reactions has provided an efficient and productive synthetic method for the synthesis of 2,3-dihydro-4(1*H*)-quinolinones. These compounds possess a variety of biological activities and can be used to treat cancer[2] **(1)**, central nervous system disorders[3] **(2)**, steroid receptor modulator problems[4] **(3)**, and inflammatory diseases such as asthma[5] **(4)** as shown in Figure 1.1. Also these compounds are useful synthetic intermediates for various pharmaceuticals and other biologically active compounds.[6,7]



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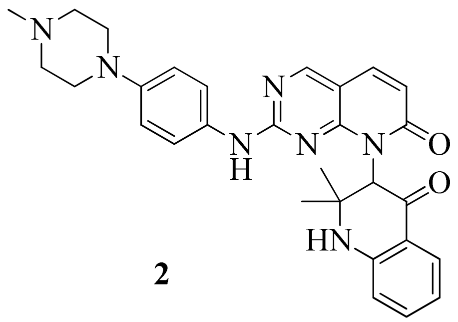

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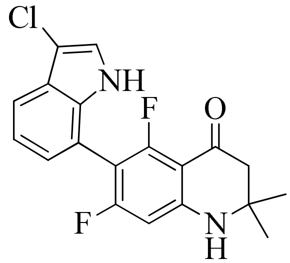

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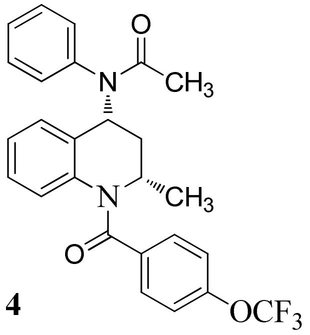

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Figure 1.1. A biologically active 2,3-dihydroquinolinones.

Different methods have been reported for the synthesis of 2-aryl-2,3-dihydro-4(1*H*)-quinolinones. Generally, it has been synthesized by cycloisomerization of substituted 2´-aminochalcone derivatives[8] in the presence of acid or base such as H_3PO_4,[9a] montmorillonite,[9b] $InCl_3$,[9c] silica gel-supported $TaBr_5$,[9d] silica gel-supported $NaHSO_4$,[9e] PEG-400[9f] or NaOEt[9g] as shown in Figure 1.2.

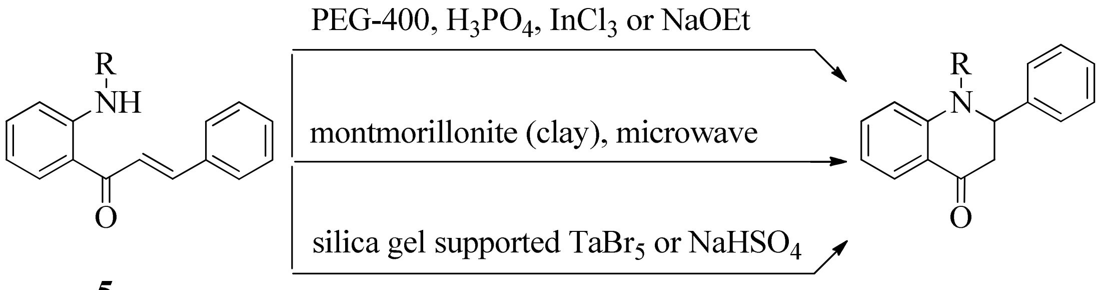

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Figure 1.2. General synthetic methods of 2-aryl-2,3-dihydro-4(1*H*)-quinolinones.

Bunce and co-workers[10] have synthesized the of 2-aryl-2,3-dihydro-4(1*H*)-quinolinones by tandem reduction-Michael addition of nitroaromatic compounds or Michael addition-nucleophilic aromatic substitution (S_NAr) in fluoroaromatic substrates. Reduction of nitroaromatic compounds has been done by catalytic hydrogenation or dissolving metal reduction using iron (Fe) in acetic acid or hydrochloric acid.[11] The intermediate amino group undergoes Michael addition to an α,β-unsaturated carbonyl compound forming the heterocyclic compound as shown in Figure 1.3. The other tandem reaction involves Michael addition and S_NAr reaction. This tandem process involves the addition of a primary amine to the electron deficient β-carbon of the enone to form a secondary amine, and then ring closure follows by nucleophilic aromatic substitution[12] as shown in Figure 1.4.

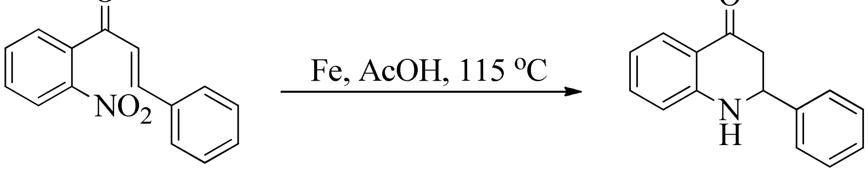

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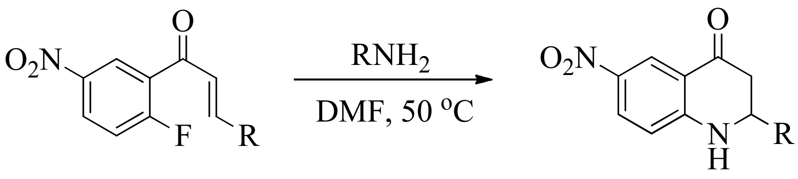
Figure 1.3. Tandem reduction of a nitroaromatic compounds.



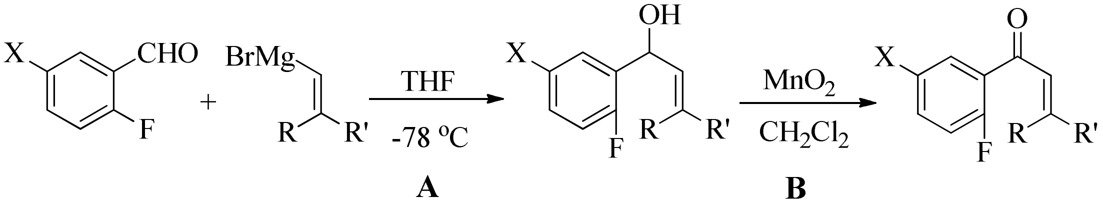
9 **10**

Figure 1.4. Tandem reaction involves Michael addition-S_NAr reactions.

In this project, we have examined the effect of substituents at the enone terminus on Michael addition-S_NAr reactions for the synthesis of 2-aryl-2,3-dihydro-4(1*H*)-quinolinone derivatives. For this study we reacted simple substrates, monomethylated and dimethylated at the β-carbon, benzylamine, hexylamine and isobutylamine.

Results and Discussion

The required cyclization substrates were prepared by a two-step sequence. The reaction of 2-fluorobenzaldehyde (**11)** and 2-fluoro-5-nitrobenzaldehyde **(12)** in THF at -78 °C with vinylmagnesium bromides **13-14** afforded the allylic alcohols **15-18** in 86-88% yields.[13] Oxidation of the allylic alcohols **15-18** with manganese(IV) oxide[14] produced the corresponding ketones in 65-84% yields as shown in Figure 1.5 and Table 1.1.



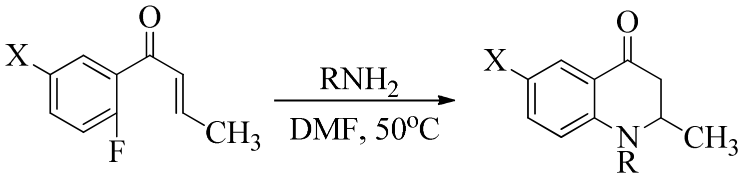
11 X = H
12 X = NO_2
13 R = H, R' = CH_3
14 R, R' = CH_3
15-18
19-20
23-24

Figure 1.5. Synthesis of the allylic alcohol and the enone derivatives.

X	R	R´	Product (%) **A**	Product (%) **B**
H	H	CH_3	**15** (88)	**19** (65)
NO_2	H	CH_3	**16** (86)	**20** (68)
H	CH_3	CH_3	**17** (81)	**23** (84)
NO_2	CH_3	CH_3	**18** (88)	**24** (81)

Table 1.1. Yields of allylic alcohol and enone derivatives.

Addition of the primary amines to the monomethylated enones **19** and **20** in DMF at 50 ºC afforded the cyclized products **21a-c** and **22a-c** in high yields, as shown in Figure 1.6 and Table 1.2. On the other hand, addition of amines to dimethylated enone **23** afforded low yields of cyclized products and the major component was unreacted starting material **23** (Figure 1.7 and Table 1.3). The low yields from dimethylated substrate **23** is due to steric hindrance at β-carbon and the weakly activated aromatic ring toward nucleophilic aromatic substitution reaction. Also, there is no significant increase in the yields of the cyclized products upon increasing the reaction temperature.



19 X = H
20 X = NO_2

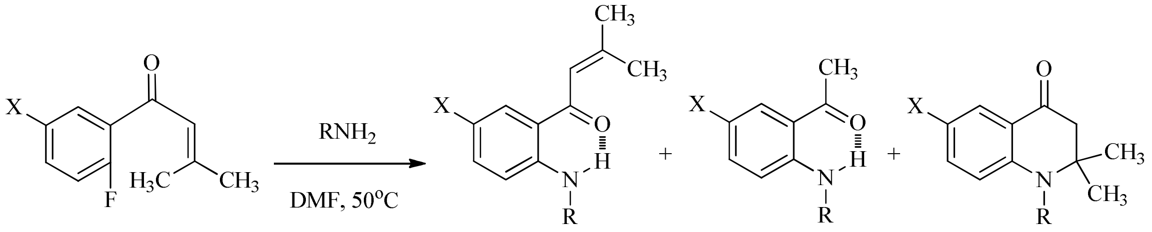
21 a-c X = H
22 a-c X = NO_2

Figure 1.6. Cyclization of substrate **19** and **20**.

X	R	Product (%)
H	$C_6H_5CH_2$	**21a** (80)
H	*n*-C_6H_{13}	**21b** (86)
H	*i*-C_4H_9	**21c** (78)
NO_2	$C_6H_5CH_2$	**22a** (97)
NO_2	*n*-C_6H_{13}	**22b** (98)
NO_2	*i*-C_4H_9	**22c** (92)

Table 1.2. Major products of cyclized mono methylated substrates **19** and **20**.

Introduction of a second electron-withdrawing group on the aromatic ring of the dimethylated substrate had a dramatic effect on the yield of cyclized product and the mechanism of the reaction at the Michael terminus.[10] Cyclization of substrate **24** afforded three products, including the target cyclized products **25c-30c**, 1-(2-alkylamino)-5-nitrophenyl)-3-methyl-2-buten-1-one derivatives (**26a**, **28a** or **30a**) and acetophenone derivatives (**26b**, **28b** or **30b**) as shown in Figure 1.7 and Table 1.3.



23 X = H
24 X = NO_2

26a, **28a**, **30a**

26b, **28b**, **30b**

25c-30c

Figure 1.7. Cyclization of substrate **23** and **24**.

Product No.	X	R	Product (%)		
			a	**b**	**c**
25	H		0	0	4
26	NO_2	$C_6H_5CH_2$	32	1	66
27	H		0	0	12
28	NO_2	*n*-C_6H_{13}	19	3	69
29	H		0	0	7
30	NO_2	*i*-C_4H_9	18	7	70

Table 1.3. Major products of cyclized substrates **23** and **24**.

Mechanistically the formation of **26a, 28a** or **30a** could arise from a direct S_NAr reaction[12] of the primary amine on the aromatic ring due to the relatively slow addition at the β-carbon of the enone. Once this addition happens, steric interaction between the amine and the side chain at the β-carbon would cause rotation about the benzylic bond to give a product stabilized by six-centered H-bonding. Further addition of excess amine to the electron deficient β-carbon would produce a secondary amine, which would fragment to form the acetophenone derivative (**26b, 28b** or **30b**) via the enol **33**. The acetone imine **34**, also formed in this process, would hydrolyze and be lost in the work-up. This mechanistic scenario is summarized in Figure 1.8.

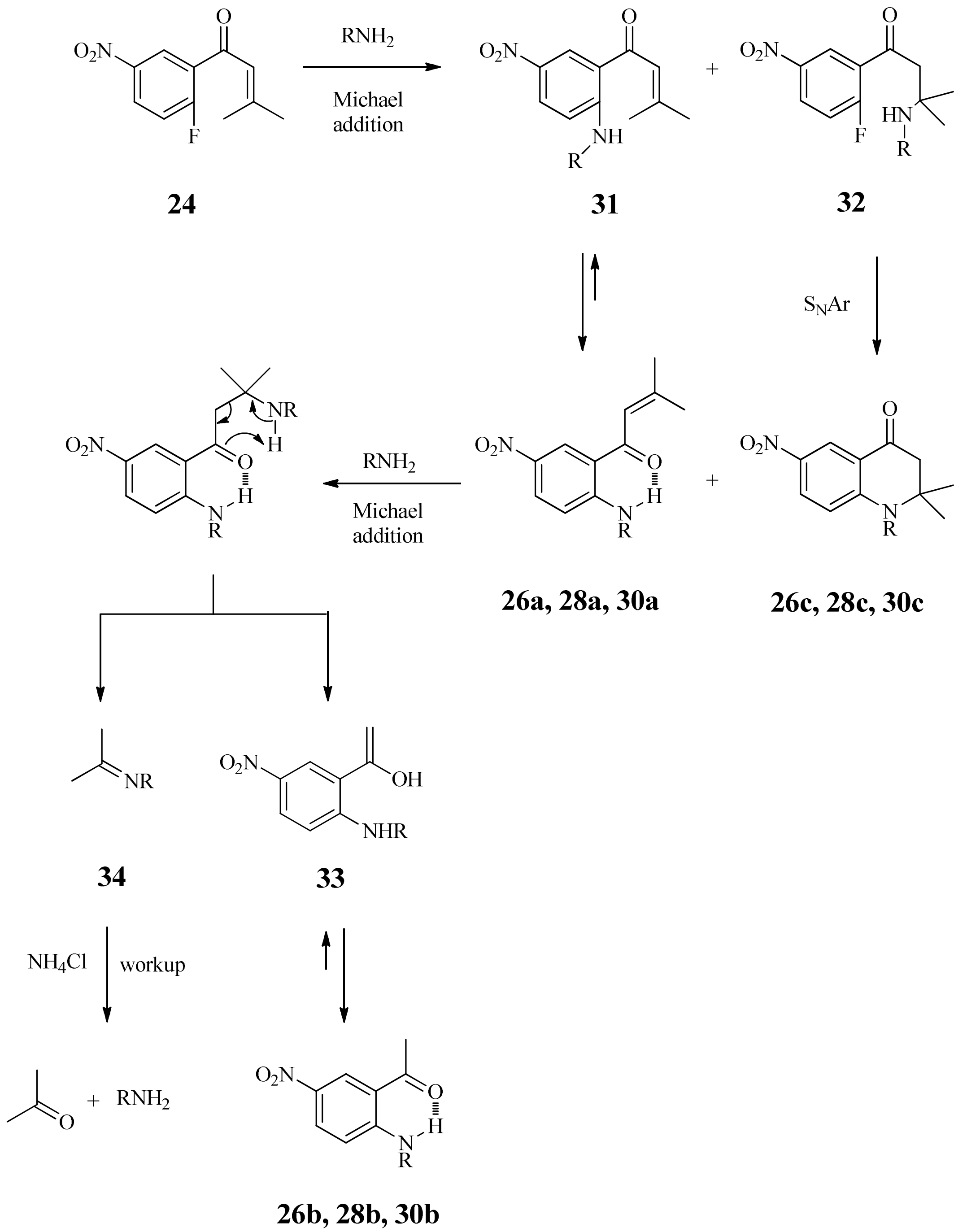


Figure 1.8. Mechanisms of the formed products.

Conclusions

A study to probe the steric and electronic factors important in the Michael- S_NAr sequence to produce 2,3-dihydro-4(1*H*)-quinolinones has been performed. Three amines (benzylamine, hexylamine and isobutylamine) have been used for this study. Substrates bearing a single methyl group at the Michael terminus gave excellent yields of the cyclized product. Increasing the steric bulk at the Michael terminus with *gem*-dimethyl slows the addition to the side chain double bond and reverses the Michael- S_NAr sequence. Introduction of an electron withdrawing group to activate the aromatic ring improves the yield of the cyclization product. Once addition to the aromatic ring occurs, steric interaction between the added amine and the side chain causes rotation about the benzylic bond and gives the H-bond-stabilized acetophenone derivatives.

Experimental Section

All solvents were distilled prior to use. Other reagents were used as received from various vendors. All reactions were run under dry nitrogen in oven-dried glassware. 1-Propenylmagnesium bromide (0.5 *M* in tetrahydrofuran) was purchased from Aldrich Chemical Company. Commercial anhydrous *N,N*-dimethylfomamide (DMF) was syringed into reactions as needed. Reactions were monitored by TLC on hard layer silica gel GF plates (Analtech No. 21521) using UV detection. Preparative separations were performed using one of the following methods: (1) PTLC on 20-cm x 20-cm silica gel GF plates (Analtech No. 02015) or (2) flash column chromatography on silica gel (Davisil®, grade 62, 60-200 mesh) containing UV-active phosphor (Sorbent Technologies No. UV-05). In each case, band elution was monitored using a hand-held UV-lamp. IR spectra were taken on thin films on NaCl disks. ^{1}H-NMR and ^{13}C-NMR spectra were measured in $CDCl_3$ at 300 MHz and 75 MHz, respectively, and were referenced to internal $(CH_3)_4Si$; coupling constants (*J*) are in Hz.

Representative Grignard Addition Procedure: (±)-(*E*)- and (±)-(*Z*)-1-(2-Fluorophenyl)-2-buten-1-ol (15). The general procedure of Danishefsky and co-workers[13] was used. A 250-mL, three-necked, round-bottomed flask, equipped with a magnetic stirrer, a septum, a reflux condenser and a nitrogen inlet was charged with 2-fluorobenzaldehyde **(11)** (1.86 g, 15.0 mmoles) in dry THF (75 mL). The solution was cooled to -78 ºC and 1-propenylmagnesium bromide **(13)** (45 mL, 0.5 *M*, 22.5 mmol) in THF was added dropwise. The reaction mixture was stirred for 3.5 h at -78 ºC and then quenched by addition of saturated aqueous NH_4Cl (50 mL) and extracted three times with ether. The combined ether extracts were washed three times with water, once with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated under vacuum to give **15** (2.19 g, 88%) as viscous yellow oil. This product mixture (*E*-**15** and *Z*-**15**) was used without further purification. IR: 3347, 1616, 1242 cm^{-1}; ^{1}H-NMR: δ 7.49 (overlapping td, 1H, *J* = 7.4, 1.6 Hz), 7.24 (m, 1H), 7.14 (td, 1H, *J* = 7.4, 1.6 Hz), 7.01 (ddd, 1H, *J* = 9.3, 1.4, 1.1 Hz), 5.83 and 5.63 (2d, 1H, *J* = 7.1, 0.5 Hz), 5.73 (m, 0.5H), 5.61 (m, 1.5H), 2.18 (br s, 1H), 1.77 and 1.70 (2d, 3H, *J* = 5.4, 4.9 Hz); ^{13}C-NMR: δ 159.9 (d, *J* = 246.2 Hz), 132.1, 131.4, 130.6 (d, *J* = 13.2 Hz), 129.0 (d, *J* = 8.3 Hz), 128.4 (d, *J* = 8.3 Hz), 127.6, 127.4 (d, *J* = 4.3 Hz), 126.9, 124.3 (d, *J* = 3.4 Hz), 115.3 (d, *J* = 21.8 Hz), 69.2 (d, *J* = 2.2 Hz), 64.1 (d, *J* = 3.4 Hz), 17.6, 13.2.

(±)-(*E*)- and (±)-(*Z*)-1-(2-Fluoro-5-nitrophenyl)-2-buten-1-ol (16). This compound (1.81 g, 86%) was prepared from **12** (1.69 g, 10.0 mmol) and 1-propenylmagnesium bromide **(13)** (30 mL, 0.5 *M*, 15.0 mmol) and isolated as a viscous yellow oil. This product was used without further purification. IR: 3378, 1629, 1530, 1350, 1247 cm^{-1}; ^{1}H-NMR: δ 8.49 and 8.46 (dd, 1H, *J* = 6.1, 2.7 Hz), 8.18 (m, 1H), 7.16 (t, 1H, *J* = 9.2 Hz), 5.84 (m, 1H), 5.68 (m, 1H), 5.51 (m, 1H), 2.55 (br s, 1H), 1.82 (dm, 1.5 H, *J* = 6.8 Hz), 1.72 (dd, 1.5H, *J* = 6.4, 0.8 Hz); ^{13}C-NMR: δ 163.2 (d, *J* = 262.8 Hz), 163.1 (d, *J* = 262.8 Hz), 144.8, 132.6 (d, *J* = 15.5 Hz), 132.4 (d, *J* = 15.5 Hz), 131.0, 130.2, 129.1, 128.5, 124.7 (d, *J* = 3.7 Hz), 124.6 (d, *J* = 3.7 Hz), 123.6 (d, *J* = 6.6 Hz), 116.3 (d, *J* = 25.0 Hz), 68.4, 63.3, 17.6, 13.2.

(±)-1-(2-Fluorophenyl)-3-methyl-2-buten-1-ol (17). This compound (2.19 g, 81%) was prepared from 2-fluorobenzaldehyde **(11)** (1.86 g, 15.0 mmoles) and 2-methyl-1-propenylmagnesium bromide **(14)** (45 mL, 0.5 *M*, 22.5 mmol) in dry THF and isolated as a yellow oil. This product was used without further purification. IR: 3353, 1618, 1224 cm^{-1}; ^{1}H-NMR: δ 7.50 (td, 1H, *J* = 7.7, 1.6 Hz), 7.22 (m, 1H), 7.14 (td, 1H, *J* = 7.7, 1.1 Hz), 7.01 (m, 1H), 5.73 (dd, 1H, *J* = 8.8, 3.3 Hz), 5.40 (dq, 1H, *J* = 8.8, 1.1 Hz), 1.95 (d, 1H, *J* = 3.3 Hz), 1.80 (s, 3H), 1.74 (s, 3H); ^{13}C-NMR: δ 159.9 (d, *J* = 245.9 Hz), 135.9, 131.1 (d, *J* = 13.2 Hz), 128.7 (d, *J* = 8.0 Hz), 127.3 (d, *J* = 4.6 Hz), 126.2, 124.2 (d, *J* = 3.4 Hz), 115.3 (d, *J* = 21.3 Hz), 65.4 (d, *J* = 3.1 Hz), 25.8, 18.2. *Anal*. Calcd. for $C_{11}H_{13}FO$: C, 73.33; H, 7.22. Found: C, 73.37; H, 7.24.

(±)-1-(2-Fluoro-5-nitrophenyl)-3-methyl-2-buten-1-ol (18). This compound (1.98 g, 88%) was prepared from **12** (1.69 g, 10.0 mmol) and 2-methyl-1-propenylmagnesium bromide **(14)** (30 mL, 0.5 *M*, 15.0 mmol) and isolated as a viscous yellow oil. This product was used without further purification. IR: 3372, 1626, 1531, 1350, 1248 cm^{-1}; ^{1}H-NMR: δ 8.49 (dd, 1H, *J* = 6.2, 2.9 Hz), 8.15 (ddd, 1H, *J* = 9.0, 4.3, 2.9 Hz), 7.15 (t, 1H, *J* = 9.0 Hz), 5.77 (d, 1H, *J* = 9.0 Hz), 5.30 (d, 1H, *J* = 9.0 Hz), 2.13 (br s, 1H), 1.84 (s, 3H), 1.76 (s, 3H); ^{13}C-NMR: δ 163.1 (d, *J* = 257.7 Hz), 144.5, 137.7, 133.1 (d, *J* = 14.7 Hz), 125.1, 124.5 (d, *J* = 10.3 Hz), 123.6 (d, *J* = 7.4 Hz), 116.3 (d, *J* = 24.2 Hz), 64.7 (d, *J* = 2.9 Hz), 25.8, 18.2 (d, *J* = 1.5 Hz). *Anal*. Calcd. for $C_{11}H_{12}FNO_3$: C, 58.67; H, 5.33; N, 6.22. Found: C, 58.72; H, 5.55; N, 6.18.

Representative Oxidation Using Manganese(IV) oxide: (*E*)- and (*Z*)-1-(2-Fluorophenyl)-2-buten-1-one (19). A 250-mL, round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser was charged with a solution of **15** (1.0 g, 6.02 mmol) in dichloromethane (25 mL). Manganese(IV) oxide (10 g) was added and the reaction mixture was stirred vigorously at 23 ºC for 4-8 h. The reaction mixture was filtered through a plug of Celite®, washed thoroughly with dichloromethane, and the solvent was concentrated. The product was purified on a 40-cm x 2.0-cm silica gel column eluted with increasing concentrations of ether in hexanes to give two bands. Band 1 gave (*Z*)-**19** (127 mg, 13%) as viscous yellow oil. IR: 1669, 1614, 1215 cm^{-1}; ^{1}H-NMR: δ 7.78 (td, 1H, *J* = 7.7, 1.6 Hz), 7.49 (m, 1H), 7.22 (t, 1H, *J* = 7.7 Hz), 7.11 (dd, 1H, *J* = 11.0, 8.2 Hz), 6.75 (dq, 1H, *J* = 11.2, 1.6 Hz), 6.44 (dq, 1H, *J* = 11.2, 7.1 Hz), 2,19 (dd, 3H, *J* = 7.1, 1.6 Hz); ^{13}C-NMR: δ 189.8, 161.1 (d, *J* = 253.9 Hz), 144.5, 133.8 (d, *J* = 8.9 Hz), 130.8 (d, *J* = 2.6 Hz), 128.2 (d, *J* = 6.0 Hz), 127.7 (d, *J* = 13.2 Hz), 124.4 (d, *J* = 3.4 Hz), 116.5 (d, *J* = 23.5 Hz), 16.4. *Anal*. Calcd. for $C_{10}H_9FO$: C, 73.17; H, 5.49. Found: C, 73.12; H, 5.51.

Band 2 gave (*E*)-**19** (516 mg, 52%) as viscous yellow oil. IR: 1667, 1619, 1215 cm^{-1}; ^{1}H-NMR: δ 7.70 (td, 1H, *J* = 7.7, 1.6 Hz), 7.48 (m, 1H), 7.22 (t, 1H, *J* = 7.7 Hz), 7.12 (dd, 1H, *J* = 11.0, 8.2 Hz), 6.99 (m, 1H), 6.76 (dq, 1H, *J* = 15.4, 1.1 Hz), 1.98 (dd, 3H, *J* = 6.6, 1.1 Hz); ^{13}C-NMR: δ 189.5, 160.9 (d, *J* = 253.1 Hz), 145.5, 135.5 (d, *J* = 8.6 Hz), 131.1 (d, *J* = 5.7 Hz), 130.7 (d, *J* = 2.9 Hz), 127.0 (d, *J* = 13.5 Hz), 124.3 (d, *J* = 3.4 Hz), 116.4 (d, *J* = 23.2 Hz), 18.5. *Anal*. Calcd. for $C_{10}H_9FO$: C, 73.17; H, 5.49. Found: C, 73.15; H, 5.47.

(*E*)- and (*Z*)-1-(2-Fluoro-5-nitrophenyl)-2-buten-1-one (20). This compound (0.67 g, *ca*. 5:1 *E*:*Z* mixture, 68%) was prepared from **16** (1.00 g, 4.74 mmol) and manganese(IV) oxide (10.0 g) in dichloromethane (25 mL) and was isolated as a light yellow oil. The product was purified on a 40-cm x 2.0-cm silica gel column eluted with increasing concentrations of ether in hexanes to give two bands. Band 1 gave (*Z*)-**20** (119 mg, 12%) as light yellow solid, mp 43-45 ºC. IR: 1675, 1612, 1532, 1355, 1246 cm^{-1}; ^{1}H-NMR: δ 8.69 (dd, 1H, *J* = 6.0, 2.7 Hz), 8.38 (dt, 1H, *J* = 9.3, 3.8 Hz), 7.31 (t, 1H, *J* = 9.3 Hz), 6.74

(dq, 1H, *J* = 11.5, 1.6 Hz), 6.57 (dq, 1H, *J* = 11.5, 7.1 Hz), 2.24 (d, 3H, *J* = 7.1 Hz); ^{13}C-NMR: δ 186.8, 163.9 (d, *J* = 264.0 Hz), 147.5, 144.5, 128.7 (d, *J* = 10.9 Hz), 128.6 (d, obscured), 127.1 (d, *J* = 4.9 Hz), 126.8 (d, *J* = 6.3 Hz), 118.0 (d, *J* = 26.1 Hz), 16.7. *Anal*. Calcd. for $C_{10}H_8FNO_3$: C, 57.42; H, 3.83; N, 6.70. Found: C, 57.49; H, 3.86; N, 6.64.

Band 2 gave (*E*)-**20** (555 mg, 56%) as light yellow solid, mp 43-45 ºC. IR: 1674, 1623, 1532, 1350, 1246 cm^{-1}; ^{1}H-NMR: δ 8.60 (dd, 1H, *J* = 6.0, 2.7 Hz), 8.37 (ddd, 1H, *J* = 9.3, 3.8, 2.7 Hz), 7.32 (t, 1H, *J* = 9.3 Hz), 7.07 (m, 1H), 6.74 (dq, 1H, *J* = 15.4, 1.6 Hz), 2.03 (dd, 3H, *J* = 7.1, 1.6 Hz); ^{13}C-NMR: δ 186.8, 163.8 (d, *J* = 263.4 Hz), 148.0, 144.3, 130.1 (d, *J* = 5.1 Hz), 128.5 (d, *J* = 10.9 Hz), 127.9 (d, *J* = 16.6 Hz), 126.9 (d, *J* = 4.9 Hz), 117.9 (d, *J* = 25.8 Hz), 18.7. *Anal*. Calcd. for $C_{10}H_8FNO_3$: C, 57.42; H, 3.83; N, 6.70. Found: C, 57.46; H, 3.85; N, 6.65.

1-(2-Fluorophenyl)-3-methyl-2-buten-1-one (23). This compound (1.82 g, 84%) was prepared from **17** (2.19 g, 12.2 mmol) and manganese(IV) oxide (22 g) in dichloromethane (45 mL). The product was purified on a 40-cm x 2.0-cm silica gel column eluted with increasing concentrations of ether in hexanes to give **23** as a yellow oil. IR: 1666, 1614, 1228 cm^{-1}; ^{1}H-NMR: δ 7.74 (td, 1H, *J* = 7.7, 1.6 Hz), 7.44 (m, 1H), 7.19 (td, 1H, *J* = 8.2, 1.1 Hz), 7.09 (dd, 1H, *J* = 10.4, 8.8 Hz), 6.64 (m, 1H), 2.25 (s, 3H), 1.99 (s, 3H); ^{13}C-NMR: δ 189.1, 160.8 (d, *J* = 252.8 Hz), 157.4, 133.3 (d, *J* = 8.9 Hz), 130.7 (d, *J* = 2.6 Hz), 128.2 (d, *J* = 4.3 Hz), 124.4 (d, *J* = 4.9 Hz), 124.2 (d, *J* = 3.4 Hz), 116.3 (d, *J* = 23.2 Hz), 28.0, 21.4. *Anal*. Calcd. for $C_{11}H_{11}FO$: C, 74.16; H, 6.18. Found: C, 74.22; H, 6.21.

1-(2-Fluoro-5-nitrophenyl)-3-methyl-2-buten-1-one (24). This compound (0.80 g, 81%) was prepared from **18** (1.00 g, 4.39 mmol) and manganese(IV) oxide (10.0 g) in dichloromethane (25 mL). The product was purified on a 20-cm x 2.0-cm silica gel column eluted with increasing concentrations of ether in hexanes to give **24** as a light yellow solid, mp 54-55 ºC. IR: 1667, 1624, 1532, 1350, 1252 cm^{-1}; ^{1}H-NMR: δ 8.64 (dd, 1H, *J* = 6.0, 2.7 Hz), 8.35 (ddd, 1H, *J* = 9.3, 3.8, 2.7 Hz), 7.29 (t, 1H, *J* = 9.3 Hz), 6.62 (q, 1H, *J* = 1.1 Hz), 2.30 (s, 3H), 2.06 (s, 3H); ^{13}C-NMR: δ 186.1, 163.9 (d, *J* = 263.4 Hz), 161.1, 144.4, 129.4, 128.2 (d, *J* = 10.9 Hz), 127.0 (d, *J* = 5.2 Hz), 123.1 (d, *J* = 5.7 Hz), 117.9 (d, *J* = 26.3 Hz), 28.3, 21.8. *Anal*. Calcd. for $C_{11}H_{10}FNO_3$: C, 59.19; H, 4.48; N, 6.28. Found: C, 59.22; H, 4.49; N, 6.25.

Representative Procedure for the Tandem Michael-S$_N$Ar Reaction: (±)-1-Benzyl-2,3-dihydro-2-methyl-4(1*H*)-quinolinone (21a). A 50-mL, round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser was charged with a solution of **19** (66 mg, 0.4 mmol) in anhydrous DMF (3 mL). To the reaction mixture was added benzylamine (51 mg, 0.052 mL, 0.40 mmol) and the solution was heated at 50 ºC for 24 h. The reaction mixture was cooled and added to saturated aqueous NaCl (25 mL) and extracted three times with ether. The combined ether extracts were washed with water, saturated aqueous NaCl, dried ($MgSO_4$) and concentrated under vacuum to afford a yellow oil. The product was purified by PTLC plate using 50-70% ether in hexanes to afford **21a** (78 mg, 80%) as a light yellow solid, mp 88-90 ºC. IR: 1673 cm^{-1}; ^{1}H-NMR: δ 7.90 (dd, 1H, *J* = 7.9, 1.7 Hz), 7.39-7.25 (complex, 6H), 6.66 (apparent t, 1H, *J* = 7.4 Hz), 6.57 (d, 1H, *J* = 8.6 Hz), 4.69 (d, 1H, *J* = 16.6 Hz), 4.37 (d, 1H, *J* = 16.6 Hz), 3.83 (m, 1H), 3.06 (dd, 1H, *J* = 16.0, 6.1 Hz), 2.55 (dd, 1H, *J* = 16.0, 3.3 Hz), 1.22 (d, 3H, *J* =

6.6 Hz); ^{13}C-NMR: δ 193.3, 149.4, 137.7, 135.7, 128.8, 127.6, 127.4, 126.4, 119.2, 116.4, 113.5, 54.7, 53.3, 44.3, 15.4; ms: *m/z* 160 (M^+-C_7H_7). *Anal*. Calc. for $C_{17}H_{17}NO$: C, 81.27; H, 6.77; N, 5.58. Found: C, 81.28; H, 6.77; N, 5.59. The yield in this reaction was the same using the *Z* isomer of the starting enone.

(±)-1-Hexyl-2,3-dihydro-2-methyl-4(1*H*)-quinolinone (21b). This compound (0.84 g, 86%) was prepared from **19** (66 mg, 0.4 mmol) and hexylamine (49 mg, 0.063 mL, 0.48 mmol). The product was purified by PTLC plate using 10% ether in hexanes to afford **21b** as a viscous yellow oil. IR: 1674 cm^{-1}; ^{1}H-NMR: δ 7.86 (dd, 1H, *J* = 8.2, 1.7 Hz), 7.35 (ddd, 1H, *J* = 8.8, 7.2, 1.7 Hz), 6.63 (d, 1H, *J* = 8.8 Hz), 6.62 (t, 1H, *J* = 7.2 Hz), 3.72 (m, 1H), 3.49 (dt, 1H, *J* = 14.8, 7.2 Hz), 3.07 (dt, 1H, *J* = 15.0, 7.4 Hz), 2.93 (dd, 1H, *J* = 15.8, 6.1 Hz), 2.47 (dd, 1H, *J* = 16.0, 3.1 Hz), 1.67 (quintet, 2H, *J* = 7.2 Hz), 1.45-1.29 (complex, 6H), 1.16 (d, 3H, *J* = 6.6 Hz), 0.91 (distorted t, 3H, *J* = 6.8 Hz); ^{13}C-NMR: δ 193.2, 149.1, 135.6, 127.7, 118.6, 115.3, 112.6, 54.5, 49.6, 44.0, 31.6, 27.9, 26.8, 22.6, 15.6, 14.0; ms: *m/z* 174 (M^+-C_5H_{11}). *Anal*. Calc. for $C_{16}H_{23}NO$: C, 78.37; H, 9.39; N, 5.71. Found: C, 78.41; H, 9.42; N, 5.67.

(±)-2,3-Dihydro-1-isobutyl-2-methyl-4(1*H*)-quinolinone (21c). This compound (68 mg, 78%) was prepared from **19** (66 mg, 0.4 mmol) and isobutylamine (29 mg, 0.040 mL, 0.48 mmol). The product was purified by PTLC plate using 10% ether in hexanes to afford **21c** as a viscous yellow oil. IR: 1674 cm^{-1}; ^{1}H-NMR: δ 7.87 (dd, 1H, *J* = 7.8, 1.8 Hz), 7,34 (ddd, 1H, *J* = 8.6, 7.0, 1.8 Hz), 6.63 (apparent t, 1H, *J* = 7.8 Hz), 6.59 (d, 1H, *J* = 8.6 Hz), 3.70 (quintet of d, 1H, *J* = 6.6, 2.3 Hz), 3.44 (dd, 1H, *J* = 14.4, 5.1 Hz), 2.99 (dd, 1H, *J* = 15.9, 6.1 Hz), 2.64 (dd, 1H, *J* = 14.4, 9.6 Hz), 2.48 (dd, 1H, *J* = 15.9, 2.3

Hz), 2.04 (m, 1H), 1.13 (d, 3H, *J* = 6.6 Hz), 1.04 (d, 3H, *J* = 6.6 Hz), 0.99 (d, 3H, *J* = 6.8 Hz); ^{13}C-NMR: δ 193.2, 149.1, 135.6, 127.7, 118.6, 115.4, 112.7, 57.7, 55.5, 43.7, 27.3, 20.4, 20.0, 14.6; ms: *m/z* 174 (M^+-C_3H_7). *Anal*. Calc. for $C_{14}H_{19}NO$: C, 77.42; H, 8.76; N, 6.45. Found: C, 77.45; H, 8.78; N, 6.40.

(±)-1-Benzyl-2,3-dihydro-2-methyl-6-nitro-4(1*H*)-quinolinone (22a). This compound (115 mg, 97%) was prepared from **20** (84 mg, 0.4 mmol) and benzylamine (51 mg, 0.052 mL, 0.48 mmol). The product was purified by PTLC plate using 10% ether in hexanes to afford **22a** as a light yellow solid, mp 118-120 ºC. IR: 1688, 1506, 1317 cm^{-1}; ^{1}H-NMR: δ 8.75 (d, 1H, *J* = 2.7 Hz), 8.09 (dd, 1H, *J* = 9.3, 2.7 Hz), 7.44-7.26 (complex, 5H), 6.64 (d, 1H, *J* = 9.3 Hz), 4.84 (d, 1H, *J* = 16.8 Hz), 4.55 (d, 1H, *J* = 16.8 Hz), 3.98 (quintet of d, 1H, *J* = 6.4, 2.7 Hz), 3.08 (dd, 1H, *J* = 15.9, 6.0 Hz), 2.64 (dd, 1H, *J* = 15.9, 2.7 Hz), 1.28 (d, 3H, *J* = 6.9 Hz); ^{13}C-NMR: δ 191.1, 152.5, 137.6, 135.7, 130.2, 129.1, 128.0, 126.2, 124.5, 117.5, 113.4, 55.0, 53.6, 43.3, 16.2; ms: *m/z* 205 (M^+-C_7H_7). *Anal*. Calc. for $C_{17}H_{16}N_2O_3$: C, 68.92; H, 5.41; N, 9.46. Found: C, 68.88; H, 5.42; N, 9.43.

(±)-1-Hexyl-2,3-dihydro-2-methyl-6-nitro-4(1*H*)-quinolinone (22b). This compound (114 mg, 98%) was prepared from **20** (84 mg, 0.4 mmol) and hexylamine (49 mg, 0.063 mL, 0.48 mmol). The product was purified by PTLC plate using 10% ether in hexanes to afford **22b** as a viscous yellow oil. IR: 1688, 1510, 1315 cm^{-1}; ^{1}H-NMR: δ 8.72 (d, 1H, *J* = 2.8 Hz), 8.17 (dd, 1H, *J* = 9.6, 2.8 Hz), 6.67 (d, 1H, *J* = 9.6 Hz), 3.88 (quintet of d, 1H, *J* = 6.6, 2.4 Hz), 3.63 (dt, 1H, *J* = 14.7, 7.2 Hz), 3.23 (dt, 1H, *J* = 14.7, 7.6 Hz), 2.98 (dd, 1H, *J* = 16.0, 6.2 Hz), 2.59 (dd, 1H, *J* =16.0, 2.5 Hz), 1.73 (quintet, 2H, *J* = 7.4 Hz), 1.46-1.32 (complex, 6H), 1.23 (d, 3H, *J* = 6.8 Hz), 0.91 (distorted t, 3H, *J* = 6.9 Hz); ^{13}C-

NMR: δ 191.2, 152.0, 136.9, 130.2, 124.8, 117.0, 112.5, 54.9, 50.4, 43.2, 31.4, 27.8, 26.6, 22.5, 16.2, 13.9; ms: *m/z* 219 (M^+-C_5H_{11}). *Anal*. Calc. for $C_{16}H_{22}N_2O_3$: C, 66.21; H, 7.59; N, 9.66. Found: C, 66.26; H, 7.62; N, 9.58.

(±)-2,3-Dihydro-1-isobutyl-2-methyl-6-nitro-4(1*H*)-quinolinone (22c). This compound (96 mg, 92%) was prepared from **20** (84 mg, 0.4 mmol) and isobutylamine (29 mg, 0.40 mL, 0.48 mmol). The product was purified by PTLC plate using 10% ether in hexanes to afford **22c** as a light yellow solid, mp 120-121 ºC. IR: 1687, 1511, 1316 cm^{-1}; ^{1}H-NMR: δ 8.74 (d, 1H, *J* = 2.8 Hz), 8.16 (dd, 1H, *J* = 9.4, 2.8 Hz), 6.66 (d, 1H, *J* = 9.4 Hz), 3.85 (quintet of d, 1H, *J* = 6.6, 2.1 Hz), 3.59 (dd, 1H, *J* = 14.5, 5.3 Hz), 3.01 (dd, 1H, *J* = 16.0, 6.1 Hz), 2.84 (dd, 1H, *J* = 14.5, 9.6 Hz), 2.60 (dd, 1H, *J* =16.0, 2.0 Hz), 2.10 (m, 1H), 1.20 (d, 3H, *J* = 6.8 Hz), 1.08 (d, 3H, *J* = 6.6 Hz), 1.04 (d, 3H, *J* = 6.6 Hz); ^{13}C-NMR: δ 191.1, 152.2, 137.0, 130.1, 124.9, 117.1, 112.7, 57.8, 55.7, 42.9, 27.5, 20.2, 20.0, 15.5; ms: *m/z* 219 (M^+-C_3H_7). *Anal*. Calc. for $C_{14}H_{18}N_2O_3$: C, 64.12; H, 6.87; N, 10.69. Found: C, 64.15; H, 6.89; N, 10.64.

1-Benzyl-2,3-dihydro-2,2-dimethyl-4(1*H*)-quinolinone (25c). A 50-mL, round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser was charged with a solution of **23** (71 mg, 0.4. mmol) in anhydrous DMF (3 mL) and benzylamine (48 mg, 0.48 mmol). The solution was heated at 50 ºC for 48 h. The reaction mixture was cooled, added to saturated aqueous NaCl (25 mL) and extracted three times with ether. The combined ether extracts were washed with water, saturated aqueous NaCl, dried ($MgSO_4$) and concentrated under vacuum to afford a yellow oil. The product was purified by PTLC plate using 10% ether in hexanes. Band 1 gave recovered starting material **23** (47 mg, 67%). Band 2 gave compound **25c** (4 mg, 4%) as a light yellow solid, mp 114-115 ºC. IR: 1676, 1605, 1364 cm^{-1}; ^{1}H-NMR: δ 7.90 (dd, 1H, *J* = 7.7, 1.6 Hz), 7.36 (d, 3H, *J* = 4.4 Hz), 7.27 (m, 3H), 6.70 (t, 1H, *J* = 7.7 Hz), 6.50 (d, 1H, *J* = 8.2 Hz), 4.54 (s, 2H), 2.77 (s, 2H), 1.34 (s, 6H); ^{13}C-NMR: δ 193.8, 150.7, 138.9, 135.7, 128.8, 127.1, 127.0, 125.8, 119.5, 116.5, 114.3, 58.4, 51.8, 49.5, 29.7, 24.8; ms: *m/z* 250 (M^+-CH_3). *Anal*. Calc. for $C_{18}H_{19}NO$: C, 81.51; H, 7.17; N, 5.28. Found: C, 81.45; H, 7.15; N, 5.33.

1-Hexyl-2,3-dihydro-2,2-dimethyl-4(1*H*)-quinolinone (27c). The procedure was the same as for **25c**. The product was purified by PTLC plate using 10% ether in hexanes. Band 1 gave recovered staring material **23** (35 mg, 50%). Band 2 gave compound **27c** (12 mg, 12%) as a yellow oil. IR: 1680, 1604, 1361 cm^{-1}; ^{1}H-NMR: δ 7.87 (dd, 1H, *J* = 7.7 Hz), 7.38 (ddd, 1H, *J* = 8.8, 7.1, 1.6 Hz), 6.67 (t, 1H, *J* = 7.1 Hz), 6.66 (d, 1H, *J* = 8.4 Hz), 3.24 (t, 2H, *J* = 7.7 Hz), 2.60 (s, 2H), 1.66 (m, 2H), 1.37 (m, 6H), 1.30 (s, 6H), 0.93 (t, 3H, *J* = 6.6 Hz); ^{13}C-NMR: δ 193.9, 150.4, 135.6, 127.4, 119.2, 115.6, 113.2, 57.9, 51.8, 45.6, 31.6, 29.5, 26.7, 24.9, 22.7, 14.0; ms: *m/z* 188 (M^+-C_5H_{11}). *Anal*. Calc. for $C_{17}H_{25}NO$: C, 78.76; H, 9.65; N, 5.41. Found: C, 78.90; H, 9.67; N, 5.32.

2,3-Dihydro-1-isobutyl-2,2-dimethyl-4(1*H*)-quinolinone (29c). The procedure was the same as for **25c**. The product was purified by PTLC plate using 10% ether in hexanes. Band 1 gave recovered starting material **23** (33 mg, 44%). Band 2 gave compound **29c** (7 mg, 7%) as a yellow oil. IR: 1679, 1604, 1366 cm^{-1}; ^{1}H-NMR: δ 7.91 (dd, 1H, *J* = 7.7, 1.6 Hz), 7.37 (ddd, 1H, *J* = 8.8, 7.1, 1.6 Hz), 6.71-6.68 (m, 2H), 3.04 (d, 2H, *J* = 7.7 Hz), 2.64 (s, 2H), 2.07 (nonet, 1H, *J* = 7.1 Hz), 1.28 (s, 6H), 1.02 (d, 3H, *J* = 6.6 Hz); ^{13}C-

NMR: δ 194.0, 151.3, 135.4, 127.5, 120.0, 116.2, 114.4, 58.6, 52.2, 30.3, 27.7, 25.1, 20.5; ms: *m/z* 188 (M^+-C_3H_7). *Anal*. Calc. for $C_{15}H_{21}NO$: C, 77.92; H, 9.09; N, 6.06. Found: C, 77.99; H, 9.12; N, 5.97.

Cyclization of compound 24. Using the procedure given for the preparation of benzyl-2,3-dihydro-2,2-dimethyl-4(1*H*)-quinolinone **(25c)**, a solution of **24** (89 mg, 0.40. mmol) and the amine (0.48 mmol) in 2.5 mL of dry DMF was heated at 50 ºC for 24 h. Workup and purification by PTLC using 10-20% ether in hexanes showed three major bands.

Benzylamine. Band 1 gave 1-(2-benzylamino-5-nitrophenyl)-3-methyl-2-buten-1-one **(26a)** (41 mg, 34%) as a light yellow solid, mp 92-94 ºC. IR: 3265, 1609, 1505, 1328 cm^{-1}; ^{1}H-NMR: δ 10.1 (br s, 1H), 8.77 (d, 1H, *J* = 2.7 Hz), 8.13 (dd, 1H, *J* = 9.4, 2.7 Hz), 7.42-7.28 (complex, 5H), 6.73 (s, 1H), 6.68 (d, 1H, *J* = 9.4 Hz), 4.55 (d, 2H, *J* = 5.5 Hz), 2.13 (s, 3H), 2.05 (s, 3H); ^{13}C-NMR: δ 193.9, 155.9, 154.9, 136.8, 135.6, 129.5, 129.1, 128.9, 127.7, 127.0, 121.6, 117.4, 111.8, 47.0, 27.8, 21.1; ms: *m/z* 219 (M^+-C_7H_7). *Anal*. Calc. for $C_{18}H_{18}N_2O_3$: C, 69.68; H, 5.81; N, 9.03. Found: C, 69.67; H, 5.80; N, 9.05.

Band 2 gave 2-benzylamino-5-nitroacetophenone **(26b)** (1 mg, 1%) as a light yellow solid, mp 85-88 ºC. IR: 3282, 1648, 1504, 1328 cm^{-1}; ^{1}H-NMR: δ 10.0 (br s, 1H), 8.76 (d, 1H, *J* = 2.7 Hz), 8.16 (dd, 1H, *J* = 9.3, 2.7 Hz), 7.42-7.27 (complex, 5H), 6.69 (d, 1H, *J* = 9.3 Hz), 4.55 (d, 2H, *J* = 6.0 Hz), 2.69 (s, 3H); ^{13}C-NMR: δ 200.6, 154.5, 136.6, 130.0, 129.8, 129.0, 127.8, 127.0, 116.2, 112.0, 47.0, 29.7, 27.9; ms: *m/z* 179 (M^+-C_7H_7). *Anal*. Calc. for $C_{15}H_{14}N_2O_3$: C, 66.67; H, 5.19; N, 10.37. Found: C, 66.70; H, 5.21; N, 10.32.

Band 3 gave 1-benzyl-2,3-dihydro-2,2-dimethyl-6-nitro-4(1*H*)-quinolinone **(26c)** (80 mg, 66%) as a light yellow solid, mp 137-138 ºC. IR: 1691, 1506, 1323 cm^{-1}; ^{1}H-NMR: δ 8.77 (d, 1H, *J* = 2.7 Hz), 8.08 (dd, 1H, *J* = 9.4, 2.7 Hz), 7.44-7.26 (complex, 5H), 6.57 (d, 1H, *J* = 9.4 Hz), 4.71 (s, 2H), 2.83 (s, 2H), 1.40 (s, 6H); ^{13}C-NMR: δ 191.7, 153.9, 137.9, 136.7, 130.1, 129.1, 127.6, 125.5, 124.0, 118.2, 114.4, 59.2, 51.1, 49.5, 25.1 (2C); ms: *m/z* 295 (M^+-CH_3). *Anal*. Calc. for $C_{18}H_{18}N_2O_3$: C, 69.68; H, 5.81; N, 9.03. Found: C, 69.72; H, 5.79; N, 9.01.

Hexylamine. Band 1 gave 1-(2-hexylamino-5-nitrophenyl)-3-methyl-2-buten-1-one **(28a)** (23 mg, 19%) as a yellow solid, mp 44-46 ºC. IR: 3262, 1644, 1610, 1505, 1327 cm^{-1}; ^{1}H-NMR: δ 9.72 (br s, 1H), 8.74 (d, 1H, *J* = 2.7 Hz), 8.18 (dd, 1H, *J* = 9.4, 2.7 Hz), 6.69 (m, 2H), 3.30 (dt, 2H, *J* = 7.1, 5.5 Hz), 2.12 (d, 3H, *J* = 1.1 Hz), 2.04 (s, 3H), 1.73 (quintet, 2H, *J* = 7.1 Hz), 1.50-1.22 (complex, 6H), 0.91 (distorted t, 3H, *J* = 6.8 Hz); ^{13}C-NMR: δ 194.0, 155.2, 155.1, 135.0, 129.6, 129.4, 121.8, 117.1, 111.2, 43.4, 28.8, 27.7, 26.7, 22.5, 21.0, 14.0; ms: *m/z* 233 (M^+-C_5H_{11}). *Anal*. Calc. for $C_{17}H_{24}N_2O_3$: C, 67.11; H, 7.89; N, 9.21. Found: C, 67.15; H, 7.93; N, 9.16.

Band 2 gave 2-hexylamino-5-nitroacetophenone **(28b)** (3 mg, 3%) as a yellow oil. IR: 3267, 1648, 1502, 1329 cm^{-1}; ^{1}H-NMR: δ 9.66 (br s, 1H), 8.73 (d, 1H, *J* = 2.7 Hz), 8.20 (dd, 1H, *J* = 9.4, 2.7 Hz), 6.71 (d, 1H, *J* = 9.4 Hz), 3.30 (dt, 2H, *J* = 7.1, 5.5 Hz), 2.67 (s, 3H), 1.72 (quintet, 2H, *J* = 7.1 Hz), 1.51-1.24 (complex, 6H), 0.91 (distorted t, 3H, *J* = 6.6 Hz); ^{13}C-NMR: δ 200.4, 154.7, 135.0, 130.1, 130.0, 115.6, 111.5, 43.0, 31.4, 28.7, 27.8, 26, 7, 22.5, 14.0; ms: *m/z* 193 (M^+-C_5H_{11}). *Anal*. Calc. for $C_{14}H_{20}N_2O_3$: C, 63.64; H, 7.58; N, 10.61. Found: C, 63.71; H, 7.62; N, 10.54.

Band 3 gave 1-hexyl-2,3-dihydro-2,2-dimethyl-6-nitro-4(1*H*)-quinolinone **(28c)** (83 mg, 69%) as a yellow solid, mp 78-79 ºC. IR: 1691, 1503, 1322 cm^{-1}; ^{1}H-NMR: δ 8.74 (d, 1H, *J* = 2.8 Hz), 8.19 (dd, 1H, *J* = 9.4, 2.8 Hz), 6.70 (d, 1H, *J* = 9.4 Hz), 3.39 (distorted t, 2H, *J* = 8.2 Hz), 2.68 (s, 2H), 1.71 (quintet, 2H, *J* = 7.7 Hz), 1.48-1.34 (complex, 6H), 1.38 (s, 6H), 0.94 (distorted t, 3H, *J* = 6.8 Hz); ^{13}C-NMR: δ 191.7, 153.3, 137.2, 130.1, 124.4, 117.8, 113.2, 58.7, 51.5, 45.9, 31.4, 29.1, 26.6, 25.3 (2C), 22.6, 13.9; ms: *m/z* 289 (M^+-CH_3). *Anal*. Calc. for $C_{17}H_{24}N_2O_3$: C, 67.11; H, 7.89; N, 9.21. Found: C, 67.16; H, 7.92; N, 9.13.

Isobutylamine. Band 1 gave 1-(2-isobutylamino-5-nitrophenyl)-3-methyl-2-buten-1-one **(30a)** (20 mg, 18%) as a light yellow solid, mp 75-77 ºC. IR: 3258, 1643, 1610, 1506, 1327 cm^{-1}.; ^{1}H-NMR: δ 9.85 (br s, 1H), 8.74 (d, 1H, *J* = 2.7 Hz), 8.17 (dd, 1H, *J* = 9.3, 2.7 Hz), 6.70 (s, 1H), 6.68 (d, 1H, *J* = 9.3 Hz), 3.13 (t, 2H, *J* = 6.6 Hz), 2.12 (s, 3H), 2.04 (s, 3H), 2.03 (septet, 1H, *J* = 6.6 Hz), 1.06 (d, 6H, *J* = 6.6 Hz); ^{13}C-NMR: δ 194.1, 155.3, 155.2, 134.9, 129.5, 129.5, 129.4, 121.8, 117.1, 111.2, 50.7, 28.0, 27.7, 21.0, 20.4 (2C); ms: *m/z* 233 (M^+-C_3H_7). *Anal*. Calc. for $C_{15}H_{20}N_2O_3$: C, 65.22; H, 7.25; N, 10.14. Found: C, 65.19; H, 7.23; N, 10.15.

Band 2 gave 2-isobutylamino-5-nitroacetophenone **(30b)** (7 mg, 7%) as a yellow oil. IR: 3272, 1652, 1509, 1328 cm^{-1}; ^{1}H-NMR: δ 9.78 (br s, 1H), 8.74 (d, 1H, *J* = 2.7 Hz), 8.20 (dd, 1H, *J* = 9.4, 2.7 Hz), 6.70 (d, 1H, *J* = 9.4 Hz), 3.13 (t, 2H, *J* = 6.6 Hz), 2.67 (s, 3H), 2.01 (septet, 1H, *J* = 6.6 Hz), 1.05 (d, 6H, *J* = 7.0 Hz); ^{13}C-NMR: δ 200.5, 154.9, 135.0, 130.1, 130.0, 115.7, 111.5, 50.7, 28.0, 27.8, 20.3 (2C); ms: *m/z* 193 (M^+-C_3H_7). *Anal*. Calc. for $C_{12}H_{16}N_2O_3$: C, 61.02; H, 6.78; N, 11.86. Found: C, 61.11; H, 6.81; N, 11.78.

Band 3 gave 1-isobutyl-2,3-dihydro-2,2-dimethyl-6-nitro-4(1*H*)-quinolione **(30c)** (77 mg, 70%) as a yellow solid, mp 126-127 ºC. IR: 1690, 1506, 1322 cm^{-1}; ^{1}H-NMR: δ 8.70 (s, 1H), 8.17 (dd, 1H, *J* = 9.3, 2.7 Hz), 6.79 (d, 1H, *J* = 9.3 Hz), 3.24 (d, 2H, *J* = 7.7 Hz), 2.71 (s, 2H), 2.12 (septet, 1H, *J* = 6.6 Hz), 1.37 (s, 6H), 1.05 (d, 6H, *J* = 6.6 Hz); ^{13}C-NMR: δ 191.8, 154.3, 137.5, 129.7, 124.4, 118.5, 114.5, 59.3, 52.2, 51.3, 28.0, 25.3 (br, 2C), 20.3 (2C); ms: *m/z* 233 (M^{+}-C_3H_7). *Anal*. Calc. for $C_{15}H_{20}N_2O_3$: C, 65.22; H, 7.25; N, 10.14. Found: C, 65.24; H, 7.25; N, 10.11.

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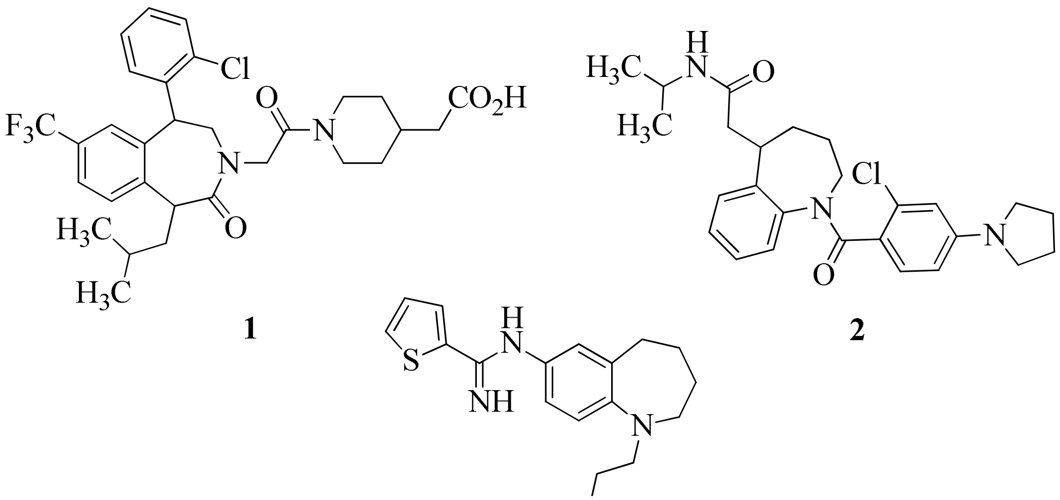
CHAPTER II

SYNTHESIS OF 2,3,4,5-TETRAHYDRO-1*H*-BENZO[*b*]AZEPINE

Introduction

The heterocyclic ring of tetrahydrobenzazepine is found in many compounds that have biological activities for the treatment of diseases. For example tetrahydrobenzo[*d*]azepine **1** (Figure 1.1) inhibits the squalene synthase enzyme.[1] This enzyme is essential for the biosynthesis of cholesterol in humans and animals.[2] Tetrahydrobenzazepins that inhibit squalene synthase might be used for the treatment and/or prevention of cardiovascular disorders such as arteriosclerosis and dyslipidaemias.[1]



1

2

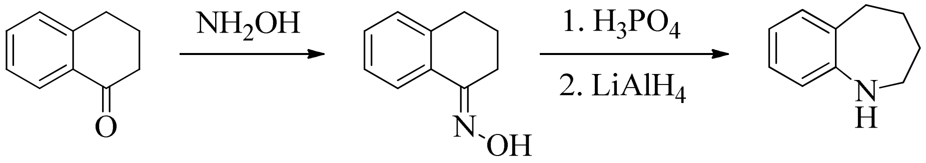
3

Figure 2.1. Biologically active tetrahydrobenzazepines.

The teterahydrobenzo[*b*]azepine **2** stimulates the vasopressin V2 receptor in the kidney.[3] Stimulation of this receptor reduces the volume of urine and, thus, these derivatives may be used in cases where a reduction of urine output is desired such as in enuresis. Compound **3** inhibits the neuronal nitric oxide synthase (nNOS) enzyme.[4] Neuronal nitric oxide is important to brain development and memory, and its overproduction causes a variety of diseases such as Alzheimer`s disease and other neurodegenerative diseases. Inhibitors of nNOS might also be used for the treatment of Parkinson's and Alzheimer's disease.[5]

Synthesis of Tetrahydrobenzo[*b*]azepines

Different methods have been employed for the synthesis of tetrahydrobenzo[*b*]azepines. Zhang and co-workers[6] reacted tetralone **(4)** with hydroxylamine to generate oxime **5**. Enlarging of the ring was accomplished by addition of polyphosphoric acid (Beckmann rearrangement), followed by reduction with lithium aluminium hydride ($LiAlH_4$) to obtain the target 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine **(6)** as shown in Figure 2.2.

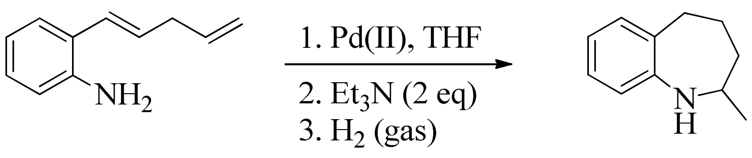


4 **5** **6**

Figure 2.2. Synthesis of tetrahydobenzo[*b*]azepine **6**.

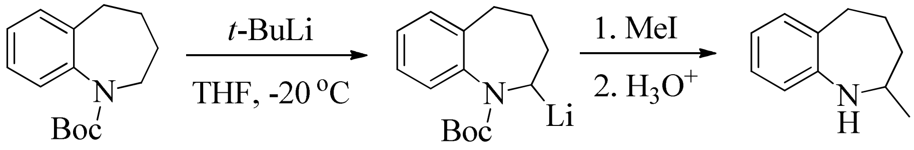
Hegedus and co-workers[7] used palladium(II) as a catalyst for the cyclization of aniline derivative **7** for the preparation of the tetrahydrobenzo[*b*]azepine **8** (Figure 2.3).

The mechanism for the formation of the heterocyclic compound involves nucleophilic attack of the amino group on the palladium(II)-olefin complex followed by hydrogenation. Meyers and co-workers[8] synthesized compound **8** by metalation of C-2 in **9** with *tert*-butyllithium and alkylation of the lithio species **10** with methyl iodide followed by deprotection of the amino group with acid as shown in Figure 2.4.



7 **8**

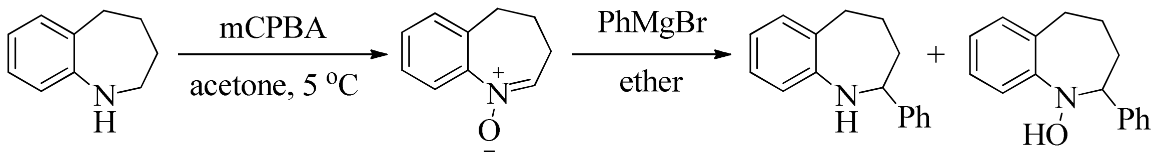
Figure 2.3. Intramolecular cyclization of 2-(1,4-pentdienyl) aniline.



9 **10** **8**

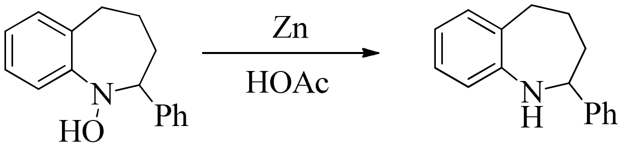
Figure 2.4. Meyers method for the synthesis of **8**.

Tufariello and co-workers[9] reported the preparation of aryl tetrahydobenzo[*b*]azepine **12** (Figure 2.5) by two different methods. The first is by oxidation of tetrahydrobenzo[*b*]azepine **(6)** to the corresponding nitrone derivative **11** with *m*-chloroperoxybenzoic acid.[10] Addition of phenylmagnesium bromide to the nitrone[11] **11** afforded **12** and **13**. The hydroxylamine derivative **13** was converted to **12** by hydrogenolysis[12] with zinc and acetic acid as shown in Figure 2.6.



6 **11** **12** **13**

Figure 2.5. Synthesis of **12** by oxidation and Grignard addition to the nitrone.



13 **12**

Figure 2.6. Hydrogenolysis of *N*-hydroxytetrahydrobenzo[*b*]azepine **11**.

The second method involved heating of *C*,*N*-diphenylnitrone **14** with excess allene **(15)** in a sealed tube at 70 °C for 60 h. Three adducts were isolated: the isoxazolidine **17** (22%), the 3-pyrroldinone **18** (23%) and the tetrahydrobenzo[*b*]azepinone **21** (31%). The latter was reduced under Wolf-Kishner conditions to afford **12** as shown in Figure 2.7. The nitrogen-oxygen bond in **16** is relatively weak and readily cleaved.[13] Additionally, in the presence of the *N*-aryl group, compound **16** undergoes spontaneous rearrangement to the tetrahydrobenzo[*b*]azepine **20**.[9]

Our approach to tetrahydrobenzo[*b*]azepines involves a tandem reduction-Michael addition process and a Michael addition-reductive amination reaction.[14,15]

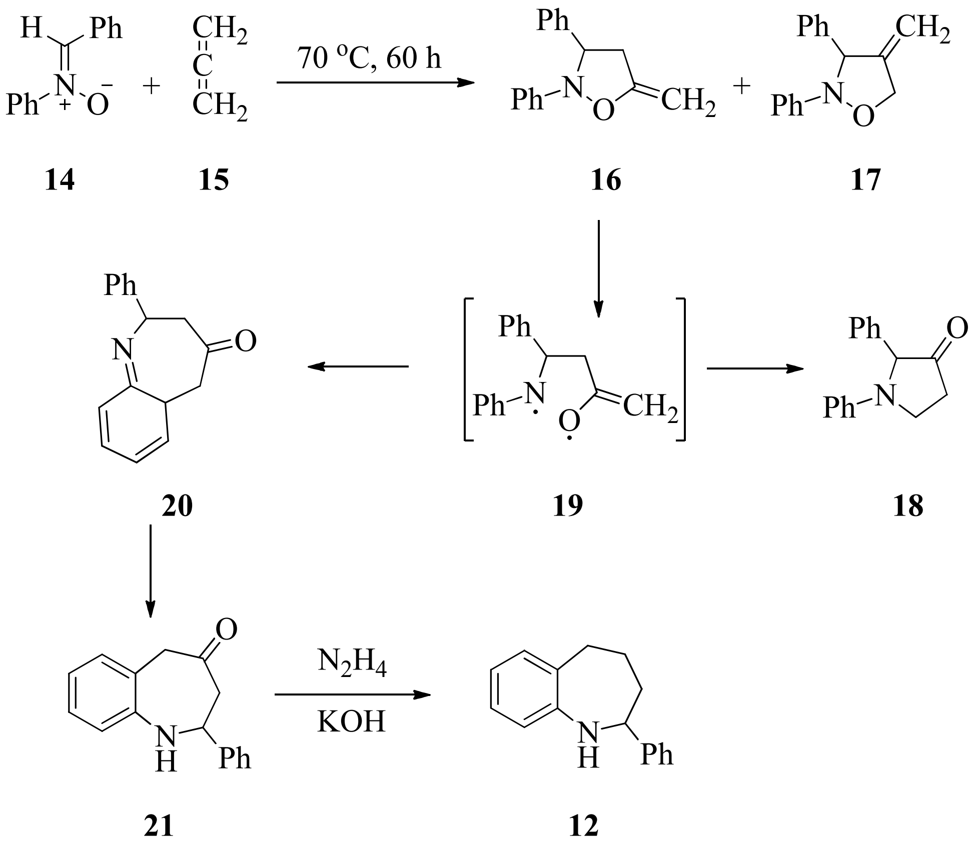
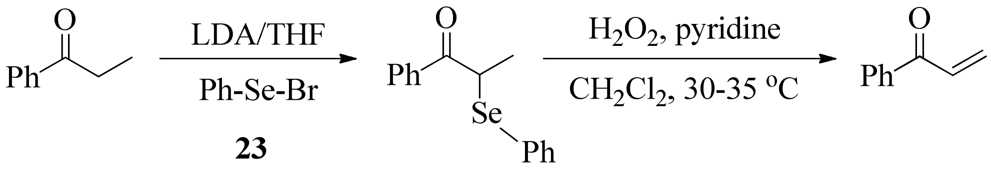


Figure 2.7. Intermolecular allene-nitrone cycloaddition.

Results and Discussion

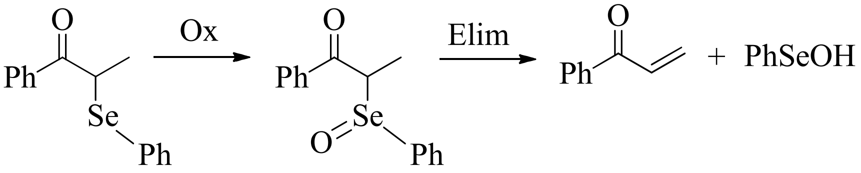
Synthesis of Phenyl Vinyl Ketone

The method of Reich *et al.*[16] was used for the preparation of phenyl vinyl ketone. Deprotonation of ketone **22** using lithium diisopropylamine (LDA) in dry THF produced the ketone enolate. Nucleophilic substitution of this enolate with benzeneselenenyl bromide **(23)** formed the α-phenylselenoketone **24** (Figure 2.8). Benzeneselenenyl bromide **(23)** was prepared by cleavage of diphenyldiselenide with bromine.[16] Oxidation of **24** using hydrogen peroxide at 30-35 ºC afforded the target substrate **25**. This reaction step involved oxidation of selenium and elimination of phenylseleninic acid **(27)** from **26** to give **25** as shown in Figure 2.9.[16]



22 **23** **24** **25**

Figure 2.8. Synthesis of phenyl vinyl ketone.



24 **26** **25** **27**

Figure 2.9. Oxidation-elimination reaction for the formation of **25**.

Synthesis of Tetrahydrobenzo[*b*]azepines

The synthesis of tetrahydrobenzo[*b*]azepines **8** and **12** is shown in Figure 2.10. Bunce and co-workers[14,15] have previously synthesized aryl-fused nitrogen heterocyclic compounds by a tandem reduction-reductive amination. Reaction of methyl (2-nitrophenyl)acetate **(28)** with K_2CO_3 in DMF generated the blue colored anion of **28**, which reacted with vinyl ketones **25** and **29** to form the ketones **30**. Basic hydrolysis of **30** with aqueous NaOH (1 *M*) formed acid **31**, which was decarboxylated to **32** using K_2CO_3 in DMF at 50 °C.[17] The target tetrahydrobenzo[*b*]azepines **8** and **12** were formed by hydrogenation of **32** using two methods. In method **A**, the reaction mixture containing

32 in methanol and 5% Pd/C as a catalyst was hydrogenated at 1 atm (balloon). In method **B**, hydrogen gas was generated *in situ* upon addition of triethylsilane (TES) to the reaction mixture containing **32** in methanol and 5% Pd/C.[18] A low yield was obtained from method **A** due to the lack of pressure during hydrogenation. Method **B** gave moderate yields of 59% and 48% for **8** and **12**, respectively.

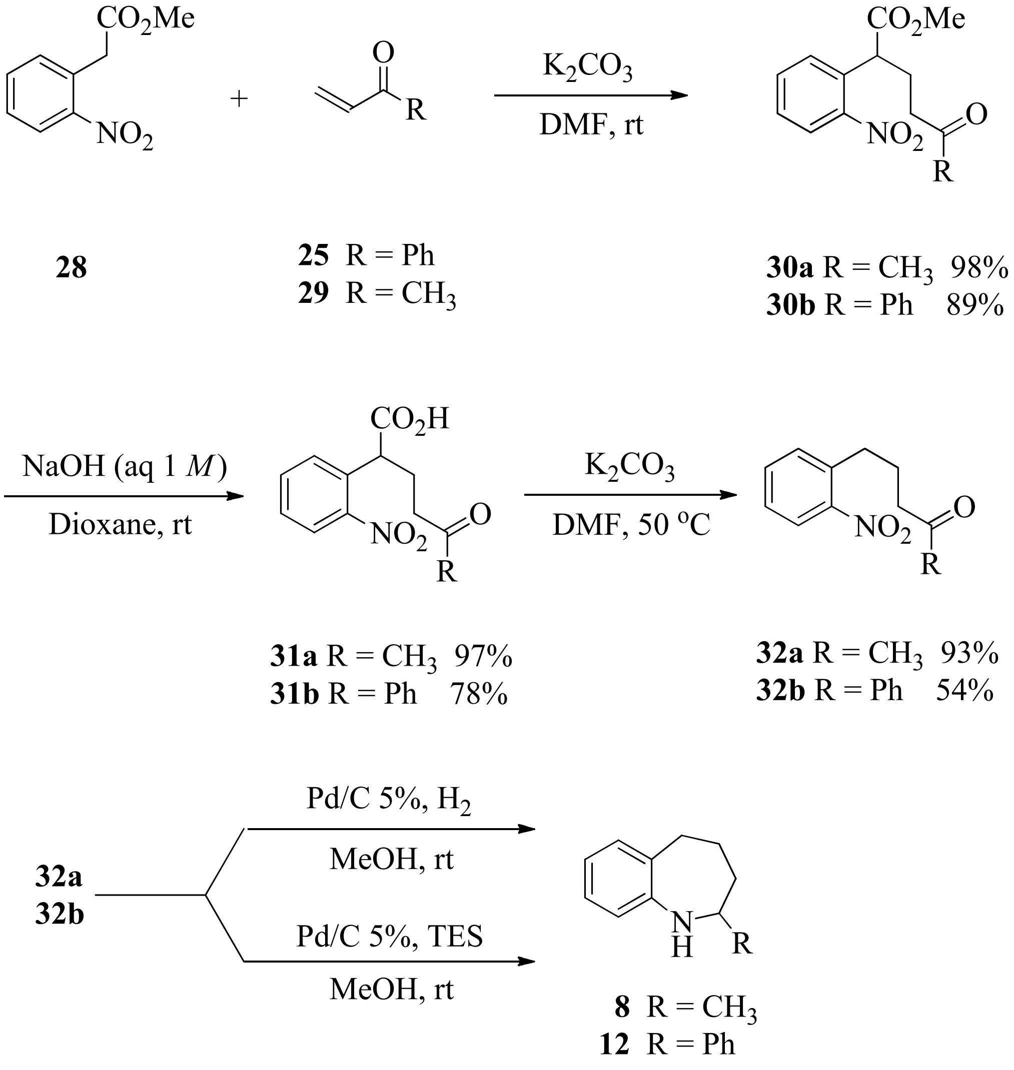
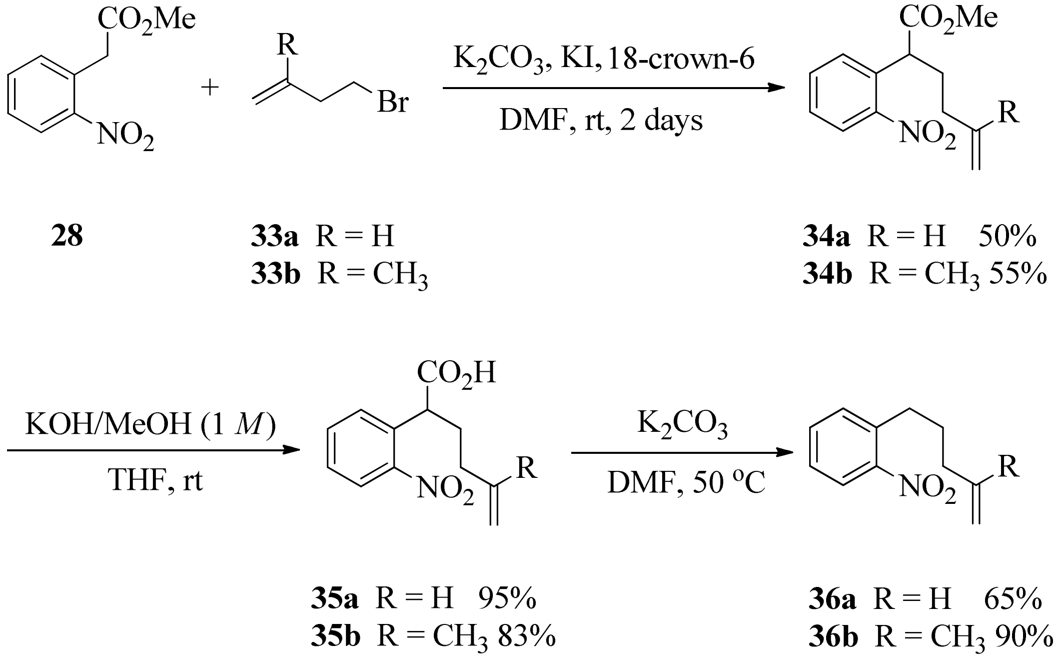


Figure 2.10. Synthesis of tetrahydrobenzo[*b*]azepines **8** and **12**.

Product No	**R**	**A**	**B**
8	CH_3	29%	59%
12	Ph	17%	48%

Table 2.1. Yield of reductive amination reaction to form **8** and **12**.

Alkylation of the blue-colored anion of methyl (2-nitrophenyl)acetate **(28)** with 4-bromobutene derivatives **33a** and **33b** using K_2CO_3 and catalytic 18-crown-6 in DMF and stirring at room temperature afforded **34a-b**.[14] Basic hydrolysis of **34a-b** with KOH in THF formed acids **35a-b**,[17] which were decarboxylated to produce **36a-b** as shown in Figure 2.11.



28

33a R = H
33b R = CH_3

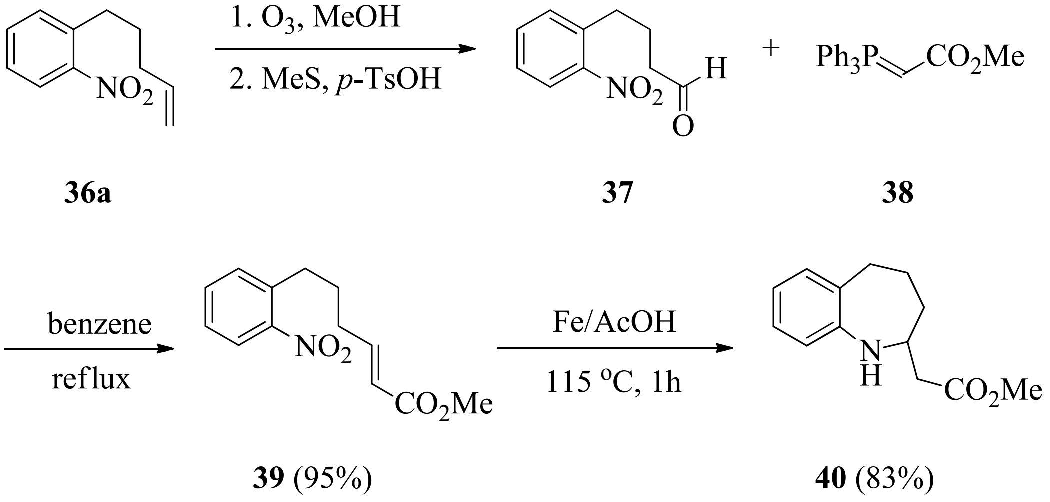
34a R = H 50%
34b R = CH_3 55%

35a R = H 95%
35b R = CH_3 83%

36a R = H 65%
36b R = CH_3 90%

Figure 2.11. Synthesis of the cyclization substrates.

Treatment of **36a** with ozone in methanol at -78 °C followed by reduction of the ozonide intermediate with dimethyl sulfide produced the aldehyde **37** (Figure 2.12).[14] Treatmet of aldehyde **37** with methyl triphenylphosphoranylidene acetate **(38)** in benzene and heating the reaction mixture formed the *E* isomer of the alkene **39** in 95% yield along with 3-5% of the *Z* isomer. Ring closure of the *E* substrate was accomplished by tandem reduction-Michael addition reactions using iron in acetic acid to produce **40** (83%) as shown in Figure 2.12.[19]



36a **37** **38**

39 (95%) **40** (83%)

Figure 2.12. Ozonolysis, Wittig reaction and reductive amination for the synthesis of **40**.

A Horner-Wadsworth-Emmons reaction of **32a** using ethyl 2-(dimethoxyphosphoryl)acetate (**41**) in the presence of NaH in THF with stirring at room temperature produced the isomeric mixture of (*E*) and (*Z*) **42**.[20] Cyclization of this mixture by reduction of nitro group with Fe/AcOH, followed by a Michael addition process, afforded product **43** (38%) as shown in Figure 2.13.[19]

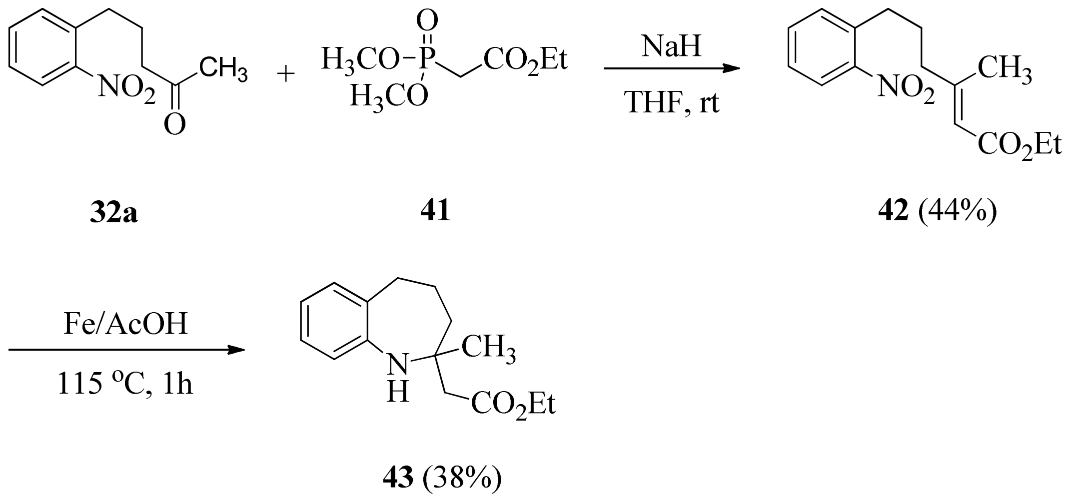


Figure 2.13. Horner-Wadsworth-Emmons reaction and reductive amination for the synthesis of **43**.

Conclusions

We have developed a synthetic method for the preparation of 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine derivatives by tandem reduction-reductive amination. Substrates for this reaction were prepared in excellent yield by a Michael addition reaction of vinyl ketone derivatives to compound **28**, followed by basic hydrolysis with potassium hydroxide and decarboxylation using K_2CO_3 in DMF. We were also able to prepare 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine derivatives by a tandem reduction-Michael addition of substrates prepared by alkylation of the substrate **28** with 4-bromobutene, followed by ozone treatment and Wittig olefination. Most reaction targets were obtained in high yields. The cyclized products were isolated in moderate yields, which might be improved by using catalytic hydrogenation under pressure.

Experimental Section

THF was distilled prior to use. All other commercial reagents and solvents were used as received. All reactions were run under dry nitrogen in oven-dried glassware. Potassium carbonate was ground to a fine powder, dried under vacuum at 120 °C for 24 h and stored in an oven at 120 °C. Commercial anhydrous *N*,*N*-dimethylfomamide (DMF) was syringed into reactions as needed. Reactions were monitored by TLC on hard layer silica gel GF plates (Analtech No. 21521) using UV detection. Preparative separations were performed using one of the following methods: (1) PTLC on 20-cm x 20-cm silica gel GF plates (Analtech No. 02015) or (2) flash column chromatography on silica gel (Davisil®, grade 62, 60-200 mesh) containing UV-active phosphor (Sorbent Technologies No. UV-05). In each case, band elution was monitored using a hand-held UV-lamp. IR spectra were run as thin films on NaCl disks. ^{1}H-NMR and ^{13}C-NMR spectra were measured in $CDCl_3$ at 300 MHz and 75 MHz, respectively, and were referenced to internal $(CH_3)_4Si$; coupling constants (*J*) are in Hz.

1-Phenyl-2-phenylseleno-1-propanone (24). The method of Reich and co-workers[16] was followed. A 250-mL, three-necked, round-bottomed flask, equipped with a magnetic stirrer, a septum and a 10-mL addition funnel was charged with freshly distilled THF (40 mL). The flask was cooled to -78 ºC, and diisopropylamine (130 g, 1.80 mL, 12.8 mmol) was added, followed by *n*-BuLi (6.0 mL, 2.5 *M*, 15.0 mmol) in hexane. A solution of propiophenone **(22)** (1.34 g, 10.0 mmol) in 5 mL of THF was added dropwise, and the solution was stirred for 15 min. Into the addition funnel was placed diphenyl diselenide (1.88 g, 6.0 mmol) as a solution in 5 mL of THF. Bromine (0.4 mL, 1.18 g, 7.4 mmol) was added dropwise to the solution, which was agitated briefly to dissolve any $PhSeBr_3$

formed. The PhSeBr solution was added rapidly to the enolate solution of **22** (immediate decolorization), and the cold reaction mixture was poured into HCl (100 mL, 0.5 *M*) and 100 mL of ether. The organic layer was washed with water, saturated $NaHCO_3$ solution, saturated aqueous NaCl, dried ($NaSO_4$), filtered, and concentrated. The residue was chromatographed using 1-3% ether in hexanes to afford **24** (2.8 g, 96%). ^1H NMR δ 7.88-7.86 (m, 2H), 7.52-7.20 (m, 8H), 4.67 (q, 1H, *J* = 7.0 Hz), 1.61 (d, 3H, *J* = 7.0 Hz).

1-Phenyl-2-propen-1-one (25). The method of Reich and co-workers[16] was followed. To a 250-mL, three-necked, round-bottomed flask, equipped with a dropping funnel, condenser, and thermometer was added a solution of **24** (1.0 g, 3.0 mmol) in 30 mL of dichloromethane containing 0.5 mL of pyridine. To the stirred solution was gradually added H_2O_2 (4.0 mL, 30% H_2O_2 in **4** mL of water), with cooling by an ice-salt bath to keep the temperature between 30 and 35 ºC. The reaction mixture was stirred vigorously at room temperature for an additional 15 min and then was added to 25 mL of dichloromethane and 10 mL of 7% $NaHCO_3$ solution. The aqueous layer was washed three times with dichloromethane (15 mL), and the combined extracts were washed with 10% HC1 (30 mL), saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated to give **25** (0.3 g, 56%), which was used for next step without further purification. ^1H NMR δ 7.93 (dd, 2H, *J* = 8.0, 2.0 Hz), 7.59-7.44 (m, 3 H), 7.20-7.11 (dd, 1H, *J* = 17.3, 10.7 Hz), 6.44 (dd, 1H, *J* = 17.3, 2.2 Hz), 5.92 (dd, 1H, *J* = 10.7, 2.2 Hz).

Methyl 2-(2-nitrophenyl)-5-oxohexanoate (30a). A 100-mL, three-necked, round-bottomed flask, equipped with a magnetic stirrer, and a reflux condenser was charged with **28** (1.00 g, 5.17 mmol) in dry DMF (25 mL), and 18-crown-6 (0.20 g) was added. To the stirred solution was added anhydrous potassium carbonate (2.5 g, 18.1 mmol).

The mixture turned blue in color and stirring was continued for 5 min. Methyl vinyl ketone **(29)** (0.50 g, 0.6 mL, 7.13 mmol) was added dropwise, and the reaction mixture was stirred for 3 h. Water (100 mL) was added, and the product was extracted three times with ether (50 mL). The ether extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed using 10-20% ether in hexane to afford **30a** (1.33 g, 98%) as a yellow oil. IR 1736, 1608, 1526, 1335, 787 cm^{-1}; ^1H NMR δ 7.89 (dd, 1H, *J* = 8.2, 1.1 Hz), 7.61 (td, 1H, *J* = 8.2, 1.1 Hz), 7.53-7.42 (m, 2H), 4.18 (t, 1H, *J* = 7.7 Hz), 3.66 (s, 3H), 2.63-2.40 (m, 3H), 2.12 (s, 3H), 2.16-2.07 (m, 1H); ^{13}C NMR δ 207.7, 173.0, 149.7, 133.5, 130.3, 128.7, 125.1, 52.6, 45.5, 41.4, 30.2, 26.9.

Methyl 2-(2-nitrophenyl)-5-oxo-5-phenylpentanoate (30b). A 100-mL, three-necked, round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser was charged with **28** (0.70 g, 3.61 mmol) in dry DMF (20 mL), and 18-crown-6 (0.20 g) was added. To the stirred solution was added anhydrous potassium carbonate (3.0 g, 21.7 mmol). The mixture turned blue in color and stirring was continued for 5 min. Phenyl vinyl ketone **(25)** (0.80 g, 6.05 mmol) was added dropwise, and the reaction mixture was stirred for 3 h. Water (100 mL) was added and the product was extracted three times with ether (50 mL). The ether extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed using 10-20% ether in hexane to afford **30b** (1.04 g, 87%) as a light yellow oil. IR 1736, 1686, 1527, 1353, 744 cm^{-1}; ^1H NMR δ 7.93 7.88 (m, 3H), 7.60-7.53 (m, 3H), 7.46-7.41 (m, 3H), 4.31 (t, 1H, *J* = 7.7 Hz), 3.67 (s, 3H), 3.18-2.95 (m, 2H), 2.70-2.58 (m, 1H), 2.35-2.23

(m, 1H); ^{13}C NMR δ 199.2, 173.1, 137.0, 133.6, 133.5, 130.4, 129.0, 128.7, 128.4, 125.2, 52.7, 45.8, 36.6, 27.5.

2-(2-Nitrophenyl)-5-oxohexanoic acid (31a). The general procedure of Bull *et al.*[17] was followed. A 100-mL, round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser was charged with ester **30a** (0.15 g, 0.46 mmol) in dioxane (15 mL). Aqueous sodium hydroxide (20 mL, 1 *M*) was added and the reaction mixture was stirred overnight at room temperature. The solvent was evaporated, water (10 mL) was added and the mixture acidified with 1 *M* HCl. The product was extracted three times with ether (10 mL), washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed using 30% ether in hexanes to afford **31a** (0.14 g, 97%) as a yellow oil. IR 1712, 1527, 1353, 787 cm^{-1}; ^{1}H NMR δ 11.00 (s, 1H), 7.92 (dd, 1H, *J* = 8.8, 1.1 Hz), 7.60 (td, 1H, *J* = 7.1, 1.1 Hz), 7.52-7.42 (m, 2H), 4.19 (t, 1H, *J* = 7.1 Hz), 2.62-2.42 (m, 3H), 2.17-2.04 (m, 1H), 2.11 (s, 3H); ^{13}C NMR δ 208.6, 178.0, 149.5, 133.8, 133.1, 130.7, 129.0, 125.3, 45.9, 41.4, 30.3, 26.4.

2-(2-Nitrophenyl)-5-oxo-5-phenylpentanoic acid (31b). The general procedure of Bull *et al.*[17] was followed. A 100-mL, round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser was charged with ester **30b** (0.15 g, 0.46 mmol) in dioxane (15 mL). Aqueous sodium hydroxide (20 mL, 1 *M*) was added and the reaction mixture was stirred overnight at room temperature. The solvent was evaporated, water (10 mL) was added and the mixture acidified with 1 *M* HCl. The product was extracted three times with ether (10 mL), washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed using 30% ether in hexanes to afford

31b (0.11 g, 78%) as light brown oil. IR 1709, 1685, 1526, 1350, 738 cm^{-1}; ^{1}H NMR δ 10.03 (s, 1H), 7.93-7.88 (m, 3H), 7.62-7.42 (m, 6H), 4.34 (t, 1H, *J* = 7.1 Hz), 3.16 (m, 2H), 2.67-2.61 (m, 1H), 2.32-2.28 (m, 1H); ^{13}C NMR δ 199.6, 149.5, 136.9, 133.9, 133.7, 133.2, 130.8, 129.0, 128.4, 125.4, 46.0, 36.6, 27.0.

5-(Nitrophenyl)pentan-2-one (32a). The general procedure of Bull *et al.*[17] was followed. A 50-mL, round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser was charged with acid **31a** (0.14 g, 0.55 mmol) in DMF (10 mL). Potassium carbonate (0.2 g) was added, and the reaction mixture stirred at 50 °C for 3 h. After cooling to room temperature, H_2SO_4 (10 mL, 0.25 *M*) was added and the mixture was extracted three times with ether (10 mL). The ether extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed using 10% ether in hexanes to afford **32a** (0.10 g, 93%) as a light brown oil. IR 1714, 1609, 1526, 1350, 745 cm^{-1}; ^{1}H NMR δ 7.89 (d, 1H, *J* = 8.2 Hz), 7.53 (td, 1H, *J* = 7.4, 1.1 Hz), 7.38-7.32 (m, 2H), 2.87 (t, 2H, *J* = 7.9 Hz), 2.53 (t, 2H, *J* = 7.1 Hz), 2.16 (s, 3H), 2.00-1.90 (m, 2H); ^{13}C NMR δ 208.6, 149.7, 137.0, 133.3, 132.3, 127.5, 125.0, 43.3, 32.3, 30.3, 24.9.

4-(2-Nitrophenyl)-1-phenylbutan-1-one (32b). The general procedure of Bull *et al.*[17] was followed. A 250-mL, round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser was charged with acid **31b** (1.09 g, 3.47 mmol) in DMF (70 mL). Potassium carbonate (3.00 g) was added and the reaction mixture stirred at 50 °C for 3 h. After being allowed to cool, H_2SO_4 (20 mL, 0.25 *M*) was added and the mixture was extracted three times with ether (50 mL). The ether extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed using 10% ether in hexanes to afford **32b (**0.54 g, 54%) as a light brown residue, which crystallized on standing, mp 43-45 ºC. IR 1686, 1598, 1524, 1346, 741 cm^{-1}; ^1H NMR δ 8.12 (dd, 1H, *J* = 7.1, 1.6 Hz), 7.97-7.89 (m, 2H), 7.62-7.33 (m, 6H), 3.08 (t, 2H, *J* = 7.1 Hz), 2.99 (t, 2H, *J* = 7.6 Hz), 2.18-2.08 (m, 2H); ^{13}C NMR δ 137.2, 134.1, 133.5, 133.4, 132.3, 130.6, 129.0, 128.9, 128.4, 127.5, 125.1, 38.3, 32.6, 25.5.

Representative Procedures for Reductive Cyclization: 2-Methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine (8).

Method A: A 100-mL, three-necked, round-bottomed flask, equipped with a magnetic stirrer, a septum, a hydrogen gas inlet and a ¼ argon-filled balloon as an outlet was charged with **32a** (0.10 g, 0.48 mmol) in methanol (30 mL). Palladium-on-carbon (5%, 0.25 g) was added, and hydrogen gas from a balloon was introduced to the flask. The reaction was stirred overnight under hydrogen. The crude reaction mixture was concentrated, diluted with ether (15 mL) and filtered through a pad of Celite 545® topped with a layer of $MgSO_4$ to remove the catalyst. The filtrate was concentrated and chromatographed using 5-10% ether in hexanes to give **8** (0.02 g, 29%) as light yellow crystals, mp 69-70 ºC. IR 3326, 2921, 1432,761 cm^{-1}; ^1H NMR δ 7.09-7.01 (m, 2H), 6.82 (t, 1H, *J* = 7.4 Hz), 6.73 (d, 1H, *J* = 7.1 Hz), 3.38 (s, 1H), 2.94-2.65 (m, 2H), 1.94-1.82 (m, 2H), 1.55-1.32 (m, 3H), 1.24 (d, 3H, *J* = 6.0 Hz); ^{13}C NMR δ 130.9, 126.9, 121.3, 120.2, 54.1, 39.7, 35.9, 26.6, 24.5.

Method B: A 100-mL, three-necked, round-bottomed flask equipped with a magnetic stirrer, a septum, and a ¼ argon-filled balloon as an outlet was charged with **32a** (0.07 g, 0.34 mmol) in methanol (30 mL). Palladium-on-carbon (5%, 0.20 g) was added, and neat triethylsilane (1.5 mL, 1.09 g, 9.39 mmol) was added dropwise. The reaction mixture was stirred overnight at room temperature. The crude reaction mixture was concentrated, diluted with ether (10 mL) and filtered through a pad of Celite 545® topped with a layer of $MgSO_4$ to remove the catalyst. The filtrate was concentrated and chromatographed to afford **8** (0.03 g, 59%).

2-Phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine (12). A 50-mL, three-necked, round-bottomed flask, equipped with a magnetic stirrer, a septum, a hydrogen gas inlet and a ¼ argon-filled balloon as an outlet was charged with **32b** (0.30 g, 0.48 mmol) in methanol (50 mL). Palladium-on-carbon (5%, 0.80 g) was added and hydrogen gas was bubbled through the mixture for hydrogenation. The reaction was stirred overnight under hydrogen by means of hydrogen-filled balloon. The crude reaction mixture was concentrated, diluted with ether (20 mL) and filtered through a pad of Celite 545® topped with a layer of $MgSO_4$ to remove the catalyst. The filtrate was concentrated and chromatographed using 5-10% ether in hexanes to give **12** (0.04 g, 17%) as a light brown oil. IR 3377, 2928, 1721, 1619, 1496, 747 cm^{-1}; ^{1}H NMR δ 7.29-7.24 (m, 2H), 7.20-7.15 (m, 3H), 7.04-7.99 (m, 2H), 6.74-6.63 (m, 2H), 3.54 (s, 1H), 2.65 (t, 2H, *J* = 7.1 Hz), 2.49 (t, 2H, *J* = 7.4 Hz), 1.77-1.60 (m, 3H); ^{13}C NMR δ 144.4, 142.9, 129.9, 128.8, 128.7, 127.3, 127.0, 126.1, 119.1, 116.0, 36.2, 31.8, 31.6, 28.7.

Method B: A 100-mL, three-necked, round-bottomed flask, equipped with a magnetic stirrer, a septum, and a ¼ argon-filled balloon as an outlet was charged with **32b** (0.1 g, 0.37 mmol) in methanol (30 mL). Palladium-on-carbon (5%, 0.30 g) was added, and neat triethylsilane (3 mL, 2.18 g, 18.78 mmol) was added dropwise. The reaction mixture was stirred overnight at room temperature. The crude reaction mixture was concentrated, diluted with ether (10 mL) and filtered through a pad of Celite 545® topped with a layer of $MgSO_4$ to remove the catalyst. The filtrate was concentrated and chromatographed to afford **12** (0.04 g, 48%).

Methyl 2-(2-nitrophenyl)hex-5-enoate (34a). A 100-mL, three-necked, round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser was charged with **28** (0.2 g, 1.02 mmol) in DMF (15 mL). Potassium carbonate (0.5 g, 3.6 mmol) and 18-crown-6 (0.20 g) were added, and the reaction was stirred for 5 min. To the resulting blue mixture were added KI (0.40 g) and a solution of 4-bromobutene **(33a)** (0.20 g, 1.48 mmol) in 3 mL of DMF. The reaction was stirred for 2 days at room temperature. Water (100 mL) was added, and the mixture was extracted three times with ether (20 mL). The ether extracts were washed with water, saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated. The oily residue was chromatographed using 5-10% ether in hexanes to afford **34a** (0.13 g, 50%) as a yellow oil. IR 1738, 1531, 1353 cm^{-1}; ^{1}H NMR δ 7.86 (dd, 1H, *J* = 8.2, 1.2 Hz), 7.62-7.53 (m, 2H), 7.43 (td, 1H, *J* = 8.5, 1.8 Hz), 5.81-5.70 (m, 1H), 5.00 (dd, 2H, *J* = 10.8, 1.6 Hz), 4.20 (t, 1H, *J* = 7.5 Hz), 3.66 (s, 3H), 2.35-2.23 (m, 1H), 2.11-1.91 (m, 3H); ^{13}C NMR δ 173.4, 149.9, 146.2, 137.4, 133.4, 130.3, 128.5, 125.1, 116.1, 52.6, 45.8, 32.4, 32.0.

Methyl 5-methyl-2-(2-nitrophenyl)hex-5-enoate (34b). A 50-mL, three-necked, round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser was charged with **28** (0.10 g, 0.51 mmol) in DMF (10 mL). Potassium carbonate (0.25 g, 1.8 mmol) and 18-crown-6 (0.20 g) were added, and the reaction was stirred for 5 min. To the resulting blue mixture a solution of 4-iodo-2-methylbutene **(33b)** (0.10 g, 0.50 mmol) in DMF (3 mL) was added. The reaction was stirred for 2 days at room temperature. Water (50 mL) was added and the mixture was ether extracted three times. The ether extracts were washed with water, saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated. The oily residue was chromatographed using 5-10% ether in hexanes to afford **34b** (74 mg, 55%) as a yellow oil. IR 1736, 1528, 1353 cm^{-1}; ^1H NMR δ 7.88 (d, 1H, *J* = 8.2 Hz), 7.65-7.56 (m, 2H), 7.45 (td, 1H, *J* = 8.7, 2.2 Hz), 4.75 (s, 1H), 4.66 (s, 1H), 4.20 (t, 1H, *J* = 7.1 Hz), 3.68 (s, 3H), 2.38-2.31 (m, 1H), 2.08-1.98 (m, 3H), 1.73 (s, 3H); ^{13}C NMR δ 173.4, 144.6, 133.8, 133.4, 130.3, 128.9, 128.5, 125.7, 111.3, 52.6, 45.9, 35.9, 31.1, 22.5.

2-(2-Nitrophenyl)hex-5-enoic acid (35a). A 250-mL, round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser was charged with **34a** (0.95 g, 3.81 mmol) in THF (50 mL), and alcoholic KOH (50 mL, 1 *M*) was added. The mixture was stirred overnight at room temperature, and the reaction progress was monitored by TLC. Water (50 mL) was added, and the mixture acidified with 1 *M* HCl solution and extracted three times with CH_2Cl_2 (50 mL). The organic extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated. The oily residue was chromatographed using 20% ether in hexanes to afford **35a** (0.86 g, 95%) as a yellow oil. IR 3678-2651, 1709, 1527, 1351 cm^{-1}; ^1H NMR δ 11.28 (br s, 1H), 7.92 (dd, 1H, *J* = 8.2, 1.6 Hz), 7.60 (td, 1H, *J* = 7.1, 1.1 Hz), 7.52 (dd, 1H, *J* = 7.5, 1.1 Hz), 7.44 (td, 1H, *J* = 8.2, 1.1 Hz), 5.81-5.68 (ddt, 1H, *J* = 9.3, 6.6 Hz), 5.00 (2d, 2H, *J* = 15.9, 12.1 Hz), 4.22 (t, 1H, *J* = 7.1 Hz), 2.35-2.24 (m, 1H), 2.10-1.19 (m, 3H); ^{13}C NMR δ 179.2, 149.7, 137.2, 133.6, 133.1, 130.7, 128.8, 125.3, 116.4, 64.1, 31.9, 31.7.

5-Methyl-2-(2-nitrophenyl)hex-5-enoic acid (35b). A 100-mL, round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser was charged with **34b** (0.20 g, 0.75 mmol) in THF (15 mL), and alcoholic KOH (10 mL, 1 *M*) was added. The mixture was stirred overnight at room temperature, and the reaction progress was monitored by TLC. Water (20 mL) was added, and the mixture acidified with 1 *M* HCl solution and was extracted three times with CH_2Cl_2 (20 mL). The organic extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated. The oily residue was chromatographed using 20% ether in hexanes to afford **35b** (0.16 mg, 83%) as a yellow oil. IR 3075, 1709, 1572, 1350 cm^{-1}; ^{1}H NMR δ 10.62, (br s, 1H), 7.91 (dd, 1H, *J* = 8.2, 1.1 Hz), 7.63-7.52 (td, 2H, *J* = 7.6, 1.1 Hz), 7.44 (td, 1H, *J* = 8.2, 1.6 Hz), 4.73 (s, 1H), 4.63 (s, 1H), 4.19 (t, 1H, *J* = 7.1 Hz), 2.39-2.31 (m, 1H), 2.04-1.93 (m, 3H), 1.69 (s, 3H); ^{13}C NMR δ 179.2, 149.7, 144.4, 133.6, 133.2, 130.7, 128.8, 125.2, 111.6, 46.2, 25.8, 30.5, 22.5.

1-Nitro-2-(pent-4-en-1-yl)benzene (36a). The general procedure of Bull *et al.*[17] was followed. A 250-mL, round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser was charged with **35a** (0.86 g, 3.65 mmol) in DMF (75 mL). Potassium carbonate (2.2 g, 15.9 mmol) was added and the reaction stirred at 50 °C for 3 h. After cooling to room temperature, H_2SO_4 (20 mL, 0.25 *M*) was added, and the mixture was extracted three times with ether (50 mL). The ether extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed using 5-10% ether in hexanes to afford **36a** (0.46 g, 65%). IR 1641, 1525, 1348 cm^{-1}; ^{1}H NMR δ 7.88 (dd, 1H, *J* = 9.3, 1.1 Hz), 7.51 (td, 1H, *J* = 8.7, 1.1 Hz), 7.33 (td, 2H, *J* = 7.1, 1.6 Hz), 5.90-5.76 (m, 1H), 5.08-4.98 (dd, 2H, *J* = 15.3, 1.6 Hz), 2.89 (t, 2H, *J* = 7.6 Hz), 2.13 (td, 2H, *J* = 7.1 Hz), 1.80-1.70 (m, 2H); ^{13}C NMR δ 138.4, 133.1, 132.3, 127.3, 125.0, 115.5, 33.9, 32.8, 30.2.

1-(4-Methylpent-4-en-1-yl)-2-nitrobenzene (36b). The general procedure of Bull *et al.*[17] was followed. A 50-mL, round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser was charged with **35b** (0.10 g, 0.40 mmol) in DMF (10 mL). Potassium carbonate (0.20 g, 1.45 mmol) was added and the reaction stirred at 50 °C for 3 h. After being allowed to cool, H_2SO_4 (10 mL, 0.25 *M*) was added, and the mixture was extracted three times with ether (10 mL). The ether extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed using 5-10% ether in hexanes to afford **36b (**0.08 g, 90%). IR 1611, 1522, 1347 cm^{-1}; ^{1}H NMR δ 7.94 (dd, 1H, *J* = 8.2, 1.1 Hz), 7.85 (dd, 1H, *J* = 7.7, 1.1 Hz), 7.49 (td, 1H, *J* = 8.7, 1.1 Hz), 7.35-7.30 (m, 1H), 4.73 (s, 1H), 4.69 (s, 1H), 2.85 (t, 2H, *J* = 7.7 Hz), 2.58 (s, 3H), 2.10 (t, 2H, *J* = 7.1 Hz), 1.83-1.72 (m, 2H); ^{13}C NMR δ 145.4, 137.7, 133.9, 133.4, 133.2, 133.1, 132.3, 127.2, 124.9, 110.8, 37.9, 32.9, 28.9, 22.6, 20.7.

Ozonolysis-Wittig Sequence: (*E*)- and (*Z*)-Methyl 6-(2-nitrophenyl)hex-2-enoate (39). The procedure of Bunce and co-workers[14] was used. A 250-mL, round-bottomed flask, was charged with **36a** (1.3 g, 6.79 mmol) in MeOH (100 mL) and the solution was ozonized at -78 °C until TLC indicated complete consumption of starting material.

Excess ozone was purged with a stream of dry N_2, and dimethyl sulfide (5.08 g, 6.00 mL, 84.9 mmol) and *p*-TsOH (200 mg) were added. The solution was gradually warmed to room temperature and stirred for 8 h. The reaction was concentrated, diluted with ether, washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl and dried ($MgSO_4$), filtered, and concentrated to afford aldehyde **37** (1.2 g, 92%) as a yellow oil. The product was used for the next reaction step without further purification. Into 50-mL, round-bottomed flask, a solution of aldehyde **37** (0.1 g, 0.50 mmol) in benzene (10 mL) was added. To the stirred solution was added methyl triphenylphosphoranylidene acetate **(38)** (0.40 g, 1.20 mmol) and the reaction was refluxed for 3 h. After cooling to room temperature, the mixture was concentrated and chromatographed using 20% ether in hexanes to afford the two isomeric products (*E*)-**39** isomer (98 mg, 83%) and (*Z*)-**39** isomer (2 mg, 2%), both as yellow oils. *E* isomer: IR: 1723, 1657, 1526, 1348 cm^{-1}; ^1H NMR δ 7.90 (dd, 1H, *J* = 8.2, 1.1 Hz), 7.53 (td, 1H, *J* = 7.7, 1.1 Hz), 7.38-7.28 (m, 2H), 7.03-6.93 (dt, 1H, *J* = 15.4, 7.1 Hz), 5.86 (dt, 1H, *J* = 17.0, 1.6 Hz), 3.73 (s, 3H), 2.90 (t, 2H, *J* = 7.7 Hz), 2.34-2.26 (m, 2H), 1.88-1.78 (m, 2H); ^{13}C NMR δ 167.3, 148.7, 137.0, 133.3, 132.2, 127.6, 125.1, 121.9, 51.8, 32.8, 32.3, 29.3.

Z isomer: ^1H NMR δ 7.91 (dd, 1H, *J* = 8.2, 1.1 Hz), 7.52 (td, 1H, *J* = 7.7, 1.1 Hz), 7.36-7.32 (m, 2H), 6.31-6.22 (dt, 1H, *J* = 11.5, 7.7 Hz), 5.82 (dt, 1H, *J* = 11.5 Hz), 3.71 (s, 3H), 2.92 (t, 2H, *J* = 7.7 Hz), 2.80-2.73 (qd, 2H, *J* = 7.7, 1.6 Hz), 1.86-1.76 (m, 2 H); ^{13}C NMR δ 166.7, 149.4, 137.0, 132.8, 132.0, 127.0, 124.7, 120.0, 51.0, 32.7, 29.8, 28.7.

Methyl 2-(2,3,4,5-Tetrahydro-1*H*-benzo[*b*]azepin-2-yl)acetate (40). The procedure of Bunce and coworkers[15] was used. Into a 100-mL, three-necked, round-bottomed flask, equipped with magnetic stirring, a reflux condenser and a nitrogen inlet were placed **(*E*)**

39 (71 mg, 0.27 mmol), acetic acid (10 mL) and iron powder (0.15 g, 2.67 mmol) (>100 mesh). The mixture was heated with stirring at 115 ºC until thin layer chromatography indicated complete consumption of the starting material. After being allowed to cool the crude reaction mixture filtered through Celite 545®. Water was added, and the mixture was extracted three times with ether (10 mL). The ether extracts were washed with saturated aqueous NaCl dried ($MgSO_4$), filtered, and concentrated. The crude material was chromatographed using 15% ether in hexanes to afford **40** (50 mg, 83%) as a yellow oil. IR 3355, 1731 cm^{-1}; ^1H NMR δ 7.08-7.01 (m, 2H), 6.84 (td, 1H, *J* = 7.1, 1.1 Hz), 6.75 (d, 1H, *J* = 7.7, 1.1 Hz), 4.23 (br s, 1H), 3.70 (s, 3H), 3.35-3.27 (m, 1H), 2.75 (m, 2H), 2.56-2.47 (dd, 1H, *J* = 9.8, 6.0 Hz), 2.41 (dd, 1H, *J* = 15.9, 3.8 Hz), 1.91-1.74 (m, 2H), 1.68-1.45 (m, 2H); ^{13}C NMR δ 173.2, 148.0, 134.6, 130.7, 127.1, 121.8, 120.9, 54.3, 52.1, 40.2, 37.8, 35.7, 25.3.

(*E*)-Ethyl 3-methyl-6-(2-nitrophenyl)hex-2-enoate (42). A 50-mL, three-necked, round-bottomed flask, equipped with a magnetic stirrer and a condenser was charged with ethyl dimethylphosphonoacetate **(4)** (0.10 g, 0.51 mmol) in dry THF (10 mL). Sodium hydride (0.03 g, 1.25 mmol) was added, while the solution was stirring under nitrogen at 0 ºC (ice bath). The reaction mixture was stirred for 1.5 h. Ketone **32a** (0.10 g, 0.48 mmol) was added, and the reaction mixture was allowed to warm to room temperature and was stirred overnight at room temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted three times with ethyl acetate (10 mL). The organic phase was washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated to afford the *E* isomers of **42** (60 mg, 44%), which was used for next reaction step without further purification. IR 1714, 1648, 1526, 1349 cm^{-1}; ^1H NMR δ 7.89 (td, 2H, *J* = 7.7, 1.1 Hz), 7.56-7.49 (m, 2 H), 7.38-7.32 (m, 4H), 5.69 (s, 2H), 4.14 (q, 4H, *J* = 7.1 Hz), 2.95-2.84 (td, 4H, *J* = 7.7 Hz), 2.75 (t, 2H, *J* = 7.7 Hz), 2.24 (t, 2H, *J* = 7.7 Hz), 2.18 (s, 6H), 1.91-1.82 (m, 4H), 1.27 (t, 6H, *J* = 7.1 Hz); ^{13}C NMR δ 167.0, 166.7, 159.7, 159.2, 149.9, 137.6, 137.2, 133.3, 133.2, 132.2, 127.5, 127.3, 125.1, 125.0, 117.1, 116.4, 59.9, 41.0, 33.5, 33.3, 32.9, 32.3, 29.3, 28.7, 25.3, 24.9, 19.0, 14.6.

Ethyl 2-(2-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-2-yl)acetate (43). The procedure of Bunce and coworkers[20] was used. Into a 100-mL, round-bottomed flask, equipped with magnetic stirring, a reflux condenser and a nitrogen inlet, was placed **42** (0.10 g, 0.36 mmol), acetic acid (25 mL) and of iron powder (0.20 g, 3.57 mmol) (>100 mesh). The mixture was heated with stirring at 115 ºC until thin layer chromatography indicated complete consumption of the starting material. After cooling to room temperature, the crude reaction mixture filtered through Celite 545®. Water was added and the mixture was extracted three times with ether (10 mL). The ether extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated. The crude material was chromatographed using 10% ether in hexanes to afford **43** (30 mg, 38%). IR 3343, 1728, 1481 cm^{-1}; ^{1}H NMR δ 7.06-7.00 (m, 2H), 6.85 (td, 1H, *J* = 7.6, 1.1 Hz), 6.76 (d, 1H, *J* = 7.6 Hz), 4.31 (s, 1H), 4.13 (q, 2H, *J* = 7.1 Hz), 2.76-2.71 (m, 3H), 2.48 (d, 1H, *J* = 14.8 Hz), 2.26 (d, 1H, *J* = 14.8 Hz), 1.78-1.63 (m, 4H), 1.28-1.23 (t, 6H, *J* = 7.1 Hz); ^{13}C NMR δ 172.4, 146.1, 134.8, 130.3, 127.0, 122.3, 121.9, 60.6, 54.5, 44.2, 43.6, 35.8, 26.9, 22.8, 14.6.

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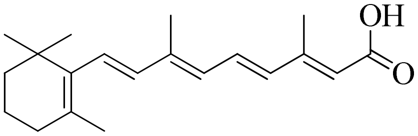
CHAPTER III

SYNTHESIS OF NITROGEN HETEROAROTINOIDS FOR ANTICANCER ACTIVITY

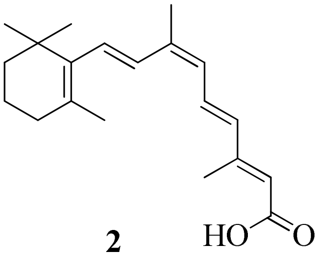
Introduction

Retinoids are a class of chemical compounds structurally related to vitamin A. Naturally occurring retinoids such as *trans*-retinoic acid **(1)**, 9-*cis*-retinoic acid **(2)** and 13-*cis*-retinoic acid **(3)** are depicted in Figure 3.1. They have medicinal use due to their importance for regulation of cell proliferation and differentiation throughout the body. Studies have shown anticancer activity of natural and synthetic retinoids against skin, breast, lung, ovarian and uterine cancer.[1] Some synthetic retinoids (Figure 3.2),[1,2] such as arotinoid TTNPB **(4)**, etretinate **(5)** and fenretinide **(6)**,[3] have shown potent anticancer activity. The application of these retinoids, however, was limited due to their teratogenicity and/or toxic manifestations such as diarrhea, hair loss, nausea, and headaches.[1-3]



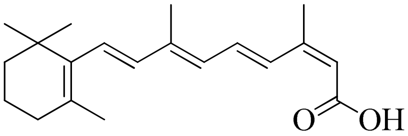
1

trans-retinoic acid (tretinoin)



2

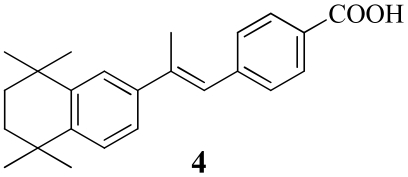
9-*cis*-retinoic cid



3

13-*cis*-retinoic cid (isotretinoin)

Figure 3.1. Naturally occurring retinoids.



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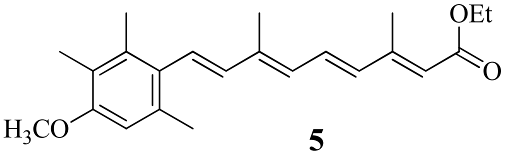
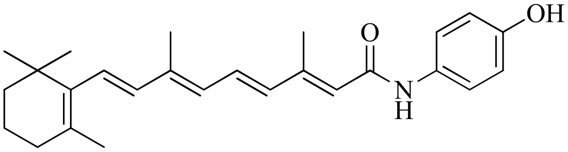
TTNPB



5

etretinate



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15-[(4-hydroxyphenyl)amino]retinal (fenretinide)

Figure 3.2. Synthetic retinoids having potent anticancer activity.

Retinoids exert their therapeutic activity by interaction with and activation of a specific group of nuclear receptors, termed retinoid receptors.[1-3] The retinoid receptors are divided into two distinct types, namely the retinoic acid receptors (RARs) and the retinoid X receptors (RXRs). For each type, three receptor subtypes, namely RARα, -*β*, and -*γ* and RXRα, -*β*, and -*γ*, have been identified for a total of six retinoid receptors.[3] These retinoid receptors belong to the hormone receptor superfamily, and, as a group, this family of proteins regulate the transcription of genes that control a variety of metabolic, developmental, and differentiation pathways. Misregulation of any one of these pathways could enhance carcinogenesis. Compounds, such as retinoids, may regulate these receptors and are, therefore, potentially chemopreventive agents.[3,4]

Other research suggested that retinoids inhibit cell growth by inhibition of ornithine decarboxylase (ODC) induction. Ornithine decarboxylase is an essential enzyme for the biosynthesis of polyamines. Polyamines, such as putrescine **(7)**, spermidine **(8)** and spermine **(9)**, comprise a family of aliphatic cations (Figure 3.3) that occur ubiquitously in nature. They are necessary for cell proliferation, differentiation and transformation and are involved in DNA, RNA, and protein synthesis, as well as in stabilizing membrane and cytoskeletal structures. Polyamines accumulate in larger amounts in cancer cells than normal cells. Therefore, depletion of polyamines causes cell apoptosis.[5,6]

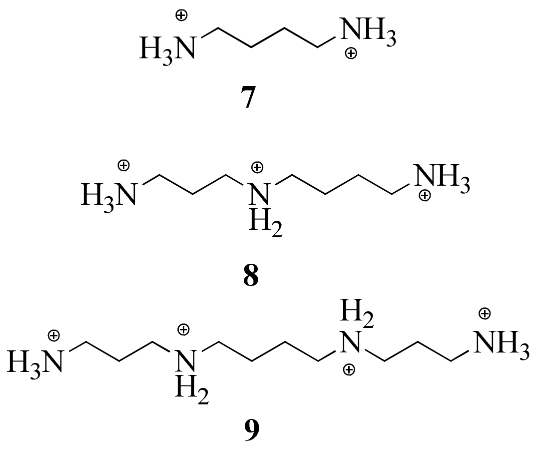
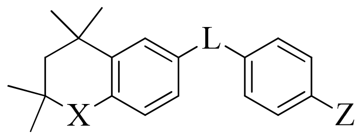


Figure 3.3. Polyamine cations.

It has also been found that treating some human erythroleukemia (HEL) cells with *trans*-retinoic acid (*t*-RA) results in cell differentiation accompanied by a 9-fold increase in tissue transglutaminase (TGase) activity.[7] Tissue transglutaminases are Ca^{2+} dependent enzymes which catalyze the crosslinking of proteins between an α-amino group of a lysine residue and a γ-carboxamide group of a glutamine residue, creating an inter- or intramolecular bond that is highly resistant to proteolysis. There is evidence to prove that TGase induction is mediated through a pathway involving retinoic acid receptors (RAR).[8]

Heteroarotinoids are a new class of synthetic retinoids structurally resembling arotinoids in that at least one aryl moiety is present within the molecular structure. They have been designed to mimic the anticancer activity of retinoids. They have been called heteroarotinoids since they possess an aryl ring fused to saturated five- or six-membered ring containing a heteroatom as shown in Figure 3.4.[9] Intensive studies on the modification of heteroarotinoid structures have been reported involving the insertion of different linkers to connect the two aryl rings. Structures with two-atom linker groups, such as an amide **13**, an alkene **14**, an ester **15** or an *N*-methoxyamide **16**, have been synthesized. Structures with three-atom linkers, such as propenone **17**, propenol **18**, *R*-hydroxyamide **19** and 1,4-diketone **20** as a four-atom linker, have also been reported (Figure 3.5). All of these heteroarotinoids have shown potent anticancer activity with low toxicity.[3,7]



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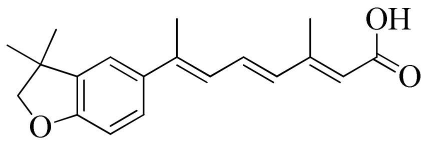
X = O, S, NR
Z = CO_2H, CO_2R
SO_3H, NO_2

L = Linking group:
amide, alkene,
ester, urea, thiourea



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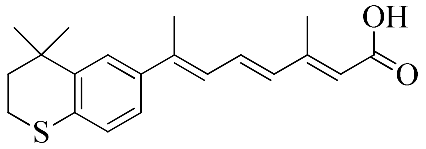

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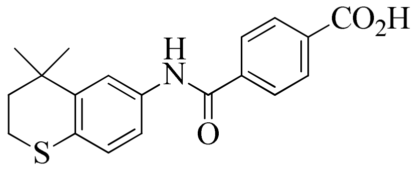

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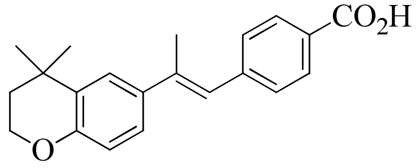

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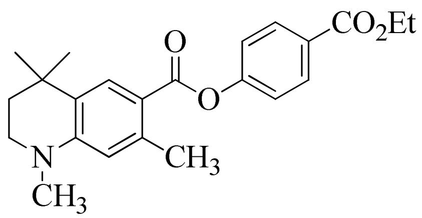

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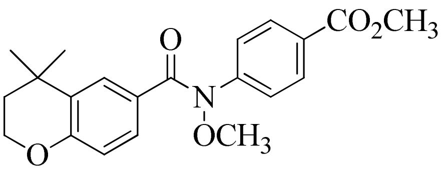

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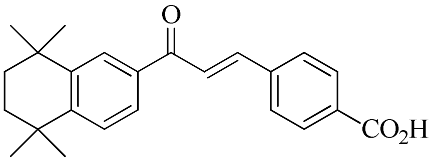
Figure 3.4. Heteroarotinoids with different linkers.



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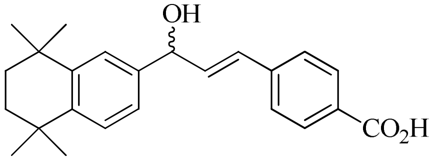

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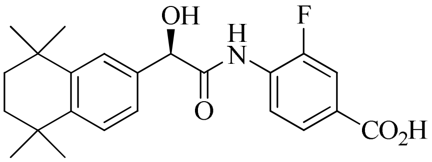

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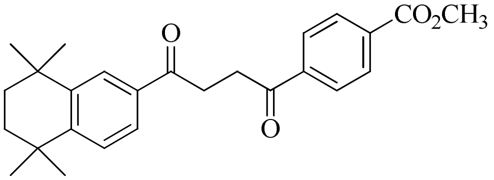

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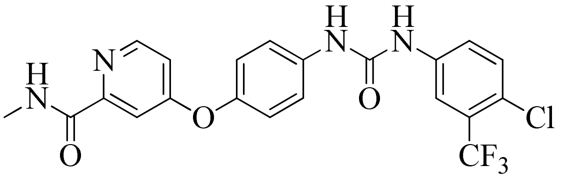
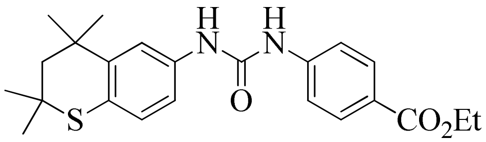
Figure 3.5. Heteroarotinoids with three- and four-atom linkers.

The search for flexible heteroarotinoids which bind freely with the receptors is the primary objective to enhance the specificity and activity of the anticancer agent. Incorporation of a more flexible linker between the aryl moieties provides more degrees of freedom that allow for better accommodation of the molecule in the receptor site. A number of urea and thiourea linkers between the aryl rings have been synthesized and have shown marked flexibility as a ligand and more H-bonding interaction with the amino acids at the receptor site (Figure 3.6). These flexible heteroarotinoids have potential anticancer activity against kidney and multiple types of cancer cells.[3,10,11] Sorafenib (BAY-43-9006) **(21)** (Figure 3.7) is a compound that was approved by the FDA and was developed to improve its hydrophilic property without losing its biological activity. It has been shown to have potent anticancer activity against kidney cancer. The enhanced hydrophilicity increases the drug concentration in the blood or plasma and consequently, delivers a higher concentration to the tumor cells.[11] Heteroarotinoids **22-25** are structural analogs to the anticancer agent sorafenib **(21)**. Molecular modeling studies have shown that sorafenib **(21)** and heteroarotinoid **25** have the same binding sites on the receptor, where, both the urea groups in Sorafenib and the thiourea group in **25** formed H-bonds with Glu501 and Asp594 as shown in Figure 3.7. Thus, it is predictable that **25** would inhibit B-Raf.[11a] B-Raf is a protein made by a human gene called BRAF. B-Raf regulates signal transduction serine/threonin-specific protien kinase that essential for cell growth and differentiation. Active B-Raf mutants cause human cancer by accelerating cell growth.[11b]



Sorafenib **(21)**



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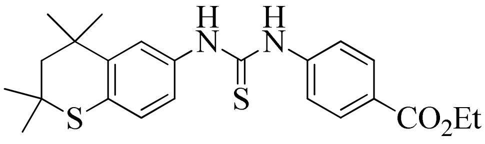

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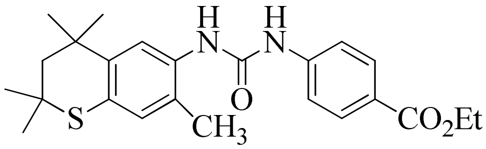

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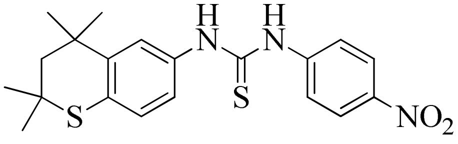


25

Figure 3.6 Heteroarotinoids with structural features similar to those in sorafenib **(21)**.

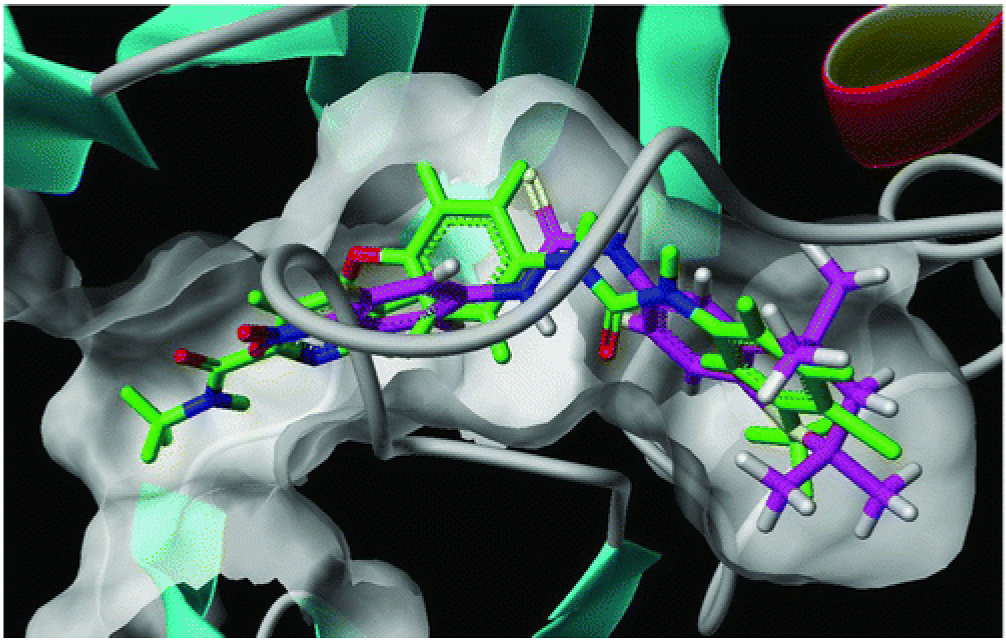


Figure 3.7. Sorafenib **(21)** and **25** docked into the binding sites of B-Raf.

Structure activity relationship studies based on the model unit **10** suggests that alteration of the heteroatom, ring size and terminal side chain (Z group) may change the efficacy and specificity toward the retinoid receptor. In general, insertion of a heteroatom in the five- or six-membered ring of the arotinoid backbone reduced the toxicity 1000-fold compared to *trans*-retinoic acid and arotinoids.[12,13] Heteroarotinoids with six-membered rings exhibited greater specificity for RARβ, while other derivatives had specificity to other receptors.[12,13]

Compound **25** exhibited more potency than the clinical agent 4-hydroxyphenylretin amide (4-HPR) against ovarian cancer.[3] Chemoprevention activity by 4-HPR is thought to induce apoptosis through a retinoic acid receptor at low concentration.[3b,3c] This high activity caused by the thiourea or urea group may be due to the natural flexibility of the three-atom linker, which might allow a good fit into the RARs and therefore enhance the activity. Moreover, a thiourea or urea function provides two -NH- groups capable of hydrogen bonding with the receptor, thus possibly improving the RAR selectivity.[3]

As a part of ongoing work on this project, we sought to insert a nitrogen atom in place of sulfur or oxygen in the arotinoid ring system. Based on the results of related heteroarotinoids, these new derivatives have great potential as agents with high anticancer activity and low toxicity. In comparison, the nitrogen atom is smaller than oxygen and sulfur. Moreover, the nitrogen atom has a greater ability to hydrogen bond, which could allow new derivatives to easily fit in and bind to the receptor site. Furthermore, to overcome the solubility problem with heteroarotinoids containing sulfur and oxygen and increase the hydrophilicity, these new heteroarotinoids are able to form quaternary ammonium salts. This would provide greater solubility and could enhance the *in vivo* activity by increasing the blood concentration of the drug for distribution to the target tissue.

Results and Discussion

Synthesis of the Amine

The synthesis of selected target compounds began with the allylation of the LDA generated anion of ethyl isobutyrate (**26**) with methylallyl iodide (**27**) in THF to afford ester **28** in a yield of 59%. Ester **28** was converted to acid **29** (96%) by basic hydrolysis using aqueous NaOH. Finally, amine **31** was prepared by the reaction of acid **29** with diphenylphosphonic azide (**30**) in the presence of Et_3N with benzene as solvent (Figure 3.8).[14] The conversion of a carboxylic acid to an amine using diphenylphosphonic azide

(**30**) and base involves a Curtius rearrangement[15] as shown in Figure 3.8. This reaction usually gives high yields of product, but with the volatile aliphatic amine **31**, the yield was 72%.

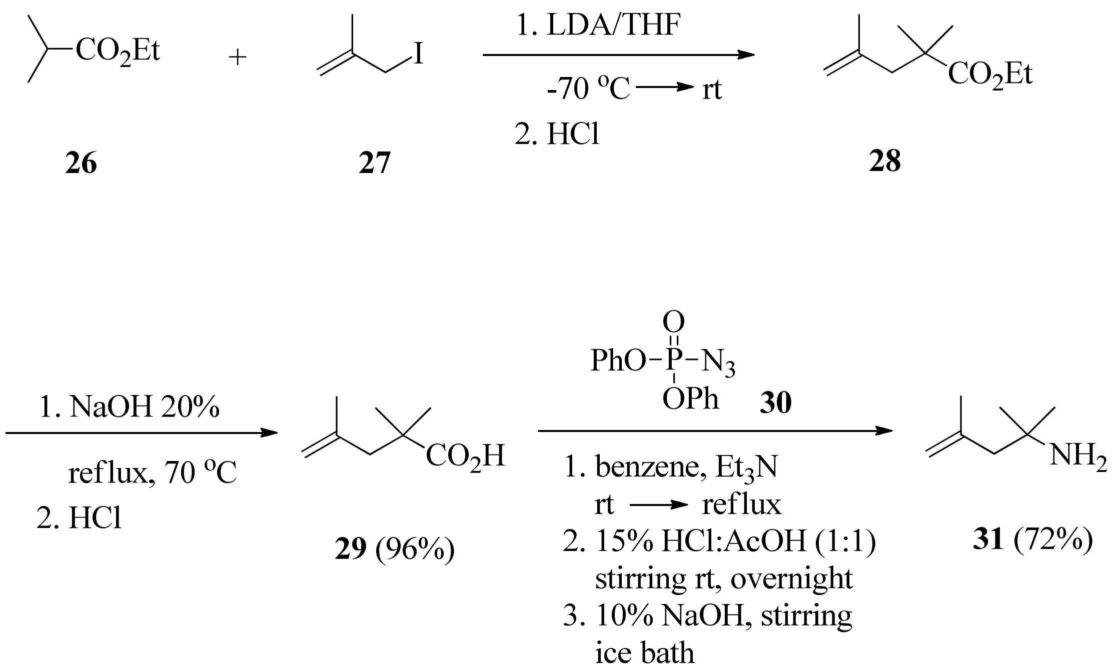


Figure 3.8. Synthesis of amine **31**.

Mechanism of the Curtius Rearrangement

The first step of the Curtius rearrangement is the formation of an acyl azide (or acyl nitrene) **32** by displacement of azide form **30** by acid **29** (carboxylate) in the presence of Et_3N and addition of azide to the resulting acyl phosphate as shown in Figure 3.9. This acyl nitrene is highly reactive and electrophilic. Thermal decomposition of acyl nitrene **32** leads to migration of the alkyl substituent from carbon to the electron deficient nitrogen atom to give isocyanate **33** with release of nitrogen gas. The isocyanate **33** was isolated and subjected to acidic hydrolysis with a mixture of 15% HCl and acetic acid (1:1) to form the carbamic acid **34**, which spontaneously decarboxylated. The free base amine **31** was released by basification of the solution containing the amine salt **35** using 10% NaOH under cooling conditions.

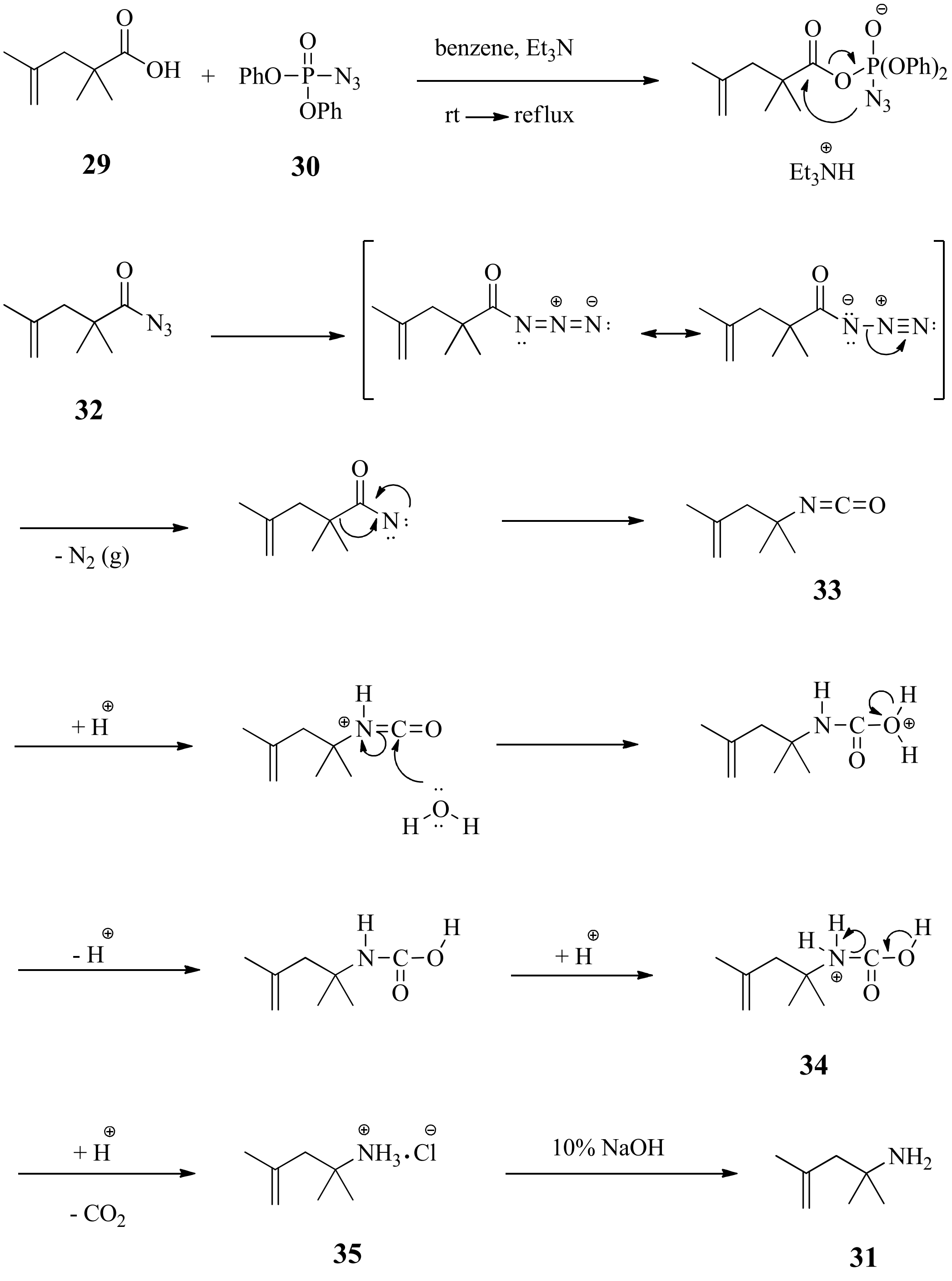
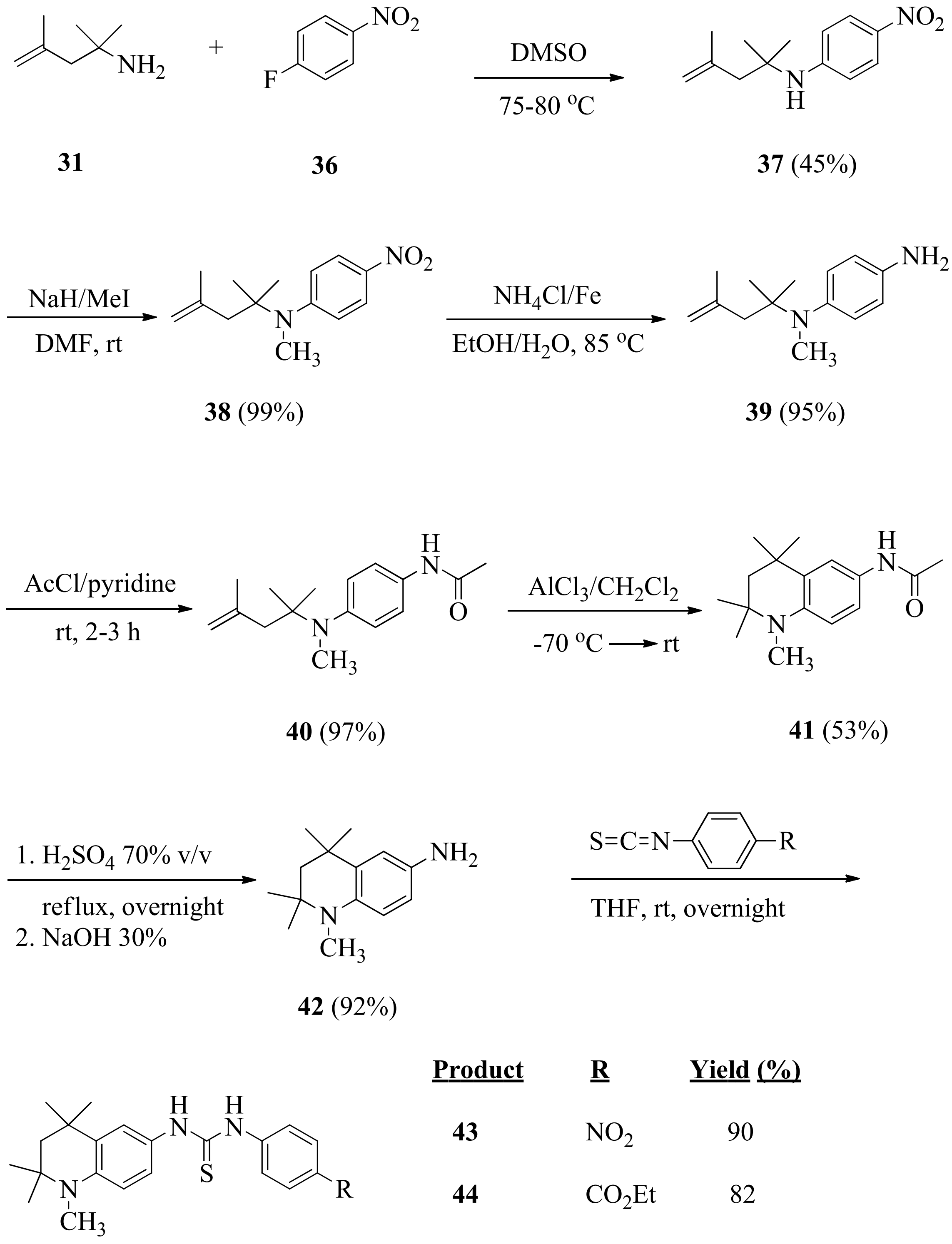


Figure 3.9. Mechanism of Curtius rearrangement for the synthesis amine **31**.

Synthesis of the Heteroarotinoids

Amine **31** was spectroscopically pure and, due to its volatility, was used directly for the next reaction step.[14] Nucleophilic aromatic substitution of **31** with **36** afforded the secondary amine **37** in 45% yield,[16] which was converted to tertiary amine **38** (99%) by methylation with MeI using NaH in DMF as solvent.[17] Compound **39** was obtained in 95% yield by reduction of the nitro compound **38** with iron powder in the presence of NH_4Cl in aqueous ethanol as solvent.[18] Protection of the amino group of **39** by acetylation with acetyl chloride in the presence of pyridine produced the acetamide derivative **40** in 97% yield. Friedel-Crafts cyclization of **40** using $AlCl_3$ in CH_2Cl_2 formed the fused-ring compound **41** (53%).[19] Deprotection of **41** was accomplished by acidic hydrolysis under reflux using 70% (v/v) H_2SO_4, followed by basification with 30% NaOH to produce diamine **42** in 92% yield. The target heteroarotinoids **43** and **44** were obtained in 90% and 82% yields, respectively, by reaction of the isothiocyanate derivatives in THF at room temperature[3] as shown in Figure 3.10.



Product	R	Yield (%)
43	NO_2	90
44	CO_2Et	82

Figure 3.10. Synthesis of the heteroarotinoids.

Conclusions

This project provides a new synthetic route for the synthesis of heteroarotinoids containing a saturated nitrogen heterocycle as a part of the core ring structure. The key step of the synthetic scheme is the formation of the new amine derivative **31**. All intermediates are stable structures formed in reasonably good yields. Deprotection of the amino group of compound **41** with 70% v/v H_2SO_4 prove the stability of the heteroarotinoid ring even under strongly acidic conditions. The target heteroarotinoids **43** and **44** were obtained as crystalline solids. These new heteroarotinoids will be screened for anticancer activity on different types of cancer cells.

Experimental Section

All solvents were distilled prior to use. Other reagents were used as received from various vendors. All reactions were run under dry nitrogen in oven-dried glassware. Reactions were monitored by TLC on hard layer silica gel GF plates (Analtech No. 21521) using UV detection. Preparative separations were performed using one of the following methods: (1) PTLC on 20-cm x 20-cm silica gel GF plates (Analtech No. 02015) or (2) flash column chromatography on silica gel (Davison®, grade 62, 60-200 mesh) containing UV-active phosphor (Sorbent Technologies No. UV-05). In each case, band elution was monitored using a hand-held UV-lamp. IR spectra were run as thin films on NaCl disks. ^{1}H-NMR and ^{13}C-NMR spectra were measured in $CDCl_3$ at 300 MHz and 75 MHz, respectively, and were referenced to internal $(CH_3)_4Si$; coupling constants (J) are in Hz.

Ethyl 2,2,4-Trimethyl-4-pentenoate (28). The method of Walborsky *et al.*[14] was followed. A 500-mL, three-necked, round-bottomed flask, equipped with a magnetic stirrer, a septum, a condenser and a nitrogen inlet, was charged with diisopropylamine (15.9 g, 22 mL, 157 mmol) in 200 mL of freshly distilled THF. The flask was cooled to -70 °C (dry ice/acetone), and *n*-butyllithium (2.5 *M*, 63 mL, 157.5 mmol) was added to the solution. After 5 min, ethyl isobutyrate (**26**, 14 g, 120.5 mmol) was added dropwise. Stirring was continued for 1 h at -70 °C. A solution of 3-iodo-2-methylpropene (**27**, 22 g, 120.5 mmol) was added dropwise, and the reaction was stirred overnight with warming to ambient temperature. The reaction mixture was poured into a mixture of ice and 1 *M* HCl, and the product was extracted with ether (3 × 100 mL). The combined ether extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated. Vacuum distillation afforded **28** (12.8 g, 64%) as colorless liquid, bp 50 ºC (1.8 mm). IR: 3078, 1729, 1645, 895 cm^{-1}; ^{1}H-NMR: δ 4.79 (s, 1H), 4.65 (s, 1H), 4.08 (q, 2H, *J* = 7.1 Hz), 2.31 (s, 2H), 1.66 (s, 3H), 1.25 (t, 3H, *J* = 7.1 Hz), 1.17 (s, 6H); ^{13}C-NMR: δ 177.7, 142.3, 113.9, 60.1, 48.2, 41.7, 25.4, 23.3, 13.9.

2,2,4-Trimethyl-4-pentenoic acid (29). A 500-mL, round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser, was charged with compound **28** (11.2 g, 66.6 mmol) in 25 mL of MeOH. An aqueous solution of NaOH (20%, 30 mL) was added to the solution, and the reaction mixture was refluxed overnight at 60-70 °C. After being allowed to cool to room temperature, 50 mL of water was added, and the mixture was acidified with 1 *M* HCl. The product was extracted with ether (3 × 100 mL), and the combined ether extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated. Vacuum distillation afforded acid **29** (9.04 g, 96%) as a colorless liquid, bp 83 °C (1.8 mm). IR: 3077, 1703, 1644, 895 cm^{-1}; ^{1}H-NMR: δ 11.15 (s, 1H), 4.82 (s, 1H), 4.70 (s, 1H), 2.34 (s, 2H), 1.71 (s, 3H), 1.21 (s, 6H); ^{13}C-NMR: δ 185.3, 142.6, 114.8, 48.5, 42.3, 25.7, 23.9.

2,4-Dimethyl-4-penten-2-amine (31). A 250-mL, three-necked, round-bottomed flask, equipped with a magnetic stirrer, a septum, a reflux condenser and a nitrogen inlet, was charged with compound **29** (2.2 g, 15.6 mmol) and TEA (2.9 g, 4 mL, 28.6 mmol) in 25 mL of dry benzene. The flask was cooled to 0 ºC (ice bath), and diphenylphosphonic azide (**30**, 6.3 g, 23.2 mmol) was added dropwise with stirring. The reaction mixture was stirred at 0 °C for 1 h, and then at room temperature for 1 h and finally at reflux for 3 h (evolution of nitrogen). The solution was cooled, ether (250 mL) was added and the organic layer was washed three times with water. The organic layer was dried (Na_2SO_4), filtered, and concentrated. To the concentrated residue was added a mixture of 15% HCl (10 mL) and AcOH (10 mL), and the reaction was stirred overnight at room temperature. Water was added, and the aqueous layer was washed with ether (3 × 50 mL). The aqueous layer was cooled (ice bath) and basified by dropwise addition of 10% NaOH solution, and the product was extracted with ether (3 × 50 mL). The combined ether extracts were washed with water, and saturated aqueous NaCl, and then dried over KOH. The solvent was evaporated to give **31** (1.2 g, 72%) as a light yellow liquid, which was used for the next step without purification. IR: 3355, 2967, 1639, 891 cm^{-1}; ^{1}H-NMR: δ 4.91 (s, 1H), 4.72 (s, 1H), 2.10 (s, 2H), 1.82 (s, 3H), 1.13 (s, 6H); ^{13}C-NMR: δ 143.4, 114.8, 52.8, 46.5, 31.3, 25.5.

***N*-(2,4-Dimethyl-4-penten-2-yl)-4-nitroaniline (37).** A 250-mL, pressure vessel (ChemGlass, CG-1880-R-03), equipped with a magnetic stirrer, was charged with the amine **31** (2.2 g, 19.7 mmol) and 1-fluoro-4-nitrobenzene **36** (2.5 g, 17.7 mmol) in 15 mL of DMSO. The vessel was sealed under nitrogen and heated at 80 °C for 48 h. After cooling to room temperature, water was added, and the product was extracted with ether (3 × 75 mL). The ether extract was washed with water and saturated aqueous NaCl, then dried (Na_2SO_4), filtered, and concentrated to give a yellow oil, which was chromatographed using 5-15% ether in hexane to afford **37** (1.8 g, 45%) as a yellow oil. IR: 3379, 1599, 1531, 1368, 834 cm^{-1}; ^{1}H-NMR: δ 8.05 (d, 2H, *J* = 9.3 Hz), 6.61 (d, 2H, *J* = 9.3 Hz), 4.94 (s, 1H), 4.72 (s, 1H), 4.63 (br s, 1H), 2.46 (s, 2H), 1.76 (s, 3H), 1.44 (s, 6H); ^{13}C-NMR: δ 152.7, 142.2, 126.6, 116.3, 113.3, 54.3, 48.4, 28.8, 24.9.

***N*-(2,4-Dimethyl-4-penten-2-yl)-*N*-methyl-4-nitroaniline (38).** A 50-mL, round-bottomed flask, equipped with a magnetic stirrer, a reflux condenser and drying tube, was charged with compound **37** (70 mg, 0.3 mmol) in 5 mL of DMF. Sodium hydride (50 mg, 2 mmol) was added, and the mixture was stirred for 5 min, and then methyl iodide (3.0 g, 0.6 mmol) was added dropwise. Stirring was continued overnight at room temperature. Aqueous NH_4Cl (10%, 5 mL) was added, and the product was extracted with ether (3 × 10 mL). The ether extracts were washed with water and saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated to give a yellow oil, which was chromatographed using 10-20% ether in hexane to afford **38** (70 mg, 99%) as a yellow oil. IR: 1591, 1502, 1307, 837 cm^{-1}; ^1H-NMR: δ 8.06 (d, 2H, *J* = 9.3 Hz), 6.95 (d, 2H, *J* = 9.3 Hz), 4.91 (s, 1H), 4.75 (s, 1H), 3.02 (s, 3H), 2.47 (s, 2H), 1.72 (s, 3H), 1.41 (s, 6H); ^{13}C-NMR: δ 156.6, 142.7, 124.8, 119.7, 115.5, 59.6, 47.2, 37.5, 28.6, 24.6.

N^1-(2,4-Dimethyl-4-penten-2-yl)-N^1-methyl-1,4-benzenediamine (39). The basic procedure of Zhao *et al.*[18] was followed. A 250-mL, round-bottomed flask, equipped with a magnetic stirrer, and a reflux condenser, was charged with compound **38** (2.0 g, 8.1 mmol), iron powder (3.0 g, 53.7 mmol, >100 mesh) and NH_4Cl (1.0 g, 18.6 mmol) in 100 mL of $EtOH:H_2O$ (3.6:1). The reaction mixture was heated to 85 °C under N_2 for 2 h. The reaction mixture was filtered through Celite 545®, treated with saturated aqueous $NaHCO_3$ (100 mL), and extracted with ethyl acetate (3 × 100 mL). The organic layer was washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated to afford a brown residue (1.67 g, 95%), which was spectroscopically pure and was used directly for the next reaction step. IR: 3348, 1551 cm^{-1}; ^1H-NMR: δ 6.97 (d, 2H, *J* = 7.8 Hz), 6.58 (d, 2H, *J* = 8.7 Hz), 4.84 (s, 1H), 4.71 (s, 1H), 3.81 (s, 2H), 2.72 (s, 3H), 2.22 (s, 2H), 1.81 (s, 3H), 1.06 (s, 6H); ^{13}C-NMR: δ 144.1, 143.5, 129.5, 115, 114.6, 113.5, 58.2, 46.5, 37.3, 25.7, 25.3.

***N*-[4-(2,4-Dimethyl-4-penten-2-yl)methylamino)phenyl]acetamide (40).** A 250-mL, two-necked, round-bottomed flask, equipped with a magnetic stirrer, a condenser and addition funnel was charged with compound **39** (1.0 g, 4.7 mmol) in 50 mL of pyridine. Acetyl chloride (3 mL) was added dropwise, and the mixture was stirred at room temperature for 2-3 h. Water (100 mL) was added, and the product was extracted with ether (3 × 50 mL). The ether extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated, to give a brown residue, which was purified by chromatography using 30% ether in hexane to afford **40** (1.2 g, 97%) as a light yellow solid, mp 74-75 ºC. IR: 3297, 1663, 887 cm^{-1}; ^{1}H-NMR: δ 7.45 (s, 1H), 7.37 (d, 2H, J = 7.1 Hz), 7.09 (d, 2H, J = 7.1 Hz), 4.86 (s, 1H), 4.73 (s, 1H), 2.75 (s, 3H), 2.23 (s, 2H), 2.15 (s, 3H), 1.82 (s, 3H), 1.08 (s, 6H); ^{13}C-NMR: δ 168.7, 147.6, 143.9, 134.3, 128.8, 120.0, 114.7, 58.1, 46.6, 37.1, 26.0, 25.2, 24.8.

***N*-(1,2,2,4,4-Pentamethyl-1,2,3,4-tetrahydroquinolin-6-yl)acetamide (41).** The basic procedure of Faure *et al.*[19] was followed. A 250-mL, three-necked, round-bottomed flask, equipped with a magnetic stirrer, a septum, a reflux condenser and a nitrogen inlet, was charged with $AlCl_3$ (5.0 g, 37.4 mmol) in 75 mL of CH_2Cl_2. The flask was cooled at -70 °C (dry ice/acetone), and amide **40** (0.9 g, 3.4 mmol) in 15 mL CH_2Cl_2 was added dropwise. Stirring was continued overnight with a gradual warming to room temperature. The reaction was monitored by TLC. The reaction mixture was poured into crushed ice, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with saturated $NaHCO_3$, water, and saturated aqueous NaCl, then dried ($MgSO_4$), filtered, and concentrated to give a brown residue, which was chromatographed using 5-20% ethyl acetate in hexane to afford semisolid **41** (0.45 g, 53%). IR: 3289, 1655, 1610, 806 cm^{-1}; ^{1}H-NMR: δ 8.08 (s, 1H), 7.28-7.22 (m, 2H), 6.52 (d, 1H, *J* = 8.2 Hz), 2.72 (s, 3H), 2.08 (s, 3H), 1.74 (s, 2H), 1.26 (s, 3H), 1.19 (s, 3H); ^{13}C-NMR: δ 169.0, 142.9, 134.4, 128.3, 125.4, 123.8, 120.1, 118.6, 112.6, 54.5, 53.2, 52.7, 32.8, 31.7, 31.5, 28.1, 27.8, 24.5.

1,2,2,4,4-Pentamethyl-1,2,3,4-tetrahydroquinolin-6-amine (42). A 50-mL, round-bottomed flask, equipped with a magnetic stirrer, and a reflux condenser, was charged with the amide **41** (0.15 g, 0.6 mmol) in 10 mL of 70% (v/v) of H_2SO_4. The reaction mixture was refluxed overnight. After being allowed to cool to room temperature, 10 mL of water was added and the mixture was basified with 30% NaOH. The amine was extracted with ethyl acetate (3 × 15 mL). The organic extracts were dried (Na_2SO_4), filtered and concentrated to give **42** (0.15 g, 92%) as a brown residue. This compound was used without further purification. IR: 3336, 1623 cm^{-1}; ^{1}H-NMR: δ 6.64 (s, 1H), 6.50 (s, 2H), 3.64 (s, 2H), 2.69 (s, 3H), 1.74 (s, 2H), 1.28 (s, 6H), 1.17 (s, 6H); ^{13}C-NMR: δ 139.3, 137.2, 135.8, 114.7, 114.2, 114.0, 53.4, 32.1, 31.7, 27.4.

3-(1,2,2,4,4-Pentamethyl-1,2,3,4-tetrahydroquinolin-6-yl)-1-(4-nitrophenyl)thiourea (43). A 50-mL, round-bottomed flask equipped with a magnetic stirrer, reflux condenser and nitrogen inlet was charged with the amine **42** (0.1 g, 0.5 mmol) in 5 mL of dry THF. To the stirred solution was added 4-nitrophenyl isothiocyanate (0.1 g, 0.5 mmol), and stirring was continued under nitrogen overnight at room temperature. The solvent was removed, and the mixture was subjected to chromatography using 20-30% ether in hexane to afford **43** (0.18 g, 90%) as orange crystals, mp 151-153 ºC. IR: 3335, 1596, 1500, 1332, 1263, 851 cm^{-1}; ^{1}H-NMR: δ 8.17 (d, 2H, *J* = 9.3 Hz), 7.86 (br s, 2H), 7.78 (d, 2H, *J* = 8.8 Hz), 7.08 (d, 1H, *J* = 2.2 Hz), 7.02 (dd, 1H, *J* = 8.8, 2.2 Hz), 6.63 (d, 1H, *J* = 8.8 Hz), 2.82 (s, 3H), 1.81 (s, 2H), 1.31 (s, 6H), 1.28 (s, 6H); ^{13}C-NMR: δ 179.6, 144.7, 125.2, 124.7, 123.4, 123.1, 113.1, 54.9, 52.3, 32.9, 31.8, 31.4, 28.4. *Anal.* Calcd. For $C_{21}H_{26}N_4O_2S$: C, 63.28; H, 6.57; N, 14.06. Found: C, 63.06; H, 6.58; N, 13.92.

1-(4-Ethoxycarbonylphenyl)-3-(1,2,2,4,4-pentamethyl-1,2,3,4-tetrahydroquinolin-6-yl)thiourea (44). A 100-mL, round-bottomed flask, equipped with a magnetic stirrer, reflux condenser and nitrogen inlet, was charged with the amine **42** (0.77 g, 3.76 mmol) in 100 mL of dry THF. To the stirred solution was added 4-ethoxycarbonylphenyl isothiocyanate (0.9 g, 4.34 mmol), and stirring was continued under nitrogen overnight at room temperature. The solvent was removed, and the mixture was subjected to column chromatography using 20-40% ether in hexane to afford **44** (1.32 g, 82%) as a yellow solid, mp 154-155 ºC. IR: 3287, 1712, 1500, 1274 cm^{-1}; ^{1}H-NMR: δ 8.18 (d, 2H, *J* = 8.8 Hz), 7.88 (s, 1H), 7.84 (s, 1H), 7.78 (d, 2H, *J* = 8.8 Hz), 7.26 (ds, 1H, *J* = 2.2 Hz), 7.20 (dd, 1H, *J* = 2.2, 8.8 Hz), 6.80 (d, 1H, *J* = 8.8 Hz), 4.52 (q, 2H, *J* = 7.1 Hz), 2.99 (s, 3H), 1.98 (s, 2H), 1.54 (t, 3H, *J* = 7.1 Hz), 1.48 (s, 6H), 1.45 (s, 6H); ^{13}C-NMR: δ 180.1, 166.4, 130.7, 125.3, 123.5, 123.3, 113.0, 61.3, 54.9, 52.4, 32.9, 31.8, 31.4, 28.4, 14.7. *Anal.* Calcd. For $C_{24}H_{31}N_3O_2S$: C, 67.72; H, 7.34; N, 9.87. Found: C, 67.44; H, 7.18; N, 9.80.

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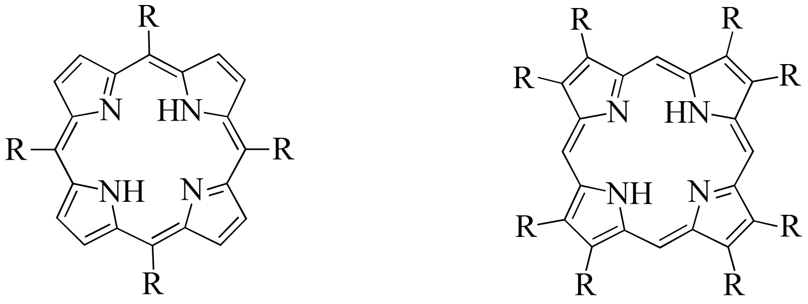
CHAPTER IV

SYNTHESIS OF CO-FACIAL PORPHYRINS

Introduction

Supramolecular chemistry has experienced rapid development within the last two decades. It is defined as chemistry beyond the molecule, bearing on the organized entities of higher complexity that result from the association of two or more chemical species held together by intermolecular forces.[1] The synthesis of well-defined molecular architectures will play a very crucial role because the incorporation of spatially-defined and orientationally-controlled steric and/or electronic features into molecules is essential for dictating non-covalent interactions. The forces responsible for the spatial organization between molecules include hydrogen bonding, metal coordination, hydrophobic interaction, van der Waals forces, π-π interaction, and electrostatic forces.[1] Studying the photophysical and electrochemical properties of these compounds is of great interest involving a variety of biomimetic, molecular self-assembly, host-guest chemistry, metal complexation, molecular machinery, and molecular imprinting… etc. The porphyrins represent ideal building blocks for the formation of supramolecular materials.[2]

Porphyrin is an aromatic system consisting of four pyrrole rings joined by four methine carbons (Figure 4.1). The electronic system of the porphyrin ring has a total of 22π electrons, only 18 of them participate in the aromatic stabilization. Due to the anisotropic effect from the porphyrin ring current, the shielded N-H protons appear at very high field (-2 to -4 ppm) in the ^{1}H-NMR spectrum, while the peripheral protons are deshielded and appear at 8-10 ppm.[3] These protons have topological diversity, minimal conformational flexibility, and can be readily functionalized at several different sites, and thus fine-tuned to self-assemble and self-organize in predefined architectures.[4]



1

2

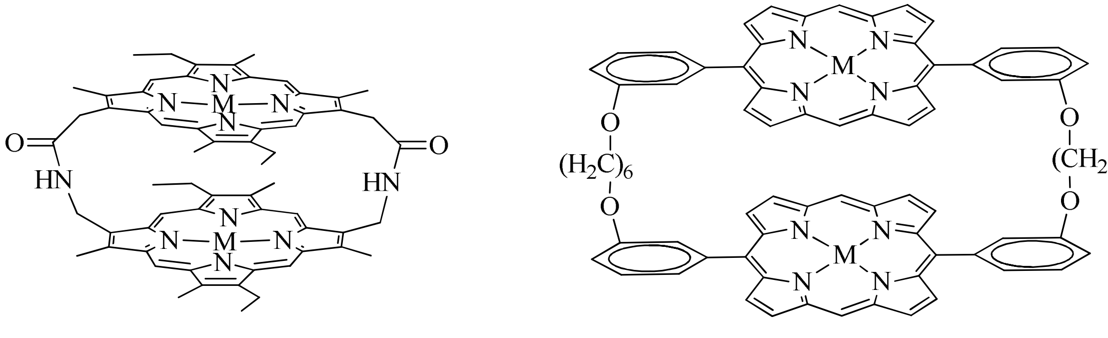
meso-substituted porphyrins

β-substituted porphyrins

Figure 4.1. Basic structures of *meso*-substituted and β-substituted porphyrins.

Porphyrins have strong absorption bands in the visible light region,[5] and their remarkable photoelectronic properties make them useful in various molecular devices. Zinc and magnesium porphyrins are coordinated by nitrogen ligands, and the coordination bond can exchange rapidly. This feature has been applied to the formation of dynamic supramolecular porphyrin complexes. Other stable metal porphyrins, such as Fe(III), Co(III), and Ru(II)CO porphyrins, also bind nitrogen ligands strongly. They are not, however, suitable for dynamic systems because their exchange rates are too slow.[5]

Aromatic stacking between porphyrins is a frequently encountered motif arising from π-stacking and/or crystal packing forces. Cofacially stacked dimetalloporphyrins have the ability to facilitate catalytic proton coupled electron transfer (PCET) for the reduction of small molecules in the binding pocket.[6] Moreover, columnar assemblies of aromatic building blocks may also be induced through interactions of peripheral substituents.[7] A number of reports showed the formation of co-facial porphyrins which were joined by different linkers (Figure. 4.2) such as an amide and ether.[8,9]



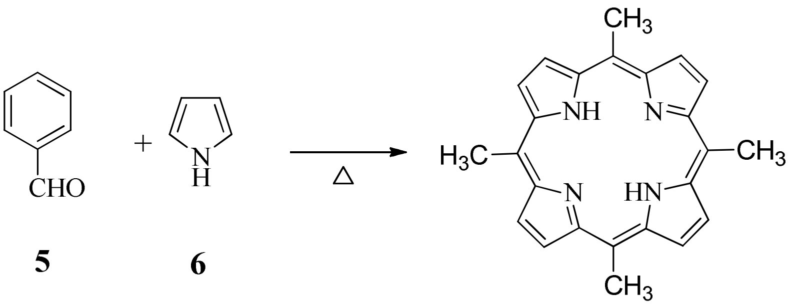
3 **4**

Figure 4.2. Face to face porphyrins with amide and ether linkages.

Synthesis of Porphyrins

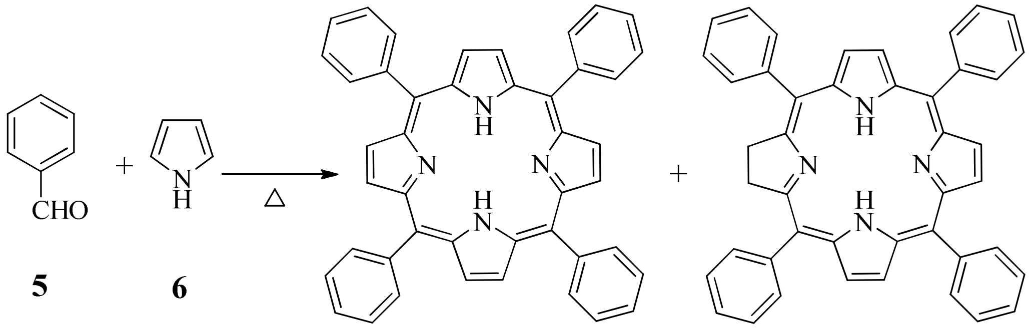
Rothemund method

The chemistry of meso-substituted porphyrins had its genesis with the work of Rothemund in 1935.[10] He first investigated the synthesis of *meso*-tetramethylporphyrin by reaction of acetaldehyde and pyrrole **(6)** in methanol at various temperatures (Figure 4.3). This method has little application because of the low yield and the production of chlorin (dihydroporphyrin) **9** as a byproduct (Figure 4.4). This method does not have any major advantages.[3]



5 6 7

Figure 4.3. Rothemund method for the synthesis of *meso*-tetramethylporphyrin.

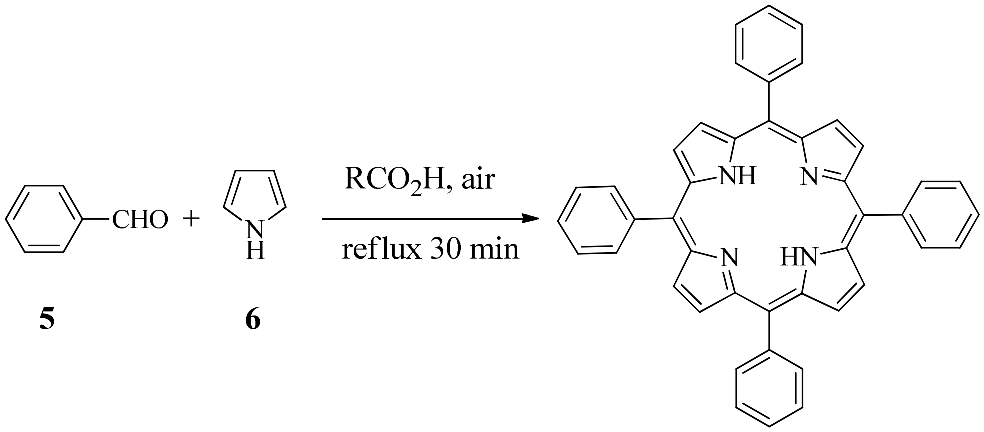


5 6 8 9

Figure 4.4. Formation of cholrin as a byproduct along with porphyrin.

Adler method

In the mid-1960s, Adler, Longo and coworkers reexamined the synthesis of *meso*-substituted porphyrins.[3,11,12] They performed a condensation of benzaldehyde **(5)** and pyrrole **(6)** (0.002 *M*) in a variety of acidic solvents at reflux in glassware open to the atmosphere (Figure 4.5). The main solvents employed were acetic acid and propionic acid, and the reaction was performed at high temperature. A number of aryl-substituted porphyrins were prepared in higher yields than the Rothemund method. This method can be used for the synthesis of porphyrins on a preparative scale from aldehydes that are relatively stable. The major limitations of the Adler method occur with aldehydes bearing substituents that do not survive refluxing with propionic acid, aryl aldehydes, (2,6-disubstitution) and aliphatic aldehydes.[3]



8

Figure 4.5. Adler method for porphyrin synthesis.

Lindsey method

The Lindsey method was performed in two steps in one flask under mild conditions.[3,13-15] In the first step, a solution of pyrrole and benzaldehyde (10 mM each) in CH_2Cl_2 at room temperature was treated with trifluoroacetic acid or BF_3-etherate (Figure 4.6). The ensuing condensation was found to plateau after 30-60 min. In the second step, a stoichiometeric quantity of DDQ or *p*-chloranil was added, causing room temperature conversion of the porphyrinogen to the porphyrin (Figure 4.6). This method has a broad scope because it provides higher yields than the previous methods. It can be used for aldehydes which are unstable under Adler conditions and with fewer by-products being generated. Lindsey's method is preferable for the preparation of porphyrins from mixed aldehydes that are hard to purify using the Adler method. The best application of the Lindesy method used 2,6-disubstituted aryl aldehydes and aliphatic aldehydes.[3,14]

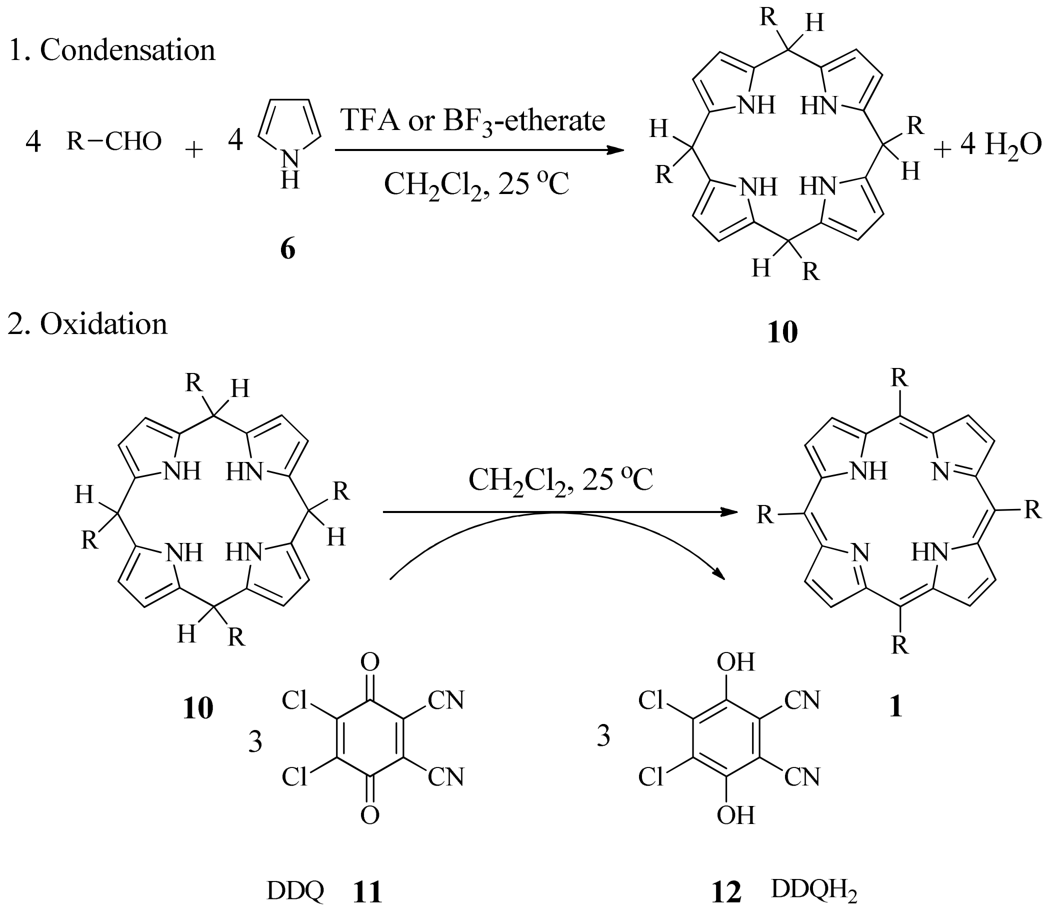


Figure 4.6. Two-step porphyrin synthesis (Lindsey method).

Besides the previous methods where pyrrole-aldehydes are the only reactants for porphyrin synthesis, porphyrins can also be synthesized via condensations of a dipyrromethane and an aldehyde (Figure 4.7). Certain *trans*-A_2B_2-porphyrins can be obtained by condensations of a dipyrromethane and an aldehyde. This condensation usually yields not only the desired *trans*-A_2B_2-porphyrin, but also other porphyrins such as *cis*-A_2B_2-isomers and A_3B porphyrins. This major limitation is due to acid-catalyzed polypyrrolic rearrangement called “scrambling” as shown in Figure 4.7.[16]

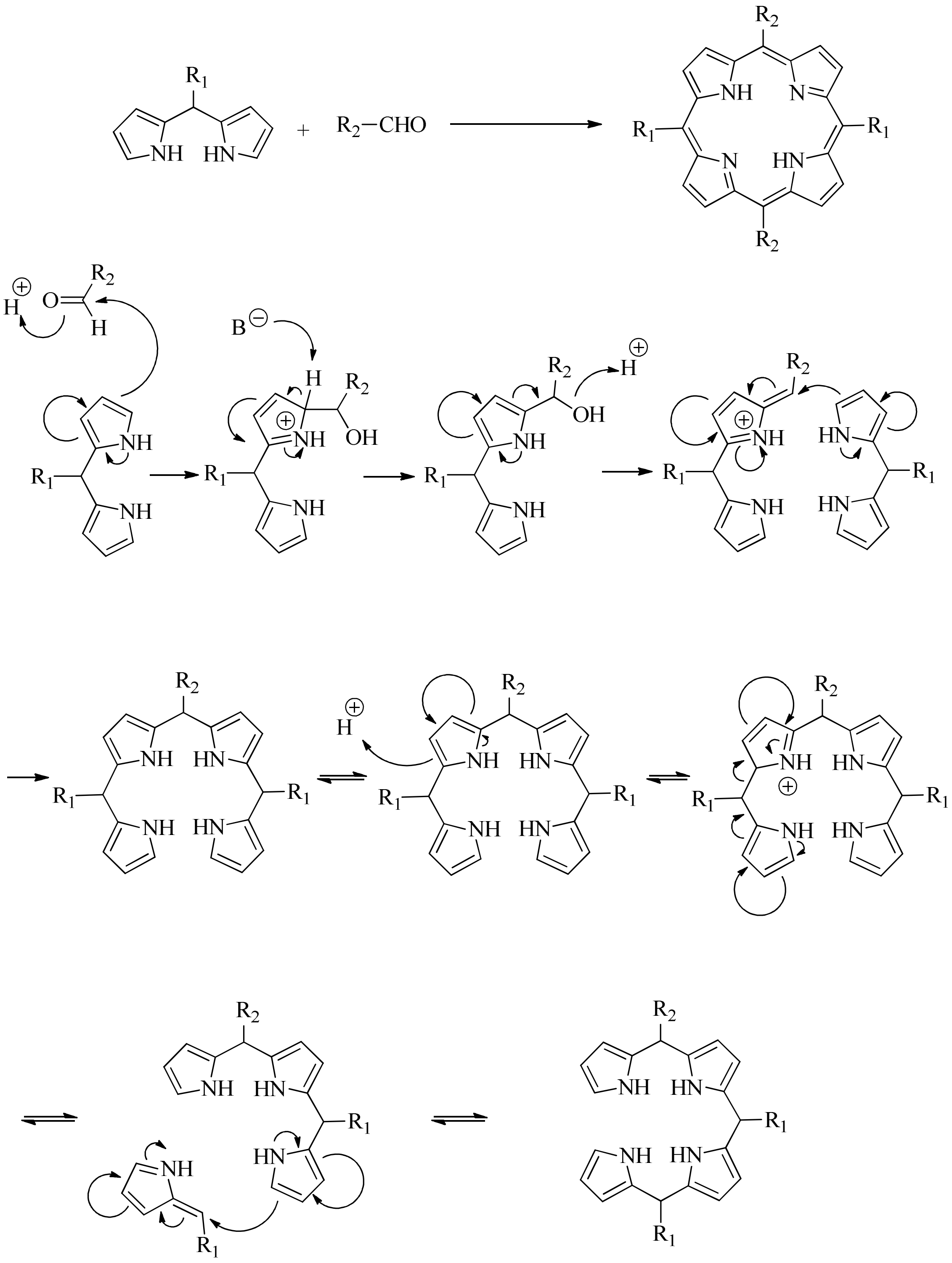


Figure 4.7. The mechanism of scrambling during the synthesis of *trans*-A_2B_2 porphyrins.

Our aim was to synthesize *trans*-A_2B_2 porphyrins substituted with polar functional groups, such as OH, NH_2, COOH and a pyridine ring and to examine their NMR, IR, UV-VIS spectroscopic and fluorescence properties. The polar functional groups have the ability to H-bond with other molecules to form a central cavity between themselves or to form flexible non-slipped, co-facially stacked porphyrins with different covalent and hydrogen bonding linkers. These structures were predicted to provide unique geometric systems that would be capable of binding small molecules in an interior pocket.

Dipyrromethanes were synthesized by heating freshly distilled pyrrole with an appropriate aldehyde with or without an acid catalyst (Figure 4.8).[15] All porphyrins in this work were prepared by a condensation of dipyrromethane derivatives with an aldehyde in acetic acid in a system open to air for oxidation. Dipyrromethanes and porphyrins were purified by column chromatography. Certain Zn(II) complexes were synthesized by reaction of Zn(II) acetate with a porphyrin in a proper solvent as shown in Figures 4.9, 4.10 and 4.11.

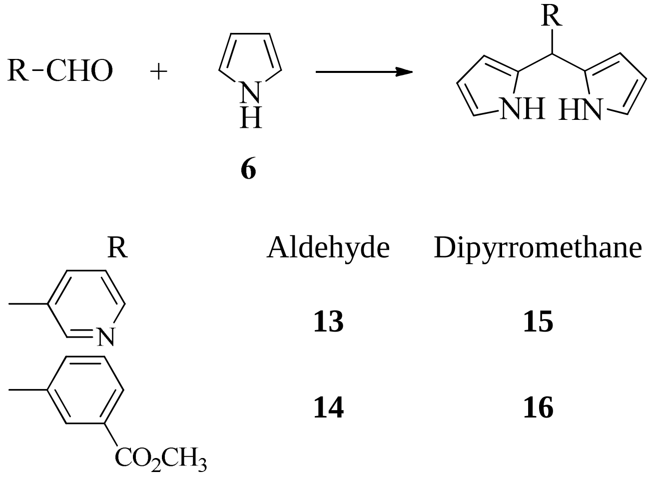


Figure 4.8. Synthesis of porphyrins via a dipyrromethane intermediate.

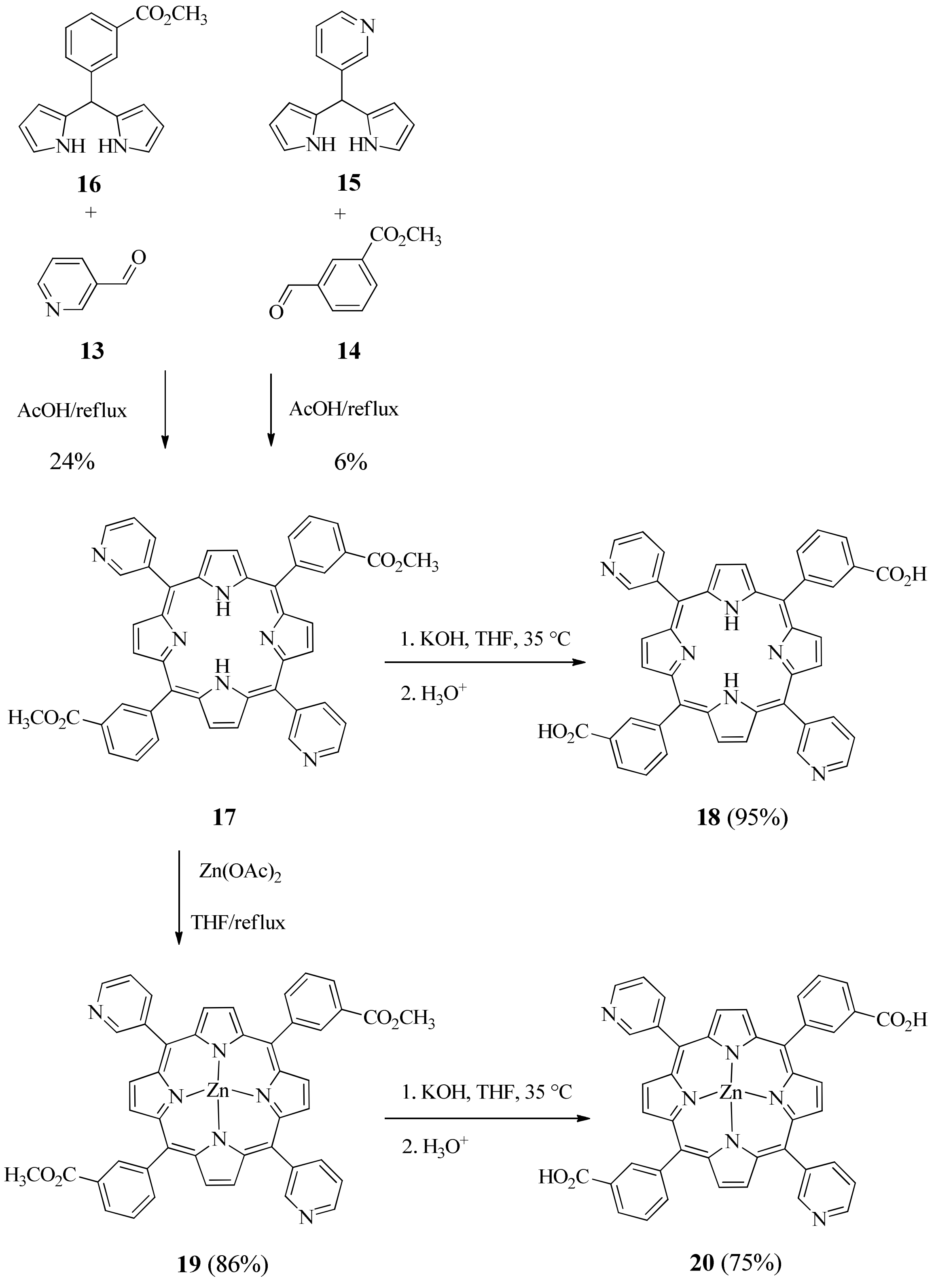


Figure 4.9. Synthesis of porphyrins **17-18** and their Zn(II) complexes **19-20**.

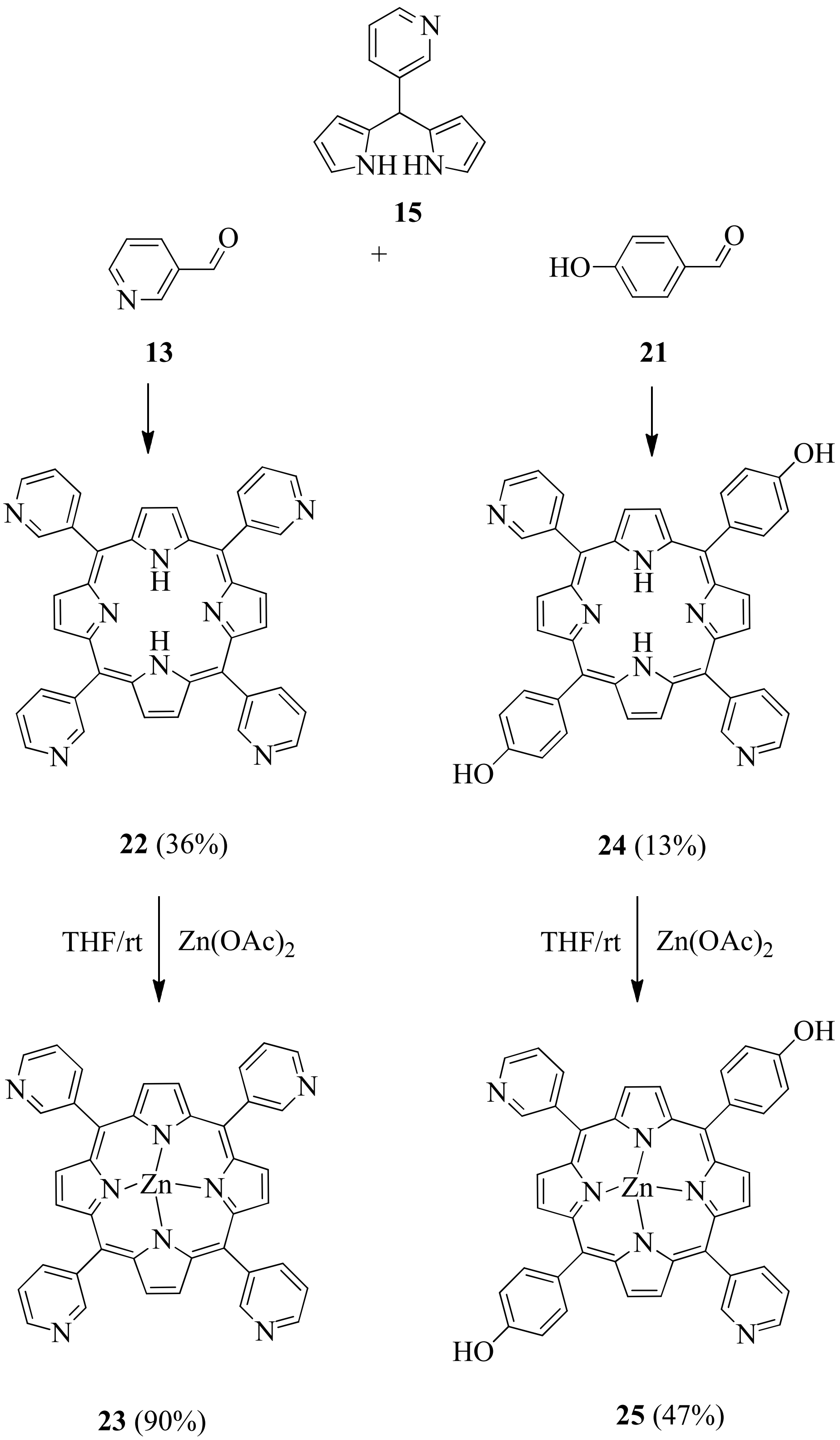
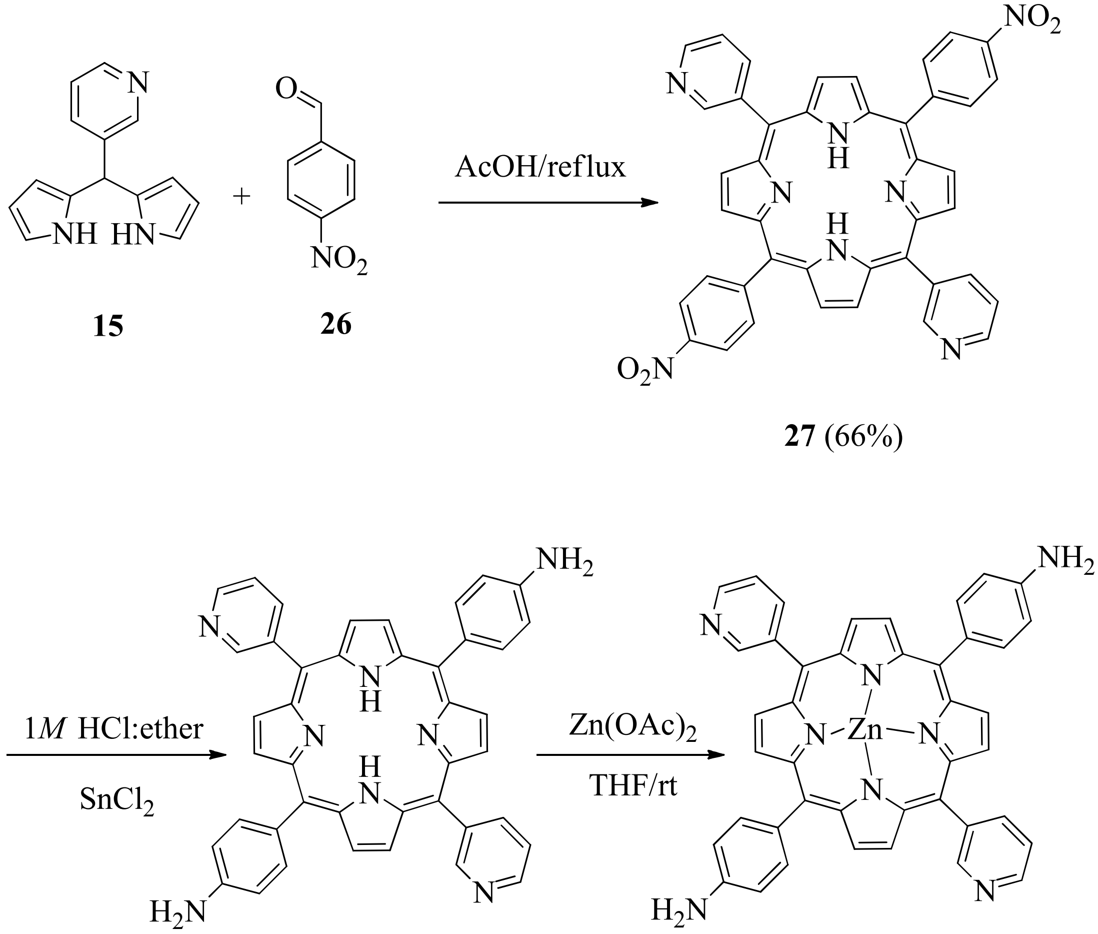


Figure 4.10. Synthesis of porphyrins **22** and **24** and their Zn(II) complexes **23** and **25**.



15 **26** **27** (66%)

28 (92%) **29** (75%)

Figure 4.11. Synthesis of porphyrins **27** and **28** and the Zn(II) complex **29**.

Results and Discussion

In this project a number of *trans*-A_2B_2-prophyrins containing pyridine moieties and phenyl groups substituted with polar functional groups, such as OH, NH_2 and CO_2H, were synthesized and characterized by NMR, IR and UV-VIS spectroscopy. The Zn(II) complexes of these polar porphyrins were solids and had limited solubility in common solvents, such as $CHCl_3$, $CH_3CO_2C_2H_5$, MeOH, CH_3CN, and DMSO, which made it difficult to study the H-bonding interactions between porphyrin systems. This impaired solubility is believed to be due to the presence of OH, NH_2, CO_2H groups and the pyridine ring in the porphyrin structure which coordinates with the Zn(II) metal of other molecules (Figure 4.12). Thus, the usual solvents sited above are, unfortunately, not usable for the study of intermolecular bonding forces.

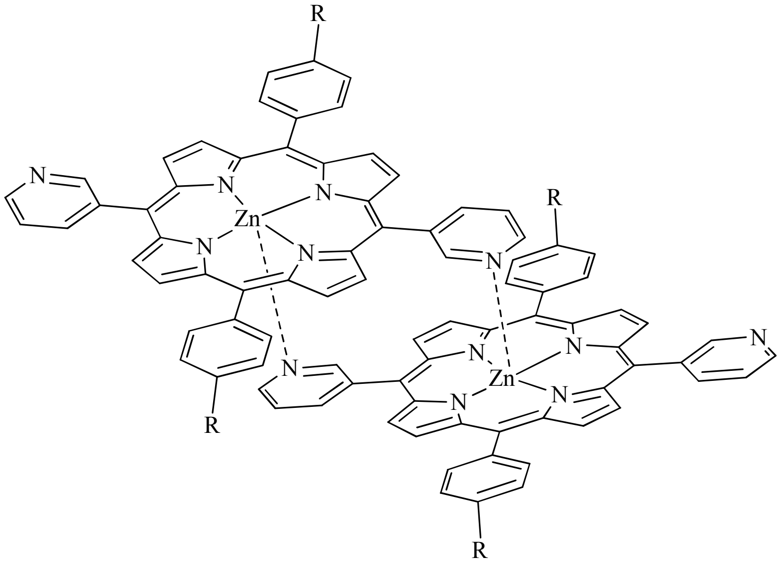


Figure 4.12. Coordination of the pyridine ring with the Zn(II) porphyrin.

Experimental Section

Chemicals were purchased from commercial sources and, unless specified, were used without further purification. Dipyrromethane derivatives were prepared from freshly distilled pyrrole. Reactions were monitored by TLC on hard layer silica gel GF plates (Analtech No. 21521) using UV detection. Column chromatography was performed on silica gel (Davisil®, grade 62, 60-200 mesh). Both ^{1}H-NMR and ^{13}C-NMR spectra were acquired in $CDCl_3$ or DMSO-d_6 using a Varian Inova 300 MHz or 400 MHz NMR spectrometer. Chemical shifts (δ) are expressed in ppm relative to residual chloroform (^{1}H: 7.26 ppm, ^{13}C:77.16 ppm) or to TMS (0.00 ppm). Fourier Transform Infrared (FT-IR) measurements were performed on a Varian 800 FT-IR spectrometer, and UV-VIS spectra were recorded on a Cary 5000 UV-VIS-NIR spectrophotometer.

3-Pyridyldipyrromethane (15). The procedure of Lindsey[15] was followed. A 500-mL, round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser was charged with nicotinaldehyde **(13)** (10.17 g, 94.95 mmol) in freshly distilled pyrrole **(6)** (100 mL). The reaction mixture was stirred at 58 ºC for 24 h. The reaction mixture was evaporated, and the product was purified by chromatography using ethyl acetate:hexane (40:60). The product was isolated as a fluffy yellow solid (12 g, 57%), mp 166 ºC (lit[15] mp 166-167 ºC). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.6 (s, 2H), 8.40-8.38 (m, 2H), 7.50 (dd, 1H, J = 7.8, 1.8 Hz), 7.30 (dd, 1H, J = 7.8, 4.8 Hz), 6.63 (d, 2H, J = 1.8 Hz), 5.91-5.89 (m, 2H), 5.65 (s, 2H), 5.40 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 149.3, 147.3, 139.1, 135.4, 132.2, 123.2, 117.2, 107.0, 106.2, 41.3.

Methyl 3-(Di(*1H*-pyrrol-2-yl)methyl) benzoate (16). Literature procedures were followed[17]. A 250-mL, three-necked, round-bottomed flask, equipped with a magnetic stirrer, a septum, a condenser and an argon inlet, was charged with methyl 3-formylbenzoate **(14)** (2 g, 12.19 mmol) in freshly distilled pyrrole (37 mL). The mixture was purged with argon for 15 min. Trifluoroacetic acid (0.2 mL) was added, and the mixture stirred for 90 min at room temperature. A saturated aqueous solution of $NaHCO_3$ was added, and the organic materials were extracted with CH_2Cl_2 (3 × 75 mL). The CH_2Cl_2 extracts were combined, washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed using ethyl acetate:hexane (30:70) to afford **16** (1.9 g, 56%) as a yellow solid mp 125-127 ºC (lit.[18] mp 124-127 ºC). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.6 (s, 2H), 7.87 (d, 2H, *J* = 9 Hz), 7.31 (d, 2H, *J* = 9 Hz), 6.62 (s, 2H), 5.91 (m, 2H), 5.66 (s, 2H), 5.45 (s, 6H), 3.83 (s, 3H).

5,10-Bis(3-pyridyl)-15,20-bis(3-methoxycarbonylphenyl)porphyrin (BPMP) (17). A 500-mL, round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser, was charged with dipyrromethane **16** (0.8 g, 2.86 mmol) and nicotinaldehyde **(13)** (0.32 g, 2.98 mmol) in acetic acid (350 mL). The reaction mixture was refluxed for 5 h. After cooling to room temperature, the reaction mixture was concentrated on a rotary evaporator. A saturated aqueous solution of $NaHCO_3$ was added to neutralize the acid, and the organic material was extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, evaporated, and then chromatographed using 20-60% ethyl acetate in hexane. Porphyrin-BPMP **17** was isolated as a purple solid (0.51 g, 24%), mp > 300 ºC. IR (neat): 3329, 2951, 1731, 1685, 1408, 1247, 802, 733, 712 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.46 (s, 2H), 9.06 (d, 2H, *J* = 4.8 Hz), 8.89-8.81 (m, 12H), 8.53-8.49 (m, H), 8.41 (d, 2H, *J* = 6 Hz), 7.86 (t, 2H, *J* =

7.8 Hz), 7.76 (t, 2H, *J* = 7.8 Hz), 3.96 (s, 6H), -2.82 (s, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 154.0, 149.6, 142.4, 141.3, 138.1, 137.9, 135.2, 129.7, 127.4, 122.4, 119.9, 116.7, 52.8.

5,10-Bis(3-pyridyl)-15,20-bis(3-carboxyphenyl)porphyrin (BPCP) (18). The procedure of Goldberg[19] was followed. A 50-mL, round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser, was charged with porphyrin-BPMP **17** (0.35 g, 0.47 mmol) in THF (10 mL) and 6% methanolic KOH (4 mL). The mixture was stirred at 35 ºC for 6 h. After cooling to room temperature, the solvent was evaporated, water (75 mL) was added, and the mixture was acidified with 1*M* HCl to a pH of 4-6. The porphyrin was extracted with ethyl acetate (3 × 100 mL). The organic extracts were evaporated to dryness to afford prophyrin **18** (0.3 g, 95%) as brown-purple solid, mp > 300 ºC. IR (neat): 3330, 1699, 1582, 1297, 1248, 972, 796 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 13.28 (s, 2H), 9.36 (s, 2H), 9.03 (dd, 2H, *J* = 3.6, 0.9 Hz), 8.83 (s, 8H), 8.67 (m, 4H), 8.47 (br s, 2H), 8.39 (d, 2H, *J* = 6 Hz), 7.95 (t, 2H, *J* = 5.7 Hz), 7.88 (t, 2H, *J* = 7.8 Hz), -2.98 (s, 2H); MS: *m/z* Calc. for $C_{44}H_{28}N_6O_4$ 704.72, Found 704.

BPMP Zn(II) Complex (19). A 100-mL, round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser, was charged with porphyrin-BPMP **17** (0.15 g, 0.20 mmol) in THF (50 mL), zinc acetate dihydrate (0.5 g) and methanol (3 mL). The reaction mixture was refluxed at 60 ºC for 2 h. The solvent was evaporated, and the product was washed with water, and dried under vacuum to afford porphyrin **19** as a purple solid (0.15 g, 92%), mp > 300 ºC.

BPCP Zn(II) Complex (20). A 50-mL, round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser, was charged with porphyrin **19** (0.10 g, 0.13

mmol) in THF (10 mL) and 6% methanolic KOH (2 mL). The mixture was stirred at 35 ºC for 6 h. After cooling to room temperature, the solvent was evaporated, water (10 mL) was added, and the mixture was acidified with 1*M* HCl to a pH of 6-7. The porphyrin was extracted with ethyl acetate (3 × 50 mL). The organic extracts were evaporated to dryness to afford porphyrin **20** (0.06 g, 66%) as purple solid mp > 300 ºC. IR (neat): 3400, 1728, 1436, 1284, 1224, 995, 794 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) 9.29 (br s, 4H), 8.96 (br s, 4H), 8.77-8.72 (dd, 8H, *J* = Hz), 8.62 (br s, 4H), 8.58 (m, 4H), 8.32-8.27 (m, 4H), 7.82 (m, 4H); MS: *m/z* Calc. for $C_{44}H_{26}N_6O_4Zn$ 767.39, Found 768.

5,10,15,20-Tetra(3-pyridyl)porphyrin (TPP) (22). A 500-mL, round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser, was charged with dipyrromethane **15** (0.40 g, 1.79 mmol) and aldehyde **13** (0.20 g, 1.86 mmol) in acetic acid (250 mL). The reaction mixture was refluxed for 5 h and, after cooling to room temperature, the reaction mixture was concentrated on a rotary evaporator. A saturated aqueous solution of $NaHCO_3$ was added to neutralize the acid, and the organic material was extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, evaporated, and then chromatographed using 20-60% ethyl acetate in dichloromethane. Porphyrin **22** (0.19 g, 17%) was isolated as a purple solid, mp > 300 ºC. IR (neat): 3307, 2952, 1668, 1406, 1183, 966 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.48 (s, 4H), 9.07 (d, 4H, *J* = 3.9 Hz), 8.88 (s, 8H), 8.5 (d, 4H, *J* = 6.6 Hz), 7.78 (t, 4H, *J* = 4.8 Hz), -2.80 (s, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 153.4, 149.2, 140.9, 137.6, 131.4, 122.0, 116.6.

TPP Zn(II) Complex (23). A 50-mL, round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser, was charged with porphyrin **22** (0.10 g, 0.16 mmol), $CHCl_3$ (15 mL), zinc acetate dihydrate (0.15 g) and methanol (3 mL). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated, and the product was washed with water and dried under vacuum to afford porphyrin **23** (0.09 g, 90%) as a purple solid, mp > 300 ºC. IR (neat): 3042, 1669, 1471, 1184, 994, 788 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6) δ 9.31 (s, 4H), 8.99 (dd, 4H, J = 4.8, 1.6 Hz), 8.77 (s, 8H), 8.58 (br s, 4H), 7.85 (td, 4H, J = 7.6, 2 Hz); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 117.6, 122.8, 132.6, 135.2, 138.9, 141.2, 149.4, 150.1, 153.4.

5,10-Bis(3-Pyridyl)-15,20-bis(4-hydroxyphenyl)porphyrin (BPHP) (24). A 500-mL, round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser was charged with dipyrromethane **15** (0.5 g, 2.24 mmol) and 4-hydroxybenzaldehyde **(21)** (0.27 g, 2.24 mmol) in acetic acid (250 mL). The reaction mixture was refluxed for 5 h and, after cooling to room temperature, was concentrated on a rotary evaporator. A saturated solution of $NaHCO_3$ was added to neutralize the acid, and the organic material was extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, evaporated and then chromatographed using 20-60% ethyl acetate in dichloromethane. The porphyrin **24** (0.1 g, 13%) was obtained as a purple solid. IR (neat): 3100, 1671, 1468, 1226, 966, 765, 711 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6) δ 9.99 (s, 2H), 9.37 (s, 2H), 9.04 (d, 2H, J = 4.8 Hz), 8.92 (d, 4H, J = 5.1 Hz), 8.81 (d, 4H, J = 5.1 Hz), 8.66 (d, 2H, J = 8 Hz), 8.01 (d, 4H, J = 7.2 Hz), 7.90 (t, 2H, J = 7.6 Hz), 7.21 (d, 4H, J = 7.2 Hz), -2.93 (s, 2H).

BPHP Zn(II) Complex (25). A 100-mL, round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser, was charged with porphyrin **24** (0.44 g, 0.67 mmol), CH_2Cl_2 (25 mL), zinc acetate dihydrate (0.20 g) and methanol (3 mL). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated, and the product was washed with water, and dried under vacuum to afford porphyrin **25** (0.22 g, 91%) as a purple solid, mp > 300 ºC. IR (neat): 3400, 1572, 1341, 1269, 994, 793, 715 cm^{-1}; ^1H-NMR (300 MHz, DMSO-d_6) δ 9.88 (s, 2H), 9.28 (s, 2H), 8.95 (d, 2H, J = 3.9 Hz), 8.86 (d, 4H, J = 4.8 Hz), 8.71 (d, 4H, J = 4.8 Hz), 8.58 (d, 2H, J = 7.2 Hz), 7.96 (d, 4H, J = 8.1 Hz), 7.85 (t, 2H, J = 6.2 Hz), 7.18 (d, 4H, J = 8.1 Hz); MS: *m/z* Calc. for $C_{42}H_{26}N_6O_2Zn$ 711.38, Found 712.

5,10-Bis(3-pyridyl)-15,20-bis(4-nitrophenyl)porphyrin (BPNP) (27). A 250-mL, round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser, was charged with dipyrromethane **15** (0.2 g, 0.89 mmol), 4-nitrobenzaldehyde **(26)** (0.13 g, mmol) and a mixture of acetic acid and propionic acid (50 mL, 32:18). The resulting solution was refluxed for 6 h, and after cooling to room temperature, the mixture was concentrated on a rotary evaporator. A saturated solution of $NaHCO_3$ was added to neutralize the acid, and the organic material was extracted with CH_2Cl_2 (3 × 25 mL). The organic extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, evaporated, and then chromatographed using 20-60% ethyl acetate in dichloromethane. The porphyrin **27** (0.19 g, 61%) was isolated as a purple solid. IR (neat): 3319, 2924, 1689, 1514, 1344, 848, 799 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ 9.43 (s, 2H), 9.07 (dd, 2H, J = 5.1, 1.8 Hz), 8.86-8.80 (m, 8H), 8.64 (d, 4H, J = 9 Hz), 8.53 (d, 2H, J = 7.5 Hz), 8.41 (d, 4H, J = 7.8 Hz), 7.78 (t, 2H, J = 6.9, 2.3 Hz), -2.84 (s, 2H).

5,10-Bis(3-pyridyl)-15,20-bis(4-aminophenyl)porphyrin (BPAP) (28). The Hatay procedure was followed.[20] A 50-mL, round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser, was charged with $SnCl_2.H_2O$ (1.5 g) and a mixture of HCl/ether (1*M*, 20 mL). Porphyrin **27** (0.1 g, 0.14 mmol) in $CHCl_3$ (10 mL) was added, and the reaction mixture was stirred at room temperature for 8 h in the dark. The resulting mixture was poured onto crushed ice and, when the ice melted, $CHCl_3$ (50 mL) was added. The organic layer was washed with water and then with 10% solution of NaOH and saturated aqueous NaCl. The organic layer was dried (Na_2SO_4), filtered, and concentrated to afford porphyrin **28** (0.083 g, 92%) as a purple solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.44 (s, 2H), 9.03 (d, 2H, *J* = 4.5 Hz), 8.97 (d, 4H, *J* = 4.5 Hz), 8.77 (d, 4H, *J* = 4.5 Hz), 8.50 (d, 2H, *J* = 7.2 Hz), 7.97 (d, 4H, *J* = 7.8 Hz), 7.74 (t, 2H, *J* = 7.5 Hz), 7.08 (d, 4H, *J* = 7.8 Hz), -2.78 (s, 2H).

BPAP Zn(II) Complex (29). A 50-mL, round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser, was charged with porphyrin **28** (0.20 g, 0.31 mmol), zinc acetate dihydrate (0.20 g) and methanol (3 mL). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated, and the product was washed with water, and dried under vacuum to afford porphyrin **29** (0.2 g, 75%) as a green solid, mp > 300 ºC. IR (neat): 3300, 1504, 1392, 831, 695 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-*d*$_6$) δ 9.25 (s, 2H), 8.93 (s, 2H), 8.89 (d, 4H, *J* = 4.8 Hz), 8.66 (d, 4H, *J* = 4.8 Hz), 8.55 (d, 2H, *J* = 6.8 Hz), 7.83-7.77 (m, 6H), 6.94 (d, 2H, *J* = 8.4 Hz), 5.46 (s, 2H); ^{13}C-NMR (100 MHz, DMSO-*d*$_6$) δ 153.5, 150.9, 149.5, 148.8, 141.2, 139.3, 135.9, 133, 131.4, 130.4, 122.7, 122.5, 119.2, 116.6, 112.9; MS: *m/z* Calc. for $C_{42}H_{28}N_8Zn$ 709.3, Found 710.

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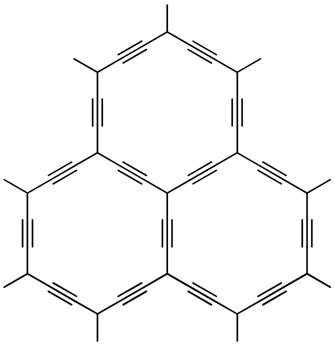
CHAPTER V

PHENYLACETYLENE MACROCYCLES

Introduction

In recent years, shape persistent arylene ethynylene macrocycles have been extensively investigated because of their potential as functional materials and host-guest systems, aggregation/adsorption phenomena, including solution state aggregation, liquid crystallinity and surface adsorption (Figure 5.1).[1] Their rigid backbones give large molecular surfaces that organize into ordered structures. These large supramolecular building blocks generate π-stacked structures in solution, noncollapsable nanoporous solids, and tubular ordered fluid phases. Conformationally, they are flexible rings which



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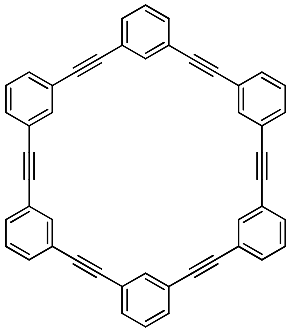

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Figure 5.1. Shape persistent arylene ethynylene macrocycles.

have a regular repeating unit with few degrees of conformational freedom. The ethynylene functional group is an attractive building block for these structures as a result of the potential for extended conjugation, simple linear geometry, pure carbon composition, and accessibility through a wide range of synthesis.[2] Moreover, the ability of the acetylene linkage to transmit electronic perturbation within conjugated systems makes them useful components in the construction of molecular wires, conjugated dendrimers and optical systems.[3-5]

Such molecules have been synthesized by homocoupling (e.g. Glaser reaction)[6] and cross-coupling reactions. Two types of monomers are required, whether for homocoupling or cross-coupling reactions for cyclooligomerization (Figure 5.2).[7] A difunctionalized monomer AB (which has two different functional groups A and B on the same molecule, and A can only react with B) is representative of cross-coupling cyclooligomerization, while a difunctionalized AA monomer (two identical functional groups A on the same molecule, and A can react with B) is representative of homocoupling cyclooligomerization. Ring closure occurs mainly by intramolecular interaction between the terminal functional groups. The main disadvantage of these coupling-based approaches is the formation of higher oligomers (overshooting) which is impossible to prevent undesired bond formation that lowers the yield of the desired product.[7]

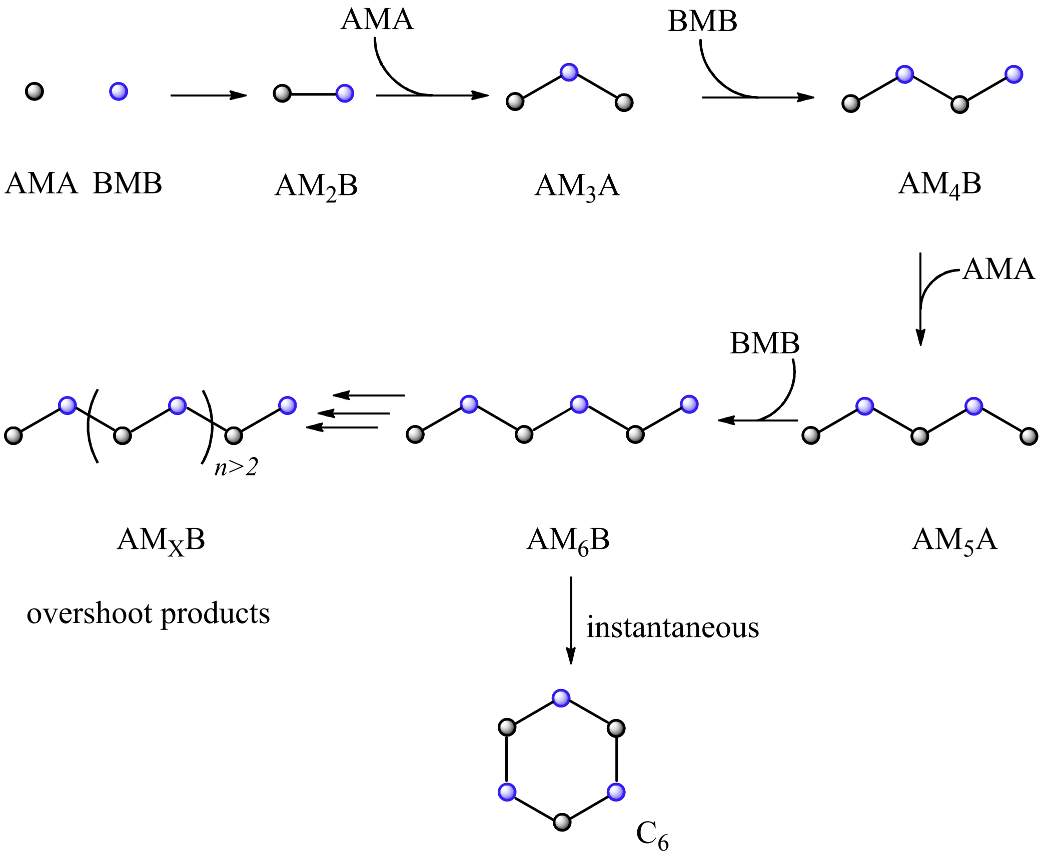

Figure 5.2. Reaction pathways for oligomerization and cyclohexamer formation from A_2- and B_2-type monomers. AMA = A monomer A **(9)** and BMB = B monomer B **(11)**.

Our aim in this project was to prepare a phenylacetylene cyclic structure with the functional group NH_2 in its central cavity. This functional group is able to complex with metals. The promise of these compounds is that they can be used for purification of water polluted with radioactive and heavy metals. They may also be able to trap small molecules.

Chemistry

Starting from aniline **3**, it was possible to obtain 4-iodoaniline (**4**) (51%) by iodination of aniline[8] via reaction with iodine and $NaHCO_3$ in aqueous solution. Acetylation of compound **4** with acetic anhydride formed the protected amine compound **5** (87%). Sonogashira coupling reaction[9] of **5** using $Pd(PPh_3)_4$, CuI and 1-hexyne produced compound **6** (84%).[10] The corresponding alkane derivative **7** (84%) was obtained by reduction of the alkyne **6** using triethylsilane (TES) and Pd/C 10% in methanol.[11] Hydrolysis of the amide group in **7** using 70% H_2SO_4 afforded the amine **8** (98%). Iodination[8] of **8** provided the diiodo derivative **9** (70%). Sonogashira coupling[9] with 2 equivalents of trimethylsilyl acetylene produced disilylated compound **10** (73%). Compound **11** was obtained (79%) by desilylation of **10** using K_2CO_3 in methanol.[12] For cyclization to form the phenylacetylene compound **12**, compounds **9** and **11** should react under Sonogashira coupling conditions (Figure 5.3).

Results and Discussion

All compounds in Figure 5.2 were obtained in high yields except for the last step. Chromatography of the reaction mixture showed that overshooting occurred and gave by-products which could not be separated.

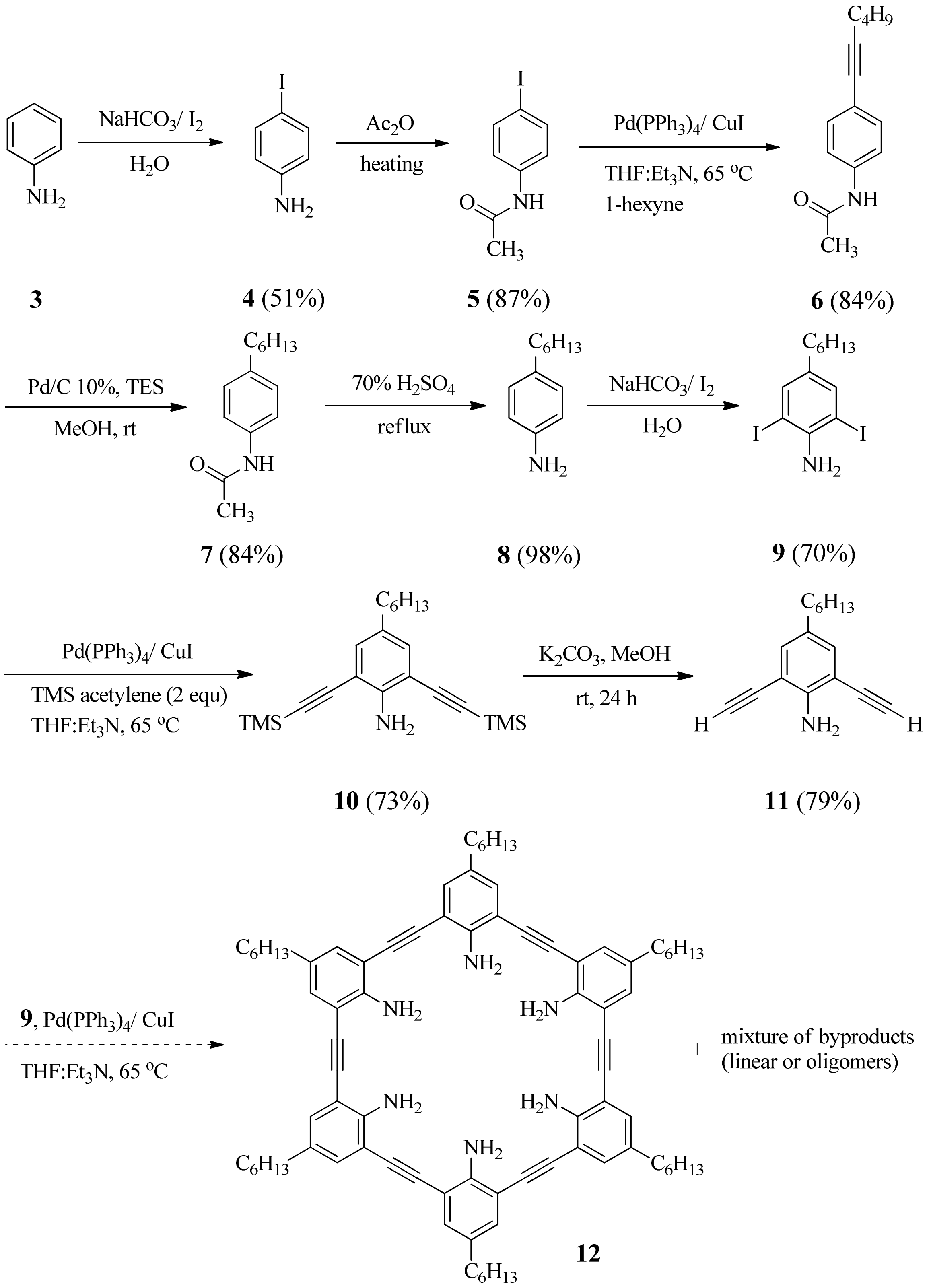

Figure 5.3. Proposed synthesis of phenylacetylene macrocycles such as **12**.

Experimental Section

Chemicals were purchased from commercial sources and, unless specified, were used without further purification. Sonogashira coupling reactions were performed under argon by using dry THF and triethylamine. Reactions were monitored by TLC on hard layer silica gel GF plates (Analtech No. 21521) using UV detection. Column chromatography was performed on silica gel (Davisil®, grade 62, 60-200 mesh). Both ^{1}H-NMR and ^{13}C-NMR spectra were acquired in $CDCl_3$ or DMSO-d_6 using a Varian Inova 300 MHz or a 400 MHz NMR spectrometer. Chemical shifts (δ) are expressed in ppm relative to residual chloroform (^{1}H: 7.26 ppm, ^{13}C: 77.16 ppm) or to TMS (0.0 ppm). Fourier Transform Infrared (FT-IR) measurements were performed on a Varian 800 FT-IR spectrometer. UV-VIS spectra were recorded on Cary 5000 UV-VIS-NIR spectrophotometer.

***N*-(4-Iodophenyl)acetamide (5).** A 250-mL, round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser, was charged with acetic anhydride (20 mL) and 4-iodoaniline **(4)** (1 g, 4.56 mmol). The mixture was heated in a water bath for 30 min. The hot solution was poured onto crushed ice, filtered, washed with water and dried under vacuum to afford **5** (1.05 g, 87%) as a yellow-white solid, mp 184 (lit.[13] 181-185 ºC).

***N*-(4-*n*-Hexyn-1-yl)phenyl)acetamide (6).).** A 250-mL, three-necked, round-bottomed flask, equipped with a magnetic stirrer, a septum, a condenser and a nitrogen inlet was charged with *N*-(4-iodophenyl)acetamide (**5**) (0.5 g, 1.90 mmol), triethylamine (10 mL) and dry THF (10 mL). The resulting solution was purged with argon for 20 min.

$Pd(PPh_3)_4$ (0.08 g, 0.07 mmol), CuI (0.032 mg, 0.16 mmol) and 1-hexyne (0.17 g, 2.07 mmol) were then added and the reaction mixture was heated at 65 ºC for 24 h. After cooling to room temperature the reaction mixture was filtered through Celite 545®, and the solvent was evaporated. The crude material was chromatographed using ethyl acetate:hexane (35:65) to afford **6** (0.35 g, 84%) as a yellow solid, mp 120-122 ºC. IR (neat): 3301, 1667, 1535, 832 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.39 (d, 2H, *J* = 8.0 Hz), 7.31 (d, 2H, *J* = 8.0 Hz), 2.36 (t, 2H, *J* = 7.6 Hz), 2.13 (s, 3H), 1.57-1.51 (septet, 2H, *J* = 7.6, 7.2 Hz), 1.47-1.41 (sextet, 2H), 0.91 (t, 3H, *J* = 7.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.5, 137.3, 132.4, 120.0, 119.5, 90.2, 80.3, 31.0, 24.8, 22.2, 19.3, 13.8.

***N*-(4-*n*-Hexylphenyl)acetamide (7).** A 100-mL, three-necked, round-bottomed flask, equipped with a magnetic stirrer, a septum, and a ¼ argon filled balloon as an outlet was charged with compound **6** (0.5 g, 2.31 mmol), MeOH (25 mL) and 10% Pd/C (0.25 g). Triethylsilane (7 mL) was added dropwise and the resulting mixture was stirred at room temperature for 4 h. The reaction mixture was filtered through Celite 545®, and the solvent was evaporated to afford **7** (0.43 g, 84%) as a white solid, mp 89-90 ºC (lit.[13] mp 91 ºC). IR (neat): 3284, 2853, 1660, 840 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35 (d, 2H, *J* = 8.4 Hz), 7.19 (s, 1H), 7.10 (d, 2H, *J* = 8.4 Hz), 2.53 (t, 2H, *J* = 7.8 Hz), 2.13 (s, 3H), 1.55 (m, 2H), 1.26 (m, 6H), 0.85 (t, 3H, *J* = 6.6 Hz); ^{13}C-NMR (57 MHz, $CDCl_3$) δ 168.0, 139.3, 135.6, 129.0, 120.1, 35.5, 31.9, 31.6, 29.1, 24.7, 22.8, 14.3.

4-*n*-Hexylaniline (8). A 250-mL, round-bottomed flask, equipped with a magnetic stirrer and a reflux condenser, was charged with **7** (1.2 g, 5.44 mmol) and 70% H_2SO_4 (75 mL). The reaction mixture was heated overnight at 100 ºC. After cooling to room temperature the mixture was neutralized with 70% aqueous NaOH and was extracted with CH_2Cl_2 (3 × 75 mL). The organic extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated to produce **8** (0.95 g, 98%) as a brown oil, (lit.[14] bp 140 ºC). IR (neat): 3427-3353, 1623, 816 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.97 (d, 2H, *J* = 8.1 Hz), 6.64 (d, 2H, *J* = 8.1 Hz), 3.53 (s, 2H), 2.51 (t, 2H, *J* = 7.6 Hz), 1.56-1.54 (m, 2H), 1.30 (m, 6H), 0.9 (t, 3H, *J* = 7.1 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 145.6, 137.5, 128.9, 115.0, 35.7, 31.8, 31.2, 28.9, 22.7, 14.1.

4-*n*-Hexyl-2,6-diiodoaniline (9). A 250-mL, round-bottomed flask, equipped with a magnetic stirrer was charged with 4-*n*-hexylaniline (**8**) (0.95 g, 5.32 mmol), $NaHCO_3$ (3.0 g) and water (45 mL). The reaction mixture was cooled to 10-12 ºC (ice bath) and iodine (5 g) was added in small portions. After complete addition, the reaction mixture was stirred for 4 h. A saturated solution of $NaHSO_3$ (75 mL) was added, and the product was extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated to afford **9** (1.32 g, 69%) as a white solid, mp 85-87 ºC. IR (neat): 3411, 1610, 865, 703 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 2H), 4.43 (s, 2H), 2.38 (t, 2H, *J* = 7.8 Hz), 1.53-1.45 (m, 2H), 1.28-1.26 (m, 6H), 0.85 (t, 3H, *J* = 7.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 144.1, 139.3, 136.5, 81.7, 34.1, 31.8, 31.6, 28.9, 22.7, 14.3; MS: *m/z* Calc. for $C_{12}H_{17}I_2N$ 429.26, found 431.

4-*n*-Hexyl-2,6-bis[(trimethylsilyl)ethynyl]aniline (10). A 250-mL, three-necked, round-bottomed flask, equipped with a magnetic stirrer, a septum, a condenser and a nitrogen inlet was charged with compound **9** (0.4 g, 0.93 mmol), triethylamine (10 mL) and dry THF (10 mL). The resulting solution was purged with argon for 20 min. $Pd(PPh_3)_4$ (0.08 g, 0.07 mmol), CuI (0.032 mg, 0.16 mmol) and trimethylsilylacetylene (0.83 g, 8.45 mmol) were then added and the reaction mixture was heated at 65 ºC for 24 h. After cooling to room temperature the reaction mixture was filtered through Celite 545®, and the solvent was evaporated. The crude product was chromatographed using ethyl acetate:hexane (20:80) to afford **10** (0.25 g, 73%) as a white solid mp 60-61 ºC. IR (neat): 3489, 3387, 2145, 1612, 1249, 843, 759 cm^{-1}; ^{1}H-NMR (400 MHz, acetone-d_6) δ 6.84 (s, 2H), 4.79 (s, 2H), 2.19 (t, 3H, J = 7.6 Hz), 1.30-1.27 (m, 2H), 1.05 (m, 6H), 0.62 (t, 3H, J = 6.6 Hz), 0.01 (s, 18H); ^{13}C-NMR (100 MHz, acetone-d_6) δ 149.2, 133.2, 131.3, 107.5, 102.3, 99.8, 34.9, 32.2, 23.0, 14.2, 0.27.

2,6-Diethynyl-4-hexylaniline (11). A 100-mL, round-bottomed flask, equipped with a magnetic stirrer was charged with compound **10** (0.24 g, mmol), K_2CO_3 (0.30 g) and methanol (25 mL). The reaction mixture was stirred overnight at room temperature. The solvent was removed under vacuum, water (25 mL) was added and the product was extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and evaporated to afford **11** (0.12 g, 79%) as a yellow solid, mp 74-76 ºC. IR (neat): 3484, 3384, 2098, 1613, 1465 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.09 (s, 2H), 4.66 (s, 2H), 3.33 (s, 2H), 2.38 (t, 3H, J = 7.6 Hz), 1.52-1.44 (m, 2H), 1.23 (m, 6H), 0.82 (t, 3H, J = 7.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.5, 133.5, 131.7, 106.3, 82.7, 80.5, 34.7, 31.5, 28.9, 22.7, 14.3; MS: *m/z* Calc. for $C_{16}H_{19}N$ 225.32, found, 226.

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