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# *APPLICATION OF COPE-TYPE HYDROAMINATION IN THE SYNTHESIS OF HYDRAZONES AND THE TOTAL SYNTHESIS OF THE BENZYLTETRAHYDROISOQUINOLINE NORRETICULINE*

**Pamela H. Cebrowski**

Thesis submitted to the Faculty of Graduate & Postdoctoral Studies, University of Ottawa
in partial fulfillment of the requirements for the M.Sc. degree in the
Ottawa-Carleton Chemistry Institute

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|---|---|
| Pamela H. Cebrowski | Prof. André M. Beauchemin |

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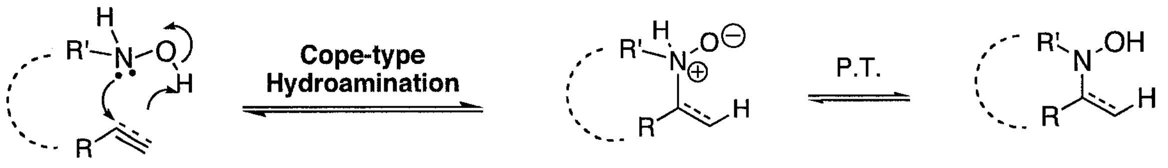
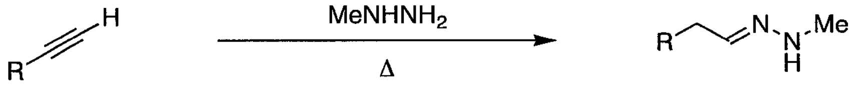
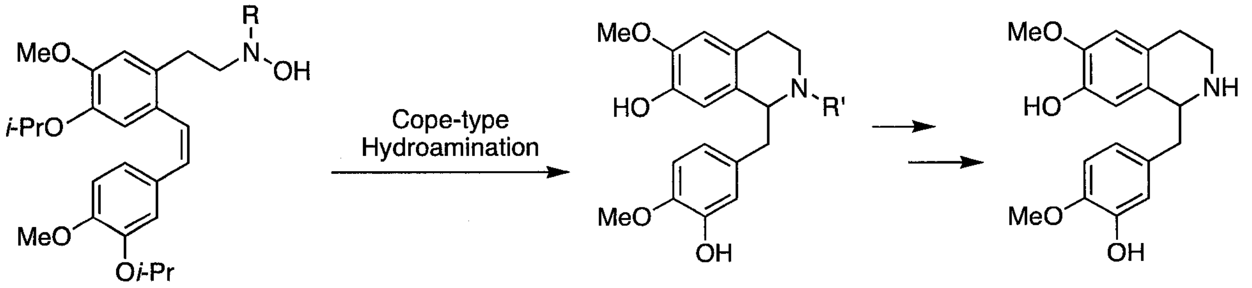
# Abstract



**1** **2** **3** (1)



**4** **5** R = aryl (2)



**6** R = H, allyl, methallyl
R' = OH, *O*-allyl, *O*-methallyl
**7**
**8**, norreticuline (3)

The hydroamination of alkenes and alkynes is a highly desirable, yet underdeveloped approach to nitrogen incorporation into molecules. Currently, this approach is predominantly limited to transition metal catalysis and suffers from limitations in substrate scope and functional group compatibility. The focus of thesis is the development of simple, metal-free hydroaminations through a different approach that is concerted in nature: the Cope-type hydroamination (eq. 1).

This transformation was applied towards the intermolecular hydroamination of alkynes with hydrazines, and is regioselective for the linear, “anti-Markovnikov” isomer **5** (eq. 2) and is presented in Chapter 2. This methodology has also been applied to intramolecular cyclizations and has been extended towards the synthesis of natural products with a specific focus on the challenging formation of 6-membered rings. The total synthesis of the benzyltetrahydroisoquinoline alkaloid norreticuline **8** through a Cope-type hydroamination key step (eq. 3) is presented in Chapter 3.

# Acknowledgements

First and foremost I would like to thank my supervisor, Prof. André Beauchemin. He remains the most enthusiastic, dedicated, and eternally-optimistic professor I know. His passion for chemistry is so contagious to his students both in the lab and in the classroom that I believe he has already made a significant contribution to increasingly populating the scientific community with new, eager chemists. Thank you for the constant support and motivation throughout the past years André!

Of course I would also like to thank all the members of the Beauchemin group. Joe, you were my first bench-mate in the group and I'll always be grateful for your guidance, your love of hockey, and your diverse collection of CDs.....I would never have listened to so much great jazz and hard rock in the same afternoon without you! Marie-Eve, it was your kindness and eagerness to help people out that truly made me feel welcome and part of the group when I first arrived. Even though your love of the Backstreet Boys and N'Sync initially threatened our ability to get along as lab neighbours, luckily the friendship we developed became much bigger than my distaste for boy bands. Joffré, I could always count on you to make me laugh when chemistry was...well...chemistry. Your 100-watt smile and infectious laugh filled the lab with your "joie de vivre," which was only intensified once you introduced us to les Têtes à Claques. Isa, you have becomes so much more of a friend than a labmate since you arrived from Sherby-ville. I'll always treasure our discreet and tasteful conversations from across the bench and your help in my immersion into French slang. Il n'y a pas l'aire d'avoir bien du monde qui est une bonne amie comme toi! I also greatly appreciate all the friendship and support of all past and present Beauchemin group members that I've had the pleasure of working with: Maria, Eric, Peter, Chris, Lili, Agnès, Anna, Marija, Elena, Anne-4, Jean, Hao, Francis, Toni and Jenn. It's because of all of you that the Beauchemin group was always such a great place to be.

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# Table of contents

# Abbreviations

| | |
|---|---|
| $\Delta G^{\ddagger}$ | activation free energy |
| AM | anti-Markovnikov |
| approx. | approximately |
| aq. | aqueous |
| Ar | argon |
| BHT | butylated hydroxytoluene |
| calcd | calculated |
| cat. | catalyst or catalyzed |
| $CHCl_3$ | chloroform |
| COSY | correlation spectroscopy |
| Cp | cyclopentadiene |
| G | Gibbs free energy |
| GCMS | gas chromatograph/mass spectrometry |
| eq. | equation |
| equiv. | molar equivalents |
| $Et_2O$ | diethyl ether |
| EtOAc | ethyl acetate |
| h | hours |
| *i*-Pr | isopropyl |
| $KMnO_4$ | potassium permanganate |
| M | Markovnikov |
| MHz | megahertz |
| mL | millilitres |
| HMBC | heteronuclear multiple bond correlation experiment |
| HMQC | heteronuclear mutltiple quantum coherence experiment |
| HRMS | high resolution mass spectrometry |
| M | molarity |
| MeOH | methanol |

| | |
|---|---|
| mg | milligrams |
| min | minutes |
| mmol | millimolar |
| *n*-Bu | normal butyl |
| NMR | nuclear magnetic resonance spectroscopy |
| NOESY | nuclear Overhauser effect spectroscopy |
| ppm | parts per million |
| $R_f$ | rate of flow (coelution coefficient) |
| r.t. | room temperature |
| *t*-Bu | tertiary butyl |
| THF | tetrahydrofuran |
| TLC | thin-layer chromatography |
| TMS | trimethylsilane |
| TS | transition state |
| μL | microlitre |
| vs | versus |

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# List of schemes

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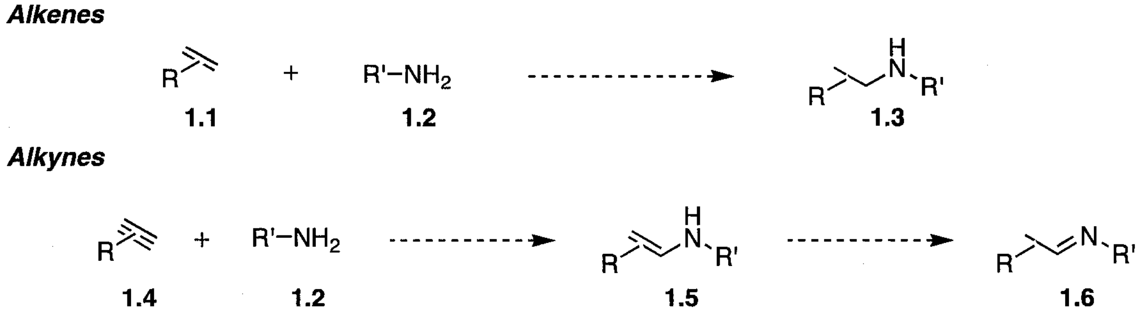
# 1

# Introduction

## 1.1 Hydroamination of alkenes and alkynes: General reactivity

The common occurrence of amines, imines, and nitrogen heterocycles in natural products, commercial pharmaceuticals and other valuable fine chemicals has rendered the formation of C-N bonds a highly desirable synthetic transformation.[1,2] There are several different methods of integrating amine functionalities into a more complex molecule. The most common include reductive animation, Mitsunobu reactions, Ritter amination, the displacement of acyl chlorides or alkyl halides, and the reduction of other nitrogen species (such as nitriles, azides, amides, and nitro functional groups). These methods, however, often involve reactive intermediates or require more than one step. In contrast, hydroamination is perhaps a simple atom-efficient method of nitrogen incorporation,[3] and is the formation of a new C-N bond via the addition of N-H across an unsaturated carbon-carbon bond (Scheme 1.1).



Scheme **1.1.** Overview of hydroamination of alkenes and alkynes

---

[1] Dugger, R. W.; Ragan, J. A.; Brown Ripin, D. H. *Org. Proc. Res. Dev.* **2005**, *9*, 253.

[2] Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337.

[3] For recent reviews on hydroamination, please see (a) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795. (b) Müller, T. E; Beller, M. *Chem. Rev.* **1998**, *98*, 675.

The hydroamination of alkenes (**1.1**) provides direct access to substituted amines (**1.3**) while the hydroamination of alkynes (**1.4**)[4] furnishes imines (**1.5**) upon tautomerization of the corresponding enamines (**1.6**). This transformation, however, has a high activation barrier due to the electrostatic repulsion between the alkene or alkyne and the lone pair on the approaching nitrogen. In the intermolecular case, hydroamination also suffers from a negative reaction entropy, which precludes simply heating the reaction to overcome this activation barrier. This process thus typically requires catalysis by either transition metals or harsh acids and is seldomly used in practical organic synthesis of complex molecules due to poor substrate scope and challenges with functional group compatibility. Intramolecular cyclization reactions are the most facile, intermolecular hydroamination of alkynes is feasible, but intermolecular hydroamination of alkenes is not yet synthetically useful as the reaction is only slightly exothermic or thermoneutral depending on the reaction conditions.[5] The current development of hydroaminaton methods is described in Section 1.2. But despite recent progress, particularly in the area of transition metal catalysis, there still lacks a general hydroamination method that effectively circumvents the issues surrounding limited reactivity and thermodynamics (alkenes).

## 1.2 Hydroamination methods under current development

### 1.2.1 Acid-catalyzed hydroamination

Acid-catalyzed hydroaminations are possible but they must overcome two substantial problems. The first is that the basicity of the nitrogen nucleophile may act as a buffer of the acid catalyst, which subsequently reduces the amount of available catalyst. The second is that once this nitrogen protonation occurs, the nitrogen loses its nucleophilicity and can no longer participate in the C-N bond forming event. Because of these obstacles, acid-catalyzed hydroaminations are often limited to biased substrates or require harsh reaction conditions[6] which then leads to poor substrate compatibility. Previously published examples of acid catalyzed hydroamination include the Ritter amination,[7] where a nitrile (**1.7**) is an effective nucleophile under strongly acidic conditions (eq. 1.1). The resulting amide could then be reduced to the corresponding amine if required.

---

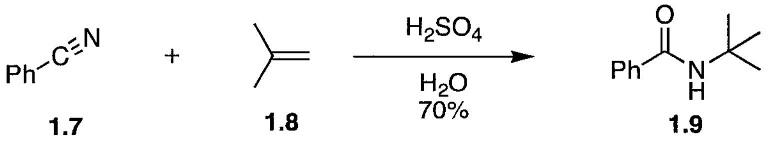
[4] For recent reviews on hydroamination of alkynes, please see (a) Nobis, M.; Drieβen-Hölscher, B. *Angew. Chem. Int. Ed.* **2001**, *40*, 3983. (b) Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104. (c) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (d) Severin, R.; Doye, S. *Chem. Soc. Rev.* **2007**, *32*, 1407. (e) Bruneau, C.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 2176. (f) Odom, A. L.; *Dalton Trans.* **2005**, 225. (g) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368.

[5] (a) Johns, A. M.; Sakai, N.; Ridder, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 9306. (b) Brunet, J. J.; Neibecker, D.; Niedercorn, F. *J. Mol. Catal.* **1989**, *49*, 235.

[6] For a review on strong acid catalysis (with section on hydroamination), please see Akiyama, T. *Chem. Rev.* **2007**, *107*, 5747.

[7] Krimen, L. I.; Cota, D. J. *Org. React.* **1969**, *17*, 213.

Similarly, protonated hydrazines can be effective nucleophiles as well, as seen in equation 1.2. In both these cases the strongly acidic conditions can suffer from poor functional group compatibility and result in a severely limited substrate scope and only Markovnikov regioselectivity is possible.



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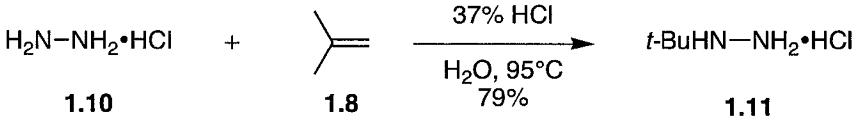


(1.2)

Examples which utilize slightly milder reaction conditions are limited to biased systems where either the alkene is more reactive (i.e. strained alkenes) or the reaction is intramolecular. The Bergman group reported the intermolecular hydroamination of a handful of activated alkenes, such as norbornene (**1.12**), and aniline (**1.13**) with only 5 mol% of catalyst (eq. 1.3).[8] The hydroamination of the alkene had a competing side reaction of hydroarylation, which could only be consistently suppressed when the aniline nucleophile was substituted with $CF_3$ groups at the 3 and 5 positions. Schlummer and Hartwig reported the intramolecular hydroamination of the tosylated amines **1.16** (eq. 1.4).[9] The cyclizations were facilitated by the use of a deactivated nitrogen nucleophile which were less likely to become completely protonated than a more electron-rich counterpart. The cyclizations were completed in up to 99% yield with a variety of aryl substituents on the alkene moiety, but could not be extended to non-deactivated nitrogen species. Later in 2006 the Hartwig group reported the intermolecular variant of this reactivity,[10] again with the use of a deactivated amine nucleophile. The reactivity was mostly explored with the sulfonamide **1.18,** whose reaction with norbornene (**1.12**) formed exclusively the exo addition product **1.19** in 91% yield (eq. 1.5). This reactivity was extended to benzylamide as the nucleophile (with an increased amount of triflic acid catalyst and slightly higher temperature) and to the cyclic alkenes cyclohexene, cyclooctene, and cyclohexadiene, albeit with lower yields. The He group also reported similar results simultaneously.[11]

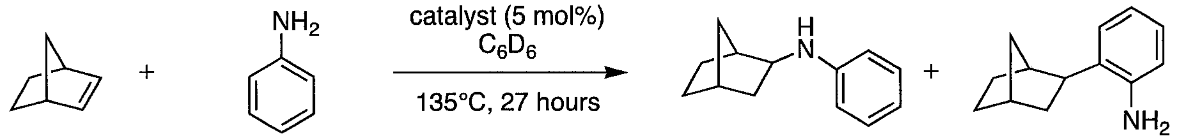
---

[8] Anderson, L. L.; Arnold, J.; Bergman, R. G. *J. Am. Chem. Soc.* **2005,** *127,* 14542

[9] Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002,** *4,* 1471.

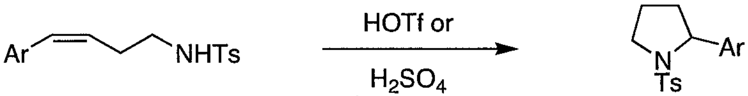
[10] Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.,* **2006,** *8,* 4179.

[11] Li, Z.; Zhang, J.; Brouwer, C.; Yang, C.-G.; Reich, N. W.; He, C. *Org. Lett.* **2006,** *8,* 4175.

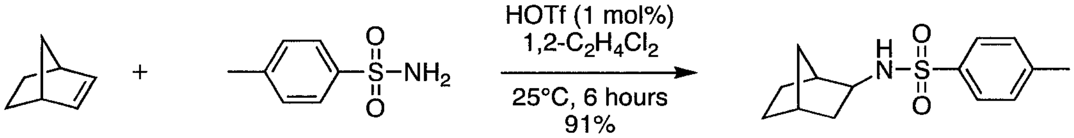


**1.12** **1.13**, 5 equiv. **1.14** **1.15** (1.3)

cat.:
$Ph_3CB(C_6F_5)_4$: 58% yield, 1:1 ratio
HOTf: 13% yield, 1:1 ratio



**1.16** (20 mol%) up to 99% yield **1.17** (1.4)



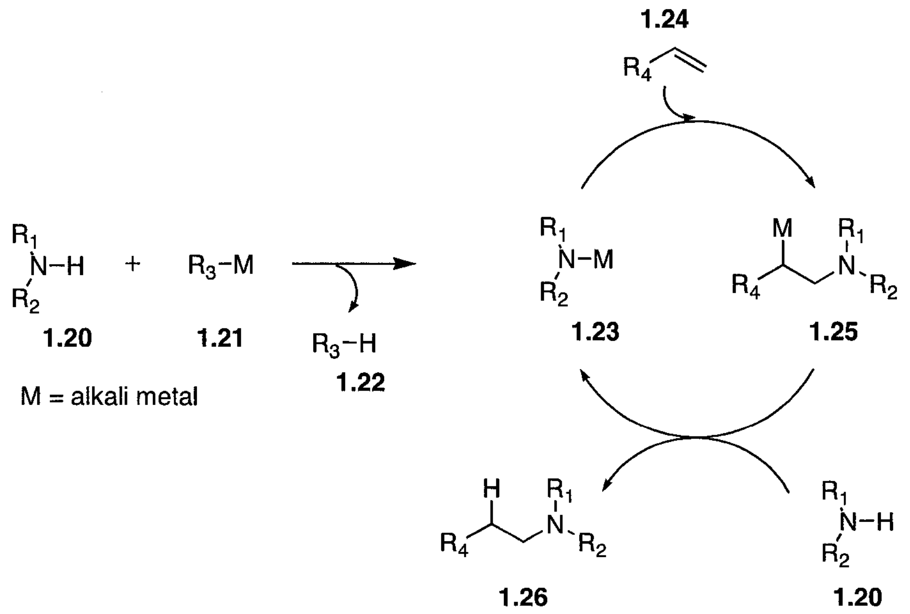
**1.12** **1.18** **1.19** (1.5)

## 1.2.2 Base/alkali metal-catalyzed hydroamination

The deprotonation of the amine nucleophile with an alkali base has also been used to effectively catalyze hydroaminations in some cases.[12] The mechanism for this catalysis resembles that of any alkyllithium reaction, where the metal counterion plays an important role in sequestering the negative charge, and is outlined in Scheme 1.2.

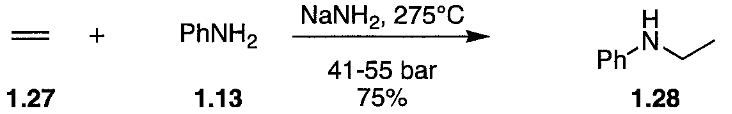
---

[12] For a recent review on base-catalyzed hydroaminations, please see Seayad, J.; Tillack, A.; Hartung, C. G.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 795.



Scheme 1.2. Catalyic cycle of the alkali base-catalyzed hydroamination of an alkene

Upon deprotonation of the amine **1.20**, the alkali metal forms the alkali amide **1.23** which is highly nucleophilic. The addition of **1.23** to the alkene (**1.24**) then generates an even more reactive organometallic species **1.25**, which subsequently deprotonates a second molecule of the amine **1.20** and generates the hydroamination product **1.26**. This type of catalysis has been reported with alkali bases such as $NaNH_2$ (eq. 1.6),[13] $LiNEt_2$/TMEDA (eq. 1.7),[14] *s*-BuLi (eq. 1.8),[15] *n*-BuLi,[15] *t*-BuOK,[16] and CsOH (eq. 1.9).[17]



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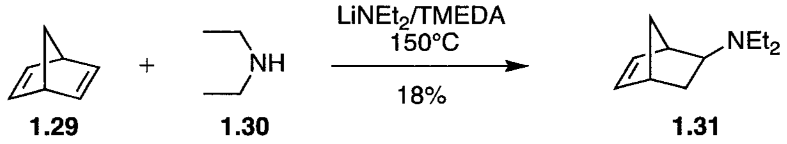

(1.7)

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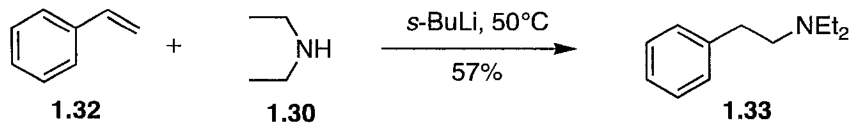
[13] Howk, B. W.; Little, E. L.; Scott, S. L.; Whitman, G. M. *J. Am. Chem. Soc.* **1954**, *76*, 1899.
[14] Lemkuhl, H.; Reinehr, D. *J. Organomet. Chem.* **1973**, *55*, 215.
[15] Schlott, R. J.; Falk, J. C.; Narducy, K. W. *J. Org. Chem.* **1972**, *37*, 4243.
[16] (a) Beller, M.; Breindl, C.; Riermeier, T. H.; Eichberger, M.; Trauthwein, H. *Angew. Chem. Int. Ed.* **1998**, *37*, 3389. (b) Beller, M.; Breindl, C.; Riermeier, T. H.; Tillack, A. *J. Org. Chem.* **2001**, *66*, 1403.
[17] Tzalis, D.; Koradin, C.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 6193.



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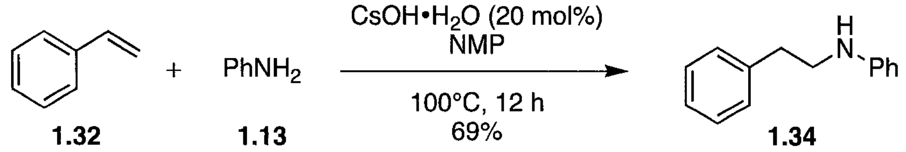


(1.9)

Similar to the acid-catalyzed variety, alkali base-catalyzed intermolecular hydroamination of alkenes generally requires forcing conditions to obtain hydroamination products, particularly when the substrate is a simple alkene that is less able to stabilize a developing negative charge. Moderate yields were obtained using styrene (**1.32**, eq. 1.8 and 1.9), but the reaction with ethylene (**1.27**) required a higher temperature and pressure to obtain comparable results (eq. 1.6). The reaction between 2,5-norbornadiene (**1.29**) and diethylamine (**1.30**) illustrates the importance of negative charge stabilization as **1.29** is a strained alkene, one might expect it to be more reactive, but it is actually much less reactive than styrene (**1.32**) because it doesn't contain that charge-stabilizing $sp^2$ carbon $\alpha$ to the alkene moiety. The synthetic utility of base/alkali metal-catalyzed hydroamination appears to be limited to electron-withdrawing alkenes and the harshness of the reaction conditions severely limit the scope due to poor substrate compatibility.

### 1.2.3 Transition metal-catalyzed hydroamination

Transition metal catalysis is by far the main focus in current hydroamination literature.[3] The use of transition metals has become an efficient method of lowering the high activation barrier that exists for hydroaminations and has been undergoing significant development with respect to both inter- and intramolecular reactions. A rapidly-growing list of both early (mostly titanium and zirconium) and late (ruthenium, rhodium, iridium, palladium, platinum, copper, gold, and zinc) transition metal catalysts as well as lanthanide and actinide-based catalysts have been reported to be effective in some type of hydroamination reaction. This long list of catalysts, however, illustrates the lack of a *general* hydroamination method that can be extended toward many different alkene and alkyne substrates with a variety of nitrogen nucleophiles.

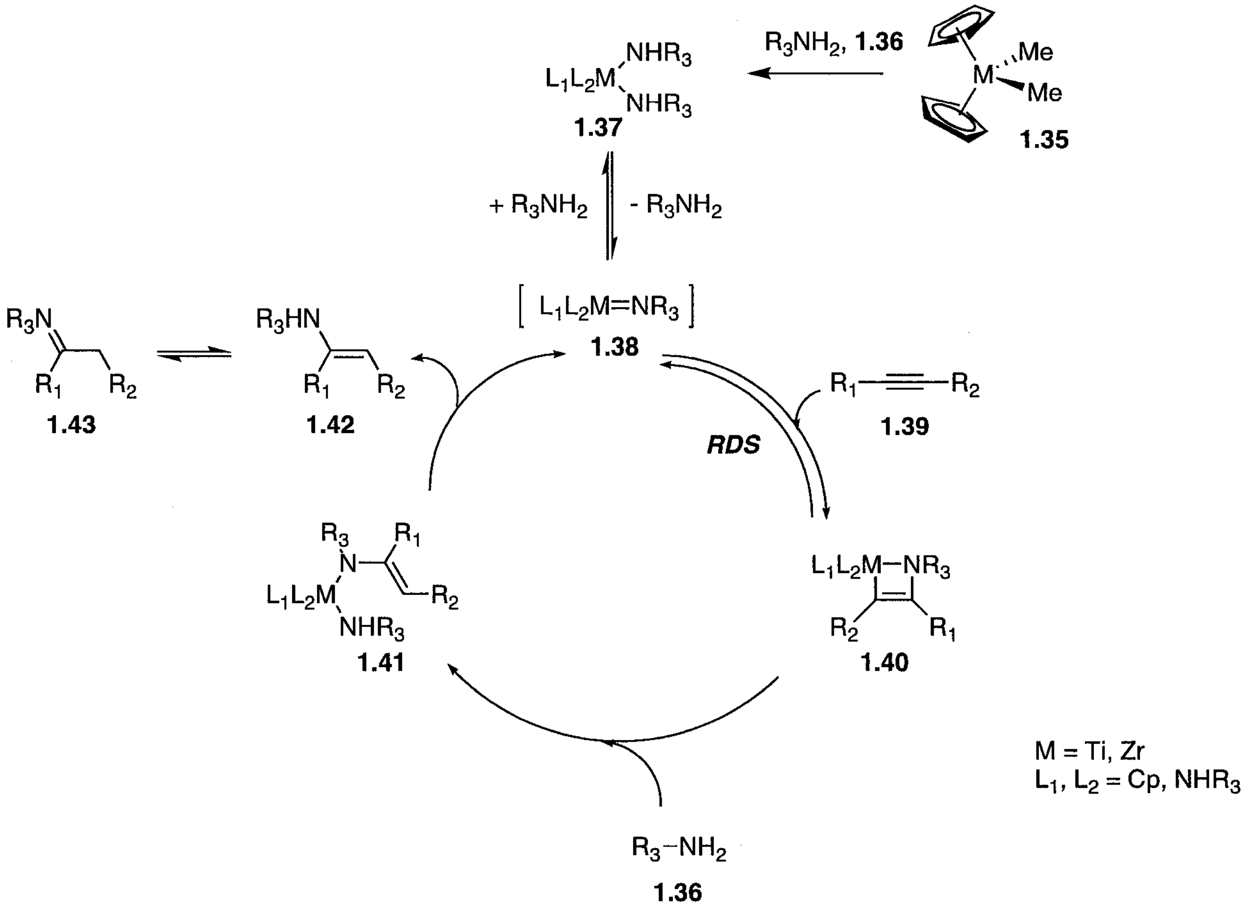
The increased reactivity of alkynes compared to alkenes has often made them desirable substrates to begin the development of a hydroamination catalyst. Early transition metal catalysts (Group 4) have been found to be particularly useful in the hydroamination of alkynes, as well as allenes. The high reactivity of these catalysts have been attributed to the reversible formation of a metal imido complex (**1.38**), which then undergoes a [2+2] cycloaddition with the alkyne (or allene) substrate to form an azametallacyclobutene intermediate **1.40**.[18] The general scheme for hydroamination of alkynes with Group 4 catalysts can be seen in Scheme 1.3.[19] Titanocene catalyzed hydroamination has dominated the literature in both the inter- and intramolecular hydroamination of alkynes. The following is a brief overview of titanocene reactivity with alkynes.

Bisamidate and cyclopentadienyl-type titanium complexes have been used extensively in the generation of pyrrolidines and piperidines, which is exemplified in equations 1.10 and 1.11, respectively.

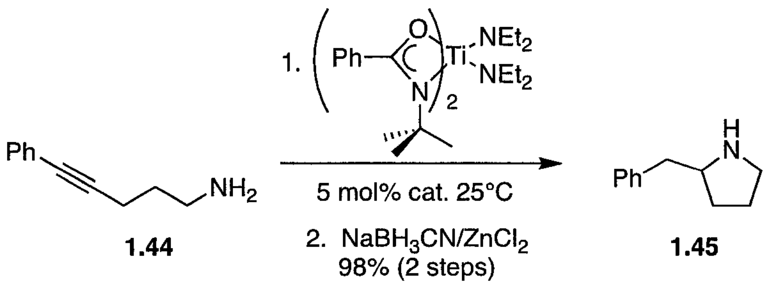
---

[18] Polse, J. L.; Andersen, R. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1998**, *120*, 13405 and references cited therein.

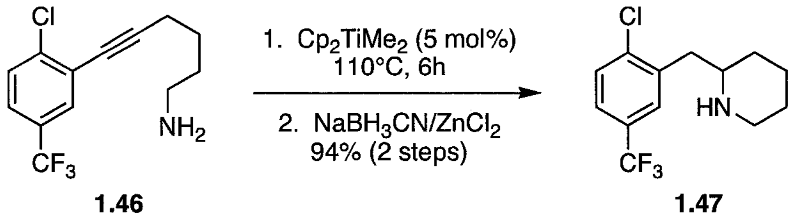
[19] (a) Ward, D. B.; Maisse-François, A.; Gade, L. H.; Mountford, P. *Chem. Commun.* **2004**, 704. (b) Michael, F. E.; Duncan, A. P.; Sweeney, Z. K.; Bergman, R. G. *J. Am. Chem. Soc.* **2005**, *127*, 1752 and references cited therein.



Scheme 1.3. Proposed catalytic cycle for the early transition metal-catalyzed hydroamination of alkynes



(1.10)



(1.11)

It was found by Li *et al.*[20] that the bisamidate titanocene catalysts exhibited excellent reactivity even under mild reaction conditions. Using this type of catalyst, the cyclization of **1.44** furnished the corresponding pyrrolidine **1.45** upon reduction, which was achieved at room temperature in 98% isolated yield over both the hydroamination and reduction steps. The formation of 6-membered piperidines such as **1.47**, however, is much less facile than the formation of 5-membered rings.[21] Bytschkov and Doye reported the cyclization (and reduction) of the aminoalkyne **1.46** in 2002 (eq. 1.11), just prior to the development of the biamidate catalysts, in 94% with a readily available cyclopentadenyl titanocene catalyst by heating to 110°C for 6 hours.[22] The *relative* ease of intramolecular hydroaminations of alkynes[23] has allowed it to become developed into a synthetically-useful transformation. Selected applications of intramolecular hydroamination of alkynes in the total synthesis of natural products are briefly explored in Section 3.2.

The intermolecular hydroamination of alkynes is a significantly more difficult tranformation, and has been developed over a wide range of alkyne substrates and amines. In many of these cases, issues regarding regioselectivity for either the Markovnikov or anti-Markovnikov isomer have been successfully addressed. The regiochemical outcome and overall reactivity of these reactions has been optimized by fine-tuning the selection of the metal, ligand(s), alkyne or the amine nucleophile which may differ in terms of sterics, electronics, or both. Recently, the Odom group has developed the catalytic intermolecular addition of arylhydrazines to alkynes[24] in the interest of developing efficient hydrazone syntheses for use in Fischer indole synthesis.[25,26] The titanocene catalysts were optimized to accommodate the change in electronics and chelating ability brought about by the electron-donating ability of the free lone pair on the β-nitrogen atom.[27] These catalysts are depicted in Figure 1.1. A series of reactions between terminal and di-substituted alkynes (**1.50-1.52**) and 1,1-dimethylhydrazine (**1.53**) was performed with each of the two catalysts (**1.48** and **1.49**). Both catalysts were effective in promoting Markovnikov reactivity with the terminal alkyne **1.50** (Entries 1 and 2). In contrast, the hydroamination of phenylacetylene (**1.51**) favoured the anti-Markovnikov product (Entries 3 and 4). Perhaps

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[20] Li, C.; Thomson, R. K.; Gillion, B.; Patrick, B. O.; Schafer, L. L. *Chem. Commun.* **2003**, 2562.

[21] Reactivity in cyclizations of 5-membered rings > 6-membered rings > 7 membered rings. For more details, please refer to Baldwin's rules for ring closure: Baldwin, J. E. *Chem. Commun.* **1976**, 734.

[22] Bytschkov, I.; Doye, S. *Tetrahedron Lett.* **2002**, *43*, 3715.

[23] When compared to intermolecular hydroaminations of alkynes and equivalent reactions with alkenes.

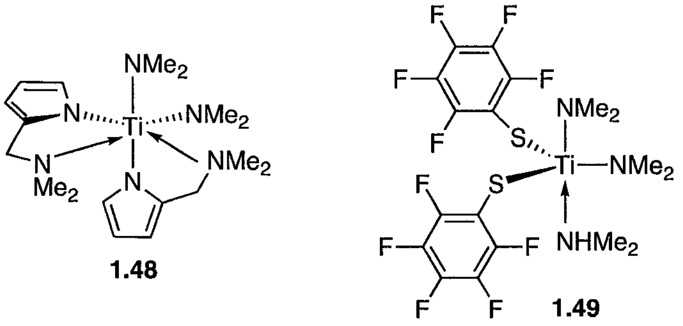
[24] Cao, C.; Shi, Y.; Odom, A. L. *Org. Lett.* **2002**, *4*, 2853–2856.

[25] Robinson, B. *The Fischer Indole Synthesis*; Wiley & Sons: Chichester, U.K., 1982.

[26] For application of hydrohydrazination towards Fischer indole synthesis, please see Banerjee, S.; Barnea, E.; Odom, A. L. *Organometallics* **2008**, *27*, 1005.

[27] For mechanistic studies with respect to the formation of titanium hydrazido and imido catalytic complexes, please see Li, Y.; Shi, Y.; Odom, A. L. *J. Am. Chem. Soc.* **2004**, *126*, 1794.

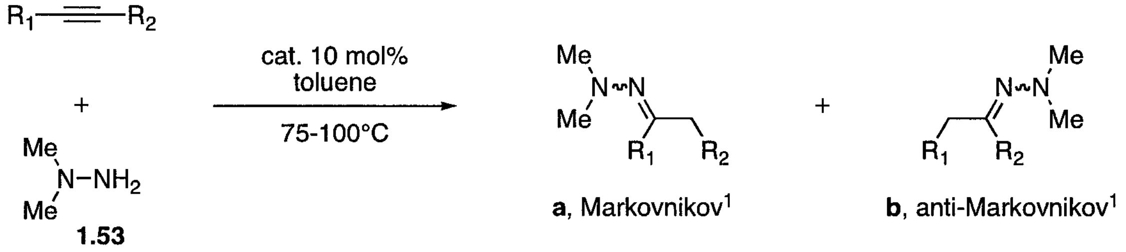
the most interesting results were the reactions with 1-methyl-2-phenylacetylene (**1.52**), which *exclusively* furnished the isomer **b**, albeit in poor yield with catalyst **1.48**. These results demonstrates how the alkyne substrate can heavily influence regioselectivity while using the same catalyst. In addition, the large difference in yield between Entries 5 and 6 (13 and 92%, respectively) with the same alkyne substrate (**1.52**) illustrates how the catalyst can also have a great impact on reactivity.



**1.48** **1.49**

Figure 1.1. Titanium catalysts for hydrohydrazination[24]

**Table 1.1.** Catalytic hydrohydrazination of alkynes



**1.53**

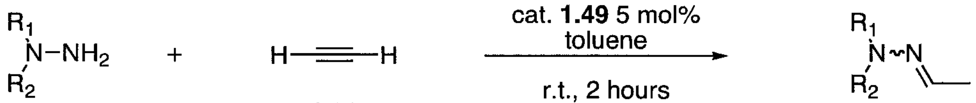
**a**, Markovnikov[1] **b**, anti-Markovnikov[1]

| Entry | R₁ | R₂ | Catalyst | Time (h) | a/b | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | **1.50** *n*-Bu | H | **1.48** | 24 | 50:1 | 79 |
| 2 | | | **1.49** | 24 | 10:1 | 72 |
| 3 | **1.51** Ph | H | **1.48** | 2 | 1:3 | 85 |
| 4 | | | **1.49** | 2 | 1:30 | 88 |
| 5 | **1.52** Ph | Me | **1.48** | 75 | 0:100 | 13 |
| 6 | | | **1.49** | 10 | 0:100 | 92 |

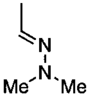
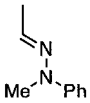
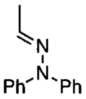
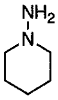
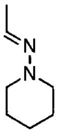
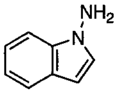
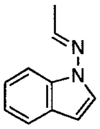
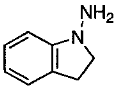
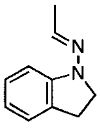
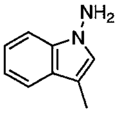
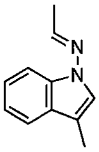
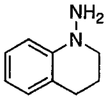
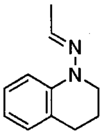
[1] The designations as Markovnikov and anti-Markovnikov do not apply to Entries 5 and 6 in this case as Me is more electron donating than Ph.

In the same account by the Odom group, the hydroamination of the highly reactive acetylene was explored using different 1,1-disubstituted hydrazines (Table 1.2). Good to excellent yields were observed for each of the attempted hydrazines (83-99% yield) although the highest were reported with hydrazines containing at least one $sp^2$ carbon a to the substituted nitrogen atom (Entries 2,3,5,6 and 7). Although the other yields were still good for Entries 1,4 and 8, it does suggest that the charge-stabilizing ability of an $sp^2$ carbon has a beneficial effect in hydrohydrazination reactions. It may thus be necessary to sequester the lone pair on nitrogen to achieve superior reactivity when using titanocene catalysts, which may ultimately limit its general applicability.

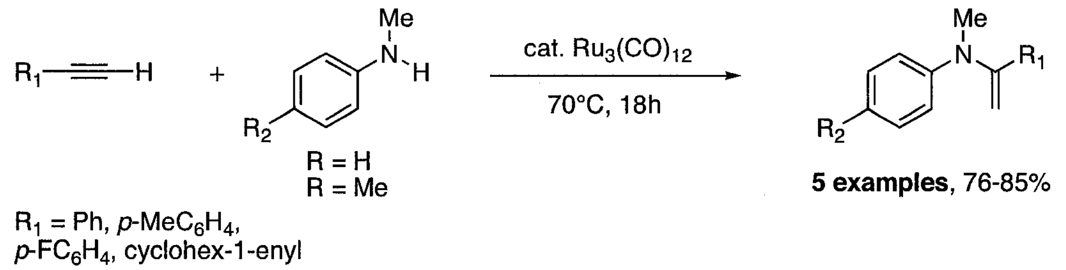
**Table 1.2.** Catalytic hydrohydrazination of acetylene with 1,1-disubstituted hydrazines



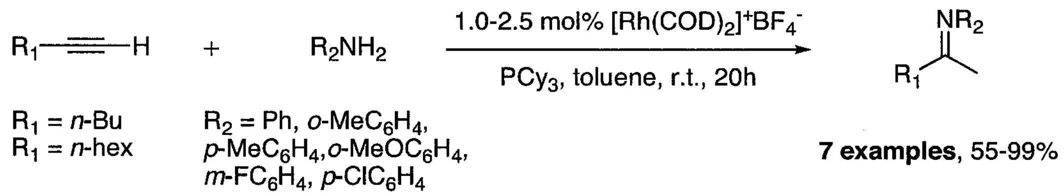
**1.66**

| Entry | Hydrazine | Product | Yield (%) |
|---|---|---|---|
| 1 | **1.53** MeNHNH$_2$ | **1.67**  | 83 |
| 2 | **1.59** Me(Ph)NNH$_2$ | **1.68**  | 97 |
| 3 | **1.60** Ph$_2$NNH$_2$ | **1.69**  | 99 |
| 4 | **1.61**  | **1.70**  | 86 |
| 5 | **1.62**  | **1.71**  | 95 |
| 6 | **1.63**  | **1.72**  | 96 |
| 7 | **1.64**  | **1.73**  | 95 |
| 8 | **1.65**  | **1.74**  | 94 |

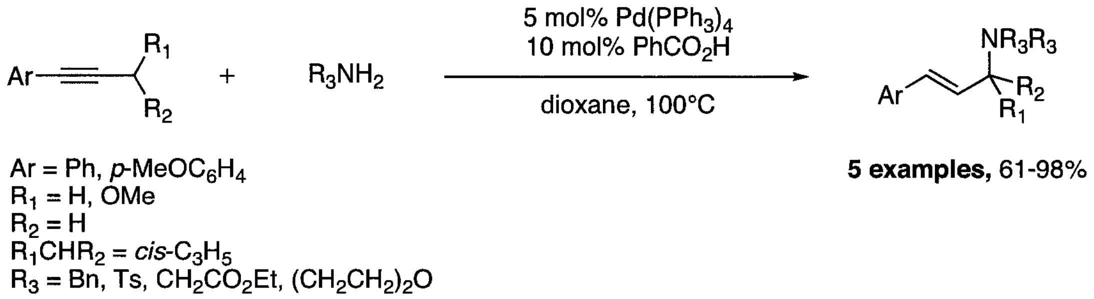
Late transition metal catalysts have also been significantly developed in the intermolecular hydroamination of alkynes as their highly Lewis acidic $d^8$ and $d^{10}$ electron configurations appear to promote high reactivities.[28] The majority of these catalysts also tend to exhibit Markovnikov selectivity, good functional group tolerance, and higher tolerance towards oxygen and moisture.[29] Below is a brief overview of the wide-range of efficient late transition metal catalysis of intermolecular hydroamination of alkynes.



(1.12)



(1.13)



(1.14)

In 1999 Uchimaru reported the hydroamination of terminal alkynes with 1-aryl-1-methylanilines using a ruthenium complex in good yields and with selectivity for the Markovnikov isomer (eq. 1.12).[30] The Beller group also obtained Markovnikov hydroamination products between terminal alkyl acetylenes and six electronically-different anilines using a cationic rhodium catalyst (eq. 1.13).[31] Palladium, which has been

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[28] Müller, T. E.; Pleier, A.-K. *J. Chem. Soc., Dalton Trans.* **1999**, 583.

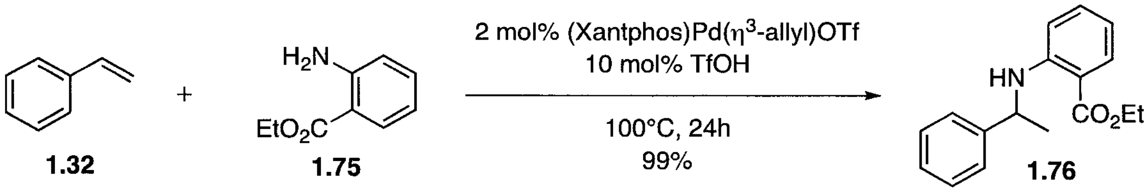
[29] Johns, A. M.; Utsunomiya, M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 1828.

[30] Uchimaru, Y. *Chem. Commun.* **1999**, 1133–1134.

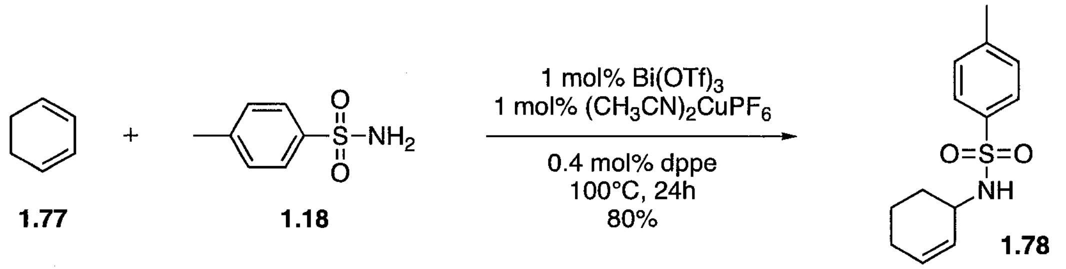
[31] Hartung, C. G.; Tillack, A.; Trauthwein, H.; Beller, M. *J. Org. Chem.* **2001**, *66*, 6339.

referred to as the most utilized metal in the hydroamination of alkynes,[4,32] effectively catalyzed the hydroamination of internal aryl alkynes and secondary amines with a palladium(0)tetrakis triphenylphosphine catalyst in the presence of benzoic acid (eq. 1.14).[33] Interestingly though, the reaction furnished the corresponding allylic amines rather than the precedent hydrazones due to the formation of a palladium π-allyl intermediate.

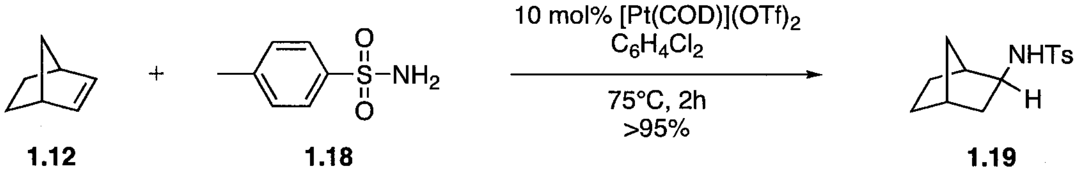
The intermolecular hydroamination of alkenes is much less developed than that for alkynes in terms of substrate scope, which is due to the increased π-bond strength relative to alkynes. Currently, intermolecular transition metal-catalyzed reactions with alkenes are predominantly limited to activated alkenes such as styrenes (eq. 1.15),[29] dienes (eq. 1.16),[34] and strained alkenes (eq. 1.17 and 1.18).[35,36]



(1.15)



(1.16)



(1.17)

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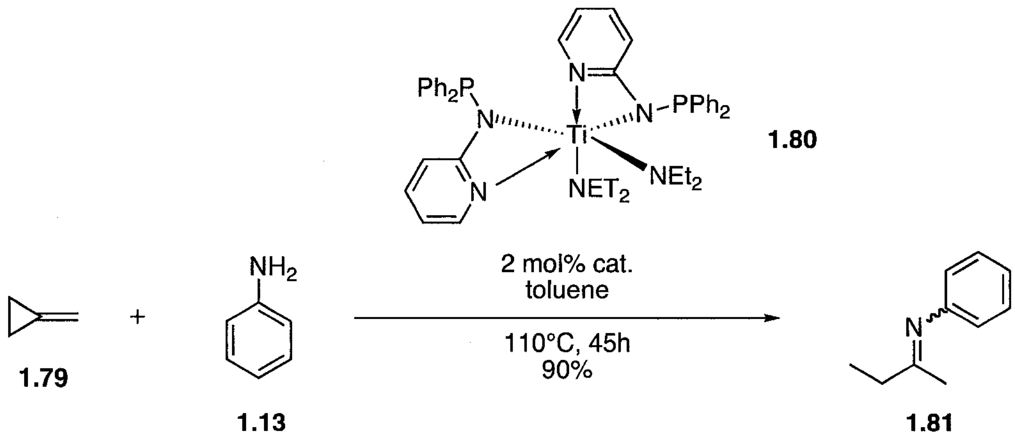
[32] Although more so for intramolecular hydroaminations.

[33] (a) Kadota, I.; Shibuya, A.; Mpaka Lutete, L.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 4570. (b) Mpaka Lutete, L.; Kadota, I.; Shibuya, A.; Yamamoto, Y. *Heterocycles* **2002**, *58*, 347.

[34] Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 1611.

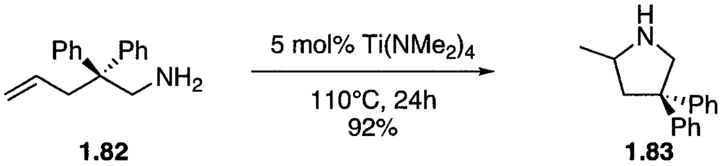
[35] Karshtedt, D.; Bell, A. T.; Tilley, T. D. *J. Am. Chem. Soc.* **2005**, *127*, 12640.

[36] (a) Smolensky, E.; Kapon, M.; Eisen, M. S. *Organometallics* **2005**, *24*, 5495. (b) Smolensky, E.; Kapon, M.; Eisen, M. S. *Organometallics* **2007**, *26*, 4510.

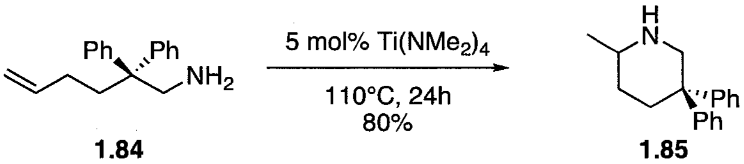


(1.18)

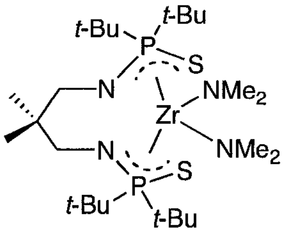
In contrast, the intramolecular hydroamination of alkenes has undergone significant advancement and has been used as a useful strategy in the total synthesis of natural products (which is briefly discussed in Section 3.1). The synthesis of nitrogen heterocycles, in particular pyrrolidine and piperidine derivatives has been shown to be viable with both early and late transition metal catalysts as well as lanthanides and actinides.[3] The majority of work has been done on the formation of 5-membered rings presumably because they are much easier to cyclize than their 6-membered counterparts.[21] Because of the greater challenge in forming 6-membered rings, there is still presently a significant opportunity for method development. Some of the leading examples of piperidine synthesis via the metal-catalyzed intramolecular hydroamination of alkenes are presented below.



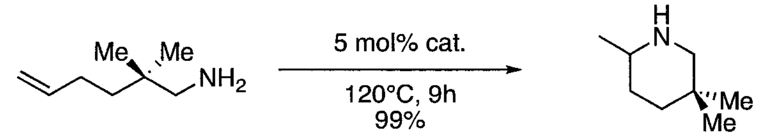
(1.19)



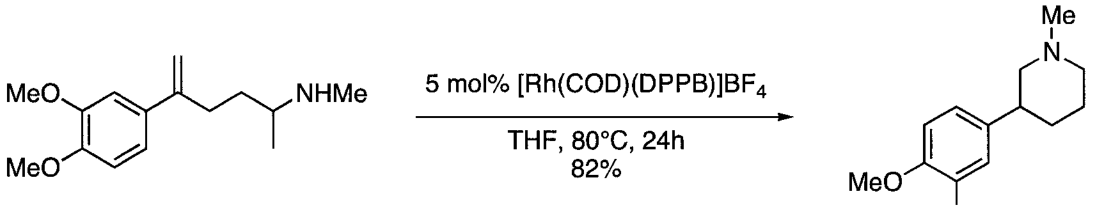
(1.20)



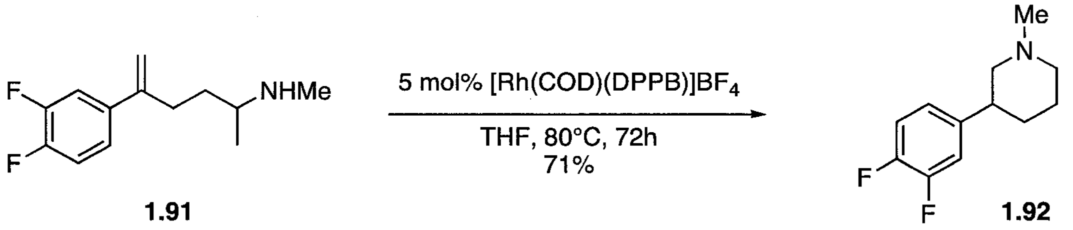
**1.87**



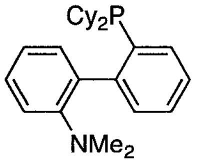
**1.86** **1.88** (1.21)



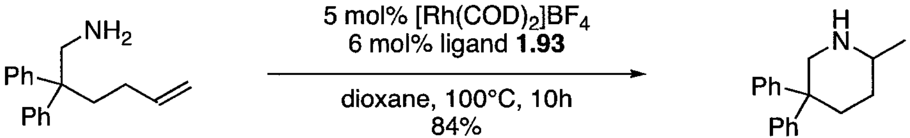
**1.89** **1.90** (1.22)



**1.91** **1.92** (1.23)



**1.93**



**1.84** **1.85** (1.24)

In 2005 the Schafer group were the first to report a $Ti(NMe_2)_4$ catalyzed intramolecular hydroamination of *gem*-disubstitution-activated primary aminoalkenes.[37] The best results were obtained in the formation of 5-membered pyrrolidines (eq. 1.19) but identical reaction conditions yielded piperidines in only slightly lower yields (eq. 1.20). Many of these reactions, however, benefitted from a significant Thorpe-Ingold effect[38] which

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[37] Bexrud, J. A.; Beard, J. D.; Leitch, D. C.; Schafer, L. L. *Org. Lett.* **2005**, *7*, 1959.

[38] From the *gem*-disubstitution on the β-carbon. Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc. Trans.* **1915**, *107*, 1080.

appeared necessary in the formation of the 6-membered piperidines. Another type of Group 4 metal catalyst, **1.87**, was also employed in the hydroamination of *gem*-disubstituted primary amines at around the same time (eq. 1.21).[39] This zirconium-based catalyst was able to promote the 6-membered cyclization of **1.86**, which has less of a Thorpe-Ingold effect than **1.84**, in a better yield (99%) and in less time (9 hours). A cationic rhodium-based catalyst was subsequently used by Takemiya and Hartwig in the hydroamination of "unactivated" aryl aminoalkenes.[40] The catalyst effectively catalyzed the reactions of both an electron-rich aryl aminoalkene **1.89** (eq. 1.22) and an electron-deficient aryl aminoalkene **1.91** (eq. 1.23) to form the corresponding piperidines (**1.90** and **1.92**, respectively). This unusual preference for the anti-Markovnikov was not rationalized at the time of publication, but the reaction was limited to 1,1-disubstitution of the alkene and also required an *N*-methyl substituent. More recently, Hartwig and Liu[41] reported efficient rhodium-catalyzed intramolecular hydroaminations of unactivated terminal and internal alkenes with both primary and secondary amines. The cyclization to the 6-membered pyrrolidine **1.85** was quite efficient in the presence of the biarylphosphine ligand **1.93** that was previously developed by the Buchwald group[42] (eq. 1.24).

In general, metal-catalyzed hydroamination methods have undergone recent significant development. The majority of this progress has been in the area of alkyne hydroamination, particularly with Group 4 transition metals. A very large number of titanium and zirconium-based catalysts have been developed, but this is perhaps due to the apparent need to tailor a different catalyst to each reaction. Late-transition metal catalysts have been much more successful in exhibiting functional group tolerance and have been more successful in catalyzing the hydroamination of alkenes. Intramolecular hydroaminations, particularly of alkenes, are much more highly developed than their intermolecular counterparts. The cyclization of 5-membered rings has been very well developed while access to 6-membered rings remains challenging. Despite the great progress that has been made in the area of metal catalyzed-hydroamination, there still lies a significant need for a *general* hydroamination method that is non-substrate specific and tolerable over a wide-range of functional groups. There is, however, a metal-free alternative to achieve metal-free reactivity.

---

[39] Kim, H.; Lee, P. H.; Livinghouse, T. *Chem. Commun.* **2005**, 5205.
[40] Takemiya, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 6042.
[41] Liu, Z.; Hartwig, J. F.; *J. Am. Chem. Soc.* **2008**, *130*, 1530.
[42] This ligand was previously developed for cross-coupling reactions. Gaertzen, O.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 465.

## 1.3 The search for a general method: The Cope-type hydroamination

The Cope-type hydroamination is simply our interpretation of the reverse Cope elimination, which is a well known and documented reaction that has not yet been developed as a hydroamination method.[43] This thesis documents two projects, one in methodology (Ch. 2) and the other in total synthesis (Ch. 3), which both involve the development of this simple, metal-free approach to hydroamination. A brief overview of current literature precedents of the Cope-type hydroamination reaction will be presented (Section 1.3.1) as well as the developments from within the Beauchemin group which provided a basis for this work (Section 1.3.2).

### 1.3.1 The mechanism, scope, and characteristics of the Cope-type hydroamination

The Cope-type hydroamination is essentially the formal addition of an N-H bond to an unsaturated C-C bond by a "bifunctional" reagent such as hydroxylamine. This transformation is known to occur through a 5-membered, concerted transition state and under relatively mild reaction conditions. Figure 1.2 shows the general reaction scheme where the substrate **1.94** (either an alkene or alkyne) reacts with the hydroxylamine **1.95** to form the hydroamination product **1.96**. The mechanism below illustrates the concerted formation of the 5-membered transition state. It was later found that this transition state, although concerted, is in fact asynchronous.[44] The concerted nature of this reaction adds an increased level of predictability compared to other hydroamination methods, which may become highly important when attempting to predict and control regioselectivity and eventually, stereoselectivity. If possible, a proton transfer step can subsequently occur to furnish the corresponding neutral product. As with other hydroaminations, the Cope-type hydroamination of alkynes results in the formation of enamines/imines and that of alkenes results in the corresponding amines. It should be considered, however, that the synthesis of enamines/imines through the Cope-type hydroamination of alkynes is methodology that is orthogonal to carbonyl chemistry. The development of such an alternative to Schiff base-type chemistry would lead to an increase in synthetic versatility with respect to starting materials, as the desired products could be equally accessed through either the corresponding carbonyls or alkynes.

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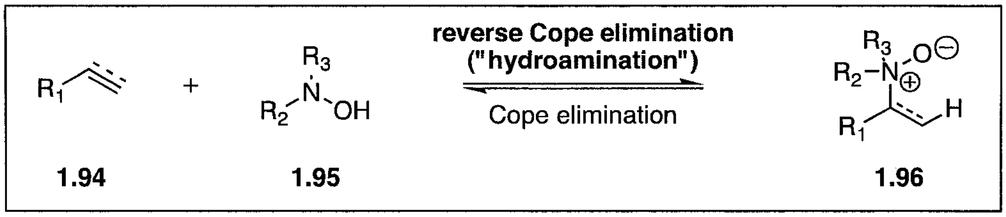
[43] For an excellent review on the reverse Cope elimination, please see Cooper, N. J.; Knight, D. W. *Tetrahedron* **2004**, *60*, 243.

[44] Beauchemin, A. M.; Moran, J.; Lebrun, M.-E.; Séguin, C.; Dimitrijevic, E.; Zhang, L.; Gorelsky, S. I. *Angew. Chem. Int. Ed.* **2008**, *47*, 1410.



***Mechanism:***

Figure 1.2. Cope-type Hydroamination: General reaction scheme and mechanism.

The intramolecular version of this reaction was first reported by House and coworkers in 1976,[45] who later suggested that the reverse Cope elimination occurred through a radical-based mechanism.[46] Observations by Black and Doyle[47] and Ciganek,[48] however, lead to the initial thinking that the mechanism may in fact be concerted.

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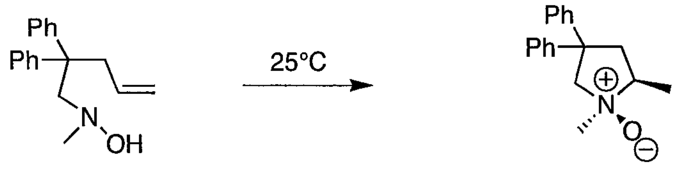
[45] House, H. O.; Manning, D. T.; Melillo, D. G.; Lee, L. F.; Haynes, O. R.; Wilkes, B. E. *J. Org. Chem.* **1976**, *41*, 855.

[46] House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863.

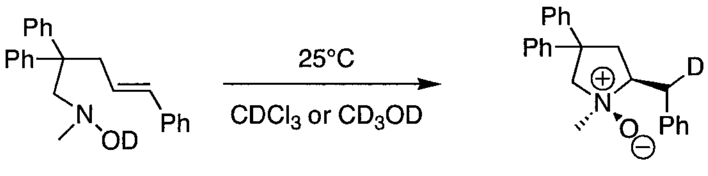
[47] No effect on rate of cyclization in the presence of radical inhibitors. Black, D. St. C.; Doyle, J. E. *Aust. J. Chem.* **1978**, *31*, 2317.

[48] Ciganek, E. *J. Org. Chem.* **1990**, *55*, 3007.



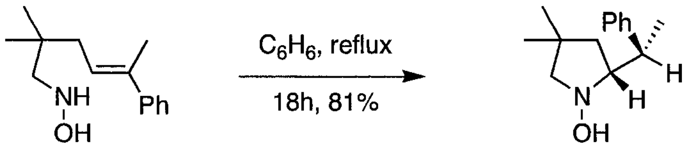
**1.101** **1.102**

(1.25)



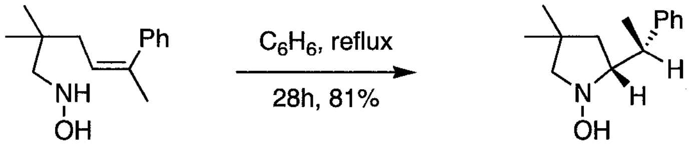
**1.103** **1.104**

(1.26)



**1.105** **1.106**

(1.27)



**1.107** **1.108**

(1.28)

The cyclization of the methyl-substituted hydroxylamine **1.101** at 25°C by Ciganek yielded the single diastereomer **1.102**, which had *cis* stereochemistry between the oxide oxygen and the methyl group (eq 1.25). This stereochemistry suggests the suprafacial delivery of the nitrogen and hydrogen atoms across the terminal alkene, which then must have occurred in a concerted fashion as to not lose the stereochemical information. The deuterated hydroxylamine **1.103** was subsequently cyclized to yield the *N*-oxide **1.104**, where Ciganek suggested the specific transfer of deuterium was consistent only with a concerted mechanism (eq 1.26). The Oppolzer group reported the cyclizations of the *E*- and *Z*-alkenylhydroxylamines **1.105** and **1.107** to provide the epimeric pyrrolidine-*N*-oxides **1.106** and **1.108**, respectively (eq 1.27 and 1.28, respectively).[49] These results strongly support a concerted mechanism, since the nitrogen and hydrogen atom addition must have occured on the same face of the alkene to form only one diastereoisomer. This mode of reactivity had been confirmed by *ab initio* and DFT calculations only for the Cope elimination.[50] However, no direct evidence could yet confirm

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[49] Oppolzer, W.; Spivey, A. C.; Bochet, C. G. *J. Am. Chem. Soc.* **1994**, *116*, 3139.

[50] (a) Komaromi, I.; Tronchet, J. M. J. *J. Phys. Chem.* **1997**, *101*, 3554. (b) Acevedo, O.; Jorgensen, W. L. *J. Am. Chem. Soc.* **2006**,

that the intermolecular Cope-type hydroamination occurs by the same transition state as the intramolecular variant, but it was assumed so due to the principle of microscopic reversibility.

At the current state of development, the Cope-type hydroamination's synthetic utility was limited to that of intramolecular cyclizations. Through many experimental observations over the years,[43] this cyclization developed a set of common characteristics that are summarized in Figure 1.3.

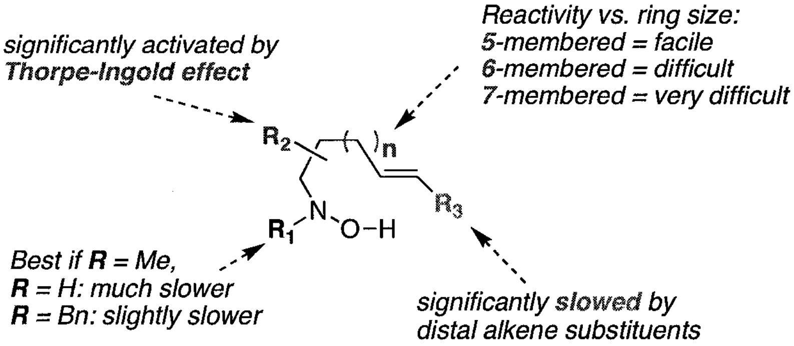
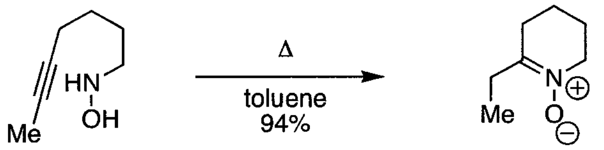


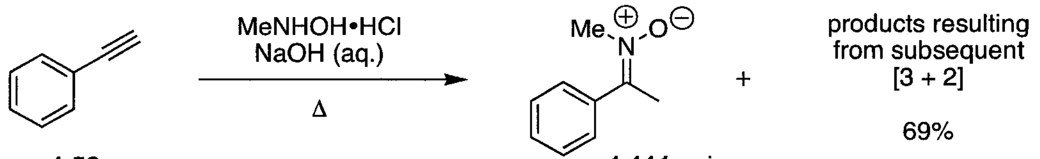
Figure 1.3. Features of the reverse Cope cyclization (hydroamination)

It had been determined that the optimal substrate for cyclization via a Cope-type hydroamination would be *N*-methyl substituted, contain substitution that would invoke the Thorpe-Ingold effect,[38] form a 5-membered ring, and be a terminal alkene. These, of course, were not all preconditions to achieving successful reactivity. The following equations illustrate the scope and limitations of the Cope-type hydroamination outside of the 5-membered intramolecular cyclization.



**1.109** **1.110**

(1.29)



**1.52** **1.111**, minor

(1.30)

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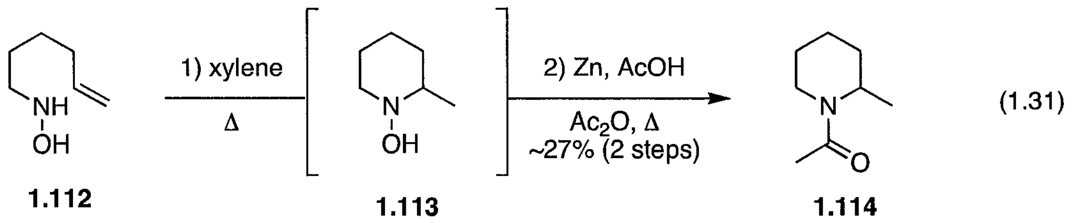
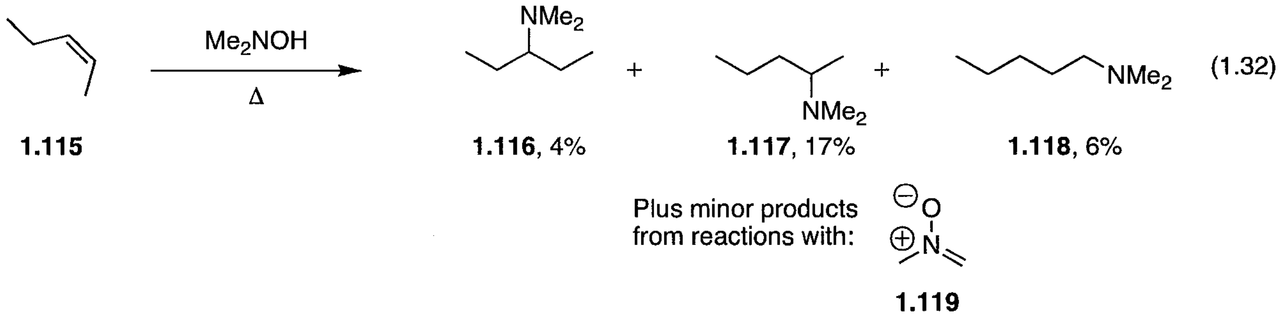
*128*, 6141.





The Holmes group discovered that the intramolecular hydroamination of the alkyne **1.109** to form the nitrone **1.110** was very efficient (eq. 1.29),[51] despite being a 6-membered cyclization and having a distal methyl substitution on the alkene. It has been shown that when there is no competing mode of cyclization, even internal alkynes can effectively cyclize into piperidine rings.[43] The intermolecular hydroamination of phenylacetylene (**1.52**) was reported by Padwa and Wong (eq. 1.30),[52] but the yield for the nitrone product **1.111** remained low due to its high tendency to subsequently react with the starting **1.52** in a [3+2] manner, and the reaction was limited to only aryl acetylenes. The intramolecular Cope-type hydroamination and subsequent formylation of the simple alkyl aminoalkene **1.112** was reported in low yield (eq. 1.31, approx. 27%).[53] This example is illustrative of the difficulty in the formation of 6-membered rings from alkene hydroamination, which greatly contrasts the facile formation of 5-membered rings. The intermolecular Cope-type hydroamination has proven to be even more elusive; the only previously-reported example was by Laughlin,[54] which was the reaction between the cis-alkene **1.115** and *N,N*-dimethylhydroxylamine (eq. 1.32). The reaction resulted in a complex mixture of products which likely would have been formed by a Cope-type hydroamination first-step. The majority of the mixture consisted of oxazoles (not shown), which would have resulted from a [3+2] reaction between the nitrone **1.119** and the starting alkene (**1.115**), with the mass balance residing in the reduction products **1.116-1.118** of Cope-type hydroaminations. The lack of control in this

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[51] Fox, M. E.; Holmes, A. B.; Forbes, I. T.; Thompson, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3379.

[52] Padwa, A.; Wong, S. K. *J. Org. Chem.* **1986**, *51*, 3125.

[53] (a) House, H. O.; Manning, D. T.; Melillo, D. G.; Lee, L. F.; Haynes, O. R.; Wilkes, B. E. *J. Org. Chem.* **1976**, *41*, 855. (b) House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863.

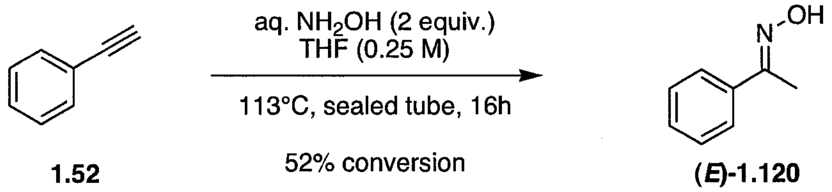
[54] Laughlin, R. G. *J. Am. Chem. Soc.* **1973**, *95*, 3295.

reaction essentially eliminated any synthetic utility, but the core reactivity was present, which presented an opportunity for further development.

These precedents in Cope-type hydroamination had shown that this approach towards nitrogen integration was quite general, and that this hydroamination strategy often occurred at temperatures similar to metal-catalyzed variants for analogous reactions. Therein was the opportunity to develop this methodology and ultimately establish a simple, efficient, general method for inter- and intramolecular hydroamination of alkenes and alkynes.

### 1.3.2. Previous Cope-type hydroamination results within the Beauchemin group

The first success in Cope-type hydroamination came at the hands of Marie-Eve Lebrun and Catherine Séguin with the intermolecular hydroamination of alkynes with aqueous hydroxylamine. Their first hit of reactivity was the reaction of phenylacetylene (**1.52**) and hydroxylamine by heating in THF at 113°C in a sealed tube overnight (eq. 1.33). A conversion of 52% was obtained for the *E*-oxime, **(*E*)-1.120**. This reaction was subsequently optimized and resulted in efficient Cope-type hydroaminations that were applicable to aryl, alkyl and alkenyl terminal acetylenes which exhibited moderate to excellent selectivities for the Markovnikov isomers (eq. 1.34).[44,55]



**1.52** **(*E*)-1.120** (1.33)

(1.34)

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[55] Including internal alkynes, this reactivity has been extended to include 22 examples. Moran, J.; Gorelsky, S. I.; Dimitrijevic, E.; Lebrun, M.-E.; Bédard, A.-C.; Séguin, C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 17893.

This significant achievement greatly increased the efficiency, generality, and synthetic utility of the intermolecular Cope-type hydroamination of alkynes over what was previously reported in literature. It had then become important to explore the possibility of developing even more control: achieving regioselectivity for the anti-Markovnikov isomer. Presented in Chapter 2 of this thesis is the development of a Cope-type hydroamination method to achieve anti-Markovnikov regiocontrol in the intermolecular reaction of alkynes. Also presented in this thesis is the total synthesis of a natural product, the benzyltetrahydroisoquinoline norreticuline, using an intramolecular Cope-type hydroamination key step to form a 6-membered ring. This synthesis, described in Chapter 3, was a unique opportunity to further develop the intramolecular Cope-type hydroamination of alkenes in a complex system.

# 2

# Intermolecular Cope-type hydroamination of alkynes

## 2.1 Regiocontrol in intermolecular hydroaminations

The development of practical and predicable intermolecular Cope-type hydroaminations depends on the achievability of regiocontrol and ultimately stereocontrol. As discussed in Section 1.3.2., the intermolecular reaction between aqueous hydroxylamine and alkynes demonstrated significant selectivity for the Markovnikov product. At this point there became a need to develop a method to achieve the complementary, anti-Markovnikov selectivity.

### 2.1.1 Regioselectivity in metal-catalyzed intermolecular hydroamination of alkynes

Much progress has already been made in the control of regioselectivity in metal-catalyzed hydroaminations.[56] Anti-Markovnikov selectivity in the metal-catalyzed hydroamination of alkynes has been achieved in excellent yields (up to 99%) and ratios (up to <99:1), but is still relatively limited in terms of scope. Zhang and Schafer have demonstrated the use of a bis-(amidate)titanium precatalyst complex to transform a range of terminal aliphatic alkynes into the corresponding aldimines (eq. 2.1).[57] Rosenthal and coworkers have similarly developed a titanocene precatalyst complex of the type $Cp_2Ti(\eta^2\text{-}Me_3SiC{\equiv}CR)$, also known as

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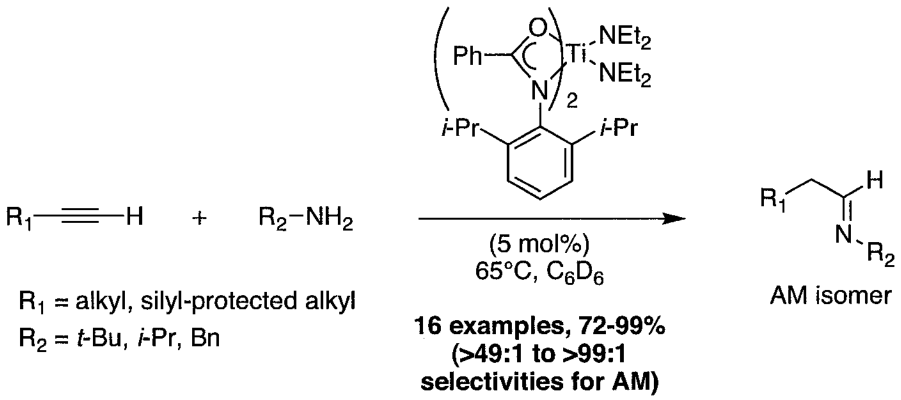
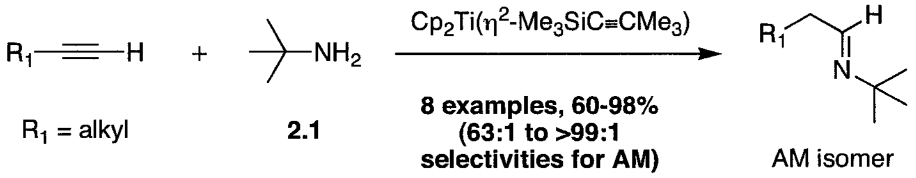
[56] For a review on the regioselectivity of catalytic additions to alkenes and alkynes, please see Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem. Int. Ed.* **2004**, *43*, 3368.
[57] Zhang, Z.; Schafer, L. L.; *Org. Lett.* **2003**, *5*, 4733.

Rosenthal's catalyst,[58] which had later afforded the anti-Markovnikov products of aliphatic alkynes, as well as phenyl acetylene, and aliphatic amines in similarly high selectivities and yields (eq. 2.2).[59] Interestingly, the use of aniline or aryl hydrazines favoured the Markovnikov isomer, as did the use of increasingly sterically hindered catalysts.[60] Based on product ratios and theoretical calculations, it was concluded that both sterics and electronics played major roles in the regioselective outcome of the reactions. However, the calculations showed that it was the steric interactions between the alkyne and the ligands on the titanium catalyst that were the greater influence in determining regioselectivity.



(2.1)



(2.2)

The perhaps most intriguing case of regioselectivity that exemplifies the sensitivity of intermolecular hydroamination is that reported by Straub and coworkers.[61] Using an organoactinide catalytic complex, the regioselectivity in the hydroamination of the aliphatic terminal alkyne **2.2** and ethyl amine (**2.3**) was controlled simply by selecting the appropriate actinide metal centre (eq. 2.3 and 2.4).

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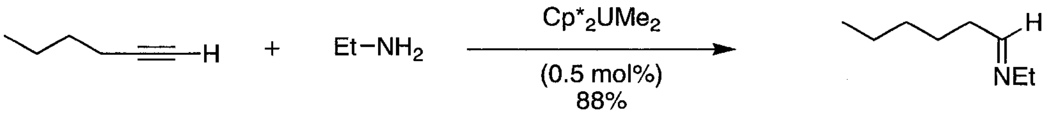
[58] For a review on the use of the "Rosenthal"-type titanocene reagents, please see Rosenthal, U.; Burlakov, V. V.; Arndt, P.; Baumann, W.; Spannenberg, A. *Organometallics* **2003**, *22*, 884.

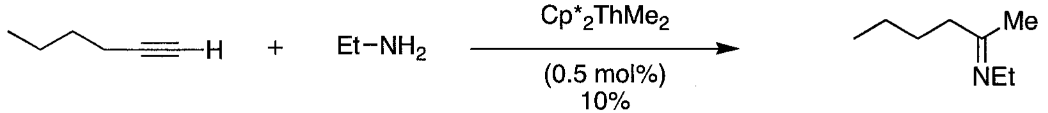
[59] Tillack, A.; Garcia Castro, I.; Hartung, C. G.; Beller, M. *Angew Chem. Int. Ed.* **2002**, *41*, 2541.

[60] Steric bulk on the catalyst was achieved through increased substitution on the cyclopentadiene moieties. Tillack, A.; Jiao, H.; Garcia Castro, I.; Hartung, C. G.; Beller, M. *Chem. Eur. J.* **2004**, *10*, 2409.

[61] Straub, T.; Haskel, A.; Neyroud, T. G.; Kapon, M.; Botoshansky, M.; Eisen, M. S. *Organometallics* **2001**, *20*, 5017.



**2.2** **2.3** **2.4** (AM isomer) (2.3)



**2.2** **2.3** **2.5** (M isomer) (2.4)

Cp* = $C_5Me_5$

The selection of the organouranium catalyst exclusively produced the anti-Markovnikov isomer, aldimine **2.4**, whereas the organothorium catalyst produced the Markovnikov isomer, ketimine **2.5**, albeit in a modest yield. Due to the lack of steric differences between the alkyne, amine and catalysts, these results illustrate how electronics do play a clear and distinct role in the regioselectivity of the hydroamination product.

In each of these metal-catalyzed cases, the catalyst generally interacts with both the alkyne and the amine in the proposed catalytic cycles. Although the exact transition states may not be known, the metal complexes are formed in such a way as to sufficiently stabilize the transition state of the reaction to evoke catalysis. Thus, when evaluating the regioselectivity of metal-catalyzed intermolecular hydroaminations of alkynes, both the sterics and electronics of the complex-containing transition state must be carefully considered.

### 2.1.2. Regioselectivity in Cope-type hydroaminations: Previous results from the Beauchemin group

In the recent efforts towards the development of the Cope-type hydroamination in the Beauchemin group, it was quickly observed that the intermolecular reaction between hydroxylamine and various alkynes exhibited a strong preference for the Markovnikov product.[62] In the work performed by Ms. Catherine Séguin, Ms. Marie-Eve Lebrun, and Ms. Anne-Cahterine Bédard (eq. 2.5), it was found that in 18 examples of alkyl, alkenyl and aryl acetylenes where both isomer products were observed there were selectivities from 4:1 to over 55:1 in favour of the Markovnikov isomer (eq 2.5). In a few examples, only the sole isolation of the Markovnikov isomer was possible.

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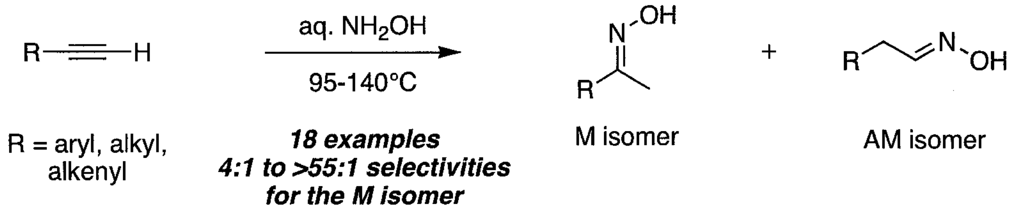
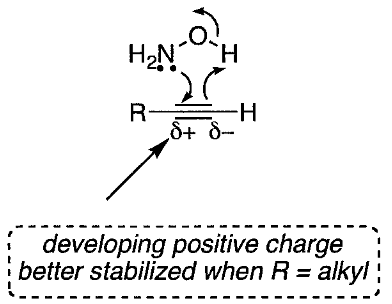
[62] Beauchemin, A. M.; Moran, J.; Lebrun, M.-E; Séguin, C.; Dimitrijevic, E.; Zhang, L.; Gorelsky, S. I. *Angew. Chem., Int. Ed.* **2008**, *47*, 1410.



(2.5)

In general, there was greater Markovnikov selectivity in alkyl acetylene substrates than in aryl acetylenes. This difference in selectivity may be explained by a greater stabilization of the developing positive charge adjacent to an alkyl sp$^3$ carbon versus an aryl sp$^2$ carbon in the transition state (Figure 2.1). The selectivity observed with 1-phenyl-1-propyne is also in agreement with this hypothesis.



developing positive charge better stabilized when R = alkyl

Figure 2.1. Alkyl substituent on acetylene stabilizing the TS

DFT calculations[63] were subsequently performed with Dr. Serge Gorelsky (University of Ottawa) to gain further understanding of the thermodynamics of the reaction between phenylacetylene (**2.6**) and hydroxylamine. These calculations had confirmed that the formation of the Markovnikov product is preferred in the intermolecular Cope-type hydroamination of hydroxylamine and phenylacetylene. The hydroamination activation free energy for the transition state ($\Delta G^{\ddagger}_{\mathrm{HA}}$) favours the Markovnikov isomer by 3.1 kcal/mol, which accounts well for the difference in selectivities of aryl acetylenes. Through the calculation of the interatomic bond distances it was determined that the concerted transition state is asynchronous (Figure 2.1). It was calculated that the proton abstraction by the oxygen atom likely preceded the addition of nitrogen to the acetylene. This transformation would thus create a partial positive charge on the carbon atom α to the phenyl

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[63] Using Prof. T. Woo's facilities at the University of Ottawa. Calculations performed at the B3LYP/TZVP level of theory in the gas phase at 298K and 1 atm.

ring. Such a developing positive charge in the transition state would be much better stabilized adjacent to either an alkyl or aryl substituent, leading to the Markovnikov product, rather than adjacent to the terminal hydrogen.

### 2.1.3 How to achieve complementary regioselectivity

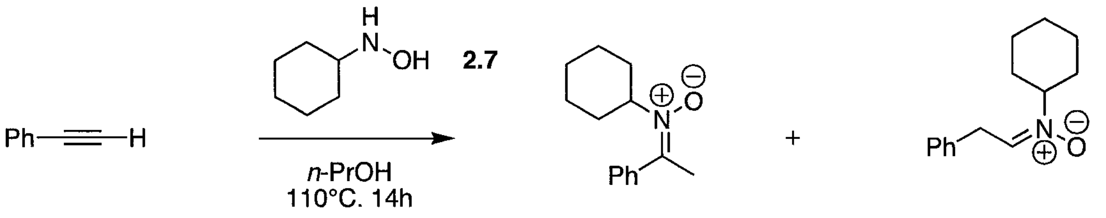
With the ability to achieve good regiocontrol for the Markovnikov product, attention was turned towards reversing this selectivity to obtain the anti-Markovnikov product. As discussed previously in Section 2.1.1 with reference to metal-catalyzed hydroamination, one possible way to achieve this would be though the use of sterics to override the electronic preference for the Markovnikov pathway. Using a substituted hydroxylamine could potentially create enough steric bulk to destabilize the transition state pictured in Figure 2.2 and result in favouring an alternative transition state. This alternative transition state would lead to the preferential formation of the anti-Markovnikov product. We rationalized that such a strategy would succeed since some anti-Markovnikov isomer can be observed with NHOH and the interactions described above could likely reverse this selectivity.

bulky R group on the hydroxylamine destabilizes the transition state

no significant destabilization of the TS leading to the anti-Markovnikov isomer

Figure 2.2. Destablization of the Markovnikov transition state through sterics

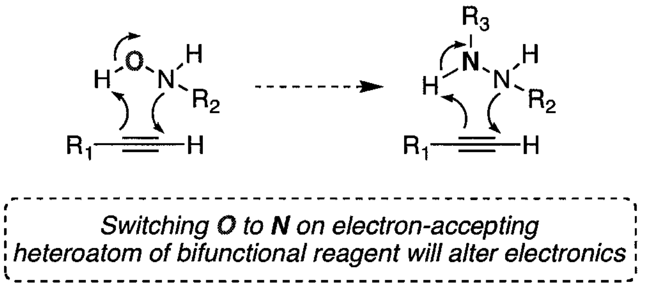
It was found by Mr. Joseph Moran, however, that the reaction of phenylacetylene (**2.6**) with *N*-cyclohexylhydroxylamine (**2.7**) afforded the Markovnikov nitrone **2.8** in 52% isolated yield whereas the detection of the anti-Markovnikov nitrone **2.9** was not reported (eq 2.6). The electronic bias towards the Markovnikov product thus did not appear to be easily overcome by sterics, although a more thorough investigation using more sterically hindered hydroxylamines would be necessary to evaluate whether selectivity is governed either predominantly or exclusively by electronics rather than sterics.



(2.6)

**2.6** **2.8** (M isomer, 52%) **2.9** (AM isomer, not reported)

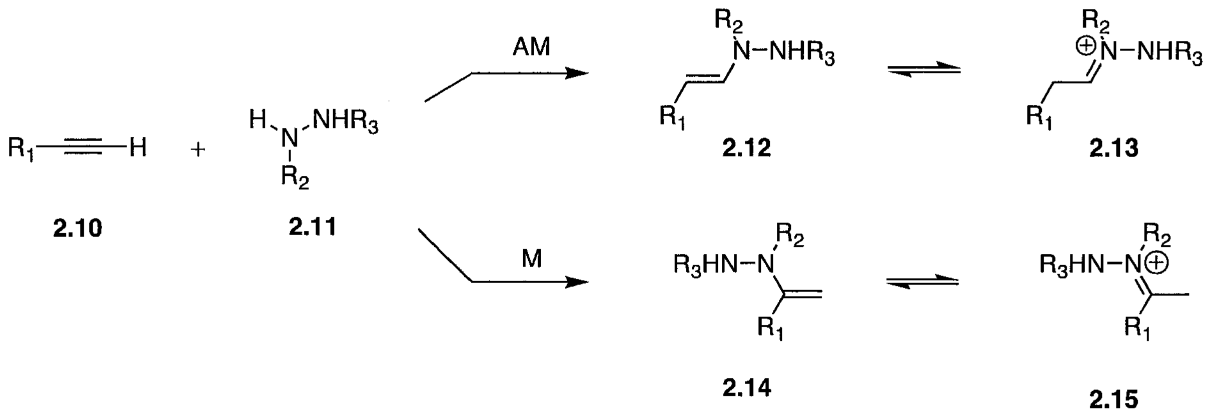
Alternatively, the complementary regioisomer could potentially be achieved by altering the electronics of the alkyne substrate. This was successfully demonstrated in the Beauchemin group in the intermolecular Cope-type hydroamination of alkenes using perfluorinated styrene as the substrate (66%, <20:1 for the AM isomer). This strategy, however, only worked significantly for the one substrate and could not possibly lead to a general method.



*Switching **O** to **N** on electron-accepting heteroatom of bifunctional reagent will alter electronics*

Figure 2.3. Changing the heteroatom of the bifunctional reagent.

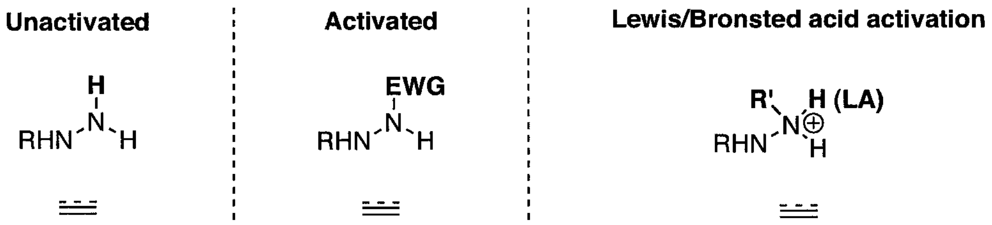
Lastly, anti-Markovnikov regioselectivity could be obtained by altering the electronics of the nitrogen-containing bifunctional reagent. Switching the electron-accepting heteroatom of the reagent from an oxygen atom to a nitrogen atom would allow for the development of anti-Markovnikov selective Cope-type hydroaminations using hydrazines (Figure 2.3). The possible hydroamination products of reacting a hydrazine with a terminal alkyne are outlined below in Scheme 2.1. The reaction pathway leading to the anti-Markovnikov product would yield upon tautomerization the corresponding aldiminium **2.13**, or the equivalent aldimine hydrazone if $R_3$ = H. Similarly, the Markovnikov pathway would produce either the ketiminium **2.15** if $R_3 \neq$ H, or the ketimine hydrazone if $R_3$ = H. Either hydroamination product could also undergo intermolecular exchange to form a more stable hydrazone (*E* vs. *Z*).



Scheme 2.1. Cope-type hydroaminations of a terminal alkyne and hydrazine

## 2.2 Intermolecular hydroamination of alkynes with hydrazines

The use of hydrazines as the nitrogen-containing bifunctional reagent in the development of intermolecular Cope-type hydroaminations of alkynes was pursued mainly because it allowed for good opportunities to "fine tune" the electronics of the system. It would also be possible to explore different steric interactions which were not possible with hydroxylamines. This electronic and steric tuning would be achieved through the incorporation of various substituents on the second nitrogen atom. Three main classes of hydrazine reagents were proposed for development (Scheme 2.2).



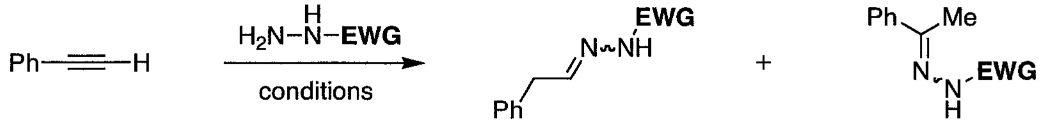
Scheme 2.2. Three different classes of hydrazine reagents for development in Cope-type hydroaminations

The unactivated hydrazines would have the necessary difference in electronics with respect to the precedent hydroxylamines as the nitrogen atom to receive the electron density is less electronegative than the corresponding oxygen atom. These hydrazines could consequently be less reactive as a reagent, but are most likely to be commercially-available and would be relatively simply to further derivatize. The results obtained for unactivated hydrazines are described in Section 2.2.2. Activated hydrazines containing an electron withdrawing group on the electron-density receiving nitrogen would be more electronically similar to the hydroxylamines and would thus be expected to be reactive. The electron withdrawing moiety could be a traditionally-used protecting group which could be easily removed at a later stage. Caution must be taken though that the group is not so labile that it is removed prematurely. The results using a variety of these hydrazines are presented in Section 2.2.1. Hydrazines which are activated via a Lewis acid or additional substitution combined with Brϕnsted acid protonation could also be seen as good bifunctional reagents as they would readily draw electron density towards the activated nitrogen. This strategy would also be most easily amenable to asymmetric versions of the Cope-type hydroamination with alkenes through the use of a chiral substituent or counterion. In this case care would have to be taken to avoid Ritter-type reactivity (as briefly described in Chapter 1). The development of this acid-activated hydrazine had been investigated prior to these efforts and these studies strongly suggested a Ritter pathway was operating.[64]

## 2.2.1 Intermolecular hydroamination of alkynes with activated hydrazines

The first attempts of intermolecular hydroamination of alkynes were performed using tosyl hydrazine. The use of this activated hydrazine was intended to bias the system towards the desired hydroamination reactivity by rendering the donor-hydrogen more acidic. These attempts, outlined in table 2.1, were mostly unsuccessful.

**Table 2.1.** Intermolecular hydroamination of alkynes with activated hydrazines



2.6 2.7 2.8

| Entry | EWG | Solvent | Temperature (˚C) | Comments[a] |
|---|---|---|---|---|
| 1 | $SO_2PhMe$ | DMSO-$d_6$ | 100 | Mostly hydrogenation to ethyl benzene |
| 2 | $SO_2PhMe$ | $CDCl_3$ | 100 | Mostly hydrogenation to ethyl benzene; possible HA; Isolated SnAr product |
| 3 | $SO_2PhMe$ | MeOD | 100 | Mostly hydrogenation to ethyl benzene; |

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[64] Beaulieu, Dornan, Moran; unpublished results.

|  |  |  |  |  |
|---|---|---|---|---|
|  |  |  |  | possible HA |
| 4 | $SO_2PhMe$ | $C_6D_6$ | 100 | Mostly hydrogenation to ethyl benzene |
| 5 | $SO_2CF_3$ | $CDCl_3$ | 100 | No reaction after 18h |
| 6 | $COCF_3$ | $CDCl_3$ | 100 | No reaction after 18h |
| 7 | $SO_2CF_3$ | DMSO-$d_6$ | 120 | Traces of hydrogenation |
| 8 | $COCF_3$ | DMSO-$d_6$ | 120 | Traces of hydrogenation |

[a] Based on analysis of $^1$H NMR spectra

It was found that the entries using tosylhydrazine (1-4) resulted in hydrogenation of the triple bonds down to the corresponding ethyl benzene. This reactivity was also observed with triflic- and trifluoroacetyl-hydrazines (entries 7 and 8) under higher reaction temperature. These results were not surprising due to the literature precedence for hydrogenation using electron-withdrawing hydrazines through the *in-situ* formation of diimide.[65] The unsuccessful attempts using activated hydrazines then prompted the pursuit of the approach using simpler, unactivated hydrazines. Without the presence of potentially labile groups, reaction conditions may be used which more closely resemble those which were successfully developed for hydroxylamines.[62]

### 2.2.2 Intermolecular hydroamination of alkynes with unactivated hydrazines: Initial results

The use of aqueous hydrazine yielded the first significant indication of successful hydroamination with alkynes and a hydrazine nucleophile (eq 2.7). Two equivalents of hydrazine were successfully reacted with phenyl acetylene (**2.6**) with methanol as the solvent, and heated to 113°C for 18 hours in a sealed tube. The major products determined by crude $^1$H NMR analysis were the two anti-Markovnikov isomers of **2.18** (*E* and *Z*). This result was in stark contrast with the selectivity observed with hydroxylamine, which favours the formation of the Markovnikov product. These hydrazone products, however, were not possible to isolate by silica column chromatography due to decomposition. Subsequent attempts at isolation of the hydrazones were unsuccessful and necessitated the addition of styrene as an internal standard for the calibration of crude $^1$H NMRs.

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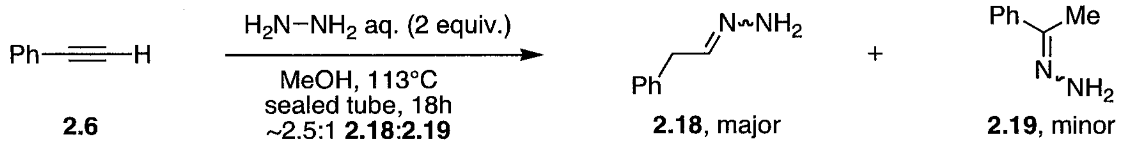
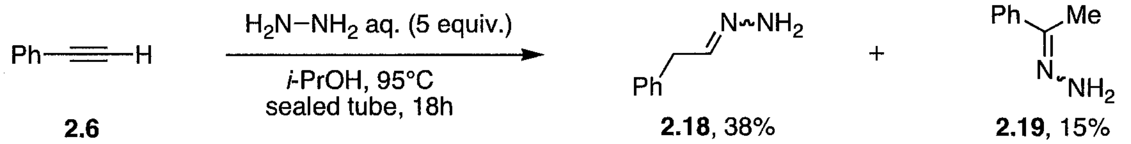
[65] Hydrogenation occurs via the hydrogen donor diimide, which is generated *in situ* upon the elimination of the electron withdrawing group. Van Tamelen, E. E.; Dewey, R. S.; Lease, M. F.; Pirkle, W. H. *J. Am. Chem. Soc.* **1961**, *83*, 3725.

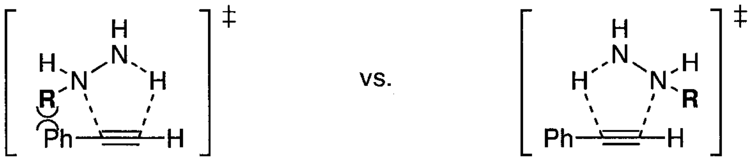


(2.7)



(2.8)

The first reaction to be calibrated with the internal standard yielded 38% conversion to the anti-Markovnikov products and 15% conversion to the Markovnikov products (eq. 2.8, 2.5:1 AM:M selectivity). The changes in reaction conditions from the initial result were done to more closely resemble the current optimal conditions in the development of the intermolecular Cope-type hydroamination of hydroxylamine and alkenes by Mr. Joseph Moran.[62] Now that it seemed the electronics were indeed in place to favour the desired anti-Markovnikov product, it was then postulated whether increased selectivity could be obtained using a *substituted* hydrazine, which would further favour the anti-Markovnikov product via steric hinderance (Figure 2.4).

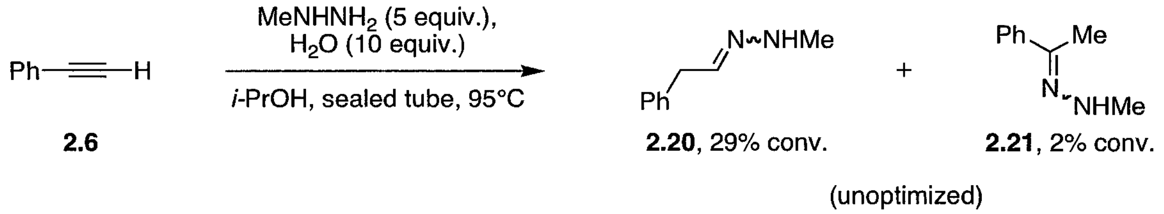


Markovnikov disfavoured

anti-Markovnikov favoured

Figure 2.4. Proposed transition states for the reaction between mono-substituted hydrazine and phenylacetylene

A preliminary result with methyl hydrazine supported this hypothesis and yielded an improved selectivity of 15:1 with 29 and 2% conversion to the anti-Markovnikov and Markovnikov products, respectively (eq. 2.9). The addition of water was utilized to mimic the same amount of water present in the hydrazine hydrate reagent used previously. Optimization studies and scope determination of this new hydroamination reactivity with methyl hydrazine were then undertaken.

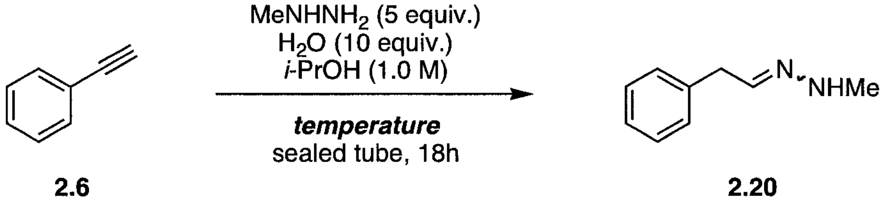


(2.9)

## 2.2.3 Intermolecular hydroamination of alkynes with methyl hydrazine: Optimization

The first optimization study was performed with respect to varying the temperature (Table 2.2). This study was aimed at quickly determining an appropriate approximate temperature range as it was previously found with the optimization of the Cope-type hydroamination of alkynes with hydroxylamine that temperature changes did not have as significant an impact on conversions as other variables.[66] The highest conversion to the desired anti-Markovnikov product **2.20** was obtained by running the reaction at 113°C (Entry 2).

**Table 2.2.** Temperature optimization with phenylacetylene and methyl hydrazine



| Entry | Temperature (°C) | % Conversion[a] |
|---|---|---|
| 1 | 70 | 11 |
| **2** | **113** | **67** |
| 3 | 140 | 43 |

[a] Calculated from analysis of $^1$H NMR spectra using styrene as internal standard (0.25 equiv.). Both *E* and *Z* anti-Markovnikov isomers were included in the calculation.

A solvent scan was performed with a series of protic and aprotic polar solvents, and in addition the effect of water as an additive was also explored (Table 2.3). Sufficiently polar solvents were necessary to efficiently solubilize the methyl hydrazine, and water was omitted due to its inability to completely solubilize the acetylene starting material.

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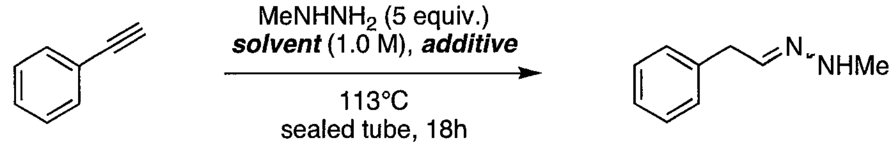
[66] Lebrun, M-E. MSc. Thesis, Department of Chemistry, University of Ottawa: Ottawa, 2008.

**Table 2.3.** Solvent scan with and without water as an additive



**2.6** **2.20**

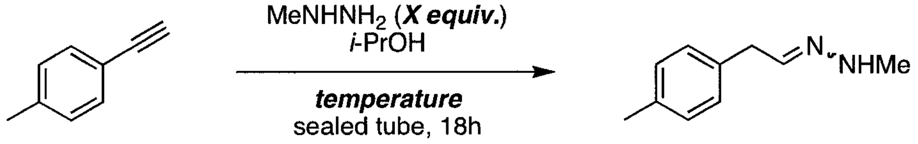
| Entry | Solvent | Additive (mol %) | % Conversion[a] |
|---|---|---|---|
| 1 | Dioxane | $H_2O$ (10 equiv.) | 56 |
| 2 | MeOH | $H_2O$ (10 equiv.) | 54 |
| 3 | EtOH | $H_2O$ (10 equiv.) | 36 |
| 4 | *n*-PrOH | $H_2O$ (10 equiv.) | 41 |
| 5 | *i*-PrOH | $H_2O$ (10 equiv.) | 59 |
| 6 | Dioxane | - | 20 |
| 7 | DMSO-$d_6$ | - | 34 |
| **8** | ***i*-PrOH** | **-** | **82** |
| 9 | $MeNO_2$ | - | 11 |

[a] Calculated from analysis of $^1H$ NMR spectra using styrene as internal standard (0.25 equiv.). Both *E* and *Z* anti-Markovnikov isomers were included in the calculation.

Isopropanol was revealed as the most efficient solvent among those with water as an additive (Entry 5, 59%). A significant increase in conversion was observed with isopropanol, however, when water was omitted from reaction mixture (Table 2.3, Entry 8). In the case of hydroxylamines, it had been already established that the hydroamination involves a high-energy proton transfer step which is greatly facilitated by a bimolecular proton donation pathway.[62] It was for this reason that protic solvents, such as isopropanol, often furnished higher conversions than their non-protic counterparts. It appeared from these results that adding water to an otherwise aprotic solvent increased the conversion. This increase was observed dioxane with water (Entry 1, 56%), which was significantly higher than when water was absent (Entry 6, 20%). The trials with polar aprotic solvents such as dimethyl sulfoxide (Entry 7, 34%) and nitromethane (Entry 9, 11%), illustrated the importance of a proton source in this transformation. The differences in conversion between the protic solvents with water (Entries 2-5) could not be easily explained using simple chemical concepts like acidity.

Having obtained a reasonably high conversion with **2.6** (Entry 8, 82%), further optimization was achieved using an alkyne that was less reactive under the current reaction conditions: *p*-tolyl acetylene (**2.21**). Optimization of the reaction conditions with respect to concentration, temperature, and hydrazine equivalents (Table 2.4) was performed.

**Table 2.4.** Optimization of temperature, concentration, and hydrazine equivalents with *p*-tolyl acetylene (**2.21**)



**2.21** **2.22**

| Entry | Temperature (°C) | Concentration (M)[a] | Equiv. Hydrazine | % Conversion[b] |
|---|---|---|---|---|
| 1 | 113 | 1.0 | 5 | 31 |
| 2 | 120 | 1.0 | 5 | 45 |
| **3** | **140** | **1.0** | **5** | **65** |
| 4 | 160 | 1.0 | 5 | 59 |
| 5 | 140 | 0.1 | 5 | 57 |
| 6 | 140 | 0.5 | 5 | 50 |
| 7 | 140 | 2.0 | 5 | 33 |
| 8 | 140 | 1.0 | 1 | 7 |
| 9 | 140 | 1.0 | 2 | 21 |
| 10 | 140 | 1.0 | 10 | not determined[c] |

---

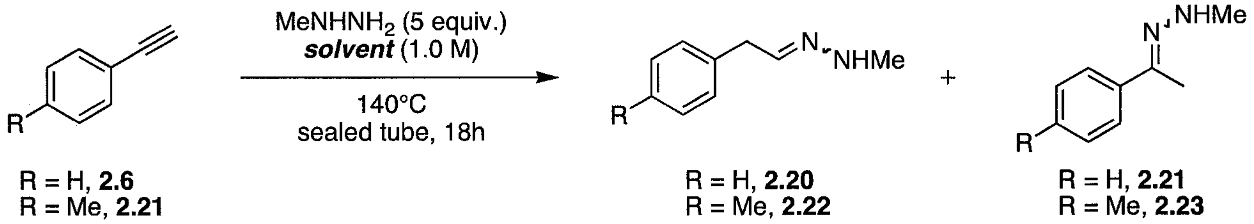
[a] Solvent concentration calculated with respect to alkyne, not considering additional volume of reagents.

[b] Calculated from analysis of $^1$H NMR spectra using styrene as internal standard (0.25 equiv.). Both *E* and *Z* anti-Markovnikov isomers were included in the calculation.

[c] High concentration of hydrazine inhibited reliable $^1$H NMR peak integration.

The best results were seen in Entry 3, with a reaction temperature of 140°C, a concentration of 1.0 M with respect to the alkyne, and using five equivalents of methyl hydrazine. The solvent was subsequently optimized for **2.21** and the regioselectivity was calculated for the anti-Markovnikov (**2.22**) and Markovnikov (**2.23**) isomers in order to note any solvent effects on the product distribution (Table 2.5). Two additional solvents (THF and toluene) were attempted with **2.6** under the slightly updated conditions (temperature increased to 140°C from the previous 113°C). The product distribution between the anti-Markovnikov and Markovnikov hydrazones (**2.20** and **2.21**, respectively) was also calculated for these solvents as well as that with isopropanol.

**Table 2.5.** Solvent scan with phenylacetylene (**2.6**) and *p*-tolyl acetylene (**2.21**)



| Entry | R | Solvent | % Conversion (**AM**:**M**)[a,b] |
|---|---|---|---|
| 1 | H | THF | 53 (7:1) |
| 2 | H | Toluene | 23 (9:1) |
| **3** | **H** | ***i*-PrOH** | **88 (14:1)** |
| **4** | **Me** | ***i*-PrOH** | **73 (8:1)** |
| 5 | Me | EtOH | 71 (8:1) |
| 6 | Me | Dioxane | 29 (4:1) |
| 7 | Me | DMSO-$d_6$ | 53 (6:1) |
| 8 | Me | neat | 0 |

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[a] Calculated from analysis of $^1$H NMR spectra using styrene as internal standard (0.25 equiv.). Both *E* and *Z* anti-Markovnikov isomers were included in the calculation.
[b] Regioselectivity was determined by $^1$H NMR.

For phenylacetylene (**2.6**), the non-polar solvents THF and toluene (Entries 1 and 2) respectively exhibited moderate and poor reactivity, but both **2.6** and **2.21** demonstrated decent selectivity for the anti-Markovnikov isomers (**2.20** and **2.22**, respectively). Comparably, the entry with isopropanol (3) achieved the highest conversion under the reaction conditions (88%) and the best regioselectivity (14:1 AM:M). Slightly lower conversions and selectivities were seen with *p*-tolyl acetylene (**2.21**), which again had the best results with isopropanol (Entry 4, 73%, 8:1 AM:M).

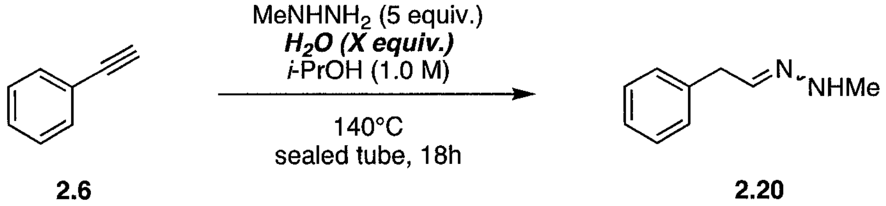
### 2.2.4 Investigations into reactivity

Control experiments were performed with phenylacetylene (**2.6**) to gain some further mechanistic insight into the reactivity. The optimized reaction conditions were used (5 equiv. $MeNHNH_2$, 1.0 M *i*-PrOH, 140°C for 18h) with the addition of chosen additives. The addition of 5 equivalents of diisopropylethylamine (Hünig's base) resulted in only a slight decrease in conversion and selectivity (35%, 8:1 AM:M). The addition of one equivalent of acetic acid also had a minimal effect on the reaction outcome (33% conversion, 7:1 AM: M selectivity). To investigate the possible generation and role of radicals, butylated hydroxytoluene (BHT) was added (5.1 equiv.) and still resulted in an overall conversion of 29%. Overall, while these investigations were limited, these results suggest that acid or base catalysis, or the generation of free radicals, do not appear likely under our reaction conditions.

### 2.2.5 Reproducibility

Upon performing the previous optimizations (Section 2.2.3), it was noted that the conversions obtained for different trials under identical reaction conditions were sometimes differing by as much as 25%. The presence of air and moisture were not previously considered in detail due to the initial inclusion of water as an additive. An investigation into the effect of water and type of atmosphere was performed in collaboration with Jean-Grégoire Roveda and the results are presented below in Table 2.6. To be certain of the amount of water present, the methyl hydrazine was dried and purified by distillation over barium oxide. Isopropanol had always been previously distilled for each optimization trial.

**Table 2.6.** Effect of water and oxygen vs. inert atmosphere in the reaction between phenylacetylene (**2.6**) and methyl hydrazine.



| Entry | Equiv. $H_2O$ | $O_2$/Ar | % Conversion[a] |
|---|---|---|---|
| 1 | 10 | $O_2$ | 43 |
| 2 | 10 | Ar | 49 |
| 3 | 2 | Ar | 38 |
| 4 | 0 | $O_2$ | 65 |
| **5** | **0** | **Ar** | **69** |

[a] Calculated from analysis of $^1$H NMR spectra using styrene as internal standard (0.25 equiv.). Both *E* and *Z* anti-Markovnikov isomers were included in the calculation.

When using both distilled solvent and methyl hydrazine and adding known amounts of water, the highest conversions to the anti-Markovnikov products were obtained when water was present under an inert atmosphere (Entry 3, 49%), but the best result was obtained in the absence of water under an inert atmosphere (Entry 5, 69%). These results suggested an oxygen atmosphere had a detrimental effect on the reaction,[67] and confirmed that the complete absence of water yielded the highest conversions in isopropanol, despite being beneficial in other conjunction with other solvents. All proceeding experiments were then conducted with distilled methyl hydrazine under an inert atmosphere of argon and were found to be significantly more consistent.

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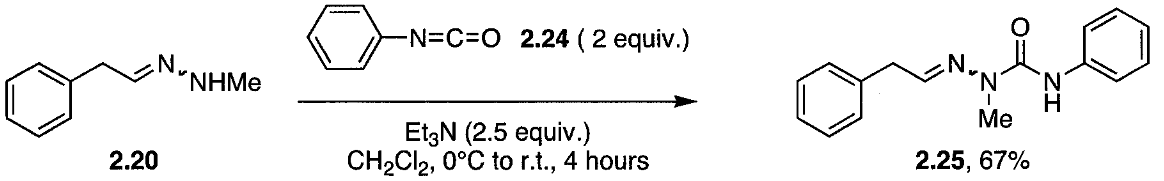
[67] Unsubstituted hydrazine is known to oxidize to diimide in air ($O_2$). Buyle, R.; Van Overstraeten, A. *Chem. Ind.* **1964**, 839.

## 2.2.6 Substrate scope and hydrazone derivatization

The substrate scope of the intermolecular hydroamination of alkynes was then to be determined under the optimized reaction conditions. The isolation of these hydroamination products, however, was challenging. The instability of the resulting linear hydrazones is well-known in literature.[68] A common solution to this problem had been to use silica gel pre-treated with 0.5-1% triethylamine. This solution was not able to be extended to these hydrazones, nor was using basic alumina column chromatography. Attention was quickly turned to possible derivatization procedures. Literature precedence for the derivatization of preformed hydrazones has been limited, as the derivatization of hydrazones usually took place in the hydrazone-formation step itself via the condensation of a derived hydrazine with the requisite ketone.[69] Attempts were made to form a Myers-inspired TBS derivative[68] but were unsuccessful. Preliminary attempts at hydrogenolysis to be followed by acylation to yield the corresponding amide were also ineffective as they resulted in decomposition. An initial trial using the derivatization procedure used by Whipp[70] for isolating acid-promoted intramolecular alkene hydroamination was met with modest success as the reaction of the phenyl acetylene-derived hydrazone **2.20** with phenyl isocyanate (**2.24**) yielded the semicarbazide **2.25** in 10% yield.[71] This semicarbazide proved to be stable enough for full characterization when kept in the freezer overnight. Mastery of the moisture-sensitive reaction conditions proceeded to give an improved yield of 67%[71] (eq. 2.10, 58% over two steps). This approach to solving the isolation problem had been previously considered in the early stages of the optimization process, but had been dismissed due to the presence of water in the hydrazine hydrate reagent or as an additive.



(2.10)

The one-pot derivatization of the resulting hydrazone to the corresponding semicarbazide proved at this point to be the most effective means of isolation and was therein used to in determining the scope of the reaction (Table 2.7). As previously reported, the conversions and regioselectivities were determined by $^1H$

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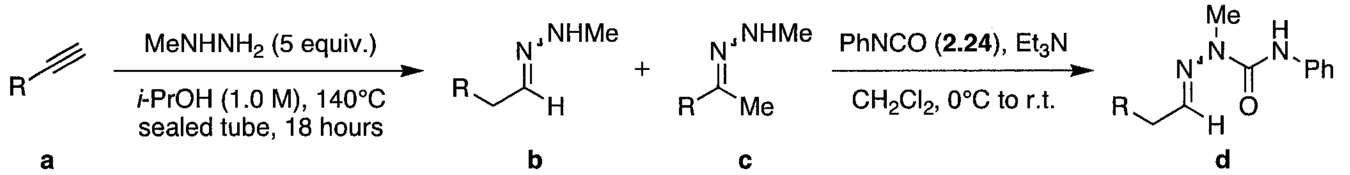
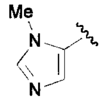
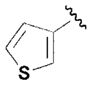
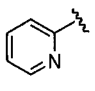
[68] Myers, A. G.; Furrow, M, E. *J. Am. Chem. Soc.* **2004**, *126*, 5436.
[69] Justo de Pomar, J. C.; Soderquist, J. A. *Tetrahedron Lett.* **2000**, *41*, 3285.
[70] Whipp, C. Honours Thesis, Department of Chemistry, University of Ottawa: Ottawa, 2007.
[71] Calculated from the conversion of anti-Markovnikov hydrazone **2.20**.

NMR using styrene as an internal standard and the reported yield is the isolated yield following column chromatography after both hydroamination and derivatization steps.

**Table 2.7.** Alkyne substrate scope



| Entry | R | % Conversion[a] (b+c) | Regioselectivity[b] (b:c) | Yield[c] (d) |
|---|---|---|---|---|
| 1 | **2.6** $C_6H_5$ | 87 | 14:1 | 58 (**2.25**) |
| 2 | **2.26** 2-Me($C_6H_4$) | 76 | 5:1 | 50 (**2.37**) |
| 3 | **2.27** 3-Me($C_6H_4$) | 77 | 15:1 | 49 (**2.38**) |
| 4 | **2.21** 4-Me($C_6H_4$) | 73 | 8:1 | 37 (**2.22**) |
| 5 | **2.28** 4-F($C_6H_4$) | 72 | 9:1 | 44 (**2.39**) |
| 6 | **2.29** 2-MeO($C_6H_4$) | 66 | 32:1 | 40 (**2.40**) |
| 7 | **2.30** 4-MeO($C_6H_4$) | 30 | 5:1 | — |
| 8 | **2.31** 3,5-($CF_3$)$_2C_6H_3$ | 77 | 10:1 | 31 (**2.41**) |
| 9[d] | **2.32**  | 76 | 25:1 | 55 (**2.42**) |
| 10 | **2.33**  | 81 | 6:1 | 45 (**2.43**) |
| 11 | **2.34**  | 68 | 32:1 | — |

| | | | | |
|---|---|---|---|---|
| 12 | **2.35** 2-NH$_2$(C$_6$H$_4$) | 0 | — | — |
| 13 | **2.36** *n*-C$_6$H$_{13}$ | 0 | — | — |

[a] Calculated from analysis of $^1$H NMR spectra using styrene as internal standard (0.25 equiv.). Both *E* and *Z* isomers for the anti-Markovnikov and Markovnikov isomers were included in the calculation.

[b] Regioselectivity was determined by $^1$H NMR.

[c] Isolated yield of both *E* and *Z* isomers for the anti-Markovnikov products. Purified by silica column chromatography.

[d] Entry added by Mr. Jean-Gregoire Roveda.

The intermolecular Cope-type hydroamination was found to be the most efficient with the unsubstituted phenyl acetylene substrate **2.6** (Entry 1, 87% conversion). Good reactivity was seen with each of the methyl-substituted isomers **2.26**, **2.27** and **2.21** (Entries 2-4), electron-withdrawing fluorinated phenyl acetylenes **2.28** and **2.31** (Entries 5 and 8), and the heterocyclic acetylenes, imidazole **2.32**, thiophene **2.33**, and pyridine **2.34** (Entries 9, 10, and 11). Moderate to poor reactivity was seen with the electron-rich phenyl acetylenes **2.29** and **2.30** (Entries 6 and 7). This decrease in reactivity may be due to increased electron density in the π system relative to the other substrates (caused by induction), which would increase the electrostatic repulsion between the alkyne moiety and the approaching nucleophilic hydrazine nitrogen. No reactivity was detected with the aniline substrate **2.35**,[72] which may be due to the very electron-rich character of the aniline, or with the alkyl acetylene **2.36** (Entry 13). It should be noted, however, that the reaction conditions for each of these two entries were not optimized at the time and that more forcing conditions have been known to be effective with less reactive substrates in the hydroamination of alkynes with hydroxylamine.[62] Each of the terminal hydrazone intermediates in Entries 1-6 and 8-10 were modestly able to be transformed into and isolated as the corresponding semi-carbazides upon reaction with phenyl isocyanate (**2.24**). In the case of the substrate **2.30** (Entry 7), the initial conversion to the hydrazone was likely too low to be viable for derivatization. The derivatization of the hydroamination between methyl hydrazine and the pyridine-substituted acetylene **2.34** (Entry 11) resulted the in apparent formation of the semi-carbazide,[73] but the product mixture underwent rapid decomposition upon purification attempts. The calculated regioselectivities of the hydroaminations ranged from 5:1 (Entries 2 and 7) to 32:1 (Entries 6 and 11), which are moderate to excellent. For each of the entries which exhibited the highest regioselectivity (6, 9 and 11), the substrate contained a heteroatom α to the alkyne

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[72] Only starting material was observed; no side reactions appeared to have taken place.

[73] The semi-carbazide was observed by crude $^1$H NMR.

moiety. These results suggest that perhaps the presence of a heteroatom helps stabilize the transition state by being able to accept electron density that builds up on the adjacent carbon.

In general, it appears that the intermolecular Cope-type hydroamination of alkynes with methyl hydrazine is effective at regioselectively producing the corresponding linear, anti-Markovnikov hydrazone with a variety of terminal aryl acetylenes (as seen in Table 2.7). The hydroamination products themselves are relatively unstable to typical purification methods but may successfully be derivatized and isolated as semi-carbazides upon reaction with phenyl isocyanate (**2.24**). Under the current reaction conditions, very electron-rich aryl acetylenes and aliphatic alkynes are not amenable to hydroamination with methyl hydrazine.

### 2.2.7 Computational calculations

Density functional theory (DFT) calculations were performed by Dr. Serge Gorelsky[74] at the University of Ottawa to gain further insight into the intermolecular Cope-type hydroamination between hydrazines and alkynes. Calculations were done for the reaction between phenyl acetylene in the gas phase at the B3LYP/TZVP level of theory. The results of these calculations are presented in Table 2.8 and Figure 2.5.

**Table 2.8.** Free energies (kcal/mol) of the reaction between methyl hydrazine ($MeNHNH_2$) and phenyl acetylene (**2.6**) at 298K and 1 atm. Free energies are relative to the free reactants.

| Species | $AM_a$ | $AM_b$ | $M_a$ | $M_b$ |
|---|---|---|---|---|
| RC[a] | 4.5 | 5.5 | 4.5 | 5.5 |
| TS[b] | 41.5 | 39.1 | 40.5 | 40.6 |
| TS[b] in MeOH[c] | 38.3 | 36.3 | 44.4 | 43.9 |

[a] Reactants complex
[b] Transition state
[c] Calculated using the polarizable continuum model (PCM)

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[74] Using Prof. T. Woo's computing facility at the University of Ottawa. Computational details are provided in the supplemental information section of Cebrowski, P. H.; Roveda, J.-G.; Moran, J.; Gorelsky, S. I.; Beauchemin, A. M. *Chem. Commun.* **2008**, 492.

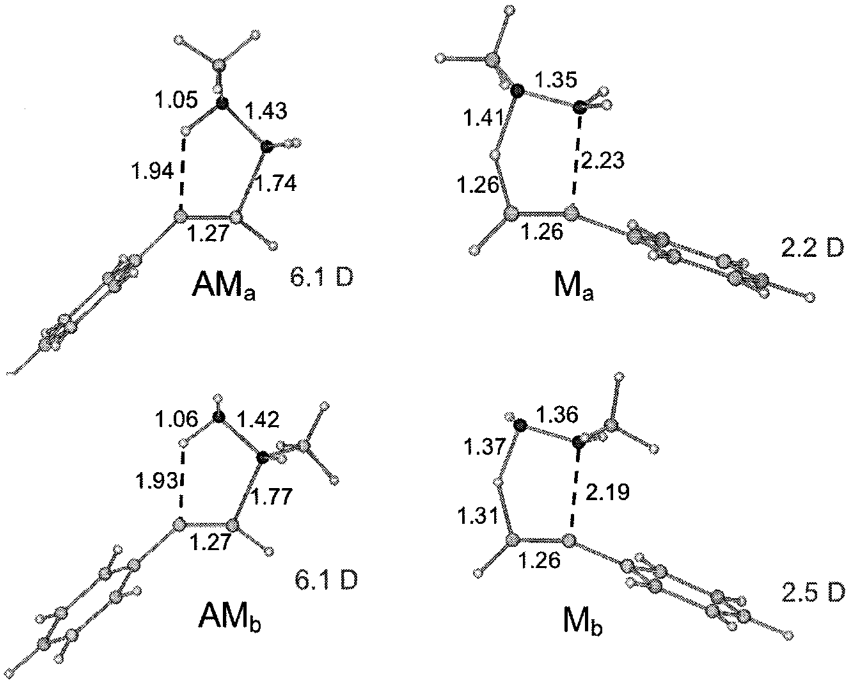

Figure 2.5. Transition state structures for the reaction between methyl hydrazine ($MeNHNH_2$) and phenylacetylene (**2.6**, $C_8H_6$). Internuclear distances (Å) are shown only for relevant chemical bonds. Calculated dipole moments (Debye) are shown in red.

When considering the reaction between phenyl acetylene (**2.6**) and methyl hydrazine, it was calculated that there are two different possible transition states each for the anti-Markovnikov and Markovnikov isomers, $AM_a$, $AM_b$ and $M_a$, $M_b$ respectively. These different transition states are possible because methyl hydrazine is asymmetrical, which means that either of the two nitrogen atoms can participate in the N-C bond forming event. Both gas phase and methanol-solvated transition state free energies predicted anti-Markovnikov selectivity, which corresponds well to the experimental observations. The free energies for each transition state in isopropanol are expected to lie somewhere between those calculated for the gas phase and for methanol. The significant difference in free energy between the gas phase and methanol-solvated models (up to 3.9 kcal/mol for the transition state of the $M_a$ isomer) indicated how greatly the solvent can affect the transition state free energy ($\Delta G^\ddagger$). In the gas phase, TS $AM_b$ has the lowest $\Delta G^\ddagger$ at 39.1 kcal/mol, and is favoured over TS $M_b$ by 1.5 kcal/mol. Although this transition state does not lead directly to the observed anti-Markovnikov product, this product can be obtained if the pathway outlined in eq. 2.11 is operational.[75] Upon attack of the methyl-

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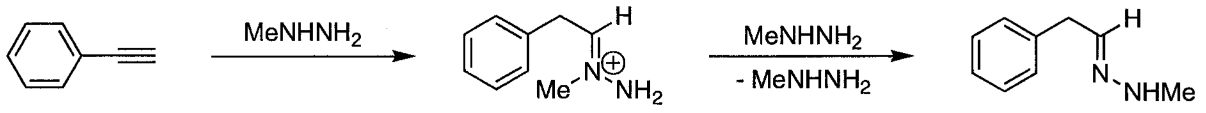
[75] Further investigation into this potential pathway would be required to support its role in this reaction.

substituted nitrogen atom through TS $AM_b$, the iminium **2.44** would be formed which could subsequently be attacked by a second equivalent of methyl hydrazine. Provided that the second equivalent of methyl hydrazine attacks through the non-methylated nitrogen atom, the elimination of the first equivalent of methyl hydrazine would then result in the observed hydrazone **2.20**.



**2.6** **2.44** **2.20**

(2.11)

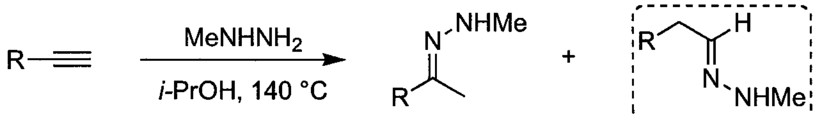
The energy difference of 1.5 kcal/mol is in good agreement with the observed regioselectivity of 14:1 for the anti-Markovnikov hydrazone (Table 2.7, Entry 1). In contrast, the TS $M_a$ showed a preference for the Markovnikov isomer by 1.0 kcal/mol in the gas phase, but when calculated in methanol, the anti-Markovnikov TS was favoured by an overwhelming 6.1 kcal/mol. Similarly, the TS $AM_b$ was favoured in methanol over TS $M_b$ by 7.6 kcal/mol and is the overall most favourable calculated transition state. These calculations did lead to the right "prediction," however, both differences in free energies, $\Delta(\Delta G^{\ddagger})$, are high enough to suggest *significantly* higher than >100:1 selectivities, which were not observed experimentally.

Examination of the internuclear distances for relevant chemical bonds for each of the transition state structures (Figure 2.5) revealed that although they are planar and concerted, they are asynchronous. The distance of approximately 1.7Å between the C and N atoms in the anti-Markovnikov transition states strongly suggested that this bond-forming event is the first to occur. In contrast, the Markovnikov transition states indicate the abstraction of the H atom from the hydrazine occurring prior to the nitrogen addition. These results are similar to the calculations corresponding to the reaction between alkynes and hydroxylamine,[66] although in the case of hydrazine they are even more asynchronous. Based on these calculations, it could be possible to better optimize the reaction through the use of increasingly nucleophilic hydrazines (increasing the electron density on the attacking nitrogen). These results also lend support as to why excessively-rich alkynes were much less reactive (or non-reactive) than electron-deficient alkynes (Table 2.7).

In general, the DFT calculations of the transition state free energies ($\Delta G^{\ddagger}$) of the reaction between phenyl acetylene (**2.6**) and methyl hydrazine showed a regioselective preference for the anti-Markovnikov isomer **2.20**. The calculations were thus in good agreement with the observed experimental results.

### 2.2.8 Conclusions

The Cope-type intermolecular hydroamination of alkynes was developed to achieve anti-Markovnikov regioselectivity which is complementary to the corresponding process with hydroxylamines.[62] The anti-Markovnikov reactivity was first observed between phenyl acetylene and hydrazine, and the reaction was subsequently developed with methyl hydrazine to achieve good yields and regioselectivities with a variety of aryl acetylenes (eq. 2.12). The optimal reaction conditions consisted of using 5 equivalents of methyl hydrazine and heating to 140°C in isopropanol for 18 hours in a sealed tube. Challenges with the isolation of the resulting linear hydrazones resulted in the development of a derivatization procedure with phenyl isocyanate to afford semicarbazides. DFT calculations were performed to gain further mechanistic insight and showed that a transition state leading to the anti-Markovnikov isomer had the lowest activation energy. Although the activation energy differences between the anti-Markovnikov and corresponding Markovnikov transition states were not quite in line with the experimental results, they did accurately predict that the reaction would be selective for an anti-Markovnikov product.



(2.12)

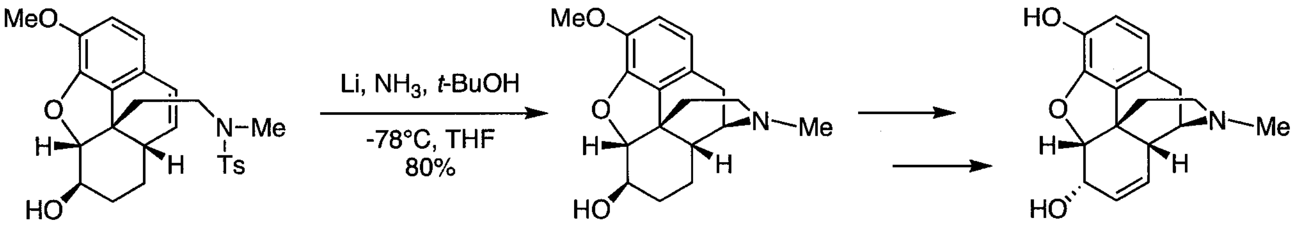
10 examples
regioselectivities 5:1 to 32:1

# 3

# Total synthesis of norreticuline

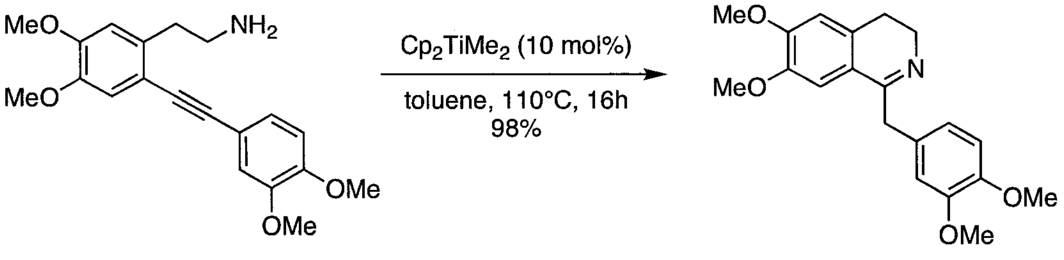
## 3.1 Cope-type and metal-catalyzed hydroaminations in alkaloid synthesis: A very difficult transformation in 6-membered systems

The total synthesis of alkaloids continues to be a highly popular area of research as alkaloids are medicinally important compounds and also present numerous synthetic challenges. As discussed earlier (Ch. 1), the integration of nitrogen into the molecule by hydroamination could be a highly efficient, and thus practical, approach. Hydroamination is seldom used in total synthesis, however, due to the lack of generally applicable procedures. The hydroamination of complex of synthetic intermediates is often too demanding and prevents application of literature methods that are documented only in significantly simpler systems. Employing a hydroamination key step could thus be particularly risky in the late stages of a total synthesis, especially if a 6-membered cycle would be formed or if the reaction involved an internal alkene. There are, however, a few instances where this desirable transformation was performed "late stage."



**3.1** **3.2** **3.3** (-)-morphine (3.1)

The formal synthesis of (–)-morphine by Parker and Fokas[76] used the Birch-like intramolecular hydroamination of the tertiary amine **3.1** as the key step to complete the final 6-membered ring of the alkaloid core structure (eq. 3.1). Mujahidin and Doye synthesized the key benzyldihydroisoquinoline intermediate **3.5** via the titanium-catalyzed hydroamination of the biaryl acetylene **3.4** in the total synthesis of both (+)-(*S*)-laudanosine (**(*S*)-3.6**) and (–)-(*S*)-xylopinine (**(S)-3.7**).[77] This strategy represents currently the best available technology to circumvent the difficulty of performing intramolecular alkene hydroamination to form 6-membered ring systems, as such cyclizations typically require the alkene to be terminal.[78] The common hydroamination precursor in this divergent synthesis was accessed by a Sonogashira coupling of the aryl acetylene **3.9** and aryl iodide **3.8** (scheme 3.1). This type of divergent approach was also to be employed in the total synthesis norreticuline (**3.24**), which would allow facile access to other benzyltetrahydroisoquinolines.



**3.4** **3.5**

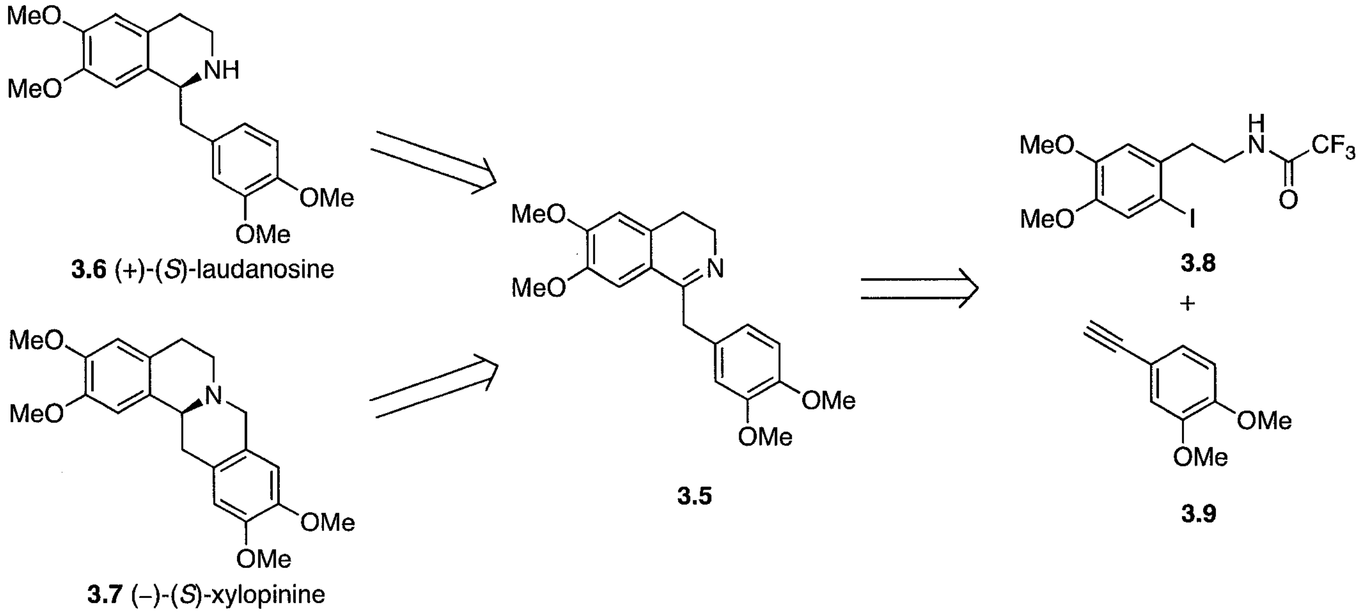
(3.2)

---

[76] Parker, K. A.; Fokas, D. *J. Org. Chem.* **2006**, *71*, 449.

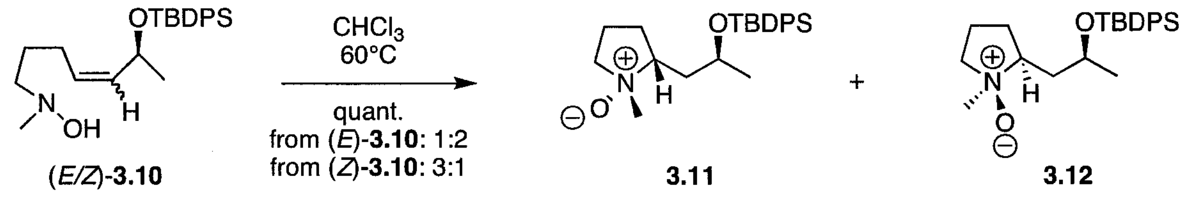
[77] Mujahidin, D.; Doye, S. *Eur. J. Org. Chem.* **2005**, 2689.

[78] Reports of 6-membered piperidine ring formation via hydroamination onto an *internal* alkene are rare. For examples, see: (a) Stubbert, B. D.; Marks, T. J. *J. Am. Chem. Soc.* **2007**, *129*, 4253. (b) Komeyama, K.; Morimoto, T.; Takaki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2938. (c) Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 1471.



Scheme 3.1. Retrosynthesis of (+)-(*S*)-laudanosine (**(*S*)-3.6**) and (–)-(*S*)-xylopinine (**(*S*)-3.7**) with hydroamination key step

The intramolecular Cope-type hydroamination method has also been applied to the total synthesis of alkaloids, but had been previously limited to the formation of 5-membered azacycles. Equations 3.3 and 3.4 illustrate the effective formation of pyrrolidines from Cope-type hydroaminations of either monosubstituted and disubstituted hydroxylamines onto substituted alkenes.[79] The limitation, however, is the inability to control the diastereoselectivity with respect to the distal oxygen substituent. Though in either case, the hydroamination products **3.11/3.14** and **3.12/3.15** are transformed into the natural products (+)-pseudohygroline (**3.16**) and (–)-hygroline (**3.17**), respectively.



(3.3)

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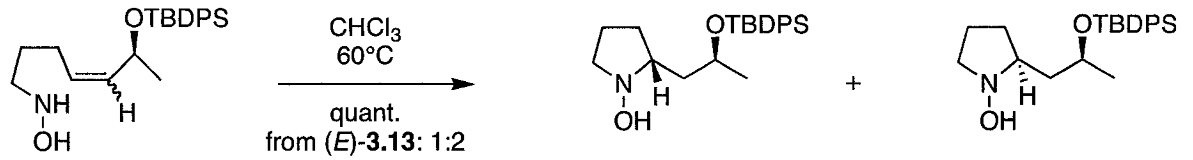
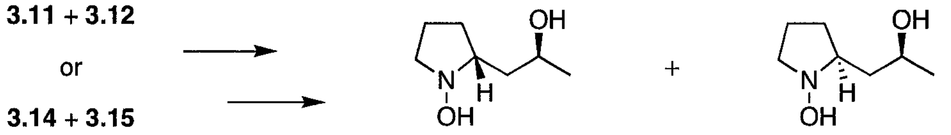
[79] Knight, D. W.; Salter, R. *Tetrahedron Lett.* **1999**, *40*, 5915.

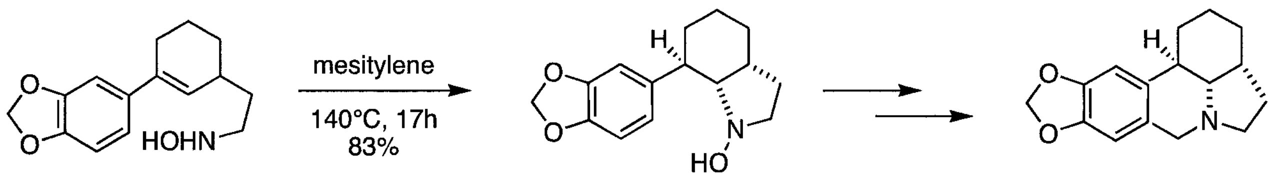


(*E*/*Z*)-**3.13** **3.14** **3.15** (3.4)

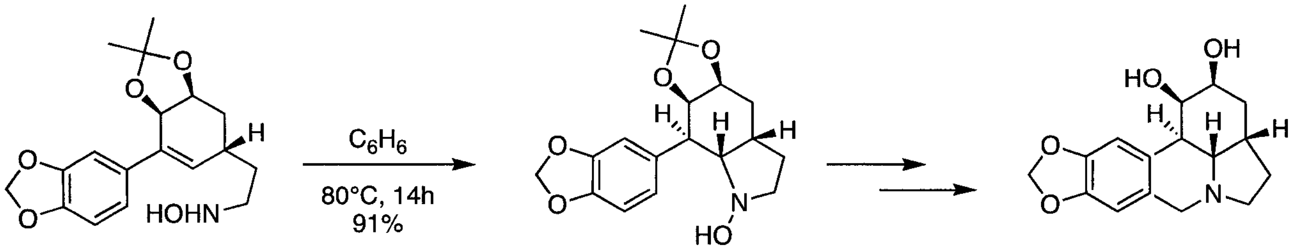


**3.16**, (+)-pseudohygroline **3.17**, (–)-hygroline (3.5)

The more complex alkaloids (±)-α-lycorane (**3.20**) and (+)-trianthine (**3.23**) were readily accessible via intramolecular Cope-type hydroaminations of internal alkenes (eq. 3.6 and 3.7).[80] In each case, the pyrrolidine formation gave a single diastereomer, which clearly illustrates the utility of the concerted nature of the transformation. These examples illustrate the robustness and utility of the 5-membered cyclization to form pyrrolidines.



**3.18** **3.19** **3.20**, (±)-α-lycorane (3.6)



**3.21** **3.22** **3.23**, (+)-trianthine (3.7)

The formation of 6-membered azacycles by a Cope-type hydroamination has been shown to be more challenging. Currently, the examples of such a cyclization are limited, as discussed in sections 1.2 and 1.3, although recent progress has been made in our group by the total synthesis of 2-epi-pumiliotoxin C,[81] which

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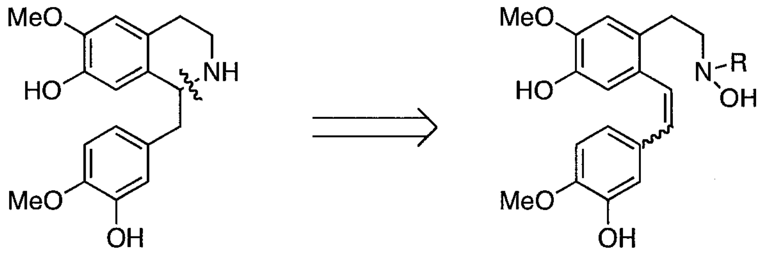
[80] Oppolzer, W.; Spivey, A. C.; Bochet, C. G. *J. Am. Chem. Soc.* **1994,** *116*, 3139.

[81] Lebrun, M.-E.; Pfeiffer, J.; Beauchemin, A. M. *Manuscript submitted for publication.*

may be the most complex example of a hydroamination key step in a bicyclic alkaloid synthesis to date. To continue to develop this important methodology in the Beauchemin group, the benzyl tetrahydroisoquinoline norreticuline (**3.24**) was chosen as the next challenging synthetic target.



**3.24**, norreticuline

**3.25**

(3.8)

Norreticuline (**3.24**) was a good synthetic target with which to further develop the Cope-type Hydroamination methodology because currently the use of hydroamination in benzyl tetrahydroisoquinolines is rare. As discussed in Section 3.1, hydroaminations are typically very substrate specific and such a transformation at the advanced stage of a synthesis could be considered risky. Typically the synthesis of these types of molecules exhibit the more classic isoquinoline synthesis reactions: Bischler-Napieralski,[82] Pictet-Spengler,[83] and Pomeranz-Fritsch.[84] These reactions are often very reliable, but they also have drawbacks such as the requirement of having electron-rich aromatic rings to enable the electrophilic aromatic substitution step common to these methods. Our methodology would allow for the synthesis of benzyl tetrahydroisoquinoline analogues with electron-poor aromatic rings and could be used as a general solution in the synthesis of otherwise poorly-reactive substrates. The formation of the 6-membered ring moiety in norreticuline (**3.24**) would allow for the further development of our Cope-type hydroamination strategy in complex systems.

## 3.2 Previous total syntheses of norreticuline and other benzyl tetrahydroisoquinolines

Norreticuline (**3.24**) is an alkaloid of the structurally diverse benzyl tetrahydroisoquinoline family. Benzyl tetrahydroisoquinolines have previously been used as versatile synthetic intermediates in the total

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[82] Bischler, A.; Napieralski, B. *Ber.* **1893**, *26*, 1903.
[83] Pictet, A.; Spengler, T. *Ber.* **1911**, *44*, 2030.
[84] (a) Fritsch, P. *Ber.* **1893**, *26*, 419. (b) Pomeranz, C. *Monatsh. Chem.* **1894**, *15*, 299. (c) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed. Blackwell Science Ltd.: Oxford, 2000, Chapter 6.

synthesis of more complex alkaloids[85] and are biosynthetic precursors of several other families such as morphinan,[86] aporphine,[87] protoberberine[88] and pavinan[89] alkaloids (figure 3.1).

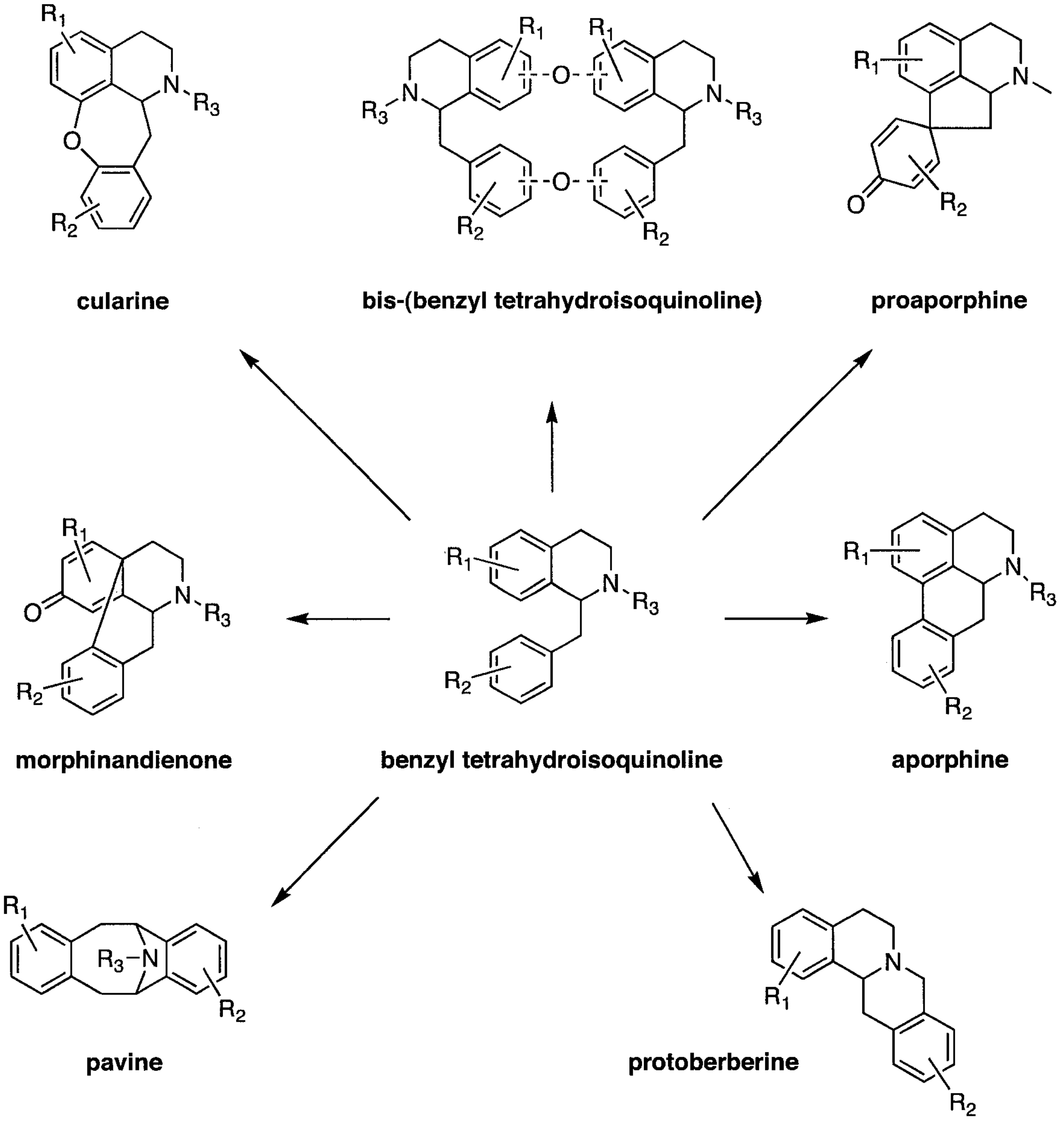

Figure **3.1**. Types of isoquinoline alkaloid structures derived from the benzyl tetrahydroisoquinoline skeleton in their respective biosyntheses.

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[85] (a) Kametani, T.; Sugahara, T.; Yagi, H.; Fukomoto, K. *Tetrahedron* **1969**, *25*, 3667. (b) Rice, K. C.; Ripka, W. C.; Reden, J.; Brossi, A. *J. Org. Chem.* **1980**, *45*, 601.

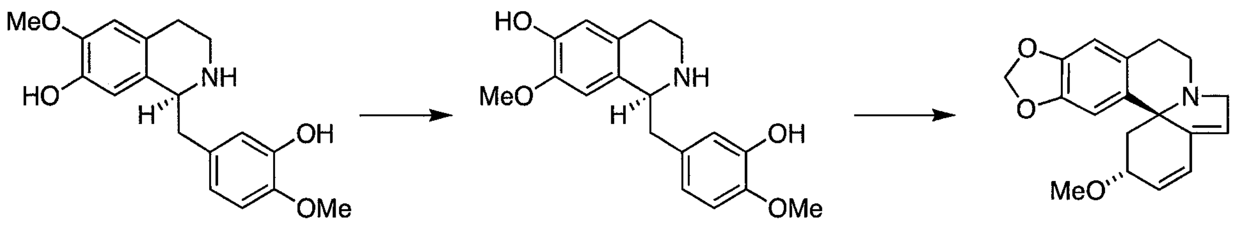
[86] Schwartz, M. A.; Pham, P. T. K. *J. Org. Chem.* **1988**, *53*, 2318.

[87] Zenk, M. H.; Rueffer, M.; Amann, M.; Deus-Neumann, B. *J. Nat. Prod.* **1985**, *48*, 725.

[88] Battersby, A. R.; Staunton, J.; Wiltshire, H. R.; Francis, R. J.; Southgate, R. J. *Chem. Soc. Perkin 1* **1975**, 1147.

[89] Rice, K. C.; Ripka, W. C.; Reden, J.; Brossi, A. *J. Org. Chem.* **1980**, *45*, 601.

In nature, (*S*)-**3.24** has been firmly established as a precursor in the biosynthesis of the spirocyclic *Erythrina*-type alkaloids,[90] which have been isolated and characterized in seven different *Erythrina* plant species.[91] The *Erythrina crista-galli* is a flowering tree in the Fabaceae family that is native to Argentina, Uruguay, Brazil and Paraguay, and pharmacological studies have demonstrated that the seed extracts from this tree possessed sedative, hypertensive, laxative and diuretic properties.[92] One of the first alkaloids of this type to have its biosynthetic pathway explored was erythraline (**3.27**), which was shown to be synthesized subsequently from (*S*)-**3.24** and (*S*)-norprotosinomenine ((*S*)-**3.26**, eq. 3.9).[93]



**(*S*)-3.24** **(*S*)-3.26** **(*S*)-3.27**

(3.9)

In 1983, Bhakuni, Gupta and Jain reported that norreticuline ((*S*)-**3.24**) is a biosynthetic precursor to the numerous tetrahydroprotoberberine alkaloids in the *Cocculus laurifolius*[94] and *Stephania glabra*[95] plants. These alkaloids, including scoulerine (**3.29**), sinactine (**3.30**), stepholidine (**3.31**), corydalmine (**3.32**), capaurine (**3.33**) and corynoxidine (**3.34**), are each synthesized via the common intermediate reticuline (**3.24**), as seen in Figure 3.2.

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[90] Maier, U. H.; Zenk, M. H. *Chem. Commun.* **1997**, 2313.

[91] Soto-Hernandez, M.; Jackson, A. H. *Planta Med.* **1994**, *60*, 175.

[92] Greshoff, M. *Chem. Ber.* **1890**, *23*, 3537.

[93] Barton, D. H. R.; James, R.; Kirby, G. W.; Turner, D. W.; Widdowson, D. A. *J. Chem. Soc. (C)* **1968**, 1529.

[94] Bhakuni, D. S.; Jain, S.; Gupta, S. *Tetrahedron* **1983**, *39*, 455.

[95] Bhakuni, D. S.; Gupta, S.; Jain, S. *Tetrahedron* **1983**, *39*, 4003.

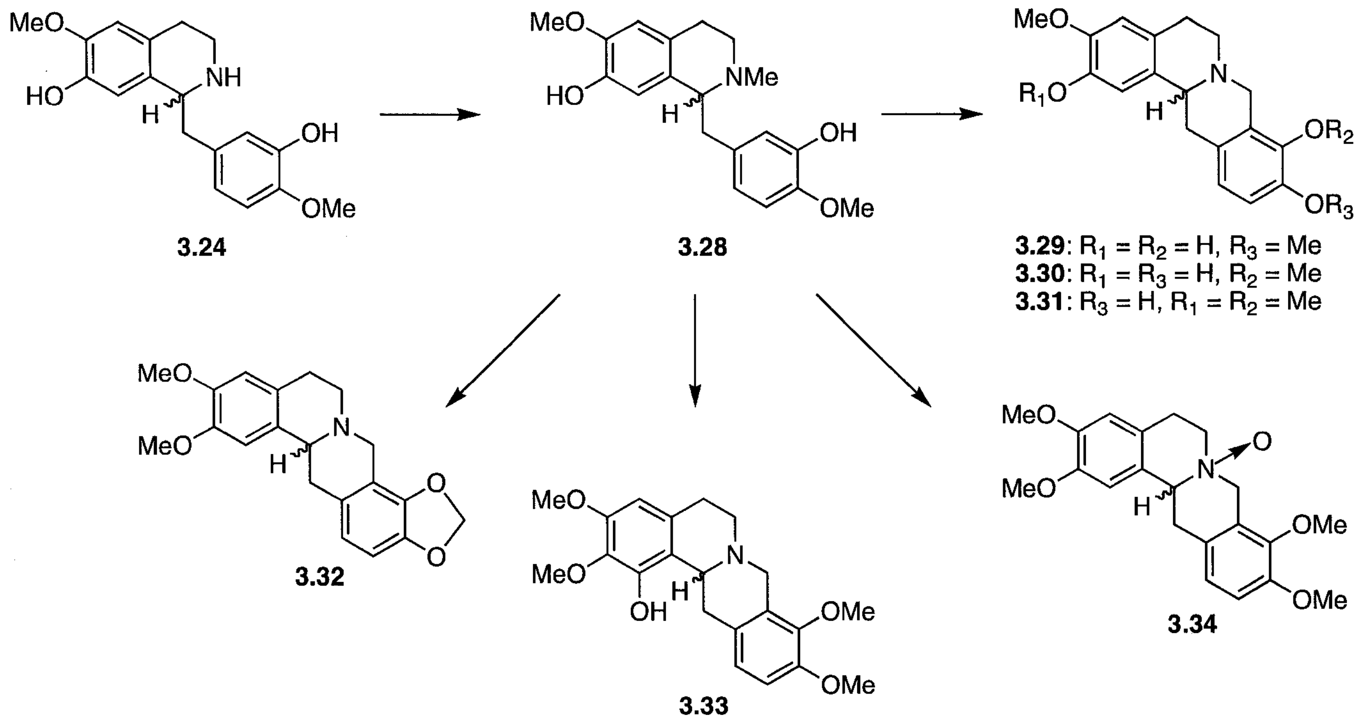

Figure 3.2. Biosynthesis of tetrahydroberberine alkaloids from norreticuline (**3.24**) and reticuline (**3.28**)

(*S*)-**3.24** is also a precursor in the biosynthesis of papaverine (**3.49**) in the opium poppy, *Papaver somniferum*, via the intermediates norlaudanidine and norlaudanosine.[96,97] It does not, however, participate in the biosynthesis of the morphinans in the opium poppy. Interestingly, (*R*)-**3.24** is thought to be a key intermediate in the biosynthesis of endogenous, mammalian morphine. It was reported by He *et al.* that (*R*)-**3.24** was converted in vitro to (*R*)-reticuline ((***R***)-**3.28**) via *N*-methylation by a mammalian enzyme.[98]

Despite being a biosynthetic precursor to numerous natural products, only a handful of distinct total syntheses of norreticuline (**3.24**) have been reported in literature to date. In each case, the key step involves an intramolecular cyclization to form the 6-membered benzyl-fused piperidine ring. This type of approach is common in the synthesis of benzyl tetrahydroisoquinolines. The earliest reported synthesis of **3.24** was by accomplished by Tomita and Kikkawa in 1956 which utilized a Bischler-Napieralski key step.[99] In 1975, Konda, Shioiri and Yamada reported using a Pictet-Spengler cyclization to form (*S*)-**3.24** as an intermediate

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[96] Battersby, A. R.; Harper, B. J. T. *J. Chem. Soc. London* **1962**, 3526.

[97] Brochmann-Hanssen, E.; Chen. C. H.; Chen, C. R.; Chiang, H. C. *J. Chem. Soc. Perkin Trans. 1* **1975**, 1931.

[98] He, X.-S.; Tadic, D.; Brzostowska, M.; Brossi, A.; Bell, M.; Creveling, C. *Helv. Chim. Acta.* **1991**, *74*, 1399.

[99] Tomita; Kikkawa, *Pharm. Bull. (Japan)* **1956**, *4*, 230.

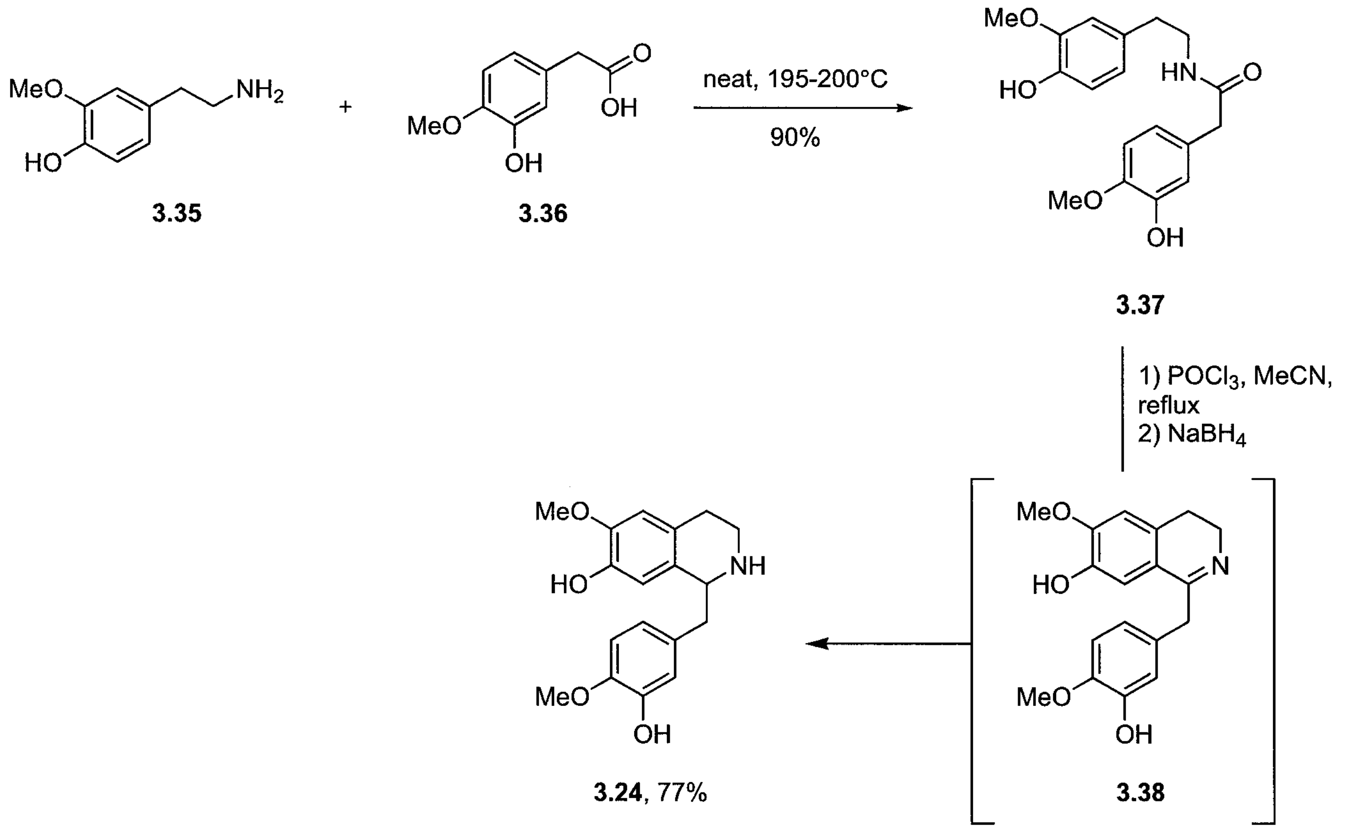
towards the asymmetric synthesis of (*S*)-reticuline, **(*S*)-3.28**.[100] Each proceeding synthesis of norreticuline (**3.24**) has used one of these methods, and these syntheses will be accounted in further detail in Sections 3.2.1 and 3.2.2, respectively. Derivatives of norreticuline have also been synthesized using Pomeranz-Fritsch and metal-catalyzed hydroamination key steps, which will be discussed in Sections 3.2.3 and 3.2.4, respectively.

### 3.2.1 Syntheses using Bischler-Napieralski

Since the synthesis by Tomita and Kikkawa in 1956, the most common approach to the synthesis of norreticuline (**3.24**) and its derivatives has been through a Bischler-Napieralski cyclization key step, followed by a reduction.[101] Battersby et al. accomplished a synthesis of **3.24** using this methodology in 1964 when exploring the biosynthetic pathways of thebaine, codeine and morphine,[102] and the same sequence was used more recently by Rice and Brossi with the goal of synthesizing *N*-substituted and 6'-bromo-*N*-norreticulines.[103] The synthetic sequence as outlined by Rice and Brossi is seen in scheme 3.2, which yielded racemic **3.24** in 41% yield over five linear steps (seven in total).

---

[100] Konda, M.; Shioiri, T.; Yamada, S.-I. *Chem. Pharm. Bull.* **1974**, *23*, 1063.
[101] Chrzanowska, M.; Rozwadowska, M. D.; *Chem. Rev.* **2004**, *104*, 3341.
[102] Battersby, A. R.; Binks, R.; Francis, R. J.; McCaldin, D. J.; Ramuz, H. *J. Chem. Soc.* **1964**, 3600.
[103] Rice, K. C.; Brossi, A. *J. Org. Chem.* **1980**, *45*, 592.

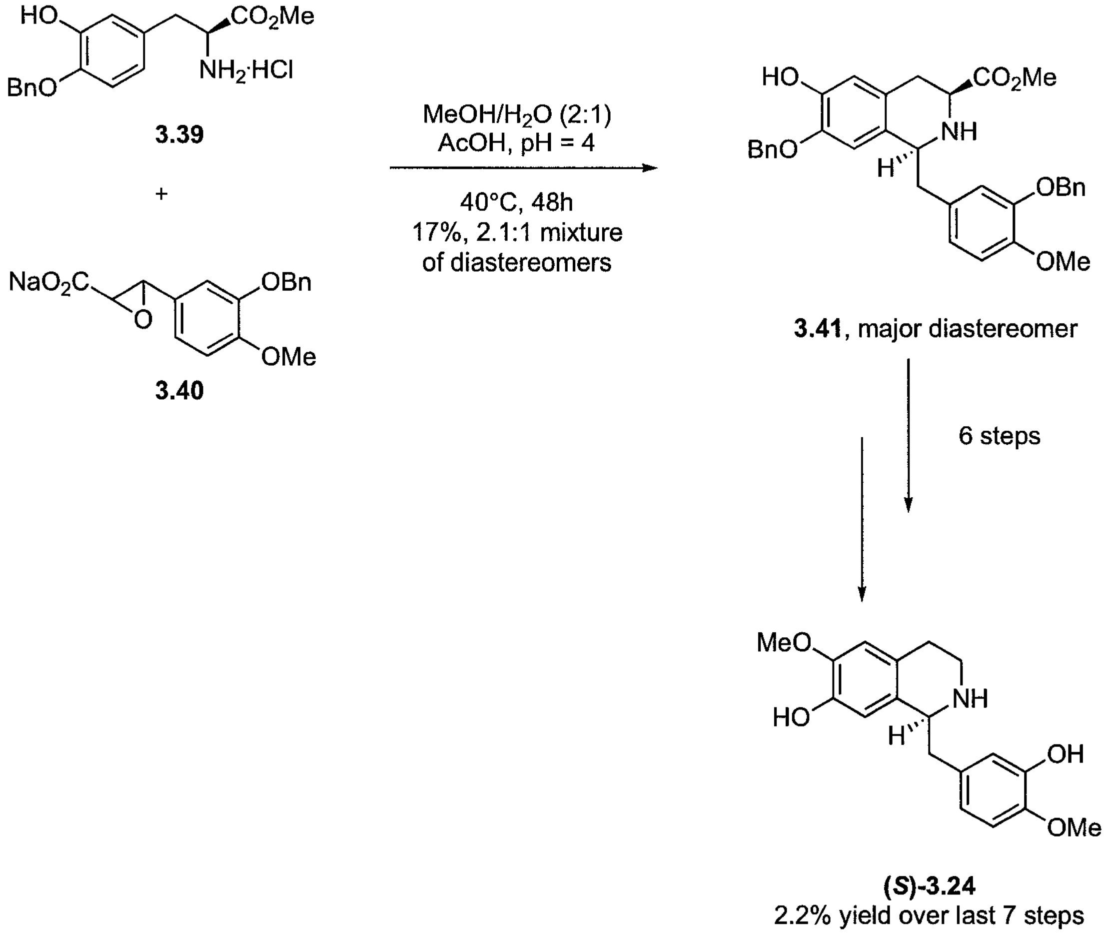


Scheme 3.2. Synthesis of **3.24** via Bischler-Napieralski/reduction sequence by Rice and Brossi

The starting primary amine **3.35**, which was synthesized from a catalytic reduction of the readily-available parent nitrile, was coupled to the carboxylic acid **3.36** in 90% to form the corresponding amide **3.37**. This amide then underwent the Bischler-Napieralski cyclization with $POCl_3$, followed by sodium borohydride reduction in one pot to give norreticuline (**3.24**) in 77% yield. This synthesis was convergent, straightforward, and efficient, but is limited to the synthesis of electron-rich derivatives. As mentioned earlier in this chapter, the cyclization step in the Bischler-Napieralski reaction requires an electron-rich adjacent phenyl ring to enable the Fridel-Crafts-type attack onto the iminium ion generated in-situ.

## 3.2.2. Synthesis using Pictet-Spengler

The Pictet-Spengler is another common route to benzyl tetrahydroisoquinolines, and was employed by Konda *et al.* in the synthesis of **(*S*)-3.24** as an intermediate in the synthesis of (*S*)-reticuline, (*S*)-**3.28**.[100] This approach (Scheme 3.3) was the first reported diastereoselective synthesis of **(*S*)-3.24**, as it had only been previously prepared by resolution.[104] The Pictet-Spengler reaction, which consisted of the condensation and subsequent cyclization between the amine hydrochloride salt **3.39** and the epoxide **3.40**, yielded a modest 2.1:1 diastereoselectivity for the (*S*)-isomer of the benzyl tetrahydroisoquinoline **3.41** with the low yield of 17% for both isomers combined.



Scheme 3.3. Synthesis of **(*S*)-3.24** by Konda *et al.* via a Pictet-Spengler cyclization

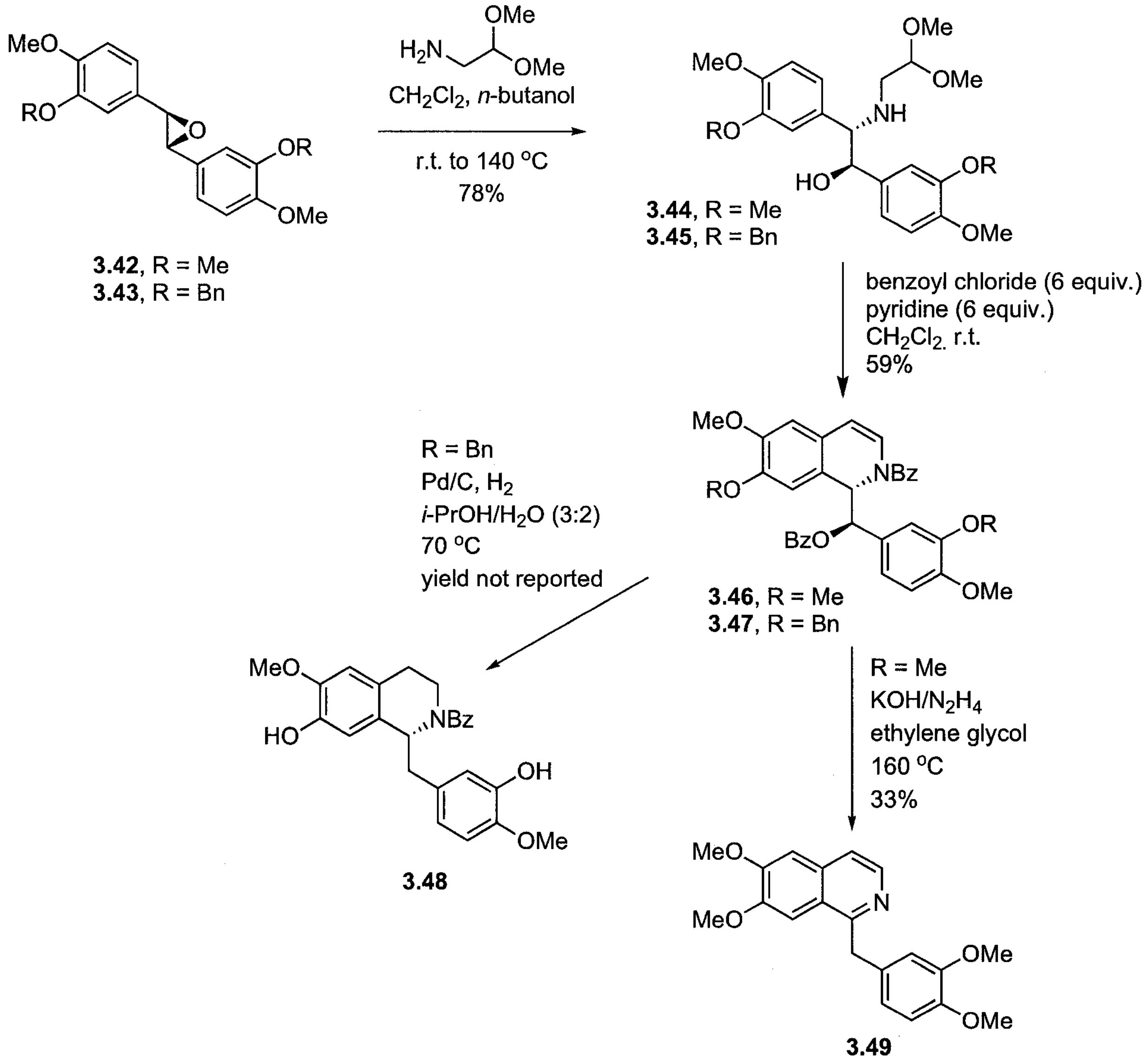
Six additional steps were needed to give rise to **(*S*)-3.24**, which was synthesized in only 2.2% yield over the last 7 steps. While this synthesis could not be described as efficient, it was the first example of a diastereoselective installation of the C1 stereocentre in norreticuline (**3.24**) or reticuline (**3.28**). The Pictet-Spengler reaction has been used more efficiently in the synthesis of other benzyl isoquinolines,[101] but as in the case of the Bischler-Naperialski, the reaction remains limited to derivatives containing an electron donating group in the *para* position relative to the cyclization to enable the Fridel-Crafts reactivity.

---

[104] Battersby, A. R.; Foules, D. M.; Binks, R. *J. Chem. Soc.* **1965**, 3323.

### 3.2.3. Synthesis using Pomeranz-Fritsch

Although the Pomeranz-Fritsch reaction has not been used in the synthesis of **3.24** itself, it had been used in the synthesis of homolgous benzyl tetrahydroisoquinolines (and papaverine, **3.49**) by Hirsenkorn in 1991 (scheme 3.4).[105]



Scheme 3.4. Hirsenkorn's synthesis of benzyl isoquinolines via a Pomeranz-Fritsch cyclization step

---

[105] Hirsenkorn, R. *Tetrahedron Lett.* **1991**, *32*, 1775.

The cyclization precursor **3.44/3.45** was synthesized in 78% yield from the stereospecific epoxide-opening of the (*E*)-stilbene derivative **3.42/3.43** and 2,2-dimethoxyethanamine. Pomeranz-Fritsch reaction occurred smoothly in the presence of excess benzoyl chloride, which facilitated the bis-protection, cyclization, and elimination events in a single step to furnish the corresponding 1,2-dihydroisoquinoline **3.46/3.47**. When R = Me, papaverine (**3.49**) is produced in 33% yield under Wolff-Kishner reducing conditions. When R = Bn, benzyl deprotection under hydrogenation conditions yields the *N*-benzoyl norreticuline derivative **3.48**. This methodology was developed to efficiently synthesize benzyl isoquinolines while avoiding side reactions leading to the corresponding pavines and isopavines.[106] This unwanted reactivity is due to the presence of the remaining OR (R = Me, Et) group of the newly cyclized unsaturated heterocyclic ring. The OR groups of the starting acetal also pose a problem in the presence of electron-withdrawing groups on the adjacent aryl ring, as they would then react preferentially with the iminium generated in-situ and form an oxazole substituent on the aryl ring in lieu of forming an isoquinoline.[107]

### 3.2.4. Synthesis using metal-catalyzed hydroamination

As mentioned earlier in this chapter (3.1), the synthesis of benzyl tetrahydroisoquinolines has been accomplished through metal-catalyzed hydroamination. Mujahidin and Doye synthesized both (+)-(*S*)-laudanosine (**(S)-3.6**) and (–)-(S)-xylopinine (**(S)-3.7**) through the titanium-catalyzed intramolecular alkyne hydroamination illustrated in Scheme 3.1. Similarly, Severin, Mujahidin, Reimer and Doye recently completed the total synthesis of laudinosine and norlausine analogues with a titanium-catalyzed alkyne hydroamination key step (Scheme 3.5),[108] but the adjacent aryl ring notably has an electron withdrawing group ($CF_3$, F) in the position *para* to where the cyclization of more traditional approaches[109] would occur. It is likely such traditional approaches using this type of substrate would not be compatible.

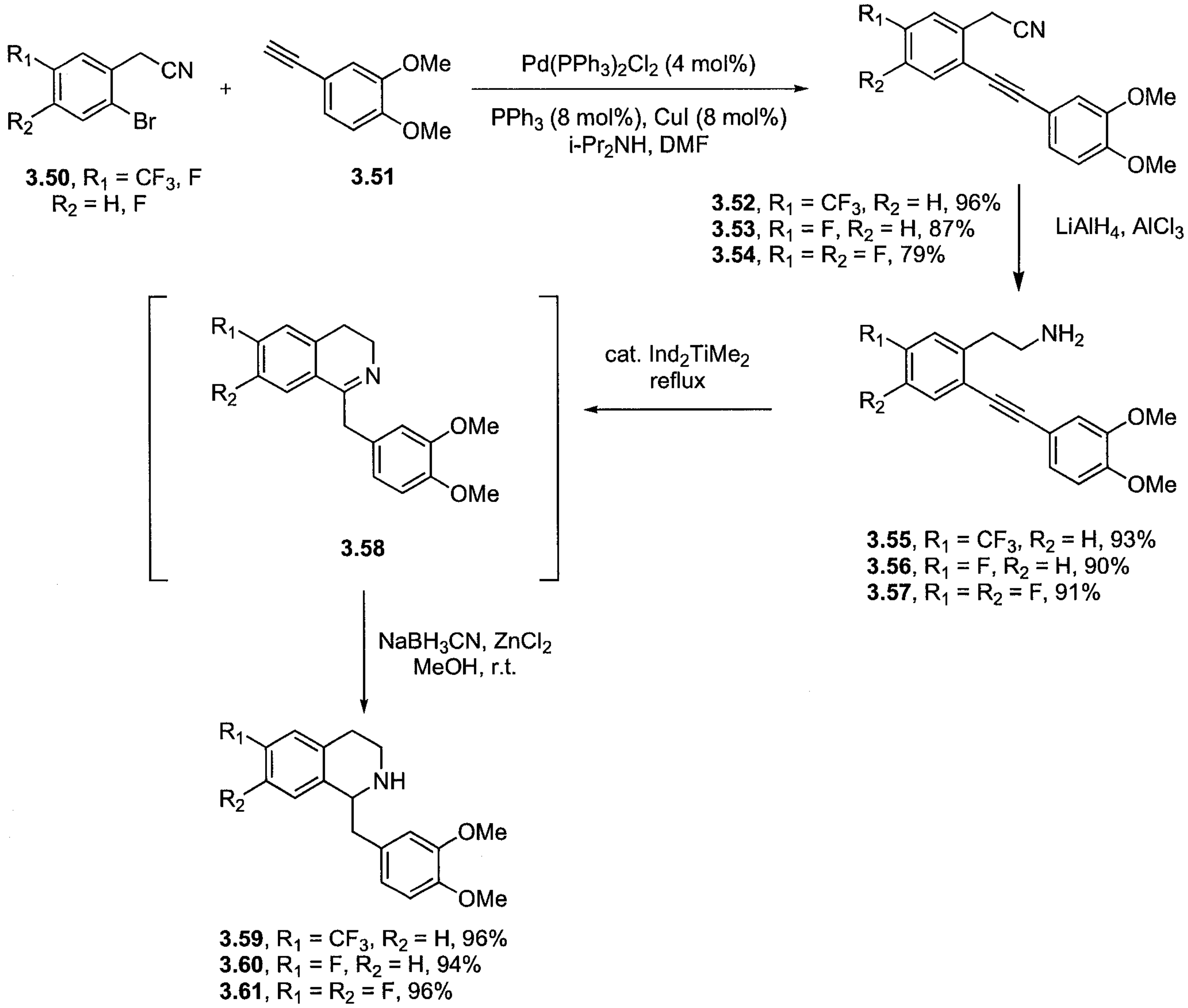
---

[106] Brown, D. W.; Dyke, S. F.; Hardy, G.; Sainsbury, M. *Tetrahedron Lett.* **1969**, *10*, 1515.

[107] Brown, E. V. *J. Org. Chem.* **1977**, *42*, 3208.

[108] Severin, R.; Mujahidin, D.; Reimer, J.; Doye, S. *Heterocycles* **2007**, *74*, 683.

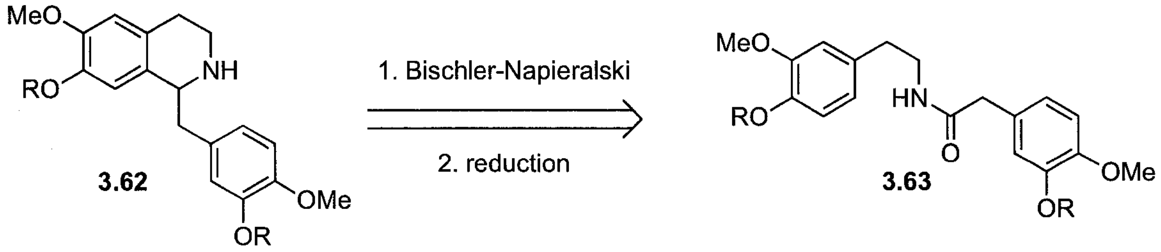
[109] Such as the aforementioned Bischler-Napieralski, Pictet-Spengler and Pomeranz-Fritsch reactions.



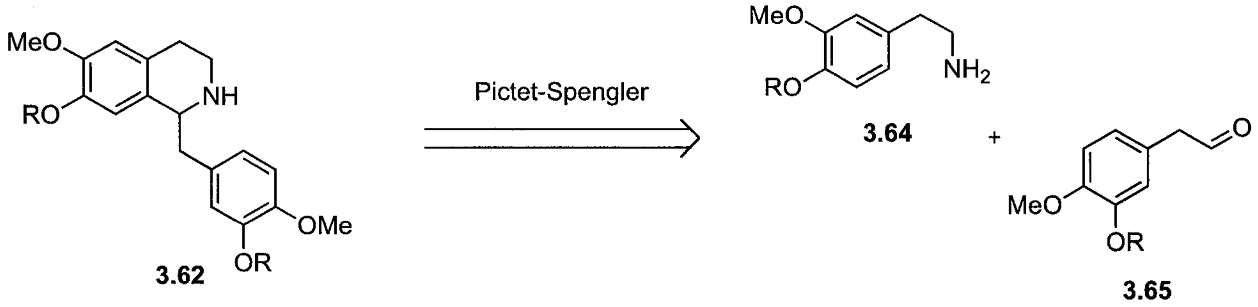
Scheme 3.5. Synthesis of electron-withdrawing laudinosine and norlausine analogues via a titanium-catalyzed intramolecular hydroamination key step.

The synthesis of the hydroamination precursor is accomplished in a similar fashion to the Doye group's previous publication[108] and the hydroamination of the various electron-withdrawing precursors **3.55**, **3.56** and **3.57** occur in excellent yields. The natural product analogues were completed upon reduction of the resulting 3,4-dihydroisoquinolines with sodium cyanoborohydride and zinc chloride, also in excellent yields. As mentioned in Chapter 1 and in Section 3.1 metal-catalyzed hydroaminations are often very substrate-specific and may not be reliable as a general approach towards the synthesis of benzyl tetrahydroisoquinolines. To date, no metal-free hydroamination has been used in the synthesis of these natural products.

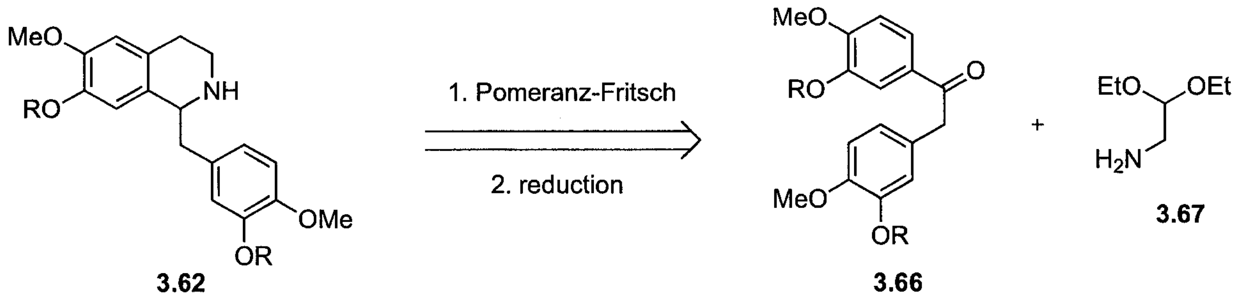
In summary, the previous approaches toward benzyl tetrahydroisoquinolines have been through Bischler-Napieralski, Pictet-Spengler, Pomeranz-Fritsch and metal-catalyzed intramolecular hydroamination key steps, and are outlined in a retrosynthetic fashion in equations 3.10, 3.11, 3.12 and 3.13, respectively.



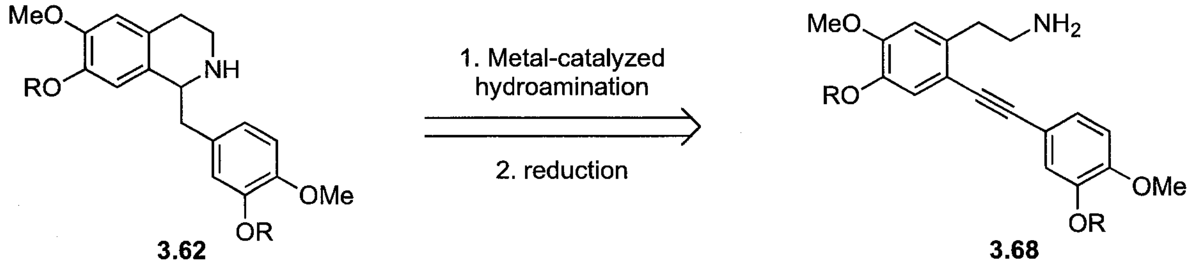
(3.10)



(3.11)



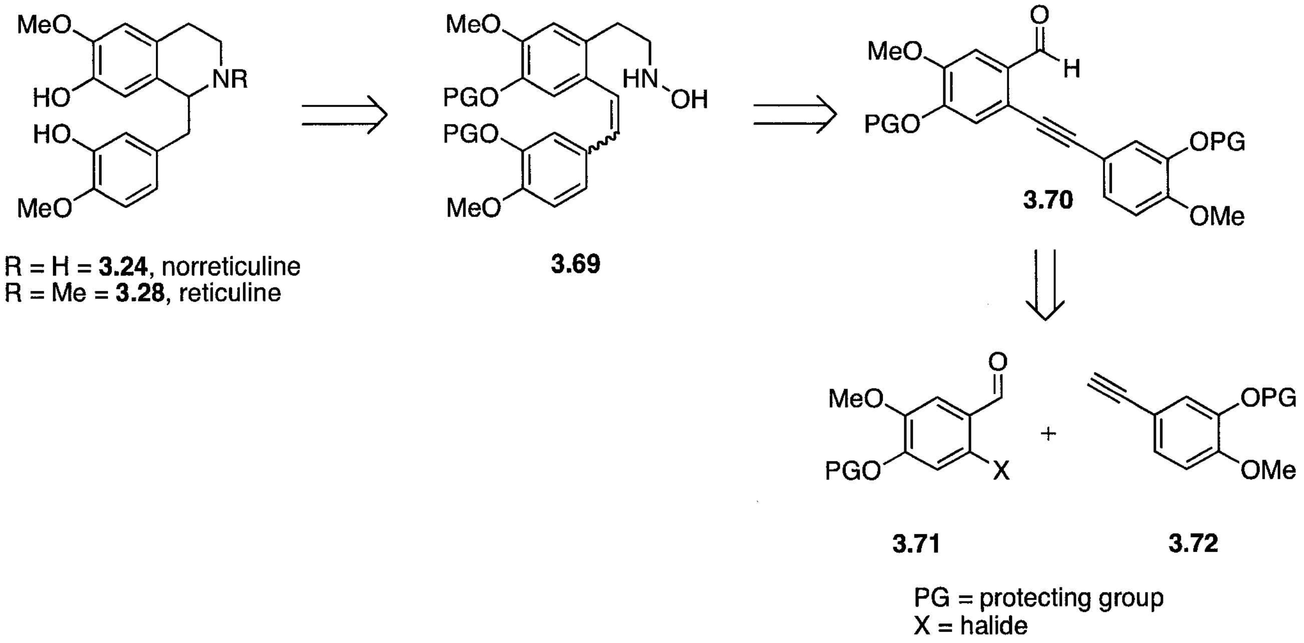
(3.12)



(3.13)

## 3.3 Retrosynthetic analysis and original synthetic plan

Building on previous work performed in the Beauchemin group toward challenging cyclizations (previously described in Chapter 1), the development of Cope-type alkene hydroaminations for the synthesis of 6-membered azacycles was to be accomplished through the total synthesis of the benzyltetrahydroisoquinoline norreticuline (**3.24**). The hydroamination key step was to be performed on the hydroxylamine **3.69**, which was to be obtained upon partial reduction of the biarylalkyne **3.70** (scheme 3.6). The key step in the synthesis of **3.70** was to be the Sonogashira cross-coupling[110] of aryl halide **3.71** and terminal alkyne **3.72**. This approach was to allow discretionary access to hydroamination precursors containing either the alkyne or alkene (*E* or *Z*) functionalities and was also sufficiently divergent to potentially synthesize a variety of benzyltetrahydroisoquinoline natural products, such as reticuline (**3.28**), scoulerine (**3.29**) and the corresponding analogues.



Scheme 3.6. Proposed retrosynthesis of norreticuline (**3.24**) and reticuline (**3.28**) with a common Cope-type hydroamination key step

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[110] Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

The initially proposed forward synthesis for the total synthesis of (±)-norreticuline (**3.24**) is outlined in scheme 3.7. Starting from commercially-available vanillin (**3.73**) and isovanillin (**3.76**), norreticuline would be obtained in 12 linear steps (14 in total). Upon protection of the phenolic OH of **3.73**, the aryl iodide **3.75** was to be synthesized via a Friedel-Crafts-type iodination using either $I_2$ and the Lewis acid $AgOCOCF_3$[111] or ICl.[112] In parallel, the aryl acetylene **3.72** could be synthesized in three steps starting from isovanillin (**3.76**) where the protection of the phenolic hydroxyl group would be followed by a two-step Corey-Fuchs alkyne synthesis[113] Sonogashira coupling of **3.72** and **3.75** would produce the biaryl acetylene **3.70**. The acetylene moiety would have then been selectively hydrogenated to the corresponding cis-olefin using either Lindlar's catalyst[114] or $Pd/BaSO_4$[115] to yield the cis-stilbene **3.78**. A one-carbon homologation would have been required to produce the aldehyde **3.79**, which was to be accomplished by a wittig olefination and subsequent hydrolysis.[116] The aldehyde **3.79** would subsequently be converted to the hydroamination precursor **3.69** by a reductive amination.[117] Following cyclization to the corresponding secondary hydroxylamineand subsequent optimization, the N-O bond would be reductively cleaved with zinc and acetic acid[118] to yield the secondary amine **3.80**. (±)-Norreticuline **3.24** would be subsequently obtained upon phenolic deprotection.

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[111] Ridley, C. P.; Reddy, M. V. R.; Rocha, G.; Bushman, F. D.; Faulkner, D. J. *Bioorg. Med. Chem.* **2002**, *10*, 3285.

[112] Feldman, K. S. *J. Org. Chem.* **1997**, *62*, 4983.

[113] Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3772.

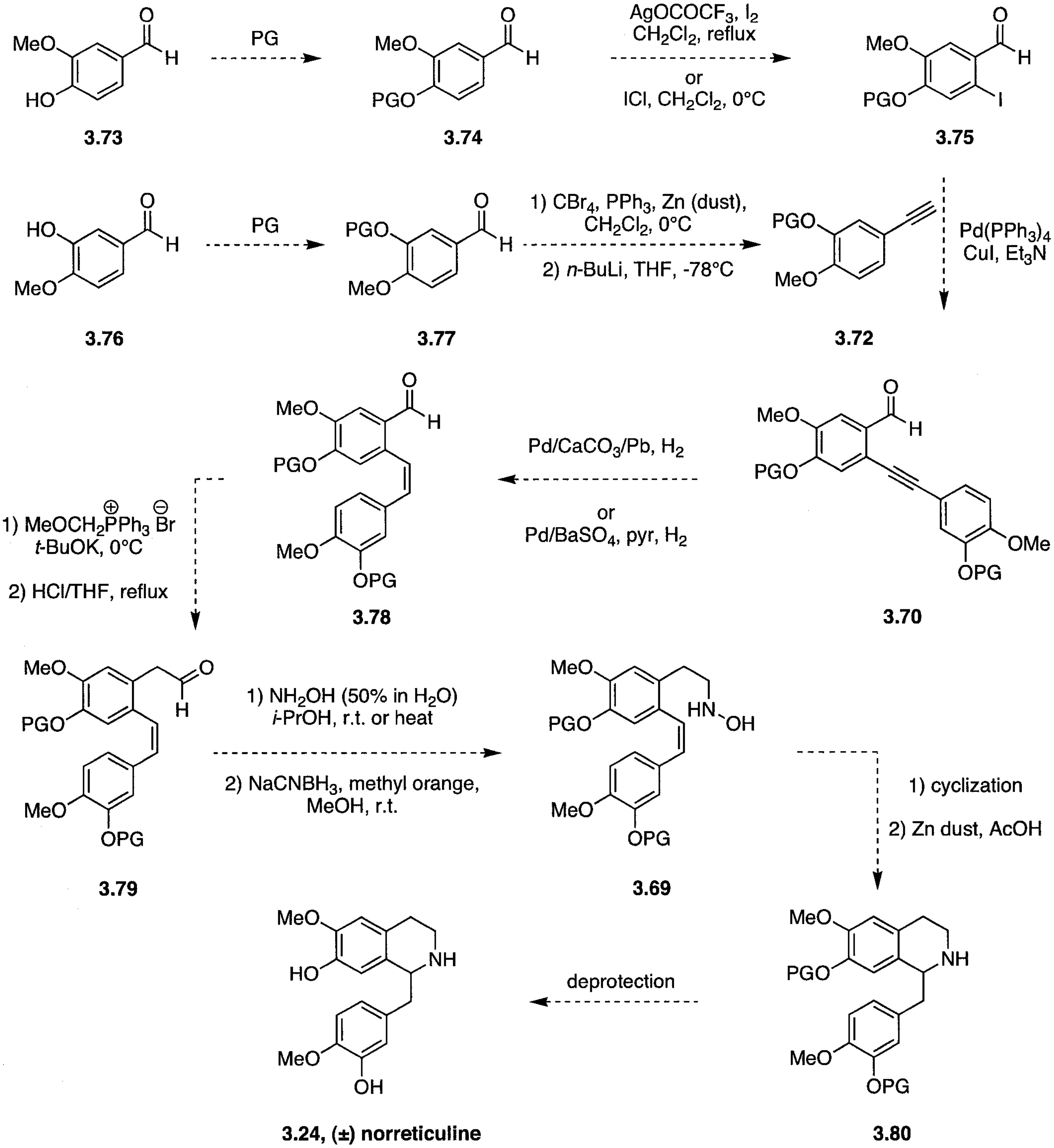
[114] (a) Lindlar, H. *Helv. Chim. Acta.* **1952**, *35*, 446. (b) Miyazaki, T.; Yokoshima, S.; Simizu, S.; Osada, H.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2007**, *9*, 4737

[115] (a) Figeys, H. P.; Gelbcke, M. *Tetrahedron Lett.* **1970**, 5139. (b) Burgstahler, A. W.; Widiger, G. N. *J. Org. Chem.* **1973**, *38*, 3652. (c) Johnson, F.; Paul, K. G.; Favara, D. *J. Org. Chem.* **1982**, *47*, 4254.

[116] Tran, V. H.; Kantharaj, R.; Roufogalis, B. D.; Duke, C. C. *Eur. J. Chem.* **2006**, 2970.

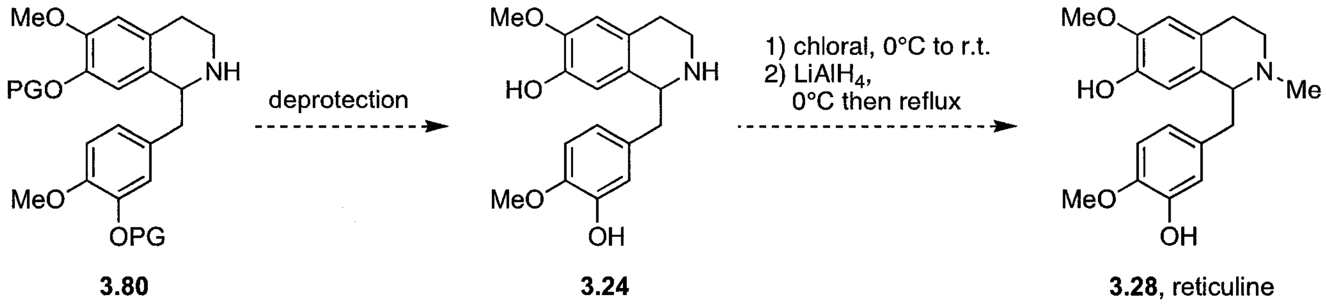
[117] (a) House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863. (b) Davison, E. C.; Forbes, I. T.; Holmes, A. B.; Warner, J. A. *Tetrahedron*, **1996**, *52*, 11601.

[118] Le Bourdonnec, B.; Goodman, A. J.; Michaut, M.; Ye, H.-F.; Graczyk, T. M.; Belanger, S.; Herbertz, T.; Yap, G. P. A.; DeHaven, R. N.; Dolle, R. E. *J. Med. Chem.* **2006**, *49*, 7278.



Scheme 3.7. Proposed forward synthesis towards norreticuline **3.24** with an intramolecular Cope-type hydroamination key step.

As alluded to earlier (section 3.1), the synthetic approach towards norreticuline was designed to be divergent and allow the synthesis of other benzyltetrahydroisoquinolines and relatives from common synthetic intermediates. Reticuline (**3.28**) could have equally been obtained from **3.80**, where deprotection and treatment with chloral would form the corresponding formamide intermediate, and a simple reduction with lithium aluminum hydride would provide the target compound.[119]



Scheme 3.8. Proposed total synthesis of reticuline from norreticuline

## 3.4 Synthesis of the Cope-type hydroamination precursor towards norreticuline

### 3.4.1 Synthesis of the di-substituted alkyne

Attempts at protecting the vanillin starting material (**3.73**) were made with a number of protecting groups with varying degrees of success. In each case, these protecting groups were chosen in consideration of the final deprotection in the presence of an *N*-methyl functional group. Upon phenolic protection, each of these intermediates (**3.81-3.86**) was then carried through to the iodination step. It was observed in certain cases that the protecting group had been subsequently cleaved by the relatively harsh iodination conditions. The results of these initial protection-iodination trials are summarized in Table 3.1. Two different iodination protocols were explored: $I_2$ with silver trifluoroacetate[111] and iodomonochloride.[112]

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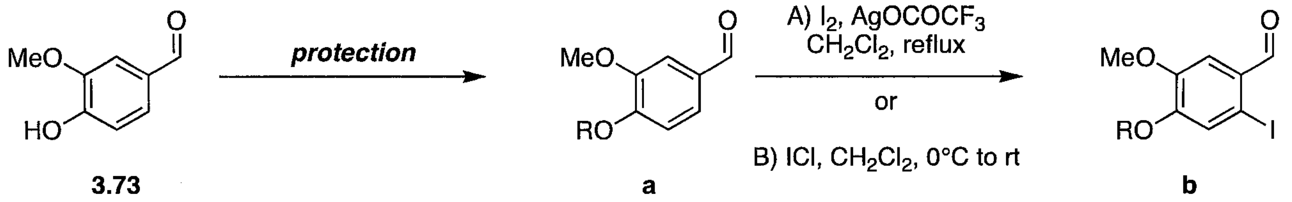
[119] Blicke, F. F.; Lu, C.-J. *J. Am. Chem. Soc.* **1952**, *74*, 3933.

**Table 3.1.** Initial protection and iodination of vanillin



| Entry | | R | Yield **a** (%) | Iodinization method (A/B) | Yield **b** (%) (aryl iodide) | Comments |
|---|---|---|---|---|---|---|
| 1 | **3.81** | TBDPS | 90[120] | A | 5 (**3.87**) | Mixture of **3.73**. **3.87** and **3.81** |
| 2 | **3.82** | Bn | 91 | A | 0[121] | Mostly **3.73** |
| 3 | **3.82** | Bn | 91 | B | 0 | Mostly **3.73**; at least 9 other spots by TLC |
| 4 | **3.83** | TBS | 23 | A | 7 (**3.88**) | Mostly **3.73** |
| 5 | **3.84** | TMSE | 15 | A | 41 (**3.89**) | Moderate amount of **3.89** |
| 6 | **3.85** | Me | n/a[122] | A | 83 (**3.90**) | Isolated pure **3.90** |
| **7** | **3.86** | ***i*-Pr** | **56** | A | **53 (3.91)** | **76% 3.91 based on recovered 3.73** |
| 8 | **3.86** | *i*-Pr | 56 | B | 20 (**3.91**) | Complex mixture containing **3.73** (not recoverable). Isolated di-iodinated product **3.98** (15%) |

In entries 1-4 it was observed that the iodination procedures were perhaps not amenable to vanillin-derivatives, despite literature precedence.[111,112] To attempt to optimize the iodination, the commercially-available and inexpensive 3,4-dimethoxybenzaldehyde (**3.90**) was first subjected to iodination conditions A. The reaction proceeded smoothly to produce the desired mono-iodinated product **3.91** in 83% yield. This result implied that the iodination may simply be protecting-group dependent, and suggested that another alkyl protecting group may be effective as long as it could be selectively deprotected later on in the synthesis. The isopropyl-protected

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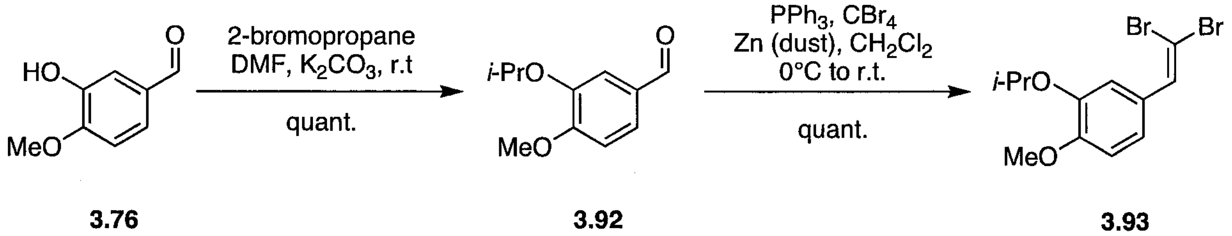
[120] Mäkelä, T.; Matikainen, J.; Wähälä, K.; Hase, T. *Tetrahedron* **2000**, *56*, 1873.

[121] Di-iodinated product was isolated (9 mg, 4% yield).

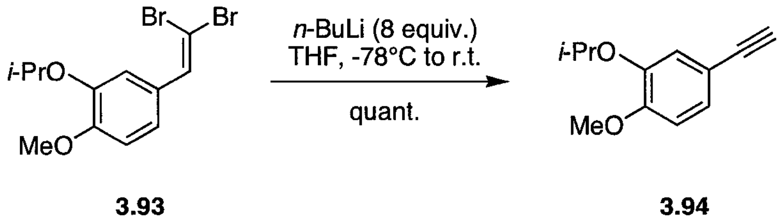
[122] Used from commercial source.

vanillin **3.89** was subsequently synthesized in 56% yield, as was the mono-iodinated derivative **3.91** (method A, 53%; 76% based on recovered **3.73**). This procedure was used previously in the preparation of lamellarin sulphate analogues by Ridley *et al,*[111] and was ultimately chosen for the continuation of the synthesis. Upon optimization of the workup, **3.89** was later obtained in quantitative yield. The isovanillin moiety was also effectively protected with an isopropyl group (**3.92**, quant. yield), and was easily carried forward in the synthesis. Using the same protecting group, the isopropyl-selective deprotection of the benzotetrahydroisoquinoline intermediate could be afforded in one step using boron trichloride, leaving the desired methoxy groups intact.[111] The conversion of isovanillin (**3.76**) to the corresponding gem-dibromide **3.93** proceeded in quantitative yield according to literature procedure (eq. 3.14).[111,113]



(3.14)

The formation of the Sonogashira coupling fragment **3.94** was obtained using a modified Corey-Fuchs alkyne synthesis procedure[113] *n*-BuLi (eq 3.15).



(3.15)

The first attempt at the Sonogashira coupling[110] of **3.94** and **3.91** produced the desired di-substituted alkyne **3.95** in a modest 11% yield (eq 3.16, 37% based on recovered starting material). The remainder of the reaction mixture appeared to be the homocoupled product **3.96**, the product of a Glaser coupling,[123] which is a known side-reaction in Sonogashira couplings.[124]

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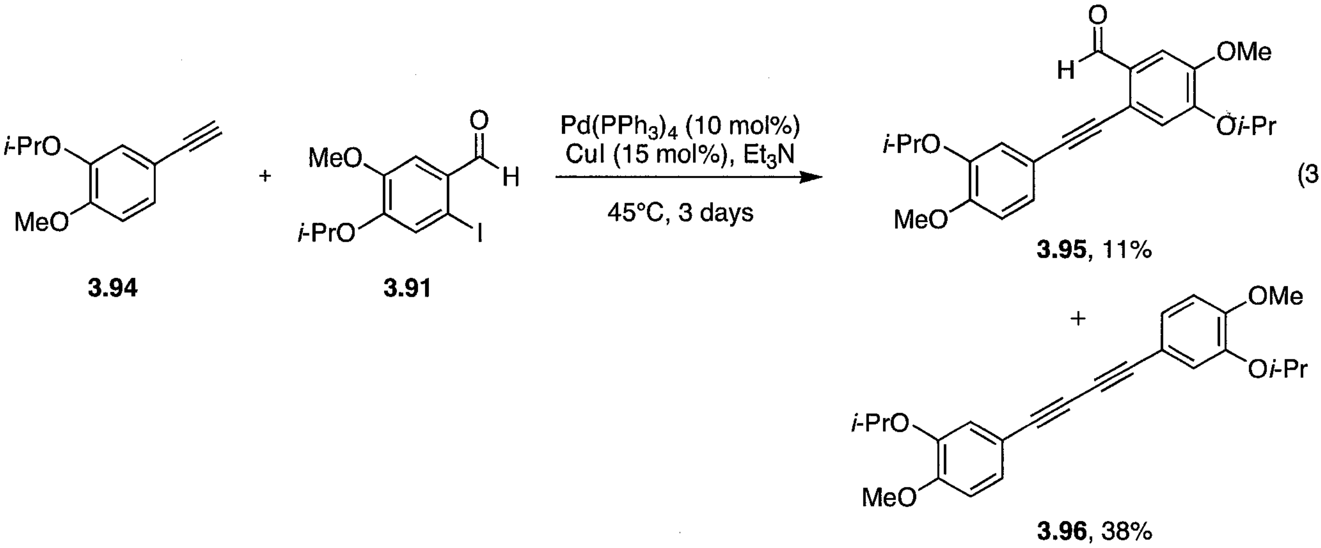
[123] Glaser, C. *Ber.* **1869**, *2*, 422.

[124] For a recent review on the Sonogashira reaction, please refer to Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874.



(3.16)

The Sonogashira step was subsequently optimized in conjunction with Anne-Catherine Bédard. In order to lower the Glaser coupling side reaction, lower reaction temperatures were explored as were solvents and equivalents of alkyne **3.94**. The optimization is summarized in Table 3.2 and the procedure was based on work previously done by Julie Simard-Mercier.[125]

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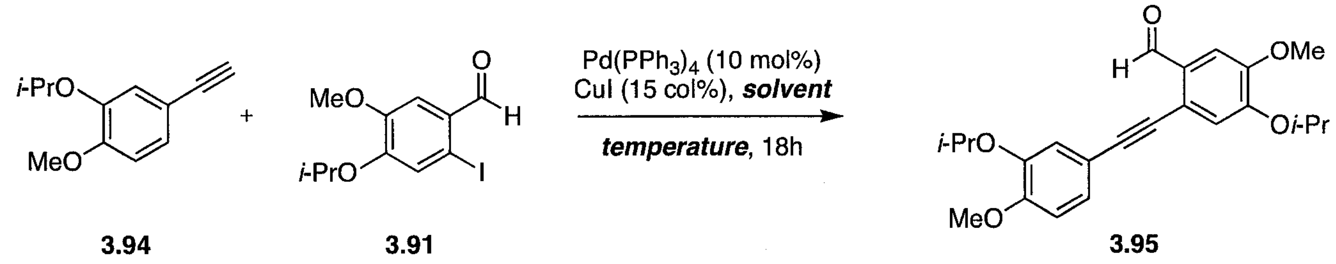
[125] Simard-Mercier, J. MSc. thesis, Department of Chemistry, University of Ottawa: Ottawa, 2008.

**Table 3.2.** Optimization of the Sonogashira coupling of **3.94** and **3.91**

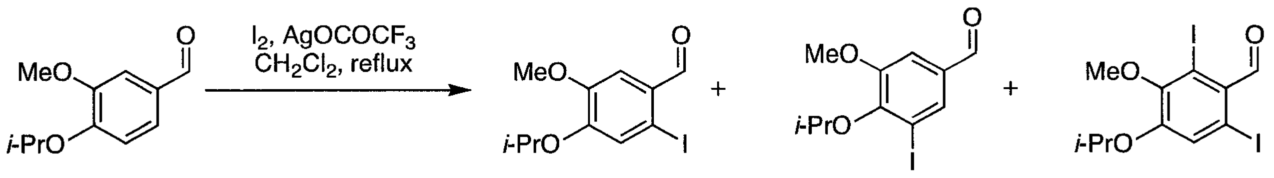


| Entry | Solvent | Temperature (°C) | Equivalents (**3.94**) | Yield (%) | Comments |
|---|---|---|---|---|---|
| 1 | $Et_3N$ | r.t. | 1.7 | 67 | Some homocoupling (minor) and aryl iodide **3.91** still present (not recovered) |
| 2 | $Et_3N$ | 5 | 1.7 | 17 | 64% recovered aryl iodide **3.91**, some homocoupling (minor) |
| 3 | $Et_3N$ | r.t. | 3 | 68[a] | Homocoupling (minor), could recover some excess alkyne **3.94** (1.13 equiv.) |
| **4** | **$Et_3N$** | **r.t.** | **2** | **71**[b] | **Homocoupling (34%)** |
| 5 | Dioxane | r.t. | 1.7 | 5 | Homocoupling (minor) |
| 6 | Dioxane | 5 | 1.7 | 8 | Homocoupling (minor) |
| 7 | $CH_2Cl_2$ | r.t. | 1.7 | - | Low conversion by TLC; not pursued |
| 8 | $CH_2Cl_2$ | 5 | 1.7 | - | Low conversion by TLC; not pursued |

[a] Reaction time of 4 days
[b] Reaction time of 2 days

It was observed that the best yields of the desired di-substituted alkyne **3.95** were obtained in triethylamine as solvent and at room temperature. It was decided that the conditions in Entry 4 would be further pursued in the continuation of the synthesis as it had the best yield despite the moderate homocoupling product **3.96**. It was later observed that the amount of **3.96** and the reaction time varied considerably with changes in environmental conditions (increased humidity yielded increased homocoupling), despite thoroughly sparging the reaction mixture with argon for ten minutes.

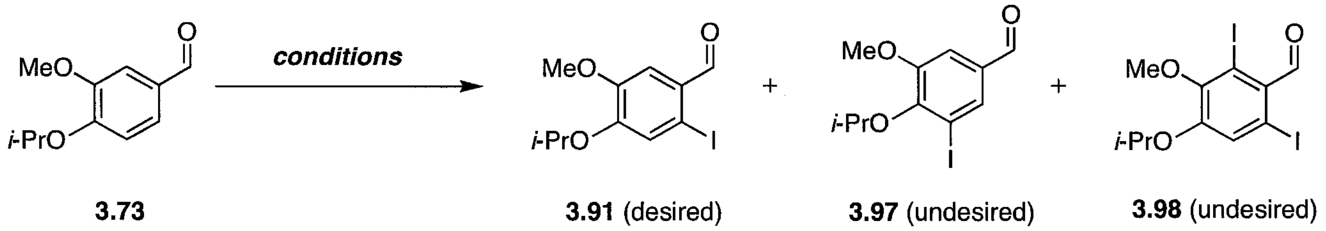
The scale-up of the terminal alkyne **3.94** and the aryl iodide **3.91** was performed predominantly by Anne-Catherine Bédard. Each synthetic intermediate was easily produced on larger scale, up to 20 grams, except for the iodination of **3.73**. It was observed that the iodination of **3.73** with $I_2$ and $AgOCOCF_3$ produced the undesired aryl iodide isomer **3.97** as well as the di-iodoinated product **3.98** (eq 3.17). The di-iodinated product **3.98** was usually present as a minor product and could be easily separated by silica gel column chromatography, but the isomer **3.97** was inseparable by chromatography. It was determined that the best results were obtained using older, less "active" sources of $AgOCOCF_3$, and this method was deemed unreliable.



**3.73** **3.91** **3.97** **3.98** (minor) (3.17)

However, the proceeding Sonogashira reaction could still be run successfully as it appeared that only the desired isomer **3.91** reacted with the aryl acetylene **3.94** to form the desired di-substituted alkyne **3.95**. The biarylalkynes that would have arose from the Sonogashira coupling of the aryl iodides **3.97** or **3.98** were never isolated. Optimization of the iodination was then attempted by Ms. Bédard and her results are presented in Table 3.3. The ratio of **3.91**:**3.97** was determined by GCMS.

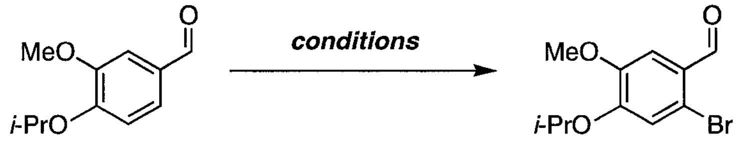
**Table 3.3.** Optimization of iodination of **3.73**.



| Entry | Reagents | Solvent | Temperature | Reaction time (h) | Result |
|---|---|---|---|---|---|
| 1 | $I_2$, $AgOCOCF_3$ | $CH_2Cl_2$ | 65 °C | 18 | 3:1 mixture of **3.91**:**3.97** |
| 2 | $I_2$, $AgOCOCF_3$ | $CH_2Cl_2$ | 60 °C | 7 | 5.7:1 mixture of **3.91**:**3.97** |
| 3 | KI, $KIO_3$, HCl | MeOH/$H_2O$ | r.t. | 3 | Only **3.73** and **3.98** |
| 4 | KI, $KIO_3$, HCl | MeOH/$H_2O$ | 0 °C for addition of HCl, then warm to r.t. | 4 | No reaction |
| 5 | $I_2$, UHP, $H_2SO_4$ | AcOH/$Ac_2O$ | 10 °C for addition of $H_2SO_4$, then warm to 40 °C | 2 | Mixture of **3.91**, **3.97** and **3.98** |
| 6 | $I_2$, $AgOCOCF_3$ (wet) | $CH_2Cl_2$ | 65 °C | 18 | Mixture of **3.91** (major), **3.97** and **3.98** |
| 7 | $I_2$ | $CH_2Cl_2$ | 65 °C | 18 | No reaction |
| 8 | NIS, $CF_3COOH$ | $CH_3CN$ | r.t. then heat to reflux | 19 | No reaction at room temp, mixture of **3.91** and **3.97** upon 1h reflux |
| 9 | NIS | $CH_3CN$ | Reflux | 3.5 | No reaction |
| 10 | NIS | $CH_3CN$ | Reflux | 18 | Only **3.73** after 5h, degraded overnight |

With limited success in optimizing the iodination of **3.73**, Ms. Bédard tried a series of bromination reactions, which are summarized in Table 3.4.

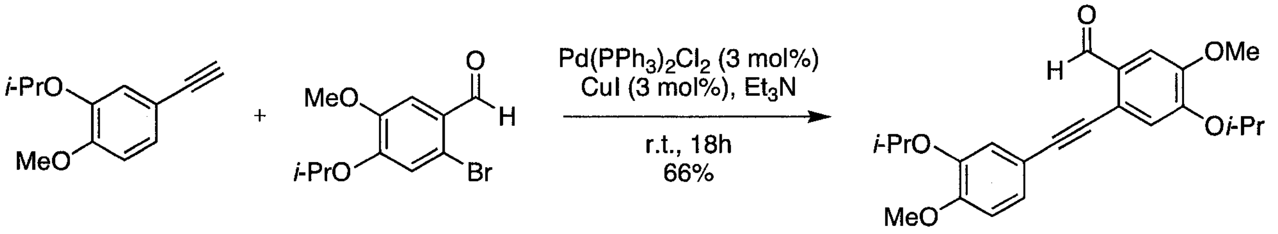
**Table 3.4.** Optimization of bromination of **3.73**.



**3.73** **3.99**

| Entry | Reagents | Solvent | Temperature | Reaction time (h) | Yield (%) |
|---|---|---|---|---|---|
| 1 | KBr, $Br_2$ | $H_2O$ | r.t. | 1 | 36 |
| 2 | $Br_2$ | MeOH | 0 °C | 1.5 | 74 |
| **3** | **$Br_2$** | **MeOH** | **0 °C for addition of $Br_2$ then r.t.** | **6** | **76** |

Using the reaction conditions[126] outlined in Entry 3, the desired aryl bromide **3.99** was obtained in 76% yield with no indication of isomers or di-bromination. **3.99** was then subjected to the previous Sonogashira conditions[125] but the desired di-substituted alkyne **3.95** was only obtained in a modest 59% yield. An improvement in yield was obtained (66%) using instead $Pd(PPh_3)_2Cl_2$ as the catalyst as outlined in the procedure by Itami *et al.* (eq. 3.18).[127] There was still, however, homocoupling observed in significant quantities.



(3.18)

**3.94** **3.99** **3.95**

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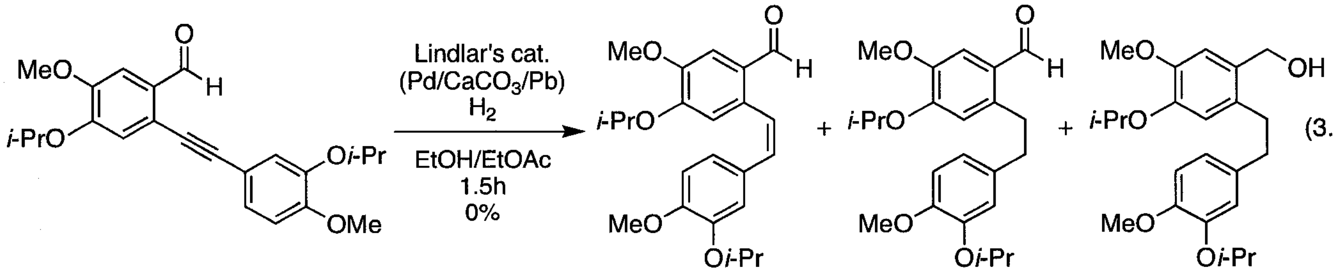
[126] Based on procedure by Appukkuttan, P.; Dehaen, W.; Van der Eycken, E. *Chem. Eur. J.* **2007**, *13*, 6452.
[127] Itami, K.; Ushiogi, Y.; Nokami, T.; Ohashi, Y.; Yoshida, J. *Org. Lett.* **2004**, *6*, 3595.

## 3.4.2 Synthesis of a Cope-type hydroamination precursor

The cis-stilbene **3.100** was prepared by the partial reduction of **3.95** using Lindlar's catalyst and $H_2$. The first attempt used conditions by the Fukuyama group in the synthesis of (+)-vinblastine and analogues to reduce a hindered alkyne.[114] The desired **3.100** was not isolated but the over-reduction products **3.101** and **3.102** were identified as likely byproducts (eq. 3.19). The *trans* alkene derivative was not detected. This reaction proved difficult to monitor by thin layer chromatography as the starting material (**3.95**) had the same Rf value as the desired product **3.100** as well as the over-reduced product **3.101**. Using vanillin as a stain it was possible to detect the emergence of **3.100** as the spot turned from brown to royal blue. Monitoring by $^1$H NMR was used in conjunction with thin layer chromatography.

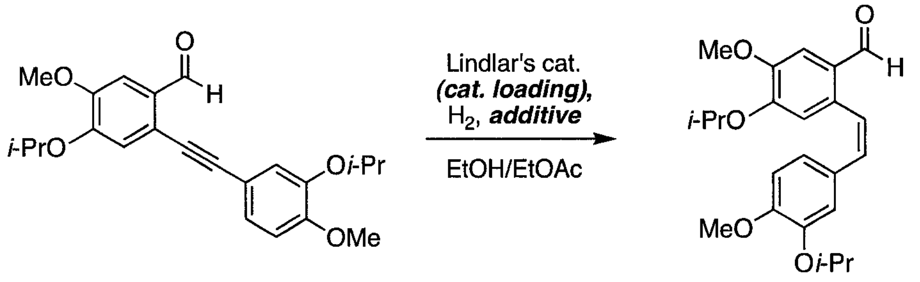


(3.19)

**3.95** **3.100** (desired) **3.101** (undesired) **3.102** (undesired)

Attempts were made to control the reaction by first lowering the catalyst loading from 20 mol% to 5 mol%, which suppressed side-product formation but was low-yielding (12%, Entry 2). Simply increasing the reaction time from 1.5 h to 4 h greatly improved the yield (98%, Entry 3) but using quinoline as an additive (5 mol%) to further poison the reaction proved to be slow (9.5 hours) and was not purified due to the intention of being used in the following step.

**Table 3.5.** Optimization of Lindlar reduction of **3.95**.



**3.95** **3.100**

| Entry | Catalyst loading (mol%) | Additive | Reaction time (h) | Yield (%) | Comments |
|---|---|---|---|---|---|
| 1 | 20 | none | 1.5 | 0 | Mixture of over-reduction products **3.101** and **3.102** |
| 2 | 5 | none | 1.5 | 12 | Purified by silica gel column impregnated with silver nitrate |
| **3** | **5** | **none** | **4** | **98** | **Purified by silica gel column impregnated with silver nitrate**[128] |
| 4 | 5 | quinoline (5 mol%) | 9.5 | - | Good conversion but was to be used as unpurified reaction mixture in following step |

The proceeding one-carbon homologation via a Wittig reaction was attempted using the commercially-available (methoxymethyl)triphenylphosphonium chloride salt (eq 3.20), as opposed to the corresponding bromide salt as indicated in the procedure by Tran *et al.*[116] Approximately 18 hours after the generation of the phosphonium ylide, the reaction was worked up despite no observable reaction. Analysis by $^{1}$H NMR revealed the presence of the starting aldehyde **3.100** (major component) and a second aldehyde byproduct that was not identified. It was also realized that **3.100** showed degradation even when stored in the freezer. Because of the lack of success with the homologation and overall handling of **3.100**, it was decided to attempt homologation of the di-substituted alkyne (**3.95**).

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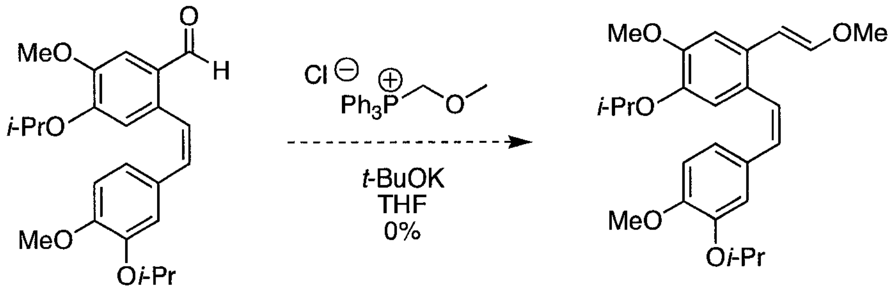
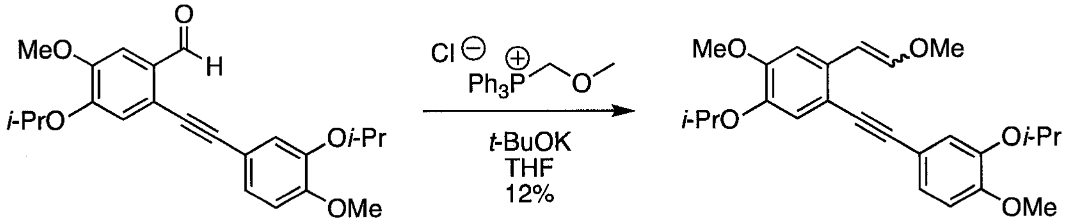
[128] Williams, C. M.; Mander, L. N. *Tetrahedron* **2001**, *57*, 425.



**3.100** **3.103**

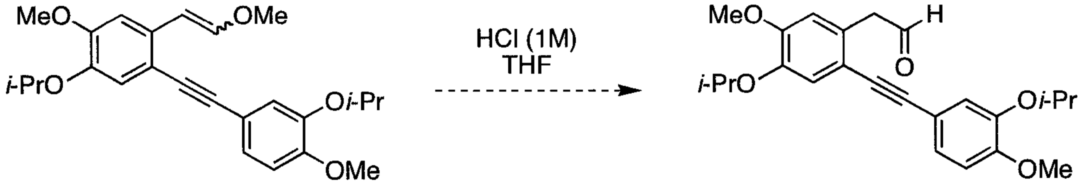
(3.20)

The same Wittig homologation conditions were attempted on **3.95** (eq. 3.21) and yielded an apparent mixture of the *E* and *Z* olefins after 9 hours (**3.104**, 12%). This mixture was of no concern, however, since the subsequent hydrolysis would proceed independently of the olefin geometry. It is possible that this lower yield was due to the initial difficulty in monitoring the reaction, as the starting **3.95** and the desired product **3.104** had the same Rf value as well as colour when stained with vanillin. It is therefore possible that the reaction was complete well before the 9 hours had elapsed and had simply begun to decompose.



**3.95** **3.104**

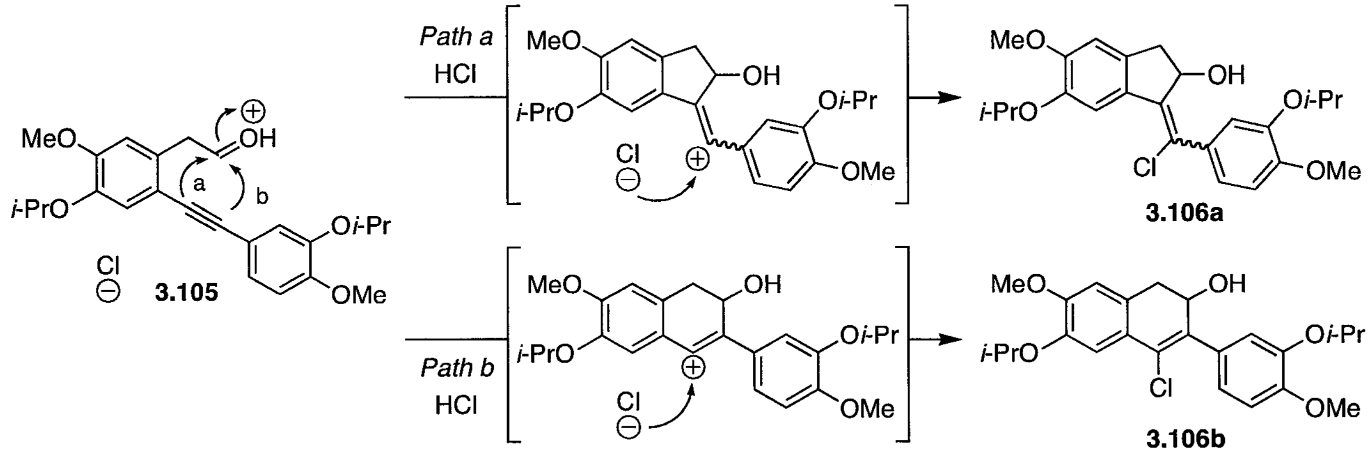
(3.21)



**3.104** **3.105**

(3.22)

The hydrolysis of the olefin mixture (**3.104**) with aqueous HCl in THF was attempted (eq. 3.22) on the 19 mg that resulted from the initial Wittig trial. The reaction was first attemped at room temperature for 4 hours, which resulted in minimal reactivity, and was then subsequently refluxed for 5.5 hours. Upon workup and purification, it was found that the desired aliphatic aldehyde **3.105** could not be isolated and the main component was possibly the result of a Prins-type cyclization[129] of **3.105** (35%, scheme 3.9) yielding either **3.106a** or **3.106b**, through either *Path a* or *Path b*, respectively. Analysis of $^1$H NMR and HRMS determined that the resulting product was likely either one of the two possible isomers, but the full characterization needed to identify which of the two isomers had been formed could not be completed because the product could not be purified sufficiently well on such small scale (7 mg).

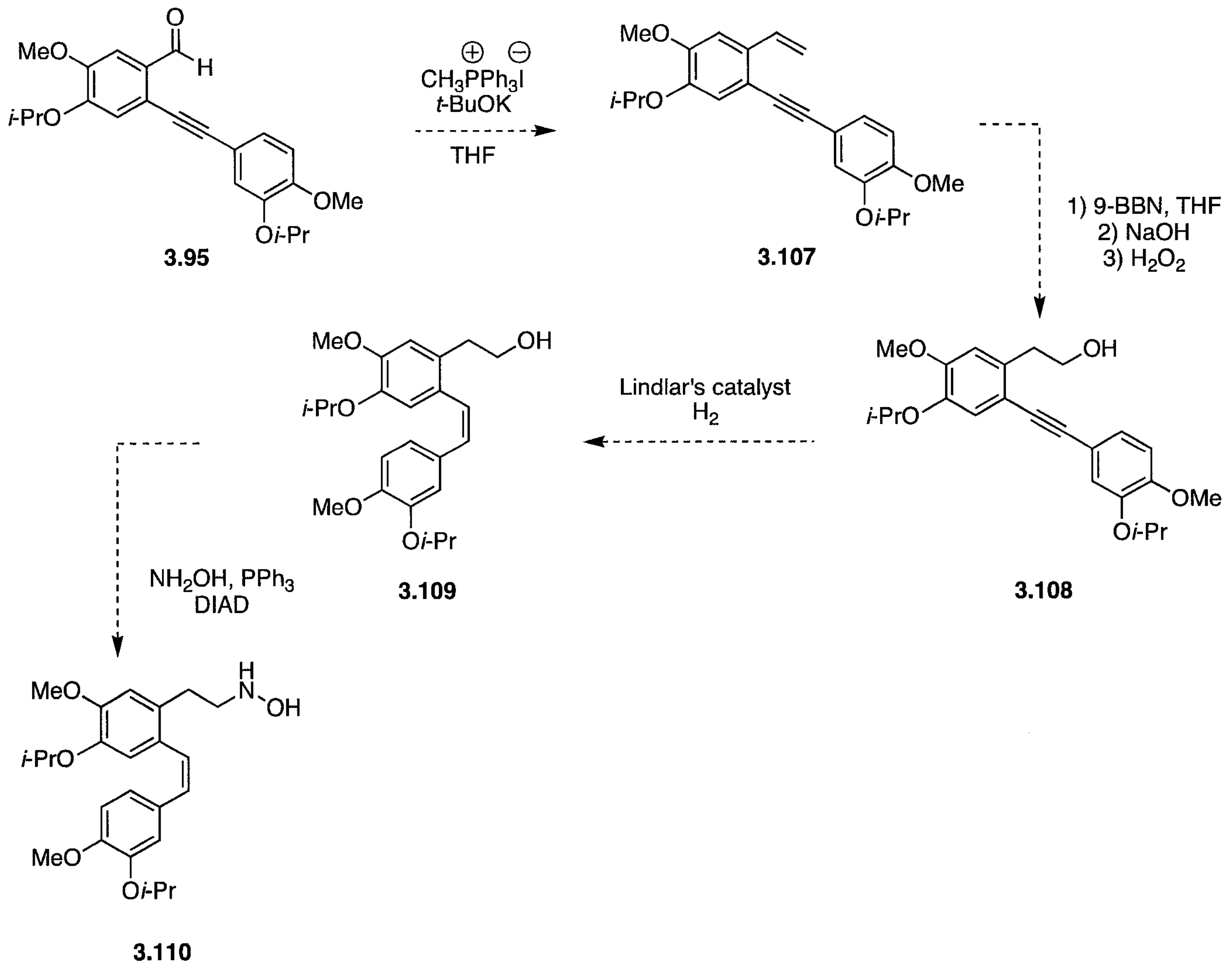


Scheme 3.9. Prins-type cyclization of the aldehyde **3.105**

Due to the high reactivity of the homologated aldehyde **3.105** under the reaction conditions, a second-generation synthesis of the hydroamination precursor was devised (scheme 3.10).

---

[129] (a) Prins, H. J. *Chem. Weekblad*, **1919**, *16*, 1072. (b) Arundale, E.; Mikeska, L. A. *Chem. Rev.* **1952**, *52*, 505.



Scheme 3.10. Proposed synthesis of the hydroamination precursor **3.110** via Wittig olefination, hydroboration, partial reduction and Mitsunobu sequence

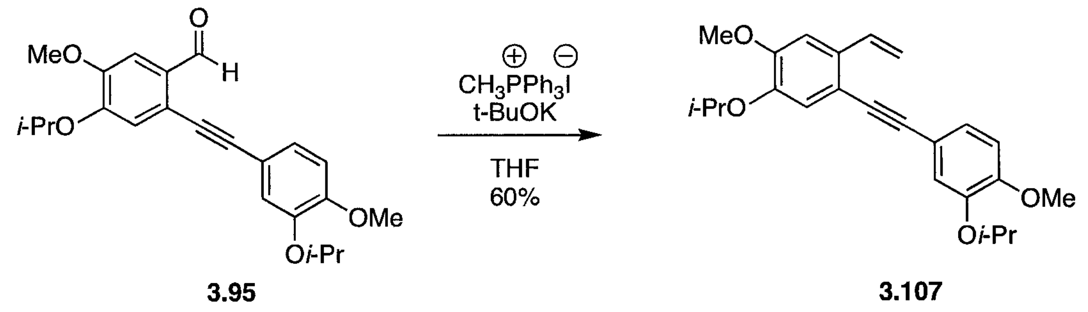
The di-substituted alkyne **3.95** was to undergo a Wittig reaction to effectuate the one-carbon homologation, producing the styrene **3.107**. Hydroboration/oxidation[130] reaction on the aryl alkene would then yield the alkyl alcohol **3.108**. The desired cyclization precursor **3.110** was then to be synthesized by a partial reduction of the triple bond to the *cis* double bond followed by a Mitsunobu reaction with hydroxylamine.[131] These last two steps could have been potentially reversed if the relative stability of each intermediate became an issue.

---

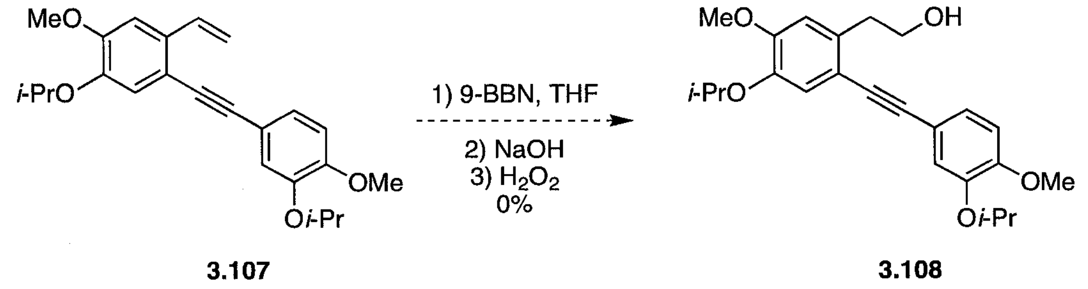
[130] Brown, H. C.; Liotta, R. *J. Org. Chem.* **1977**, *42*, 17.

[131] DiGrandi, M. J.; Tilley, J. W. *Tetrahedron. Lett.* **1996**, *37*, 4327.

The Wittig on aldehyde **3.95** proceeded according to procedure to produce the desired styrene derivative **3.107** (60%, eq. 3.23). The following step of the hydroboration was attempted twice (30 mg and 100 mg scale), but in each case the desired alcohol could not be isolated (eq. 3.24).

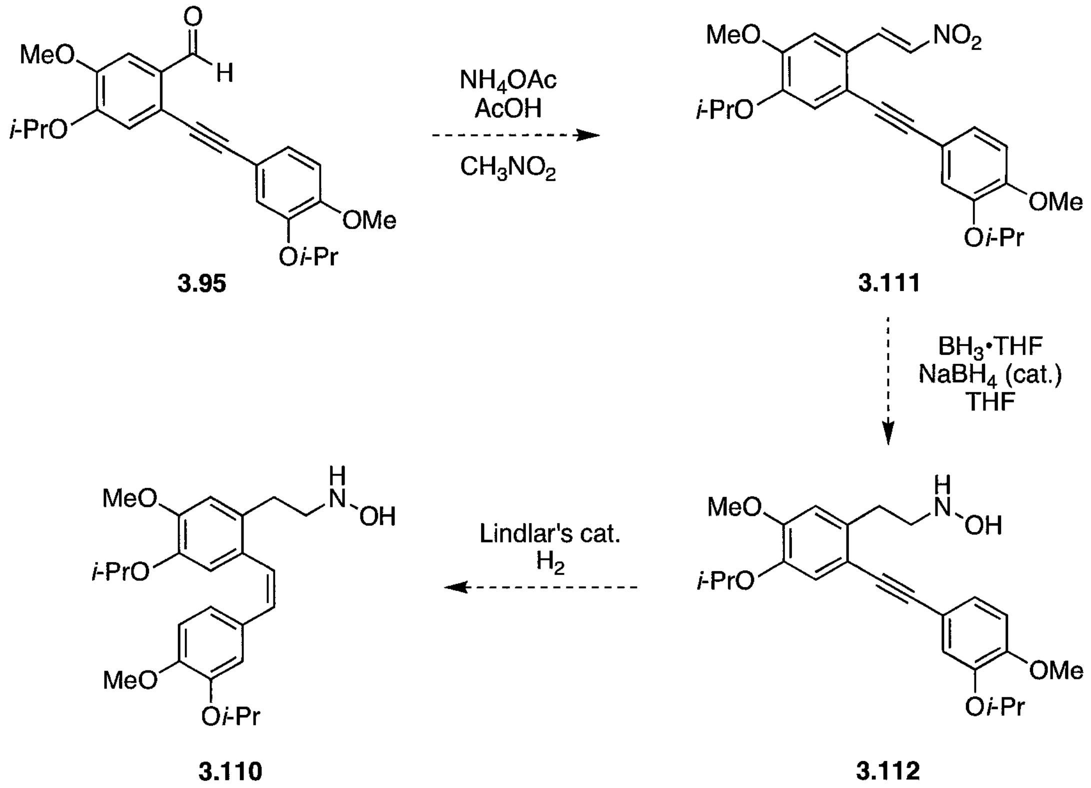


(3.23)



(3.24)

The bulky 9-BBN was used as the hydroboration agent in order to increase selectivity for the least hindered position on the alkene (anti-Markovnikov) and also effectuate selectivity for the alkene over the less accessible alkyne functionality. The unpurified reaction mixtures were complex and still contained a significant amount of starting material. The potential for selectivity issues and lack of evidence of promising reactivity lead to the development of a third-generation approach (scheme 3.11).



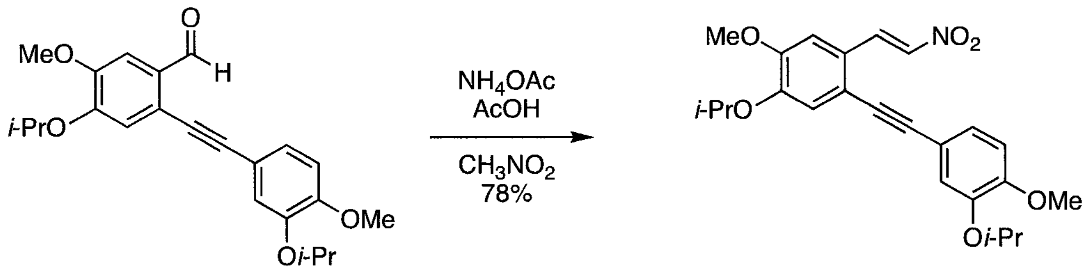
Scheme 3.11. Proposed synthesis of alkene cyclization precursor **3.110** via a Henry reaction and subsequent reductions of the resulting nitroalkene and alkyne moieties

This third synthetic approach was to begin with a modified Henry reaction on the di-substituted alkyne **3.95** to produce the corresponding nitroalkene **3.111**.[132] The reduction of **3.111** to the primary hydroxylamine was to be accomplished using borane and a catalytic amount of a borohydride reagent, a protocol which was developed by the Kabalka group.[133] The subsequent partial reduction of the triple bond to the *cis* double bond was to have furnished the desired Cope-type hydroamination precursor **3.111**. The Henry reaction on **3.95** proceeded smoothly in 78% yield (eq. 3.25) and proved to be a reliable reaction on small to medium scale (up to 500 mg).

---

[132] (a) Henry, L. *C. R. Acad. Sci. Ser. C.* **1895**, *120*, 1265. (b) Coté, A.; Lindsay, V. N. G.; Charette, A. B. *Org. Lett.* **2007**, *9*, 85.

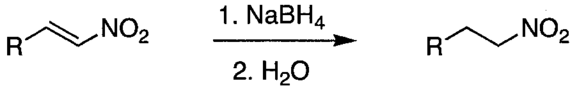
[133] (a) Mourad, M. S.; Varma, R. S.; Kabalka, G. W. *J. Org. Chem.* **1985**, *50*, 133. (b) Kabalka, G. W.; Guindi, L. H. M.; Varma, R. S. *Tetrahedron* **1990**, *46*, 7443.



**3.95** **3.111**

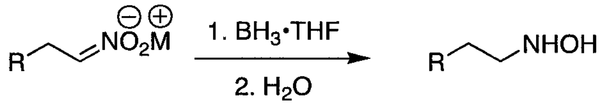
(3.25)

The synthesis of the hydroxylamine **1.112** was to be accomplished by the convenient one-pot synthesis of alkyl hydroxylamines from nitroalkenes by Kabalka *et al.*[133] This protocol was based on two known transformations: the sodium borohydride reduction of α,β-unsaturated nitroalkenes to the corresponding nitroalkanes (eq. 3.26),[133] and the reduction of nitro salts (nitronates) to hydroxylamines by borane complexes (eq. 3.27).[133] It was noted that the nitro compounds themselves were unreactive to borane complexes.



**3.113** **3.114**

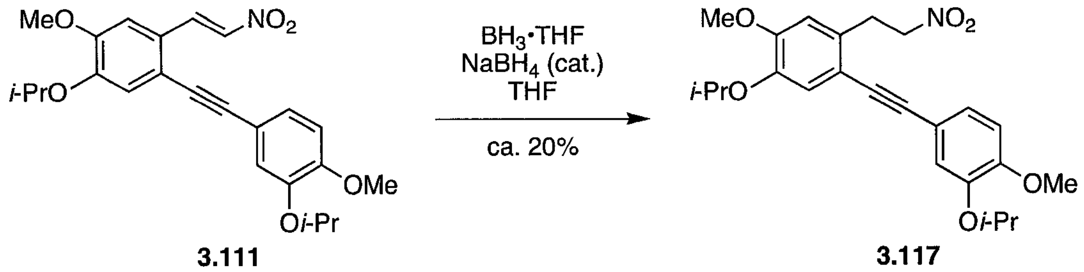
(3.26)



**3.115** **3.116**

(3.27)

Kabalka presumed that the nitronate **3.115** would be a common intermediate in the reduction of the nitroalkene by sodium borohydride (eq. 3.26) and discovered that sodium borohydride catalyzed the reaction of borane complexes with α,β-unsaturated nitro compounds at room temperature. The reduction of the nitroalkene (**3.111**) to the alkyl hydroxylamine (**3.112**) was attempted first on 10 mg by treating a solution of **3.111** with one equivalent of borane-THF complex and a catalytic amount of sodium borohydride, and the resulting borate ester was to be hydrolyzed upon reflux with water acidified by HCl. The main product, however, was the corresponding nitroalkane (**3.117**, eq. 3.28). This result indicated that the borane-THF complex did not react as intended, and it was possible that moisture was a factor on this small scale. The repetition of the reaction on a larger scale (50 mg), however, produced a similar result.

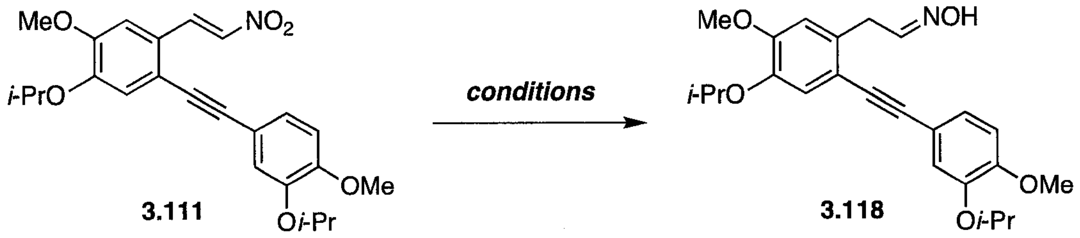


(3.28)

Rather than optimize the reaction conditions, it was decided to synthesize the alkyl hydroxylamine moiety in two steps, going through an oxime intermediate. This method was chosen because the reduction of oximes to hydroxylamines with sodium cyanoborohydride and HCl/MeOH was frequently performed in the Beauchemin group and has been deemed to be reliable. The corresponding oxime (**3.118**) was also found to be stable when stored at −20°C for at least up to a month, and therefore became a good advanced intermediate at which to store larger amounts of stock material.

Reduction of the nitroalkene **3.111** to the oxime **3.118** was optimized using two sets of reducing conditions: Zn/AcOH[134] and tin (II) chloride hydrate.[133] The results are outlined in Table 3.6.

Table 3.6. Reduction of nitroalkene **3.111** to oxime **3.118**.



| Entry | Reagent | Solvent | Yield 3.118 (%) |
|---|---|---|---|
| 1 | Zinc (dust)[a] | AcOH (4M) | 3 |
| 2 | Zinc (dust)[b,c] | AcOH (4M) | 24 |
| 3 | Zinc (dust)[b,d] | AcOH (4M) | 27 |
| **4** | **$SnCl_2 \cdot 2H_2O$** | **EtOAc** | **59** |
| 5 | $SnCl_2 \cdot 2H_2O$ | Acetone | 47 |

[a]Unactivated zinc, [b]Zinc activated with 1,2-dibromoethane, TMSCl, [c]Small scale (30 mg), [d]Larger scle (100 mg)

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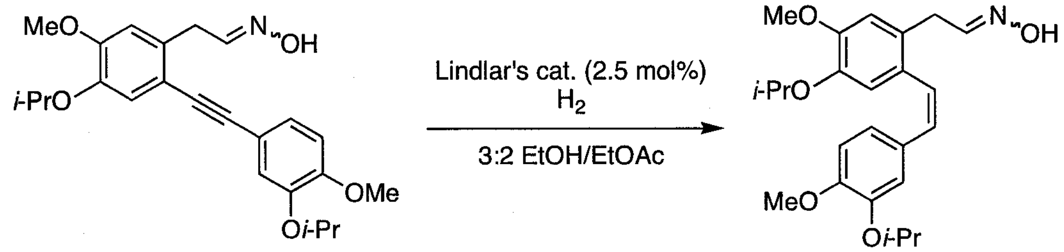
[134] Ghosh, A. K.; Gong, G. *Org. Lett.* **2007**, *9*, 1437.

The reduction with zinc and acetic acid required activation of the zinc dust[135] to get even modest yields (Entries 2,3; 24%, 27% respectively), which was partly due to more complex crude reaction mixtures, whereas the reduction with tin (II) chloride dihydrate yielded more moderate results (Entries 4,5; 59%, 47% respectively). In each case, a mixture of *E* and *Z* oxime isomers was observed. The use of the tin reduction of the nitroalkene **3.111** to the oxime **3.118** (in ethyl acetate) was then employed for the remainder of the synthesis. Slightly lower yields were experienced during scale up (above 1 gram, approx. 40%) due to increasingly difficult workups with tin salt emulsions despite the employment of larger extractions/washes and the use of brine and/or solid NaCl.

Following the reduction to the oxime **3.118**, the following step in the synthesis was to further reduce down to both the alkene and hydroxylamine functionalities. Primary hydroxylamines, however, are known to be unstable due to their sensitivity to oxygen and decomposition via bimolecular pathways.[136] The synthesis of the hydroxylamine moiety had to be the last step before the Cope-type hydroamination, which meant that the reduction of the alkyne functionality to the corresponding alkene was to occur first. The unsaturated oxime **3.118** was subjected to hydrogenation conditions with Lindlar's catalyst and resulted in the synthesis of the cis-stilbene **3.119** (eq. 3.29). No purification was performed before the next step due to the inseparable nature of the starting oxime, the desired cis-alkene, and the corresponding alkane (over-reduction product). The reduction could be controlled through careful monitoring by $^1$H NMR, and over-reduction could be observed by thin layer chromatography as a darker purple spot when stained with vanillin (vs yellow/brown spot). Conversions typically ranged from 75-95% conversion based on $^1$H NMR and mass recovery.



**3.118** **3.119**

(3.29)

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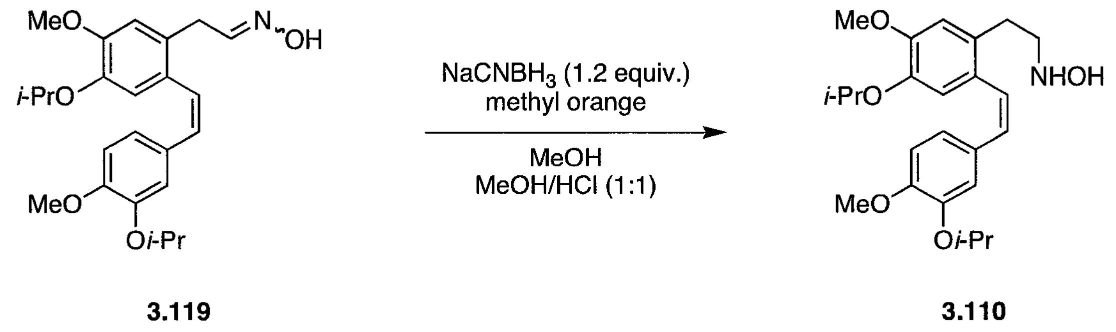
[135] Zinc activation according to the procedure by P. Knochel, M. J. Rozema, C. E. Tucker. *Organocopper Reagents: A Practical Approach* (Ed.: R. J. K. Taylor), Oxford University Press, Oxford, U.K., 1994, pp. 85.

[136] Horiyama, S.; Suwa, K,; Yamaki, M.; Kataoka, H.; Katagi, T.; Takayama, M.; Takeuchi, T. *Chem. Pharm. Bull.* **2002**, *50*, 996.

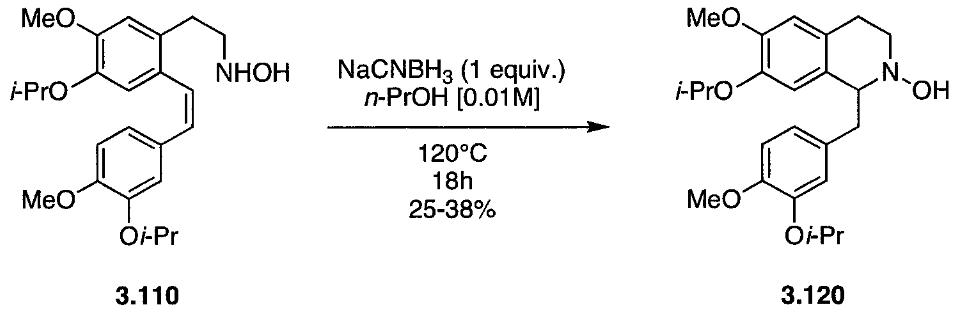
Reduction of the oxime functionality of **3.119** to the corresponding hydroxylamine **3.110** was accomplished by typical sodium cyanoborohydride reducing conditions (eq. 3.30).[117] The unpurified hydroxylamine (**3.110**) was immediately used without purification in the Cope-type hydroamination step due to its inherent instability[134,136,137] but conversions were consistently near-quantitative.[138]



(3.30)

## 3.5 Intramolecular Cope-type hydroamination attempts

The intramolecular Cope-type hydroamination of the primary hydroxylamine moiety onto the *cis* double bond in **3.110** was attempted in 5 mg scale using a set of reaction conditions that had previous been effective in the Beauchemin group (eq. 3.31). Delightfully, this initial trial furnished a 25% isolated yield for the Cope-type hydroamination product **3.120**.



(3.31)

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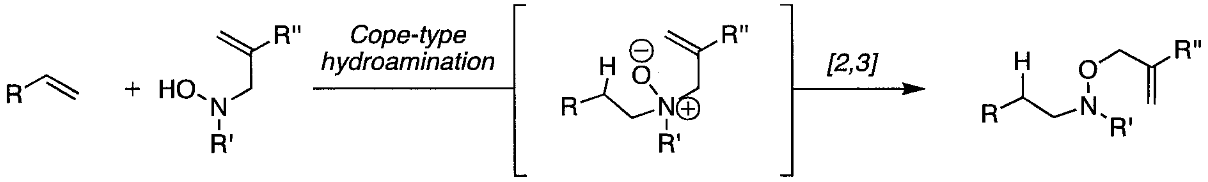
[137] Attempts at purification were unsuccessful.

[138] Based on $^1$H NMR and mass balance.

The solvent of choice was *n*-propanol because it had been shown previously in our group that alcoholic solvents mediates the bimolecular proton transfer step in the formation of the hydroamination products,[139] and *n*-propanol was the optimized solvent for the intermolecular variant with alkenes.[140] The use of sodium cyanoborohydride as an additive had also been met with success in the intermolecular hydroamination of hydroxylamines onto alkenes within our group, although the exact nature of its role is still under current investigation. Extensive optimization of the key hydroamination step with a primary hydroxylamine in the total synthesis of coniine by Isabelle Dion had previously shown that a low concentration of 0.01 M was an ideal compromise between avoiding competing side reactions and practicality.[141] The hydroamination of coniine was optimized between 140-150°C, but was considered less energetically favourable than the hydroamination of **3.110**,[142] therefore the lower temperature of 120°C was attempted. On a slightly larger scale (75 mg), the cyclization of **3.110** was achieved in 38% yield.

Instead of extensively optimizing the reaction conditions for this substrate, attention was instead given to the tandem Cope-type hydroamination / [2,3] Meiseinheimer rearrangement sequence that was being developed concurrently in the group by Joffré Bourgeois and Isabelle Dion.[143] The [2,3] rearrangement sequence was developed to provide an excellent thermodynamic sink for the otherwise "thermoneutral" hydroamination process with alkenes,[144] and would trap the hydroamination product as an *O*-allyl derivative (eq. 3.32). Under optimized thermodynamic conditions, the final sequence product could thus be formed exclusively.



(3.32)

**3.121** **3.122** **3.123** **3.124**

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[139] Beauchemin, A. M.; Moran, J.; Lebrun, M.-E.; Séguin, C.; Dimitrijevic, E.; Zhang, L.; Gorelsky, S. I. *Angew. Chem. Int. Ed.* **2008**, *47*, 1410.

[140] Moran, J.; Gorelsky, S. I.; Dimitrijevic, E.; Lebrun, M.-E.; Bédard, A.-C.; Séguin, C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 17893.

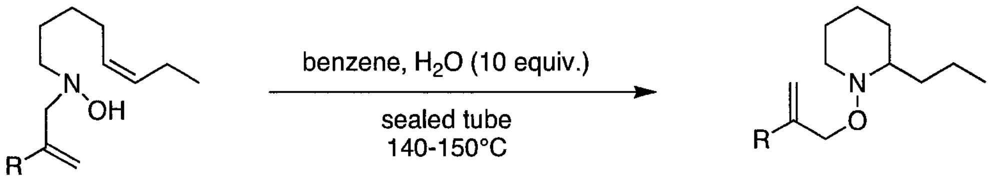
[141] Bourgeois, J.; Dion, I.; Cebrowski, P. H.; Loiseau, F.; Bédard, A.-C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *ASAP*.

[142] Coniine does not benefit from the Thorpe-Ingold effect as does the case reported herein.

[143] (a) Meisenheimer, J. *Ber.* **1919**, *52B*, 1667. (b) Bourgeois, J.; Dion, I.; Cebrowski, P. H.; Loiseau, F.; Bédard, A.-C.; Beauchemin, A. M. *Manuscript submitted for publication.*

[144] Johns, A. M.; Sakai, N.; Ridder, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 9306.

The optimization of this tandem sequence for the intramolecular variant was performed by Ms. Dion in her total synthesis of coniine (eq. 3.33) and attempted cyclizations with both allyl and methallyl hydroamination precursors (**3.125** and **3.126**, respectively). Even though the intramolecular hydroaminations are thermodynamically favourable, this sequence would be beneficial as it involves a more stable reactant, and ultimately forms a more stable hydroamination product.



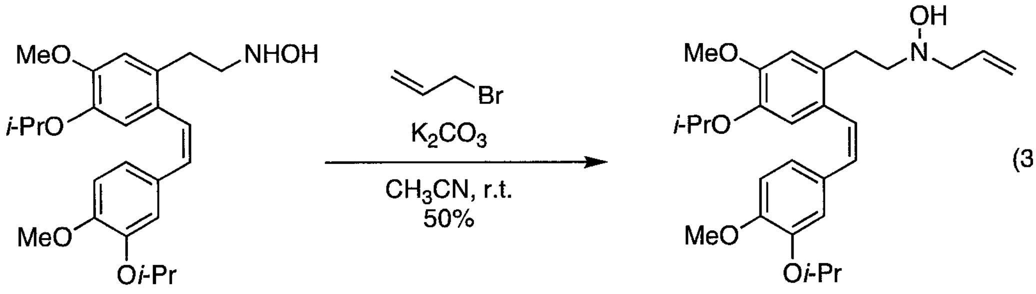
**3.125**, R = H
**3.126**, R = Me

**3.127**, R = H, 47%
**3.128**, R = Me, 31%

(3.33)

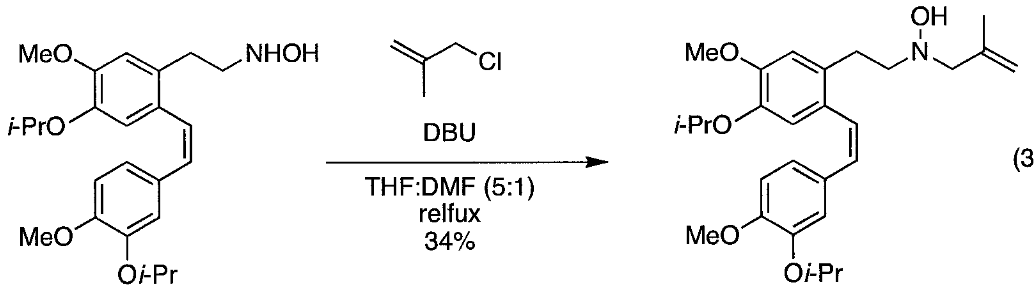
She found that similarly to the NHOH cyclization, a low concentration of 0.01 M in deoxygenated solution was critical in minimizing side reactions. The optimal solvent was found to be benzene, which perhaps rendered the allylated hydroxylamine more soluble and also minimized decomposition of the starting materials. The addition of 10 equivalents of water was beneficial to the reaction, although not absolutely necessary, which may have helped stabilize the *N*-oxide intermediate prior to the rearrangement. The cyclization of the allylhydroxylamine precursor **3.125** and the methallylhydroxylamine precursor **3.126** provided the hydroamination/[2,3] tandem sequence products **3.127** and **3.128** in 47% and 31% yields, respectively.

It was determined that the tandem sequence conditions developed by Ms. Dion could be employed as a starting point in the optimization of a Cope-type hydroamintion/[2,3] sequence key step towards the total synthesis of norreticuline (**3.24**). The allyl- and methallyl-hydroxylamine derivatives (**3.129** and **3.130**, respectively) were prepared from the previous hydroamination precursor **3.110** with modest yields. The primary hydroxylamine was allylated with allyl bromide (eq. 3.34) or methallylated with 3-chloro-2-methylpropene (eq. 3.35).[37b] Each of these cyclization/rearrangement precursors was relatively more stable than the parent primary hydroxylamine (**3.110**), but were nonetheless difficult to purify without decomposition and were usually used in the next step either crude or upon rapid purification by silica column chromatography.



**3.110** **3.129**

(3.34)

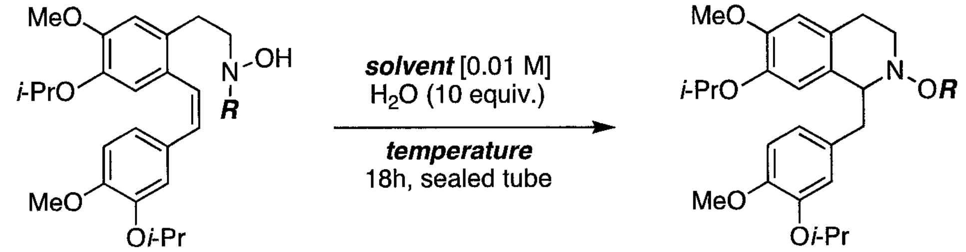


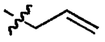
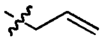
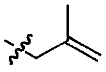
**3.110** **3.130**

(3.35)

The cyclization of the allyl and methallyl derivatives with respect to the NHOH version is shown in Table 3.7. Similar to the conditions optimized by Ms. Dion, the solvent chosen was benzene as it would minimize undesired side reactions and starting material decomposition, and 10 equivalents of water were also added to help stabilize the *N*-oxide intermediate.

Table 3.7. Cyclization of NHOH, allyl and methallyl hydroxylamine derivatives.

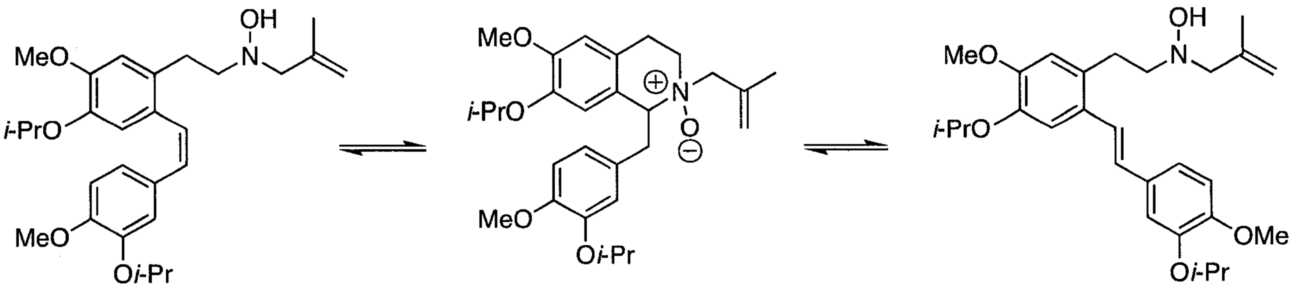


| Entry | R | Solvent | Temperature (°C) | Yield (%)[a] |
|---|---|---|---|---|
| 1 | **3.110** H | *n*-PrOH | 120 | 38 (**3.120**) |
| 2 | **3.129**  | benzene | 100 | 29 (**3.131**) |
| 3 | **3.129**  | benzene | 120 | 61 (**3.131**) |
| **4** | **3.130**  | **benzene** | **120** | **82 (3.132)** |

[a]Yield is adjusted to compensate for the presence of over-reduction product in the starting material.

The tandem Cope-type hydroamination/Meisenheimer rearrangement sequence proved more efficient than the simple hydroamination of the NHOH cyclization precursor (Entry 1) even at lower temperature (Entry 2). It was observed that the higher temperature of 120°C (Entry 3) provided a considerably higher yield than 100°C (Entry 2) for the allyl cyclization precursor **3.129**. This higher temperature was then employed in the methyallyl cyclization (precursor **3.130**), which was found to be the superior system, affording the very respectable yield of 82% (Entry 4).

In the methallylhydroxylamine cyclization, two side products were observed in addition to the desired cyclization product **3.132**. It was determined by Rf and $^1$H NMR that one was a cyclized product and the other remained uncyclized (eq. 3.36) The uncyclized product was determined to be the *E*-alkene derivative of the cyclization precursor (**3.130**), primarily due to the coupling constant of 15 Hz between the two alkene protons. This product was fully characterized by Ms. Dion following her succession of the norreticuline optimization. It was suspected that the *E*-alkene **3.134** could have been formed upon the Cope elimination of the *N*-oxide **3.133**.[37b] This was confirmed by a reversibility study conducted by Ms. Dion. It was speculated upon further discussion with Ms. Dion also that the cyclized product was the *N*-oxide intermediate but this could not be fully confirmed at the time. The conditions for the cyclization of the methyallyl precursor **3.130** underwent optimization but the 82% could not be reproduced. One discrepancy was that the starting materials during the trial where the 82% yield was obtained were less pure in that they also contained the corresponding hydroxylamines of the alkyne starting material and the alkane over-reduction product from the hydrogenation step. It was unknown exactly what effect having these "additives" would have had on the reaction, but the possibility exists that they did have a beneficial effect in this case.



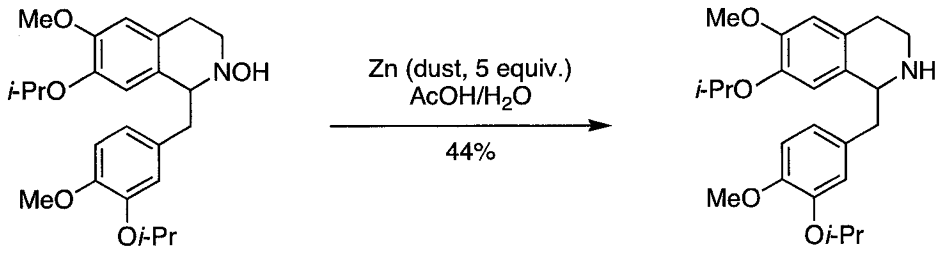
(3.36)

**3.130** **3.133** **3.134**

## 3.6 Final steps towards norreticuline

### 3.6.1 N-O bond cleavage and final deprotection

The cleavage of the N-O bond of the Cope-type hydroamination product **3.120** and the tandem hydroamination/Meisenheimer rearrangement product **3.131** was performed under typical reducing conditions using zinc dust and a mixture of AcOH and water (eq. 3.37 and 3.38).[145]



(3.37)

**3.120** **3.135**

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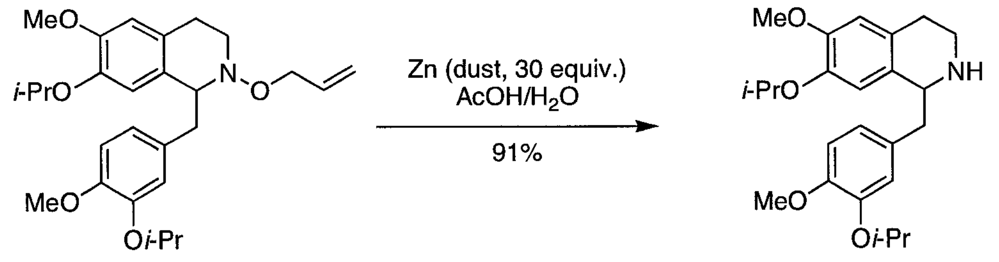
[145] Le Bourdonnec, B.; Goodman, A. J.; Michaut, M.; Ye, H.-F.; Graczyk, T. M.; Belanger, S.; Herbertz, T.; Yap, G. P. A.; DeHaven, R. N.; Dolle, R. E. *J. Med. Chem.* **2006**, *49*, 7278.

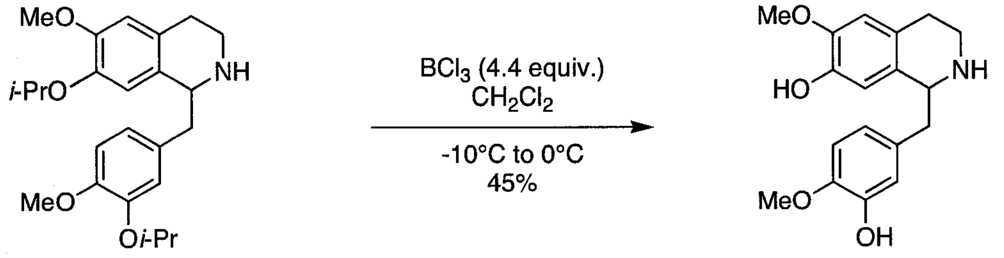


**3.131** **3.135**

(3.38)

The reduction of the N-O bond of the secondary hydroxylamine **3.120** was performed in 44% whereas the N-O-allyl bond of **3.131** was cleaved in 91% yield. The difference in yields may be accounted for by the relative instability of the hydroxylamine **3.120** with respect to the allylated **3.131**. The N-O bond cleavage of the methallyl cyclization product **3.132** was cleaved in 78% yield under the same conditions.

Norreticuline (**3.24**) was subsequently obtained upon deprotection of the isopropyl protecting groups with $BCl_3$ as described by Ridley *et al.* (eq. 3.39).[111] This reaction was quite clean by TLC and unpurified $^1H$ NMR and resulted in good, near quantitative mass balance before purification. Upon purification, however, the mass balance decreased significantly and resulted in decreased isolated yields and sometimes a lower degree of purity in the isolated product. This difficulty could be due to the polarity of the desired product and its co-elution with silica gel impurities dissolved in $CH_2Cl_2$/MeOH solvent systems. An attempt to form the HCl salt of the amine was unsuccessful due to the small scale (approx. 5 mg) and similar polarities between the HCl salt and the free base. The isolated norreticuline free base (**3.24**) was sufficiently pure, however, to be compared to literature spectroscopic data and to also be fully characterized in a different, more practical NMR solvent ($CD_3OD$ as opposed to a 4:1 mixture of $CDCl_3$:DMSO-$d_6$).



**3.135** **3.24**, norreticuline

(3.39)

### 3.6.2 Structural confirmation of norreticuline

Confirmation of the final structure of **3.24** was performed by comparison of $^1$H NMR and MS data to that found in literature[146] and also by definitive 1D and 2D NMR experiments. The comparison of $^1$H NMR data alone could not be used to definitively confirm the structure mainly because of the limited spectroscopic data available. Rice and Brossi[146a] reported $^1$H NMR data only in a 4:1 mixture of $CDCl_3$ and DMSO-$d_6$, which was an undesirable solvent system because of the limited amount of material synthesized (5 mg) and was used only once all other spectroscopic data had been collected. It was also found that the deuterated DMSO used had a water content that proved to be significant on such a small scale. Due to the nature of DMSO, however, this sample was not recoverable to attempt with a drier solvent. The final spectrum obtained for comparison was clean enough considering the scale, but additional characterization was performed in MeOD for final confirmation. The reported $^1$H NMR data in the account by Zenk et al.[146b] was only provided only for an isopically-enhanced, HCl salt, which as indicated previously was not successfully obtained. This data, however, was in MeOD and was similar to the $^1$H obtained for **3.24** in MeOD, and could be considered as additional evidence to support the structural confirmation. The $^1$H and $^{13}$C data in MeOD as well as full characterization can be seen in the Appendix and Experimental sections, respectively.

Major spectroscopic evidence in support of the structure of **3.24** was obtained by HMQC, HMBC, COSY and NOESY NMR data. The most definitive evidence was found in the HMBC (Heteronuclear Multiple Bond Correlation Experiment), whose long-range $^1$H/$^{13}$C correlations are seen in Figure 3.3.

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[146] (a) Rice, K. C.; Brossi, A. *J. Org. Chem.* **1980**, *45*, 592. (b) Maier, U. H.; Rodl, W.; Deus-Neumann, B.; Zenk, M. H. *Phytochemistry* **1999**, *52*, 373. (c) Konda, M.; Shiori, T.; Yamada, S. *Chem. Pharm. Bull.* **1975**, *23*, 1063.

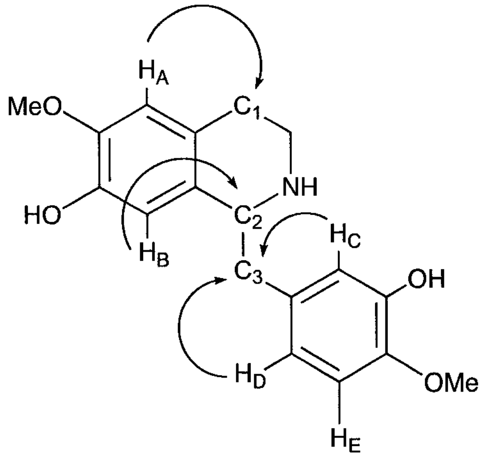
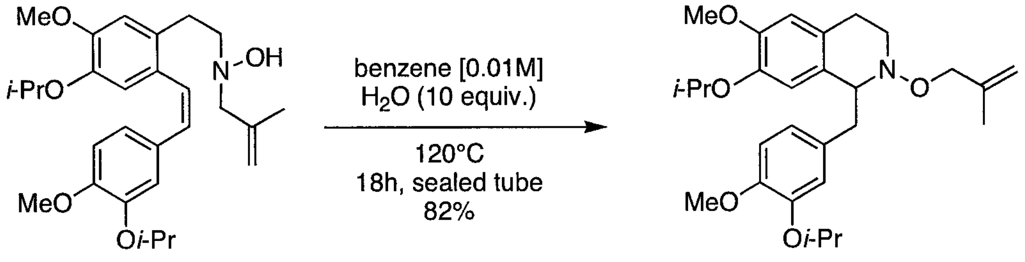


Figure 3.3. Significant HMBC correlations between $^1$H and $^{13}$C

The assignments of each proton and carbon were previously assigned using the aforementioned NMR experiments. The HMBC would give information about weak $^1$H/$^{13}$C J-couplings, which would indicate a correlation signal of a proton that is two, three, or four bonds away from the carbon and therefore gives information as to which protons may be near a particular carbon in space and not directly bonded to it (as with the HMQC). The purpose of this HMBC experiment was to prove that the Cope-type hydroamination event indeed yielded a 6-membered ring, and not an unlikely 7-membered ring. The correlation between $H_B$ and $C_2$ and a lack of correlation between $H_B$ and $C_3$, indicates that the western aryl ring is closest to the methine CH, as opposed to the benzyl $CH_2$. Similarly, the positive correlation between $H_C$ and $H_D$ with the benzyl $C_3$ and no correlation with the methine $C_2$ indicates that the benzyl $CH_2$ is closest to the southern benzyl ring. These HMBC correlations were instrumental in confirming the definitive structure of **3.24** as the natural product norreticuline.

## 3.7 Conclusion

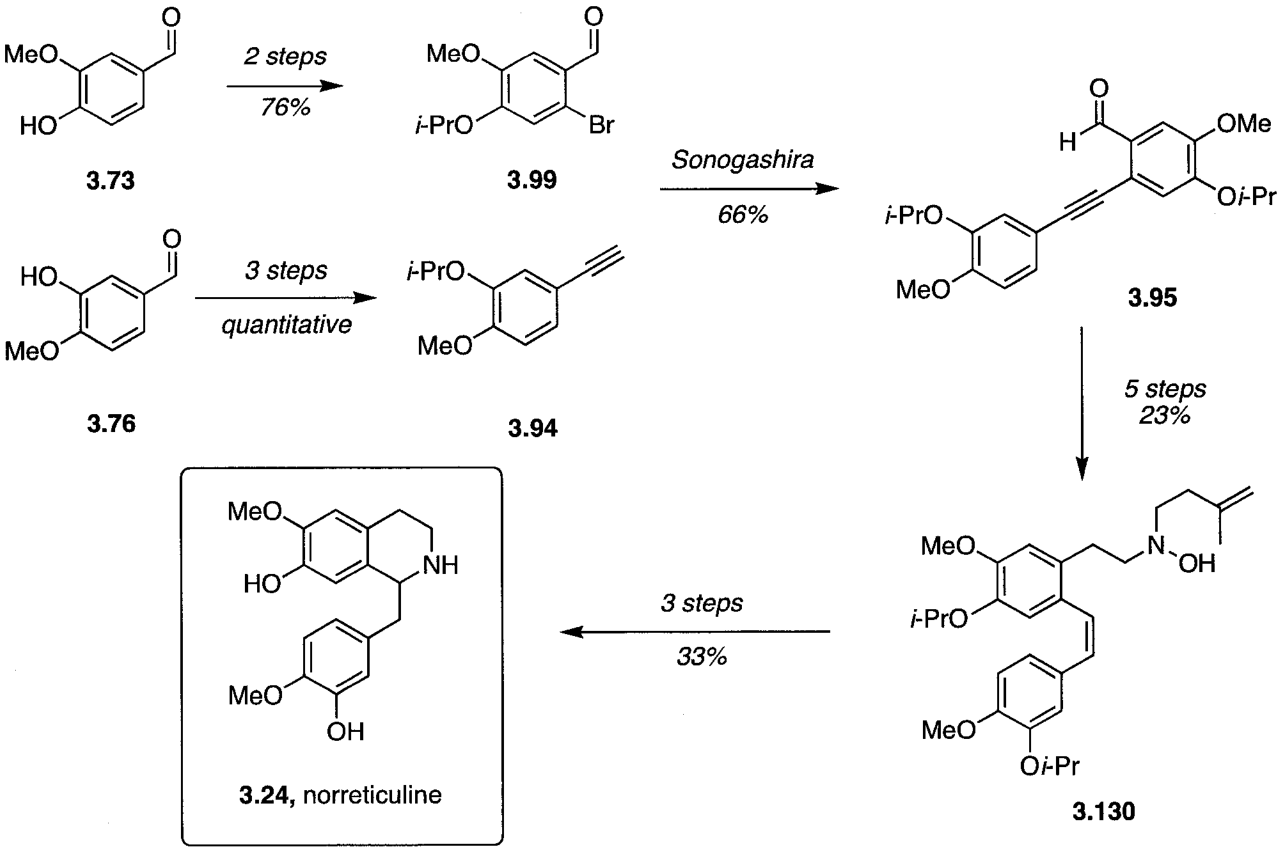
The total synthesis of norreticuline (**3.24**) was successfully completed via a difficult Cope-type hydroamination key step. The greatest success was obtained using a tandem Cope-type hydroamination/[2,3] Meisenheimer rearrangement sequence, where the cyclization step was completed in 82% isolated yield (eq. 3.40). The reaction was performed in a sealed tube by heating at 120°C for 18 hours in deoxygenated benzene with a concentration of 0.01 M and with the addition of 10 equivalents of water. Following cyclization, the target compound was obtained following the N-O bond cleavage under zinc and acetic acid reducing conditions and final deprotection of the phenolic isopropyl groups with boron trichloride.



**3.130** **3.132**

(3.40)

The cyclization precursor was synthesized in 9 linear steps from the commercial and inexpensive starting materials vanillin (**3.73**) and isovanillin (**3.76**) (Scheme 3.12). The synthesis was convergent at the Sonogashira coupling step between the aryl bromide **3.99** and the aryl alkyne **3.94**, which potentially allows for the facile synthesis of benzyl tetrahydroisoquinoline analogues.



Scheme 3.12. Synthesis of norreticuline (**3.24**) via the tandem Cope-type hydroamination/[2,3] Meisenheimer rearrangement sequence precursor from simple starting materials vanillin (**3.73**) and isovanillin (**3.76**)

The overall synthesis was completed in 3.8% over 12 linear steps. This result is difficult to compare to recent literature syntheses of **3.24** and other benzyl tetrahydroisoquinolines[147] because they tend to be asymmetric, but the Cope-hydroamination strategy involved a novel key step which has greater potential to accommodate derivatization and may also be developed as an asymmetric variant in the future. This method could be the first known metal-free hydroamination in the total synthesis of a benzyl tetrahydroisoquinoline and could be among the most complex examples of a hydroamination key step in alkaloid syntheses.[139] The completion of this synthesis demonstrated that the Cope-type hydroamination has the potential to be used as a general method in the formation of 6-membered azacycles and that the tandem Cope-type hydroamination/[2,3] Meisenheimer rearrangement could also be employed to drive more difficult cyclizations forward by forming a more thermodynamically favourable product (when compared with the *N*-oxide) and expand the reach of intramolecular Cope-type hydroamination.

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[147] For a review on the asymmetric synthesis of isoquinoline alkaloids, please see Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341.

# 4

# Conclusions

## 4.1 General Conclusions

The work presented in this thesis has described the development of certain aspects of intermolecular Cope-type hydroamination of alkynes and intramolecular Cope-type hydroamination of alkenes. The goal of this work was in line with attempts to ultimately develop a simple, metal free hydroamination method that is general to all types of alkene and alkyne substrates.

In Chapter 2, a methodology project was presented on the intermolecular hydroamination of alkynes with hydrazines. The development of Cope-type hydroaminations achieved good to excellent anti-Markovnikov regioselectivities with a variety of terminal aryl acetylenes to furnish the linear hydrazone (aldimine). The hydroamination product was isolable as the corresponding semicarbazide, which was moderate in yield but provided the opportunity to confirm the occurrence of the hydroamination and to fully characterize the products. Initial studies into reactivity were performed which suggested that the hydroamination was not operating through any acid, base or radical-based mechanism. Further studies would be necessary to fully characterize this reactivity. DFT calculations supported the general regioselectivity for the anti-Markovnikov isomer. The development of this method with hydrazines successfully complemented the regioselectivity that was previously obtained for the intermolecular Cope-type hydroamination of alkynes with hydroxylamines.

In Chapter 3, the total synthesis of the benzyltetrahydroisoquinoline norreticuline was accomplished using an intramolecular alkene Cope-type hydroamination as a key step. The synthesis was completed in 3.8% overall yield over 12 linear steps using a divergent approach that could accommodate the synthesis of similar natural products or analogues. This synthesis provided a good scaffold to develop the intramolecular hydroamination of alkenes in complex systems, as the current state of development of this area is limited. The hydroamination step was optimized using a tandem Cope-type hydroamination/[2,3]-Meisenheimer rearrangement sequence and obtained the hydroamination product in 82% yield. It was shown that the Cope-type hydroamination can be used as an efficient intramolecular alkene hydroamination method in complex systems encountered in natural product synthesis.

## 4.2 Contributions to research:

1. Was implicated in the first examples of intermolecular metal-free Cope-type Hydroamination of aryl alkynes with hydrazines and obtained anti-Markovnikov selectivity, which is rare in transition metal catalysts.
2. Further developed an approach to isolate the otherwise unstable hydroamination products of alkynes and hydrazines as semicarbazides.
3. Obtained initial results in probing the mechanistic pathway of the Cope-type hydroamination with hydrazines with respect to possible acid, base, and radical involvement. Also obtained DFT results which suggested a concerted, asynchronous transition state where the C-N bond formation precedes the C-H bond formation.
4. Applied a challenging intramolecular alkene Cope-type hydroamination to form a 6-membered ring in the total synthesis of norreticuline.

### 4.2.1 Publications

1. Cebrowski, P. H.; Roveda, J.-G.; Moran, J.; Gorelsky, S.; Beauchemin, A. M. "Metal-Free Intermolecular Hydroamination of Alkynes Using Hydrazines" *Chem. Commun.*, **2008**, 492.
2. Bourgeois, J.; Dion, I.; Cebrowski, P. H.; Loiseau, F.; Bédard, A.-C.; Beauchemin, A. M. "The Tandem Cope-type Hydroamination/[2,3]-Rearrangement Sequence: A Strategy to Favor the Formation of Intermolecular Hydroamination Products and Enable Difficult Cyclizations" *J. Am. Chem. Soc.* **2009**, ***ASAP***.

### 4.2.2 Presentations

1. “Application of Cope-Type Hydroamination Towards the Synthesis of N-Norreticuline and Hydrazones" Pamela H. Cebrowski, Anne-Catherine Bédard, Jean-Grégoire Roveda, Joseph Moran, Serge Gorelsky, André M. Beauchemin, Synthesis Day, University of Ottawa, Ottawa, ON, June 2008 (poster)

2. “Application of Cope-Type Hydroamination Towards the Synthesis of Reticuline and Hydrazones" Pamela H. Cebrowski, Anne-Catherine Bédard, Jean-Grégoire Roveda, Joseph Moran, Serge Gorelsky, André M. Beauchemin, OCCI Day, University of Ottawa, Ottawa, ON, May 2008 (poster)

3. “Hydroamination of Alkynes Using Hydrazines” Pamela Cebrowski, Jean-Grégoire Roveda, Joseph Moran, André M. Beauchemin. QOMSBOC, Université de Montréal, Montréal QC, December 2007 (poster)

4. “Progress Towards Metal-Free Hydroaminations using Hydrazines” Pamela Cebrowski, Chris Whipp, Eric Beaulieu, André M. Beauchemin, Synthesis Day, University of Ottawa, Ottawa, ON, June 2007 (poster)

# 5

# Experimental

## 5.1 Intramolecular Cope-type hydroamination of alkynes (Experimental for Chapter 2)

### 5.1.1 General information

All reactions were performed in flame-dried or oven-dried glass round-bottomed flasks. Purification of reaction products was carried out by flash column chromatography using silica gel (40-63 μm). Analytical thin layer chromatography was performed on aluminum sheets pre-coated with silica gel 60 F254, cut to size. Visualization was accomplished with UV light or by an aqueous $KMnO_4$ or vanillin solution followed by heating.

$^1$H NMR spectra were recorded on a Bruker AVANCE 300 or 400 MHz spectrometer at ambient temperature. Chemical shifts are reported in ppm from tetramethylsilane and are reported in ppm using solvent as the internal standard ($CDCl_3$ at 7.26 ppm, $C_6D_6$ at 7.15 ppm or DMSO-*d6* at 2.50 ppm). Data are reported as: multiplicity (ap = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration and coupling constant(s) in Hz. $^{13}$C NMR spectra were recorded at 75 or 100 MHz. Chemical shifts are reported in ppm from tetramethylsilane, with the solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm, $C_6D_6$ at 128.02 ppm or DMSO-*d6* at 39). High resolution mass spectroscopy (HRMS) was performed at the Ottawa-Carleton Mass Spectrometry Centre. Infrared (IR) spectra were obtained as neat thin films on a sodium chloride disk and were recorded on a Bomem Michelson 100 Fourier transform infrared spectrometer (FTIR). Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected.

**Materials.** Dichloromethane, isopropanol, and toluene were dried by distillation over calcium hydride. Tetrahydrofuran, diethyl ether, and dioxane were dried by distillation over sodium/benzophenone ketyl. Methyl hydrazine was dried by distillation over barium oxide, phenyl isocyanate was dried by distillation over phosphorus pentoxide, and the bases diisopropylamine and triethylamine were dried by distillation over calcium hydride. Unless otherwise noted, all other commercial materials were used without further purification.

### 5.1.2 Procedures

**General Procedure for hydroamination of alkynes with activated hydrazines (Table 2.1).** An oven-dried sealed tube equipped with a magnetic stir bar was charged with phenylacetylene **2.6** (55 μL, 0.50 mmol), the electron–deficient hydrazine (1.00 mmol), and deuterated solvent (500 μL, 1.0 M relative to the alkyne). The sealed tube was then closed and heated to 100°C for 18 hours with vigorous stirring. The reaction was allowed to cool to room temperature and an aliquot was transferred to an NMR tube. The unpurified reaction mixture was analyzed directly by $^1$H NMR.

**Equation 2.7, Procedure for initial reaction between phenylacetylene (2.6) and hydrazine hydrate.** An oven-dried sealed tube equipped with a magnetic stir bar was charged with phenylacetylene **2.6** (110 μL, 1.00 mmol), hydrazine hydrate (97 μL, 2.0 mmol), and methanol (1.0 mL, 1.0 M). The sealed tube was then closed and heated to 113°C for 18 hours with vigorous stirring. The reaction was allowed to cool to room temperature. The crude was concentrated under reduced pressure and re-dissolved in $CDCl_3$. An $^1$H NMR spectra of the solution was recorded and the relative product ratio was calculated and a ratio of approximately 2.5:1 for the anti-Markovnikov isomer was obtained.

**Equation 2.8, Procedure for first reaction between phenylacetylene (2.6) and hydrazine hydrate in isopropanol.** An oven-dried sealed tube equipped with a magnetic stir bar was charged with phenylacetylene **2.6** (110 μL, 1.00 mmol) followed by hydrazine hydrate (243 μL, 5.00 mmol), and isopropanol (1.0 mL, 1.0 M). The sealed tube was then closed and heated to 95°C for 18 hours with vigorous stirring. The reaction was allowed to cool to room temperature. The crude was concentrated under reduced pressure and re-dissolved in $CDCl_3$. Styrene (0.25 equivalents) was added as an internal standard for crude NMR analysis. $^1$H NMR spectra of these solutions were recorded, and the % conversion calculated based on the ratio of the styrene alkene (1H) resonance at 5.78 ppm to the resonance corresponding to the product's hydrazone CH proton resonance (1H) at approximately 7.00 ppm or the product's $CH_2$ proton resonance (2H) at approximately 3.75 ppm. The method is estimated to have an error of approximately ±5%. The conversion for the anti-Markovnikov isomer was 38%

and that for the Markovnikov isomer was 15% (2.5:1 AM:M ratio).

**Equation 2.9, Procedure for first reaction between phenylacetylene (2.6) and methyl hydrazine.** An oven-dried sealed tube equipped with a magnetic stir bar was charged with phenylacetylene **2.6** (110 µL, 1.00 mmol) followed by methyl hydrazine (266 µL, 5.00 mmol), isopropanol (1.0 mL, 1.0 M), and water (180 µL, 10.0 mmol). The sealed tube was then closed and heated to 95°C for 18 hours with vigorous stirring. The reaction was allowed to cool to room temperature. The crude was concentrated under reduced pressure and re-dissolved in $CDCl_3$. The crude was concentrated under reduced pressure and re-dissolved in $CDCl_3$. Styrene (0.25 equivalents) was added as an internal standard for $^1H$ NMR analysis, and the spectrum was analyzed as described in the general procedure for Equation 2.7. The conversion for the anti-Markovnikov isomer was 29% and that for the Markovnikov isomer was 2% (14:1 AM:M ratio).

**General Procedure for the first temperature optimization (Table 2.2).** An oven-dried sealed tube equipped with a magnetic stir bar and was charged with isopropanol (1.0 mL, 1.0 M), followed by methyl hydrazine (266 µL, 5.00 mmol), phenylacetylene **2.6** (110 µL, 1.00 mmol), and water (180 µL, 10.0 mmol). The sealed tube was then closed and heated to the chosen temperature for 18 hours with vigorous stirring. The reaction was allowed to cool to room temperature. The crude was concentrated under reduced pressure and re-dissolved in $CDCl_3$. The crude was concentrated under reduced pressure and re-dissolved in $CDCl_3$. Styrene (0.25 equivalents) was added as an internal standard for $^1H$ NMR analysis, and the spectrum was analyzed as described in the general procedure for Equation 2.7.

**General Procedure for the solvent scan with and without water (Table 2.3).** An oven-dried sealed tube equipped with a magnetic stir bar was charged with the solvent (1.0 mL, 1.0 M), followed by methyl hydrazine (266 µL, 5.00 mmol), phenylacetylene **2.6** (110 µL, 1.00 mmol), and if necessary, water (180 µL, 10.0 mmol). When water was not added no adjustment to the total reaction volume was made as it was considered negligible. The sealed tube was then closed and heated to 113°C for 18 hours with vigorous stirring. The reaction was allowed to cool to room temperature. The crude was concentrated under reduced pressure and re-dissolved in $CDCl_3$. Styrene (0.25 equivalents) was added as an internal standard for $^1H$ NMR analysis, and the spectrum was analyzed as described in the general procedure for Equation 2.7.

**General Procedure for the optimization of temperature, concentration, and hydrazine equivalents with *p*-tolyl acetylene (2.21) (Table 2.4).** An oven-dried sealed tube equipped with a magnetic stir bar was charged with isopropanol according to the chosen dilution factor with respect to the alkyne, followed by the chosen number of equivalents of methyl hydrazine, and *p*-tolyl acetylene **2.21** (127 μL, 1.00 mmol). The sealed tube was then closed and heated to the chosen temperature for 18 hours with vigorous stirring. The reaction was allowed to cool to room temperature. The crude was concentrated under reduced pressure and re-dissolved in $CDCl_3$. Styrene (0.25 equivalents) was added as an internal standard for $^1H$ NMR analysis, and the spectrum was analyzed as described in the general procedure for Equation 2.7.

**General Procedure for the second solvent scan (Table 2.5).** An oven-dried sealed tube equipped with a magnetic stir bar was charged with the solvent (1.0 mL, 1.0 M), followed by methyl hydrazine (266 μL, 5.00 mmol) and either phenylaceylene **2.6** (110 μL, 1.00 mmol) or *p*-tolyl acetylene **2.21** (127 μL, 1.00 mmol). The sealed tube was then closed and heated to 140°C for 18 hours with vigorous stirring. The reaction was allowed to cool to room temperature. The crude was concentrated under reduced pressure and re-dissolved in $CDCl_3$. Styrene (0.25 equivalents) was added as an internal standard for $^1H$ NMR analysis, and the spectrum was analyzed as described in the general procedure for Equation 2.7.

**Section 2.2.4, Investigation into acid, base or radical involvement.** An oven-dried sealed tube equipped with a magnetic stir bar and a rubber septum was purged with argon for 15 minutes and kept under an argon atmosphere with a balloon. The sealed tube was charged with isopropanol (1.0 mL, 1.0 M), followed by methyl hydrazine (266 μL, 5.0 mmol) and phenylaceylene **2.6** (110 μL, 1.00 mmol). One of the following additives was subsequently added: diisopropylethylamine (871 μL, 5.00 mmol), acetic acid, (59 μL, 1.0 mmol), or butylated hydroxytoluene (BHT, 1.124 g, 5.101 mmol). The sealed tube was then closed and heated to 140°C (trials with diisopropylehtylamine and acetic acid) or 115°C (trial with BHT) for 18 hours with vigorous stirring. The reaction was allowed to cool to room temperature. The crude was concentrated under reduced pressure and re-dissolved in $CDCl_3$. Styrene (0.25 equivalents) was added as an internal standard for $^1H$ NMR analysis, and the spectrum was analyzed as described in the general procedure for Equation 2.7.

**General Procedure for the effect of water and oxygen (Table 2.6).** For trials to be done under an argon atmosphere, an oven-dried sealed tube equipped with a magnetic stir bar and a rubber septum was purged for 15 minutes with argon and kept under an argon atmosphere with a balloon. By addition through a gas-tight microsyringe, isopropanol (1.0 mL, 1.0 M), followed by methyl hydrazine (266 μL, 5.00 mmol) and phenylaceylene **2.6** (110 μL, 1.00 mmol) was added. For trials with the presence of water, water was then added by microsyringe (180 or 36 μL, 10.0 or 2.0 mmol, respectively). The sealed tube was then quickly sealed with its Teflon cap and heated to 140°C for 18 hours with vigorous stirring. The same setup was performed for trials to be done under and oxygen atmosphere except the sealed tube was not purged with argon and was left open to air during the addition of the reagents. The reaction was allowed to cool to room temperature. The crude was concentrated under reduced pressure and re-dissolved in $CDCl_3$. Styrene (0.25 equivalents) was added as an internal standard for $^1H$ NMR analysis, and the spectrum was analyzed as described in the general procedure for Equation 2.7.

**General Procedure for alkyne substrate scope (Table 2.7).** An oven-dried sealed tube equipped with a magnetic stir bar and a rubber septum was purged with an argon balloon and an outlet for 10 minutes. Isopropanol (1.0 mL) was added, followed by methyl hydrazine (266 μL, 5.00 mmol) and the alkyne (1.00 mmol). The sealed tube was then closed and heated to 113 or 140°C for 18 hours with vigorous stirring. The reaction was allowed to cool to room temperature. The crude was concentrated under reduced pressure and re-dissolved in $CDCl_3$. Styrene (0.25 equivalents) was added as an internal standard for $^1H$ NMR analysis, and the spectrum was analyzed as described in the general procedure for Equation 2.7.

**General Procedure for derivitization to semicarbazide (Table 2.7).** Prepared from a modified procedure by Bailey.[148] A flame-dried round bottomed flask charged with a magnetic stir bar and the hydrazone (0.60 mmol) was purged with argon for 15 minutes. Methylene chloride (6.0 mL) was added and the solution was cooled to 0°C. Triethylamine (209 μL, 1.20 mmol) was added, followed by phenyl isocyanate (130 μL, 1.50 mmol). The reaction was allowed to warm to room temperature, and stirred for another 3 hours. The crude reaction mixture was concentrated under reduced pressure and purified by silica gel chromatography to give the semicarbazide.

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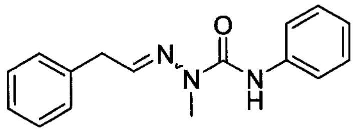
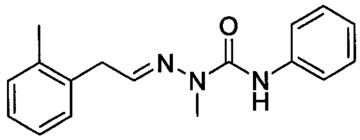
[148] Bailey, M. D.; Halmos, T.; Goudreau, N.; Lescop, E.; Llinas-Brunet, M. *J. Med. Chem.* **2004**, *47*, 3788.

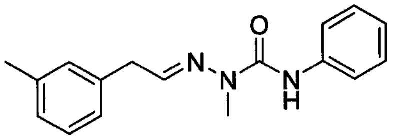
### 5.1.3 Characterization



**2-Methyl-4-phenyl-1-(2-phenylethylidene)semicarbazide (2.25, Table 2.7, Entry 1).** The crude yellow oil was purified by column chromatography (40% Et$_2$O/hexanes) and isolated as a colourless oil (777 mg, 58% yield). TLC *R*$_f$ 0.27 (40% Et$_2$O/hexanes); $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 8.66 (br, 1H), 7.54 (ap dd, *J* = 8.61, 1.03 Hz, 2H), 7.46-7.27 (m, 8H), 7.08 (td, *J* = 14.77, 1.13 Hz, 1H), 7.03 (t, *J* = 5.26, 5.26 Hz, 1H), 3.75 (d, *J* = 5.23 Hz, 2H), 3.28 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 153.0, 138.6, 138.5, 136.8, 129.1, 128.9, 128.8, 126.9, 122.9, 119.2, 39.5, 27.7; IR (film): 3378, 1690, 1591, 1524, 1442, 1124, 1014, 754, 693 cm$^{-1}$; HRMS (EI): Exact mass calcd for C$_{16}$H$_{17}$N$_3$O [M]$^+$: 267.1372. Found: 267.1392.

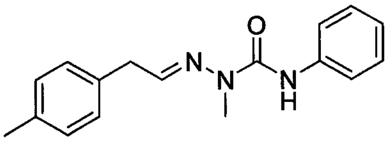


**2-Methyl-4-phenyl-1-(2-o-tolylethylidene)semicarbazide (2.37, Table 2.7, Entry 2).** Procedure as indicated above except used 1.5 equivalents of triethylamine (421 μL, 3.02 mmol) and 1.2 equivalents of phenylisocyanate (264 μL, 2.42 mmol). The crude yellow oil was purified by column chromatography (20% EtOAc/hexanes) and isolated as a colourless oil (370 mg, 50% yield). TLC *R*$_f$ 0.50 (30% EtOAc/hexanes); $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 8.53 (br, 1H), 7.44 (dd, *J* = 8.8, 1.2 Hz, 2H), 7.32-7.27 (m, 2H), 7.25-7.18 (m, 4H), 7.04 (tt, *J* = 7.6, 1.2 Hz, 1H), 6.97 (t, *J* = 5.2 Hz, 1H), 3.71 (d, *J* = 4.8 Hz, 2H), 3.25 (s, 3H), 2.35 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 152.9, 138.6, 137.7, 136.6, 135.2, 130.5, 129.6, 128.8, 127.1, 126.3, 122.8, 119.0, 37.2, 27.5, 19.6; IR (film): 3381, 3351, 1692, 1591, 1526, 1442, 1123, 1014, 751, 693 cm$^{-1}$; HRMS (EI): Exact mass calcd for C$_{17}$H$_{19}$N$_3$O [M]$^+$: 281.1528. Found: 281.1531.

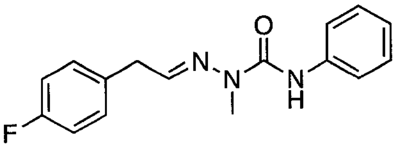


**2-Methyl-4-phenyl-1-(2-m-tolylethylidene)semicarbazide (2.38, Table 2.7, Entry 3).** The crude yellow oil was purified by column chromatography (10-30% EtOAc/hexanes) and isolated as a pale yellow oil (339 mg, 49% yield). TLC *R*$_f$ 0.39 (30% EtOAc/hexanes); $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 8.63 (br, 1H), 7.50 (ap dd,

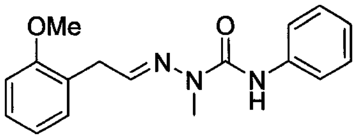
$J$ = 8.8, 1.2 Hz, 2H), 7.31 (dd, $J$ = 10.0, 8.4 Hz, 2H), 7.26 (t, $J$ = 7.6 Hz, 1H), 7.12-7.02 (m, 4H), 6.99 (t, $J$ = 5.6 Hz, 1H), 3.68 (d, $J$ = 5.2 Hz, 2H), 3.26 (s, 3H), 2.37 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 153.0, 138.6, 138.6, 138.5, 136.7, 129.7, 128.9, 128.7, 127.6, 126.0, 122.9, 119.1, 39.4, 27.6, 21.4; IR (film): 3366, 2925, 1686, 1593, 1522, 1443, 1310, 1231, 1123, 1009, 753, 691 cm$^{-1}$; HRMS (EI): Exact mass calcd for $C_{17}H_{19}N_3O$ [M]$^+$: 281.1528. Found: 281.1530.



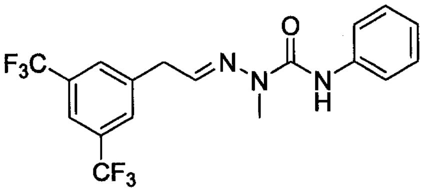
**2-Methyl-4-phenyl-1-(2-p-tolylethylidene)semicarbazide (2.22, Table 2.7, Entry 4).** The crude yellow oil was purified by column chromatography (20-50% EtOAc/hexanes) and isolated as a colourless oil (104 mg, 37% yield). TLC $R_f$ 0.49 (30% EtOAc/hexanes); $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 8.63 (br, 1H), 7.49 (ap dd, $J$ = 8.7, 1.2 Hz, 2H), 7.34-7.29 (m, 2H), 7.21-7.14 (m, 4H), 7.05 (tt, $J$ = 14.7, 1.2 Hz, 1H), 6.96 (t, $J$ = 5.1 Hz, 1H), 3.68 (d, $J$ = 5.1 Hz, 2H), 3.25 (s, 3H), 2.37 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 152.9, 138.7, 138.6, 136.5, 133.7, 129.4, 128.9, 128.8, 122.8, 119.0, 39.0, 27.5, 21.0; IR (film): 3381, 3340, 1690, 1591, 1526, 1442, 1123, 1014, 753, 693 cm$^{-1}$; HRMS (EI): Exact mass calcd for $C_{17}H_{19}N_3O$ [M]$^+$: 281.1528. Found: 281.1514.



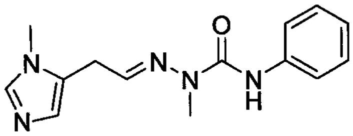
**1-(2-(4-Fluorophenyl)ethylidene)-2-methyl-4-phenylsemicarbazide (2.39, Table 2.7, Entry 5).** The crude yellow oil was purified by column chromatography (20-50% EtOAc/hexanes) and isolated as a white solid (528 mg, 44% yield, mp = 185-188 °C). TLC $R_f$ 0.45 (30% EtOAc/hexanes); $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 8.61 (br, 1H), 7.50 (d, $J$ = 7.7 Hz, 2H), 7.31 (t, $J$ = 7.9 Hz, 2H), 7.27-7.17 (m, 2H), 7.10-7.01 (m, 3H), 6.96 (t, $J$ = 7.7 Hz, 1H), 3.67 (d, $J$ = 5.2 Hz, 2H), 3.24 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 161.7 (d, $J$ = 248.9 Hz), 152.7, 138.4, 138.1, 132.4 (d, $J$ = 3.3 Hz), 130.4 (d, $J$ = 7.9 Hz), 128.8, 122.8, 119.0, 115.4 (d, $J$ = 21.4 Hz), 38.4, 27.4; IR (film): 3376, 1688, 1591, 1527, 1509, 1443, 1221, 1125, 1015, 753, 693 cm$^{-1}$; HRMS (EI): Exact mass calcd for $C_{16}H_{16}FN_3O$ [M]$^+$: 285.1277. Found: 285.1265.



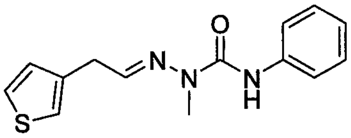
**2-Methyl-4-phenyl-1-(2-(2-methoxyphenyl)ethylidene)semicarbazide (2.40, Table 2.7, Entry 6).** Procedure as indicated above except used 1.5 equivalents of triethylamine (318 μL, 2.28 mmol) and 1.2 equivalents of phenylisocyanate (218 μL, 1.83 mmol). The crude yellow oil was purified by column chromatography (20% EtOAc/hexanes) and isolated as a yellow oil (276 mg, 40% yield). TLC $R_f$ 0.47 (30% EtOAc/hexanes); $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 8.62 (br, 1H), 7.48 (d, $J$ = 7.6 Hz, 2H), 7.32-7.28 (m, 3H), 7.21 (dd, $J$ = 7.2, 1.6 Hz, 1H), 7.06-7.01 (m, 2H), 6.97 (t, $J$ = 7.6 Hz, 1H), 6.93 (d, $J$ = 8.4 Hz, 1H), 3.71 (d, $J$ = 5.2 Hz, 2H), 3.86 (s, 3H), 3.24 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 157.3, 153.0, 138.7, 138.5, 130.4, 128.8, 128.2, 125.4, 122.7, 120.6, 119.0, 110.5, 55.4, 34.0, 27.5; IR (film): 3375, 2941, 1690, 1591, 1526, 1442, 1244, 1122, 1015, 753, 695 cm$^{-1}$; HRMS (EI): Exact mass calcd for $C_{17}H_{19}N_3O$ [M]$^+$: 294.1477. Found: 297.1483.



**1-(2-(3,5-Bis(trifluoromethyl)phenyl)ethylidene)-2-methyl-4-phenylsemicarbazide (2.41, Table 2.7, Entry 8).** The crude yellow oil was purified by column chromatography (20-45% EtOAc/hexanes) and isolated as a yellow solid (260 mg, 31% yield, mp = 173-175 °C). TLC $R_f$ 0.38 (30% EtOAc/hexanes); $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 8.46 (br, 1H), 7.83 (s, 1H), 7.73 (s, 2H), 7.46 (ap d, $J$ = 8.1, 2H), 7.30 (ap t, J = 7.5, 2H), 7.05 (t, $J$ = 7.5 Hz, 1H), 6.97 (t, J = 5.1, 1H), 3.84 (d, $J$ = 5.1, 2H), 3.27 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 152.6, 139.4, 138.3, 135.8, 132.2 (q, $J$ = 33.4 Hz), 129.3 (ap d, $J$ = 2.7 Hz), 129.0, 123.24, 123.22 (q, J = 272.8 Hz), 121.2-121.0 (m), 119.3, 39.0, 27.9; IR (film): 3383, 3058, 2948, 1694, 1593, 1528, 1444, 1378, 1279, 1172, 1131, 1016, 892, 754, 684 cm$^{-1}$; HRMS (EI): Exact mass calcd for $C_{18}H_{15}F_6N_3O$ [M]$^+$: 403.1119. Found: 403.1123.



**2-Methyl-1-(2-(1-methyl-1H-imidazol-5-yl)ethylidene)-4-phenylsemicarbazide (2.42, Table 2.7, Entry 9).** The crude yellow oil was purified by column chromatography (5% MeOH/$CH_2Cl_2$) and isolated as a colourless oil (421 mg, 55% yield). TLC $R_f$ 0.17 (5% MeOH/$CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 8.45 (br, 1H), 7.47-7.40 (m, 3H), 7.28 (t, $J$ = 7.9, Hz, 2H), 7.02 (ap t, $J$ = 7.4 Hz, 1H), 6.91-6.84 (m, 2H), 3.66 (d, $J$ = 4.8 Hz, 2H), 3.55 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 152.5, 138.3, 138.2, 135.2, 128.8, 127.7, 126.6, 122.9, 118.9, 31.4, 28.0, 27.6; IR (film): 3374, 1686, 1591, 1526, 1443, 1234, 1123, 1013, 755, 694 cm$^{-1}$; HRMS (EI): Exact mass calcd for $C_{14}H_{17}N_5O$ [M]$^+$: 271.1433. Found: 271.1459.



**2-Methyl-4-phenyl-1-(2-(thiophen-3-yl)ethylidene)semicarbazide (2.43, Table 2.7, Entry 10).** The crude yellow oil was purified by column chromatography (20-50% EtOAc/hexanes) and isolated as a colourless oil (341 mg, 45% yield). TLC $R_f$ 0.46 (30% EtOAc/hexanes); $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 8.63 (br, 1H), 7.51 (ap dd, $J$ = 8.4, 1.2 Hz, 2H), 7.36-7.92 (m, 3H), 7.10-7.01 (m, 3H), 6.98 (t, $J$ = 5.2 Hz, 1H), 3.72 (d, $J$ = 5.2 Hz, 2H), 3.25 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 152.8, 138.4, 137.7, 136.7, 128.7, 128.2, 126.0, 122.8, 121.9, 119.0, 33.8, 27.5; IR (film): 3378, 1686, 1590, 1523, 1442, 1313, 1230, 1123, 1014, 752, 692 cm$^{-1}$; HRMS (EI): Exact mass calcd for $C_{14}H_{15}N_3OS$ [M]$^+$: 273.0936. Found: 273.0935.

### 5.1.4 Computational details

Density functional theory (DFT) calculations have been performed using the *Gaussian 03* program.[149] Optimized molecular geometries were calculated using the B3LYP[150] exchange-correlation functional. The

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[149] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Lyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision C.01*, Gaussian, Inc.: 2003.

[150] Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

triple-zeta TZVP[151] basis set were used for calculations. Wave function stability calculations were performed to confirm that the calculated wave functions corresponded to the ground state. Harmonic frequency calculations were performed to ensure that the stationary points were true energy minima or transition states (TSs) and to calculate free energies of the species. Reaction coordinate scans[152] were performed to verify that the calculated TSs connected the correct minima for a given reaction step. The unscaled vibrational frequencies were used for calculating Gibbs free energies of the species (at 298K and 1 atm). The basis set superposition errors (BSSE) were evaluated using the Boys-Bernardi counterpoise method.[153] However, because all calculated corrections were sufficiently low (less than 0.6 kcal/mol) for the basis set employed, the corrections were not included in the calculation of the energies of the species.

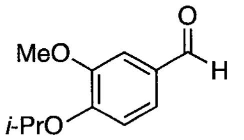
Solvation free energies of all species in methanol were calculated to probe the solvent effect for reaction barriers using the polarizable continuum model (PCM)[154] with the united atom topological radii (UAHF). The calculated solvation free energies were used to calculate the free energies of the species in solution.

## 5.2 Total synthesis of norreticuline (Experimental for Chapter 3)

### 5.2.1 General Information

Please refer to Section 5.1.1. The *n*-butyllithium was titrated prior to use with salicylaldehyde phenylhydrazone.[155]

### 5.2.2 Procedures and Characterization



**4-Isopropoxy-3-methoxybenzaldehyde (3.86, Table 3.1, Entry 7).** The title compound was prepared according to the procedure by Ridley et al.[111] In a flame-dried round-bottomed flask equipped with a magnetic

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[151] Schafer, A.; Huber, C.; Ahlrichs, R. *J. Chem. Phys.* **1994**, *100*, 5829-5835.

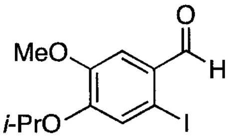
[152] (a) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154. (b) Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523.

[153] Boys, S. F.; Bernardi, F. *Mol. Phys.* **1970**, *19*, 553.

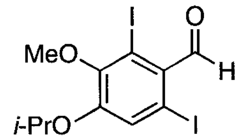
[154] Cossi, M.; Scalmani, G.; Rega, N.; Barone, V. *J. Chem. Phys.* **2002**, *117*, 43.

[155] Procedure according to Love, B. E.; Jones, E. G. *J. Org. Chem.* **1999**, *64*, 3755.

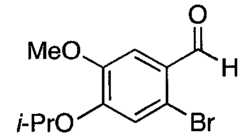
stir bar vanillin **3.73** (20.0 g, 132 mmol) was suspended in DMF (100 mL). Isopropyl bromide (19.0 mL, 203 mmol) and $K_2CO_3$ (29.2 g, 211 mmol) were subsequently added and the reaction mixture flushed with argon and stirred at room temperature for 48 hours. The resulting crude mixture was poured into water and extracted into diethyl ether. The organics were washed with 5% aq. NaOH, dried over $MgSO_4$, filtered, and concentrated by rotory evaporator. The resulting crude oil was purified by silica column chromatography (20% EtOAc/hexanes) and yielded a clear, light yellow oil (25.5 g, quant.). TLC $R_f$ 0.34 (20% EtOAc/hexanes); $^1H$ NMR (400 MHz, $CDCl_3$) δ ppm 9.84 (s, 1H), 7.43 (dd, *J* = 8.05, 1.95 Hz, 1H), 7.41 (d, *J* = 1.76 Hz, 1H), 6.97 (d, *J* = 8.03, 1H), 4.69 (sept, *J* = 6.16, 1H), 3.92 (s, 3H), 1.43 (d, *J* = 6.09, 6H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 190.8, 153.1, 150.4, 129.7, 126.6, 112.9, 109.6, 71.4, 56.0, 21.9; IR (film): 2979, 2937, 2834, 2728, 1689, 1584, 1506, 1268, 1134, 1108, 1033, 945, 730 cm$^{-1}$; HRMS (EI): Exact mass calcd for $C_{11}H_{14}O_3$ $[M]^+$: 194.0943. Found: 194.0954.



**2-Iodo-4-isopropoxy-5-methoxybenzaldehyde (3.91, Table 3.1, Entry 7).** The title compound was synthesized based on the procedure by Ridley et al.[111] Silver trifluoroacetate (0.218 g, 0.986 mmol) was placed in a flame-dried, 3-necked flask equipped with a stir bar, a condenser, and a dropping funnel. The flask was purged with argon, flame dried and allowed to cool to room temperature under argon. The 4-isopropoxy-3-methoxybenzaldehyde **3.86** (0.545 g, 2.81 mmol) was placed in a separate flame-dried round bottomed flask, purged with argon, and dissolved in $CH_2Cl_2$ (18.0 mL). This solution was added dropwise to the flask containing the silver trifluoroacetate by cannula with stirring. In a separate oven dried round bottomed flask $I_2$ was dissolved in $CH_2Cl_2$ (44 mL), transferred to the dropping funnel, put under argon, and was added dropwise to the reaction mixture. Once the addition of $I_2$ was complete, the reaction was stirred at room temperature for 2.5 hours and then at 65°C for 12 hours. The reaction was allowed to cool to room temperature, filtered, washed with an aqueous saturated solution of sodium thiosulfate, water, and brine. The organics were dried with $Na_2SO_4$, filtered and concentrated. The crude brown oil was purified by silica column chromatography (2.5-5% EtOAc/hexanes) to yield pale yellow crystals (0.480 g, 53% yield; 76% based on recovered starting material), mp 123-124°C (recrystallized from 9:1 hexanes/ethyl acetate). TLC $R_f$ 0.35 (10% EtOAc/hexanes); $^1H$ NMR (500 MHz, $CDCl_3$) δ ppm 9.85 (s, 1H), 7.42 (s, 1H), 7.31 (s, 1H), 4.46 (sept, *J* = 6.00, 1H), 3.89 (s, 3H), 1.43 (d, *J* = 6.00, 6H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 194.9, 153.2, 150.5, 128.0, 124.0, 111.6, 92.7, 71.9, 56.0, 21.8; IR (film): 2973, 2934, 2846, 1680, 1585, 1496, 1376, 1263, 1103, 865, 732 cm$^{-1}$; HRMS (EI): Exact mass calcd for $C_{11}H_{13}IO_3$ $[M]^+$: 319.9909. Found: 319.9899.



**2,6-Diiodo-4-isopropoxy-3-methoxybenzaldehyde (3.98)** was obtained in approximately 5-10% yield as a side product in the iodination procedure to form **3.91**. TLC $R_f$ 0.45 (10% EtOAc/toluene); $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 10.45 (s, 1H), 6.90 (s, 1H), 4.56 (sept, $J$ = 6.00, 1H), 3.91 (s, 3H), 1.44 (d, $J$ = 6.00, 6H); $^{13}$C NMR ($C_6D_6$, 100 MHz) δ 186.8, 155.2, 146.1, 132.5, 123.7, 114.9, 71.6, 60.0, 21.4; IR (film): 2913, 2850, 1695, 1570, 1478, 1375, 1297, 1268, 1109, 1061, 1002, 928, 825 cm$^{-1}$; HRMS (EI): Exact mass calcd for $C_{11}H_{12}I_2O_3$ $[M]^+$: 445.8876. Not found with EI.



**4-Isoproproxy-2-bromo-5-methoxybenzaldehyde (3.99).** The title compound was synthesized based on the procedure by Appukkuttan et al.[156] 4-Isopropoxy-3-methoxybenzaldehyde **3.73** (0.600 g, 3.09 mmol) was dissolved in MeOH (15 mL) in a flame-dried round-bottomed flask equipped with a magnetic stir bar. The reaction mixture was cooled to 0°C and bromine (0.162 mL, 3.24 mmol) was added. The reaction was then allowed to warm to room temperature and was stirred for 6 hours until completion. Methylene chloride was added, the organics were washed twice with an aqueous saturated solution of $Na_2S_2O_3$, followed by one wash with brine. The resulting organics were dried with $Na_2SO_4$, filtered and concentrated. The crude orange oil was purified by silica column chromatography (5-10% EtOAc/hexanes) to yield light yellow crystals (0.589 g, 76% yield), mp 116-117°C (recrystallized from 4:1 hexanes/ethyl acetate. TLC $R_f$ 0.53 (20% EtOAc/toluene); $^1$H NMR (300 MHz, $CDCl_3$) δ ppm 10.13 (s, 1H), 7.37 (s, 1H), 7.01 (s, 1H), 4.63 (sept, $J$ = 6.00, 1H), 3.86 (s, 3H), 1.40 (d, $J$ = 6.08, 6H); $^{13}$C NMR ($C_6D_6$, 100 MHz) δ 189.7, 153.5, 150.4, 126.8, 119.9, 117.7, 111.3, 71.4, 55.1, 21.5; IR (film): 2975, 2929, 2846, 1675, 1594, 1499, 1393, 1273, 1105, 988, 865 cm$^{-1}$; HRMS (EI): Exact mass calcd for $C_{11}H_{13}BrO_3$ $[M]^+$: 272.0048. Found: 272.0072.

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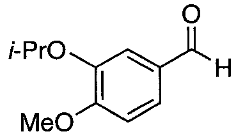
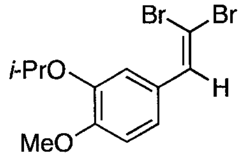
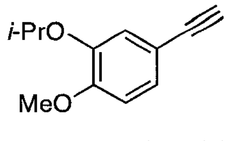
[156] Appukkuttan, P.; Dehaen, W.; Van der Eycken, E. *Chem. Eur. J.* **2007**, *13*, 6452.



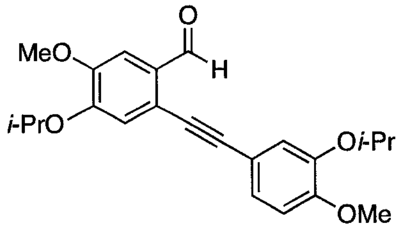
**3-Isopropoxy-4-methoxybenzaldehyde (3.92).** The title compound was prepared according to the procedure by Ridley et al.[111] In a flame-dried round-bottomed flask equipped with a magnetic stir bar isovanillin **3.76** (20.0 g, 132 mmol) was suspended in DMF (100 mL). Isopropyl bromide (19.0 mL, 203 mmol) and $K_2CO_3$ (29.2 g, 211 mmol) were subsequently added and the reaction mixture flushed with argon and stirred at room temperature for 48 hours. The resulting crude mixture was poured into water and extracted into diethyl ether. The organics were washed with 5% aq. NaOH, dried over $MgSO_4$, filtered, and concentrated by rotory evaporator. The resulting crude oil was purified by silica column chromatography (10% EtOAc/hexanes) and a clear, light yellow powder was obtained (26.0 g, quant.). The spectral data corresponded to that reported in literature.[111]



**4-(2,2-Dibromovinyl)-2-isopropoxy-1-methoxybenzene (3.93).** The following procedure followed in accordance to that of Ridley et al.[111] Carbon tetrabromide (2.76 g, 8.31 mmol) was dissolved in methylene chloride (10 mL) in a flame-dried round bottomed flask under argon and cooled to 0°C. 3-Isopropoxy-4-methoxybenzaldehyde **3.92** (0.414 g, 2.13 mmol) was dissolved in methylene chloride (3 mL) in a separate round bottomed flask and was cannulated into the $CBr_4$ solution. Two rinses with methylene chloride made up a total volume of 15 mL in the reaction flask. Triphenylphosphine (2.18 g, 8.31 mmol) and zinc dust (0.543 g, 8.31 mmol) were subsequently and quickly added and the resulting reaction mixture was allowed to stir at 0°C for 5 minutes. The reaction was then allowed to warm to room temperature and stirred under argon for an additional 30 minutes. The crude reaction mixture was poured into pentane, filtered and concentrated. The crude yellow oil was purified by silica column chromatography (5% EtOAc/hexanes) to yield a pale yellow solid (0.742 g, quant.). The spectral data corresponded to that reported in literature.[111]



**4-Ethynyl-2-isopropoxy-1-methoxybenzene (3.94).** The title compound was synthesized based on the following procedure which was modified from that by Ridley et al.[111] 4-(2,2-Dibromovinyl)-2-isopropoxy-1-methoxybenzene **3.93** (8.47 g, 24.9 mmol) was added to a flame-dried round-bottomed flask equipped with a magnetic stir bar, purged with argon for 10 minutes, and dissolved in THF (24 mL). The reaction was cooled to –78°C with a dry ice/acetone bath and stirred for 5 minutes. A solution of *n*-BuLi in hexanes (80.0 mL, 194 mmol) was added dropwise and the reaction was stirred at –78°C for 30 minutes. The reaction was allowed to warm to room temperature and was stirred for an additional 60 minutes. The crude was diluted with a saturated solution of ammonium chloride and the aqueous phase was extracted three times with ether. The combined organics were dried with $MgSO_4$, filtered and concentrated. The crude alkyne was purified by silica column chromatography (10% $Et_2O$/hexanes) and a pale yellow powder was obtained (4.60 g, quant.). The spectral data corresponds to that reported in literature.[111]



**4-Isopropoxy-2-[2-(3-isopropoxy-4-methoxyphenyl)ethynyl]-5-methoxybenzaldehyde (3.95).**

**Procedure A:** The title compound was prepared according to the literature procedure by Itami et al.[157] To a flame-dried round bottomed flask equipped with a magnetic stir bar was added 4-isoproproxy-2-bromo-5-methoxybenzaldehyde **3.99** (0.310 g, 1.14 mmol), $Pd(PPh_3)_2Cl_2$ (0.025 g, 0.036 mmol), CuI (0.0070 g, 0.036 mmol), $Et_3N$ (6 mL) and the 4-ethynyl-2-isopropoxy-1-methoxybenzene **3.94** (0.250 g, 1.31 mmol). The reaction mixture was sparged with argon for 15 minutes and was stirred at room temperature in the dark under argon for 18 hours. To the reaction mixture was added an aqueous saturated solution of ammonium chloride and diethyl ether and the resulting phases were separated. The aqueous layer was extracted with diethyl ether. The combined organics were washed with brine, dried with $MgSO_4$, filtered and concentrated. The resulting brown crude oil was purified by silica column chromatography (10-20% EtOAc/hexanes) and resulted in a pale yellow oil (0.286 g, 66%).

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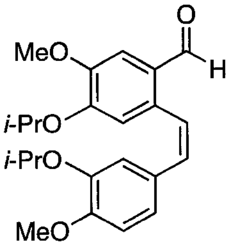
[157] Itami, K.; Ushiogi, Y.; Nokami, T.; Ohashi, Y.; Yoshida, J. *Org. Lett.* **2004**, *6*, 3595.

**Procedure B:** The title compound was prepared according to the procedure by Simard-Mercier.[158] To a flame-dried round bottomed flask purged with argon was added $Pd(PPh_3)_4$ (0.097 g, 0.084 mmol), CuI (0.024 g, 0.13 mmol), and triethylamine (11 mL). 2-Iodo-4-isopropoxy-5-methoxybenzaldehyde **3.91** (0.270 g, 0.843 mmol) was added and the solution sparged with argon for 10 minutes. 4-ethynyl-2-isopropoxy-1-methoxybenzene **3.94** (0.321 g, 1.69 mmol) was subsequently added and the reaction was stirred under an argon atmosphere at room temperature for 48 hours. The solution was diluted with diethyl ether and washed successively with a 0.1N HCl solution, saturated sodium bicarbonate solution, and brine. The organics were dried with $MgSO_4$, filtered and concentrated to yield a dark brown oil. The crude oil was purified by silica column chromatography (10% EtOAc/hexanes) to yield a pale yellow oil (229 mg, 71%). TLC $R_f$ 0.35 (20% EtOAc/hexanes); $^1$H NMR (400 MHz, $C_6D_6$) δ ppm 11.0 (s, 1H), 7.55 (s, 1H), 7.24 (d, $J$ = 1.91 Hz, 1H), 7.21 (dd, $J$ = 8.24, 1.96 Hz, 1H), 7.05 (s, 1H), 6.45 (d, $J$ = 8.29 Hz, 1H), 4.20 (sept, $J$ = 6.06 Hz, 1H), 4.07 (sept, $J$ = 5.73 Hz, 1H), 3.28 (s, 3H), 3.21 (s, 3H), 1.12 (d, $J$ = 6.05 Hz, 6H), 1.01 (d, $J$ = 6.04 Hz, 6H); $^{13}$C NMR ($C_6D_6$, 100 MHz) δ 189.5, 152.7, 152.3, 151.3, 148.0, 130.6, 125.6, 121.7, 119.1, 116.9, 115.3, 112.5, 109.3, 95.6, 84.5, 71.3, 71.0, 55.3, 55.1, 22.1, 22.1, 21.7, 21.7; IR (film): 2978, 2941, 2842, 1770, 1682, 1593, 1514, 1270, 1110, 775, 733 cm$^{-1}$; HRMS (EI): Exact mass calcd for $C_{23}H_{26}O_5$ $[M]^+$: 382.1780. Found: 382.1768.



**(Z)-2-(3-Isopropoxy-4-methoxystyryl)-4-isopropoxy-5-methoxybenzaldehyde (3.100). Table 3.X, Entry 3.** The title compound was prepared by the modification of a procedure by the Fukuyama group.[159] In a flame dried round bottomed flask equipped with a magnetic stir bar was added 4-isopropoxy-2-[2-(3-isopropoxy-4-methoxyphenyl)ethynyl]-5-methoxybenzaldehyde **3.95** (0.050 g, 0.13 mmol) and Lindlar's catalyst (5% $Pd/CaCO_3/Pb$, 0.014 g, 0.0065 mmol). The flask was then purged with argon and a 3:2 mixture of ethanol:ethyl acetate (7 mL) was added. Using a 3-way valve attached to a high vacuum source and an argon source, the flask was evacuated and subsequently purged with hydrogen three times. The reaction was vigorously stirred under an atmosphere of hydrogen for 4 hours. An additional 5 mL of ethyl acetate was added to the mixture

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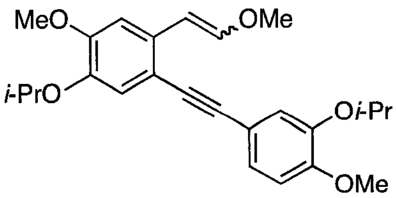
[158] Simard-Mercier, J. MSc. thesis, Department of Chemistry, University of Ottawa: Ottawa, 2008.
[159] Miyazaki, T.; Yokoshima, S.; Simuzu, S.; Osada, H.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2007**, *9*, 4737.

and was then filtered over celite with rinsing three times with ethyl acetate. The crude reaction mixture was concentrated under reduced pressure to yield a pale yellow oil which was then purified by silica gel impregnated by silver nitrate. The title compound was obtained as a pale yellow oil (49 mg, 98%). TLC $R_f$ 0.36 (30% EtOAc/hexanes). The unpurified oil was used in the next step due to the co-elution of the product with the starting material and the over-reduction side products.



**1-Isopropoxy-5-[2-(3-isopropoxy-4-methoxyphenyl)ethynyl]-2-methoxy-4-[(*E/Z*)-2-methoxyvinyl]benzene (3.104)**. The title compound was prepared according to the procedure by Tran et al.[160] In a flame dried round bottomed flask equipped with a magnetic stir bar purged with argon was added (methoxymethyl)triphenylphosphonium chloride (0.411 g, 2.00 mmol) and THF (5 mL). The suspension was cooled to 0°C and a 1 M solution of *t*-BuOK (2.00 mL, 2.00 mmol) was added dropwise while under an argon atmosphere. The solution turned deep red in colour and was stirred at 0°C for 1 hour. A solution of 4-isopropoxy-2-[2-(3-isopropoxy-4-methoxyphenyl)ethynyl]-5-methoxybenzaldehyde **3.95** (0.153 g, 0.400 mmol) in THF (1 mL) was cannulated into the reaction flask under argon and the reaction was allowed to stir at room temperature for 9 hours. The solution was cooled in an ice bath, quenched dropwise with water, acidified with an aqueous solution of HCl (2 N), and extracted twice with ethyl acetate. The organics were combined, washed with water, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude yellow oil was purified by silica gel column chromatography (30% EtOAc/hexanes) and resulted in a pale yellow oil (19 mg, 12%). TLC $R_f$ 0.55 (30% EtOAc/hexanes). Complete characterization was not possible due to decomposition of the product balance that was not used immediately in the trial in the subsequent step. Due to the unsuccessfulness of the next step and subsequent revision of this synthetic sequence, this product was not re-synthesized for the purpose of characterization.

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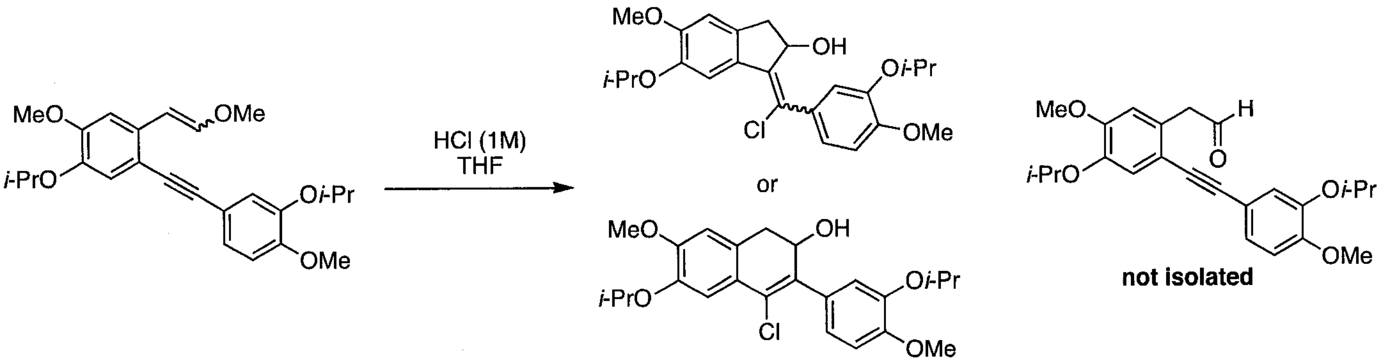
[160] Tran, V. H.; Katharaj, R.; Roufogalis, B. D.; Duke, C. C. *Eur. J. Org. Chem.* **2006**, 2970.



**(*E*/*Z*)-1-Chloro(3-isopropoxy-4-methoxyphenyl)methylene)2,3-dihydro-6-isopropoxy-5-methoxy-1*H*-inden-2-ol or 4-chloro-1,2-dihydro-6-isopropoxy-3-(3-isopropoxy-4-methoxyphenyl)-7-methoxynaphthalen-2-ol (3.106a or 3.106b, respectively).** The title compound was found to be the only isolable product in the attempted synthesis of 2-(4-isopropoxy-2-(2-(3-isopropoxy-4-methoxyphenyl)ethynyl)-5-methoxyphenyl)acetaldehyde **3.105** by the procedure below. In a round bottomed flask equipped with a magnetic stir bar and a reflux condenser was charged 1-isopropoxy-5-[2-(3-isopropoxy-4-methoxyphenyl)ethynyl]-2-methoxy-4-[(*E*/*Z*)-2-methoxyvinyl] benzene **3.104** (0.019 g, 0.046 mmol), THF (1 mL) and a 1 M aqueous solution of HCl (0.25 mL). The mixture was stirred at room temperature for 1 hour to monitor for any reactivity. With no sign of reaction, the mixture was refluxed for a total of 5.5 hours with monitoring by TLC. Upon the disappearance of most of the starting material, the reaction was allowed to cool to room temperature, quenched with an aqueous solution of sodium bicarbonate, diluted with diethyl ether, and washed with water and brine. The organics were dried with $Na_2SO_4$, filtered and concentrated. The crude oil was purified by silica column chromatography (30% EtOAc/hexanes) and yielded an orange oil (7 mg, 35%). TLC $R_f$ 0.24 (30% EtOAc/hexanes); $^1H$ NMR (400 MHz, $C_6D_6$) δ ppm 7.15 (d, *J*= 2.01, 1H), 7.09 (dd, *J*= 2.05, 8.24 Hz, 1H), 6.57 (d, *J*= 8.26 Hz, 1H), 6.45 (s, 1H), 6.43 (s, 1H), 5.47 (ap d, *J*= 7.13 Hz, 1H), 4.18 (sept, *J*= 5.95 Hz, 1H), 4.08 (sept, *J*= 6.23 Hz, 1H), 3.38 (s, 3H), 3.36 (s, 3H), 3.21 (dd, *J*= 7.11, 17.22, 1H), 3.08 (dd, *J*= 1.57, 16.92, 1H), 2.77 (d, *J*= 2.88, 1H), 1.17-1.14 (m, 12H); $^{13}C$ NMR ($C_6D_6$, 100 MHz) δ 193.9, 152.2, 146.9, 138.4, 116.4, 112.6, 110.9, 108.4, 75.0, 70.8, 70.6, 55.3, 55.1, 39.4, 22.0, 21.9, 21.8, 21.8 (signal-to-noise ratio insufficient to unambiguously assign 4 remaining quaternary carbons)[161]; HRMS (EI): Exact mass calcd for $C_{24}H_{29}O_5Cl$ $[M]^+$: 434.1674. Found: 434.1645. Although full characterization was not possible to perform due to the small amount of sample remaining, either of the proposed structures are supported by the data acquired.

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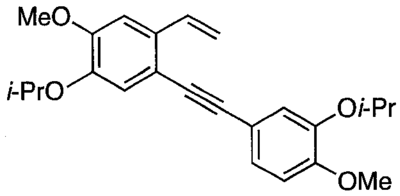
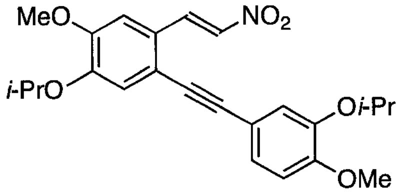
[161] Due to small sample remaining after re-purification of initial 7 mg isolation. Sample remaining for NMR <2 mg.



**2-Isopropoxy-4-(2-(5-isopropoxy-4-methoxy-2-vinylphenyl)ethynyl)-1-methoxybenzene (3.017).** In a flame dried around bottomed flask, methyltriphenylphosphonium iodide (0.106 g, 0.261 mmol) was diluted with THF (1.3 mL) and purged with argon. The suspension was cooled to 0°C and a 1 M solution of *t*-BuOK was added dropwise. The mixture turned colour from white to bright yellow and was stirred at room temperature for 1 hour. The reaction was cooled back down to 0°C and 4-isopropoxy-2-[2-(3-isopropoxy-4-methoxyphenyl)ethynyl]-5-methoxybenzaldehyde **3.95** (0.050 g, 0.13 mmol) was added as a solution in THF (0.26 mL) by cannula. After stirring for 20 minutes, the reaction was quenched dropwise with water while still in the ice bath, followed by an aqueous solution of HCl (2 N) and was extracted twice with ethyl acetate. The combined organics were dried with $MgSO_4$, filtered and concentrated. The crude orange oil was purified by silica column chromatography (15% EtOAc/hexanes) and yielded a pale yellow oil (30 mg, 60%). TLC $R_f$ 0.34 (15% EtOAc/hexanes); $^1$H NMR (400 MHz, $C_6D_6$) δ ppm 7.76 (dd, *J*=10.1, 16.6, 1H), 7.30-7.27 (m, 2H), 7.23 (s, 1H), 7.03 (s, 1H), 6.46 (d, *J* = 8.80 Hz, 1H), 5.71 (dd, *J*= 1.01, 17.58, 1H), 5.28 (dd, *J*=1.01, 11.0, 1H), 4.22-4.13 (m, 2H), 3.32 (s, 3H), 3.27 (s, 3H), 1.11 (d, *J* = 6.05 Hz, 6H), 1.10 (d, *J* = 6.04 Hz, 6H); $^{13}$C NMR ($C_6D_6$, 100 MHz) δ 151.8, 151.7, 148.1, 148.0, 135.6, 133.0, 125.4, 119.2, 118.8, 116.4, 115.6, 113.2, 112.5, 108.4, 93.7, 87.2, 71.2, 71.0, 55.3, 52.2, 22.1, 22.1, 22.0, 22.0; IR (film): 2979, 2918, 2846, 1592, 1512, 1265, 1242, 1136, 1109, 1021, 932, 854 cm$^{-1}$; HRMS (EI): Exact mass calcd for $C_{24}H_{28}O_4$ $[M]^+$: 380.1988. Found: 380.1974.



**1-Isopropoxy-5-[2-(3-isopropoxy-4-methoxyphenyl)ethynyl]-2-methoxy-4-[(*E*)-2-nitrovinyl]benzene (3.111).** The title compound was prepared according to the procedure by Côté et al.[162] A round bottomed flask equipped with a magnetic stir bar and a condenser was flame-dried and placed under an argon atmosphere.

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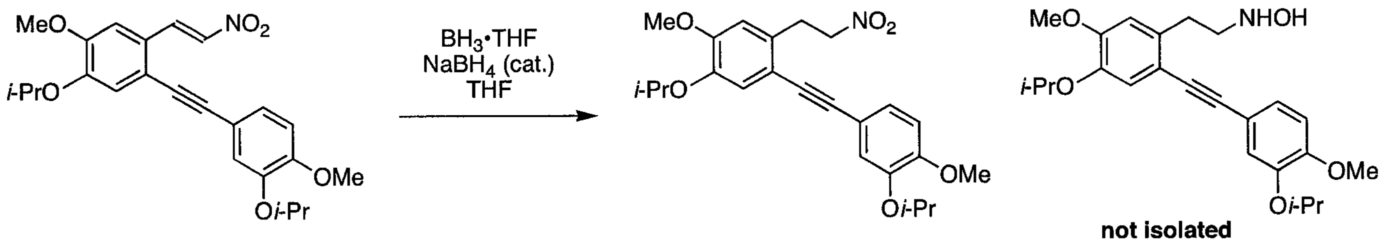
[162] Côté, A.; Lindsay, V. N. G.; Charette, A. B. *Org. Lett.* **2007**, *9*, 85.

Ammonium acetate (0.571 g, 7.40 mmol) was dissolved in acetic acid (4.3 mL), and nitromethane (1.15 mL, 21.3 mmol) and 4-isopropoxy-2-[2-(3-isopropoxy-4-methoxyphenyl)ethynyl]-5-methoxybenzaldehyde **3.95** (1.18 g, 3.09 mmol) were subsequently added. The reaction was stirred at room temperature for 30 minutes and was then heated to 100°C for 6 hours. The reaction was allowed to cool to room temperature, then was poured into water and neutralized to pH 7 with an aqueous solution of NaOH. The resulting aqueous phase was extracted 4 times with EtOAc. The combined organics were dried with $MgSO_4$, filtered and concentrated. A crude brown solid resulted which was purified by silica gel chromatography (100% $CH_2Cl_2$). The title compound was isolated as a bright yellow solid (1.0 g, 76%), mp 144-145°C (recrystallized from 4:1 hexanes:ethyl acetate). TLC $R_f$ 0.34 (20% EtOAc/hexanes); $^1H$ NMR (400 MHz, $C_6D_6$) $\delta$ ppm 8.80 (d, $J$ = 13.7 Hz, 1H), 7.52 (d, $J$ = 13.7 Hz, 1H), 7.39 (d, $J$ = 1.89 Hz, 1H), 7.37 (dd, $J$ = 8.15, 1.96 Hz, 1H), 7.03 (s, 1H), 6.42 (d, $J$ = 8.20 Hz, 1H), 6.37 (s, 1H), 4.36 (sept, $J$ = 6.08 Hz, 1H), 4.04 (sept, $J$ = 6.24 Hz, 1H), 3.27 (s, 3H), 3.19 (s, 3H), 1.20 (d, $J$ = 6.04 Hz, 6H), 1.02 (d, $J$ = 6.04 Hz, 6H); $^{13}C$ NMR ($C_6D_6$, 100 MHz) $\delta$ 152.1, 151.0, 150.6, 148.0, 136.8, 136.4, 125.1, 124.2, 119.8, 118.3, 116.7, 114.8, 112.4, 110.2, 96.9, 85.9, 71.0, 70.8, 55.1, 55.1, 21.9, 21.9, 21.6, 21.6; IR (film): 2975, 2930, 2839, 1596, 1512, 1329, 1265, 1246, 1136, 1105, 946 $cm^{-1}$; HRMS (EI): Exact mass calcd for $C_{24}H_{27}NO_6$ $[M]^+$: 425.1838. Found: 425.1817.



**1-Isopropoxy-5-(2-(3-isopropoxy-4-methoxyphenyl)ethynyl)-2-methoxy-4-(2-nitroethyl)benzene 3.117.** The title compound was isolated as the only product in the attempted synthesis of *N*-hydroxy-2-(4-isopropoxy-2(2-(3-isopropoxy-4-methoxyphenyl)ethynyl)-5-methoxyphenyl)ethanamine **3.112** by the following procedure.[163] A flame dried round bottomed flask equipped with a magnetic stir bar and condenser was charged with 1-isopropoxy-5-[2-(3-isopropoxy-4-methoxyphenyl)ethynyl]-2-methoxy-4-[(*E*)-2-nitrovinyl]benzene **3.111** (0.050 g, 0.12 mmol) and THF (2.5 mL) while under an argon atmosphere. The flask was cooled to 0°C in an ice bath and a solution of borane (1 M in THF, 0.118 mL, 0.118 mmol) was added with a gas-tight syringe. The ice bath was removed and a catalytic amount of $NaBH_4$ was added quickly by spatula. The reaction was stirred at room temperature overnight. Ice water was added to the reaction, which was then

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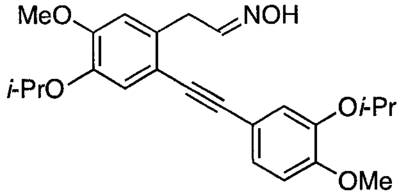
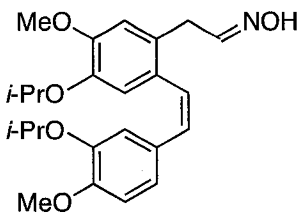
[163] Kalbalka, G. W.; Guindi, L. H. M.; Varma, R. S. *Tetrahedron* **1990,** *46,* 7443.

acidified with a 10% aqueous solution of HCl. The mixture was stirred and heated to 60°C for 2 hours to complete the hydrolysis. Once allowed to cool to room temperature, the acidic layer was washed with diethyl ether three times, and any of the formed hydroxylamine **3.112** was to be liberated upon washing with an aqueous solution of NaOH (1 M). Solid NaCl was added and the product was extracted into diethyl ether. The organic layers were dried with $Na_2SO_4$, filtered and concentrated. The resulting dark yellow oil was purified by silica column chromatography (20% EtOAc/hexanes) and resulted in another yellow oil (approx. 10 mg, 20%). TLC $R_f$ 0.29 (20% EtOAc/hexanes); $^1$H NMR (400 MHz, $CDCl_3$) δ ppm 7.11 (dd, *J*= 1.94, 8.28 Hz, 1H), 7.07 (d, *J*= 1.89 Hz, 1H), 7.04 (s, 1H), 6.86 (d, *J*= 8.35 Hz, 1H), 6.74 (s, 1H), 4.71 (dd, *J*= 7.17, 8.25 Hz, 2H), 4.56 (sept, *J*= 6.11 Hz, 1H), 4.55 (sept, *J*= 6.11, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.49 (dd, *J*= 7.82, 7.58, 2H), 1.40 (d, *J*= 6.09 Hz, 6H), 1.38 (d, *J*= 6.09 Hz, 6H); $^{13}$C NMR ($C_6D_6$, 100 MHz) δ 152.0, 151.6, 148.2, 147.3, 131.0, 125.2, 119.2, 119.0, 115.8, 115.7, 113.7, 112.6, 94.0, 86.2, 75.3, 71.3, 71.2, 55.5, 55.3, 33.0, 22.13, 22.13, 22.0, 22.0; IR (film): 2975, 2930, 2842, 1551, 1514, 1242, 1135, 1109, 1021 cm$^{-1}$; HRMS (EI): Exact mass calcd for $C_{24}H_{29}NO_6$ $[M]^+$: 427.1995. Found: 427.1975.

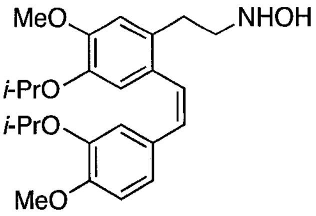


**1-Isopropoxy-5-[2-(3-isopropoxy-4-methoxyphenyl)ethynyl]-2-methoxy-4-[(*E/Z*)-acetaldehyde oxime]benzene (3.118) (Table 3.6, Entry 4).** The following procedure was based on that of Kabalka et al.[163] 1-Isopropoxy-5-[2-(3-isopropoxy-4-methoxyphenyl)ethynyl]-2-methoxy-4-[(*E*)-2-nitrovinyl]benzene **3.111** (0.127 g, 0.298 mmol) was dissolved in ethyl acetate (1.5 mL), and tin(II)chloride dihydrate (0.135 g, 0.597 mmol) was added. The reaction was stirred at room temperature open to air and was complete after 1.5 hours. The reaction was poured into ice water and the resulting solution was made slightly basic (pH 7-8) upon the addition of 5% aq. $NaHCO_3$. Diethyl ether was added, and the layers separated. The aqueous layer was extracted with diethyl ether three times and the combined organics were washed with brine, dried with $MgSO_4$, filtered, and concentrated to yield a dark orange oil. The crude was purified by silica column chromatography (40% EtOAc/hexanes) to yield the desired compound as a yellow oil (0.072 g, 59%). TLC $R_f$ 0.40 (50% EtOAc/hexanes); $^1$H NMR (400 MHz, $CDCl_3$, isolated as a 52:48 mixture of *E* and *Z* oximes); Oxime 1: δ ppm 8.04 (br, 1 H), 7.62 (t, *J*= 6.20, 6.20 Hz, 1H), 7.09 (dd, *J*= 1.93, 4.81 Hz, 1H), 7.05 (s, 1 H), 7.04 (d, *J*= 2.13 Hz, 1H), 6.84 (d, *J*= 4.97 Hz, 1H), 6.72 (s, 1H), 4.48-4.61 (m, 1H), 3.90 (d, *J*= 5.12 Hz, 2H), 3.87 (s, 3H), 3.86

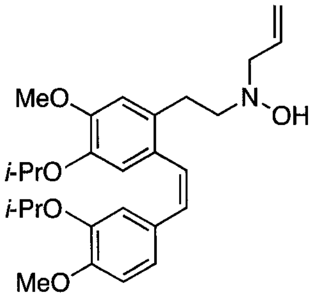
(s, 3H), 1.39 (d, $J$= 5.23 Hz, 6H), 1.37 (d, $J$= 5.21 Hz, 6H); Oxime 2: δ ppm 7.54 (br, 1H), 7.11 (dd, $J$= 1.94, 4.81 Hz, 1H), 7.04 (d, $J$= 2.04 Hz, 1H), 7.04 (s, 1H), 6.93 (t, $J$= 5.10 Hz, 1H), 6.82 (d, $J$= 4.96 Hz, 1H), 6.76 (s, 1H), 4.48-4.61 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.72 (d, $J$= 6.20 Hz, 2H), 1.38 (d, $J$= 6.09 Hz, 12H); $^{13}$C NMR ($CDCl_3$, 100 MHz, isolated as a mixture of *E* and *Z* oximes) δ 151.1, 150.9, 150.9, 150.8, 150.8, 147.0, 146.0, 145.9, 132.1, 131.5, 125.0, 125.0, 118.9, 118.8, 118.5, 118.5, 115.5, 115.5, 115.2, 115.1, 112.9, 112.7, 111.8, 92.6, 92.4, 86.1, 86.0, 71.7, 71.6, 71.6, 56.0, 56.0, 34.4, 30.5, 22.1, 22.1; IR (film): 3473, 2976, 2930, 2846, 1514, 1242, 1135, 1112, 1025, 976, 866, 813 cm$^{-1}$; HRMS (EI): Exact mass calcd for $C_{24}H_{29}NO_5$ $[M]^+$: 411.2046. Found: 411.2022.



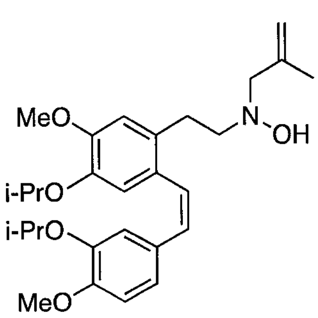
**(*Z*)-2-[2-(3-Isopropoxy-4-methoxystyryl)-4-isopropoxy-5-methoxyphenyl](*E*/*Z*)acetaldehyde oxime ((*Z*)-3.119):** The title compound was prepared by the modification of a procedure by the Fukuyama group.[159] In a flame dried round bottomed flask equipped with a magnetic stir bar was added 1-isopropoxy-5-[2-(3-isopropoxy-4-methoxyphenyl)ethynyl]-2-methoxy-4-[(*E*/*Z*)-acetaldehyde oxime]benzene **3.118** (0.062 g, 0.15 mmol) and Lindlar's catalyst (5% $Pd/CaCO_3/Pb$, 0.007 g, 0.004 mmol). The flask was then purged with argon and a 3:2 mixture of ethanol:ethyl acetate (9 mL) was added. Using a 3-way valve attached to a high vacuum source and an argon source, the flask was evacuated and subsequently purged with hydrogen three times. The reaction was vigorously stirred under an atmosphere of hydrogen for 4 hours with very diligent monitoring by $^1$H NMR at a minimum of every hour due to co-elution of the desired product by TLC with both the starting material and the over-reduction alkane product. An additional 10 mL of ethyl acetate was added to the mixture and was then filtered over celite with rinsing three times with ethyl acetate. The crude reaction mixture was concentrated under reduced pressure to yield a pale yellow oil. The title compound was obtained as a colourless oil (62 mg, 97%). TLC $R_f$ 0.29 (40% EtOAc/hexanes). The unpurified oil was used in the next step due to the co-elution of the product with the starting material and the over-reduction side product. The ratio of these compounds was taken into consideration in subsequent steps until purification could be done efficiently.



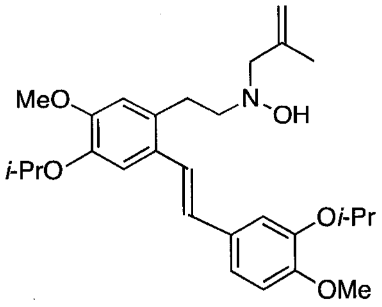
**(Z)-2-[2-(3-Isopropoxy-4-methoxystyryl)-4-isopropoxy-5-methoxyphenyl]-*N*-hydroxyethanamine ((*Z*)-3.110):** Based on House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863. In an oven-dried round bottomed flask equipped with a magnetic stir bar (*Z*)-2-[2-(3-isopropoxy-4-methoxystyryl)-4-isopropoxy-5-methoxyphenyl](*E*/*Z*)acetaldehyde oxime **(*Z*)-3.119** (0.186 g, 0.450 mmol) was dissolved in MeOH (0.450 mL) and sodium cyanoborohydride (0.034 g, 0.54 mmol) and a small amount of methyl orange indicator were added. The orange solution was purged with argon and a 1:1 solution of MeOH/conc. HCl was added dropwise so that the solution remained a consistent bright pink colour for 30 minutes. A 2.5% solution of aq. NaOH was added to bring the solution to pH 8. The mixture was extracted 3 times with $CH_2Cl_2$, the combined organics were dried with $Na_2SO_4$, filtered and concentrated. The unpurified oil was used directly in the following step without further purification due to instability.



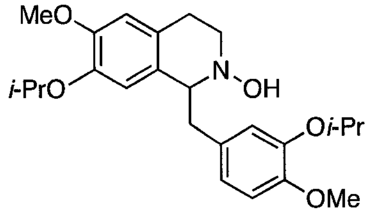
**(Z)-*N*-(2-(3-Isopropoxy-4-methoxystyryl)-4-isopropoxy-5-methoxyphenethyl)-*N*-hydroxyprop-2-en-1-amine ((*Z*)-3.129).** In a flame-dried round bottomed flask equipped with a magnetic stir bar was added (*Z*)-2-[2-(3-isopropoxy-4-methoxystyryl)-4-isopropoxy-5-methoxyphenyl]-*N*-hydroxyethanamine **(*Z*)-3.110** (0.042 g, 0.10 mmol) which was dissolved in acetonitrile (0.5 mL). Potassium carbonate (0.042, 0.30 mmol) and distilled allyl bromide (0.026 mL, 0.30 mmol) were subsequently added and the solution was purged with argon. The reaction was stirred overnight under argon. The reaction was diluted with ethyl acetate, filtered (rinsing with ethyl acetate) and concentrated. The resulting crude oil was purified by silica gel chromatography (50% EtOAc/hexanes) and yielded a colourless oil (0.023 g, 50%). TLC *R*f 0.51 (50% EtOAc/$CH_2Cl_2$). The unpurified oil was used directly in the next step due to instability.



**(Z)-*N*-(2-(3-Isopropoxy-4-methoxystyryl)-4-isopropoxy-5-methoxyphenethyl)-*N*-hydroxy-2-methylprop-2-en-1-amine ((*Z*)-3.130).** In a flame-dried round bottomed flask equipped with a magnetic stir bar was added (*Z*)-2-[2-(3-isopropoxy-4-methoxystyryl)-4-isopropoxy-5-methoxyphenyl]-*N*-hydroxyethanamine **(*Z*)-3.110** (0.129 g, 0.310 mmol) which was dissolved in a 5:1 mixture of THF:DMF (1.25 mL). DBU (0.049 mL, 0.33 mmol) and 3-chloro-2-methylpropane (0.091 mL, 0.93 mmol) were subsequently added and the solution was purged with argon. The reaction was heated and stirred under reflux for 1 hour. The reaction was allowed to cool to room temperature and diluted with ethyl acetate. The mixture was washed 5 times with a 50:50 mixture of water and brine. The organics were dried with $Na_2SO_4$, filtered and concentrated. The resulting crude oil was purified by silica gel chromatography (20% EtOAc/hexanes) and yielded a pale yellow oil (0.050 g, 34%). TLC $R_f$ 0.85 (50% EtOAc/$CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$ δ ppm 6.75 (s, 1H), 6.73 (dd, *J*= 1.76, 8.23 Hz, 1H), 6.69 (d, *J*= 6.54 Hz, 1H), 6.68 (s, 1H), 6.65 (d, *J*= 1.52 Hz, 1H), 6.57 (d, J= 11.89 Hz, 1H), 6.49 (d, *J*= 12.02 Hz, 1H), 4.83 (s, 1H), 4.80 (s, 1H), 4.25-4.21 (m, 1H), 4.13-4.09 (m, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 3.26 (s, 2H), 2.91-2.79 (m, 4H), 1.72 (s, 3H), 1.20-1.15 (m, 12H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ ppm 149.3, 149.1, 146.5, 145.5, 141.2, 130.5, 130.1, 129.7, 129.4, 127.1, 122.2, 116.5, 115.4, 114.3, 113.3, 111.3, 71.0, 70.8, 67.2, 60.0, 56.0, 55.8, 31.1, 21.8, 21.8, 21.8, 21.8, 21.1; IR (film): 3493, 3245, 2975, 2934, 2836, 1602, 1511, 1267, 1091, 1029, 731 cm$^{-1}$; HRMS (EI): Exact mass calcd for $C_{28}H_{39}NO_5$ $[M]^+$: 469.2828. Found: 469.28322.



**(*E*)-*N*-(2-(3-Isopropoxy-4-methoxystyryl)-4-isopropoxy-5-methoxyphenethyl)-*N*-hydroxy-2-methylprop-2-en-1-amine ((*E*)-3.134).** Isolated as a side product of the cyclization reaction of (*Z*)-*N*-(2-(3-isopropoxy-4 methoxystyryl)-4-isopropoxy-5-methoxyphenethyl)-*N*-hydroxy-2-methylprop-2-en-1-amine **(*Z*)-3.130**.[164] TLC $R_f$ =0.05 (5% EtOAc/$CH_2Cl_2$); $^1$H NMR (500 MHz, $C_6D_6$) δ ppm 7.64 (d, *J*= 16.05 Hz, 1H), 7.48 (s, 1H), 7.37 (d, *J*= 1.93 Hz, 1H), 7.15 (1H), 7.11 (d, *J*= 16.01 Hz, 1H), 6.65 (s, 1H), 6.62 (d, *J*= 8.29 Hz, 1H), 4.89 (s, 1H), 4.81 (s, 1H), 4.55-4.47 (m, 1H), 4.46-4.40 (m, 1H), 3.42 (s, 3H), 3.39 (s, 3H), 3.38-3.12 (m, 2H), 3.13 (s, 2H), 2.92-2.89 (m, 2H), 1.70 (s, 3H), 1.28 (d, *J*= 6.04 Hz, 6H), 1.25 (d, *J*= 6.05 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ ppm 150.2, 131.0, 128.7, 128.0, 124.0, 120.0, 113.9, 113.8, 113.6, 112.1, 100.0, 71.5, 70.9, 67.3, 60.1, 56.0, 56.0, 31.1, 22.2, 22.1, 21.9, 21.1; HRMS (EI): Exact mass calcd for $C_{28}H_{39}NO_5$ $[M]^+$: 469.2828. Found: 469.28565.



**1-(3-Isopropoxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-7-isopropoxy-6-methoxyisoquinoline-*N*-hydroxide (3.120) (Table 3.7, Entry 1).** In an oven-dried sealed tube equipped with a magnetic stir bar was dissolved (Z)-2-[2-(3-isopropoxy-4-methoxystyryl)-4-isopropoxy-5-methoxyphenyl]-*N*-hydroxyethanamine **(*Z*)-3.110** (64 mg, 0.15 mmol) in *n*-PrOH (18 mL). Sodium cyanoborohydride (11 mg, 0.18 mmol) was added and the reaction mixture was sparged with argon for 15 minutes through a septum. The septum was quickly replaced by a Teflon screw cap and the reaction vessel was sealed. The reaction was heated at 120°C for 18 hours. The reaction was then cooled, transferred to a separate round bottomed flask, rinsed three times with additional *n*-PrOH, and the solvent was evaporated. The crude residue was purified by silica column chromatography (50-70% EtOAc/hexanes) and resulted in a clear, colourless oil (24 mg, 38%).[165] TLC $R_f$ 0.37 (70% EtOAc/hexanes); $^1$H NMR (400 MHz, $C_6D_6$) δ ppm 6.94 (d, *J*= 1.95 Hz, 1 H), 6.81 (dd, *J*= 1.88, 8.13 Hz, 1 H), 6.63 (s, 1 H), 6.61 (d, *J*= 8.21 Hz, 1 H), 6.38 (s, 1 H), 4.31-4.37 (m, 2H), 4.20-4.27 (m, 1H), 3.39 (s, 3H), 3.38 (s, 3H), 3.28-3.34 (m, 2H), 3.06-3.15 (m, 2H), 2.78 (ddd, *J*= 5.63, 5.63, 12.16 Hz, 1 H), 2.67 (ddd, *J*= 6.13, 6.13, 16.41 Hz, 1 H), 1.20 (d, *J*= 6.00 Hz, 3 H), 1.20 (d, *J*= 6.04 Hz, 3 H), 1.19 (d, *J*= 6.02 Hz, 3 H), 1.17 (d, *J*= 6.09 Hz, 3 H); $^{13}$C NMR ($C_6D_6$, 100 MHz) δ 150.1, 150.0, 148.0, 146.3, 132.8, 129.5, 122.81, 118.9, 116.4,

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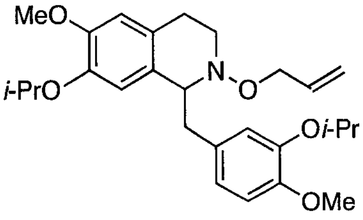
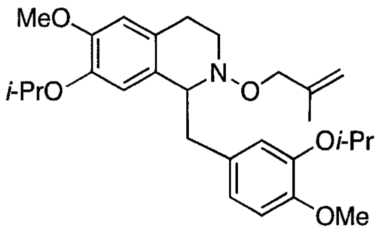
[164] Isolated and fully characterized by Ms. Isabelle Dion.

[165] Yield % calculation based on purity of starting material.

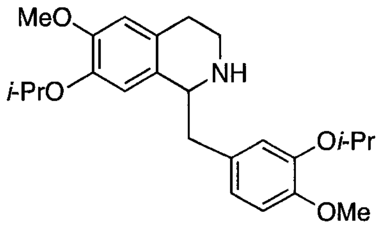
113.0, 112.6, 71.5, 71.3, 68.7, 55.7, 55.5, 51.9, 26.6, 22.4, 22.4, 22.3, 22.1; IR (film): 2979, 2934, 2842, 1607, 1512, 1445, 1261, 1235, 1109, 1033, 934, 858, 813, 771 cm$^{-1}$; HRMS (EI): Exact mass calcd for $C_{13}H_{18}NO_3$ [M – 3-isopropoxy-4-methoxybenzyl]$^+$: 236.1287. Found: 236.1268.



**1-(3-Isopropoxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-7-isopropoxy-6-methoxyisoquinoline-*N*-(2-allyloxide) (3.131) (Table 3.7, Entry 3).** In an oven-dried sealed tube equipped with a magnetic stir bar was dissolved (*Z*)-N-(2-(3-isopropoxy-4-methoxystyryl)-4-isopropoxy-5-methoxyphenethyl)-N-hydroxyprop-2-en-1-amine **(*Z*)-3.129** (0.014 g, 0.031 mmol) in benzene (3.0 mL). Distilled water (0.005 mL, 0.3 mmol) was added and the reaction mixture was sparged with argon for 15 minutes through a septum. The septum was quickly replaced by a Teflon screw cap and the reaction vessel was sealed. The reaction was heated at 120°C for 16 hours. The reaction was then cooled, transferred to a separate round bottomed flask, rinsed three times with additional benzene, and the solvent was evaporated. The crude residue was purified by silica column chromatography (10-40% EtOAc/hexanes) and resulted in a clear, colourless oil (0.0047 mg, 61%).[165] TLC $R_f$ 0.80 (30% EtOAc/hexanes); $^1$H NMR (500 MHz, $C_6D_6$) δ ppm 6.97 (d, *J*= 1.92 Hz, 1H), 6.83 (dd, *J*= 1.98, 8.15 Hz, 1H), 6.61 (d, *J*= 8.21 Hz, 1H), 6.59 (s, 1H), 6.40 (s, 1H), 5.97 (tdd, *J*= 5.91, 10.5, 16.3, 1H), 5.20 (dd, *J*= 1.72, 17.3 Hz, 1H), 5.03 (dd, *J*= 1.83, 10.4 Hz, 1H), 4.50 (t, *J*= 6.11, Hz, 1H), 4.39-4.32 (m, 1H), 4.31-4.28 (m, 2H), 4.26-4.18 (m, 1H), 3.39 (s, 3H), 3.38 (s, 3H), 3.32-3.27 (m, 2H), 3.20 (ddd, *J*= 5.32, 5.32, 12.0, 1H), 3.06 (dd, *J*= 6.59, 14.08, 1H), 2.95-2.89 (m, 1H), 2.54 (ddd, *J*= 5.11, 5.11, 16.0 Hz, 1H), 1.21 (d, *J*= 6.05 Hz, 1H), 1.20 (d, *J*= 6.33 Hz, 1H), 1.19 (d, *J*= 6.47 Hz, 1H), 1.17 (d, *J*= 6.06 Hz, 1H); $^{13}$C NMR ($C_6D_6$, 75 MHz) δ 150.1, 149.9, 147.9, 146.3, 135.4, 133.0, 129.6, 126.9, 122.8, 118.9, 117.0, 116.6, 112.8, 112.6, 73.6, 71.4, 71.2, 66.8, 55.6, 55.5, 48.5, 41.0, 26.2, 22.4, 22.4, 22.3, 22.3; IR (film): 2975, 2926, 2830, 1614, 1566, 1512, 1265, 1219, 1139, 1105, 1033, 991, 919, 843 cm$^{-1}$; MS (Electrospray): Exact mass calcd for $C_{27}H_{37}NO_5$ [M+1H]: 455.2672. Found: 455.6.

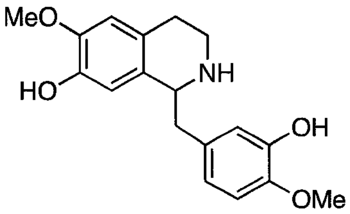


**1-(3-Isopropoxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-7-isopropoxy-6-methoxyisoquinoline-*N*-(2-methylallyloxide) (3.132) (Table 3.7, Entry 4).** In an oven-dried sealed tube equipped with a magnetic stir bar was dissolved (*Z*)-*N*-(2-(3-isopropoxy-4-methoxystyryl)-4-isopropoxy-5-methoxyphenethyl)-*N*-hydroxy-2-methylprop-2-en-1-amine **(*Z*)-3.130** (0.033 g, 0.067 mmol) in benzene (9.6 mL). Distilled water (0.017 mL, 0.96 mmol) was added and the reaction mixture was sparged with argon for 15 minutes through a septum. The septum was quickly replaced by a Teflon screw cap and the reaction vessel was sealed. The reaction was heated at 120°C for 16 hours. The reaction was then cooled, transferred to a separate round bottomed flask, rinsed three times with additional benzene, and the solvent was evaporated. The crude residue was purified by silica column chromatography (20% EtOAc/hexanes) and resulted in a clear, colourless oil (0.027 mg, 82%).[165] TLC $R_f$ 0.27 (30% EtOAc/hexanes); $^1$H NMR (500 MHz, $C_6D_6$) δ ppm 6.97 (d, *J*= 1.92 Hz, 1H), 6.83 (dd, *J*= 1.98, 8.15 Hz, 1H), 6.61 (d, *J*= 8.21 Hz, 1H), 6.59 (s, 1H), 6.41 (s, 1H), 5.09 (d, *J*= 1.02 Hz, 1H), 4.87 (d, *J*= 0.55 Hz, 1H), 4.52 (t, *J*= 6.02 Hz, 1H), 4.35 (sept, *J*= 6.01 Hz, 1H), 4.22 (q, *J*= 11.9 Hz, 2H), 4.21 (sept, *J*= 6.01 Hz, 1H), 3.39 (s, 6H), 3.28-3.35 (m, 2H), 3.18-3.24 (m, 1H), 3.07 (dd, *J*= 6.68, 14.09 Hz, 1H), 2.91 (ddd, *J*= 5.29, 8.19, 15.61 Hz, 1H), 2.56 (ddd, *J*= 5.24, 5.24, 16.05 Hz, 1H), 1.72 (s, 1H), 1.21 (d, *J*= 6.05 Hz, 1H), 1.20 (d, *J*= 6.11 Hz, 1H), 1.19 (d, *J*= 6.15 Hz, 1H), 1.16 (d, *J*= 6.06 Hz, 1H); $^{13}$C NMR ($C_6D_6$, 75 MHz) δ 150.1, 149.9, 147.9, 146.3, 142.6, 133.0, 129.7, 126.9, 122.8, 118.9, 116.5, 112.8, 112.6, 76.7, 71.4, 71.2, 66.8, 55.6, 55.5, 48.5, 40.9, 26.4, 22.4, 22.3, 20.2; IR (film): 3428, 2975, 2934, 2835, 1607, 1508, 1261, 1223, 1109, 1033, 892, 854, 801, 775 cm$^{-1}$; MS (Electrospray): Exact mass calcd for $C_{28}H_{39}NO_5$ [M+1H]: 469.2828. Found: 470.6.



**1-(3-Isopropoxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-7-isopropoxy-6-methoxyisoquinoline (3.135).** Based on a procedure by Le Bourdonnec *et al. J. Med. Chem.* **2006**, *49*, 7278. 1-(3-Isopropoxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-7- isopropoxy-6-methoxyisoquinoline-*N*-hydroxide **3.131** (24 mg, 0.058

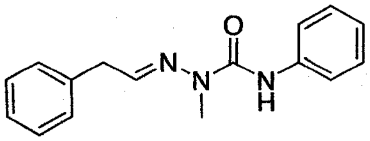
mmol) was dissolved in a 1:1 (v/v) of AcOH and water (1.0 mL) and zinc dust (19 mg, 0.29 mmol) was added. The reaction flask was capped with a rubber septum with an outlet needle and the reaction was stirred vigorously at room temperature for 1.5 hours. The reaction was filtered over celite and rinsed through with hot methanol. The solvent was evaporated and the reaction was basified upon the dropwise addition of aq. $NaHCO_3$, which resulted in vigorous bubbling. The product was subsequently extracted 3 times with EtOAc, the combined organics were washed with brine, dried with $Na_2SO_4$, filtered and concentrated. The resulting crude yellow oil was used directly in the next step without further purification (21 mg, 91%). %). TLC $R_f$ 0.13 (5% MeOH/$CH_2Cl_2$); $^1$H NMR (500 MHz, $C_6D_6$) d ppm 6.91 (d, *J*= 1.85 Hz, 1H), 6.90 (s, 1H), 6.81 (dd, *J*=1.87, 8.10 Hz, 1H), 6.63 (d, *J*= 8.14 Hz, 1H), 6.46 (s, 1 H), 4.38 (sept, *J*= 6.03 Hz, 1 H), 4.35 (sept, *J*= 6.13 Hz, 1 H), 4.23 (dd, *J*= 4.04, 8.95 Hz, 1 H), 3.41 (s, 3H), 3.41 (s, 3H), 3.21 (dd, *J*= 4.19, 13.50 Hz, 1 H), 2.92-3.01 (m, 2H), 2.66-2.75 (m, 2H), 2.50-2.56 (1H), 1.26 (d, *J*= 6.07 Hz, 6H), 1.21 (d, *J*= 6.04 Hz, 3H), 1.21 (d, *J*= 6.04 Hz, 3H); $^{13}$C NMR ($C_6D_6$, 100 MHz) δ 150.2, 150.2, 148.2, 146.2, 132.2, 131.5, 129.2, 122.5, 118.5, 116.5, 113.6, 113.1, 71.9, 71.2, 57.3, 55.7, 55.6, 42.9, 41.7, 30.3, 22.5, 22.4, 22.3, 22.3; IR (film): 3401, 2979, 2930, 2831, 1611, 1584, 1512, 1257, 1235, 1111, 1022, 1018 cm$^{-1}$; HRMS (EI): Exact mass calcd for $C_{13}H_{18}NO_2$ [M – 3-isopropoxy-4-methoxybenzyl]$^+$: 220.1338. Found: 220.1303.



***N*-Norreticuline (3.24).** Based on the procedure by Ridley *et al.* J. *Bioorg. Med. Chem.* **2002**, *10*, 3285. In a flame-dried round bottomed flask equipped with a magnetic stir bar was dissolved 1-(3-isopropoxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-7-isopropoxy-6-methoxyisoquinoline **3.135** (14 mg, 0.035 mmol) in methylene chloride (3.5 mL) under an argon atmosphere. The reaction flask was cooled to -10°C in a brine and ice bath and a solution of boron trichloride (0.154 mL, 0.154 mmol, 1.0 M solution in $CH_2Cl_2$) was added dropwise. Upon this addition, the brine and ice bath was replaced with a regular ice bath and the reaction was stirred at 0°C for 2 hours. The reaction was quenched with water, the layers separated, and the aqueous layer was extracted 3 times with methylene chloride. The combined organics were washed with brine, dried with $Na_2SO_4$, filtered and concentrated. The crude colourless oil was purified by silica column chromatography (15% MeOH/$CH_2Cl_2$) and yielded the title compound as a white solid (5 mg, 45%). The spectral data was in good agreement with the literature.[100,103]

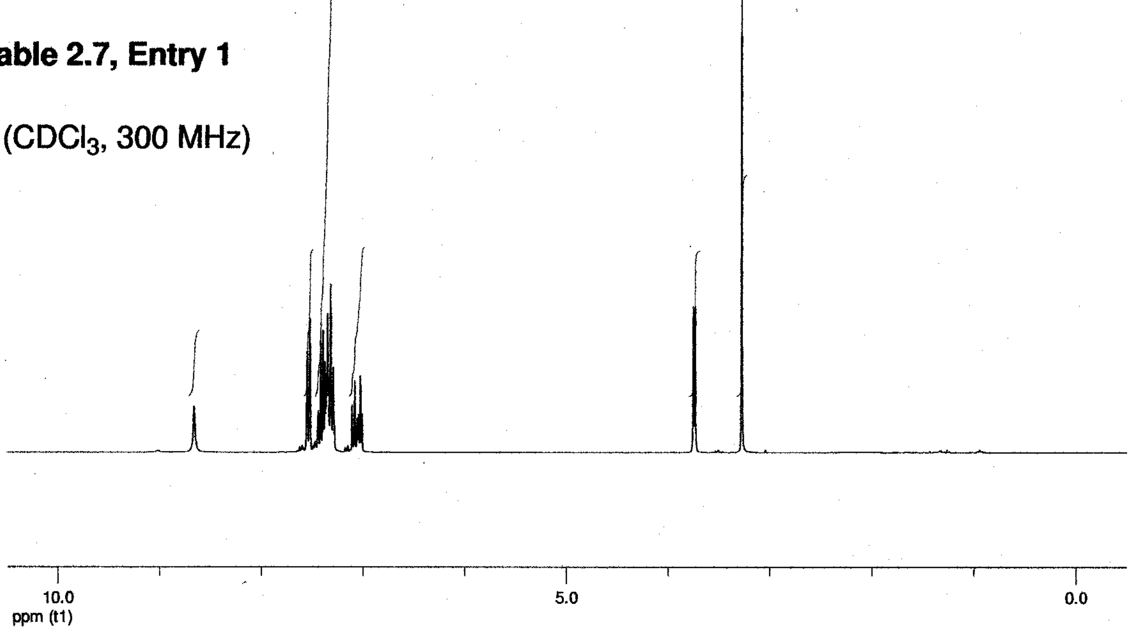
# Appendix:

# $^{1}$H and $^{13}$C NMR spectra

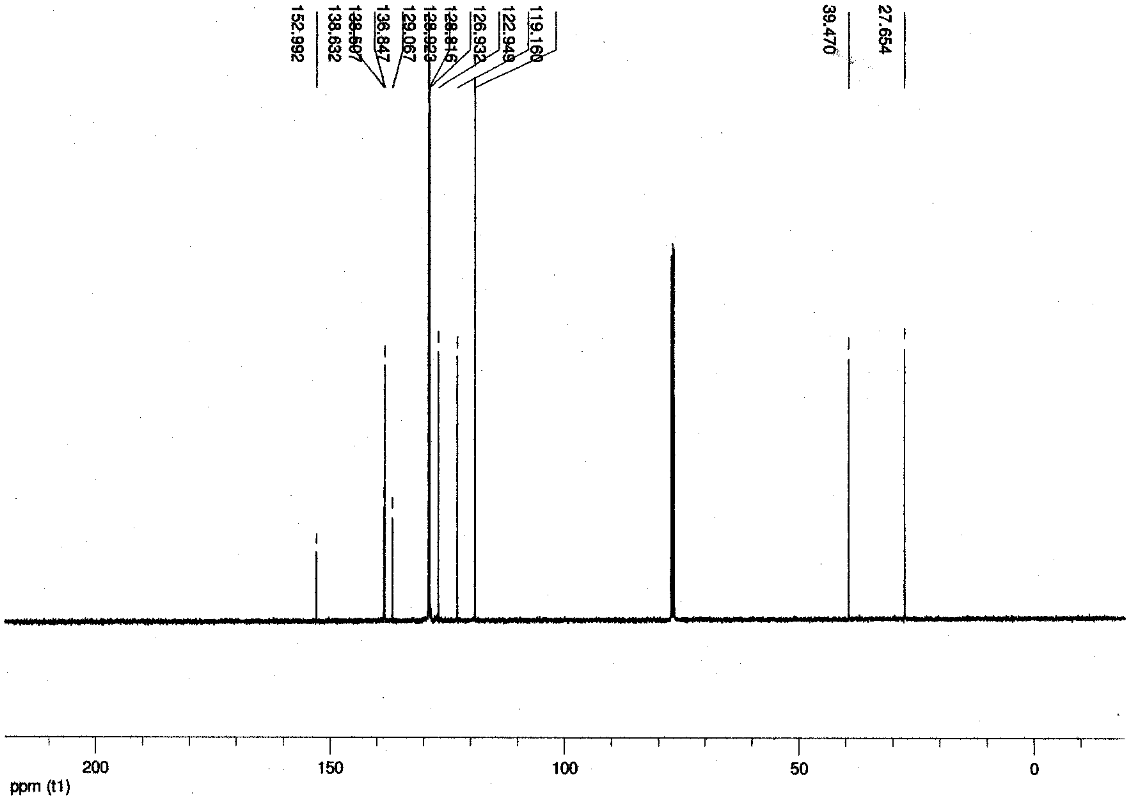


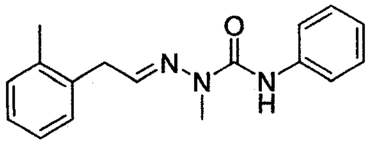
**2.25, Table 2.7, Entry 1**

**$^1$H NMR** (CDCl$_3$, 300 MHz)



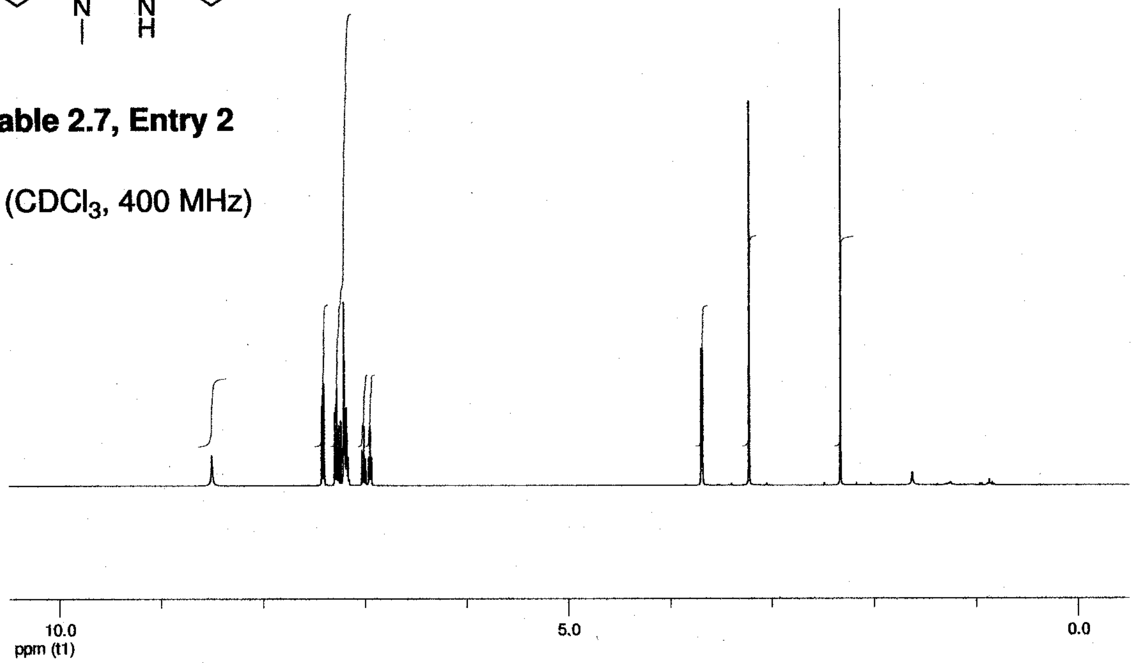
**$^{13}$C NMR** (CDCl$_3$, 100 MHz)



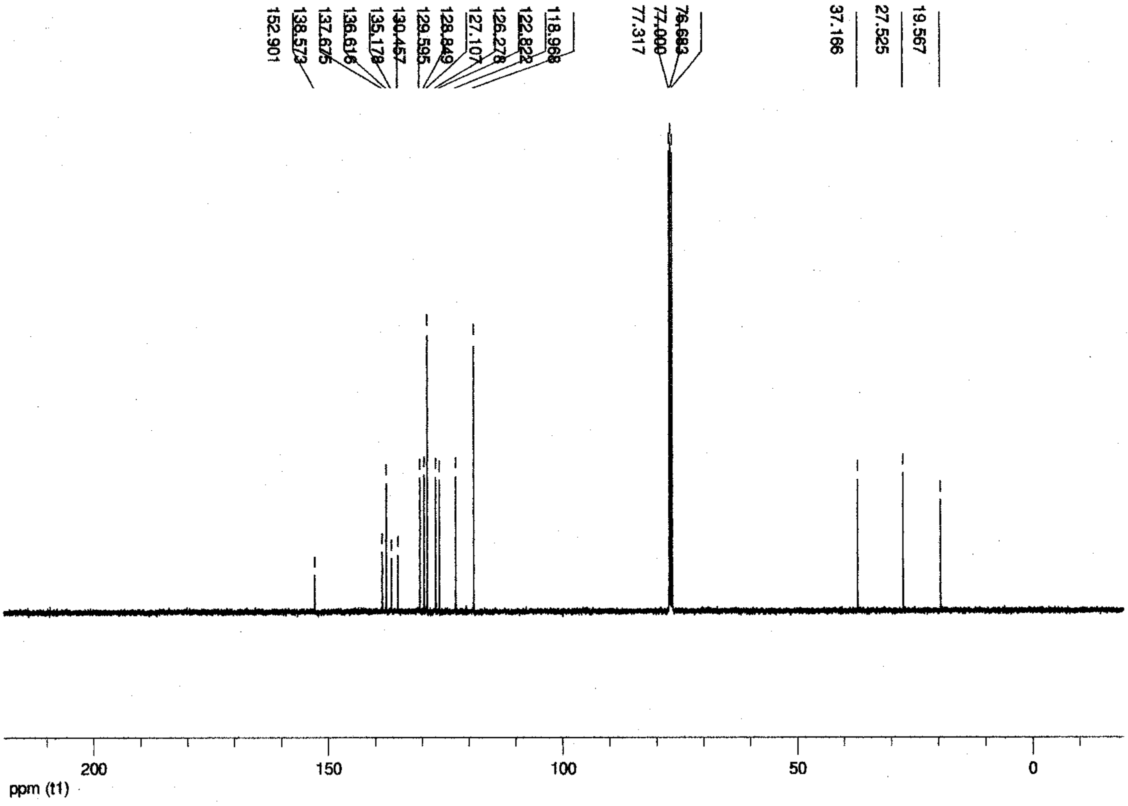


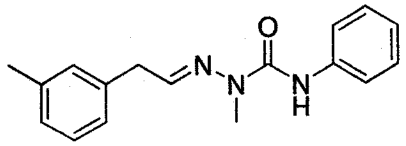
**2.37, Table 2.7, Entry 2**

**$^1$H NMR** (CDCl$_3$, 400 MHz)



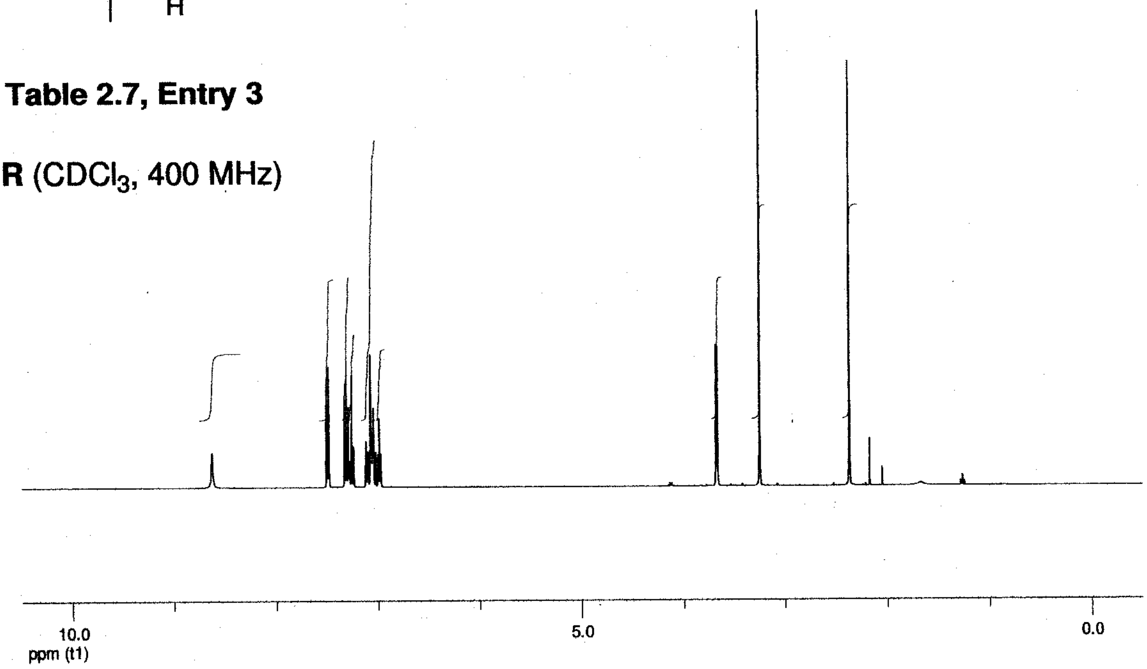
**$^{13}$C NMR** (CDCl$_3$, 100 MHz)



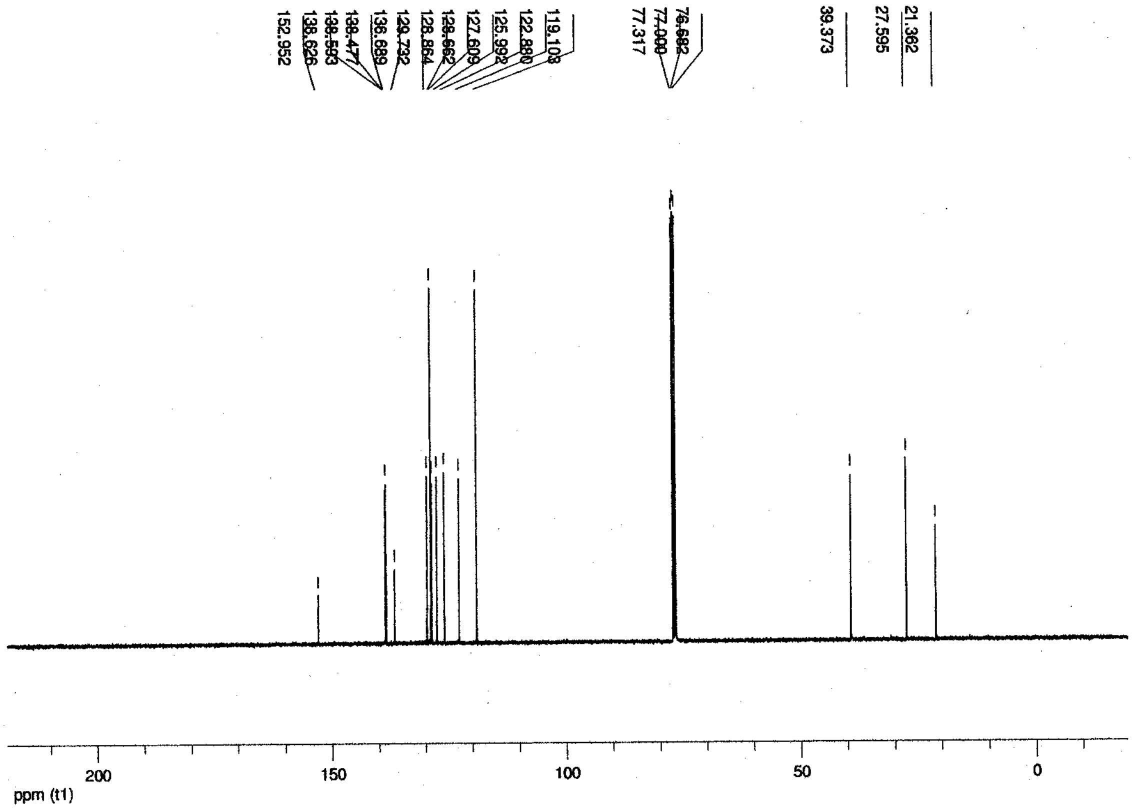


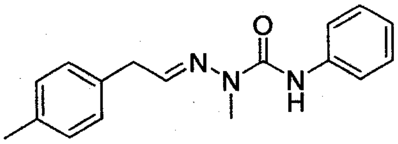
**2.38, Table 2.7, Entry 3**

**$^1$H NMR** (CDCl$_3$, 400 MHz)



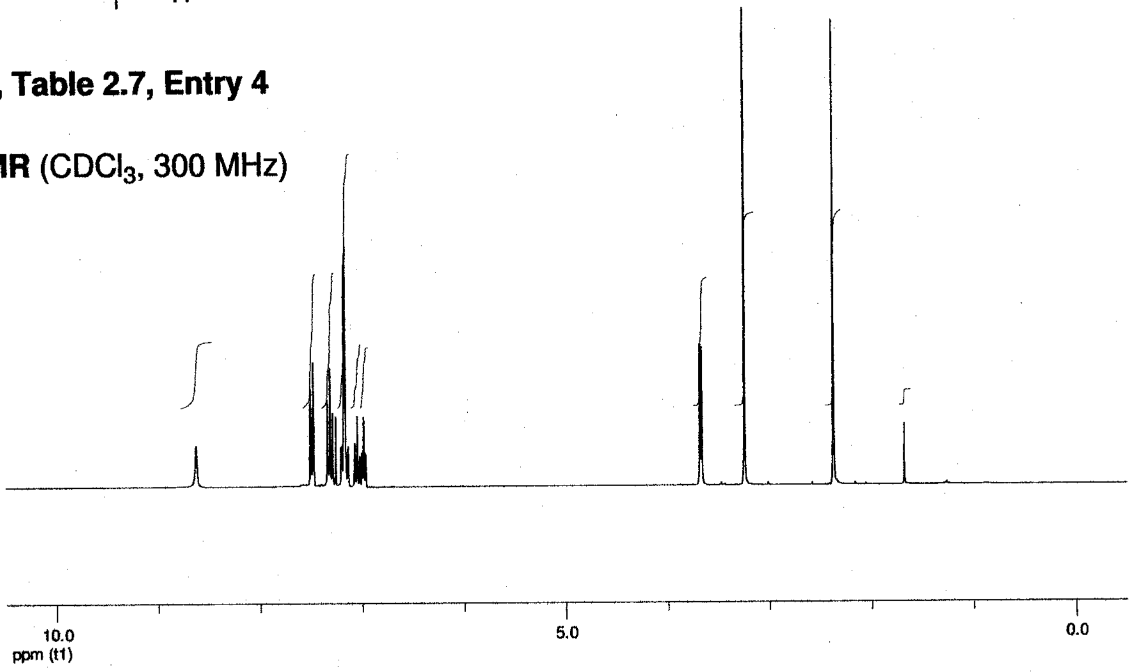
**$^{13}$C NMR** (CDCl$_3$, 100 MHz)



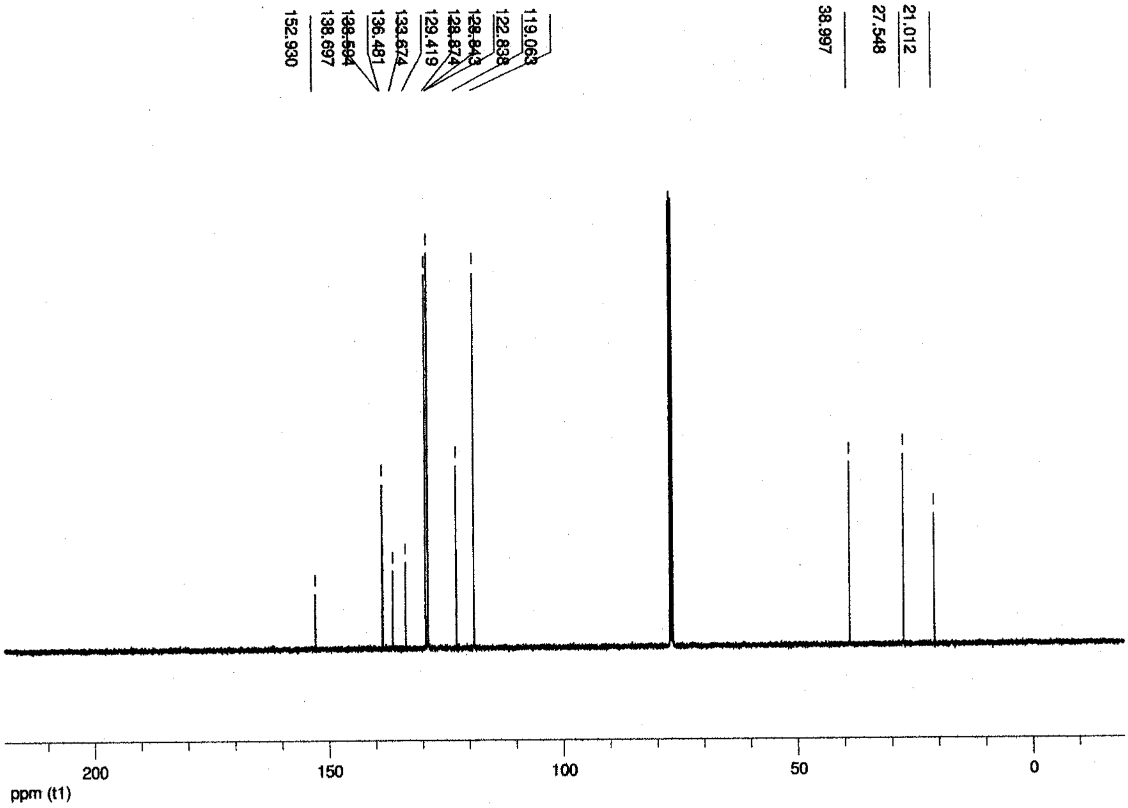


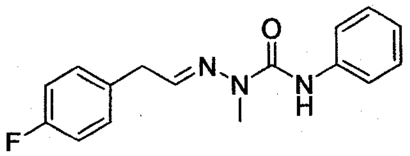
**2.22, Table 2.7, Entry 4**

**$^{1}$H NMR** (CDCl$_3$, 300 MHz)



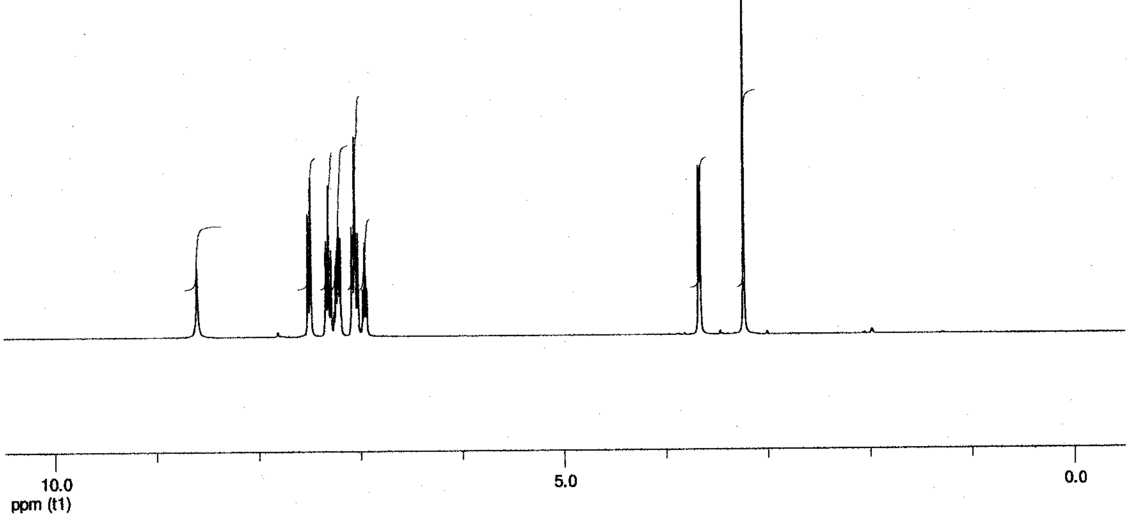
**$^{13}$C NMR** (CDCl$_3$, 75 MHz)



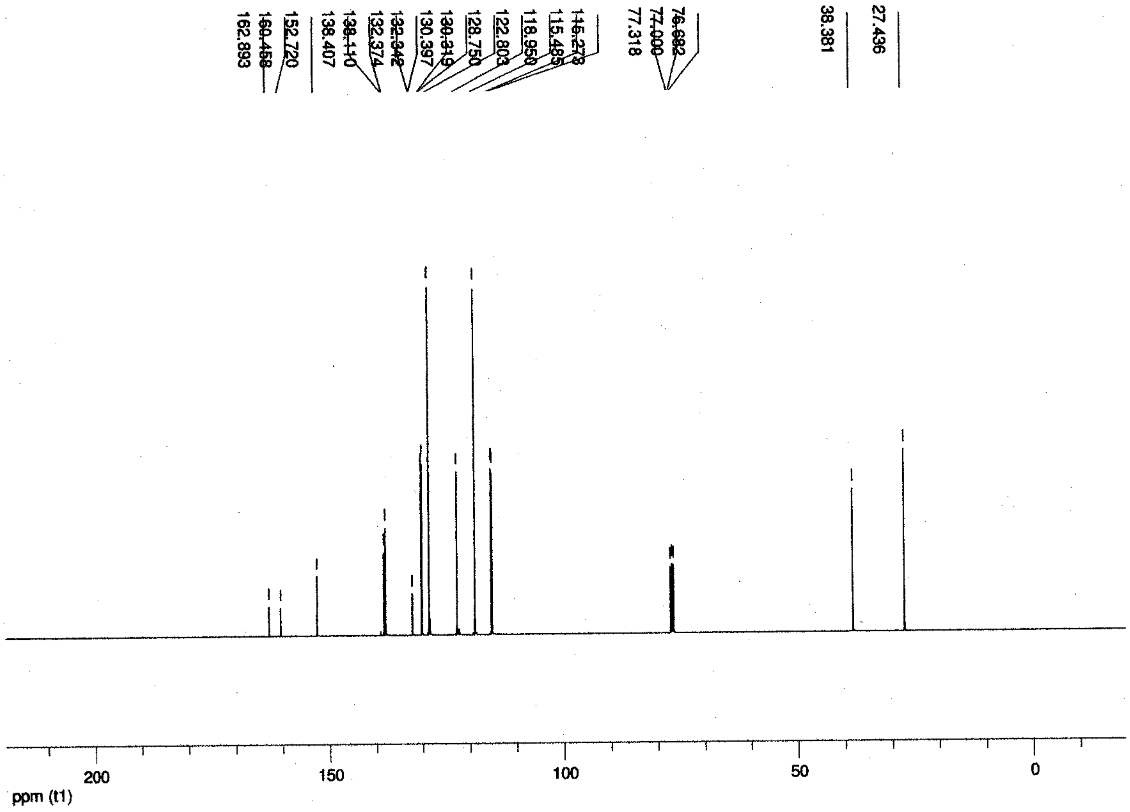


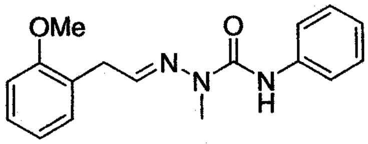
**2.39, Table 2.7, Entry 5**

**$^1$H NMR** ($CDCl_3$, 300 MHz)



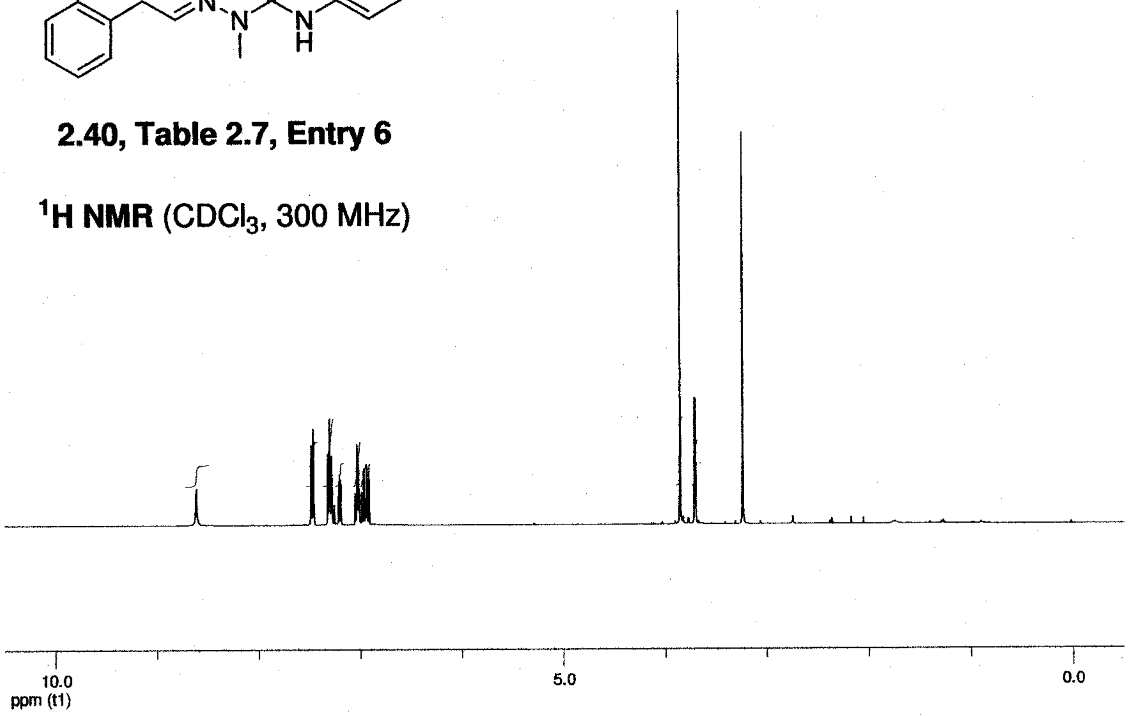
**$^{13}$C NMR** ($CDCl_3$, 100 MHz)



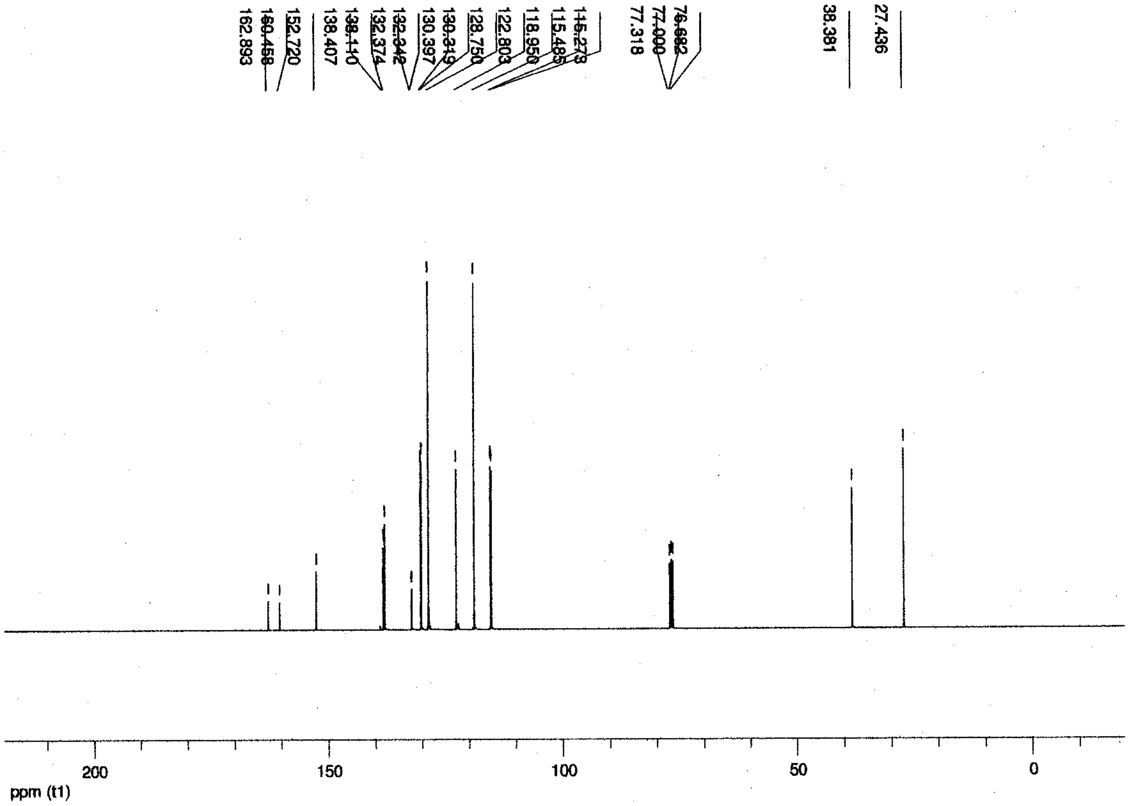


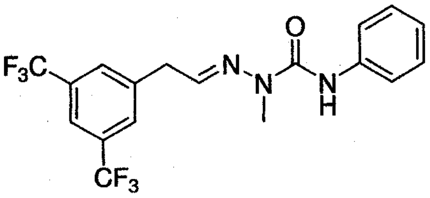
**2.40, Table 2.7, Entry 6**

**$^1$H NMR** (CDCl$_3$, 300 MHz)



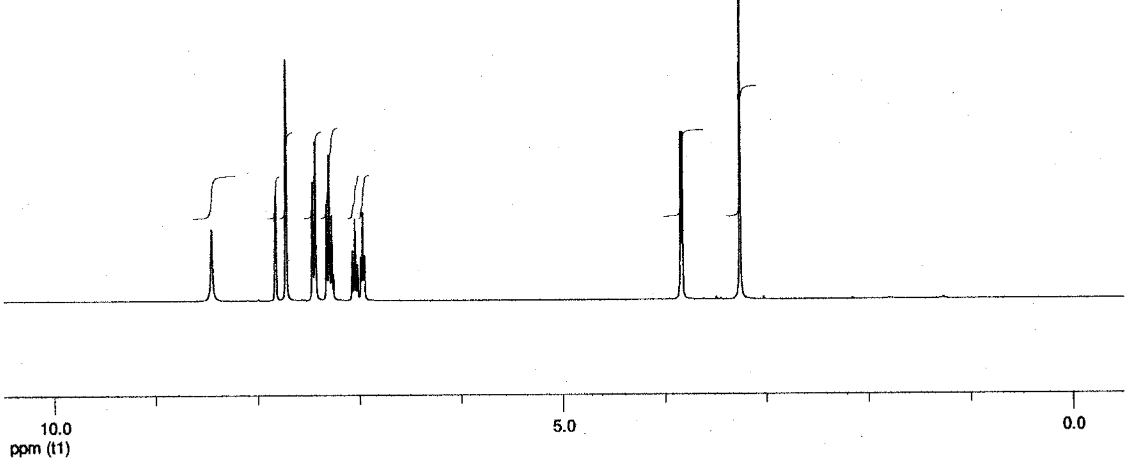
**$^{13}$C NMR** (CDCl$_3$, 100 MHz)



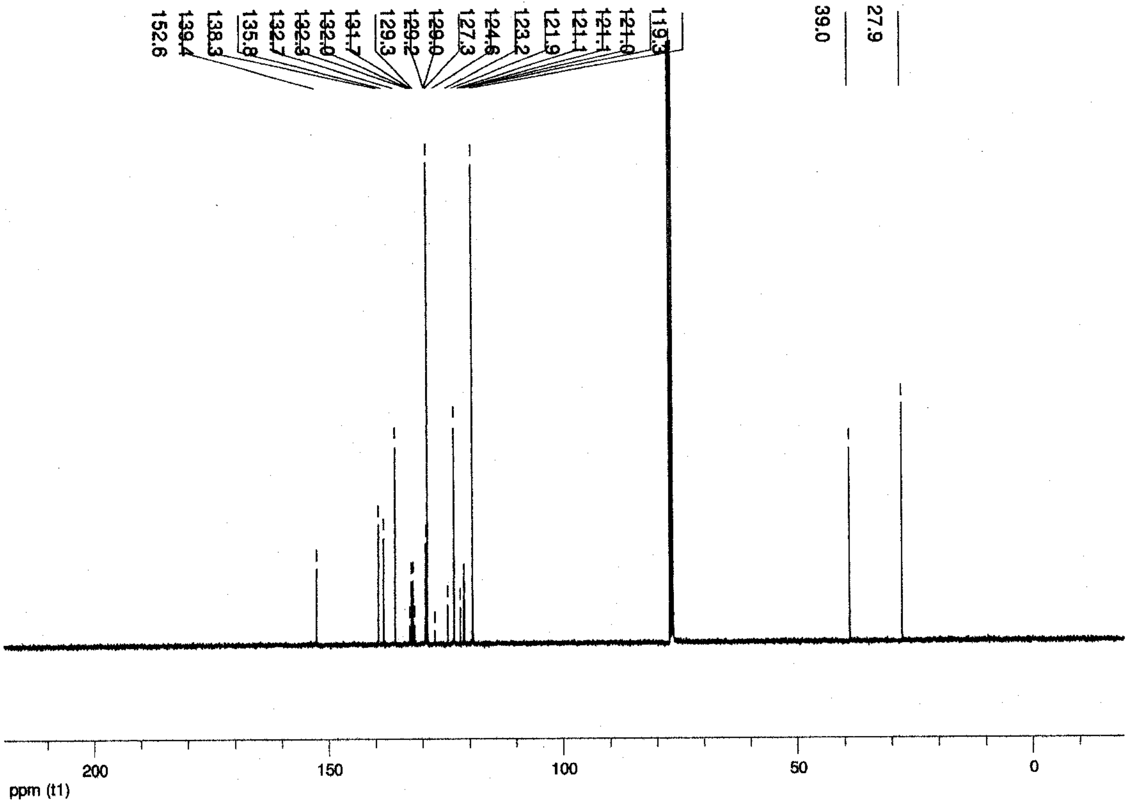


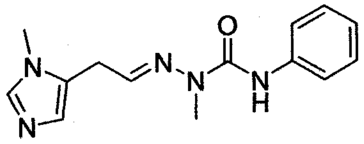
**2.41, Table 2.7, Entry 8**

**$^1$H NMR** ($CDCl_3$, 300 MHz)



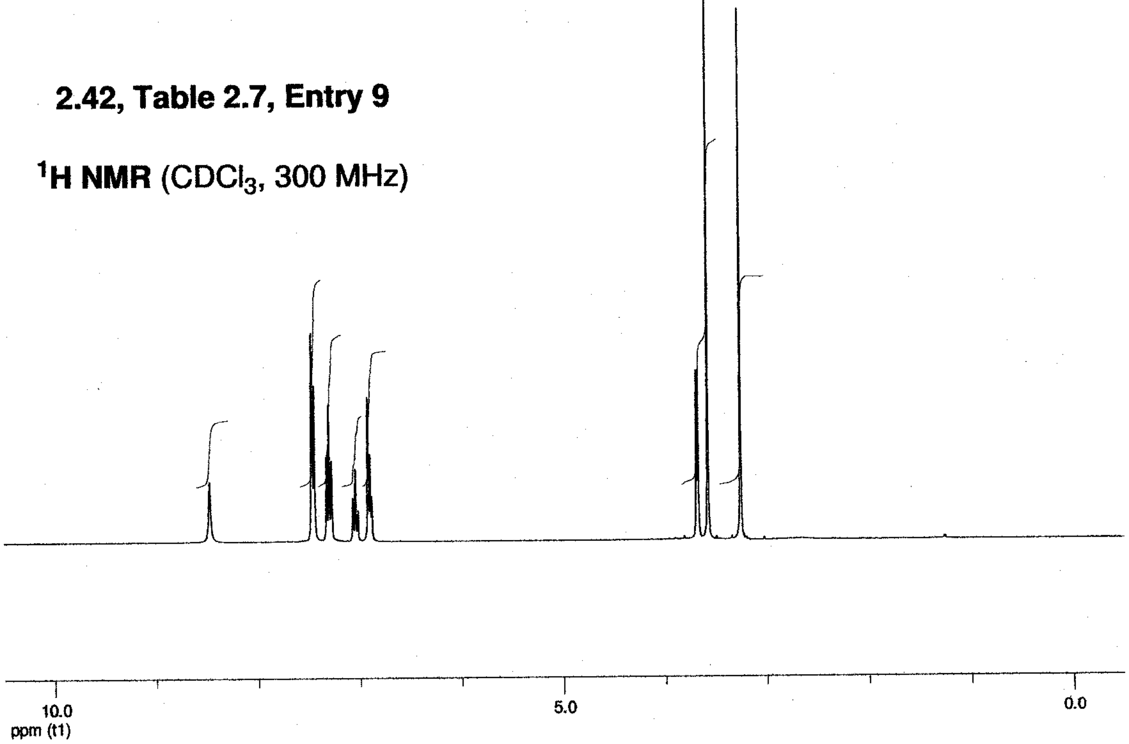
**$^{13}$C NMR** ($CDCl_3$, 100 MHz)



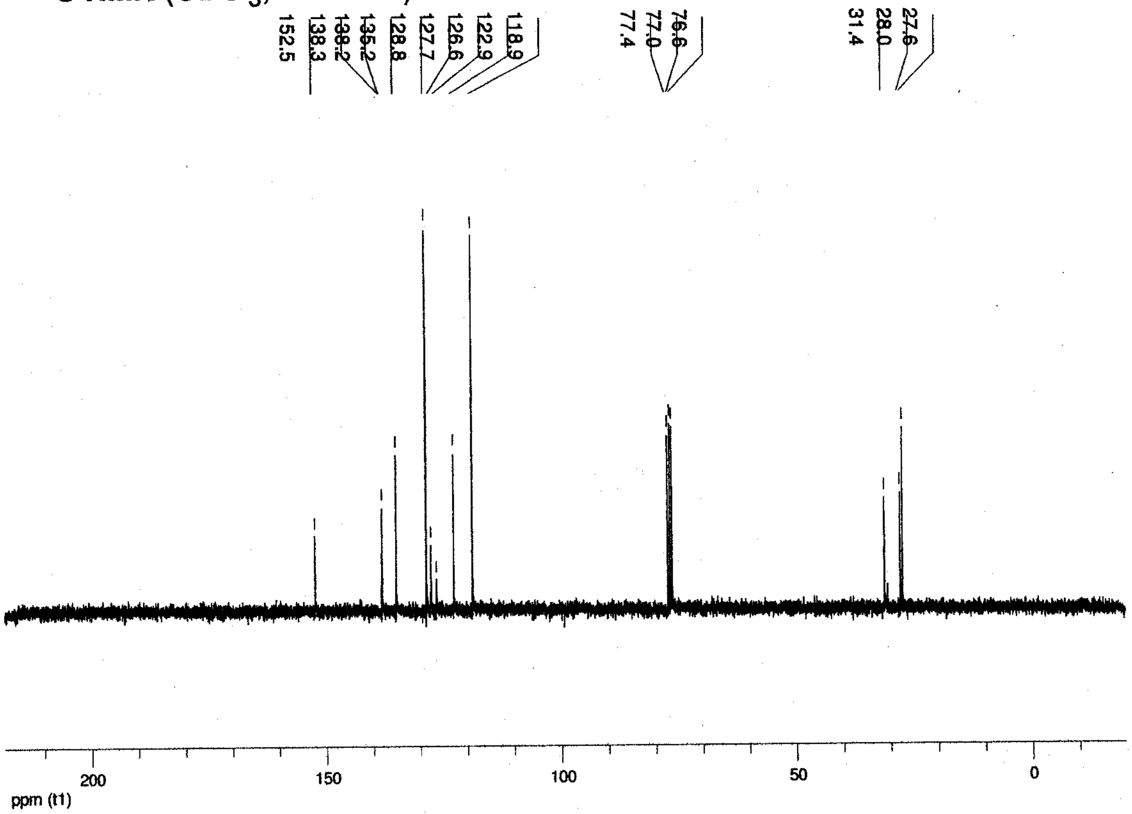


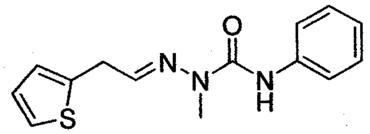
**2.42, Table 2.7, Entry 9**

**$^1$H NMR** (CDCl$_3$, 300 MHz)



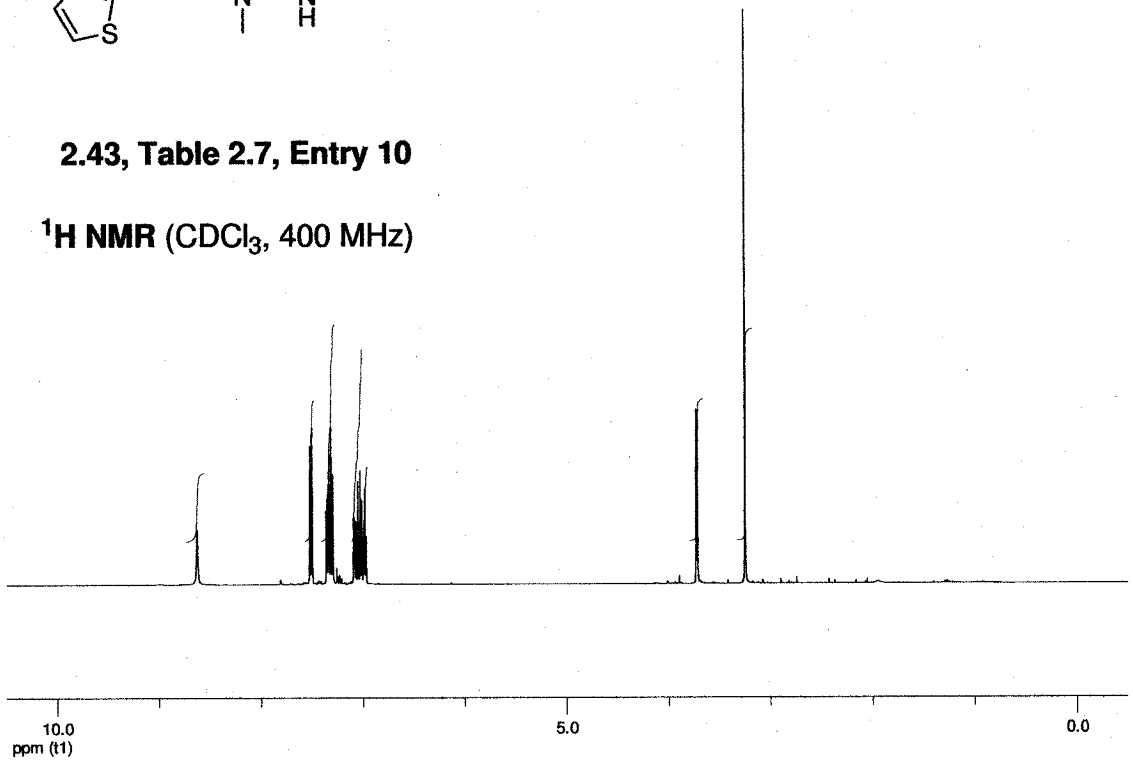
**$^{13}$C NMR** (CDCl$_3$, 100 MHz)



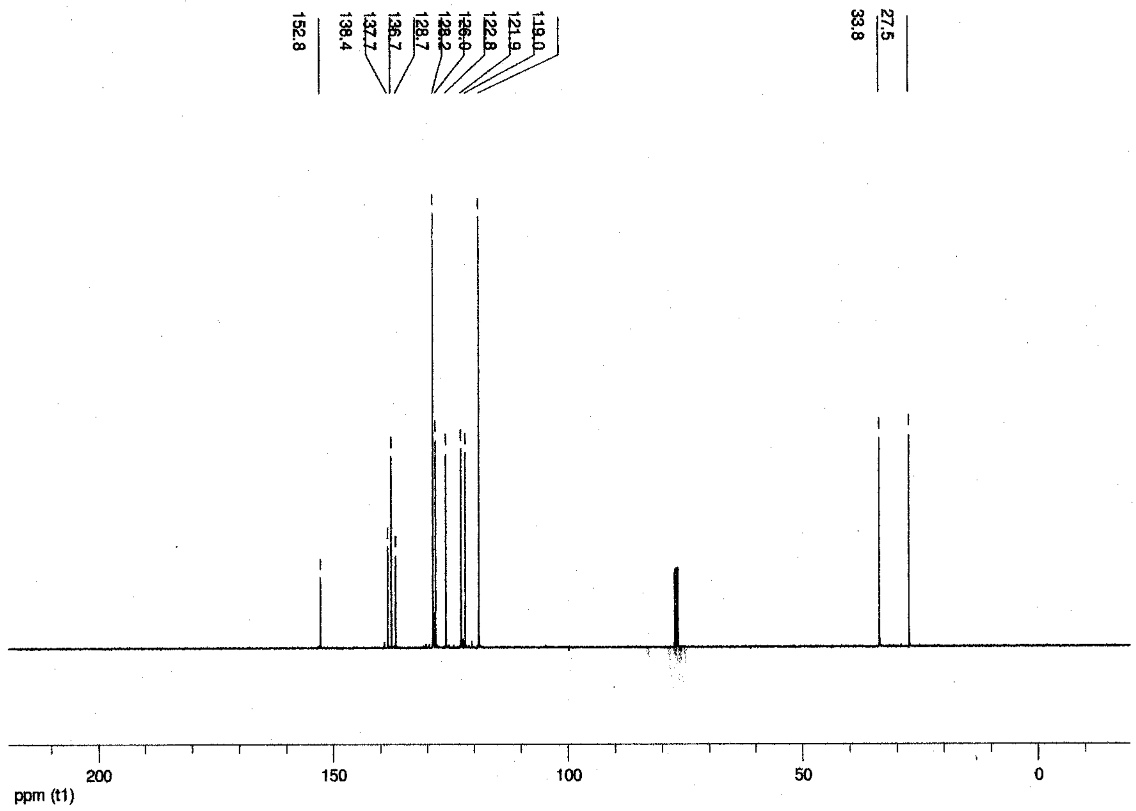


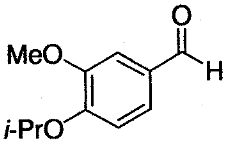
**2.43, Table 2.7, Entry 10**

**$^1$H NMR** (CDCl$_3$, 400 MHz)



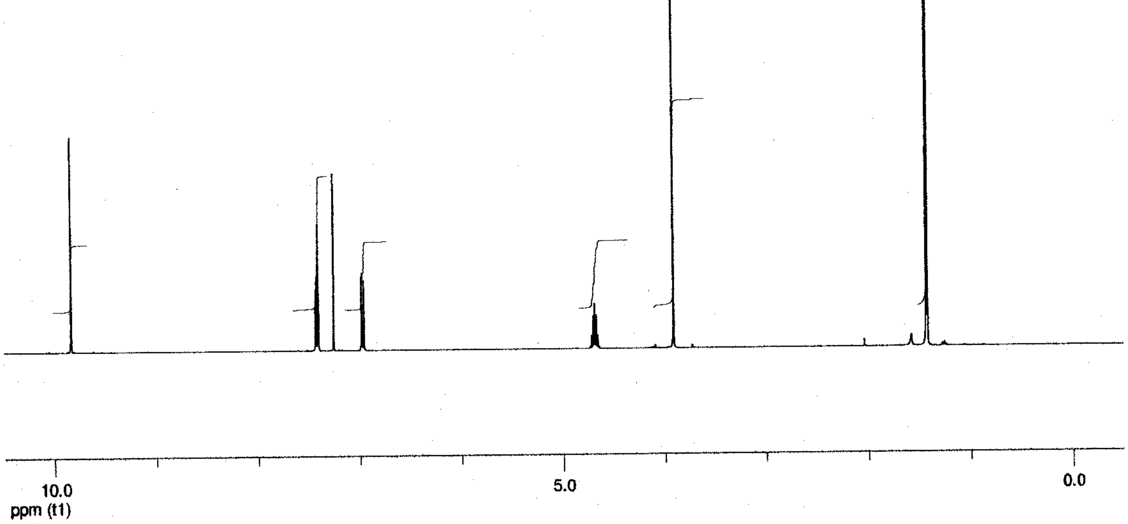
**$^{13}$C NMR** (CDCl$_3$, 100 MHz)



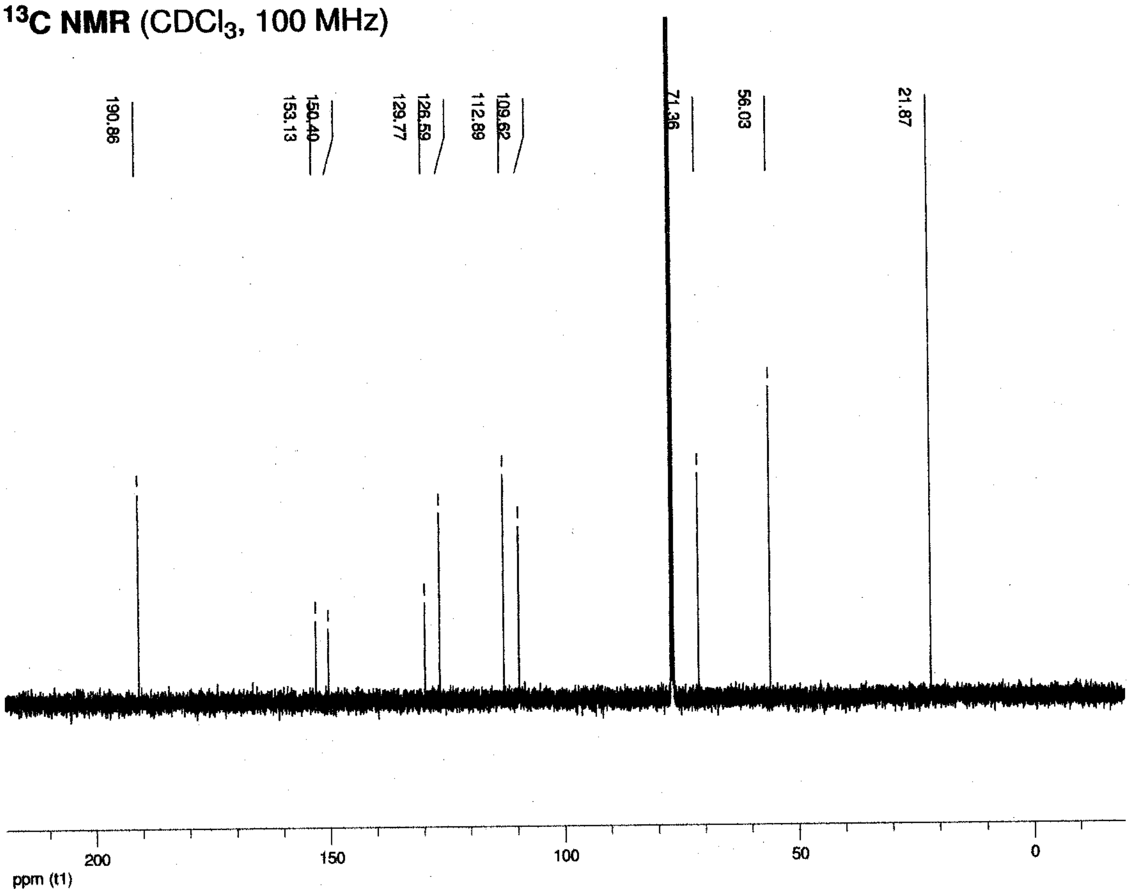


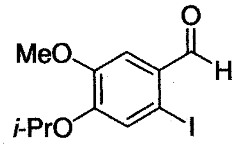
**3.86, Table 3.1, Entry 7**

**$^1$H NMR** (CDCl$_3$, 400 MHz)



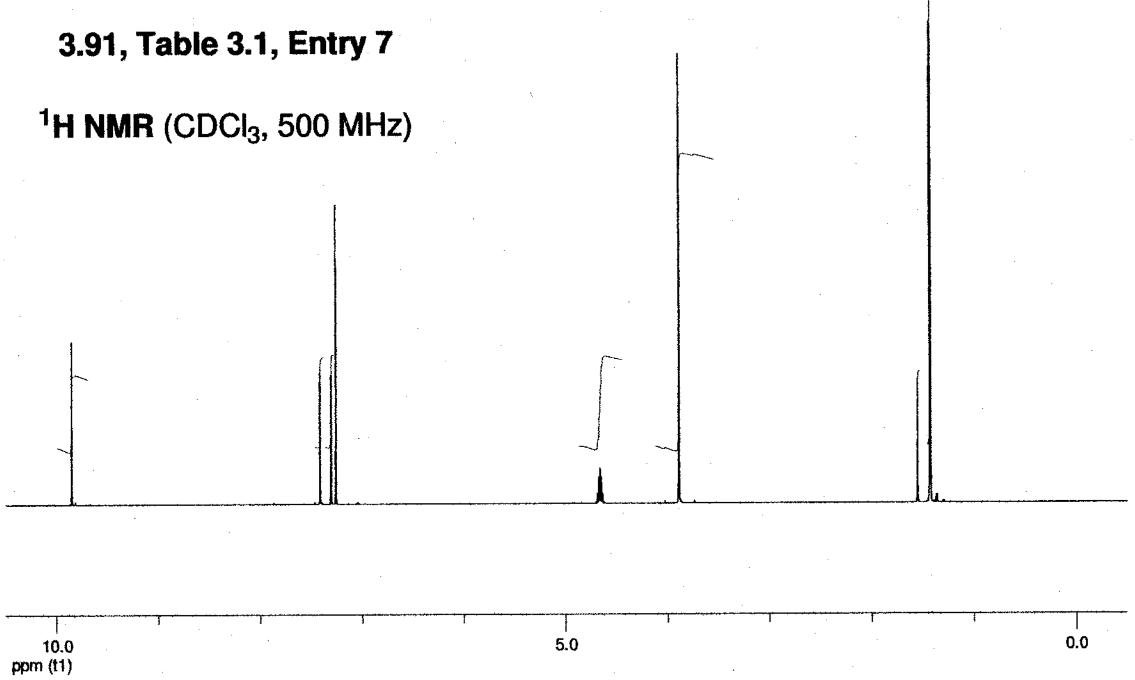
**$^{13}$C NMR** (CDCl$_3$, 100 MHz)



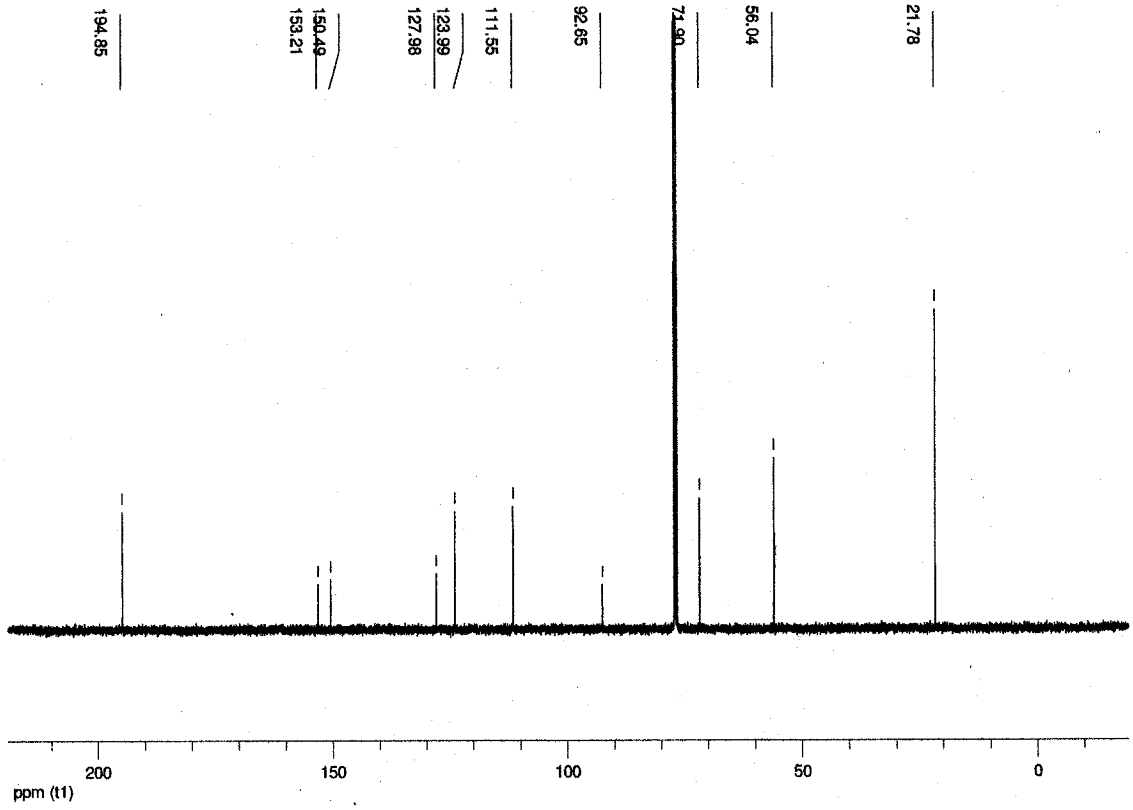


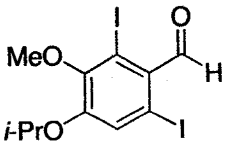
**3.91, Table 3.1, Entry 7**

**$^1$H NMR** (CDCl$_3$, 500 MHz)



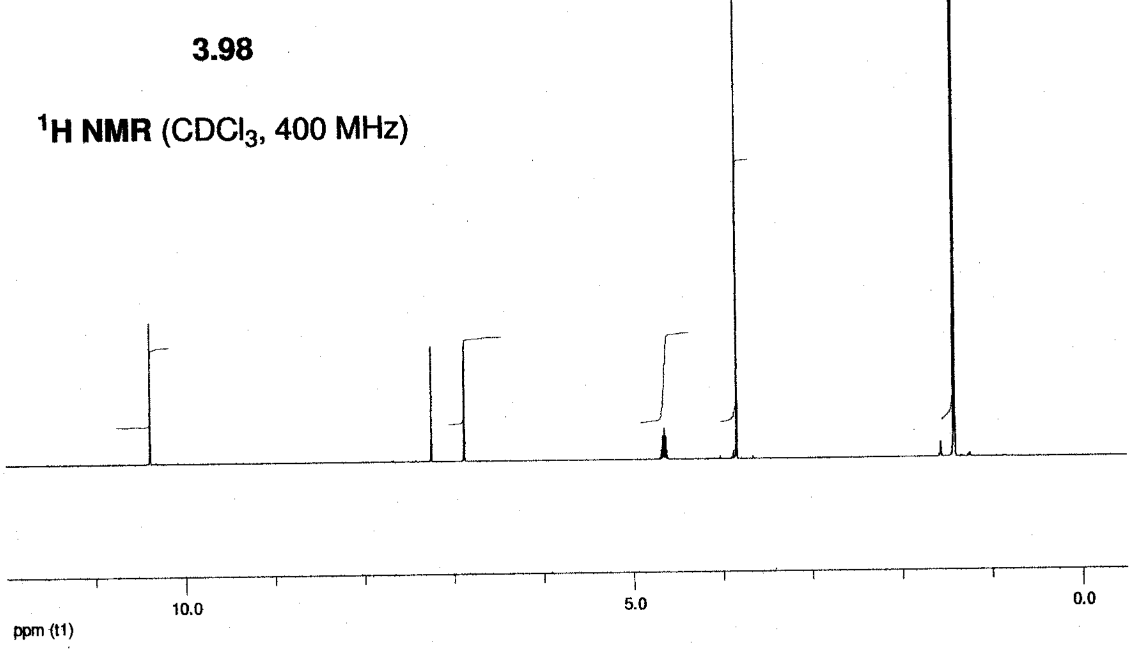
**$^{13}$C NMR** (CDCl$_3$, 100 MHz)



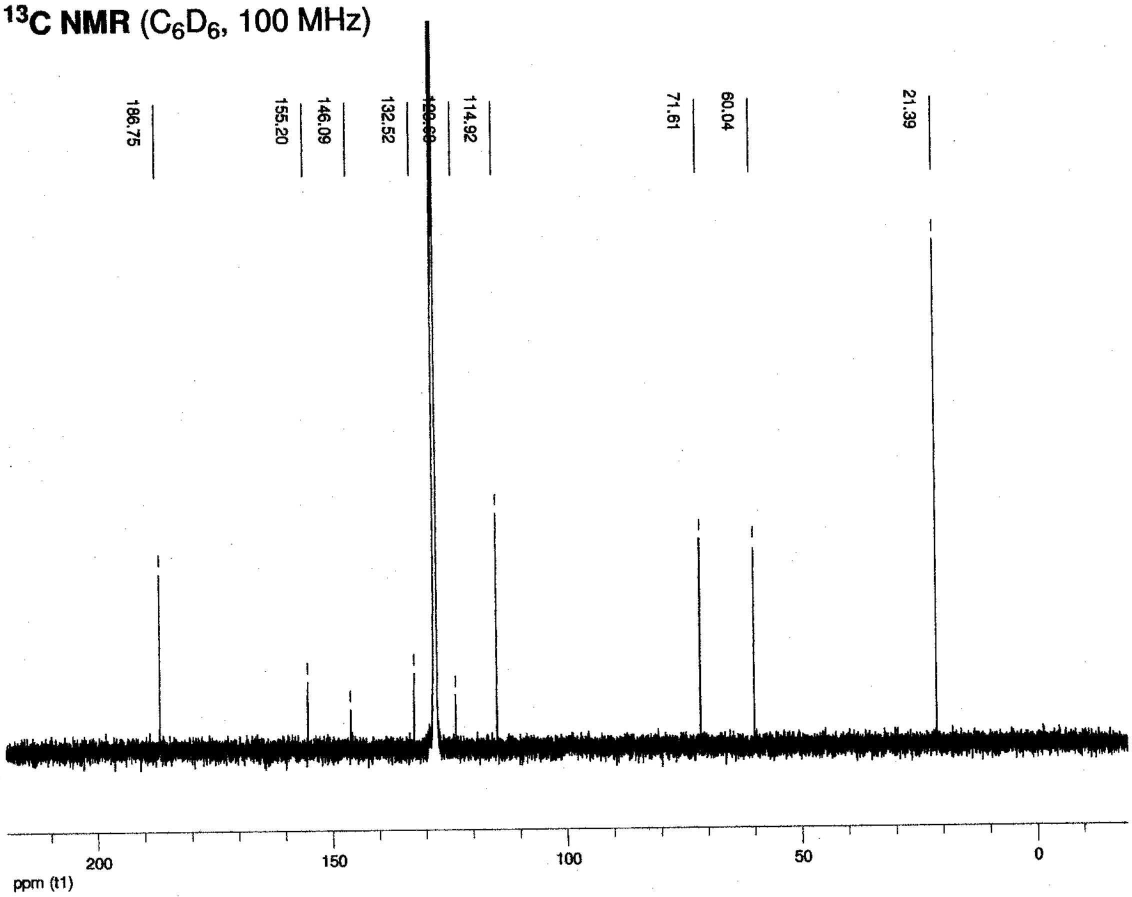


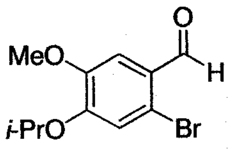
**3.98**

**$^1$H NMR** (CDCl$_3$, 400 MHz)



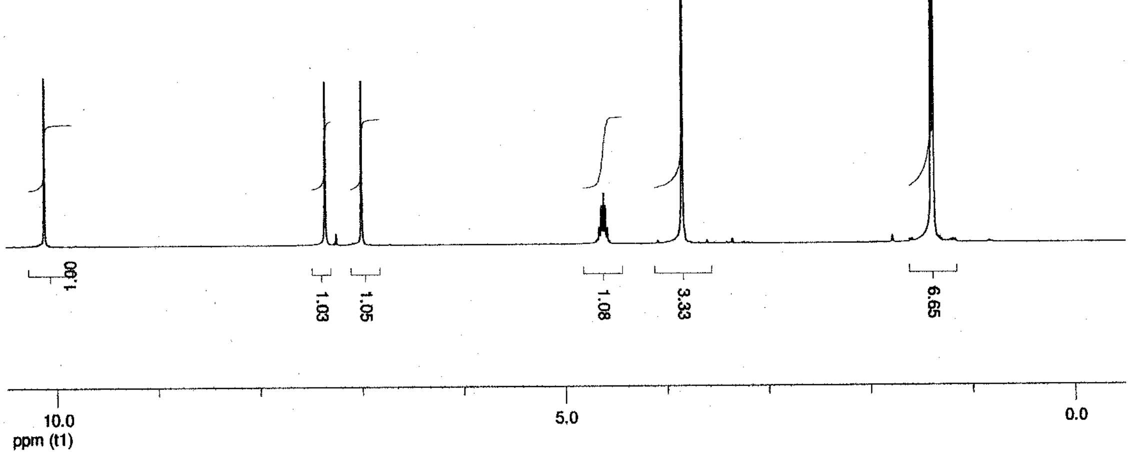
**$^{13}$C NMR** ($C_6D_6$, 100 MHz)



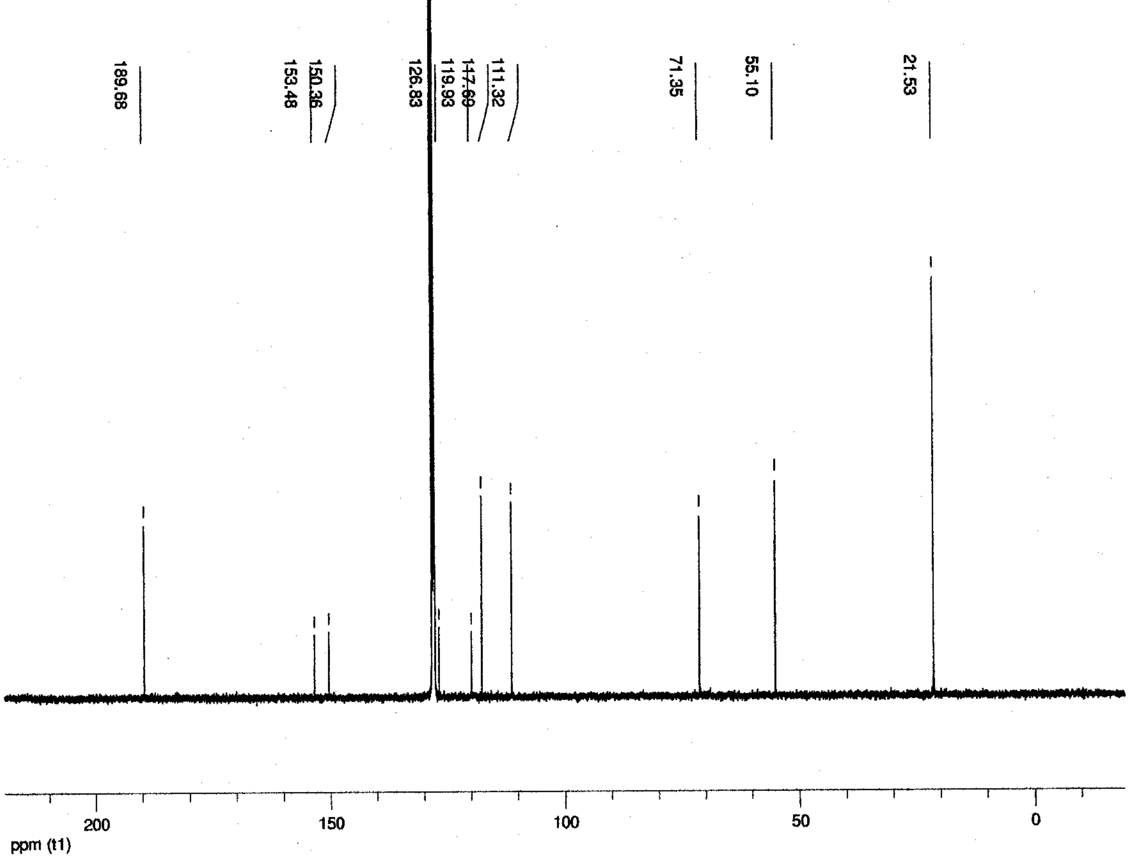


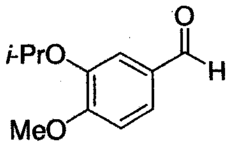
**3.99**

**$^1$H NMR** (CDCl$_3$, 300 MHz)



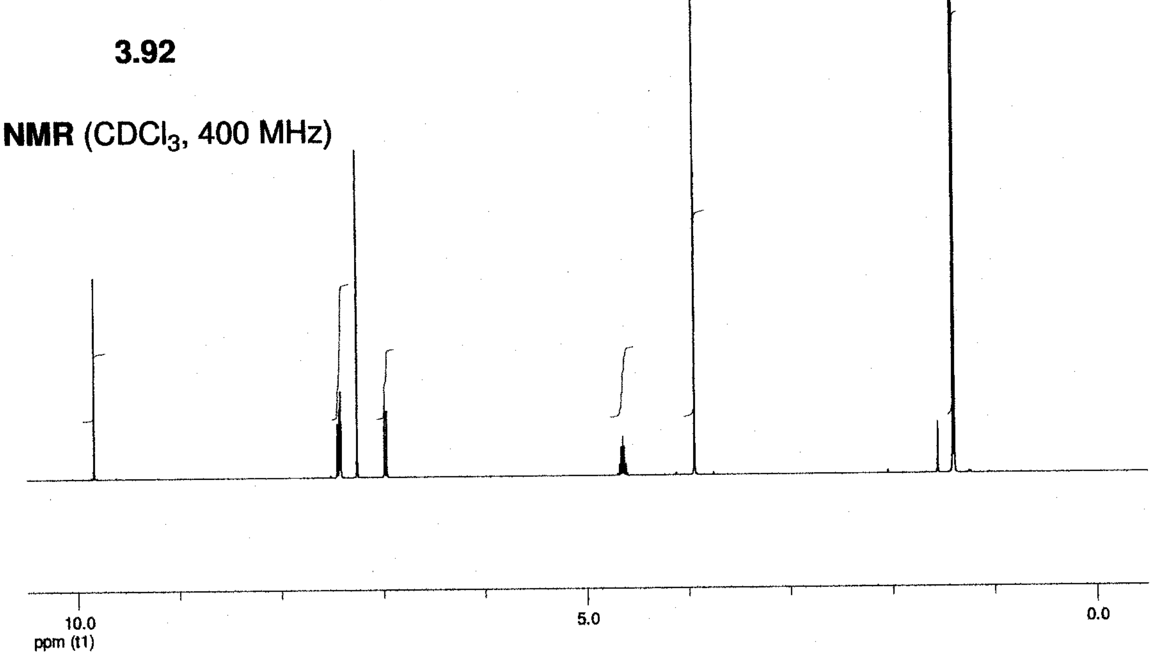
**$^{13}$C NMR** (C$_6$D$_6$, 100 MHz)



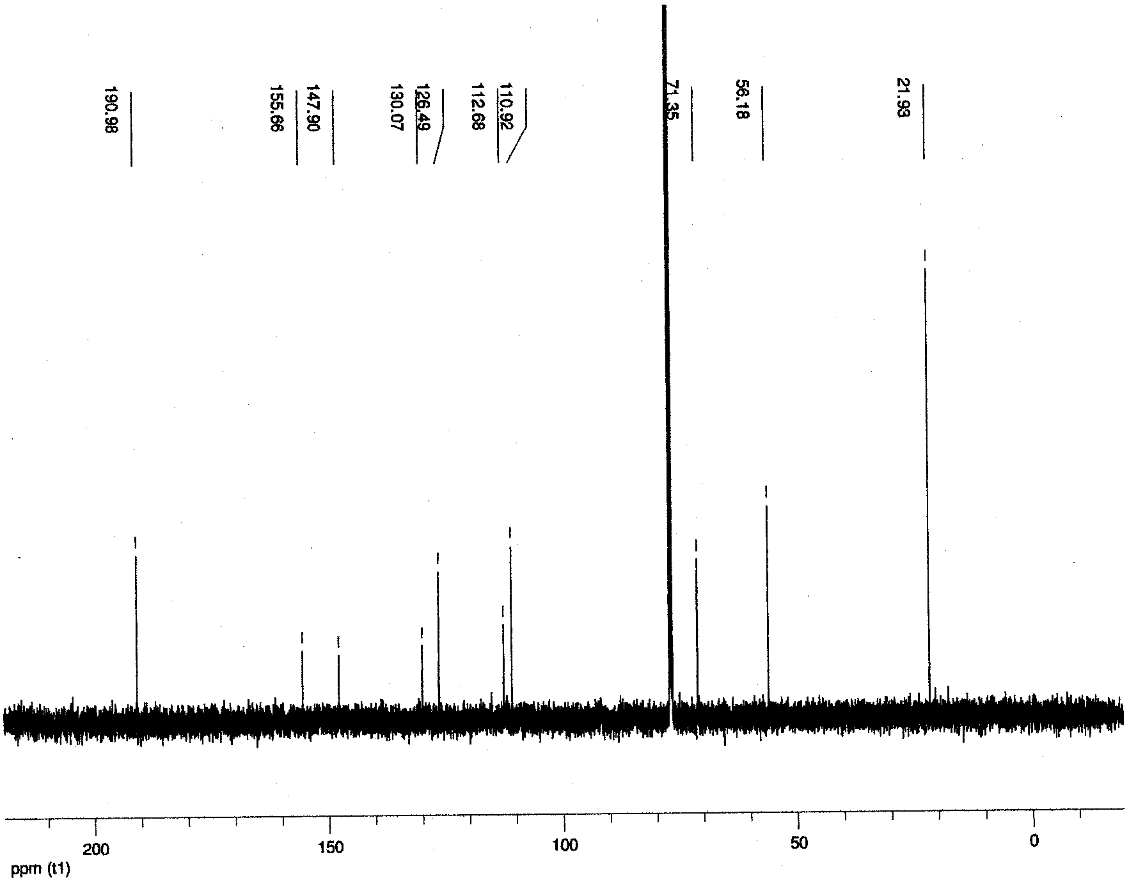


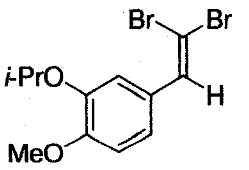
**3.92**

**$^1$H NMR** (CDCl$_3$, 400 MHz)



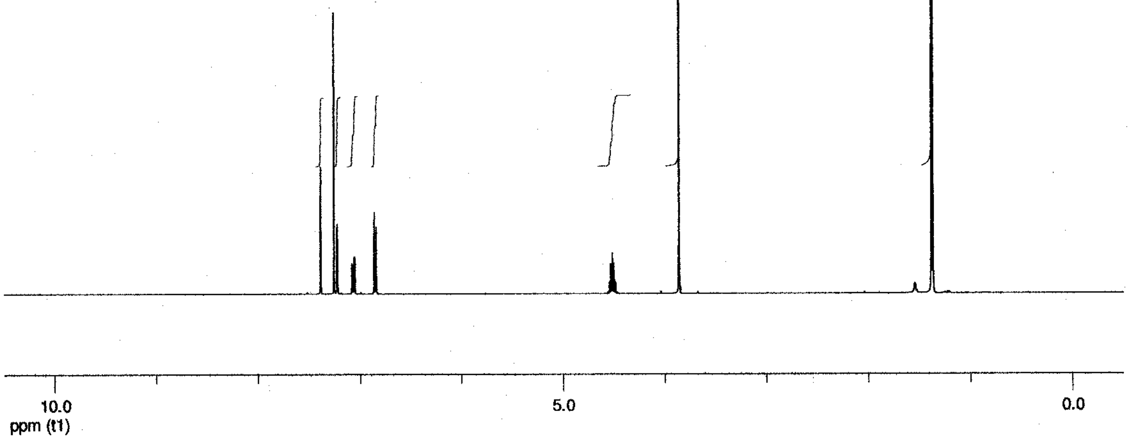
**$^{13}$C NMR** (CDCl$_3$, 100 MHz)



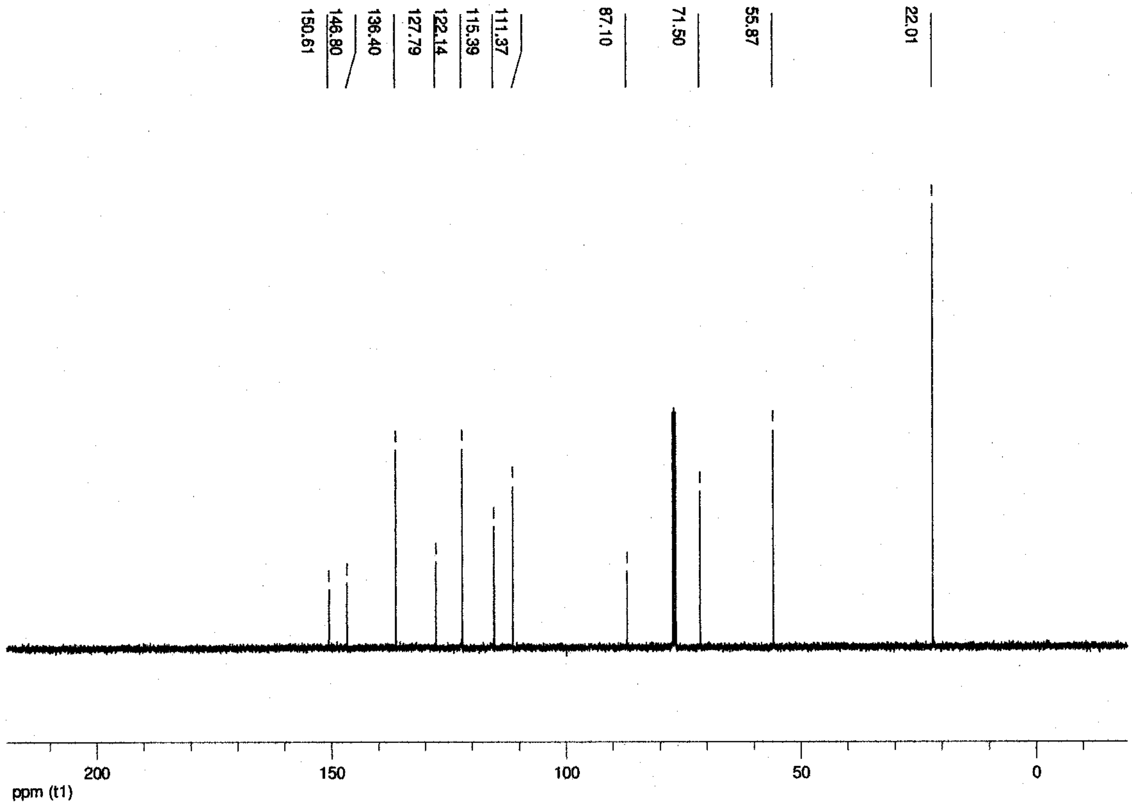


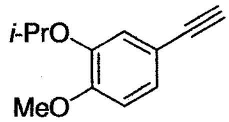
**3.93**

**$^1$H NMR** (CDCl$_3$, 400 MHz)



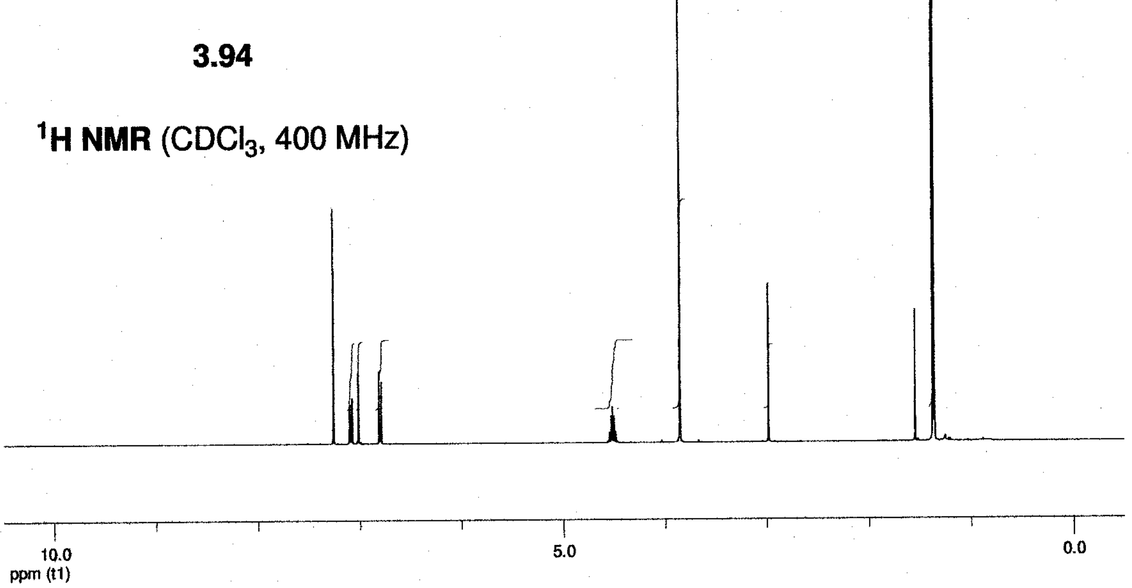
**$^{13}$C NMR** (CDCl$_3$, 100 MHz)



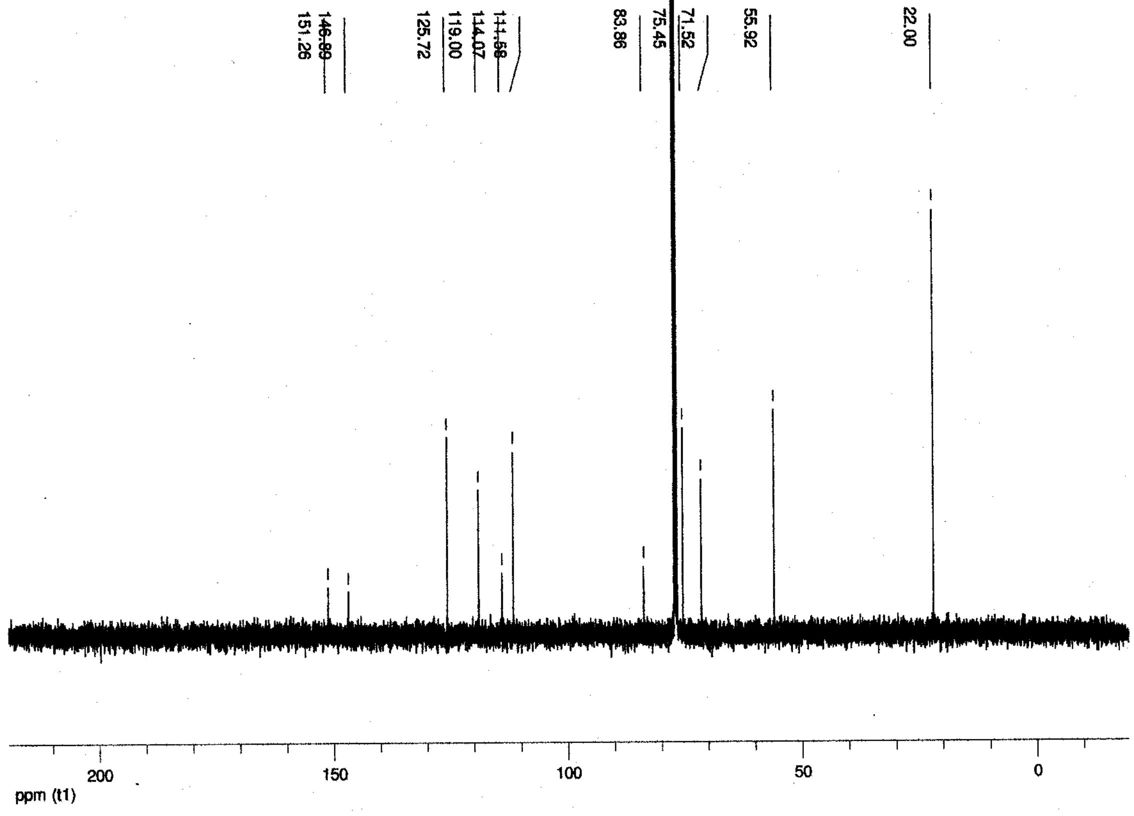


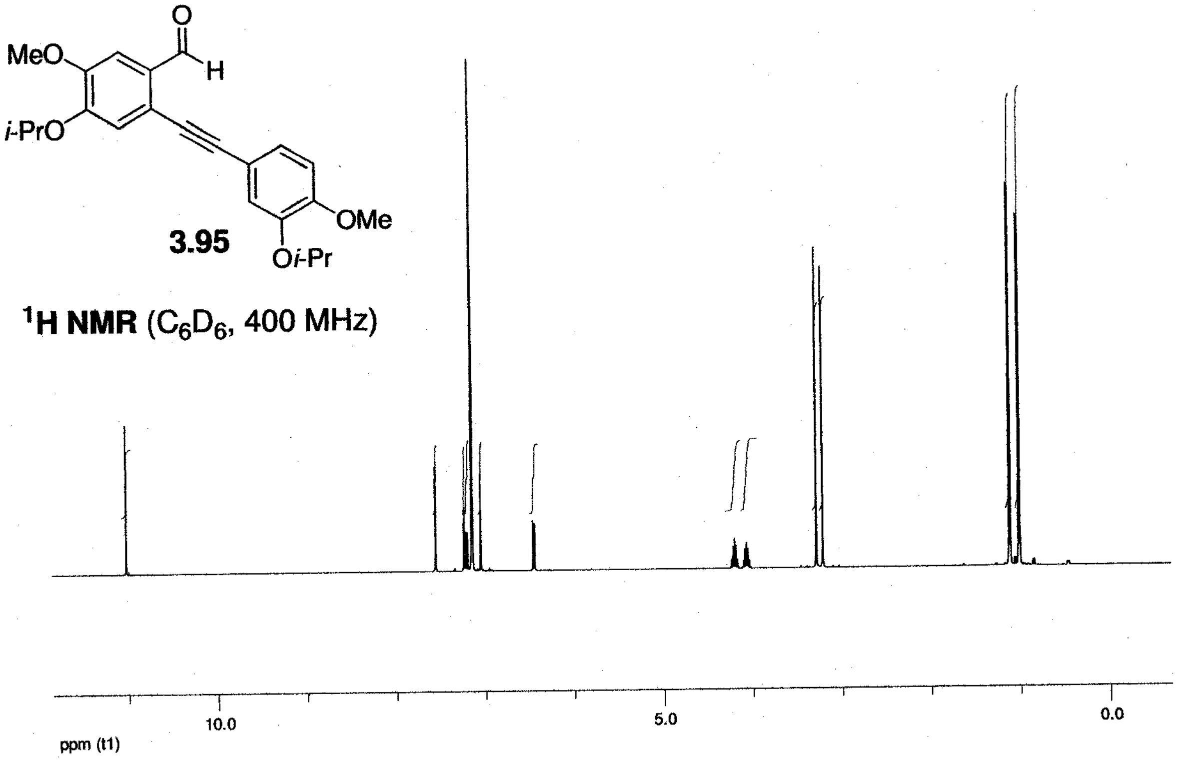
**3.94**

**$^1$H NMR** (CDCl$_3$, 400 MHz)



**$^{13}$C NMR** (CDCl$_3$, 100 MHz)

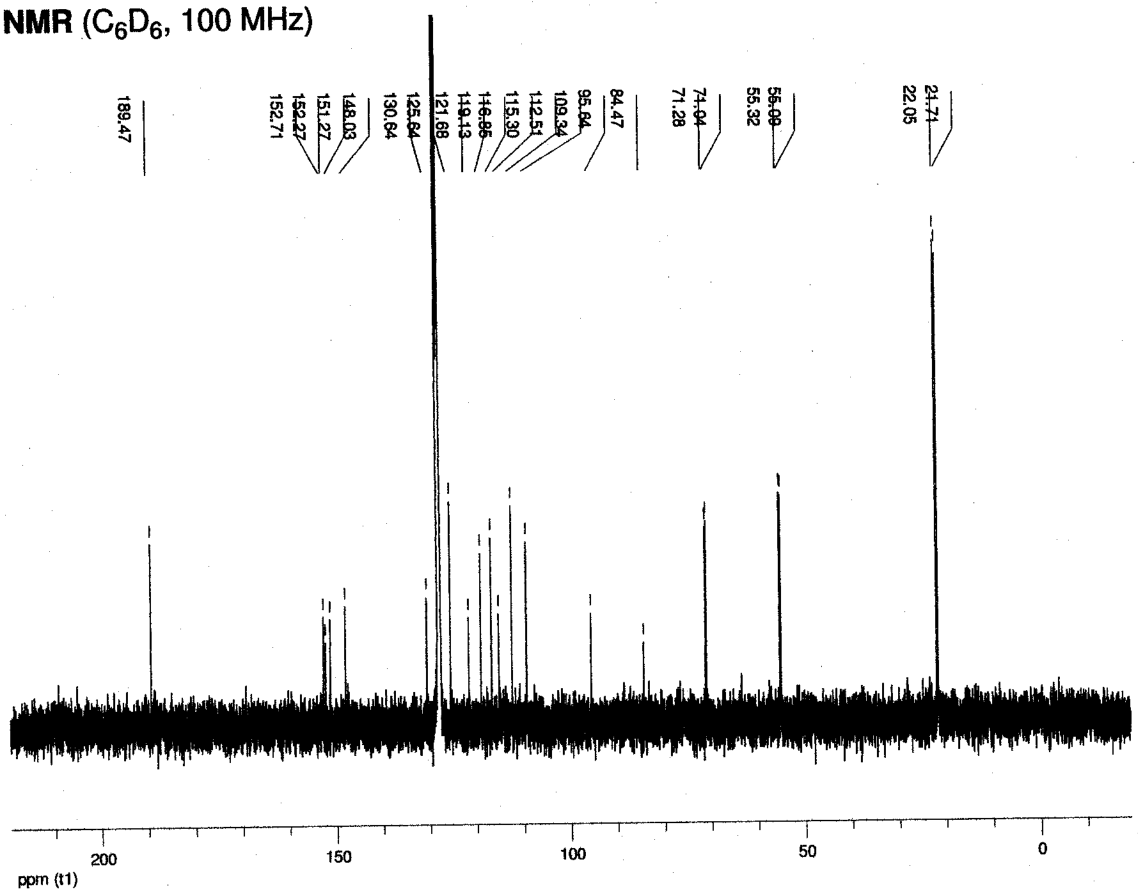


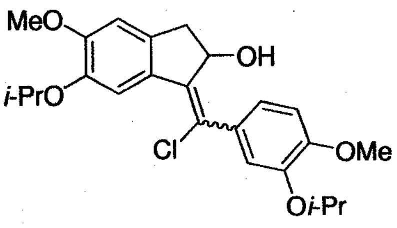


**3.95**

**$^1$H NMR** ($C_6D_6$, 400 MHz)

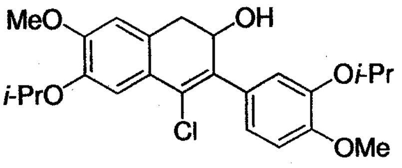
**$^{13}$C NMR** ($C_6D_6$, 100 MHz)





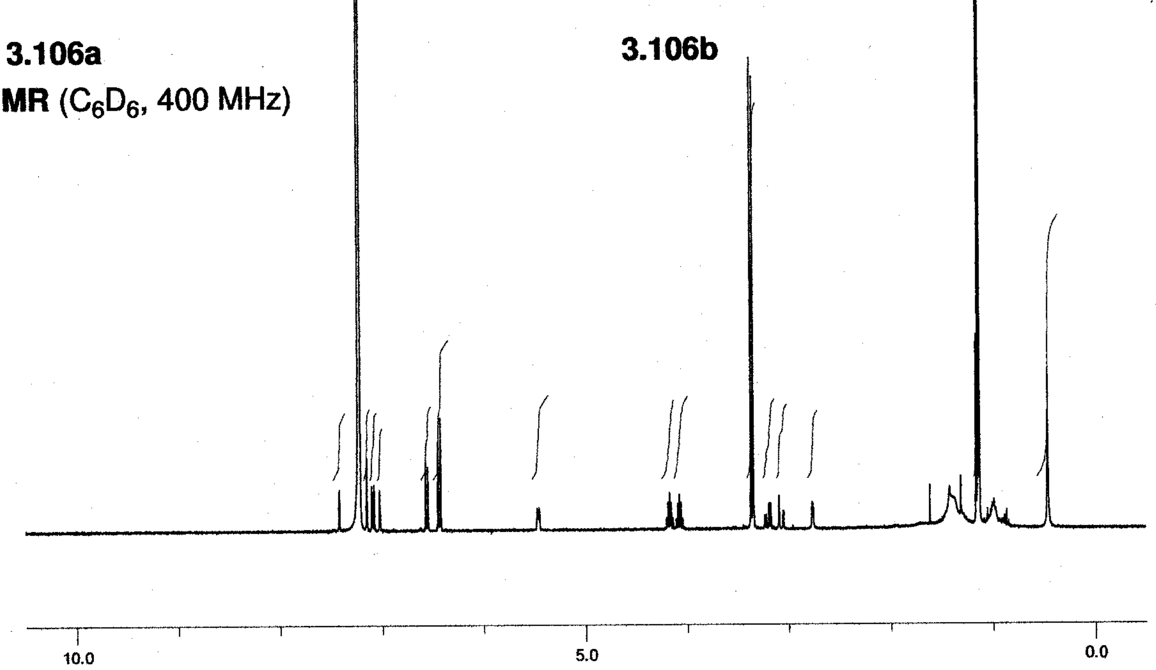
**3.106a**

**OR**

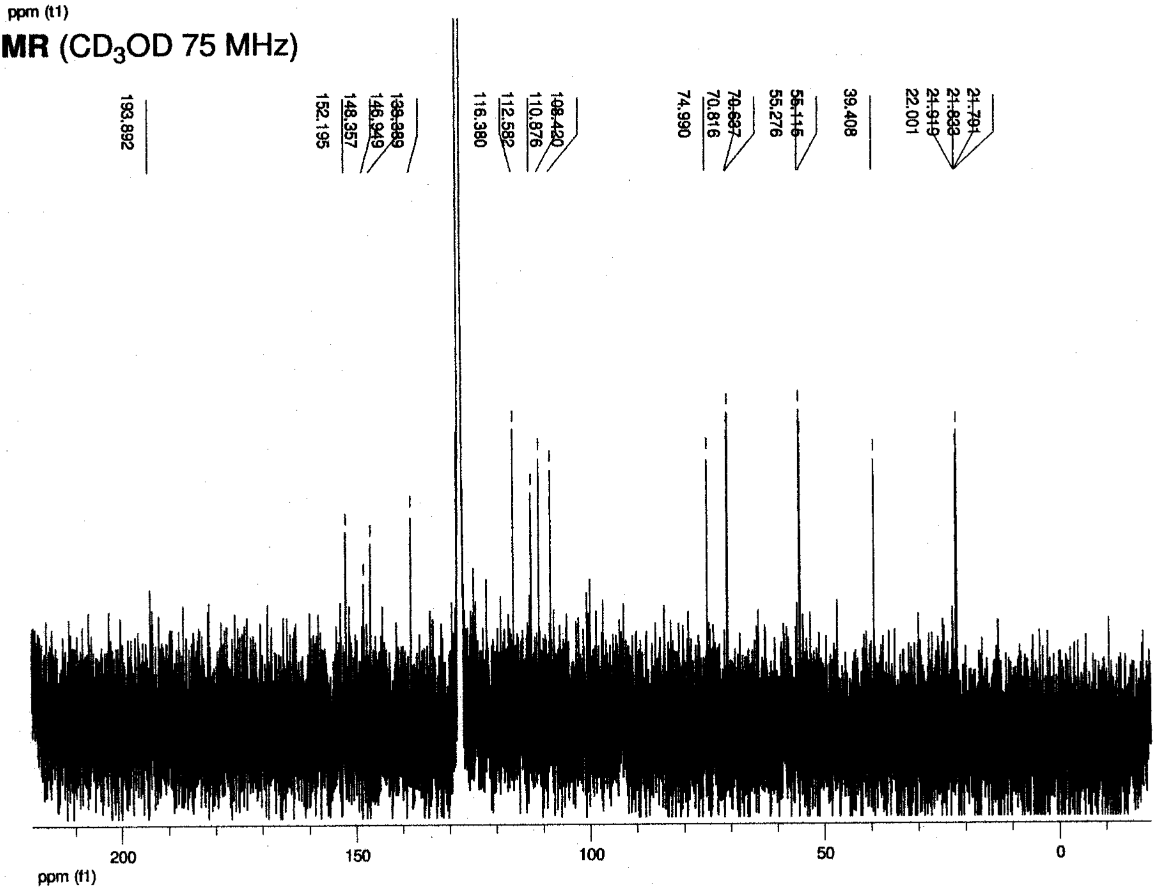


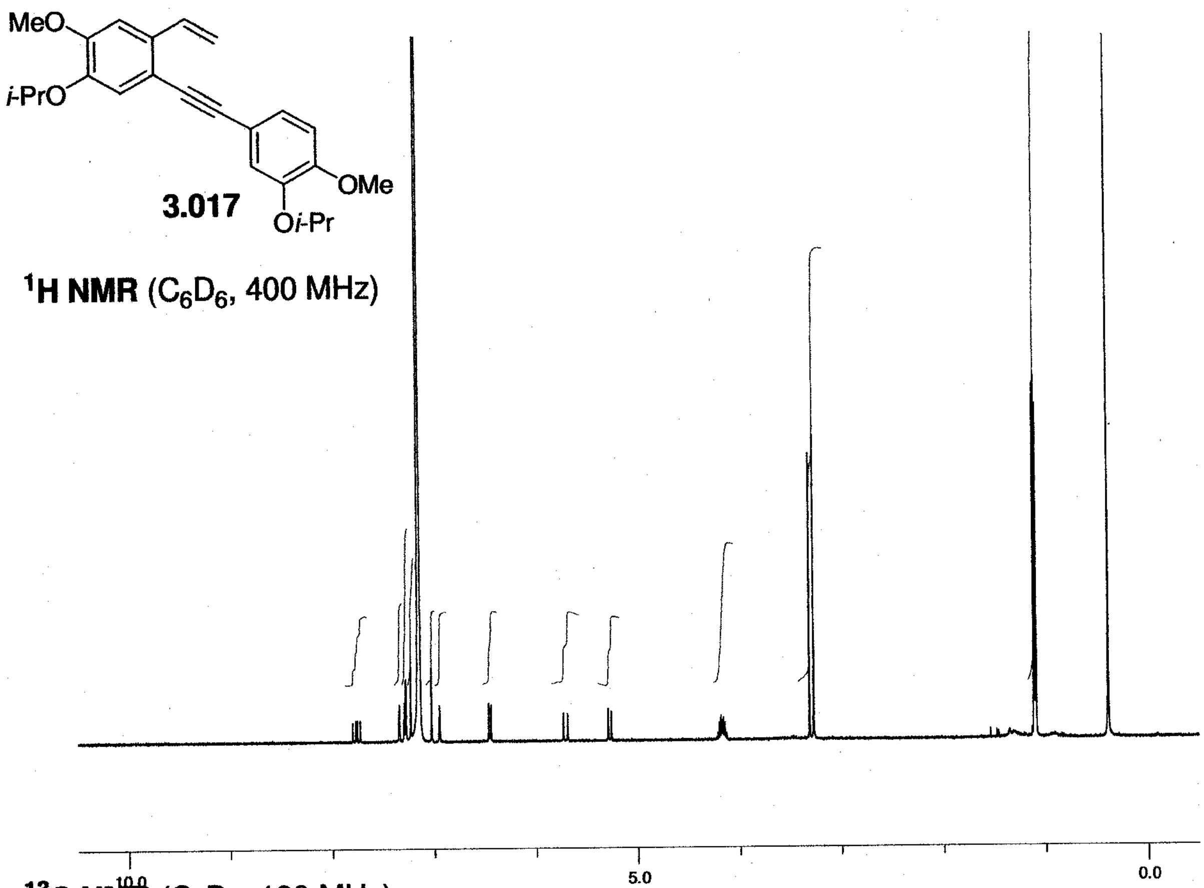
**3.106b**

**$^1$H NMR** ($C_6D_6$, 400 MHz)



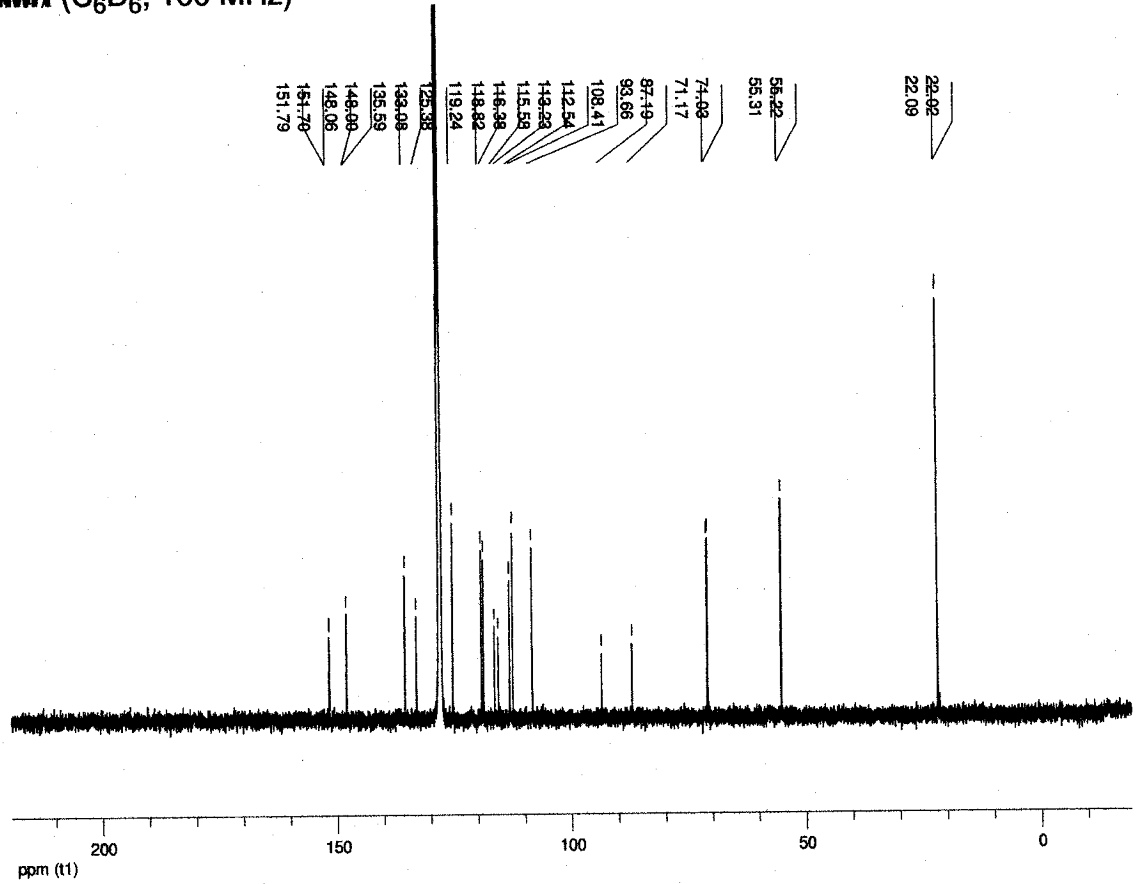
**$^{13}$C NMR** ($CD_3OD$ 75 MHz)

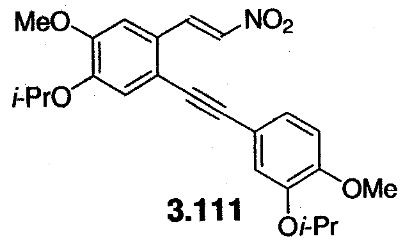



**3.017**

**$^1$H NMR** ($C_6D_6$, 400 MHz)

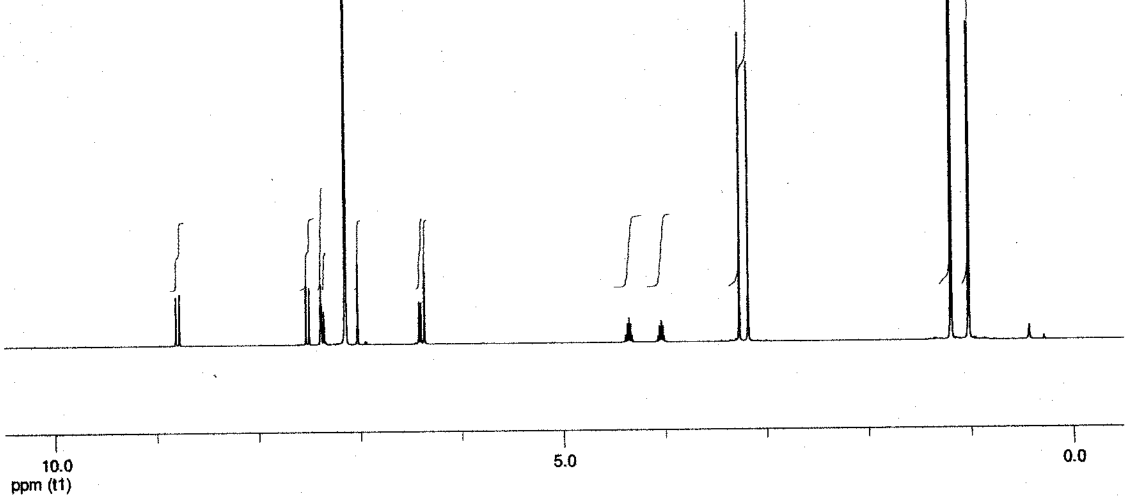
**$^{13}$C NMR** ($C_6D_6$, 100 MHz)



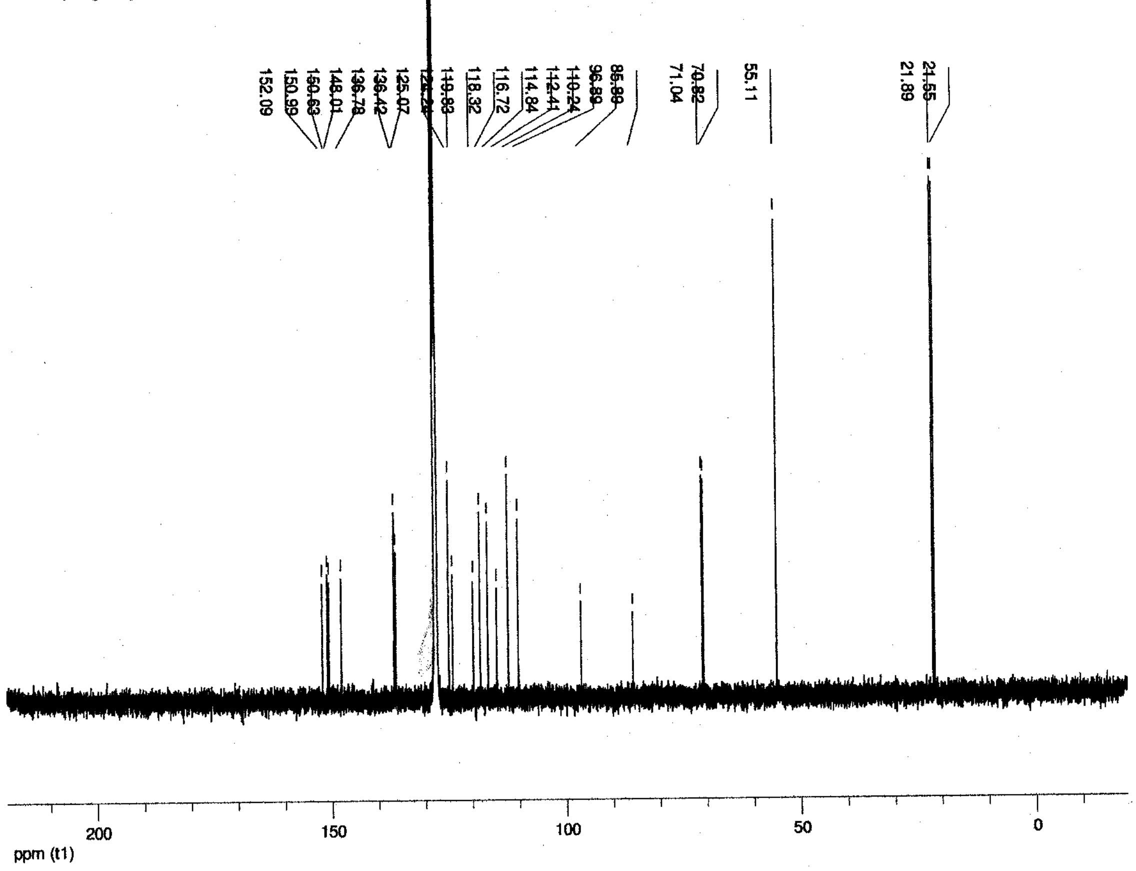


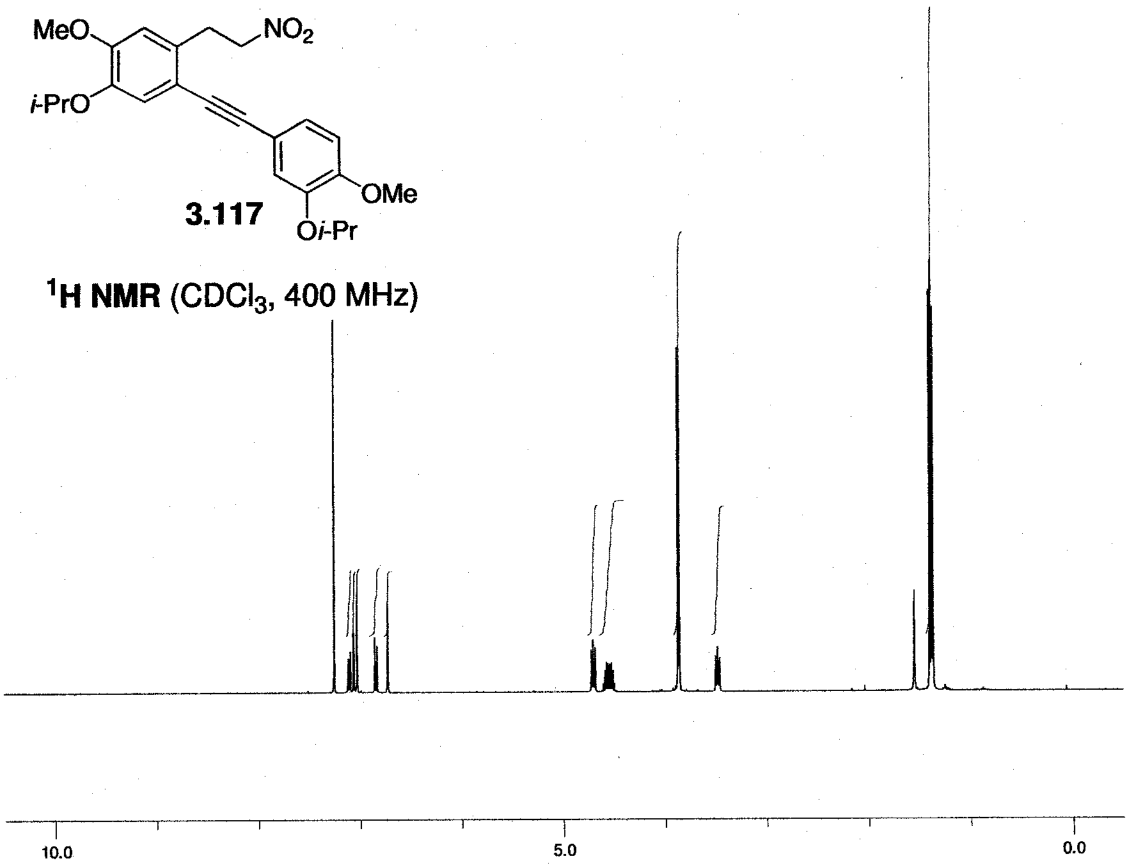
**3.111**

**$^1$H NMR** ($C_6D_6$, 400 MHz)



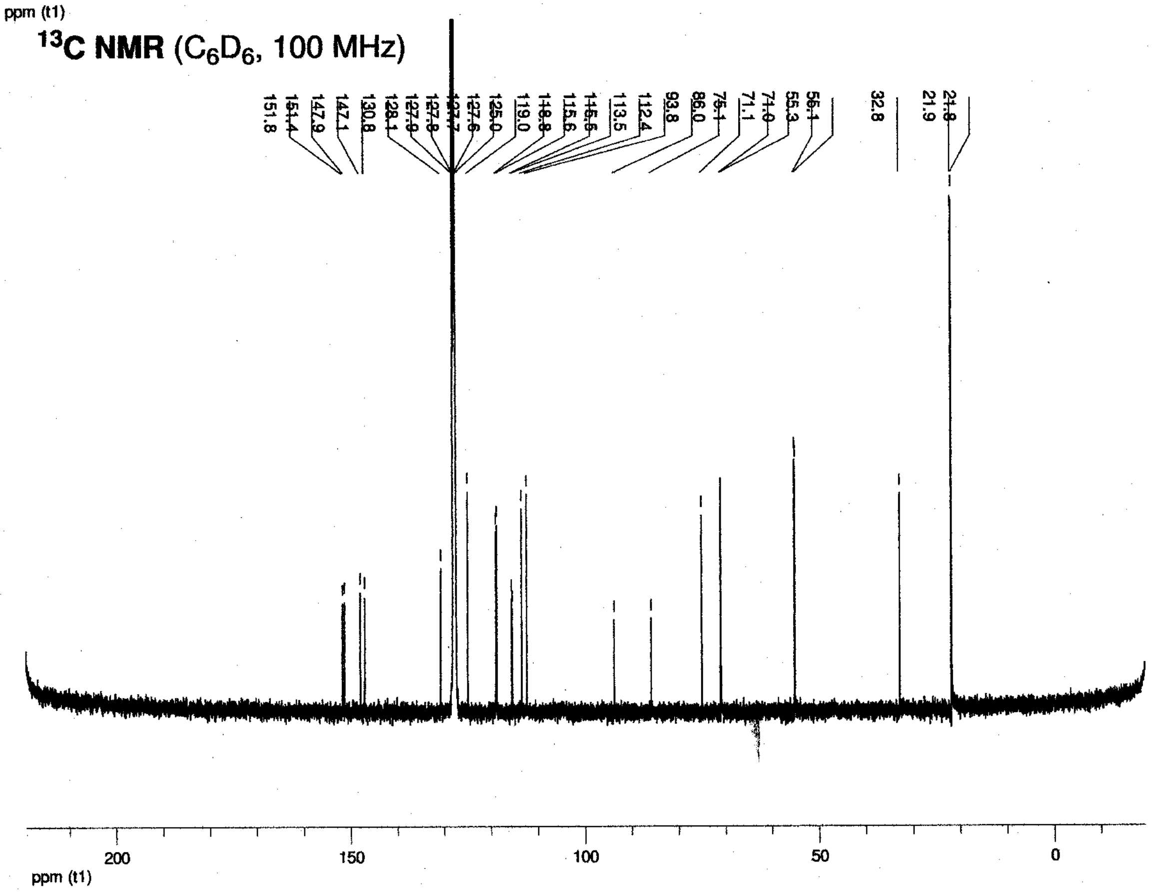
**$^{13}$C NMR** ($C_6D_6$, 100 MHz)



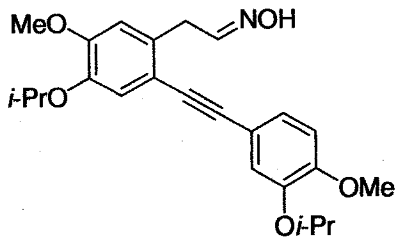


**3.117**

**$^1$H NMR** ($CDCl_3$, 400 MHz)

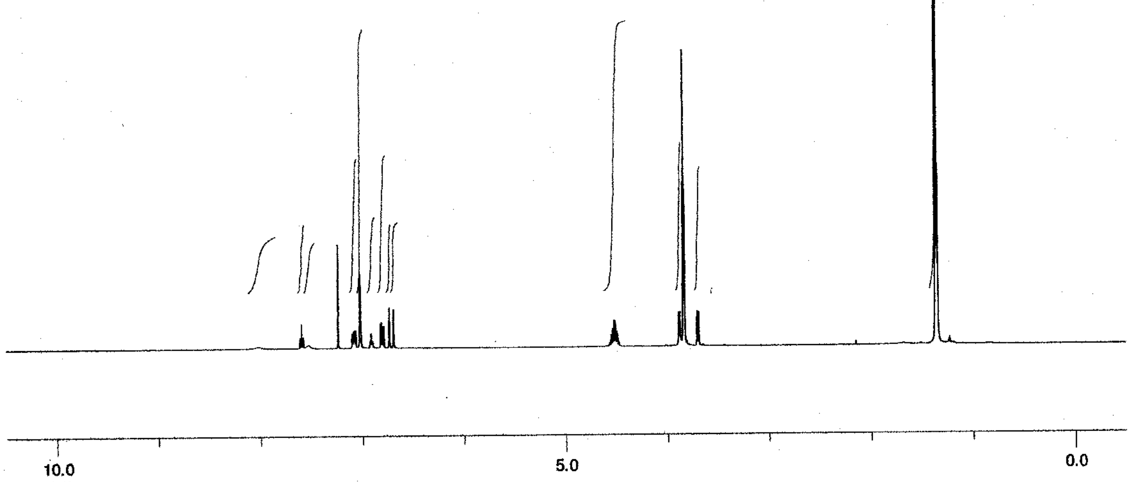


**$^{13}$C NMR** ($C_6D_6$, 100 MHz)

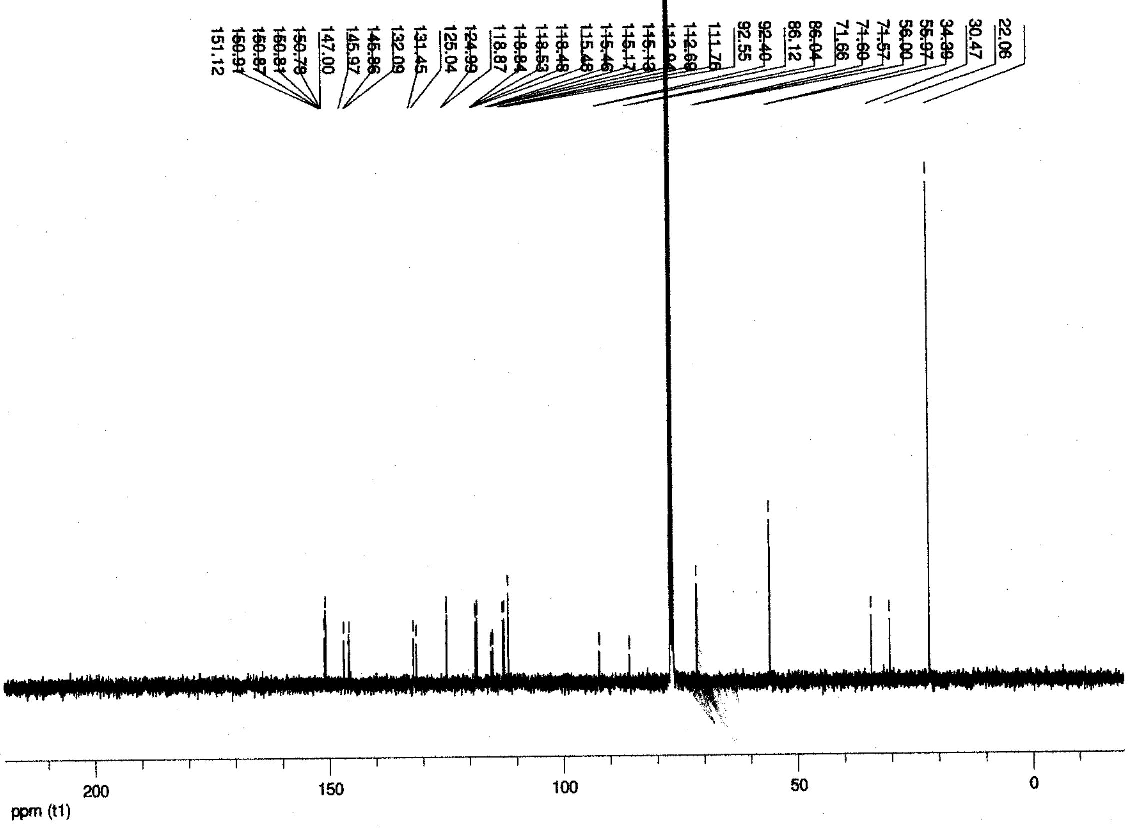


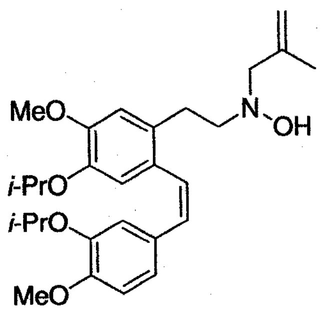
**3.118, Table 3.6, Entry 4**

**$^1$H NMR** (CDCl$_3$, 400 MHz)



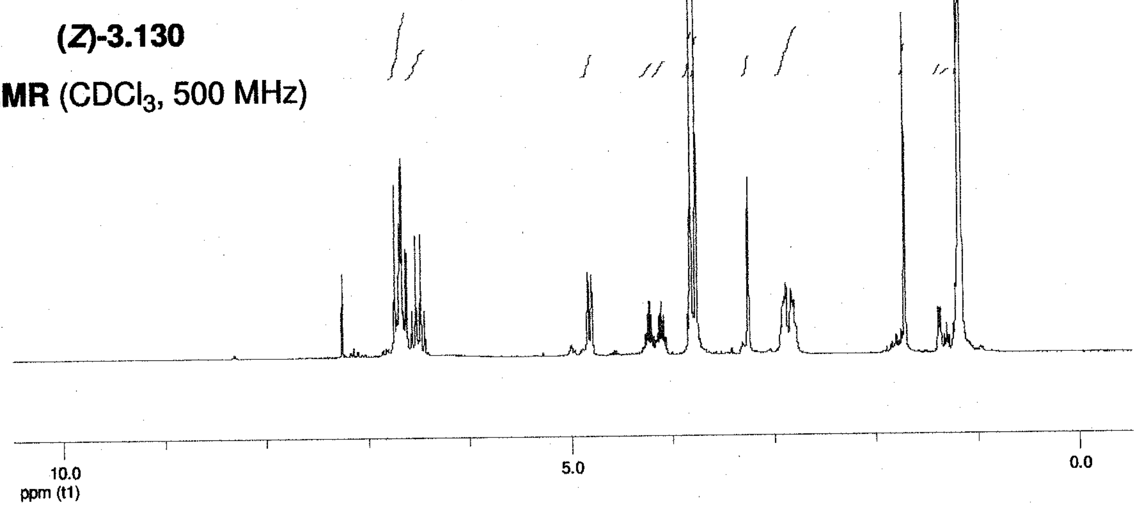
**$^{13}$C NMR** (CDCl$_3$ 100 MHz)



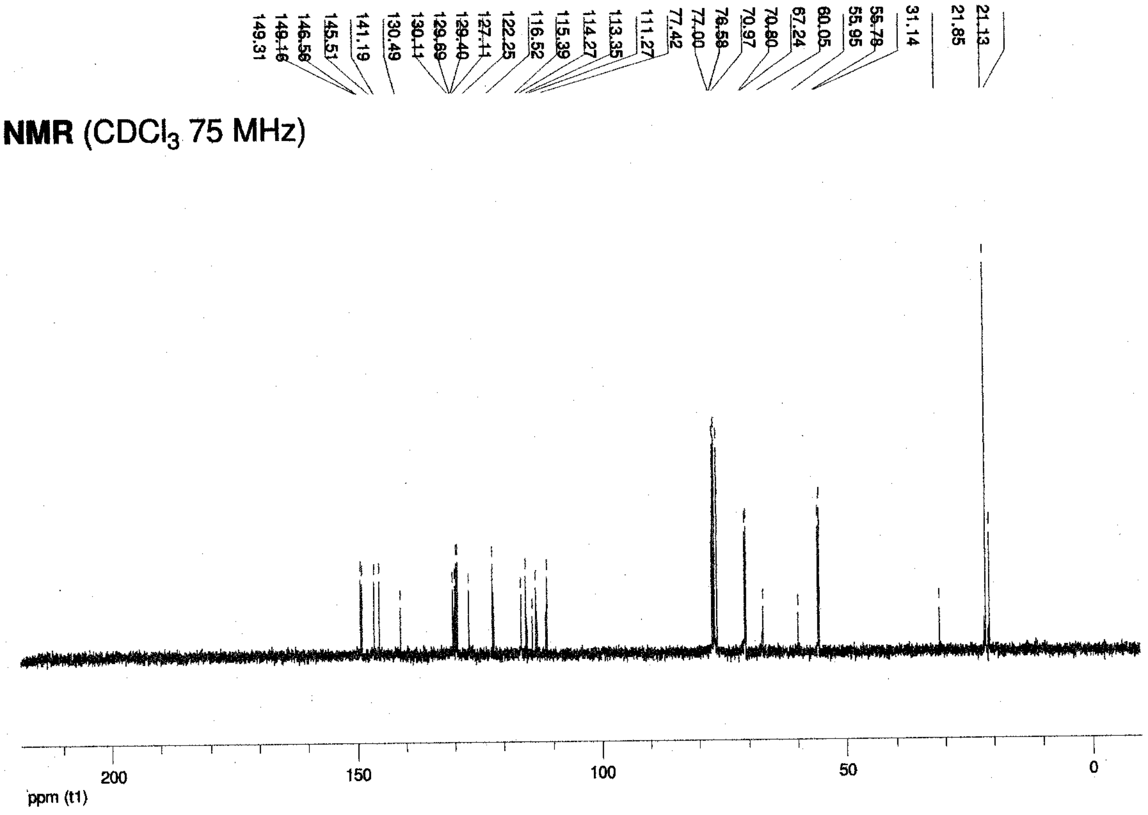


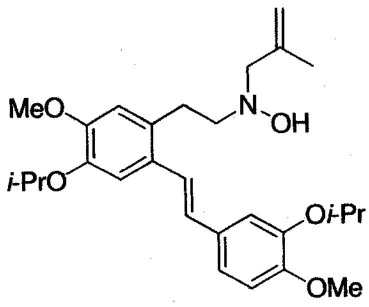
**(Z)-3.130**

**$^1$H NMR** (CDCl$_3$, 500 MHz)



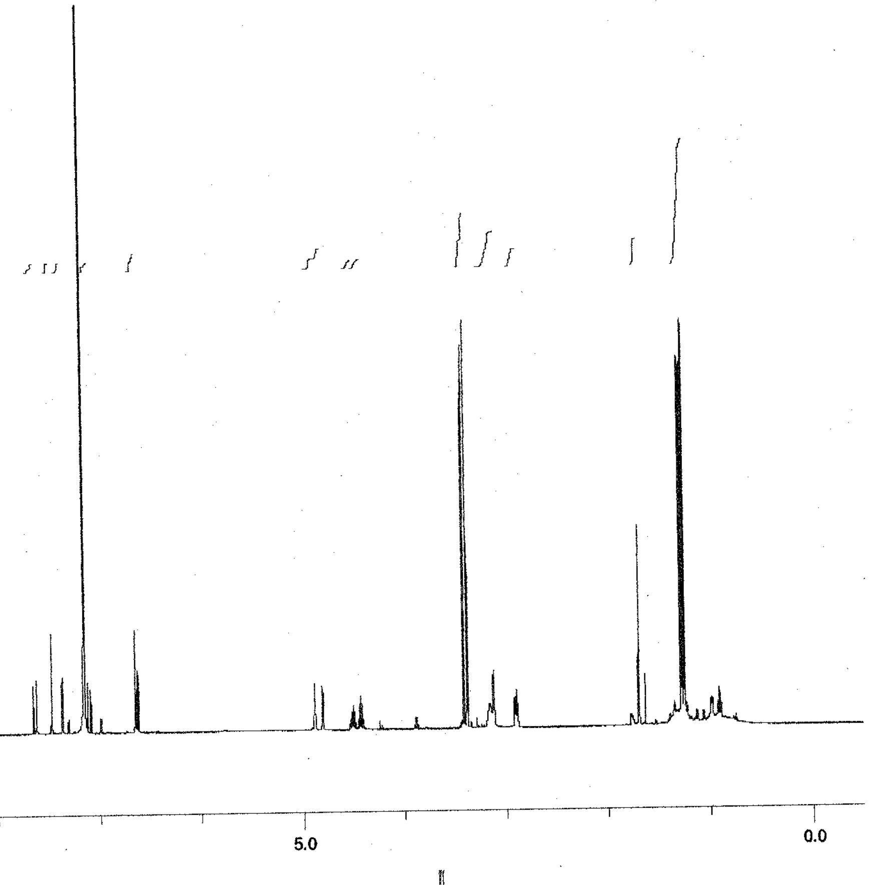
**$^{13}$C NMR** (CDCl$_3$ 75 MHz)



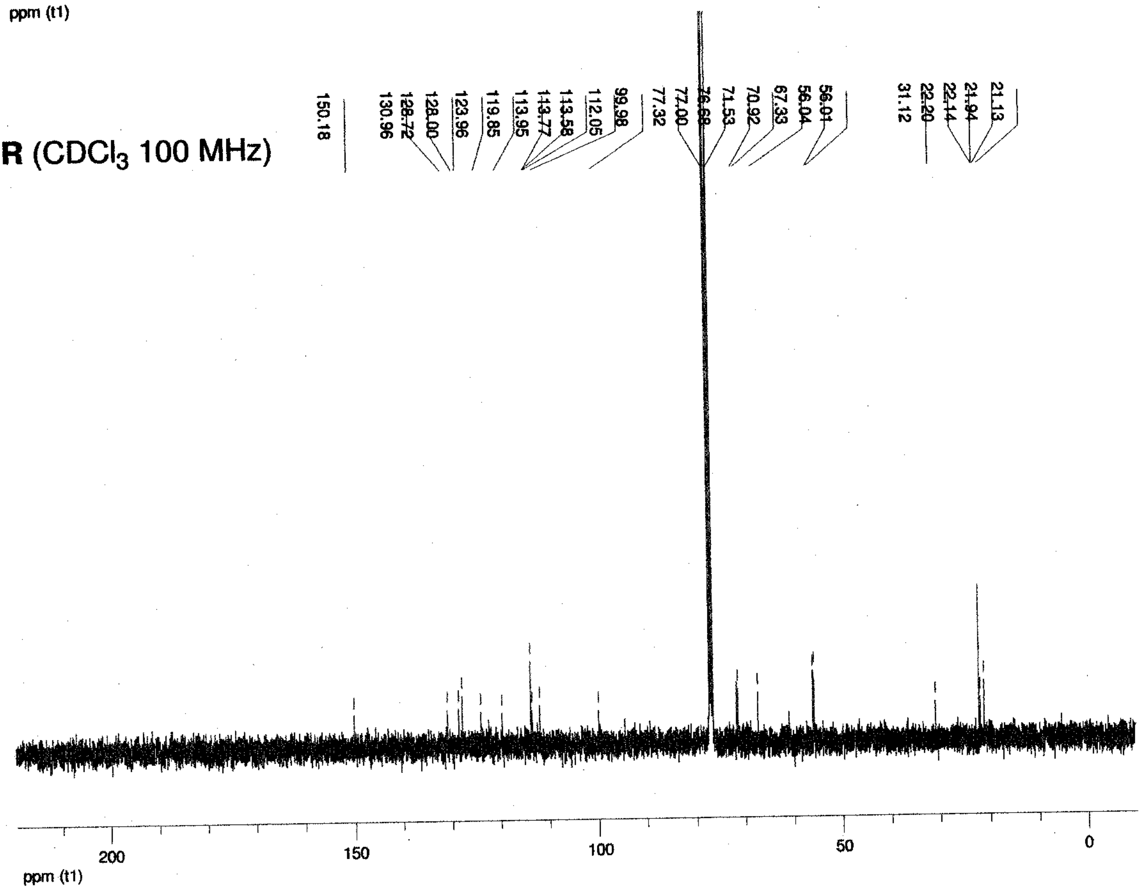


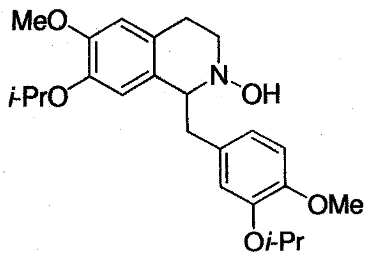
**(*E*)-3.134**

**$^1$H NMR** ($C_6D_6$, 500 MHz)



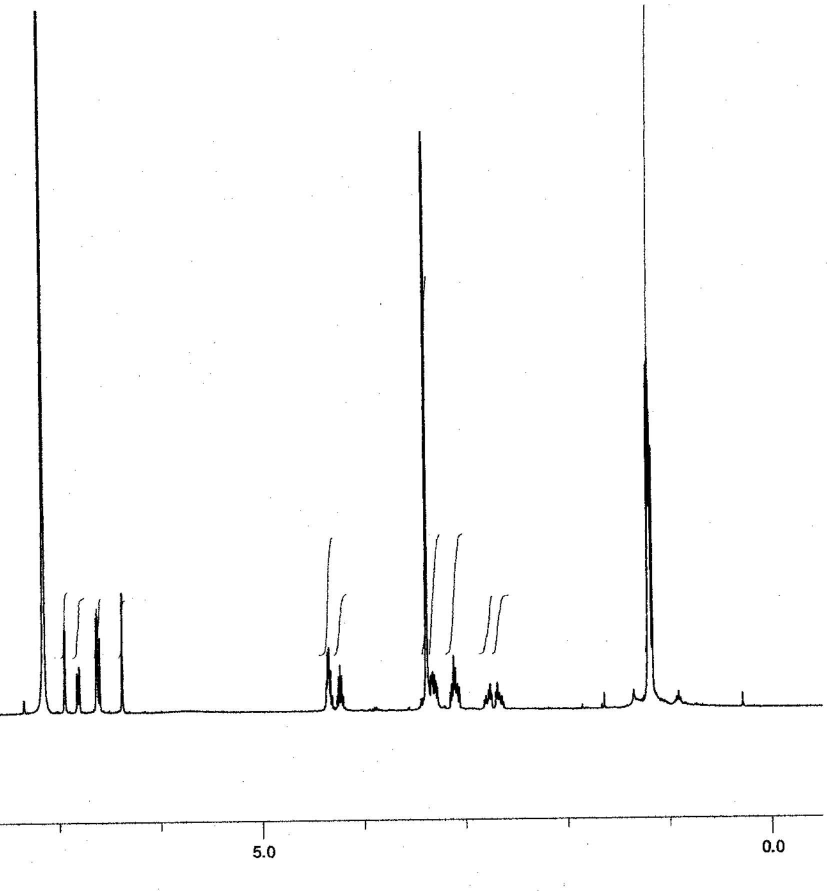
**$^{13}$C NMR** ($CDCl_3$ 100 MHz)



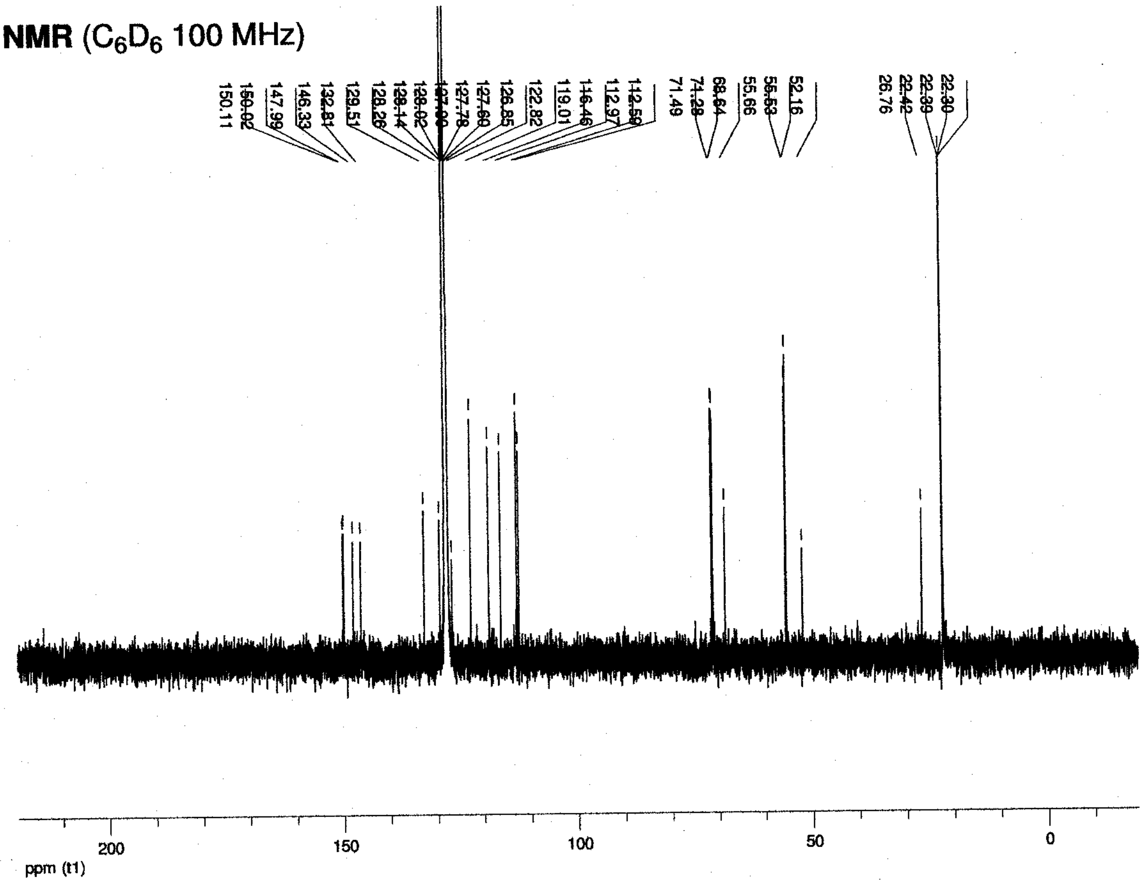


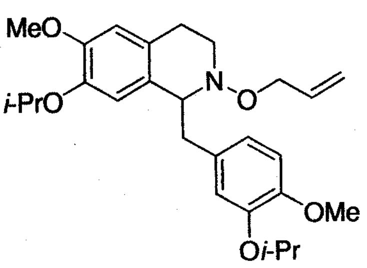
**3.120, Table 3.7, Entry 1**

**$^1$H NMR** ($C_6D_6$, 400 MHz)



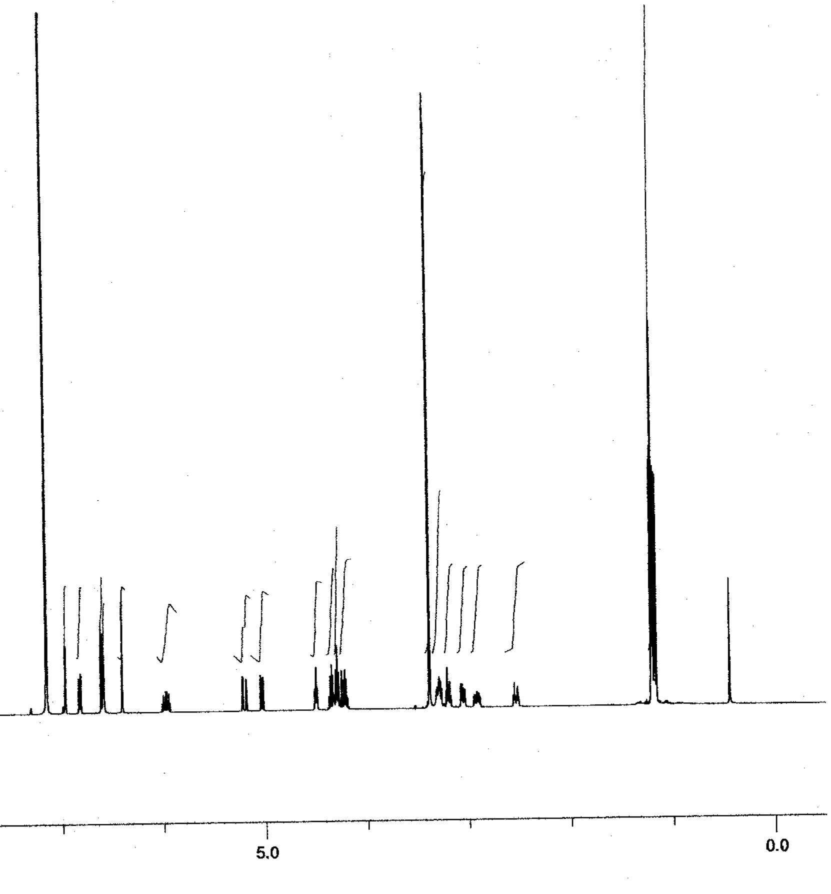
**$^{13}$C NMR** ($C_6D_6$ 100 MHz)



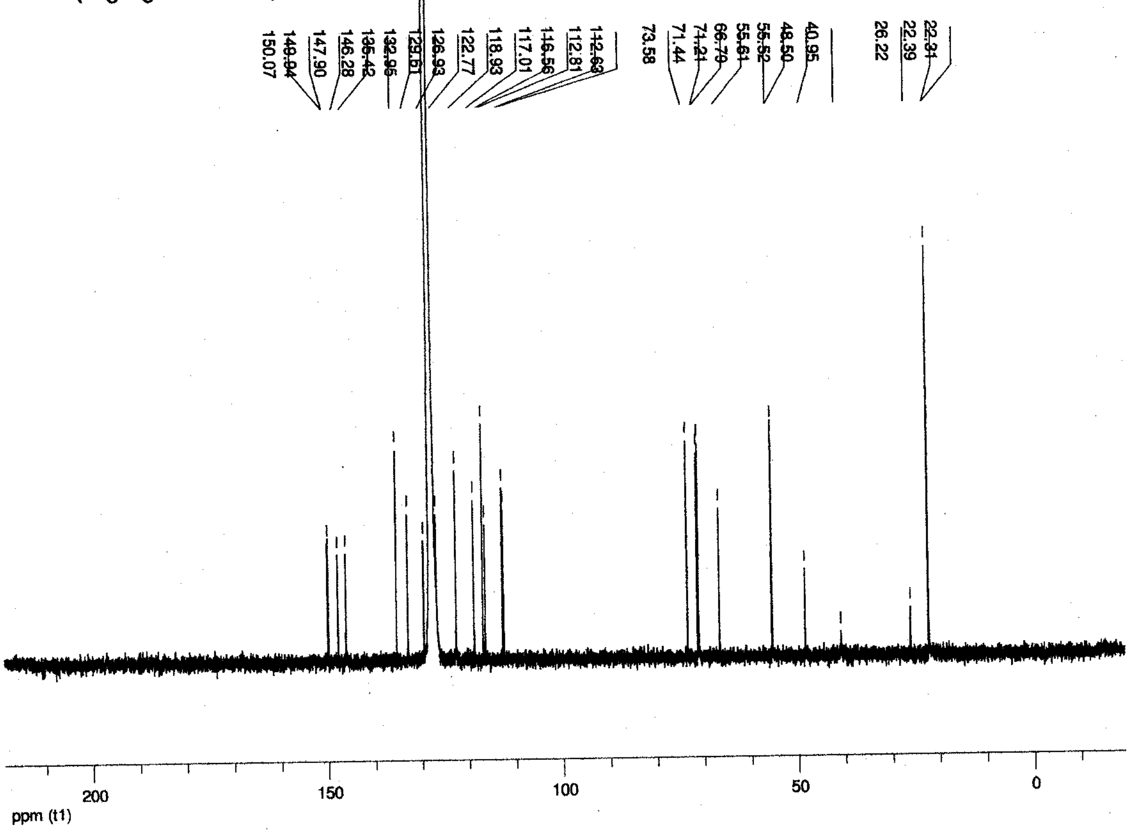


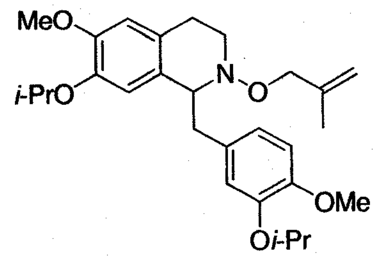
**3.131, Table 3.7, Entry 3**

**$^{1}$H NMR** ($C_6D_6$, 500 MHz)



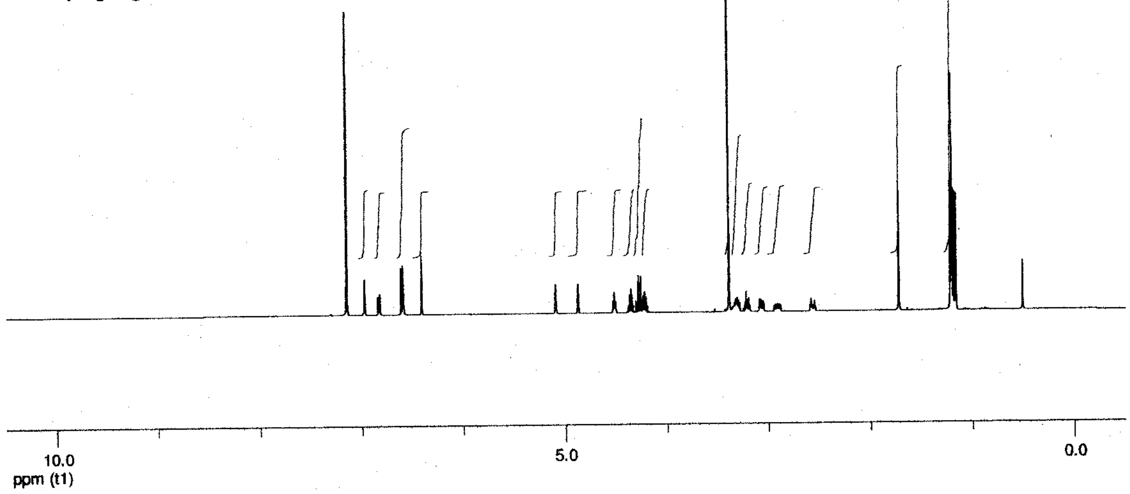
**$^{13}$C NMR** ($C_6D_6$ 75 MHz)



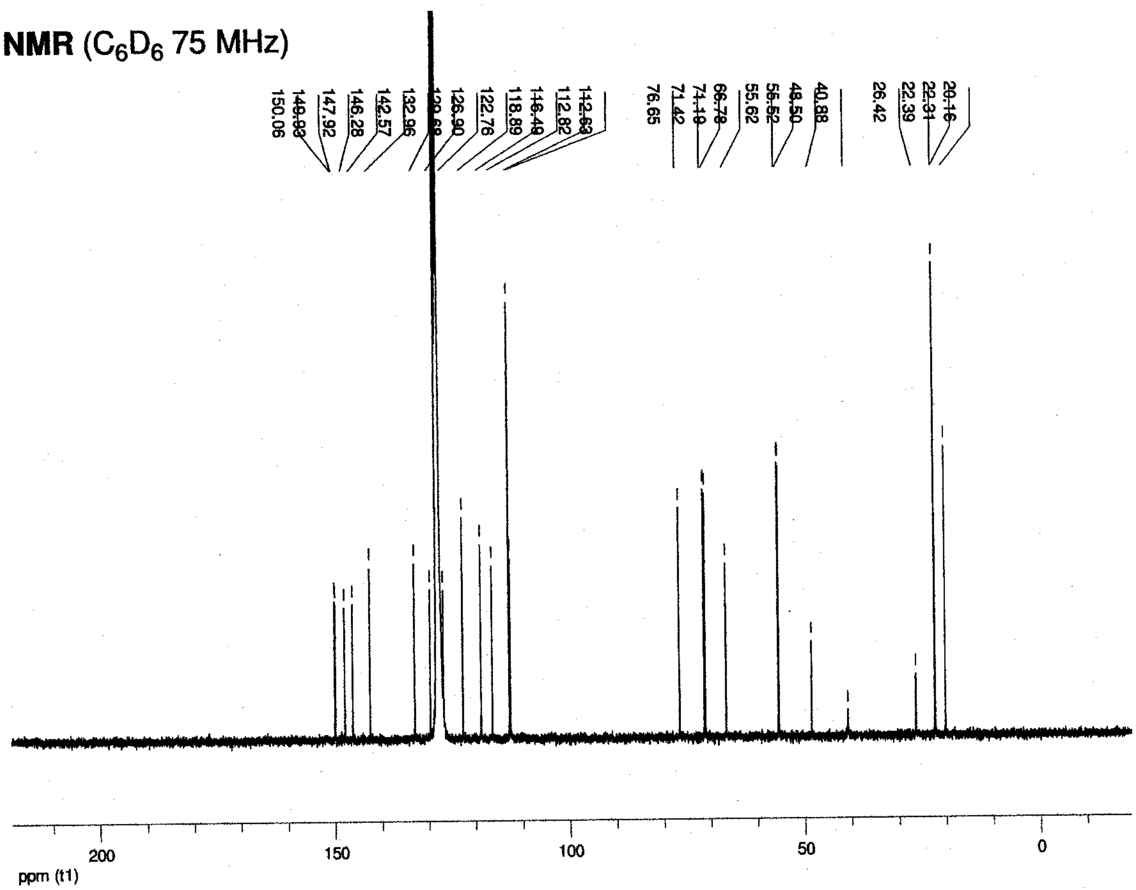


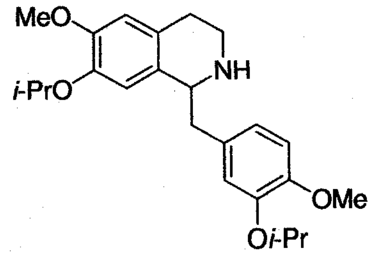
**3.132, Table 3.7, Entry 4**

**$^1$H NMR** ($C_6D_6$, 500 MHz)



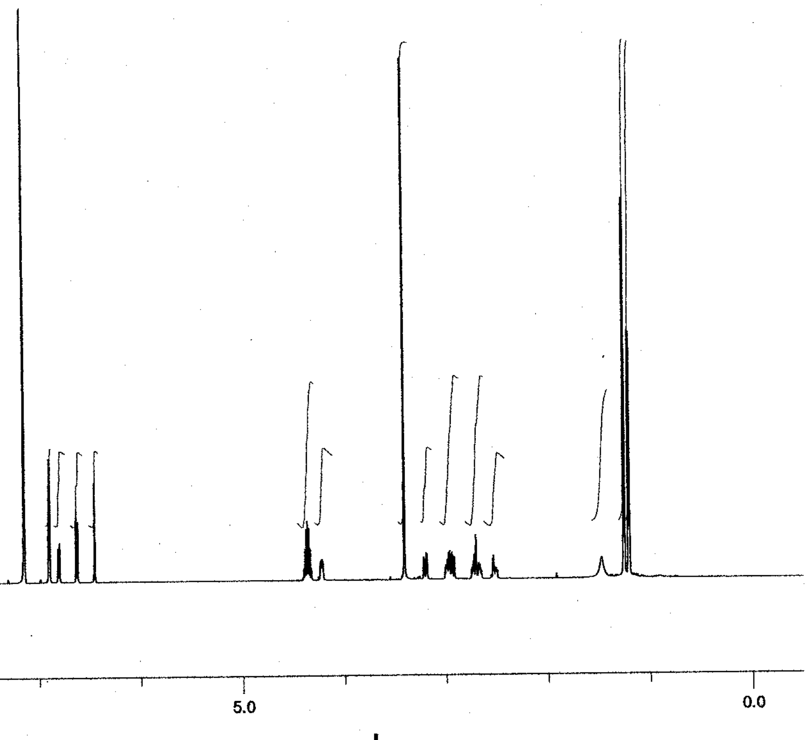
**$^{13}$C NMR** ($C_6D_6$ 75 MHz)



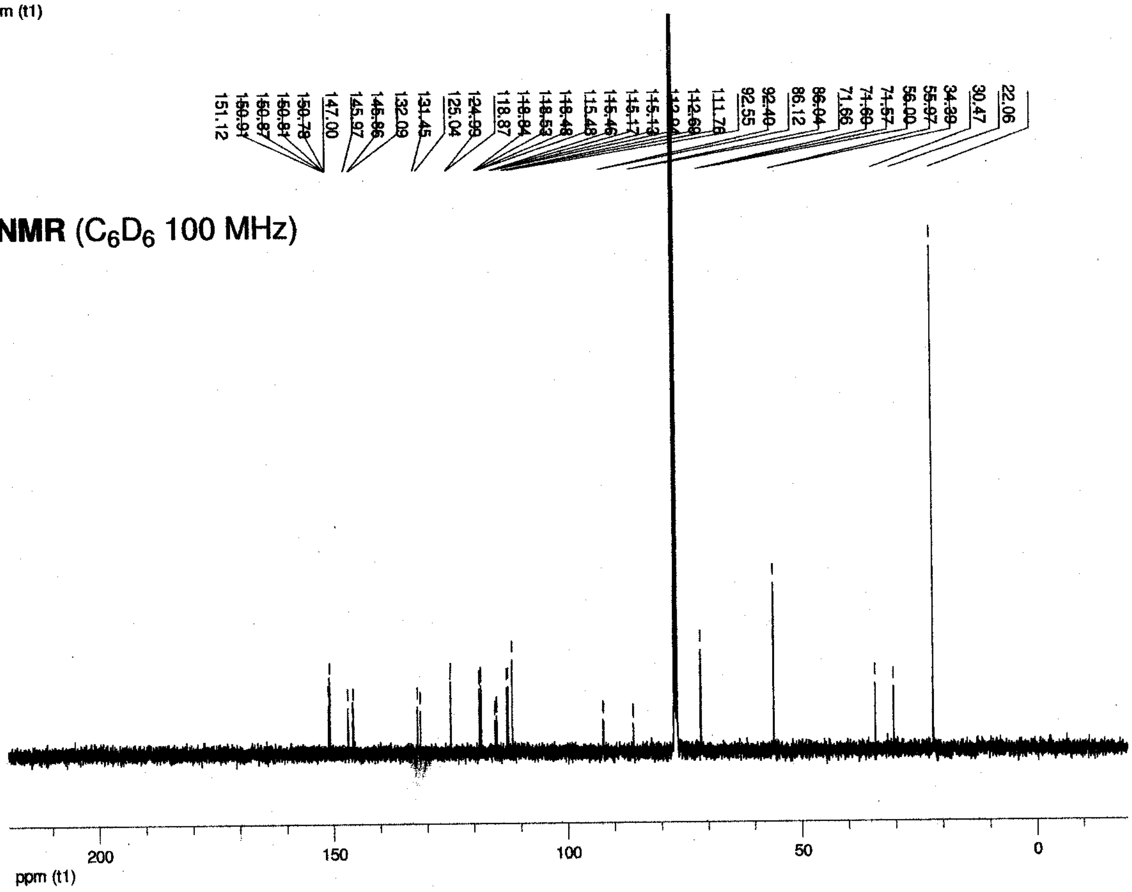


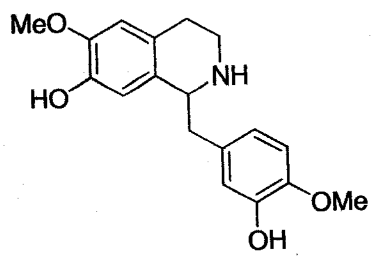
**3.135**

**$^1$H NMR** ($C_6D_6$, 500 MHz)



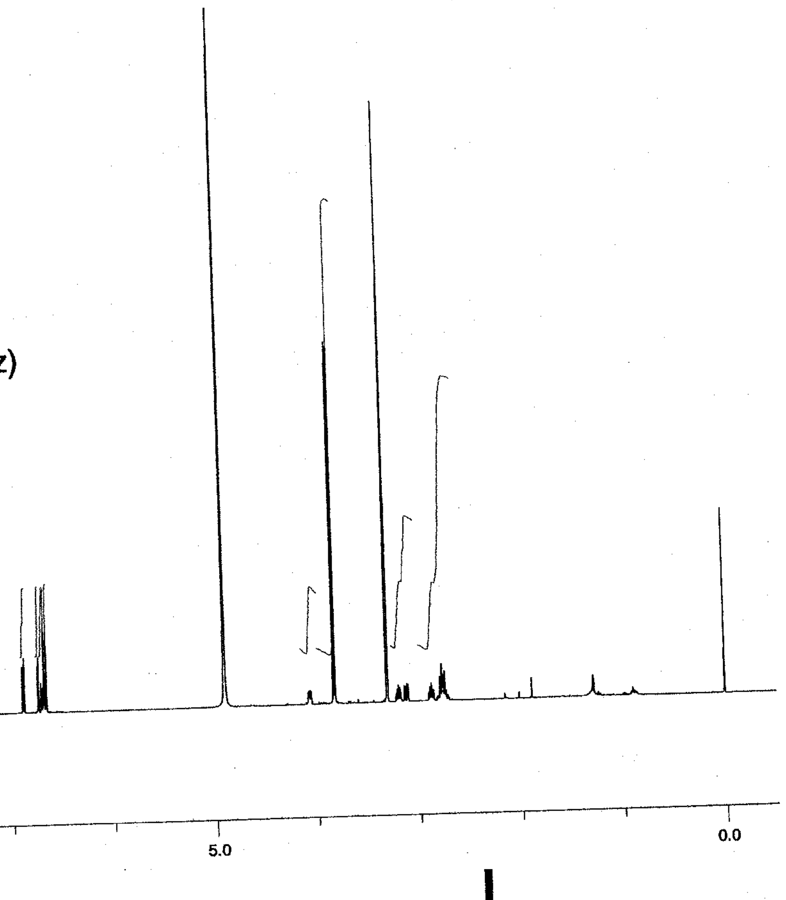
**$^{13}$C NMR** ($C_6D_6$ 100 MHz)



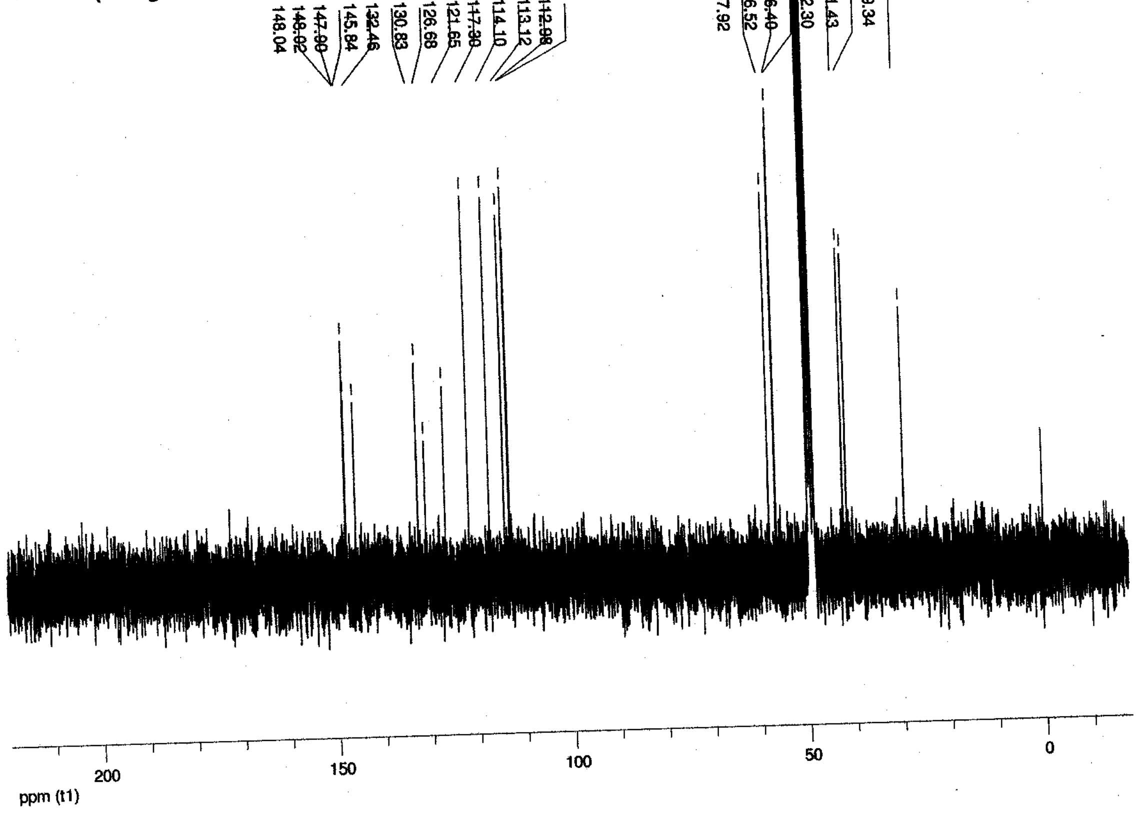


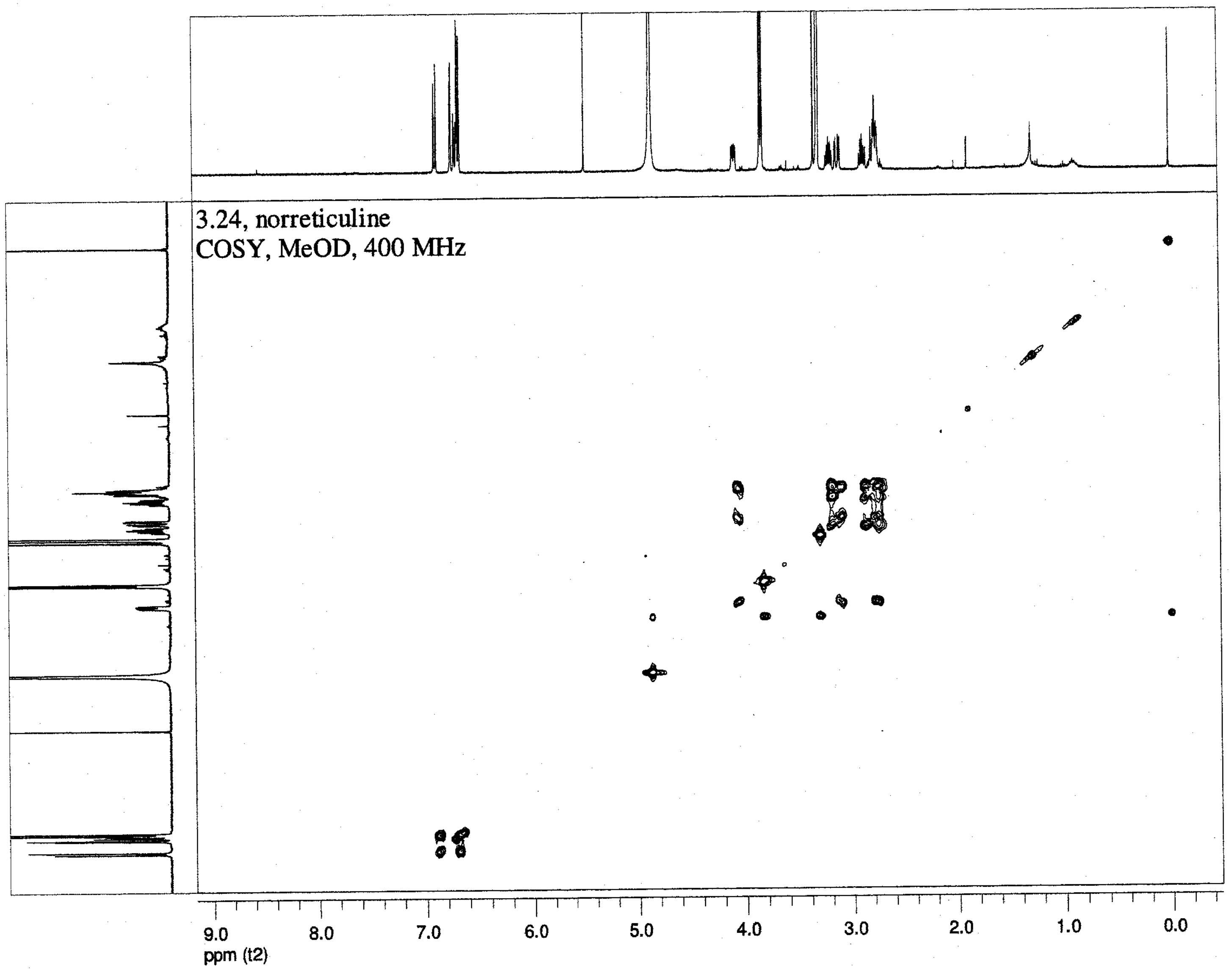
**3.24,** norreticuline

**$^1$H NMR** (CD$_3$OD, 500 MHz)

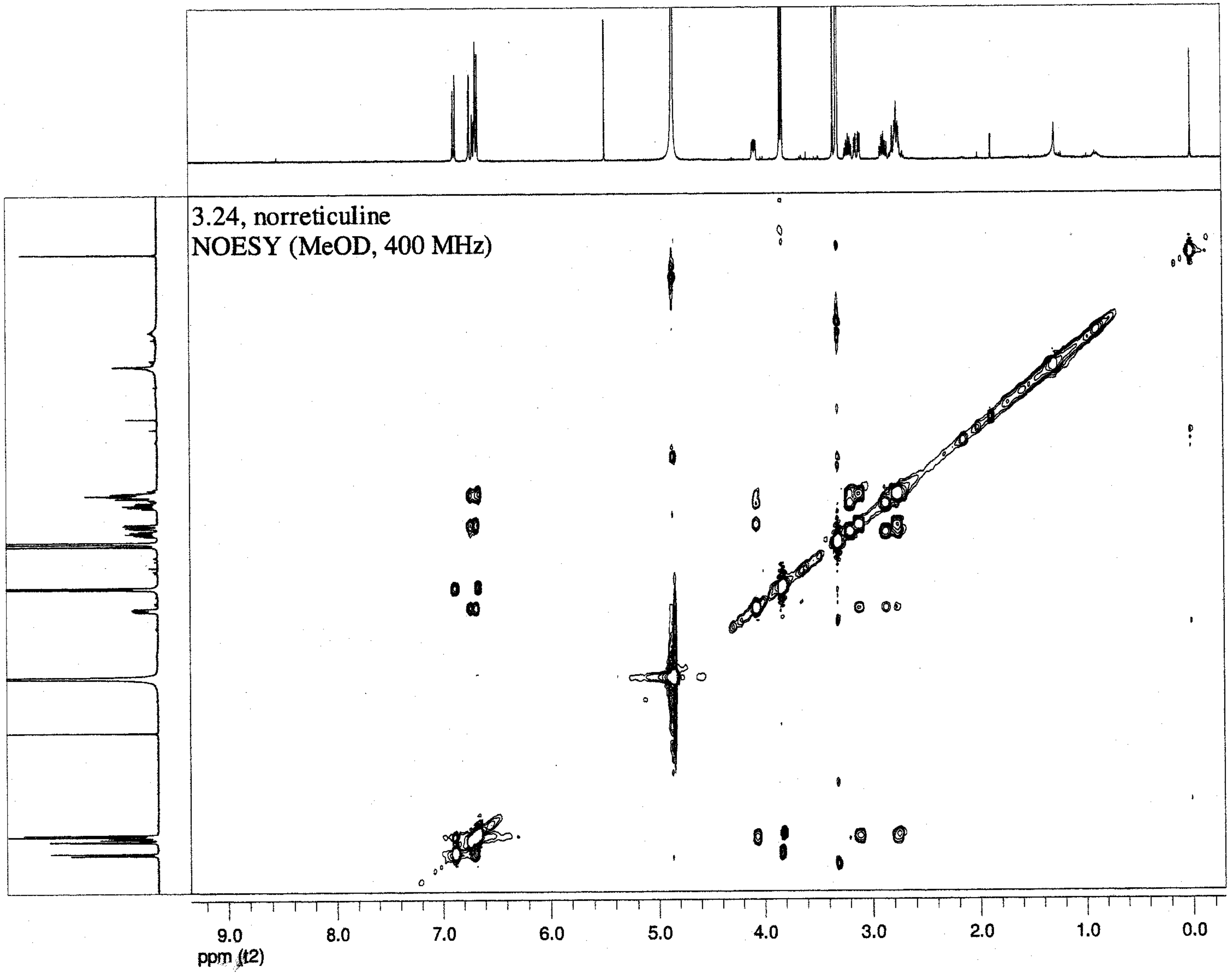


**$^{13}$C NMR** (CD$_3$OD 75 MHz)

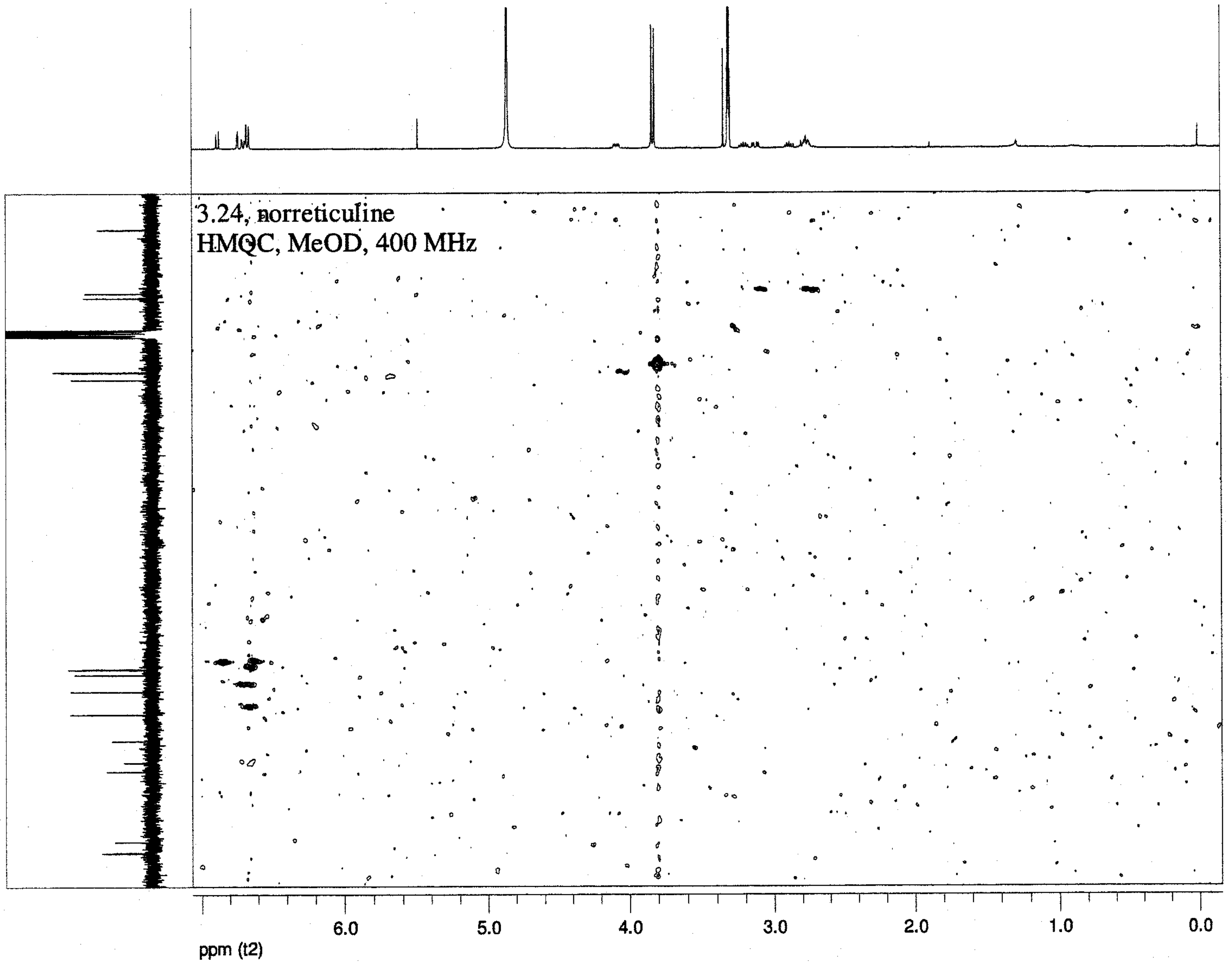




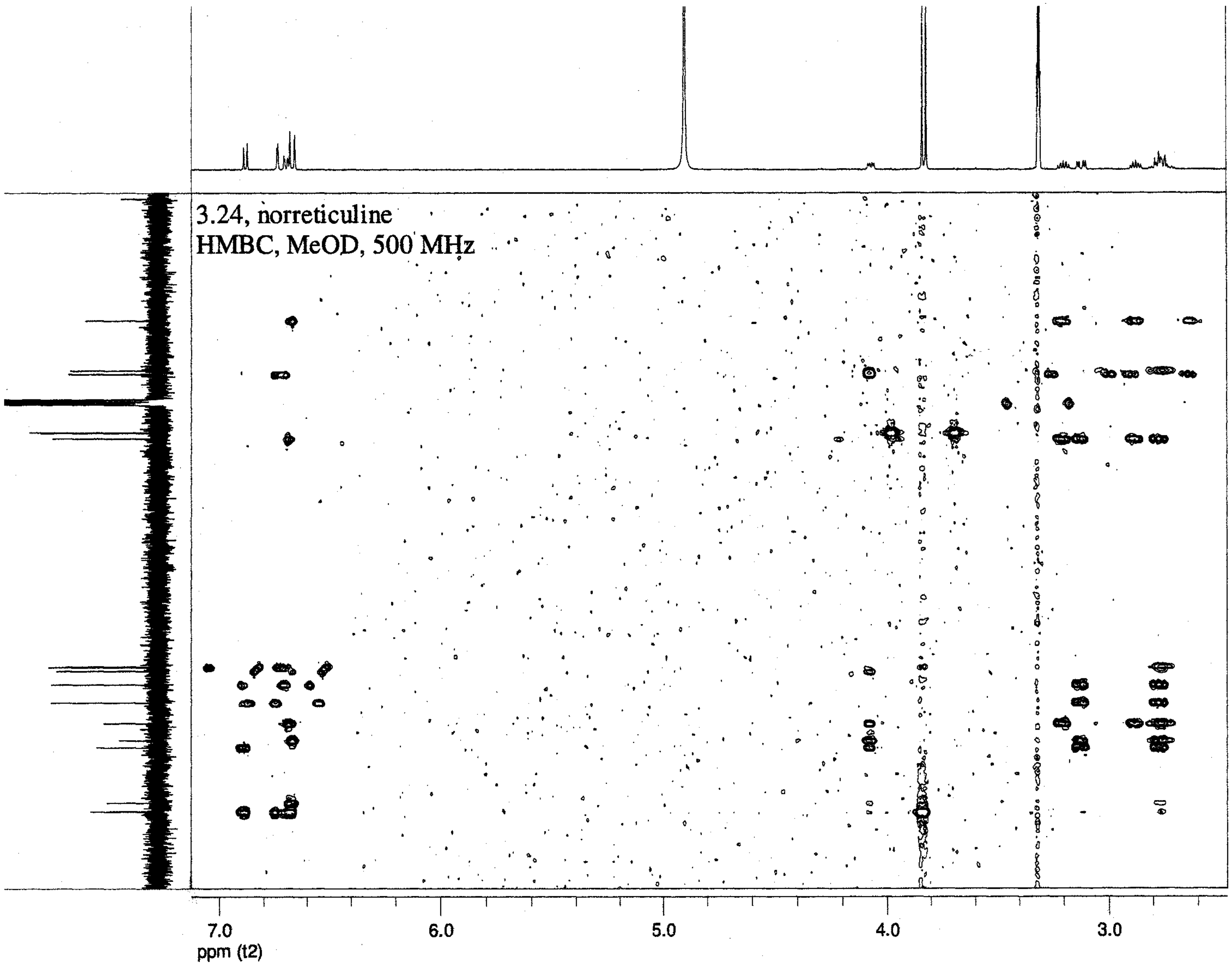
3.24, norreticuline
COSY, MeOD, 400 MHz



3.24, norreticuline
NOESY (MeOD, 400 MHz)



3.24, norreticuline
HMQC, MeOD, 400 MHz



3.24, norreticuline
HMBC, MeOD, 500 MHz