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# Synthesis of the Bicyclic Core of Pyrrolizidine Alkaloids

by

Fatmagul Tuluoglu

Thesis

Submitted to the Department of Chemistry

Eastern Michigan University

in partial fulfillment of the requirements

for the degree of

MASTER OF SCIENCE

in

Chemistry

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April 22, 2009

Ypsilanti, Michigan

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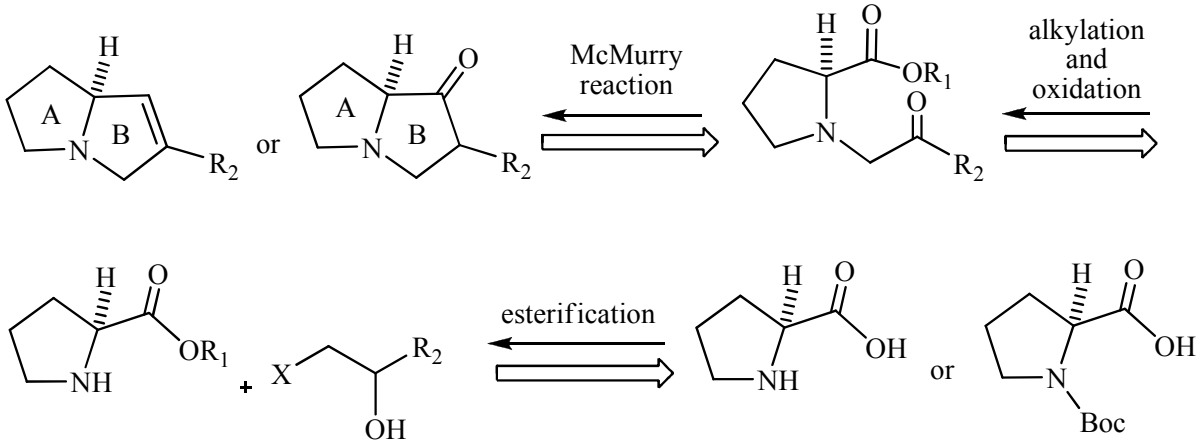
I would like to take this opportunity to thank many people who supported me intellectually, morally, and financially during my Master Degree in Science. First of all, I would like to thank Dr. Harriet Lindsay for not only giving me the chance to perform organic synthesis reactions and to work on a very important project but also for her patience and understanding. I would like to thank Dr. Harriet Lindsay and Eastern Michigan University for providing financial support for me to pursue my education. Also, I would like to thank the Chemistry Department Head; Dr. Ross Nord, the Department Graduate Advisors; former and present, Dr. Krish Rengan and Dr. Timothy Brewer; and the Chemistry faculty members for their mentoring and guidance. I would like to thank my thesis committee members, Dr. Arthur Howard and Dr. Timothy Friebe, for their outstanding assessments. I would like to thank Dr. Cory Emal, Dr. Gregg Wilmes, and their research groups for creating a pleasant working environment. I would like to thank all the research group members of Dr. Harriet Lindsay for their contributions, endeavors, and teamwork. Finally, I would like to thank my all beloved ones especially my husband for their unconditional love and support.

## ABSTRACT

Pyrrolizidine alkaloids are a large class of natural products whose members exhibit a variety of biological properties including potential applications toward the treatment of cancer, diabetes, and viral infections such as HIV. In addition, some of these compounds exhibit insect antifeedant activity, and so have potential applications in the agricultural industry for the protection of crops.

For these reasons, we were interested in developing a method to form the bicyclic alkaloid core that could be functionalized to generate many pyrrolizidine alkaloids. Specifically, our goal was to synthesize the pyrrolizidine B-ring by a novel McMurry cyclization strategy (**Scheme 1**). The synthesis of the McMurry reaction precursors and efforts at optimizing the key McMurry reaction will be described.

**Scheme 1**



## TABLE OF CONTENTS

Acknowledgements……ii

Abstract……..……..iii

List of Tables……..……...……vi

List of Figures…….....viii

Chapter 1: Introduction……..1

Chapter 2: Literature Review…….5

I. Introduction……....5

A. McMurry reaction: discovery and initial optimization……..…….....5

B. Mechanism……7

II. Examples of Intramolecular McMurry reactions……..…..…….....9

A. Aldehyde-aldehyde cyclizations……...9

B. Aldehyde-ketone cyclizations…….14

1. Cembranoid diterpene macrocyclizations……..14

2. Other aldehyde-ketone cyclizations……...17

C. Ketone-ketone cyclizations……19

D. Ketone-amide cyclizations……..…….....25

E. Ketone-ester cyclizations…….……...……..27

III. Summary……29

Chapter 3: Results and Discussion……...31

I. Synthesis of proline esters……...31

II. Alkylation and oxidation of proline esters…….34

III. McMurry reductive coupling reaction…….....51

IV. Identification of McMurry products……...58

V. New directions……...…….62

VI. Conclusion…….66

Chapter 4: Experimental……..67

References……79

## LIST OF TABLES


Table Page

1 Intermolecular reductive coupling of cyclododecanone (**23**) using Ti/K reagent system……..6

2 Intramolecular dicarbonyl coupling with $TiCl_3$, Zn(Cu) reagent system……...……...7

3 McMurry reaction of keto-aldehyde **83a-c**……19

4 McMurry reaction of diketones **86a-c**…….……..20

5 McMurry reactions of diketones **88**……...……21

6 McMurry reaction of ammonium diketones **96**…….……..23

7 McMurry reaction of keto esters **110**…….28

8 McMurry reaction of keto diesters **116**…..……..……...29

9 Attempts at one-step formation of proline benzyl ester **14c**……..33

10 Alkylation of proline methyl ester **14a** and proline ethyl ester **14b** with 2-iodoethanol…. ……...……36

11 Oxidation of amino alcohol **120a** …….……....37

12 Cleavage of the crude 1,2-diol **120b**……..……..40

13 Microwave-assisted alkylation of proline ethyl ester **14b** with (2,3-epoxypropyl) benzene…..…….....…….41

14 Oxidation of amino alcohol **128**……..…...…...……...43

15 Oxidation of amino alcohol **131**……...……. ……..44

16 Oxidation of amino alcohol **133**…….……..……46

17 Microwave-assisted alkylation of proline benzyl ester **14c** with (2,3-epoxypropyl)benzene…….……..49

18 McMurry reaction of keto ester **13a** with $TiCl_4$-Zn-THF reagent system……...…54

19 McMurry reaction of keto ester **13a** with various Ti(II) sources……..……56

20 McMurry reaction of keto ester **13d** and **13f** with $TiCl_4$-Zn-THF reagent system……...57

21 McMurry reaction of keto ester **13a** and **13f** using microwave heating…..……..…58

22 Alkylation of prolinol **151** with 2-bromoacetophenone or chloroacetone……65

## LIST OF FIGURES


Figure Page

1 Pyrrolizidine alkaloids isolated from *Achusa strigosa*……...…….....……1

2 Pyrrolizidine alkaloids lasiocarpine (**3**) and europine (**4**)……..…..…2

3 Pyrrolizidine alkaloids integerrimine (**5**), integerrimine *N*-oxide (**6**), heliovicine (**7**), and lycopsamine (**8**)…..…….……...…2

4 Pyrrolizidine alkaloids alexine (**9**) and casuarine (**10**)...……...……..…….....3

5 The bicyclic core structure of pyrrolizidine alkoloids.……...…….3

6 McMurry precursors …….51

## Introduction

Pyrrolizidine alkaloids comprise a large class of natural products whose members have been subjected to many studies due to their potential biological applications in the treatment of cancer, diabetes, and viral infections such as HIV. In addition, some of these compounds exhibit antifeedant activity against several insects, and so have applications in the agricultural industry.[1, 2, 3, 4] By definition, antifeedant activity of a chemical is to repel insects without being toxic to the insect or the plant.

Natural pyrrolizidine alkaloids (PA) are found in plant families such as *Boraginaceae*, *Leguminoseae*, *Asteraceae*, and *Apocynaceae*.[4, 5a] Pyrrolizidine alkaloids **1** and **2** isolated from *Achusa strigosa* exhibit antifeedant activity against the *Spodoptera exigua* herbivore insect. Interestingly, perhaps due to the presence of pyrrolizidine alkaloids, the *Achusa strigosa* plant is used as an analgesic, a sedative, and an anti-inflammatory agent in some cultures (**Figure 1**).[4]

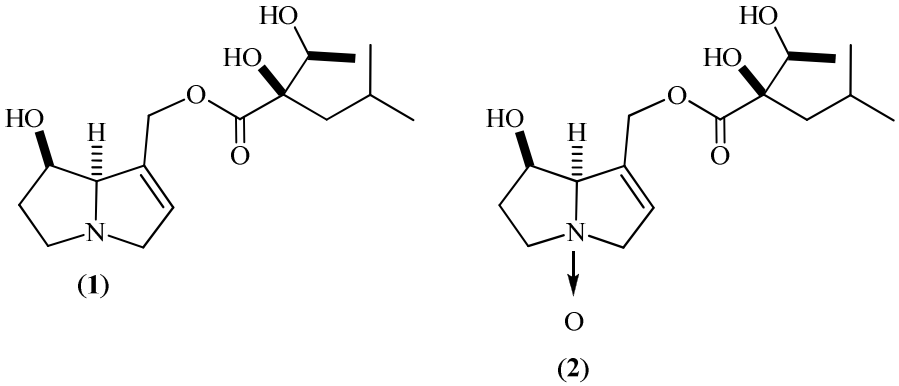



**Figure 1.** Pyrrolizidine alkaloids isolated from *Achusa strigosa*.

Lasiocarpine (**3**) and europine (**4**), which are extracted from *Heliotropium bovei*, also function as deterrents to insect feeding. In addition, these molecules show general antimicrobial activity and antifungal activity against *Fusarium moniliforme*.[5a]

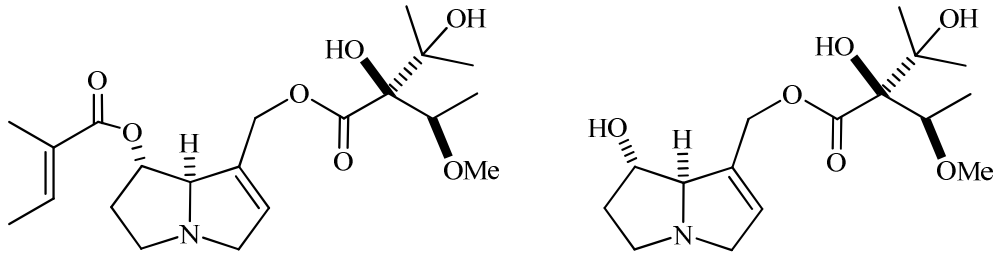



**Figure 2.** Pyrrolizidine alkaloids lasiocarpine (**3**) and europine (**4**).

Integerrimine (**5**), a pyrrolizidine cyclodiester, is found in the plants of the *Asteraceae* and shows strong antifeedant activity against the Colorado potato beetle. However, the *N*-oxide (**6**) is toxic to it (**Figure 3**).[5b] Heliovicine (**7**) and lycopsamine (**8**) have been isolated from the *Heliotropium floridum* and the *Heliotropium megalanthum* plants, respectively, and also show antifeedent activity against the Colorado potato beetle (**Figure 3**).[1, 5c]

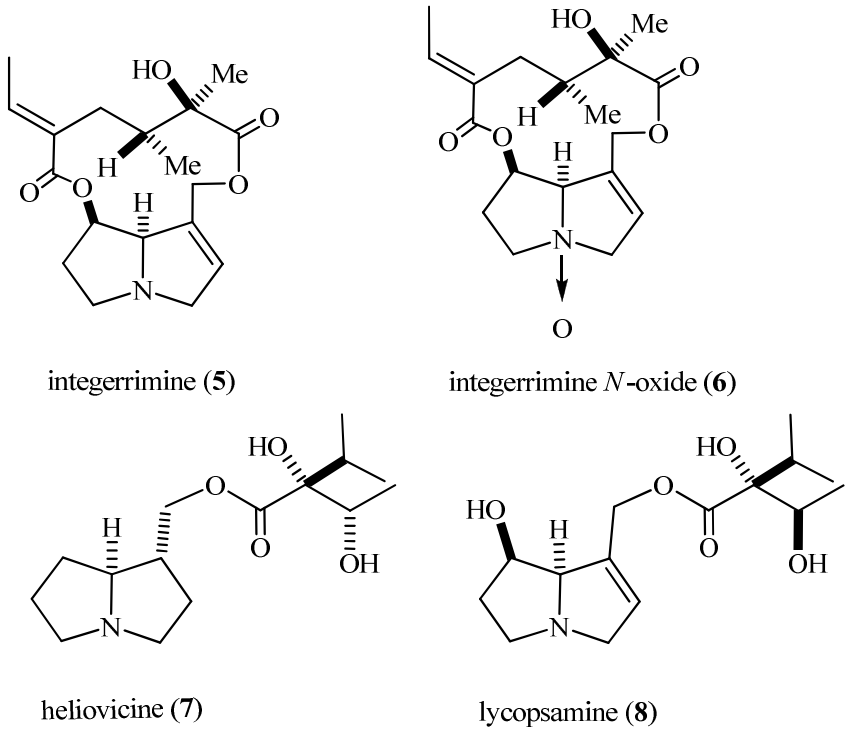



**Figure 3.** Pyrrolizidine alkaloids integerrimine (**5**), integerrimine *N*-oxide (**6**), heliovicine (**7**), and lycopsamine (**8**).

A number of PAs contain hydroxyls at multiple positions. Alexine (**9**), isolated from *Alexa canaracunensis*, has potential in the treatment of HIV-1.[3] Casuarine (**10**), which has been isolated from *Casuarina equisetifolia* and *Eugenia jambolana*, has shown potential for the treatment of breast cancer, bacterial infections, and diabetes (**Figure 4**).[3]

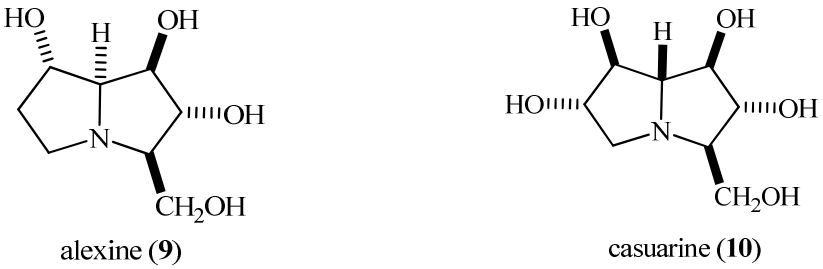
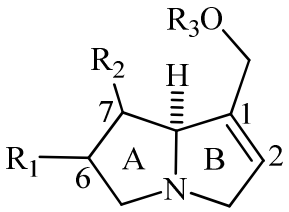



**Figure 4.** Pyrrolizidine alkaloids alexine (**9**) and casuarine (**10**).

Many syntheses of the compounds described above have been published.[1, 6, 7, 8] However, we were interested in developing a synthetic plan to form the bicyclic alkaloid core which could be then be converted to many pyrrolizidine alkaloids. The core structure of the bicyclic alkaloid features two important structural variables that could be tailored to a particular natural product target: saturation and unsaturation at C1-C2 and presence or absence of oxidation at C6 and/or C7 (**Figure 5**).



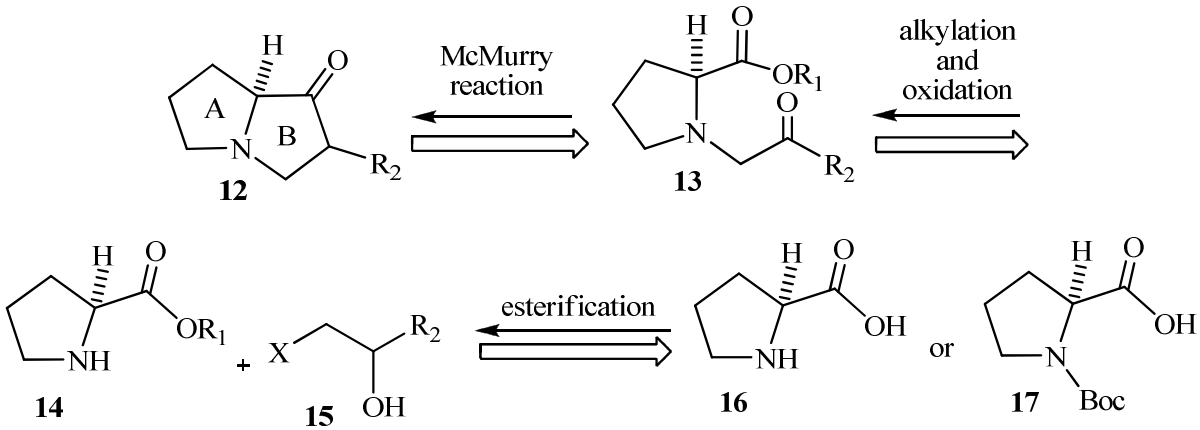

**11**

**Figure 5**. The bicyclic core structure of pyrrolizidine alkoloids.

The goal of our project is to synthesize the five-membered B-ring present in the backbone of naturally occurring pyrrolizidine alkaloids by a novel McMurry reaction (**Scheme 1**). According to our retrosynthetic analysis, McMurry reductive coupling of a keto

ester would afford pyrrolizidinone **12**. Alkylation and subsequent oxidation of amino ester **14** would result in the formation of the correct carbon skeleton required for the B-ring synthesis. Commercially available L-proline **16** or boc-L-proline **17** would be used to form proline esters. The five-membered A-ring of the pyrrolizidine alkaloids and stereochemistry at C8 would be in place from the start of the synthesis (**Scheme 1**).

**Scheme 1**



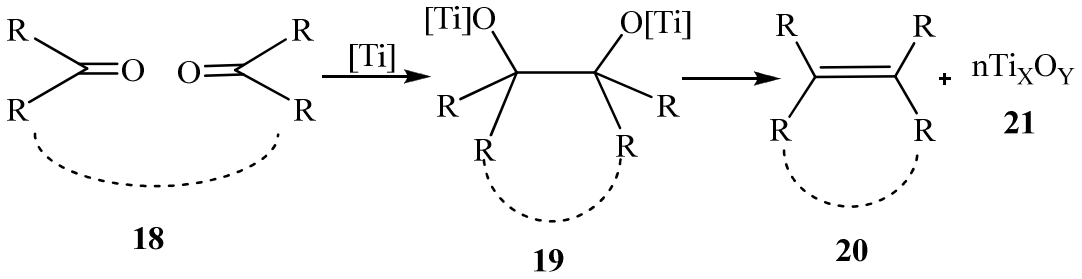
## Literature Review

### I. Introduction

### A. McMurry reaction: discovery and initial optimization

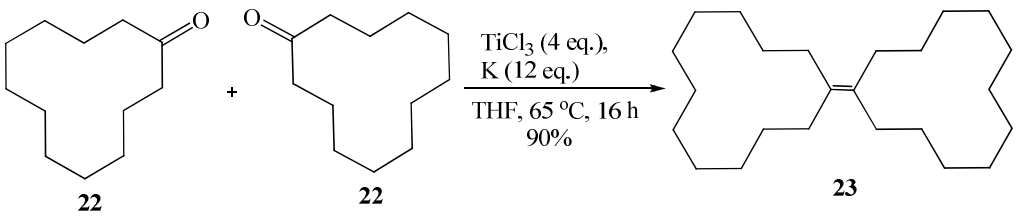
In the early 1970s, McMurry developed the reductive coupling reaction of carbonyl compounds to form carbon-carbon bonds (**Scheme 2**).[9-12] The reaction may be inter- or intramolecular, leading to acyclic or cyclic alkenes. Typically these reactions proceed by the *in situ* formation of a low-valent titanium reagent via reduction of Ti (III) or Ti (IV) with an appropriate reducing agent. Substrates are then added to the low-valent Ti reagent to effect the reductive coupling.

**Scheme 2**




In his initial investigation, McMurry examined several reducing agents. The $TiCl_3$-$LiAlH_4$ reagent combination was used for the reductive coupling of aryl and alkyl ketones. The $TiCl_3$-$LiAlH_4$ reagent system was later replaced with a $TiCl_3$-potassium metal reagent system because $LiAlH_4$ often caused side reductions. The $TiCl_3$-K reagent system was optimized using cyclododecanone (**11**) (**Scheme 3**, **Table 1**, entries 1-7). $TiCl_3$/K/ketone in the ratio of 4:12:1 in refluxing THF was found to be the best set of conditions, providing alkene **23** in 90% yield (**Table 1**, entry 7).[9] This reagent system was used for the intermolecular coupling of a number of aldehydes and sterically hindered ketones, giving alkenes in good to excellent yields (**Scheme 4**).

**Scheme 3**

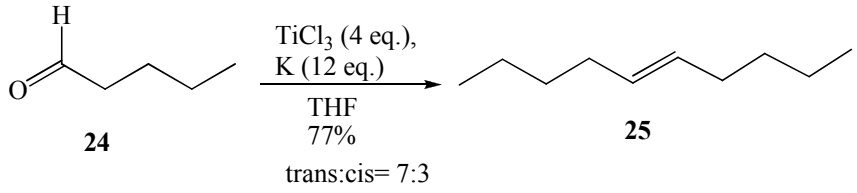



**22** **22** **23**

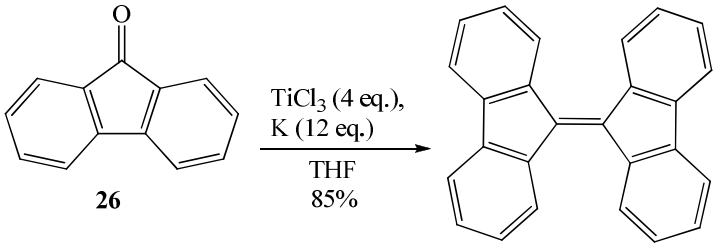
**Table 1**. Intermolecular reductive coupling of cyclododecanone (**23**) using Ti/K reagent system.[9]

| Entry | $TiCl_3$/K/ketone molar ratio | Solvent | Time, h | Yield % |
|---|---|---|---|---|
| 1 | 2:6:1 | THF | 18 | 59 |
| 2 | 2:4:1 | THF | 16 | 38 |
| 3 | 2:2:1 | THF | 16 | 28 |
| 4 | 2:6:1 | DME | 15 | 49 |
| 5 | 4:14:1 | THF | 17 | 76 |
| 6 | 4:18.8:1 | THF | 13 | 71 |
| 7 | 4:12:1 | THF | 16 | 90 |

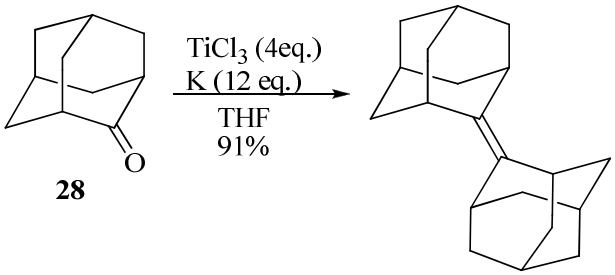
**Scheme 4**




**24** **25**



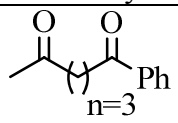
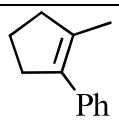
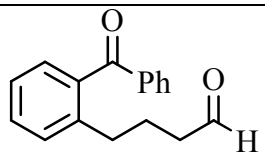
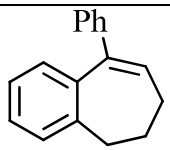
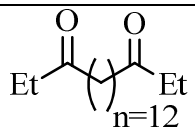
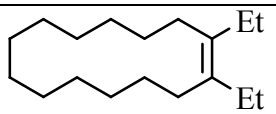

**26** **27**




**28** **29**

Because the reduction of $TiCl_3$ with potassium was potentially hazardous, McMurry looked to the $TiCl_3$-Li reagent system as a safer alternative. Applying analogous conditions, he also obtained alkenes in similar yields from the reactions of ketones and aldehydes that were also used as substrates for the $TiCl_3$-K induced reactions. However, the use of $TiCl_3$-Li reagent system did not provide satisfying yields for the intramolecular reductive coupling reaction of dicarbonyl compounds. On the other hand, when the $TiCl_3$-Zn(Cu) reagent system was used, cycloalkenes were formed in good yields regardless of the ring size of products (**Table 2**).[10] Because this system also worked well for intermolecular reactions, McMurry preferred the $TiCl_3$-Zn(Cu) reagent system for both inter- and intramolecular carbonyl couplings. It is noteworthy that in spite of the advantages of this reagent system, one disadvantage is that a much greater excess was required: 11.2 eq. $TiCl_3$, 25.7 eq. Zn(Cu) compared with 4 eq. $TiCl_3$, 12 eq. K.

**Table 2**. Intramolecular dicarbonyl coupling with $TiCl_3$, Zn(Cu) reagent system.[10]

| Entry | Dicarbonyl | Product | Yield% |
|---|---|---|---|
| 1 |  |  | 70 |
| 2 |  |  | 80 |
| 3 |  |  | 75 |

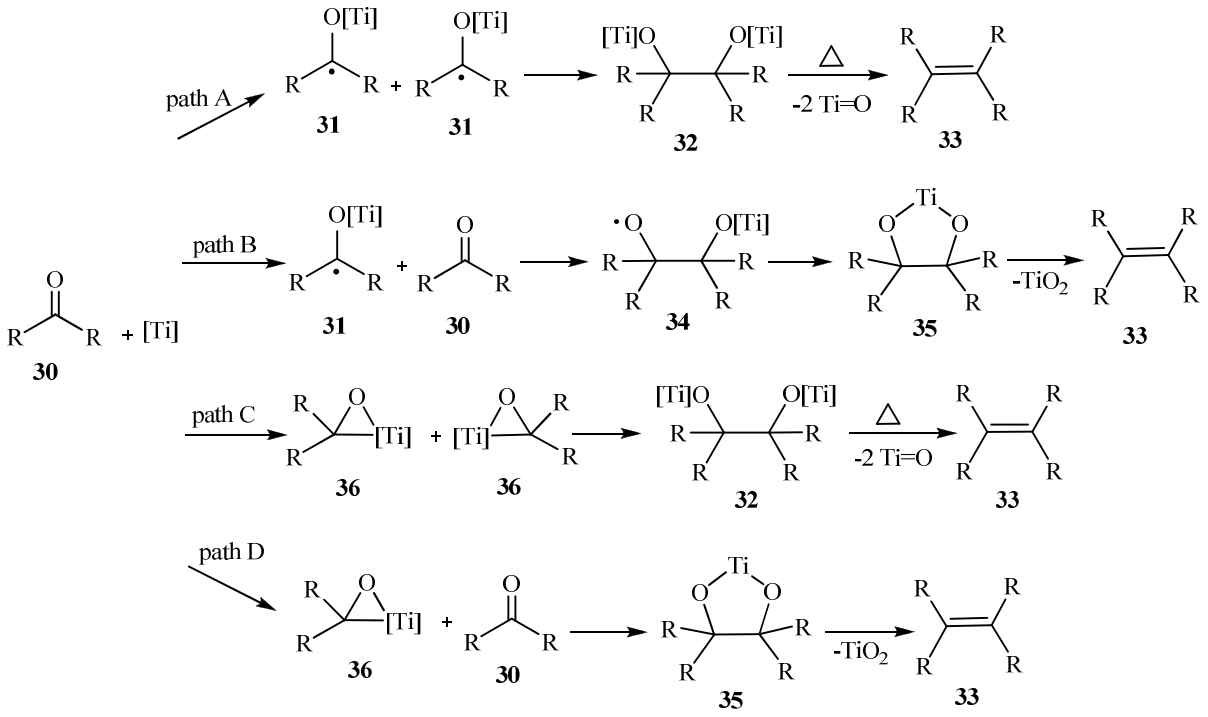
**B. Mechanism**

Four possible mechanisms have been proposed for the McMurry reaction. (**Scheme 5**).[12] Paths A and B invoke a single electron transfer mechanism, while paths C and D use a double electron transfer mechanism. In path A, a single electron reduction occurs with the

coordination of low-valent titanium to each of the carbonyl oxygens, forming the ketyl radicals that couple to form titanapinacolate intermediate **32**. In path B, coordination and reaction of the second carbonyl carbon with the ketyl radical forms the radical pinacolate **34**, which then cyclizes to give the five-membered ring intermediate **35**. After formation of the carbon-carbon bond, deoxygenation of the intermediate **32** or **35** produces the alkene **33** and $Ti^{4+}$ species.[12]

By contrast to the single electron transfer, a double electron transfer creates titanaoxiranes **36** that form intermediate **32** in path C. In path D, coordination and reaction of the second carbonyl carbon with titanaoxirane **36** generate the five-membered ring intermediate **35**. As with paths A and B, deoxygenation of the intermediate **32** or **35** produces the alkene **33** and $Ti^{4+}$ species in path C or D.[12]

**Scheme 5**



In the laboratory, McMurry reactions are often performed by a stepwise procedure. The first step is the reduction of the $TiCl_3$ or $TiCl_4$ to an active titanium species using appropriate reducing agents such as Zn, Zn(Cu), Mg, $LiAlH_4$, Al-$AlCl_3$, or alkali metals. After the titanium has been reduced, the carbonyl compounds are added.[12, 13a, 14]

In contrast to stepwise addition, the reducing agent, $TiCl_3$ or $TiCl_4$, and the carbonyl compounds may be added in one step. In this so-called instant method, the active titanium species is formed in the presence of the carbonyl compounds. The instant method has been used for both inter- and intramolecular McMurry couplings of aldehydes, ketones, amides, and nitriles. The instant method can be performed in a variety of solvents, including ethyl acetate, acetonitrile, and DMF.[13a, 14]

The goal of this research project is to develop a novel intramolecular McMurry reaction for the synthesis of pyrrolizidine alkaloids. Consequently, the following review of the literature will examine the scope of the intramolecular McMurry reaction to demonstrate the contribution of the present study to this body of work. Specifically, intramolecular McMurry reactions between two aldehydes, an aldehyde and ketone, two ketones, a ketone and an amide, and a ketone and an ester will be reviewed.

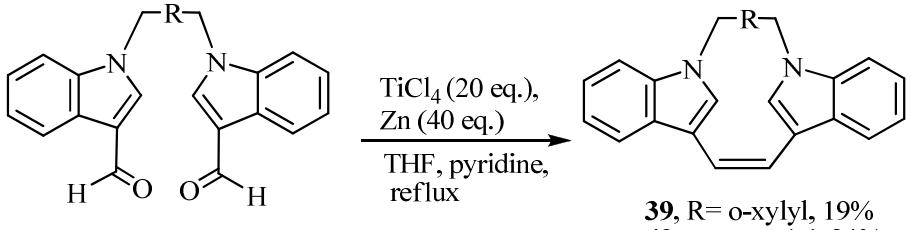
## II. Examples of intramolecular McMurry reactions

### A. Aldehyde-aldehyde cyclizations

Intramolecular McMurry reductive coupling of aldehydes has been frequently used to generate cyclic alkenes having a variety of ring sizes.[14] For example, Rajakumar, who worked on the synthesis of the indole-based cyclophanes, found that a large excess of $TiCl_4$ (20 equiv.) and Zn (40 equiv.) were required for the intramolecular cyclization of symmetrical dialdehydes **37** and **38** (**Scheme 6**).[15] The cyclization reaction was performed in

refluxing THF using pyridine as an additive. Depending on the substitution pattern of the xylyl linker, the cyclic alkenes **39** and **40** were formed in 19 and 24% yields, respectively. Other solvents, including DMF, toluene, and dioxane, were used in an effort to improve yields. Unfortunately these reactions resulted in complex mixtures.[15]

**Scheme 6**

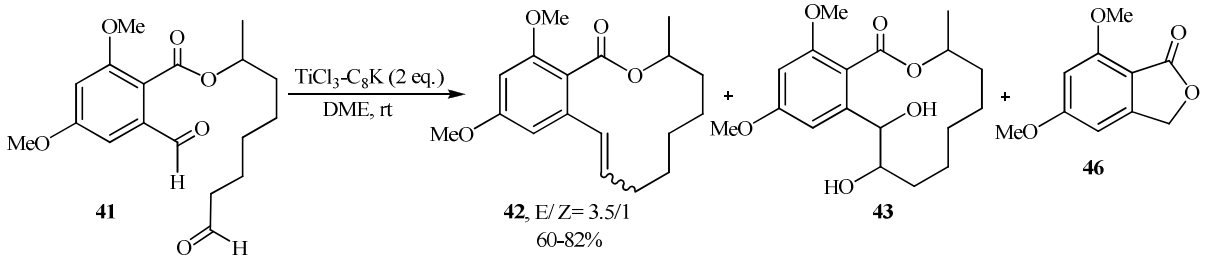



**37**, R= o-xylyl
**38**, R= m-xylyl

**39**, R= o-xylyl, 19%
**40**, R= m-xylyl, 24%

Furstner compared the ring closing metathesis reaction to the McMurry reaction to accomplish the cyclization of dialdehyde **41** (**Scheme 7**).[16] In this case, $TiCl_3$-$C_8K$ in DME at room temperature was used for the reductive coupling. Although the best results were obtained using two equivalents of the titanium complex, the yield of alkene **42** varied between in 60-82% yield as a 3.5:1 mixture of *E* and *Z* isomers. However, the McMurry reaction was problematic because it gave unreproducible yields and generated byproducts **43** and **46**. Incomplete reductive elimination led to the formation of pinacol intermediate **43**. Dimethoxy benzofuranone **46** arose from $TiCl_3$-induced reduction of the aldehyde followed by lactonization.

**Scheme 7**




**41**

**42**, E/ Z= 3.5/1
60-82%

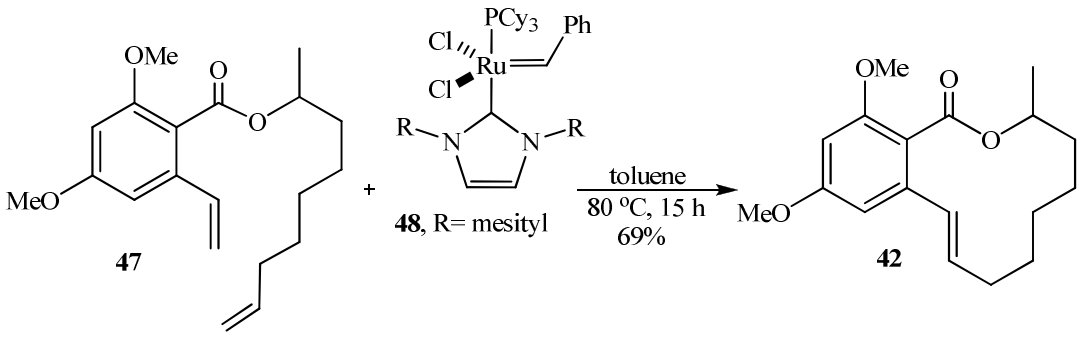
**43**

**46**

To avoid these complications, Furstner ultimately used a ring closing metathesis

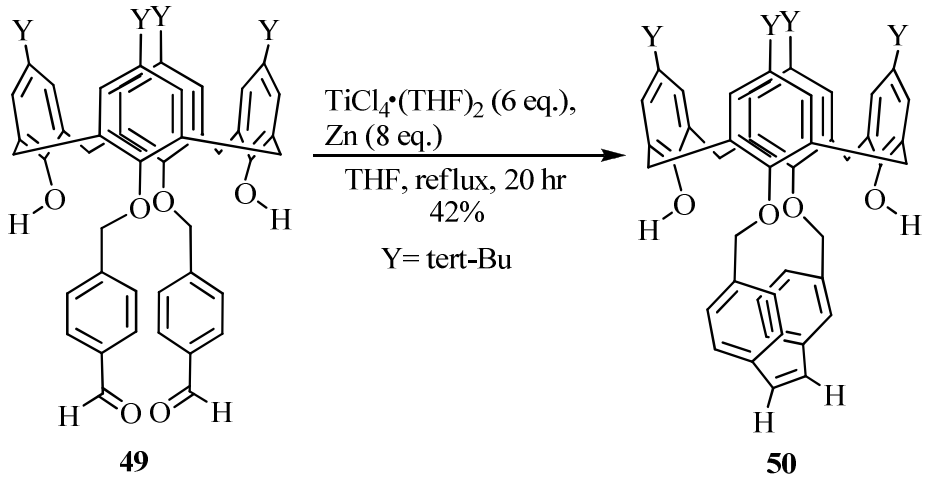
reaction with a ruthenium carbene catalyst **48**. This procedure afforded the desired alkene **42** in 69% yield as only the *E* isomer (**Scheme 8**).

**Scheme 8**




Strained alkenes can also be synthesized using low-valent titanium reagents.[12, 14] Lhotak used this process to form highly strained cyclic oligomers, calix[4]arenes. Calix[4]arenes may be used as receptors towards neutral and charged molecules.[17] Cyclization of dialdehyde **49** was accomplished by treatment with $TiCl_4 \cdot (THF)_2$ complex and Zn in refluxing THF (**Scheme 9**). This application of the "instant method" afforded the desired macrocycle **50** in 42% yield.

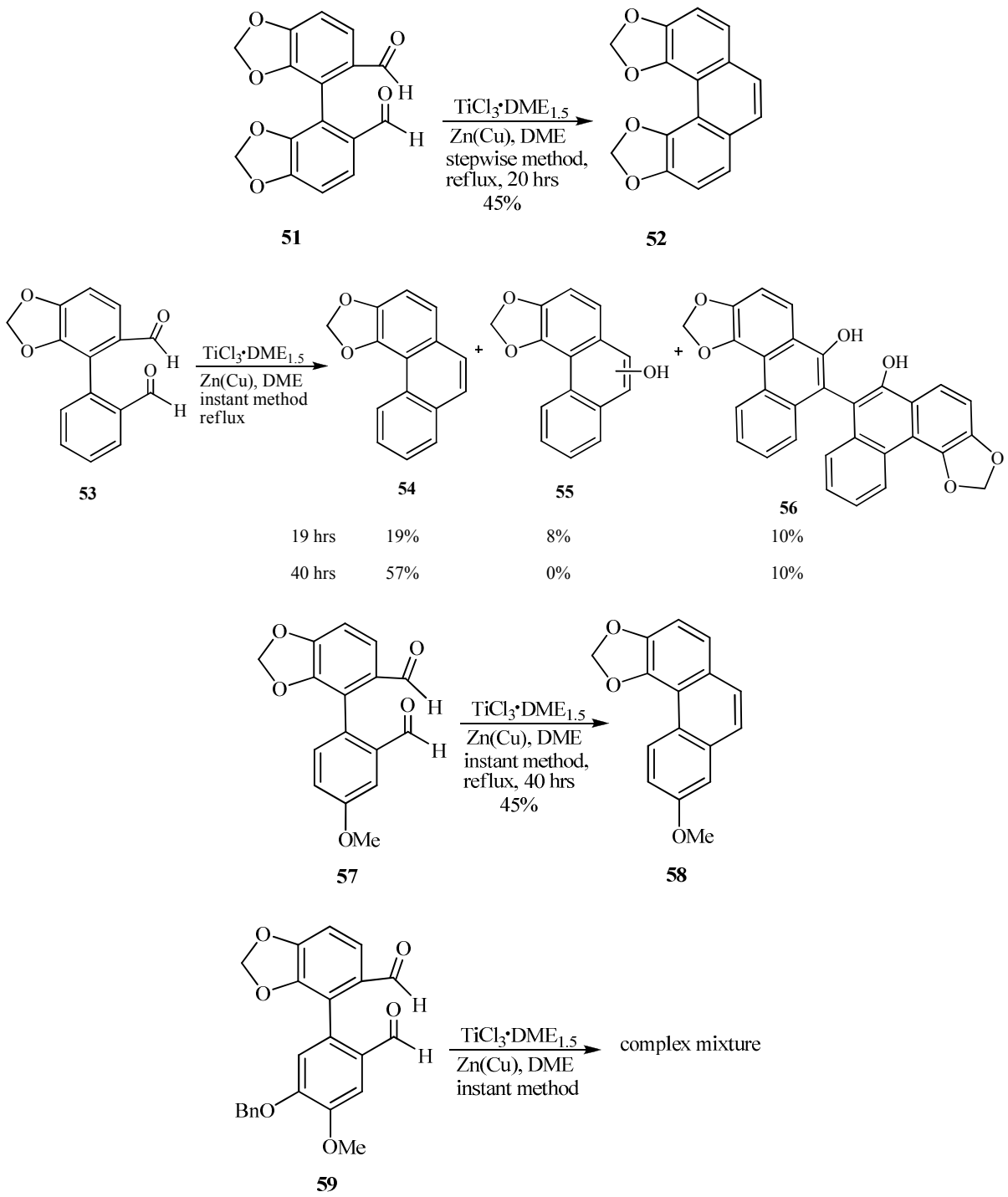
**Scheme 9**




Pfeffer worked on the synthesis of polyoxygenated phenanthrenes via McMurry

coupling of the corresponding aldehydes.[18] Cyclizations of the symmetrical and non-symmetrical bis-benzaldehydes were performed by the instant method or the stepwise addition of reactants method using the $TiCl_3$-$DME_{1.5}$-Zn(Cu) reagent system at reflux for 20 or 40 hours. While cyclization of dialdehyde **51** was accomplished by the stepwise procedure, the instant method proved more effective for the reaction of dialdehydes **53**, **57**, and **59** (**Scheme 10**). Although cyclization of dialdehyde **59** resulted in a complex mixture, cyclization of dialdehydes **51**, **53**, and **57** provided the phenanthrenes **52**, **54**, and **58** in 45%, 57%, and 45% yield, respectively. When the cyclization of dialdehyde **53** was performed for 19 hours, byproducts **55** in 8% yield and **56** in 10% yield were generated. However, running the reaction for 40 hours increased the yield of **54** from 19% to 57%.[18] Under these reaction conditions, **55** was not detected and the yield of **56** did not change. The reason for the formation of byproducts was not stated clearly.

**Scheme 10**




In the preceding examples, the McMurry reaction of highly strained dialdehydes afforded the desired *cis*-indolophanes and *cis*-calix[4]arene. However, the cyclization of poly-oxygenated dialdehydes was a particular challenge and afforded the products in moderate yields and also resulted in the formation of byproducts.

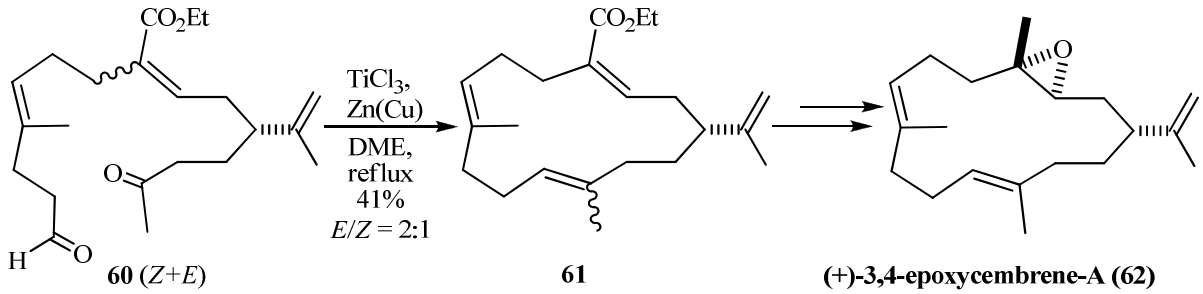
**B. Aldehyde-ketone cyclizations**

**1. Cembranoid diterpene macrocyclizations**

McMurry inter- or intramolecular reductive coupling reactions are very effective methods for the synthesis of natural and non-natural products.[12] For example, McMurry reactions have been used in cyclizations to form highly substituted macrocycles such as cembranoid diterpenes, which contain fourteen-membered ring systems.[14] Cembranoid diterpenes isolated from marine sources exhibit antitumor activity against many tumor promoters and consequently have been the target of numerous total syntheses.[19a, b, c, d]

Li used $TiCl_3$-Zn(Cu) for the macrocyclization in the synthesis of (+)-3,4-epoxycembrene-A (**62**) (**Scheme 11**).[19a] After pre-reduction of $TiCl_3$ with Zn(Cu), the cyclization of keto-aldehyde **60** afforded macrocyclic alkene **61** in 41% yield in a 2:1 ratio of *E* and *Z* isomers.

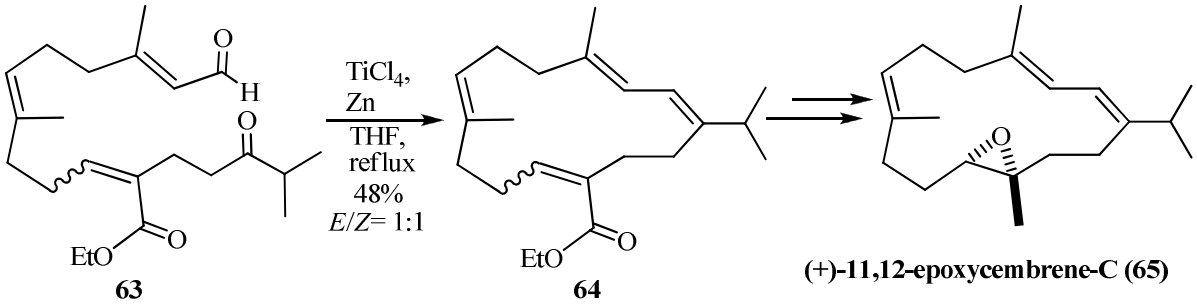
**Scheme 11**




**60** (*Z*+*E*) **61** **(+)-3,4-epoxycembrene-A (62)**

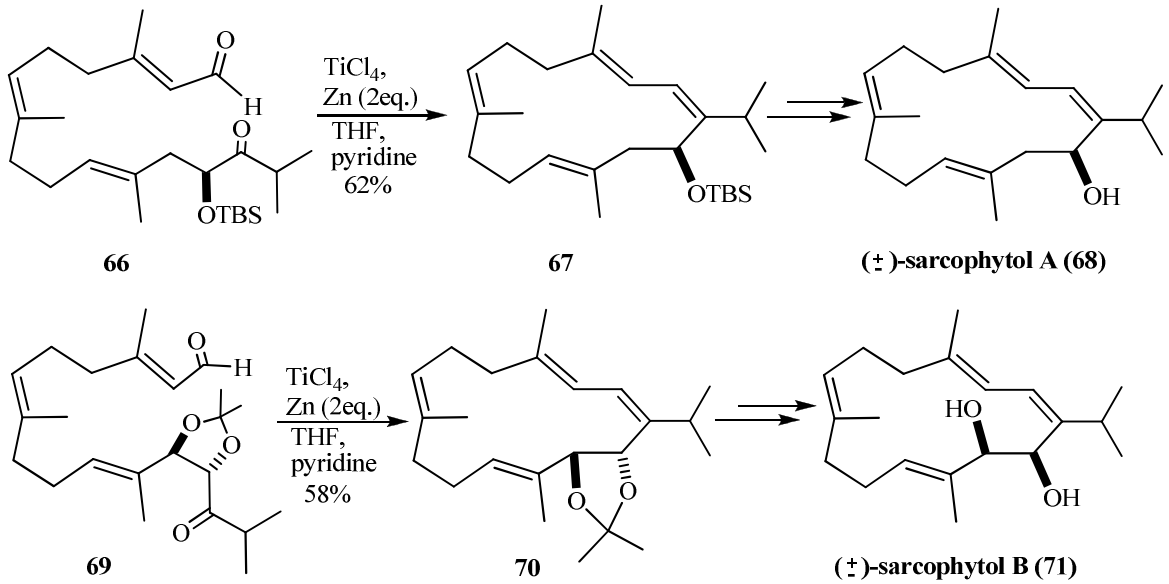
The synthesis of (+)-11,12-epoxycembrene-C (**65**) was also accomplished using a McMurry reaction for the macrocyclization.[19b] After pre-reduction of $TiCl_4$ with Zn in THF, the macrocyclization of keto-aldehyde **63** was accomplished in the presence of an α,β-unsaturated ester, affording alkene **64** in 48% yield as a 1:1 mixture of *E* and *Z* isomers (**Scheme 12**).[19b]

**Scheme 12**



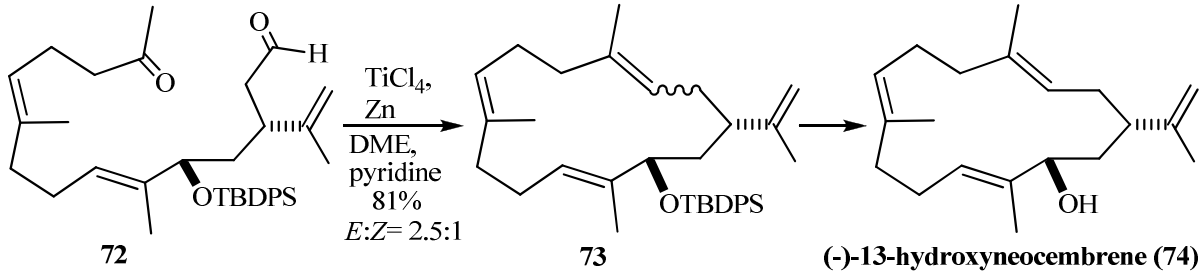

Li also used McMurry reactions for the synthesis of hydroxylated cembrenoids sarcophytol-A (**68**) and sarcophytol-B (**71**) (**Scheme 13**).[19c] Both cyclization reactions were performed in refluxing THF and used pyridine as an additive. After pre-reduction of $TiCl_4$ with Zn, the McMurry reaction of keto-aldehyde **66** afforded the macrocycle **67** in 62% yield (**Scheme 13**). Similarly, when Li attempted to synthesize sarcophytol-B (**71**), the macrocyclization of keto-aldehyde **69** with the same reagent and conditions afforded product **70** in 58% yield. In both cases, the McMurry reaction favored the desired *Z* double bond, although the ratio of *E*/*Z* isomers was not reported.

**Scheme 13**



When Li synthesized (-)-13-hydroxyneocembrene (**74**), DME was used as a solvent for the key reductive coupling (**Scheme 14**).[19d] After pre-reduction of $TiCl_4$ with Zn in refluxing DME and using pyridine as an additive, McMurry reaction of keto-aldehyde **72** afforded alkene **73** in 81% yield as a 2.5:1 mixture of *E* and *Z* isomers (**Scheme 14**).

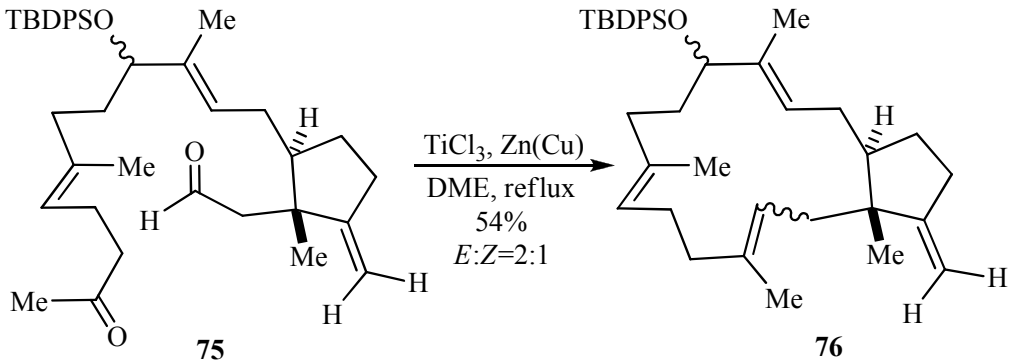
**Scheme 14**




**72** **73** **(-)-13-hydroxyneocembrene (74)**

Heissler also used McMurry coupling for the synthesis of a related diterpene.[20] $TiCl_3$-graphite or $TiCl_3$/Zn(Cu) in DME was used for the cyclization of keto-aldehyde **75**. The use of $TiCl_3$-$C_8K$ reagent system provided the product **76** in 10-15% yield. According to Heissler, the alkene **76** might have been absorbed on the graphite, resulting in the poor observed yield. However, $TiCl_3$/Zn(Cu) in DME yielded alkene **76** in 54% yield as a 2:1 mixture of *E* and *Z* diastereomers (**Scheme 15**).

**Scheme 15**




**75** **76**

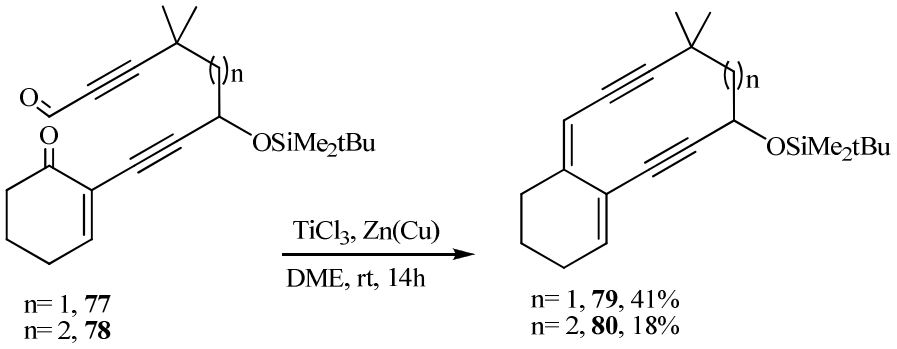
In these studies, the McMurry macrocyclization reactions proceeded in average to good yields, although the *E*/*Z* stereoselectivities were poor. While the undesired

stereoisomers could be removed by chromatography, the poor stereoselectivities reduced the overall yield and effectiveness of the total synthesis. Nonetheless, the McMurry reaction is a powerful method for the synthesis of both macrocyclic natural products and highly strained molecules. In addition, these efforts demonstrate that functional groups such as acetals, alcohols, alkenes, silyl ethers, esters, and ethers are tolerated by the McMurry reaction.[11]

**2. Other aldehyde-ketone cyclizations**

In addition to the examples shown above, intramolecular reductive coupling of aldehydes and ketones can also provide access to both medium and small rings. For example, Bruckner used the intramolecular McMurry reaction of keto-aldehydes **77** and **78** for the synthesis of enediyne antibiotics (**Scheme 16**).[21] Following pre-reduction of $TiCl_3$ with Zn(Cu) and slow addition of conjugated enediyne keto-aldehydes **77** or **78**, cyclic dienediynes **79** and **80** were produced in 41% and 18% yield, respectively.[21]

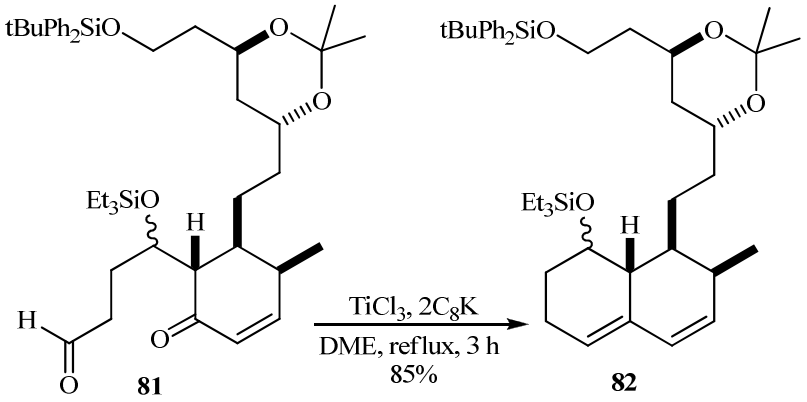
**Scheme 16**




McMurry cyclization of highly oxygenated compounds has proved difficult due to complicating Lewis acid-base interactions between the low-valent titanium species and ether moeities located elsewhere in the molecule.[14] For example, Clive used $TiCl_3$-graphite for the cyclization of keto-aldehyde **81** (**Scheme 17**).[22] Other reagent combinations such as $TiCl_3$-Zn(Cu), $TiCl_3$-$LiAlH_4$–TEA were attempted, but resulted in low yields due to coordination

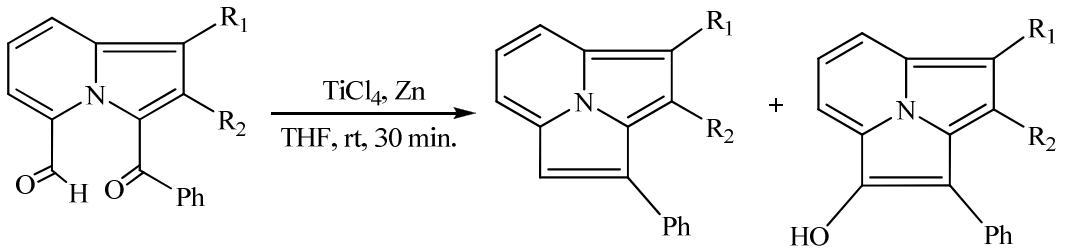
between ether oxygens and low-valent titanium. After pre-reduction of $TiCl_3$ with $C_8K$ in DME, slow addition of keto-aldehyde **81** at room temperature for 5 hours and refluxing the reaction mixture for 3 hours afforded diene **82**, a key intermediate in the synthesis of the natural product compactin, in 85% yield.[22] These results are similar to those obtained by Furstner, who also used the $TiCl_3 \cdot C_8K$ reagent system to obtain good yields in reductive coupling reactions where other Lewis bases are present (cf. **Scheme 7**).

**Scheme 17**




Hu applied the McMurry reaction to the synthesis of pyrrolo indolizines.[23] After pre-reduction of $TiCl_4$ with Zn in THF, cyclization of keto-aldehydes **83a-c** at room temperature resulted in the desired pyrrolo indolizines **84a-c** and also byproducts **85a-c**, which arose from dehydration of the pinacol intermediate (**Scheme 18**). Hu made changes in the reaction conditions including addition of pyridine and refluxing the reaction.[23] Addition of pyridine increased the yield of **84a** from 30% to 39%. However, refluxing the reactions actually lowered the yield of **84a**. Similar results were obtained for keto-aldehydes **83b** and **83c**. Notably, when an extra electron withdrawing group was present, the yield of byproduct **85c** increased at the expense of the desired product **84c** (**Table 3**, entry 3).

**Scheme 18**




**83 a-c** **84 a-c** **85 a-c**

**Table 3**. McMurry reaction of keto-aldehyde **83a-c**.[23]

| Entry | Keto-aldehyde | $R_1$ | $R_2$ | Yield | Yield |
|---|---|---|---|---|---|
| 1 | **83a** | CN | H | **84a**, 30% | **85a**, 29% |
| 2 | **83b** | $CO_2Me$ | H | **84b**, 38% | **85b**, 41% |
| 3 | **83c** | $CO_2Et$ | $CO_2Et$ | **84c**, 20% | **85c**, 55% |

In Hu's study, cyclization of keto-aldehydes **83a-c** was performed in the presence of potentially competitive functional groups including nitrile and an ester. However, in this study, evidence of inter- nor intramolecular reductive coupling involving esters or nitriles was not observed. McMurry has demonstrated that nitriles react with low-valent titanium species slowly compared to aldehydes and ketones,[11] which gives further support for Hu's observed chemoselectivity.

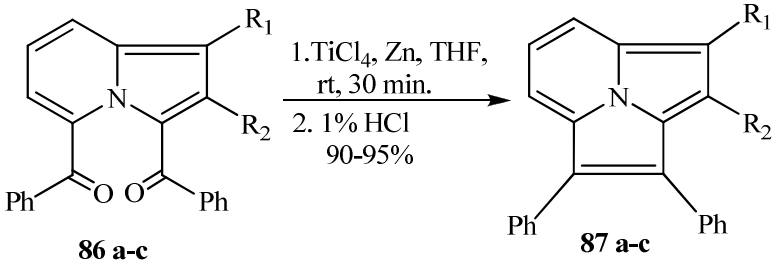
As seen in Bruckner's work,[21] the McMurry reaction of aldehyde-ketones **77** and **78** that contain C≡C bonds resulted in low yields, but the extent of C≡C bonds' electronic influence on that yield is not known. Finally, Clive demonstrated that a McMurry reaction could be accomplished in the presence of Lewis acid-labile silyl ethers and acetals. [22]

**C. Ketone-ketone cyclizations**

Intramolecular reductive couplings of diketones often give alkenes in good yield.[12] Hu also synthesized pyrrolo indolizines by cyclization of diketones **86a-c** (**Scheme 19**).[23] After pre-reduction of $TiCl_4$ with Zn in THF, cyclization of diketones **86a-c** was performed at

room temperature for 30 minutes. Pyrrolo indolizine alkaloids **87a-c** were formed in 90-95% yields (**Table 4**, entries 1-3).[23] By contrast to Hu's reductive couplings using similar keto-aldehydes (cf. **Scheme 18**), yields were excellent and no pinacol-derived byproduct was observed.

**Scheme 19**



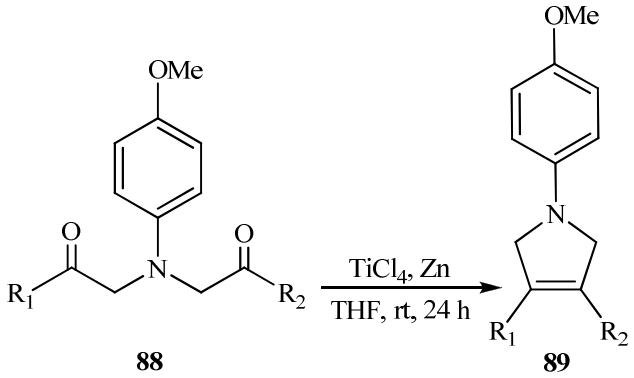

**86 a-c** **87 a-c**

**Table 4**. McMurry reaction of diketones **86a-c**.[23]

| Entry | diketone | $R_1$ | $R_2$ | Yield |
|---|---|---|---|---|
| 1 | **86a** | CN | H | **87a**, 95% |
| 2 | **86b** | $CO_2Me$ | H | **87b**, 90% |
| 3 | **86c** | $CO_2Et$ | $CO_2Et$ | **87c**, 90% |

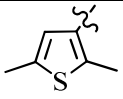
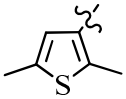
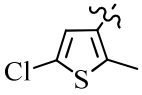
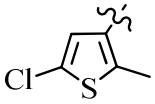
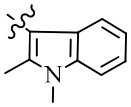
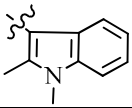
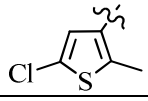
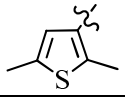
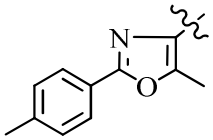
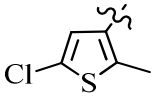
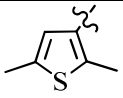
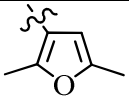
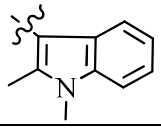
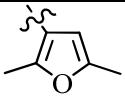
McMurry reactions have been used for the synthesis of photochromic compounds that undergo a photoinduced cyclization when they are exposed to UV light. Ideally the reaction may be reversed when the cyclized compound is exposed to visible light.[24, 25] Chen[24] and Shepelenko[25] used the McMurry reaction to generate diarylethenes and diheterylethenes to examine their photochromium properties. After pre-reduction of $TiCl_4$ with Zn refluxing in THF, Chen performed the cyclization of diketones **88** at room temperature for 24 hours, affording diarylethenes **89** in good yields (**Scheme 20**, **Table 5**, entries 1-7).[24]

**Scheme 20**



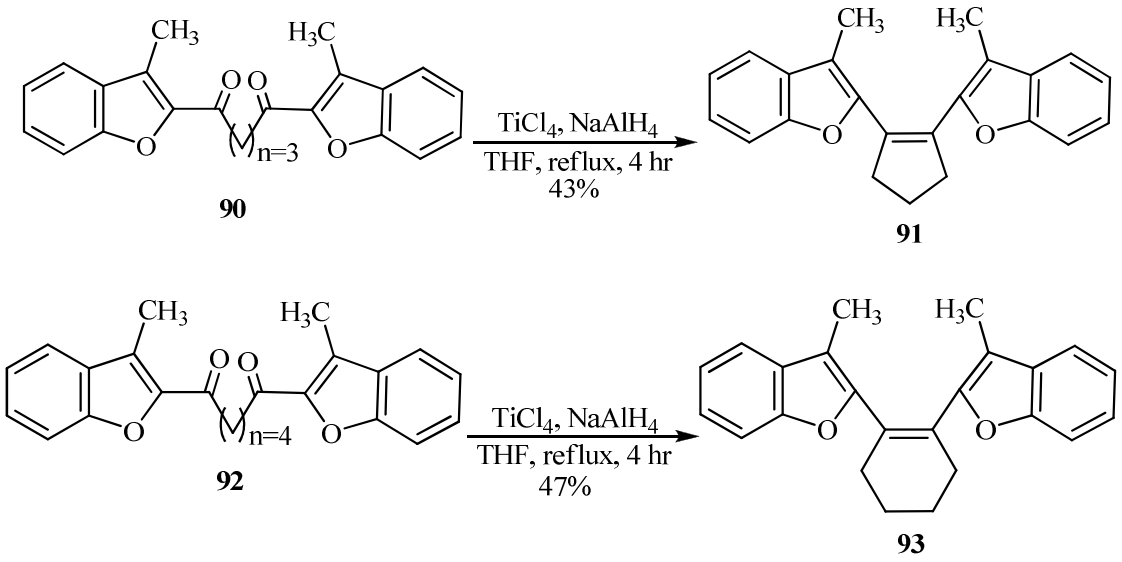

**88** **89**

**Table 5**. McMurry reactions of diketones **88**.[24]

| Entry | $R_1$ | $R_2$ | **89**, yield% |
|---|---|---|---|
| 1 |  |  | 85 |
| 2 |  |  | 84 |
| 3 |  |  | 85 |
| 4 |  |  | 85 |
| 5 |  |  | 61 |
| 6 |  |  | 60 |
| 7 |  |  | 82 |

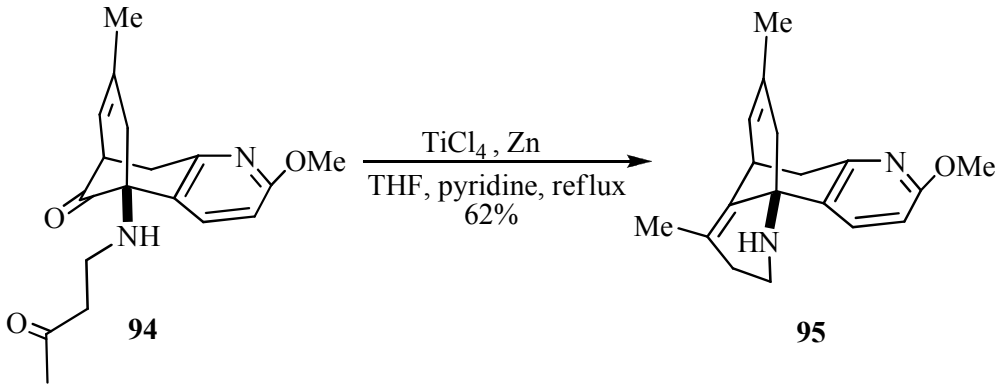
Shepelenko[25] used diketones **90** and **92** (**Scheme 21**) to synthesize diarylethenes **91** and **93**. First, pre-reduction of $TiCl_4$ with $NaAlH_4$ was accomplished in THF at 0-2 $^oC$. Refluxing diketones **90** or **92** in this mixture for 4 hours afforded cycloalkenes **91** and **93** in 43% yield and 47% yield, respectively.[25]

**Scheme 21**



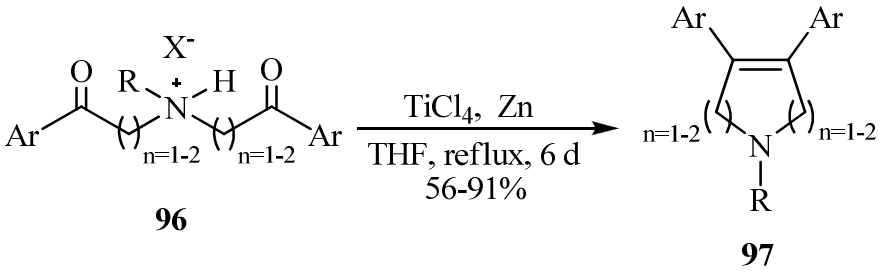

Kozikowski described a strategy to synthesize a new analog of huperzine A and huperzine B, molecules that have demonstrated neuroprotective effects and potential in the treatment of Alzheimer's disease.[26] McMurry cyclization of diketone **94** was performed by the pre-reduction of $TiCl_4$ with Zn and addition of pyridine (**Scheme 22**). Addition of diketone **94** to this mixture afforded the amino alkene **95** in 62% yield.[26] Significantly, the reductive coupling occurs in spite of the presence of a Lewis basic secondary amine.

**Scheme 22**



Feng was able to accomplish a McMurry cyclization in the presence of an amine protected as its ammonium salt.[27] After pre-reduction of $TiCl_4$ with Zn in THF, diketones **96** were added into the reaction mixture and refluxed for 6 days to obtain azacycloalkenes **97** in the 56-91% yield (**Scheme 23**, **Table 6**). Yields were higher when bromide was used as the ammonium salt counterion. The reason for this difference is not obvious and was not elaborated on by the authors.

**Scheme 23**




**96** **97**

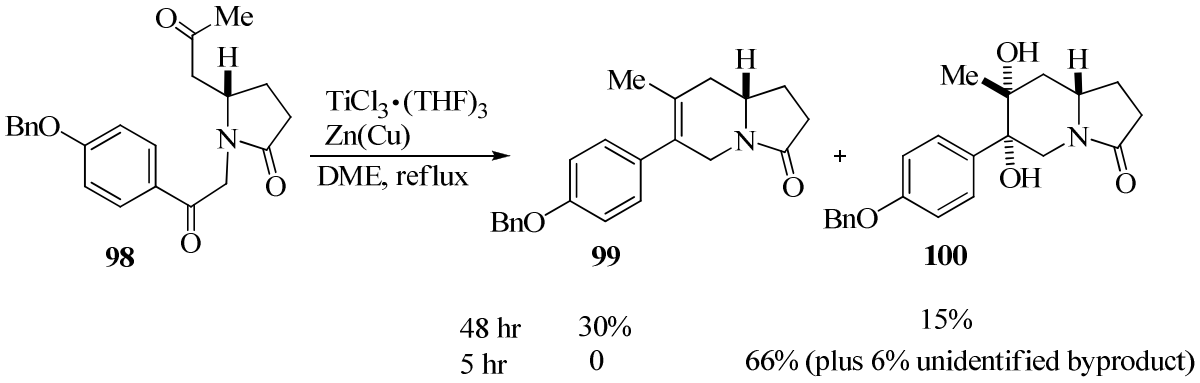
**Table 6**. McMurry reaction of ammonium diketones **96**.[27]

| | Ar | R | n | X | Yield |
|---|---|---|---|---|---|
| **a** | Ph | $CH_2Ph$ | 1 | Br | **97a**, %90 |
| **b** | Ph | 4-$CH_3C_6H_4$ | 1 | Br | **97b**, %91 |
| **c** | Ph | $CH_3$ | 2 | Cl | **97c**, %63 |
| **d** | Ph | Et | 2 | Cl | **97d**, %60 |
| **e** | Ph | n-Bu | 2 | Cl | **97e**, %66 |
| **f** | 4-$CH_3C_6H_4$ | $CH_3$ | 2 | Cl | **97f**, %56 |

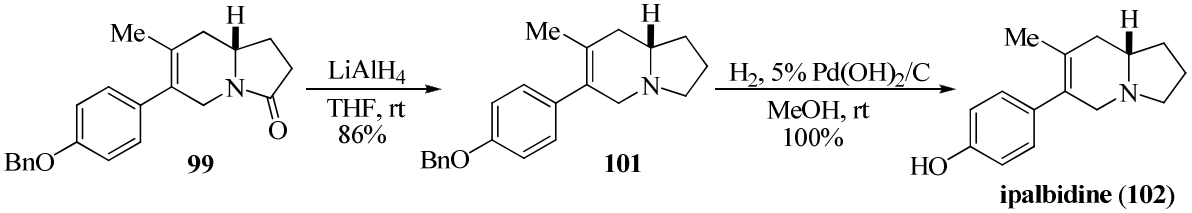
Honda also accomplished a McMurry reaction in the presence of a non-Lewis basic nitrogen in his efforts to synthesize the indolizidine alkaloid ipalbidine (**102**) (**Scheme 24**).[7] After pre-reduction of the $TiCl_3 \cdot (THF)_3$ complex with Zn(Cu) in DME, reaction of diketone **98** in refluxing DME for 48 hours resulted in indolizidinone **99** in 30% yield and pinacol byproduct **100** in 15% yield. However, running the reaction for 5 hours with the same reagent system caused the reaction to stop at the pinacol intermediate and afforded the *cis*-diol **100** in

66% yield and an unidentified byproduct in 6% yield.[7] Ipalbidine (**102**) was then accessed via reduction of amide **99** followed by benzyl ether deprotection. Significantly, Honda was able to convert the pinacol byproduct **100** into the desired alkene **99** via an acetal formation-elimination sequence (**Scheme 26**).

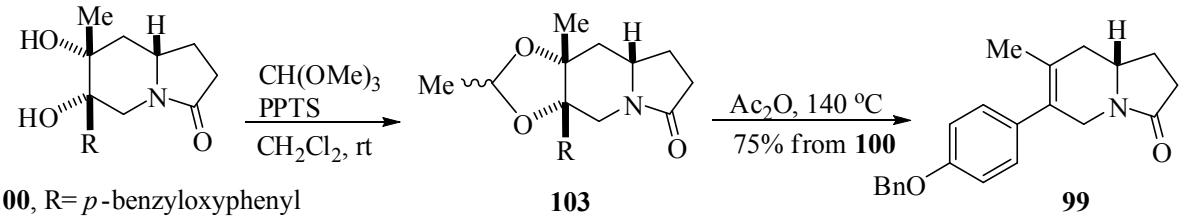
**Scheme 24**




**Scheme 25**




**Scheme 26**




Hu's results demonstrate that ketone-ketone coupling can be higher yielding than the analogous aldehyde-ketone coupling. Comparing the yields of the other studies reveals that yields seem to be substrate-dependent. Significantly, Chen,[24] Shepelenko,[25] Kozikowski,[26]

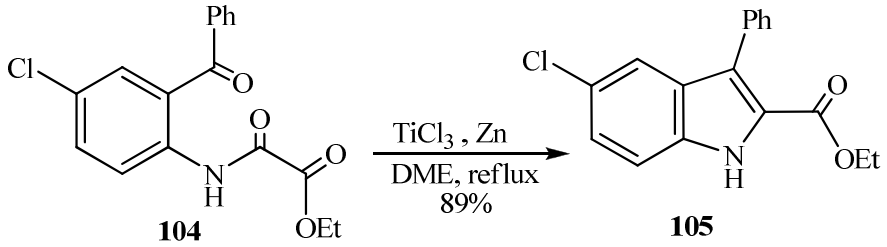
and Honda[7] were able to accomplish the McMurry reaction in the presence of a Lewis basic heteroatom. This is particularly noteworthy in Kozikowski's example where the amine is not protected or the lone pair resonance delocalized.

**D. Ketone-amide cyclizations**

McMurry reactions may be accomplished using carbonyl compounds in higher oxidation states. Indeed, the synthesis of indoles via McMurry coupling of amides and ketones has been reported.[13a, 13b, 14, 28a]

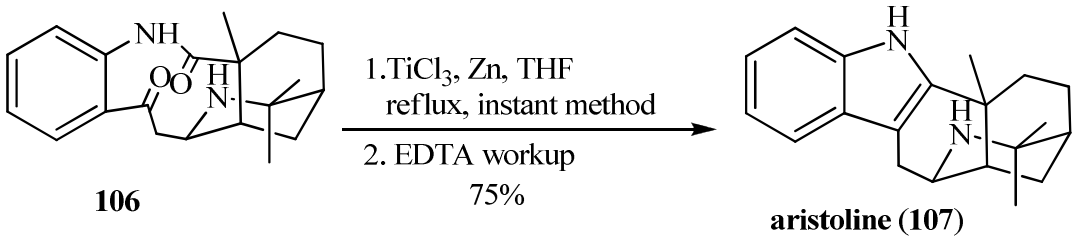
Furstner used the instant method for the McMurry reaction of keto-amide **104** (**Scheme 27**).[13b] Treatment of keto-amide **104** with $TiCl_3$-Zn in refluxing DME for 2 hours afforded the indole **105** in 89% yield. Significantly, no side reaction involving the α-ethyl ester was reported.

**Scheme 27**




Furstner also used the instant method in the synthesis of aristoline (**107**) (**Scheme 28**).[13a] Treatment of keto-amide **106** with $TiCl_3$ and Zn in refluxing THF afforded the desired natural product **107** in 75% yield. Because the aristoline (**107**) coordinated with the titanium salt strongly, the reaction mixture had to be washed with an EDTA solution to allow for product isolation.[13a] Similar to the Kozikowski study (cf. **Scheme 22**), Furstner accomplished the McMurry cyclization of keto-amide **106** in the presence of a Lewis-basic free amine.

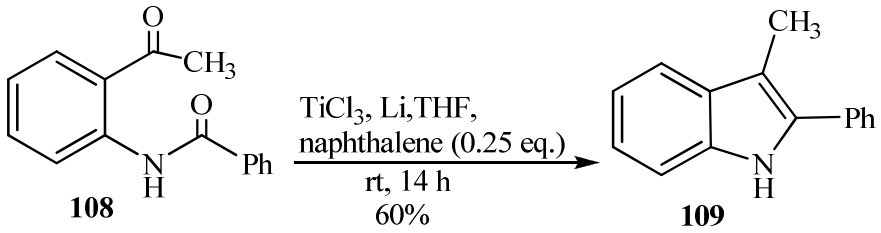
**Scheme 28**




**106** **aristoline (107)**

Chattopadhyay examined the effect of naphthalene on the activation of $TiCl_3$.[28a] After pre-reduction of $TiCl_3$ with Li in THF, naphthalene was added into the slurry at room temperature (**Scheme 29**). In addition to activating the low-valent titanium, naphthalene was used to increase the solubility of $TiCl_3$-Li in THF to provide a homogeneous solution of low-valent titanium reagent. Addition of keto-amide **108** to this solution at room temperature afforded indole **109** in 60% yield.[28a]

**Scheme 29**




**108** **109**

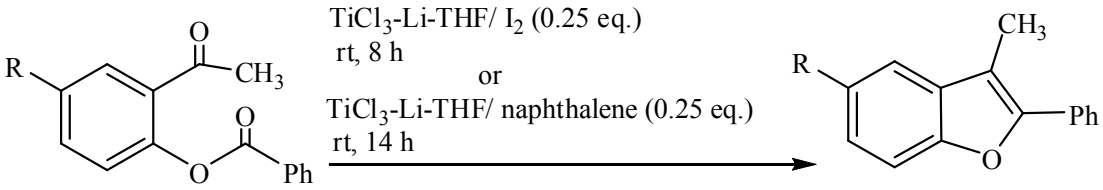
In Furstner's and Chattopadhyay's studies, cyclization of several keto-amides was accomplished. Some of these cyclizations were performed in the presence of aryl chloride, ester, and free amine functional groups. Furstner's study also demonstrates that the keto-amide cyclization was accomplished successfully in a chemoselective way; the formation of a five-membered ring is favored over that of a six-membered ring and/or the amide-ketone cyclization is favored over that of an ester-ketone cyclization.

**E. Ketone-ester cyclizations**

Although in Furstner's example of a chemoselective keto-amide McMurry cyclization reaction between the ketone and ester did not occur (cf. **Scheme 27**), coupling of keto-esters using low-valent titanium has been accomplished. Keto-esters are coupled to give enol ethers and provide ketones upon acidic workup.[14] The cyclization of keto-esters has been used for the formation of five-, six-, and seven-membered rings.

Chattopadhyay[28a] and Banerji[28b] examined the effect of iodine or naphthalene on the reaction as a means for activating low-valent titanium. As seen with amide-ketone coupling, naphthalene was chosen as an activator in hopes that it would also increase the solubility of $TiCl_3$-Li in the organic solvent. After pre-reduction of $TiCl_3$ with Li in THF, a sub-stoichiometric amount of iodine or naphthalene was added at room temperature (**Scheme 30**). McMurry reaction of keto-esters **110a** and **110b** afforded the cyclized products **111a** and **111b** in moderate yields (**Table 7**).[28a, 28b] Thus, addition of naphthalene or iodine to the $TiCl_3$-Li-THF reagent system and performing the McMurry reaction at room temperature provided comparable results with those analogous reactions previously done using conventional McMurry reaction.[28a, 28b]

**Scheme 30**



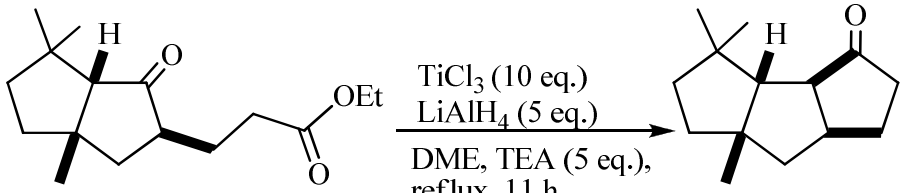

**110a, b** **111a, b**

**Table 7**. McMurry reaction of keto esters **110**.[28a]

| Keto-ester | R | Ti sources | Yield |
|---|---|---|---|
| **110a** | H | $TiCl_3$-Li- naphthalene –THF | **111a**, 55% |
| **110b** | OMe | $TiCl_3$-Li- naphthalene –THF | **111b**, 52% |
| **110a** | H | $TiCl_3$-Li-THF-$I_2$ | **111a**, 62% |
| **110b** | OMe | $TiCl_3$-Li-THF-$I_2$ | **111b**, 55% |

Iyoda used $TiCl_3$ to synthesize tricyclic ketone **113**.[29] After pre-reduction of $TiCl_3$ with $LiAlH_4$ in DME containing TEA, keto-ester **112** was added into the reaction mixture and the reaction afforded ketone **113** in 72% yield (**Scheme 31**).[29] The authors claim that the reaction was completely cis-stereoselective and assign the stereochemistry following conversion to a known natural product.

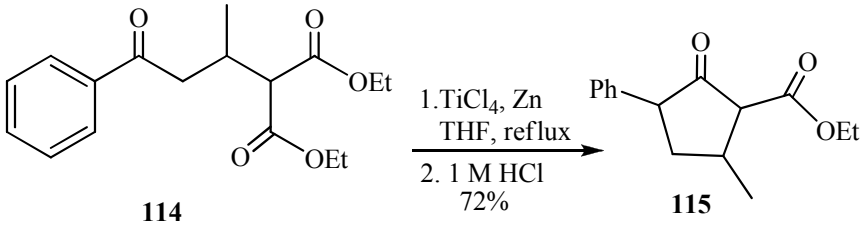
**Scheme 31**




**112** **113**

Pedersen used the McMurry reaction for the cyclization of keto-diethyl ester **114**.[30] After pre-reduction of $TiCl_4$ with activated Zn in THF, cyclization of **114** followed by acidic workup afforded ketone **115** in 72% yield (**Scheme 32**). Although the McMurry reaction was accomplished, stereoselectivity of the reaction was not stated by the authors.

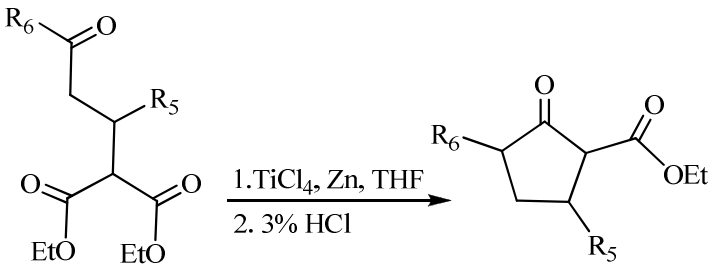
**Scheme 32**




**114** **115**

Chen also accomplished cyclization of a similar keto-diethyl esters **116a-c**.[31] After pre-reduction of $TiCl_4$ with Zn in THF, refluxing keto-diethyl ester **116a-c** followed by acidic workup provided the cyclic keto-esters **117a-c** in good yields (**Scheme 33**, **Table 7**). In Chen's study, stereoselectivity of the reaction was not reported.

**Scheme 33**




**116a-c** **117a-c**

**Table 8.** McMurry reaction of keto diesters **116**.[31]

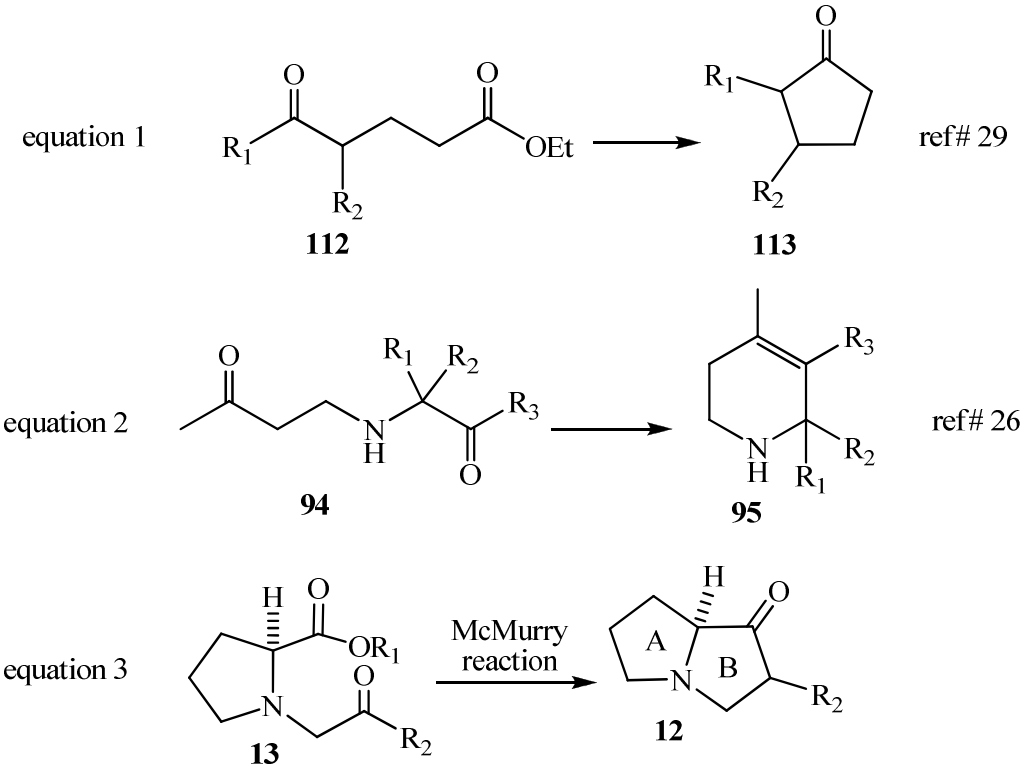
| Keto-ester | $R_5$ | $R_6$ | Yield |
|---|---|---|---|
| **116a** | $C_6H_5$ | $C_6H_5$ | **117a**, 81% |
| **116b** | $C_6H_5$ | 4-$CH_3C_6H_4$ | **117b**, 87% |
| **116c** | 3,4-$Cl_2C_6H_3$ | 4-$CH_3C_6H_4$ | **117c**, 78% |

## III. Summary

The use of low-valent titanium species in combination with different reducing agents has been employed for the reductive coupling of different carbonyl compounds in varying oxidation states to form C-C bonds. Rings ranging from 5 to 14 members have been formed using this reaction. Specifically, our interest was the formation of pyrrolizidinone **12** via the

McMurry reaction of keto ester **13**. Iyoda has demonstrated that reductive coupling of aliphatic keto-esters can be accomplished (**Scheme 34**, equation 1). Kozikowski has shown that the McMurry reaction works in the presence of a Lewis basic amine (**Scheme 34**, equation 2). Thus, encouraged by these relevant results, we were interested in developing a novel McMurry reaction for the cyclization of a keto-ester in the presence of a free amine in the ring to form the bicyclic alkaloid core that could be then functionalized to synthesize many pyrrolizidine alkaloids (**Scheme 34,** equation 3).

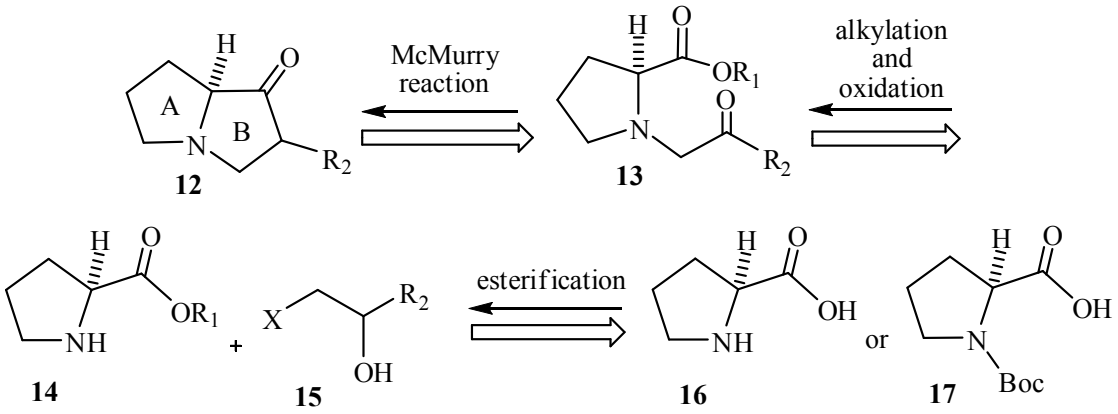
**Scheme 34**



## Results and Discussion

The goal of our project is to synthesize the five-membered B-ring present in the backbone of naturally occurring pyrrolizidine alkaloids by a novel McMurry reaction. According to the retrosynthetic analysis, reductive coupling of keto ester **13** by McMurry reaction would afford pyrrolizidinone **12** (**Scheme 1**). Alkylation of amino ester **14** followed by oxidation would result in the formation of the requisite carbon skeleton for the B-ring synthesis. Commercially available L-proline **16** or boc-L-proline **17** would be used to form proline esters. Thus, the five-membered A-ring of the pyrrolizidine alkaloids and stereochemistry at C8 would be in place from the start of the synthesis (**Scheme 1**).

**Scheme 1**

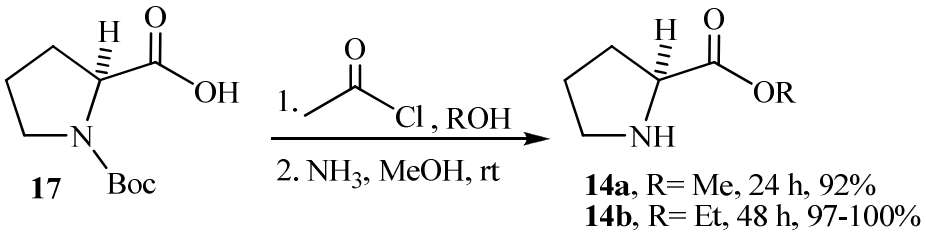



### I. Synthesis of proline esters

In **Scheme 35**, the sequential boc-deprotection and esterification reactions to synthesize proline methyl ester **14a** and ethyl ester **14b** are shown. Boc-proline was treated with 3 equivalents (eq.) of acetyl chloride in 10 ml of either methanol or ethanol at room temperature for 2 days.[32] Ammonia in MeOH was used to neutralize the proline ester HCl salt formed in the course of the reaction. When we used MeOH to form proline methyl ester

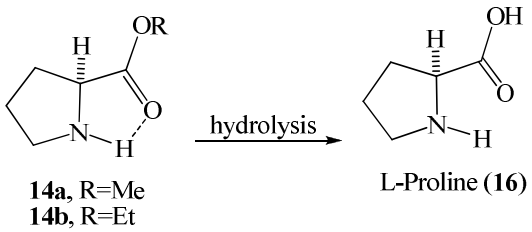
**14a**, we observed the presence of proline in the crude product mixture according to $^1$H NMR analysis. Because of our unwillingness to incorporate approximately 8% impurity into our product at the first step in the synthesis and because of facile ester hydrolysis during all purification attempts, we turned our attention to the synthesis of proline ethyl ester **14b**, which we hoped might be more stable. The sequential esterification and boc-deprotection under similar conditions except using EtOH provided ethyl ester **14b**. $^1$H NMR analysis of proline ethyl ester **14b** showed no proline. However, subsequent reactions revealed the presence of ammonium chloride in the crude reaction mixture. Unfortunately, as was the case with methyl ester **14a**, proline ethyl ester **14b** was also hydrolytically unstable during purification attempts. Consequently we were forced to continue the synthesis without removal of the ammonium chloride impurity. This ultimately proved to be a serious complication in our initial synthetic route (*vide infra*).

**Scheme 35**




We did attempt to purify proline ethyl ester **14b** using a short chromatography column or by extracting with water. However, even under these mild conditions, ester hydrolysis occurred. The ease of hydrolysis likely occurred because of intramolecular hydrogen bonding between the carbonyl oxygen and the amine proton which would activate the ester toward nucleophilic attack (**Scheme 36**). Because of this issue, we set out to synthesize what we hoped would be a more stable starting material, proline benzyl ester **14c**.

**Scheme 36**




**14a**, R=Me
**14b**, R=Et

L-Proline (**16**)

**Scheme 37** shows the reaction conditions attempted to directly form benzyl ester **14c**. Commercially available L-proline **16** was treated with 1 eq. of benzyl alcohol, 5 drops of concentrated $H_2SO_4$, silica gel, and microwave heating at 120 $^oC$ for 30 minutes (**Scheme 37**).[33] Following extractive workup, the $^1H$ NMR spectra showed only a mixture of proline and benzyl alcohol. We were not sure if the reaction occurred or if proline benzyl ester **14c** hydrolyzed during the workup. We also attempted to form proline benzyl ester **14c** by treating L-proline **16** with 4.3 eq. of benzyl alcohol and 1.5 eq. of $SOCl_2$ and stirring at 90 $^oC$ for 24 hours.[34] After extractive workup, $^1H$ NMR of the crude reaction mixture also contained almost entirely benzyl alcohol and proline. This procedure resulted in only 6% yield of proline benzyl ester **14c** after purification by column chromatography.

**Scheme 37**

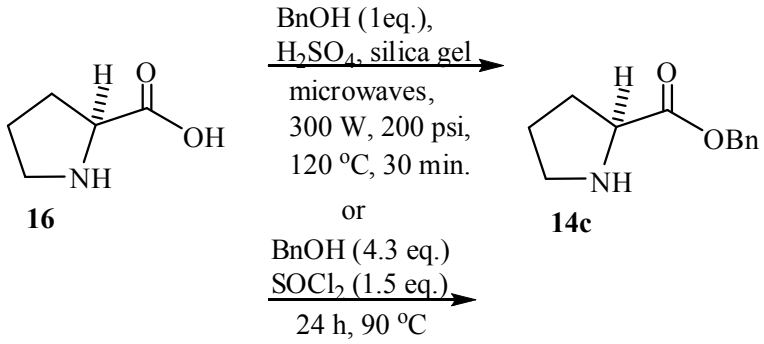
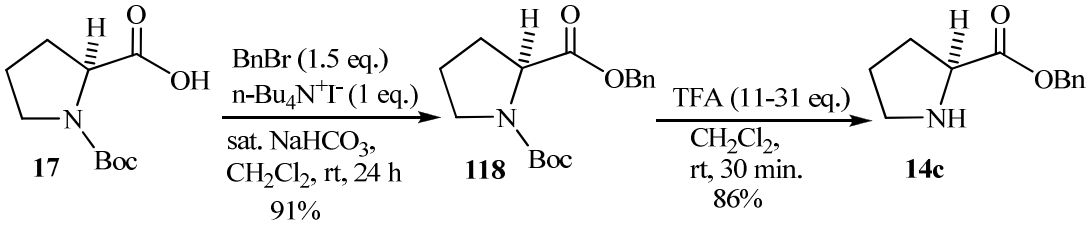



**Table 9.** Attempts at one-step formation of proline benzyl ester **14c**.

| Entry | Mass of Proline (**16**) used (g) | Comment | Notebook (NB) page |
|---|---|---|---|
| 1 | 1.3 | no reaction | FT-II-122 |
| 2 | 2.0 | 6% yield | FT-II-135 |

As seen, we needed another approach to increase the yield of proline benzyl ester **14c**. Therefore, we elected to perform a two-step alkylation-deprotection sequence. To that end, approximately 2 g of boc-L-proline **17** was treated with 1.5 eq of benzyl bromide, saturated $NaHCO_3$ solution, and 1 eq. of tetrabutyl ammonium iodide ($n\text{-}Bu_4N^+I^-$) in $CH_2Cl_2$ at room temperature overnight to afford the boc-proline benzyl ester **118** in 91% yield (**Scheme 38**).[35a] The deprotection of boc-proline benzyl ester **118** was performed with 11-31 eq. of TFA stirring at room temperature for 30 minutes. For the workup, the reaction mixture had to be added into a cold, saturated $NaHCO_3$ solution. Evaporation of the solvent after workup had to be performed using low heat, and proline benzyl ester **14c** had to be stored in $CH_2Cl_2$ solution at 4 $^oC$ all to suppress ester hydrolysis. Following this procedure, proline benzyl ester **14c** could be produced in 86% yield (**Scheme 38**). The reaction was performed using 0.5 g to 2 g of ester **118**. and the structure was confirmed by comparison of the $^1H$ NMR spectrum to that of the commercially available material.[35b]

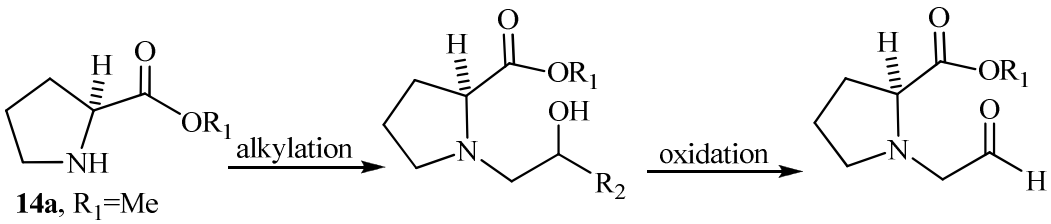
**Scheme 38**




**II. Alkylation and oxidation of proline esters**

The next step was to add the carbon chain necessary for the pyrrolizidine skeleton synthesis. Our initial plan was the alkylation of the proline methyl ester **14a** or proline ethyl ester **14b** to form amino alcohol **119a** or **120a** or amino diol **119b** or **120b** which could then be oxidized to form the desired amino aldehyde **121a** or **121b** (**Scheme 39**).

**Scheme 39**



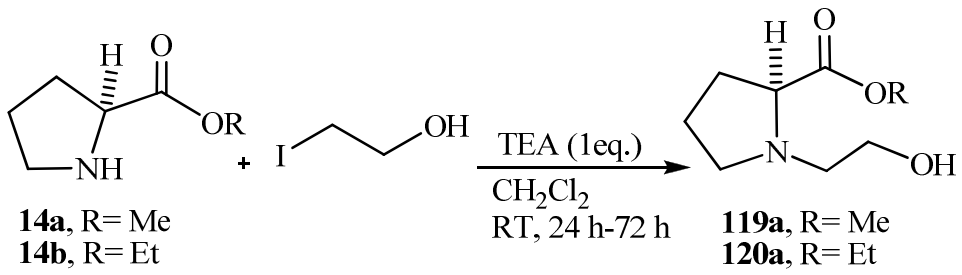

**14a**, $R_1$=Me
**14b**, $R_1$=Et

**119a**, $R_1$= Me, $R_2$= H
**119b**, $R_1$= Me, $R_2$= $CH_2OH$
**120a**, $R_1$=Et, $R_2$= H
**120b**, $R_1$=Et, $R_2$= $CH_2OH$

**121a**, $R_1$=Me
**121b**, $R_1$=Et

The alkylation reaction conditions of proline methyl ester **14a** and proline ethyl ester **14b** with 2-iodoethanol are shown in **Scheme 40**. The alkylation reaction follows an $S_N2$ mechanism with subsequent deprotonation by TEA. Although proline methyl ester **14a** provided no conversion to product (**Table 10,** entries 1 and 2), proline ethyl ester **14b** gave amino alcohol **120a** in modest yields (**Table 10,** entries 3-5). The percent conversion was improved when reaction time was increased from 24 to 48 hours but was not improved when time increased to 72 h. Because later steps in this route proved problematic (*vide infra*), these reactions were only done once and so the reproducibility of these results was not investigated.

**Scheme 40**




**14a**, R= Me
**14b**, R= Et

**119a**, R= Me
**120a**, R= Et

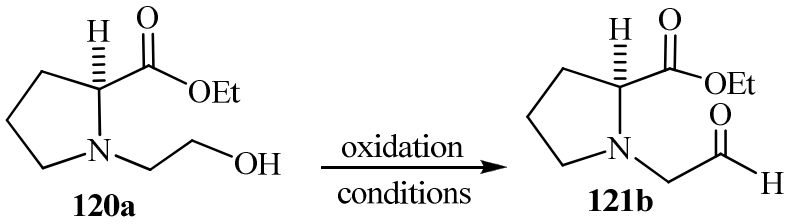
**Table 10.** Alkylation of proline methyl ester **14a** and proline ethyl ester **14b** with 2-iodoethanol.

| Entry* | SM | 2-iodoethanol, eq. | Time (h) | Comment | NB page |
|---|---|---|---|---|---|
| 1 | **14a** | 2.4 | 24 | starting material and hydrolyzed ester | FT-I-49 |
| 2 | **14a** | 1.2 | 72 | same as entry 1 | FT-I-62 |
| 3 | **14b** | 1.2 | 24 | 25% isolated yield | FT-I-53-55 |
| 4 | **14b** | 1.2 | 48 | 39% isolated yield | FT-I-97-101 |
| 5 | **14b** | 1.2 | 72 | 24% isolated yield | FT-I-61 |

*Reactions performed using 100-200 mg proline ester.

The next step was the oxidation of amino alcohol **120a**. $SO_3$·pyridine complex with DMSO (Parikh-Doering conditions),[36] oxalyl chloride/TEA/DMSO (Swern conditions),[37] and Dess-Martin periodinane[37, 38] were all used in an attempt to oxidize primary amino alcohol **120a** (**Scheme 41**). Subjecting alcohol **120a** to Parikh-Doering conditions for 2.5 h gave no reaction (**Table 11**, entry 1). Extended reaction times provided small amounts of aldehyde according to $^1$H NMR analysis, but purification of the crude product by chromatography resulted in no recovery of product (**Table 11,** entry 2-3). Swern oxidation of amino alcohol **120a** resulted in a complex mixture (**Table 11**, entry 4). Attempts using Dess-Martin periodinane gave similar results when run at 0 $^o$C or room temperature (**Table 11**, entries 5-7).

**Scheme 41**




**120a** **121b**

**Table 11.** Oxidation of amino alcohol **120a** .

| Entry | Reagents (eq.) and reaction conditions | Comment | NB page |
|---|---|---|---|
| 1[a] | $SO_3$·pyr. (3.4), TEA (3.4), DMSO, RT, 2.5 h | no evidence of aldehyde by $^1$H NMR | FT-I-73-74 |
| 2[a] | $SO_3$·pyr. (3.4), TEA (3.4), DMSO, RT, 15 h | trace amount of aldehyde by $^1$H NMR | FT-I-79 |
| 3[a] | $SO_3$·pyr. (3.4), TEA (3.4), DMSO, RT, 18 h | trace amount of aldehyde by $^1$H NMR | FT-I-84-89 |
| 4[a] | Oxalyl chloride (3.1), TEA (8.0), DMSO, RT, 1 h | complex mixture | FT-I-113 |
| 5[b] | Dess-Martin periodinane (2.0), $CH_2Cl_2$, RT, 25 min. | complex mixture | FT-I-102 |
| 6[b] | Dess-Martin periodinane (2.0), $CH_2Cl_2$, RT, 10 min. | complex mixture | FT-I-104 |
| 7[b] | Dess-Martin periodinane (2.0), $CH_2Cl_2$, 0 $^oC$, 10 min | complex mixture | FT-I-105 |

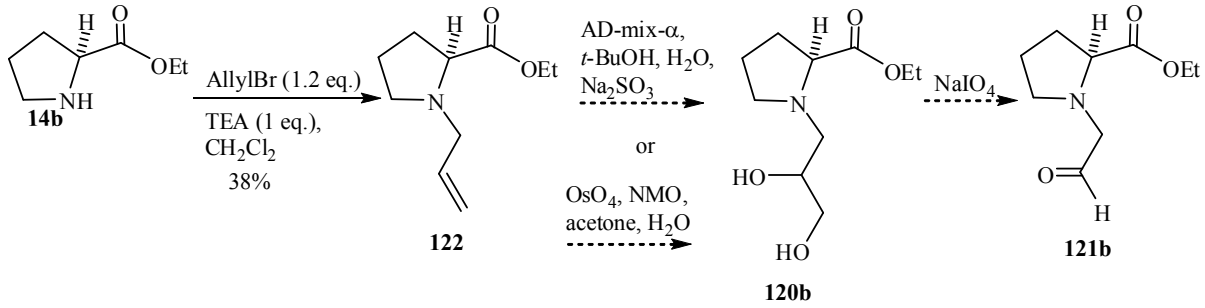
[a]Reactions performed using 75-175 mg amino alcohol.

[b]Reactions performed using 25 mg amino alcohol.

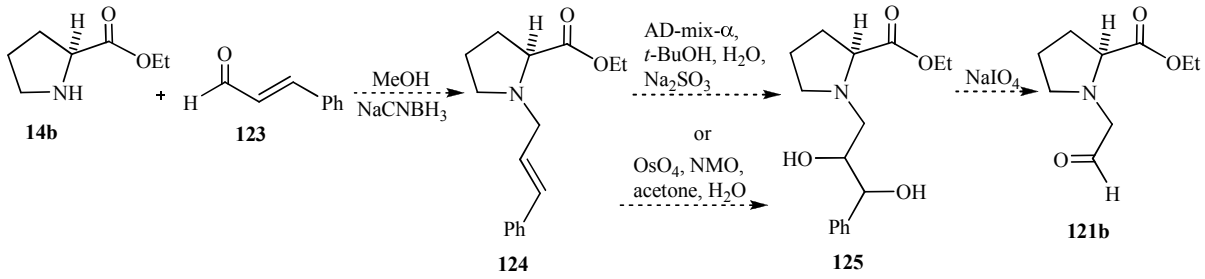
The attempted oxidations of the primary alcohol did not provide amino aldehyde **121b**. Therefore, we aimed to synthesize amino aldehyde **121b** via oxidative cleavage of a 1,2-diol **120b** (**Scheme 42**). First, proline ethyl ester **14b** was treated with 1.2 eq. of allyl bromide and 1 eq. of TEA at room temperature for 48 h, affording amino alkene **122** in 38% yield.[39] When NaI was used as a catalyst in order to increase the electrophilicity of the allyl bromide, yields were not improved. After alkylation of proline ethyl ester **14b**, we attempted dihydroxylation of amino alkene **122** to convert it to 1,2-diol **120b**, which could then be oxidatively cleaved to give the desired aldehyde. However, attempts at dihydroxylation of alkene either with $OsO_4$[40] or AD-mix-α[41] did not provide amino 1,2-diol **120b** (**Scheme 42**). Moreover, we had hoped that reductive amination[42] of proline ethyl ester **14b** with

cinnamaldehyde **123** could be followed by a better-precedented dihydroxylation, but in our hands the reductive amination failed (**Scheme 43**).

**Scheme 42**

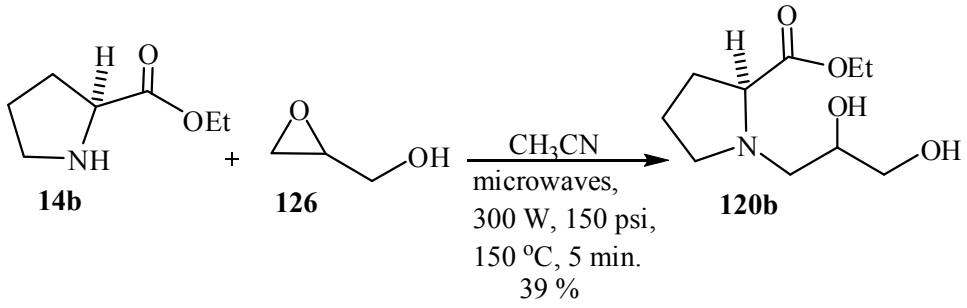



**Scheme 43**




Microwave-assisted alkylation of proline ethyl ester **14b** with glycidol was our next choice to synthesize 1,2-diol **120b**. Proline ethyl ester **14b** was treated with 1 eq. of glycidol **126** in $CH_3CN$ and heated using microwaves at 100 $^oC$ for 5 minutes (**Scheme 44**).[43] In this reaction, the amine attacks the less hindered carbon of the epoxide according to an $S_N2$ mechanism. The $2^o$ amino alcohol is easily distinguished from the undesired aminolysis regioisomer by the characteristic $^1H$ NMR resonances of the α-methylene protons, which appear as a pair of doublets at ca. 2.5 ppm.[43] This aminolysis reaction was initially run using MeOH, but this resulted in trans-esterification to form the proline methyl ester. However, the use of $CH_3CN$ afforded 1,2-diol **120b** in 39% yield following purification by column chromatography. No trace of the amino alcohol regioisomer was detected according to $^1H$ NMR analysis of the crude reaction mixtures.

**Scheme 44**




We attempted the oxidative cleavage reaction either on crude or purified 1,2-diol **120b** with $NaIO_4$[40] or $NaIO_4$ supported on silica gel [44] (**Scheme 45**). Reaction of 1,2-diol **120b** with $NaIO_4$ was carried out at room temperature for 30 minutes or 60 minutes, but no aldehyde was formed according to $^1$H NMR analysis (**Table 12**, entries 1 and 2).[40] By contrast, the analogous reaction of 1,2-diol **120b** performed using $NaIO_4$ supported on silica gel gave encouraging results at room temperature or 0 °C for 15 and 30 minutes (**Table 12**, entries 3-5).[44] Two reactions were performed in $CDCl_3$ to avoid the need to concentrate the reaction mixture (entries 4 and 5). Instead the reaction mixture was filtered and $^1$H NMR of filtrate was acquired. However, if the filtrate was concentrated, the aldehyde peaks disappeared. We also diluted the $CDCl_3$ filtrate containing the aldehyde in $CH_2Cl_2$, stored it overnight, and then acquired a $^1$H NMR spectrum. Unfortunately, this also resulted in the loss of the aldehyde resonance in the $^1$H NMR spectrum. From this, it appears that the product was labile in either concentrated form or when stored as a dilute solution.

**Scheme 45**

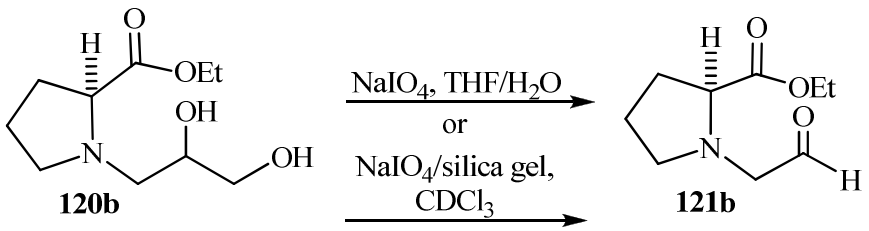



**Table 12.** Cleavage of the crude 1,2-diol **120b**.

| Entry | Reagents, eq. | Reaction conditions and comments | NB page |
|---|---|---|---|
| 1[a] | $NaIO_4$ (1.45), $THF/H_2O$ | RT, 1h, complex mixture | FT-I-124 |
| 2[a] | $NaIO_4$ (1.45), $THF/H_2O$ | RT, 30 min., complex mixture | FT-I-132 |
| 3[b] | $NaIO_4$/silica gel (9.4), $CDCl_3$ | RT, 30 min., mixture with aldehyde present | FT-I-137 |
| 4[b] | $NaIO_4$/silica gel (9.4), $CDCl_3$ | 0 $^oC$, 15 min., same as # 3 | FT-I-140 |
| 5[a] | $NaIO_4$/silica gel (9.4), $CDCl_3$ | RT, 15 min., 100% conversion to aldehyde | FT-I-134 |
| 6[b] | $NaIO_4$/silica gel (9.4), $CH_2Cl_2$ | 0 $^oC$, 15 min., polymerization upon concentrating | FT-I-141 |

[a]Reactions performed using 100 mg amine diol.

[b]Reactions performed using 50 mg amine diol.

As described above, formation of amino aldehyde proved difficult primarily because of aldehyde instability. Consequently, we turned our attention to the synthesis of keto esters in the hope that they would be more stable.

Microwave-assisted alkylation of proline ethyl ester **14b** with 1 eq. of (2,3-epoxypropyl)benzene **127** afforded a single aminolysis regiosiomer,[43] amino alcohol **128,** along with significant amounts of byproduct identified as chlorohydrin **129**[45] (**Scheme 46**). The chlorohydrin was presumably produced by reaction of the epoxide with residual $NH_4Cl$ from the boc-deprotection-esterification (**Scheme 35**). The isolated yields of chlorohydrin ranged from 20-35% and varied with the batch of proline ethyl ester. This alkylation was attempted at different reaction times and in different solvents including $CH_3CN$, toluene, and

isopropyl alcohol in an effort to increase the yield (**Table 13**). Chromatography afforded amino alcohol **128** in 20-35% yield (**Table 13**, entries 1-5), demonstrating that the solvent provided little difference in yield. To compensate for the side reaction leading to chlorohydrin **129**, 2 eq. of (2,3-epoxypropyl)benzene were used in an effort to improve the yield. In that case, chromatography afforded amino alcohol **128** in 46% yield (**Table 13**, entry 6). Running this reaction at 250 $^{o}$C in toluene resulted in ester hydrolysis (**Table 13**, entry 7).

**Scheme 46**

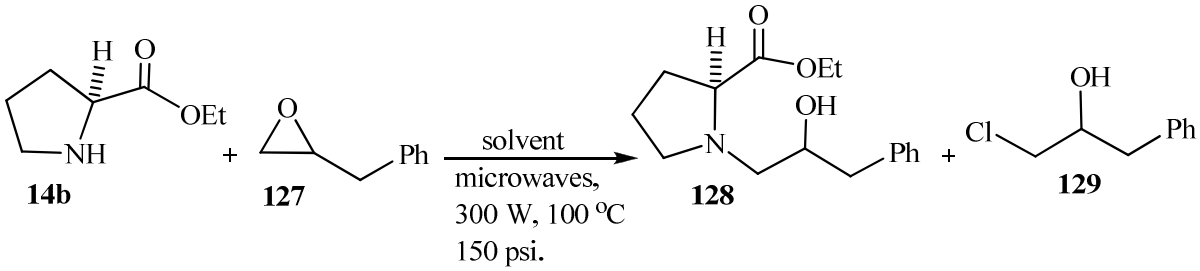



**Table 13.** Microwave-assisted alkylation of proline ethyl ester **14b** with (2,3-epoxypropyl)benzene.

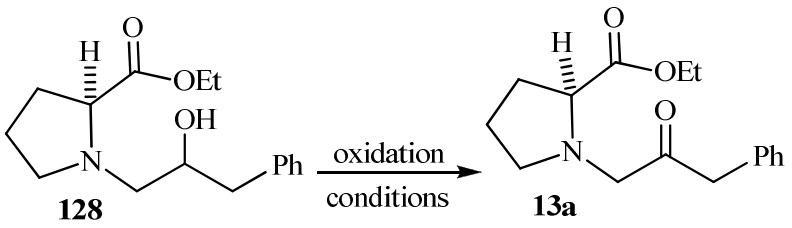
| Entry[a] | Solvent | Temp., $^{o}$C | Hold time, min. | Purified % yield | NB page |
|---|---|---|---|---|---|
| 1 | $CH_3CN$ | 100 | 10 | 20 | FT-II-104 |
| 2 | $CH_3CN$ | 100 | 60 | 27 | FT-II-112 |
| 3 | Toluene | 100 | 30 | 32 | FT-II-164 |
| 4 | Toluene | 100 | 20 | 35 | FT-II- 132 |
| 5[b] | iPrOH | 100 | 10 | 35 | FT-II-134 |
| 6[c] | Toluene | 100 | 30 | 46 | FT-II-154 |
| 7 | Toluene | 250 | 30 | ester hydrolysis | FT-II- 131 |

[a]All reactions performed using 285 mg (2 mmol) proline ethyl ester.
[b] Microwave pressure set at 200 psi.
[c] 2 equivalents of epoxide used.

The oxidation of amino alcohol **128** was performed either on crude or purified amino

alcohol **128** by using Parikh-Doering conditions,[36] Swern conditions,[37] Dess-Martin periodinane,[37, 38] or pyridinium chlorochromate (PCC)[46] (**Scheme 47**). When the oxidation of amino alcohol **128** was performed with 4 eq. of $SO_3$·pyridine complex on the purified amino alcohol **128**, extractive workup provided keto ester **13a** in 85% yield (**Table 14**, entry 1). The oxidation using Swern conditions also afforded keto ester **13a**, but in a much lower yield (**Table 14**, entry 2). Oxidation reactions with PCC resulted in decomposition (**Table 14**, entries 3-5). The oxidation reaction with Dess-Martin periodinane was performed at room temperature, 0 $^{o}$C for 15 minutes, 1.5, or 5 hours. However, all three trials resulted in ester hydrolysis (**Table 14**, entries 6-8). The Parikh-Doering oxidation was consequently used as the oxidation method of choice for this synthetic route, providing reproducible yields (ca. 85%) of keto-ester **13a**.

**Scheme 47**




**128** **13a**

**Table 14.** Oxidation of amino alcohol **128**.

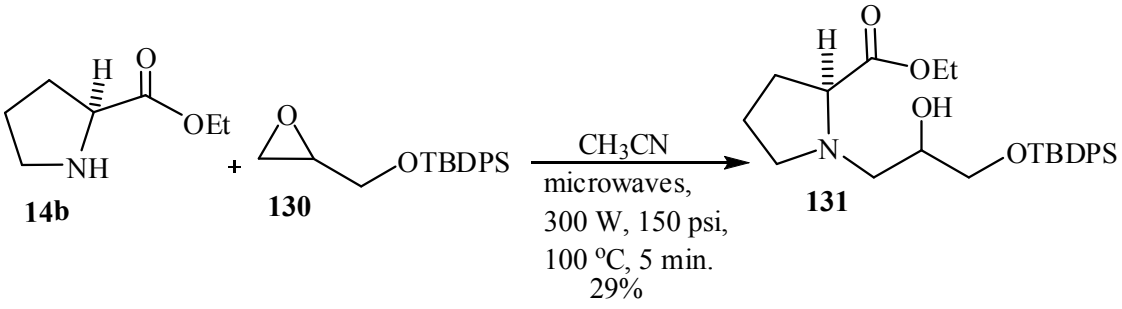
| Entry | SM mass | Oxidation reagents (eq.) and reaction conditions | Comment | NB page |
|---|---|---|---|---|
| 1 | 360 mg, purified | $SO_3$·pyridine complex (4.0) TEA (4.0), DMSO, RT, 18 h | 85% yield | FT-III-2 |
| 2 | 200 mg, purified | $(COCl)_2$ (3.1), TEA (7.75) DMSO, $CH_2Cl_2$, RT, 17 h | 14% yield | FT-II-64 |
| 3 | 50 mg, crude | PCC (2), $CH_2Cl_2$, 0 $^oC$, 5 h | complex mixture | FT-II-114 |
| 4 | 50 mg, crude | PCC (2), $CH_2Cl_2$, RT, 24 h | complex mixture | FT-II-115 |
| 5 | 50 mg, crude | PCC (2), $CH_2Cl_2$, RT, 3 h | complex mixture | FT-II-111 |
| 6 | 50 mg, crude | Dess-Martin periodinane (2) $CH_2Cl_2$, 1.5 h, RT | ester hydrolysis | FT-II-72 |
| 7 | 100 mg, crude | Dess-Martin periodinane (2) $CH_2Cl_2$, 5 h, RT | ester hydrolysis | FT-II-87 |
| 8 | 100 mg, crude | Dess-Martin periodinane (2) $CH_2Cl_2$, 15 min., 0 $^oC$ | ester hydrolysis | FT-II-86 |

We were also interested in the synthesis of other McMurry reaction precursors that contain protected functional groups that could be deprotected and further functionalized after the McMurry reaction. Syntheses of proline-derived TBDPS ether **13b** or proline-derived benzyl ether **13c** were accordingly chosen (**Scheme 49** and **51**).

In the microwave-assisted alkylation reaction,[43] proline ethyl ester **14b** was treated using 1 eq. of epoxide **130**, itself available in quantitative yield from glycidol.[47] This reaction

resulted in 29% purified yield of amino alcohol **131** (**Scheme 48**). Extending reaction time did not improve the yield.

**Scheme 48**




Oxidation of amino alcohol **131** was performed by using Parikh-Doering conditions[36] or Dess-Martin periodinane[37, 38] (**Scheme 49**). While the oxidation of amino alcohol **131** by using Parikh-Doering conditions provided no reaction (**Table 15**, entry 1), Dess-Martin periodinane resulted in ester hydrolysis, as evidenced by the presence of only proline in the $^1$H NMR spectrum of the crude reaction mixture (**Table 15**, entry 2).

**Scheme 49**

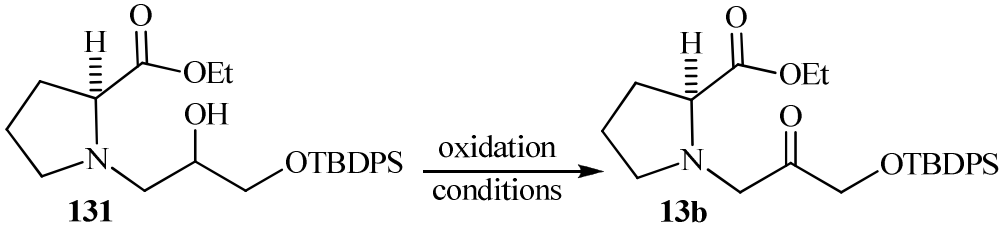


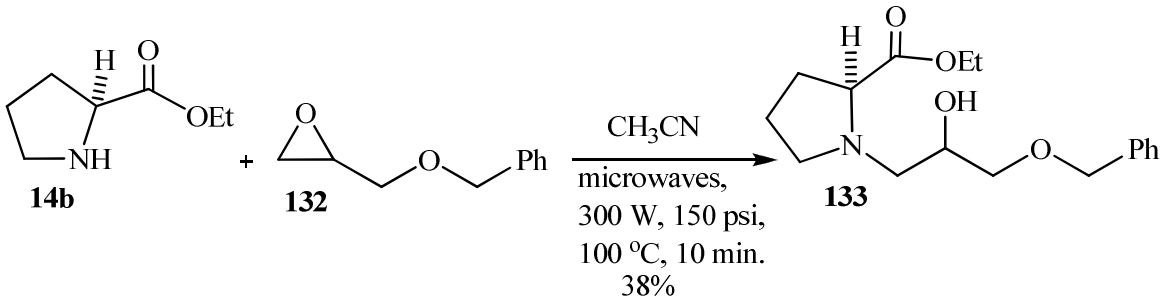

**Table 15.** Oxidation of amino alcohol **131**.

.

| Entry | SM mass | Oxidation reagents (eq.) and reaction conditions | Comment | NB page |
|---|---|---|---|---|
| 1 | 250 mg, purified | $SO_3$·pyr. complex (3.4) TEA (3.4), DMSO, RT, 18 h | no reaction | FT-II-13-19B |
| 2 | 50 mg, crude | Dess-Martin periodinane (2) $CH_2Cl_2$, RT, 3 h | ester hydrolysis | FT-II-90 |

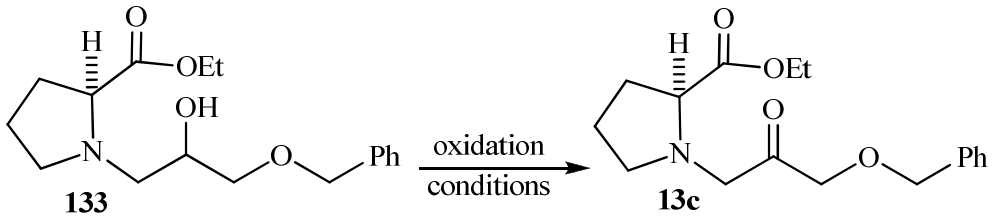
Because of the problems with oxidation of amino alcohol **131**, we decided to pursue the synthesis of the proline-derived benzyl ether **133**. As before, in the microwave-assisted alkylation reaction,[43] proline ethyl ester **14b** (2 mmol) was treated with 1 eq. of epoxy benzyl ether **132**, itself available from glycidol in 74% yield according to a known procedure.[48] Following chromatography, amino alcohol **133** was produced in 38% purified yield (**Scheme 50**).

**Scheme 50**




The oxidation of amino alcohol **133** was attempted using Parikh-Doering conditions, Swern conditions, and Dess-Martin periodinane either on crude or purified amino alcohol **133** (**Scheme 51**). Unfortunately, all attempts resulted in decomposition or ester hydrolysis (**Table 16**).

**Scheme 51**



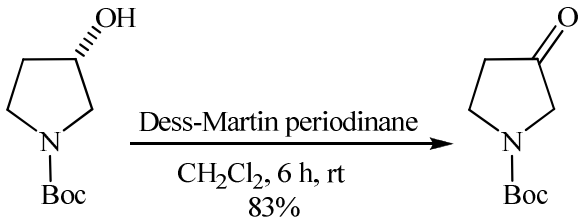

**133** **13c**

**Table 16.** Oxidation of amino alcohol **133**.

| Entry | SM mass | Oxidation reagents (eq.) and reaction conditions | NB page |
|---|---|---|---|
| 1 | 200 mg, crude | $SO_3$·pyr. complex (3.4), TEA (3.4), DMSO, RT, 21 h | FT-II-76 |
| 2 | 200 mg, purified | $SO_3$·pyr. complex (3.4), TEA (3.4), DMSO, RT, 18 h | FT-II-80 |
| 3 | 50 mg, crude | Dess-Martin periodinane (2), $CH_2Cl_2$ , RT, 3 h | FT-II-79 |
| 4 | 25 mg, purified | Dess-Martin periodinane (2), $CH_2Cl_2$ , RT, 30 min. | FT-II-81 |
| 5 | 100 mg, crude | Dess-Martin periodinane (2), $CH_2Cl_2$, 0 $^oC$, 15 min. | FT-II-84 |
| 6 | 200 mg, crude | Oxalyl chloride (3.1), TEA (7.8), DMSO, $CH_2Cl_2$, RT, 5 h | FT-II-89 |

As described previously, we attempted to use Dess-Martin periodinane (0.3 M in $CH_2Cl_2$) for the oxidation of 1,2-diol, secondary and primary alcohols. However, all trials resulted in ester hydrolysis. In order to check the viability of the Dess-Martin reagent, we treated boc-pyrrolidinol **134** with 2 eq. of Dess-Martin periodinane in $CH_2Cl_2$ at room temperature for 6 hours. Extractive workup afforded the expected boc-pyrrolidinone **135** in 83% yield (**Scheme 52**). We concluded that Dess-Martin periodinane reagent was viable.

**Scheme 52**

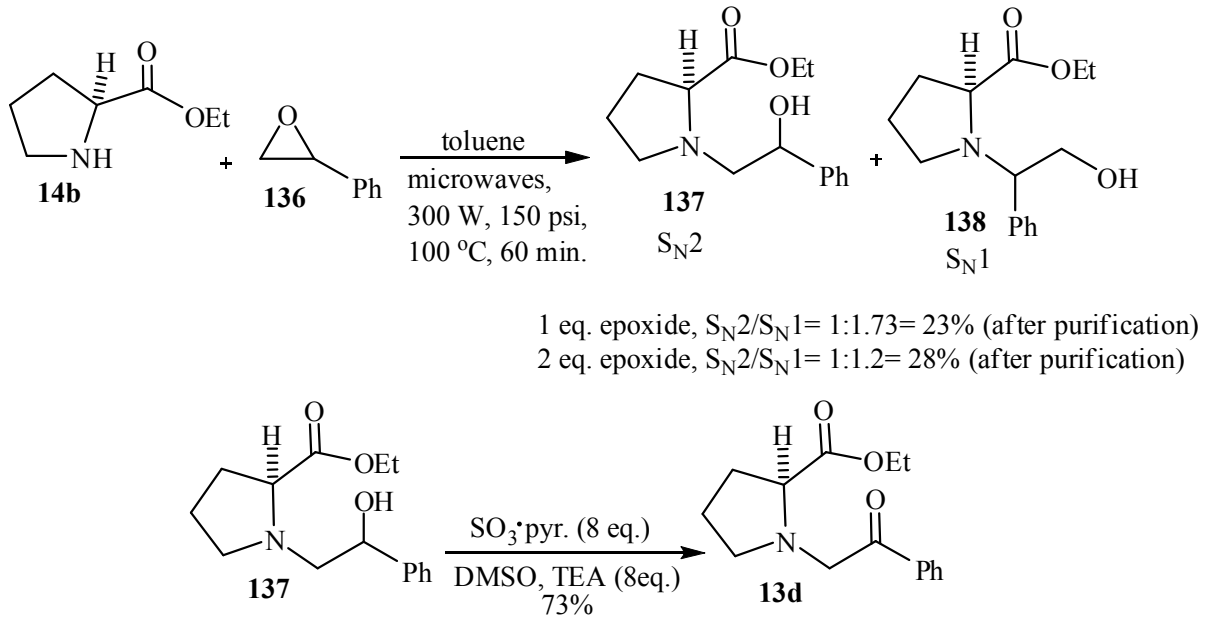



**134** **135**

As discussed earlier, microwave-assisted alkylation of proline ethyl ester **14b** with (2,3-epoxypropyl)benzene followed by oxidation provided keto ester **13a** (**Scheme 46** and

**47**). To provide a variety of precursors for the key reductive coupling sequence (*vide infra*), the analogous alkylation and oxidation were performed using styrene oxide as the epoxide. The alkylation reaction of proline ethyl ester **14b** with styrene oxide could occur by $S_N2$ or $S_N1$ mechanism. According to previous work from our group, using toluene as a solvent favors $S_N2$ selectivity.[43] However, this did not hold true for this reaction. In the microwave-assisted alkylation reaction, proline ethyl ester **14b** was treated with 1 eq. of styrene oxide **136** in toluene at 100 $^oC$ for 60 minutes (**Scheme 53**). $^1H$ NMR analysis of the crude reaction mixture showed a slight (1.7:1) selectivity for the $S_N1$ pathway. As before, regioisomeric assignments were based on the chemical shift of the amino alcohol side-chain methylene. These resonances were located at approximately 2.5 ppm for the desired amino alcohol **137** and at 3.5 ppm for the primary alcohol **138**. Nonetheless, chromatography afforded the desired amino alcohol **137** in 23% yield. To account for the presence of residual $NH_4Cl$ as before, proline ethyl ester **14b** was treated with 2 eq. of styrene oxide **136** in toluene at the same settings, but chromatography afforded amino alcohol **137** in only 28% yield. The oxidation of amino alcohol **137** was performed using 8 eq. of $SO_3$·pyridine complex and extractive workup afforded the product **13d** in 73% yield.

**Scheme 53**




As described above, alkylation and oxidation reactions were performed using proline ethyl ester **14b**. However, these esters suffered from hydrolytic instability and the presence of unremovable $NH_4Cl$, which lowered yields in alkylation steps. Consequently, the microwave-assisted alkylation of proline benzyl ester **14c** with (2,3-epoxypropyl)benzene provided an attractive option for synthesizing the analogous keto ester (**Scheme 54**). The microwave-assisted alkylation of proline benzyl ester **14c** with (2,3-epoxypropyl)benzene would not require the excess (2,3-epoxypropyl)benzene, because we were able to purify the ester **14c** prior to alkylation. Therefore, we treated proline benzyl ester **14c** with 1 eq. of (2,3-epoxypropyl)benzene **127** in $CH_3CN$ at 100 °C for different hold times (**Table 17**, entries 1-3).[43] When this reaction was run for 30, 60, and 90 minutes, we only obtained ~10% conversion to amino alcohol **139**. The crude reaction mixture contained unreacted (2,3-epoxypropyl)benzene, proline benzyl ester **14c**, along with trace amounts of proline and benzyl alcohol, indicating hydrolysis of the ester. Moreover, 5 hours hold time caused

formation of the lactone **140** (**Scheme 54**). In spite of the low product yield, an oxidation was attempted. Using Parikh-Doering oxidation conditions, amino alcohol **139** was treated with 8 eq. of $SO_3$·pyridine complex in DMSO at room temperature for 18 hours. Extractive workup afforded the keto ester **13e** in 74% yield.

**Scheme 54**

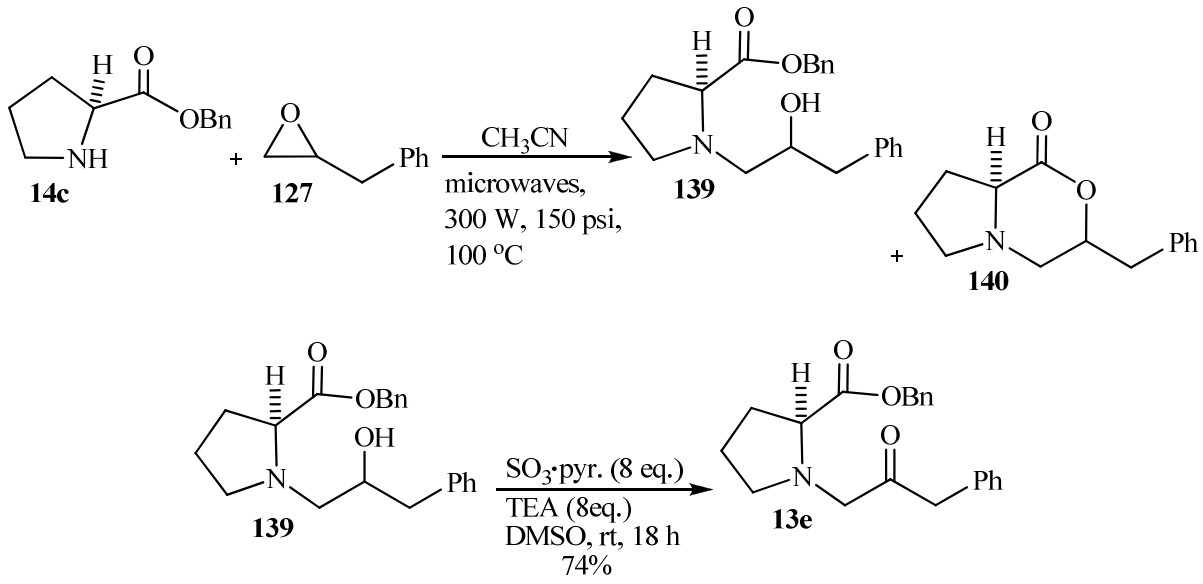


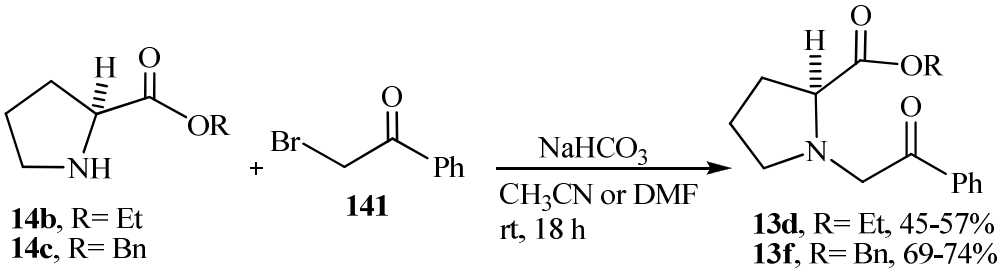

**Table17.** Microwave-assisted alkylation of proline benzyl ester **14c** with (2,3-epoxypropyl)benzene.

| Entry | SM mass | Hold time, min. | Comment | NB page |
|---|---|---|---|---|
| 1 | 275 mg | 30 | 8% yield | FT-II-130 |
| 2 | 300 mg | 30 | ~10% conversion, 50% unreacted, epoxide, 30% SM, trace benzyl alcohol, proline | FT-II- 177 |
| 3 | 200 mg | 60 | same as entry 2 | FT-II-183 |
| 4 | 200 mg | 300 | 80% lactone and trace amount of benzyl alcohol | FT-II-185 |

Because of the low-yielding alkylation step in the sequence leading to keto ester **13d**, we looked for an alternative procedure. Direct formation of keto ester **13d** via alkylation of proline ethyl ester **14b** with 2-bromoacetophenone **141** provided satisfying results.[49] This

procedure allowed us to avoid the oxidation step. It also proved successful for the synthesis of keto ester **13f** from benzyl ester **14c** (**Scheme 55**). In this alkylation reaction, proline ethyl ester **14b** or proline benzyl ester **14c** was treated with 1.0-1.3 eq. of 2-bromoacetophenone **141** in DMF or $CH_3CN$ at room temperature for 18 hours.[49] Extractive workup with water and chromatography afforded the keto ester **13d** in 45-51% yield and keto ester **13f** in 69-74% yield. During chromatography, 1% TEA had to be added into the solvent system and the keto esters **13d** and **13f** had to be stored at -78 $^oC$ in $CH_2Cl_2$ solution to avoid decomposition.

**Scheme 55**




**14b**, R= Et
**14c**, R= Bn

**13d**, R= Et, 45-57%
**13f**, R= Bn, 69-74%

Applying two, three, or four-step procedures, we synthesized four different precursors for McMurry reactions. Keto ester **13a** was synthesized by applying a three-step procedure in 31% yield; keto ester **13e** was synthesized by a four-step procedure in 5% yield. Initially, we were able to access keto ester **13d** by a three-step process in 17% overally yield. However, we later found a more efficient two-step process that provided **13d** in 50% yield. Finally, keto ester **13f** was synthesized in 54% yield using a three-step procedure (**Figure 6**). With these compounds in hand, we were ready to attempt the McMurry reaction to form the five-membered B-ring.

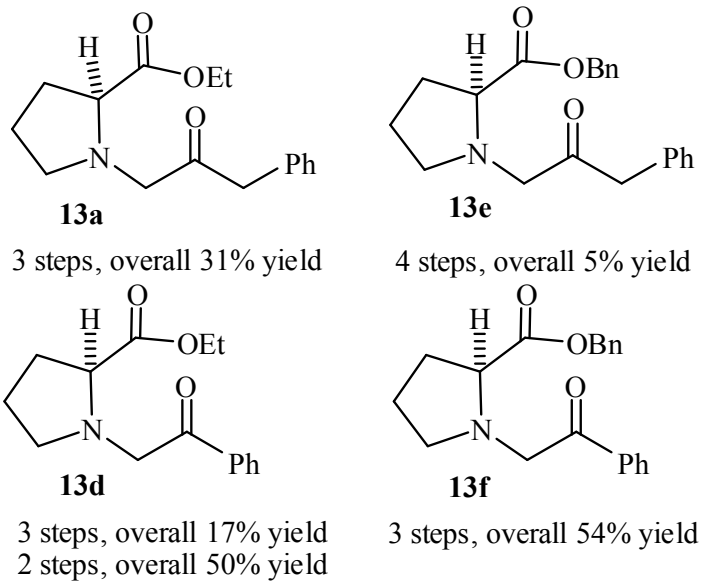



**Figure 6**. McMurry precursors

### III. McMurry reductive coupling reaction

Using the stepwise addition of reactants[50] or the instant method[13b] and different reaction conditions, these reactions were performed with keto esters **13a**, **13d**, or **13f**. Although keto ester **13e** was stored at -78 $^{o}$C, it decomposed before the McMurry reaction could be performed. In the stepwise method, a pre-reduction of titanium species with zinc metal was performed, followed by the addition of the keto ester into the reaction mixture. The resulting solution was refluxed or stirred at room temperature. In contrast to the stepwise method, the instant method was performed by adding all reactants including the keto ester in one step followed by heating conventionally or with microwave irradiation.[51]

While $TiCl_4$-Zn-THF was used for keto ester **13d** or **13f**, different titanium species, reducing agents, and solvent combinations including $TiCl_4$-Zn-THF, $TiCl_3$-Zn-DME, $TiCl_4$-$LiAlH_4$-THF, $TiCl_4$-Zn-pyridine-THF, and $TiCl_4 \cdot (THF)_2$-Zn-THF reagent systems were examined for the McMurry reaction of keto ester **13a**.

Our first series of attempts at the reductive cyclization employed the $TiCl_4$-Zn-THF reagent system in combination with keto ester **13a** (**Scheme 56**). Using the stepwise method, keto ester **13a** was added to a solution of 3 eq. of low-valent Ti in refluxing THF. After quenching with HCl-EtOH solution, neutralization, extractive workup, and chromatography using silica gel afforded a 14% yield of a product tentatively identified as pyrrolizidinone **12a** (**Table 18**, entry 1). An alternative extractive workup using saturated $NaHCO_3$ solution followed by flash chromatography using silica gel afforded the same compound in 31-39% yield (**Table 18**, entries 2-4). Changing the concentration of the keto ester had no significant effect on conversion (**Table 18**, entry 4). We considered that the modest yields might be due in part to incomplete formation of the required low-valent titanium species. To ensure that the reduction of Ti (IV) was occurring, we attempted to activate the zinc metal[30] (**Table 18**, entry 5) and also to extend the pre-reduction time to 5.5 hours (**Table 18**, entry 6). Both experiments resulted in complex mixtures.

Varying the amount of low-valent Ti had an effect on the amount of product formed. When 3 eq. of $TiCl_4$ were used, the crude product contained some unreacted keto ester **13a** (**Table 18**, entries 1-4). Therefore, 6 eq. of $TiCl_4$ were used to increase the conversion of keto ester **13a** to pyrrolizidinone **12a**. However, using the stepwise method for the McMurry reaction followed by extractive workup with $NaHCO_3$ and chromatography using silica gel afforded pyrrolizidinone **12a** in only 17% yield (**Table 18**, entry 7).

In the reactions described above, the reductive coupling step of the reaction was performed in refluxing THF. To examine if the temperature were important in the McMurry reaction, the reductive coupling was performed at room temperature using of 6 eq. of $TiCl_4$. Extractive workup with $NaHCO_3$ and chromatography using silica gel afforded

pyrrolizidinone **12a** in 31% yield (**Table 18**, entry 8). Finally, the instant method was also attempted for this keto ester cyclization. Accordingly, keto ester **13a** was treated with 6 eq. of $TiCl_4$ and 12 eq. of Zn in refluxing THF for 18 hours. However, extractive workup with $NaHCO_3$ followed by $^1H$ NMR analysis revealed only a complex mixture (**Table 18**, entry 9).

The preliminary structural assignments from the reactions described above were based on correlation of the $^1H$ NMR spectra of both the crude and purified product mixtures and were consistent with the estimated $^1H$ NMR spectrum generated by ChemDraw prediction software. It should be noted that in all McMurry coupling results reported herein, further characterization of the reaction mixtures was not possible (*vide infra*). Consequently, the structural assignments for all pyrrolizidinones remain tentative.

**Scheme 56**

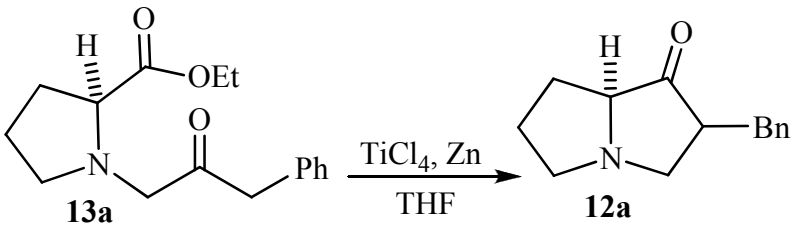



**Table 18**. McMurry reaction of keto ester **13a** with $TiCl_4$-Zn-THF reagent system.

| Entry | SM mass, (g/100ml) | $TiCl_4$, eq. | Zn, eq. | Pre-reduction, h | Temp., $^oC$ and time, h | Comment | NB page |
|---|---|---|---|---|---|---|---|
| 1[a] | 140 mg, (1.57) | 3 | 6 | 2 | 65 $^oC$, 15 | 14% yield | FT-II-34-36 |
| 2 | 250 mg, (1.49) | 3 | 6 | 2 | 65 $^oC$, 16 | 39% yield | FT-II-47-57 |
| 3 | 150 mg, (1.36) | 3 | 6 | 2 | 65 $^oC$, 17 | 34% yield | FT-II-62 |
| 4 | 275 mg, (0.34) | 3 | 6 | 2 | 65 $^oC$, 16 | 31% yield | FT-II-92 |
| 5[b] | 50 mg, (0.71) | 3 | 6 | 2 | 65 $^oC$, 17 | complex mixture | FT-II-158 |
| 6 | 100 mg, (0.83) | 3 | 6 | 5.5 | 65 $^oC$, 16 | complex mixture | FT-II-101 |
| 7 | 50 mg, (0.42) | 6 | 12 | 2 | 65 $^oC$, 18 | 17% yield | FT-II-106 |
| 8 | 50 mg, (0.31) | 6 | 12 | 2 | 25 $^oC$, 18 | 31% yield | FT-II-108 |
| 9 | 50 mg, (0.31) | 6 | 12 | none | 65 $^oC$, 18 | complex mixture | FT-II-109 |

[a] Reaction quenched with HCl-EtOH
[b] Activated Zn used

$TiCl_3$-Zn-DME, $TiCl_4$-$LiAlH_4$-THF, $TiCl_4$-Zn-pyridine-THF, and $TiCl_4 \cdot (THF)_2$-Zn-THF reagent systems were also used in an attempt to optimize the McMurry reaction of keto ester **13a** (**Scheme 57**, **Table 19**). Unfortunately, unlike the results reported using the $TiCl_4$-Zn reagent combination, all these attempts (described below) resulted in complex mixtures.

The experiments using $TiCl_3$, which is more reactive than $TiCl_4$, were prepared in a glove bag. The instant method was attempted using the $TiCl_3$-activated Zn-DME reagent system in refluxing DME. Extractive workup was performed with $NaHCO_3$ (**Table 19**, entry 1). The stepwise method using $TiCl_3$-Zn-DME at room temperature also resulted in a complex mixture after extractive workup with either $NaHCO_3$ or EDTA solution (**Table 19**, entry 2). Extraction with EDTA solution has been demonstrated to be useful for dissociating the free amine in the product from the Lewis acidic Ti species.[13a]

Besides Zn, $LiAlH_4$ was examined as a reducing agent. Keto ester **13a** was treated with $TiCl_4$-$LiAlH_4$-THF reagent system (**Table 19**, entry 3). After 2-hour pre-reduction of $TiCl_4$, keto ester **13a** was added into the slurry, and the resulting solution was refluxed for 2 hours. Extractive workup was performed using $Na_2CO_3$ solution.

Pyridine was used as a back-bonding ligand to stabilize $TiCl_4$ and to increase the electron density on the active titanium species.[26] After allowing pre-reduction of $TiCl_4$ with Zn and pyridine in THF for 2 hours, keto ester **13a** was added into the slurry and the resulting solution was stirred at room temperature for 15 hours. Again, $NaHCO_3$ solution was used for the extractive workup (**Table 19**, entry 4).

$TiCl_4 \cdot (THF)_2$ was chosen in McMurry reaction due to ease of handling. After 2 or 6 hours pre-reduction of $TiCl_4 \cdot (THF)_2$ with Zn in THF, keto ester **13a** was added into the slurry and the reaction mixture was stirred at room temperature (**Table 19**, entry 5) or refluxed at 65 $^{o}$C (**Table 19**, entries 6-7). However, both trials resulted in complex mixtures.

**Scheme 57**

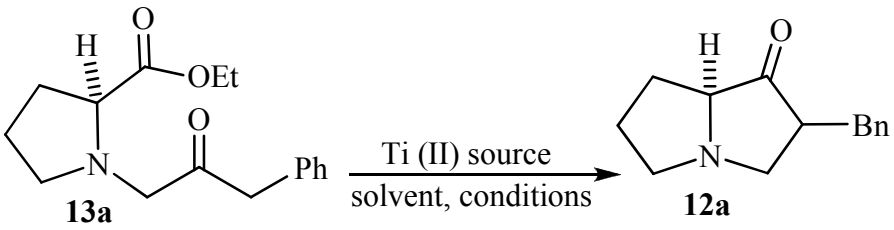



**Table 19**. McMurry reaction of keto ester **13a** with various Ti(II) sources.

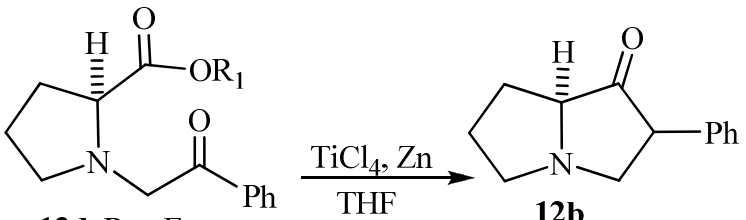
| Entry | SM mass, (g/100ml) | Ti, eq. | Zn, eq. | Solvent | Pre-reduction Time, h | Temp., °C and time, h | NB page |
|---|---|---|---|---|---|---|---|
| 1[a] | 50 mg, (0.83) | $TiCl_3$ (2) | 4 | DME | none | 85 °C, 18 | FT-II-159 |
| 2[b] | 75 mg, (1.54) | $TiCl_3$ (2) | 4 | DME | 3 | 25 °C, 18 | FT-II-160 |
| 3 | 50 mg, (1.00) | $TiCl_4$ (4) | --[c] | THF | 2 | 65 °C, 2 | FT-II-155 |
| 4[d] | 45 mg, (0.75) | $TiCl_4$ (6) | 12 | THF | 2 | 25 °C, 15 | FT-II-120 |
| 5 | 25 mg, (0.21) | $TiCl_4 \cdot (THF)_2$ (6) | 12 | THF | 2 | 25 °C, 18 | FT-II-110 |
| 6 | 70 mg, (0.70) | $TiCl_4 \cdot (THF)_2$ (3) | 6 | THF | 6 | 65 °C, 16h | FT-II-102 |
| 7 | 125 mg, (1.17) | $TiCl_4 \cdot (THF)_2$ (3) | 6 | THF | 2 | 65°C, 16 | FT-II-77 |

[a] Activated Zn used.
[b] Workup with $NaHCO_3$ or EDTA.
[c] 3 eq. of $LiAlH_4$ used instead of Zn and workup with $Na_2CO_3$.
[d] 7 eq. of pyridine added into the 6 eq. of $TiCl_4$.

Because of the success of the stepwise method using $TiCl_4$ and Zn, we applied these conditions to the cyclization of keto esters **13d** and **13f**. After pre-reduction of $TiCl_4$ with Zn in THF for 2 hours, keto ester **13d** or **13f** was added into the slurry and refluxed overnight or for 4 hours (**Scheme 58**). In all trials, extractive workup with $NaHCO_3$ afforded in modest yields a compound whose $^1H$ NMR spectrum was consistent with that estimated for pyrrolizidinone **12b** (**Table 20**, entries 1-3). To prevent protonation of the tertiary amine and

maintain neutral reaction conditions, 3 eq. of TEA were added into the reaction mixture. However, extractive workup afforded pyrrolizidinone **12b** in only 31% yield (**Table 20**, entry 4). Unfortunately, attempts at purification of the crude pyrrolizidinone **12b** using silica gel, florisil, or preparative TLC with addition of 0.5-1% of TEA to the solvent system resulted in complete product decomposition.

**Scheme 58**




**13d**, $R_1$= Et
**13f**, $R_1$= Bn

**12b**

**Table 20**. McMurry reaction of keto ester **13d** and **13f** with $TiCl_4$- Zn-THF reagent system.

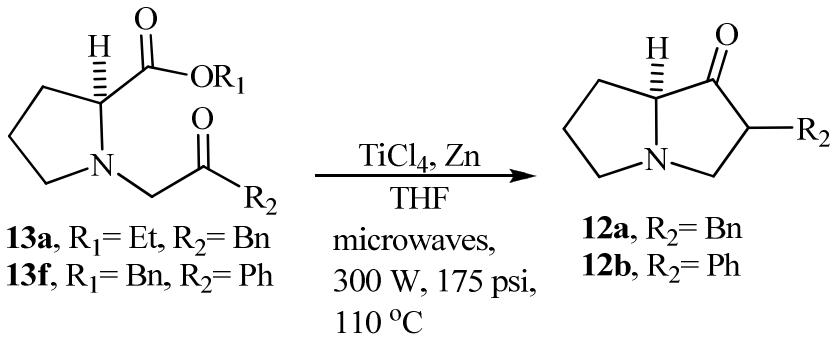
| Entry | SM mass, (g/100ml) | $TiCl_4$, eq. | Zn, eq. | Reduction time, h | Temp., $^oC$ and time, h | % Yield | NB page |
|---|---|---|---|---|---|---|---|
| 1 | 140 mg, (1.55) | 3 | 6 | 2 | 65 $^oC$, 18 | 50 | FT-III-38 |
| 2 | 150 mg, (1.43) | 3 | 6 | 2 | 65 $^oC$, 4 | 58 | FT-III-63 |
| 3 | 157 mg, (1.83) | 3 | 6 | 2 | 65 $^oC$, 18 | 67 | FT-III-54 |
| 4[a] | 150 mg, (1.88) | 3 | 6 | 2 | 65 $^oC$, 18 | 31 | FT-III-56 |

[a] Addition of 3 eq. of TEA into the $TiCl_4$.

We were also interested in using microwave heating[51] to reduce the reaction time (**Scheme 59**). The instant method was used for all microwave-assisted McMurry reactions we attempted. Reactions of keto ester **13a** or **13f** were performed with varying equivalences of low-valent Ti, varying concentrations of keto ester, and with varying hold times (**Table 21**, entries 1-4). Treating keto ester **13a** with 1.2 eq. of $TiCl_4$ and 2.4 eq. of Zn and irradiation for

10 minutes produced pyrrolizidinone **12a** in 15% yield after extractive workup with $NaHCO_3$ solution (**Table 21**, entry 1). For this reaction, $^1H$ NMR analysis showed unreacted keto ester **13a**. However, using excess $TiCl_4$ and/or increasing the reaction time did not improve the yields (**Table 21**, entries 2-4). McMurry reaction with keto ester **13f** was performed using similar reaction conditions, but the yields were also low (**Table 21**, entry 5-7).

**Scheme 59**




**13a**, $R_1$= Et, $R_2$= Bn
**13f**, $R_1$= Bn, $R_2$= Ph

**12a**, $R_2$= Bn
**12b**, $R_2$= Ph

**Table 21**. McMurry reaction of keto ester **13a** and **13f** with $TiCl_4$-Zn-THF using microwave heating.

| Entry | Keto ester, g/100 ml | $TiCl_4$, eq. | Zn, eq. | Hold time, min. | Comment | NB page |
|---|---|---|---|---|---|---|
| 1 | **13a** (10.41) | 1.2 | 2.4 | 10 | 15% percent yield | FT-II-51-54 |
| 2 | **13a** (10.41) | 1.2 | 2.4 | 30 | same as # 1 | FT-II-56 |
| 3 | **13a** (5.51) | 2.0 | 4.0 | 30 | same as # 1 | FT-II-58 |
| 4 | **13a** (4.59) | 2.0 | 4.0 | 60 | same as # 1 | FT-II-59 |
| 5 | **13f** (10.00) | 1.2 | 2.4 | 15 | 9% yield | FT-III-44 |
| 6 | **13f** (8.25) | 1.2 | 2.4 | 45 | same as # 5 | FT-III-45 |
| 7 | **13f** (7.00) | 1.2 | 2.4 | 30 | same as # 5 | FT-III-42 |

## IV. Identification of McMurry products

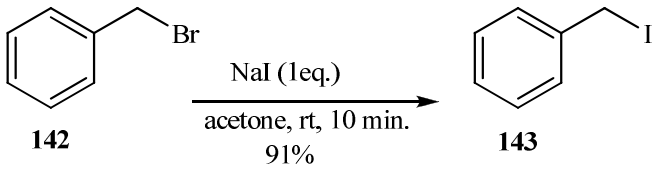
As reported above, the McMurry reaction provided compounds with spectra that were consistent with the estimated $^1H$ NMR spectra for pyrrolizidinones **12a** and **12b**, but these data are insufficient to make a structural assignment. More data were needed to identify these products. Pyrrolizidinone **12a** could be purified by chromatography, although the

presumed diastereomers proved inseparable. However, purification of pyrrolizidinone **12b** failed due to its instability in the presence of any Lewis acidic sorbent no matter how mild. Elimination of the chiral carbon in pyrrolizidinone **12a** and formation of a more stabile analog to pyrrolizidinone **12a** were our planned solutions to these characterization and purification issues.

Initially, we attempted an enolate alkylation of pyrrolizidinone **12a** to eliminate the chiral center and to deconvolute the $^{1}H$ and $^{13}C$ NMR spectra. Paquette has demonstrated that enolization of a similarly substituted bicyclo[3.3.0]octanone using KHMDS followed by alkylation using allyl bromide occurred exclusively at the non-bridgehead α-carbon.[52] Consequently, we employed these conditions for our alkylation attempt.

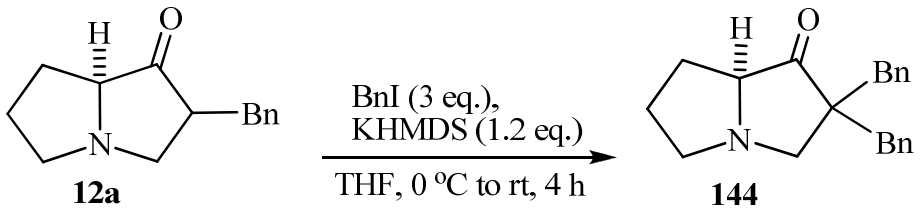
For the preparation of our alkylating reagent, a Finklestein reaction was performed to form benzyl iodide **143**. In this reaction, benzyl bromide was treated with 1 eq. of NaI in acetone at room temperature for 10 minutes. Benzyl iodide **143** was isolated in 91% yield following extractive workup (**Scheme 60**).

**Scheme 60**



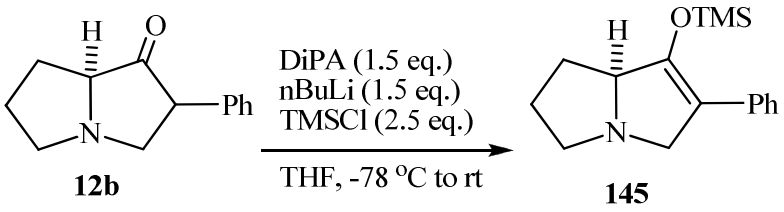

In the alkylation reaction, pyrrolizidinone **12a** was treated with 1.2 eq. of KHMDS (potassium hexamethyldisilylazide) and 3 eq. of benzyl iodide **143** in THF at 0 $^{o}C$, and the mixture was stirred under nitrogen at room temperature for 4 hours (**Scheme 61**).[52] After extractive workup with $NaHCO_3$, $^{1}H$ NMR analysis showed the disappearance of the α-methine, but the crude product decomposed when subjected to column chromatography.

**Scheme 61**




The next strategy to eliminate the chiral center was the formation of silyl enol ether (**Scheme 62**). In this reaction, lithium diisopropyl amide (1.5 eq.) was made *in situ*, and a solution of pyrrolizidinone **12b** was added to that reaction mixture at -78 °C to form the enolate. TMSCl (2.5 eq.) was then added to form the silyl enol ether. However, extractive workup with $NaHCO_3$ resulted in a complex mixture. Consequently, these attempts at reducing the complexity of the $^1H$ NMR and $^{13}C$ NMR spectra failed.

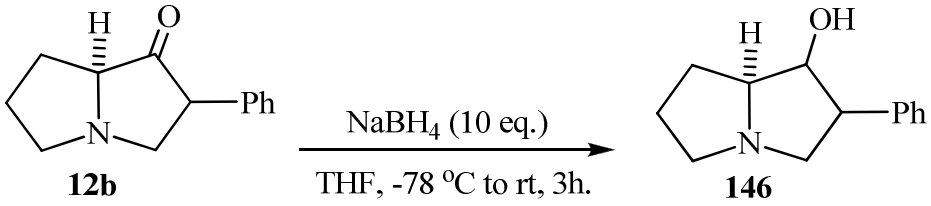
**Scheme 62**




Different reduction reactions were attempted on the crude pyrrolizidinone **12b** using $NaBH_4$[53] or $LiAlH_4$[54] to create more stable compounds. The reduction of ketone **12b** using $NaBH_4$ or $LiAlH_4$ would create another chiral center that would cause the $^1H$ NMR spectrum to become more complex. However, good diastereoselectivity in the reduction was likely and chromatographic separation of the mixture of stereoisomers might be accomplished. When we used $NaBH_4$,[53] the crude pyrrolizidinone **12b** (0.2 mmol) was treated with 10 eq. of $NaBH_4$ in THF at -78 °C and reaction mixture was stirred at room temperature for 3 hours.

Quenching the mixture with 10% $NH_4OH$ followed by extractive workup provided a crude reaction mixture whose $^1H$ NMR spectrum showed a complex coupling pattern around 3.5 ppm, consistent with a secondary carbinol. However, no separation was obtained during chromatography (**Scheme 63**).

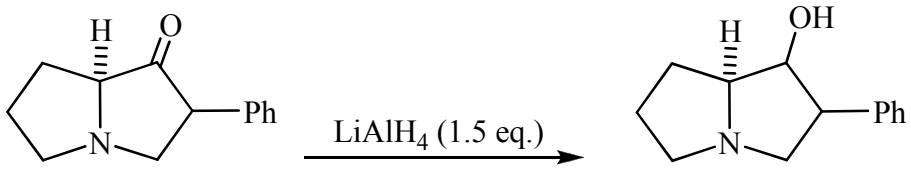
**Scheme 63**




**12b** **146**

$LiAlH_4$[54] also provided similar encouraging results for the reduction of pyrrolizidinone **12b** (**Scheme 64**). The crude pyrrolizidinone **12b** (0.4 mmol) was treated with 1.5 eq. of $LiAlH_4$ in refluxing THF for 2 hours. After quenching the reaction mixture with 20% KOH, $^1H$ NMR analysis again showed a complex multiplet near 3.5 ppm, consistent with the expected chemical shift for pyrrolizinol **146**. However, the crude product mixture decomposed during column chromatography using silica gel. No separation of the presumed diastereomers was obtained using florisil as a sorbent.

**Scheme 64**

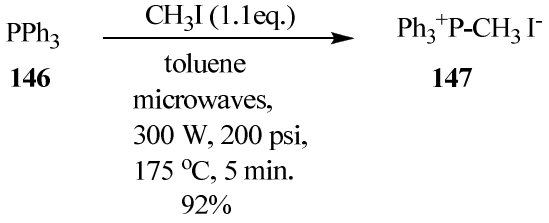



**12b** **146**

Our last approach was the use of a Wittig reaction to form an alkene.[55] This reaction does not create a new chiral center and the alkene peaks appear at a distinctive $^1H$ NMR chemical shift. In order to perform the Wittig reaction, first the Wittig reagent was

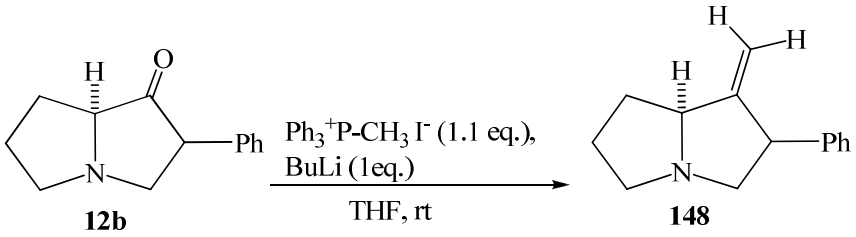
synthesized. Triphenyl phosphine **146** (1 mmol) was treated with 1.1 eq. of methyl iodide in toluene using microwaves at 175 $^{o}$C for 5 minutes. Filtration and washing the solid with hexanes afforded methyl triphenyl phosphonium iodide **147** in 92% yield (**Scheme 65**).

**Scheme 65**




In the second step of Wittig reaction, methyl triphenyl phosphonium iodide **147** (0.8 mmol) was treated with 1 eq. of nBuLi in THF at 0 $^{o}$C to form the ylide. Pyrrolizidinone **12b** (0.7 mmol) dissolved in THF was added to the reaction mixture and stirred at room temperature for 2 hours or overnight (**Scheme 66**). Extractive workup with $NaHCO_3$ resulted in complex mixtures regardless of reaction time.

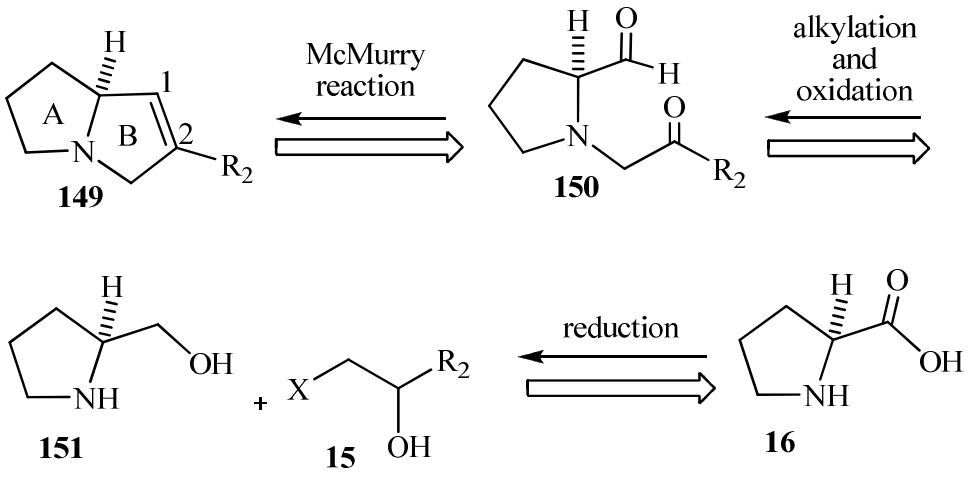
**Scheme 66**




**V. New directions**

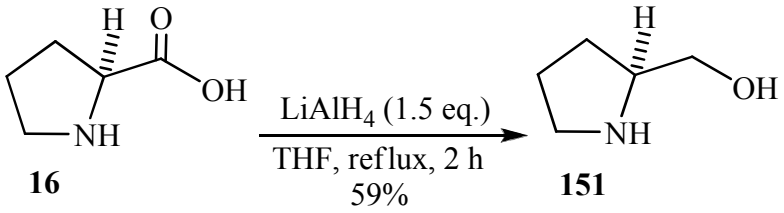
We were also interested in performing McMurry reactions using a keto aldehyde to obtain pyrrolizidine **149** that contains unsaturation at C1 and C2. This route would eliminate the purification and characterization issues posed by the previous approach (**Scheme 1**), as the target contains only one chiral carbon and does not involve the formation of the unstable presumed pyrrolizidinone moeity.

**Scheme 1**



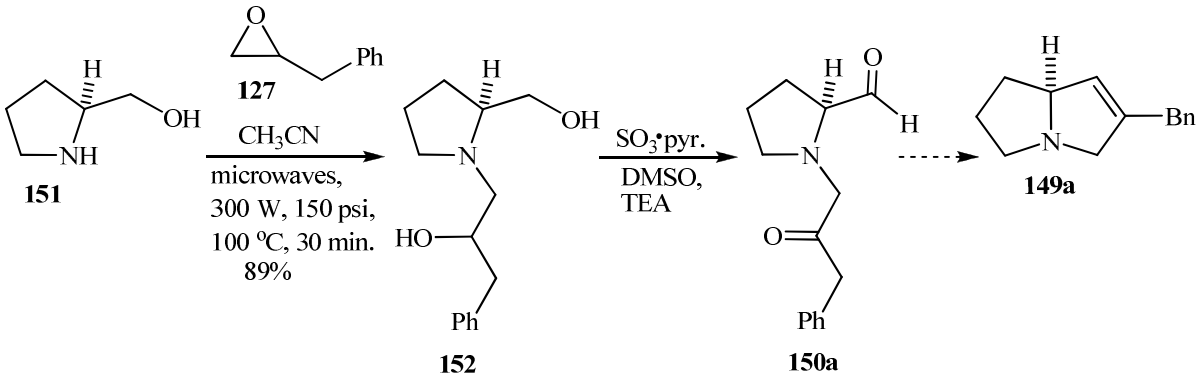

This synthesis began with the reduction of L-proline **16** using $LiAlH_4$ (**Scheme 67**). According to a known procedure,[54] L-proline **16** (8.7 mmol) was treated with 1.5 eq. of $LiAlH_4$ in refluxing THF for 2 hours followed by quenching with 20% KOH. Workup and Kugelrohr distillation of the crude product provided prolinol **151** in 59% yield.

**Scheme 67**




In the microwave-assisted alkylation reaction,[43] prolinol **151** (2 mmol) was treated with 1 eq. of (2,3-epoxypropyl)benzene **127** in $CH_3CN$ at 100 $^oC$ for 30 minutes and concentrated to afford amino alcohol **152** in 89% yield (**Scheme 68**). Oxidation of amino alcohol **152** using Parikh-Doering conditions, however, did not provide keto aldehyde **150a**. Furthermore, the aqueous workup conditions for this oxidation caused problems with the recovery of the starting material due to its water solubility.

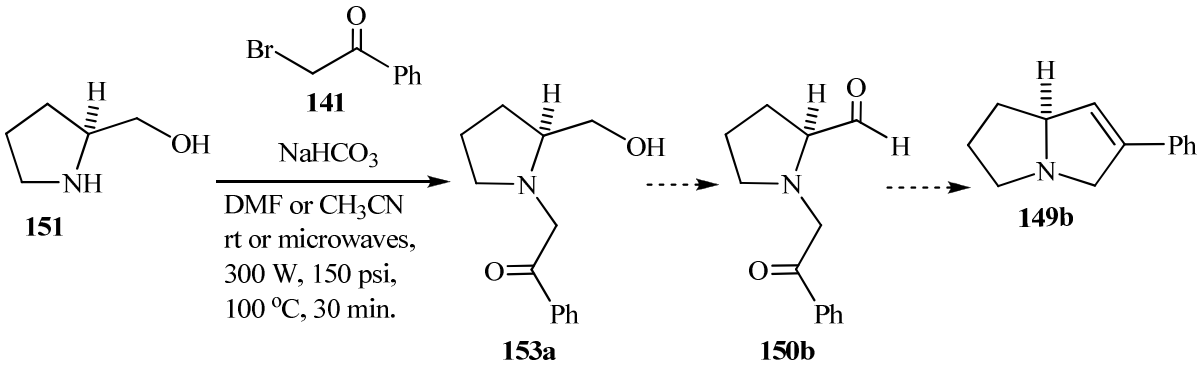
**Scheme 68**




Because of the problems with the oxidation of amino alcohol **152**, synthesis of keto aldehyde **150b** and **150c** was attempted by alkylation of prolinol **151** with 2-bromoacetophenone (**Scheme 69**) or chloroacetone (**Scheme 70**), respectively.[49] When prolinol **151** was treated with 1.3 eq. of 2-bromoacetophenone in DMF at room temperature overnight, $^{1}$H NMR analysis revealed a mixture of products (**Table 22**, entry 1). Unfortunately, chromatography resulted in decomposition. Moreover, running this reaction under microwave heating for 30 minutes resulted in a complex mixture (**Table 22**, entries 2-3).

Alkylation of prolinol **151** with chloroacetone at room temperature in DMF (**Table 22**, entry 5) or in refluxing ethanol[56] resulted in complex mixtures (**Table 22**, entry 4). In these trials, the distinctive methyl ketone peak was not observed in $^{1}$H NMR analysis.

**Scheme 69**




**Scheme 70**

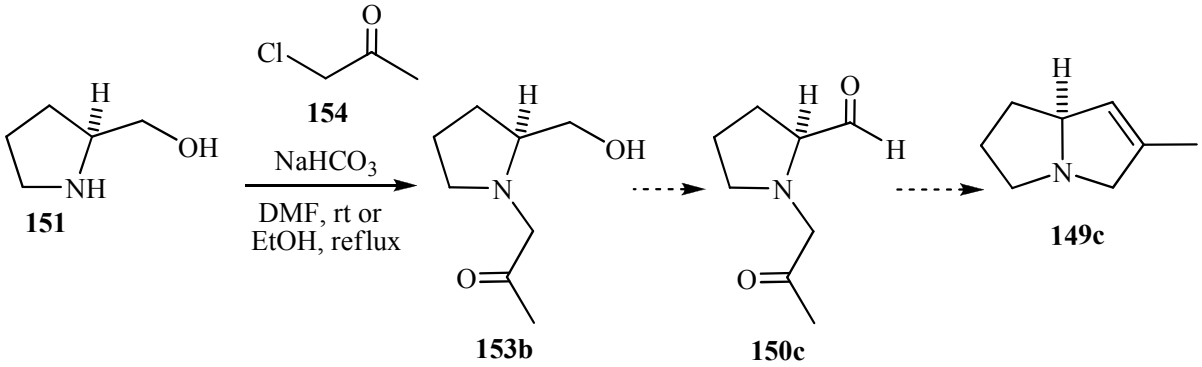



**Table 22**. Alkylation of prolinol **151** with 2-bromoacetophenone or chloroacetone.

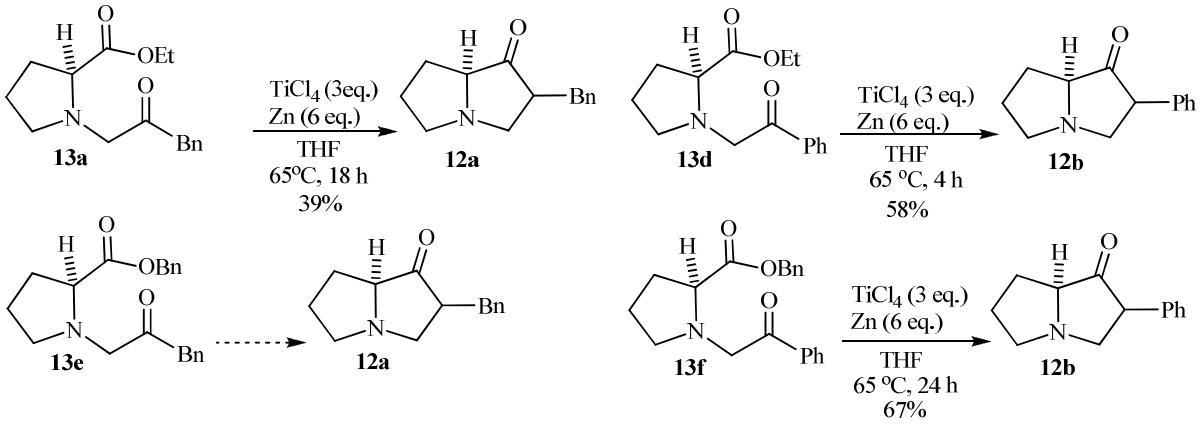
| Entry | Reagents, eq. | Comment | NB page |
|---|---|---|---|
| 1[a] | 2-bromoacetophenone (1.3)<br>$NaHCO_3$ (1.3), DMF | RT, 24 h, decomposition after chromatography | FT-III-15 |
| 2[b] | 2-bromoacetophenone (1.3)<br>$NaHCO_3$ (1.3), DMF | microwaves, 30 min.<br>complex mixture | FT-III-22 |
| 3[b] | 2-bromoacetophenone (1.1)<br>$NaHCO_3$ (1.1), $CH_3CN$ | microwaves, 30 min.<br>complex mixture | FT-III-28 |
| 4[a] | Chloroacetone (1.0)<br>$NaHCO_3$ (1.3), EtOH | reflux, 24 h,<br>complex mixture | FT-III-23 |
| 5[a, c] | Chloroacetone (1.3) , $NaHCO_3$ (1.3), DMF | RT, 24 h,<br>complex mixture | FT-III-24 |

[a]Reaction performed using 100 mg prolinol
[b]Reaction performed using 50 mg prolinol
[c] NaI used as a catalyst.

## VI. Conclusion

Commercially available boc-L-proline or L-proline was used as the source of the A-ring of the bicyclic core of pyrrolizidine alkaloids. Formation of the necessary five-membered chain for the correct carbon skeleton of the B-ring was accomplished using alkylation and oxidation or direct alkylation reactions. Although formation of amino aldehyde proved difficult, oxidation of the secondary alcohols using Parikh-Doering conditions afforded the keto ester McMurry precursors in satisfying yields. The novel McMurry reaction with keto ester **13a**, **13d**, and **13f** using the stepwise method in refluxing THF or the instant method using microwave heating provided compounds with spectra that were consistent with the estimated $^{1}$H NMR spectra for pyrrolizidinones **12a** and **12b**. Different strategies were applied to identify McMurry products **12a** and **12b** more thoroughly. However, our attempts to form stable McMurry products failed, and so the structural assignments remain tentative. Studies in this area are ongoing.

**Scheme 71**



## Experimental

### General Procedures

All commercially available compounds were purchased from Aldrich Chemical Company or Acros and used as received unless otherwise specified. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Purification of compounds was performed by using silica gel or florisil. TLC analyses were performed on silicagel 60 $F_{254}$ plates (250 μm thicknesses). Microwave-assisted reactions were performed using a CEM Discover ™ reactor. Microwave reactor vials and caps were purchased from CEM Corporation. Triethyl amine was dried over potassium hydroxide and used freshly distilled. Dimethyl sulfoxide was dried over calcium hydride and distilled. All $^{1}H$ NMR and $^{13}C$ NMR spectra were obtained on a 400 MHz JEOL ECX instrument and chemical shifts (δ) reported relative to residual solvent peak $CDCl_3$. All NMR spectra were obtained at room temperature.

### (7aS)-2-Benzylhexahydro-1H-pyrrolizin-1-one (12a)

**Stepwise method:** To a 25 mL round-bottom flask equipped with a magnetic stirring bar and a nitrogen atmosphere were added zinc dust (0.3388 g, 5.18 mmol) and THF (11 mL). The solution was cooled in an ice bath, and titanium tetrachloride (0.519 g, 2.5908 mmol) was added slowly. The resulting suspension was refluxed for 2 hours. Keto ester **13a** (0.2378 g, 0.8636 mmol) dissolved in 5 mL of THF was added into the black slurry. The solution was refluxed for 18 h. The reaction mixture was dissolved in $CH_2Cl_2$ (50 mL), extracted with saturated $NaHCO_3$ (2x 20 mL), and washed with distilled water (25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography using MeOH-$CH_2Cl_2$-hexanes (5:45:50) afforded the title compound as a reddish brown oil (0.0578 g, 39%). $^{1}H$ NMR (The spectrum consists of at least the presumed

mixture of diastereomers in an undetectable ratio so integral values are not reported): (400 MHz, $CDCl_3$): δ 7.26 (m, broad), 3.71 (m), 3.5 (m), 3.18 (m), 3.03 (m), 2.65 (m, broad), 2.38 (dd, J= 10.1, 11.0 Hz), 2.13 (m), 1.75 (m, broad).

**Instant method:** To a 10 mL microwave reactor vial equipped with a magnetic stirring bar and a nitrogen atmosphere were added zinc dust (0.148 g, 2.2689 mmol), THF (1.5 mL), titanium tetrachloride (0.2079 g, 1.134 mmol), and keto ester **13a** (0.22603 g, 0.9454 mmol) dissolved in THF (1 mL). The vial was sealed with a cap and placed in the microwave reactor. The reaction was carried out with the following input parameters: temperature: 110 $^oC$, pressure: 175 psi, power: 300 W. After 10 minutes' hold time and a cooling period, the reaction mixture was dissolved in $CH_2Cl_2$ (50 mL), extracted with saturated $NaHCO_3$ (2x20 mL), and washed with distilled water (25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography on silica gel using MeOH-$CH_2Cl_2$-hexanes (5:45:50) afforded a substance tentatively identified as the title compound as a reddish brown oil (0.0296 g, 15%).

**(7aS)-2-Phenylhexahydro-1H-pyrrolizin-1-one (12b)**

**Stepwise method:** To a 25 mL round-bottom flask equipped with a magnetic stirring bar and a nitrogen atmosphere were added zinc dust (0.2101 g, 3.2142 mmol) and THF (7 mL). The solution was cooled in an ice bath, and titanium tetrachloride (0.3114 g, 1.6071 mmol) was added slowly. The resulting suspension was refluxed for 2 hours. Keto ester **13d** (0.14 g, 0.5357 mmol) dissolved in THF (3 mL) was added into the black slurry. The solution was refluxed for 18 h. The reaction mixture was dissolved in $CH_2Cl_2$ (50 mL), extracted with saturated $NaHCO_3$ (2x20 mL), and washed with distilled water (25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a

substance tentatively identified as the title compound as a reddish brown oil (0.3232 g, 50%). $^{1}$H NMR (The spectrum consists of at least the presumed mixture of diastereomers in an undetectable ratio so integral values are not reported): (400 MHz, $CDCl_3$): δ 7.24 (m, broad), 3.71 (m), 3.54 (m), 3.18 (t, J= 9.60 Hz), 3.15 (m), 2.65 (m, broad), 2.41 (dd, J= 10.1, 11.0 Hz), 2.15 (m), 1.80 (m, broad).

**Stepwise method:** To a 25 mL round-bottom flask equipped with a magnetic stirring bar and a nitrogen atmosphere were added zinc dust (0.190 g, 2.9124 mmol) and THF (6 mL). The solution was cooled in an ice bath, and titanium tetrachloride (0.2768 g, 1.4562 mmol) was added slowly. The resulting suspension was refluxed for 2 hours. Keto ester **13f** (0.157 g, 0.4854 mmol) dissolved in THF (3 mL) was added into the black slurry. The solution was refluxed for 18 h. The reaction mixture was dissolved in $CH_2Cl_2$ (50 mL), extracted with saturated $NaHCO_3$ (2x20 mL), and washed with distilled water (25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a substance tentatively identified as the title compound as a reddish brown oil (0.0658 g, 67%).

**(S)-Ethyl 1-(2-oxo-3-phenylpropyl) pyrrolidine-2-carboxylate (13a)**

To a 25 mL round-bottom flask equipped with a magnetic stirring bar at 0 $^{o}$C were added amino alcohol **128** (0.361 g, 1.3015 mmol) in DMSO (2 mL), and TEA (0.523 g, 5.2062 mmol). $SO_3$·pyr. (0.8286 g, 5.2062 mmol) dissolved in DMSO (2 mL) was added to the stirring solution after 15 minutes. The resulting solution was stirred at room temperature for 18 h. The mixture was poured into ice and extracted with $CH_2Cl_2$ (3x25 mL). Combined organic layers were washed with 50% citric acid/water solution (10 mL), saturated $NaHCO_3$, and distilled water, then dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the

title compound as a reddish brown oil (0.3032 g, 85%). $^1$H NMR: (400 MHz, $CDCl_3$): δ 7.30 (m, 5 H), 4.14 (q, J= 6.87 Hz, 2 H), 3.75 (s, 1 H), 3.74 (s, 1 H), 3.68 (d, J= 17.4 Hz, 1 H), 3.47 (d, J= 17.40 Hz, 1 H), 3.42 (dd, J=8.70 Hz, 5.04 Hz, 1 H), 3.06 (m, 1 H), 2.61 (d, J= 7.79 Hz, 1 H), 2.16 (m, 1 H), 1.97 (m, 3 H), 1.24 (t, J= 6.87 Hz, 3 H).

**S)-Ethyl 1-(2-oxo-2-phenylethyl) pyrrolidine-2-carboxylate (13d)**

**Method A:** To a 25 mL round-bottom flask equipped with a magnetic stirring bar at 0 $^oC$ were added amino alcohol **137** (0.2628 g, 0.9979 mmol), DMSO (2 mL), and TEA (0.8059 g, 7.9838 mmol. $SO_3$·pyr. (1.27 g, 7.9838 mmol) dissolved in DMSO (4 mL) was added to the stirring solution after 15 minutes. The resulting solution was stirred at room temperature for 18 h. The mixture was poured over ice and extracted with $CH_2Cl_2$ (3x25 mL). The combined organic layers were washed with 50% citric acid/water solution (10 mL), saturated $NaHCO_3$, and distilled water, then dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the title compound as a reddish brown oil (0.1915 g, 73%).

**Method B:** To a 25 mL round-bottom flask equipped with a magnetic stirring bar were added proline ethyl ester **14b** (0.5 g, 3.4921 mmol), $NaHCO_3$ (0.3755 g, 4.4698 mmol), and 2-bromoacetophenone (0.8897 g, 4.4698 mmol) in DMF (16 mL). The mixture was stirred at room temperature for 24 hours, poured into ice-water (20 mL), and extracted with $CH_2Cl_2$ (3x25 mL). The combined organic layers were washed with distilled water (4x100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography on silica gel using EtOAc-hexanes (10:90) and 1% TEA afforded the title compound as a reddish brown oil (0.5227 g, 57%). $^1$H NMR: (400 MHz, $CDCl_3$): δ 8.03 (m, 2 H), 7.57 (m, 2 H), 7.46 (m, 1 H), 4.34 (d, J= 16.94 Hz, 1 H), 4.20 (q, J= 7.33 Hz, 2 H), 3.99 (d, J= 16.94 Hz, 1 H), 3.59 (dd, J= 5.50 Hz, 5.95 Hz, 1 H), 3.18 (m, 1 H), 2.77 (d, J= 7.79 Hz,1 H), 2.25 (m, 1 H), 2.01

(m, 3 H), 1.27 (t, J= 7.32 Hz, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 197.2, 174.0, 135.9, 133.2, 128.7, 128.6, 64.6, 60.6, 59.4, 53.2, 29.7, 23.6, 14.3.

**(S)-Benzyl 1-(2-oxo-3-phenylpropyl) pyrrolidine-2-carboxylate (13e)**

To a 25 mL round-bottom flask equipped with a magnetic stirring bar at 0 $^{o}$C were added amino alcohol **139** (0.1043 g, 0.3072 mmol), DMSO (2 mL), and TEA (0.2468 g, 2.4582 mmol) in the ice-water bath. $SO_3$·pyr. (0.3912 g, 2.4582 mmol) dissolved in DMSO (2 mL) was added into the stirring solution after 15 minutes. The resulting solution was stirred at room temperature for 18 h. The mixture was poured over ice and extracted with $CH_2Cl_2$ (3x25 mL). Combined organic layers were extracted with 10 mL of 50% citric acid/water solution, saturated $NaHCO_3$, and distilled water, then dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the title compound as a reddish brown oil (0.0768 g, 74%). $^{1}$H NMR: (400 MHz, $CDCl_3$): δ 7.34 (m, 10 H), 5.15 (d, J= 12.36 Hz, 2 H), 3.71 (d, J= 15.11 Hz, 1 H), 3.69 (d, J= 17.86 Hz, 1 H), 3.66 (dd, J= 13.28 Hz, 2 H), 3.51 (dd, J= 5.04 Hz, 8.70 Hz, 1 H), 3.46 (d, J= 17.40 Hz, 1 H), 2.62 (d, J= 7.79 Hz, 1 H), 2.18 (m, 1 H), 2.01 (m, 3 H).

**(S)-Benzyl 1-(2-oxo-2-phenylethyl) pyrrolidine-2-carboxylate (13f)**

To a 25 mL round-bottom flask equipped with a magnetic stirring bar were added proline benzyl ester **14c** (1 g, 4.8721 mmol), $NaHCO_3$ (0.4043 g, 4.8721 mmol), and 2-bromoacetophenone (0.9697 g, 4.8721 mmol) in DMF (49 mL). The mixture was stirred at room temperature for 24 hours. The resulting solution was poured into ice-water (20 mL) and extracted with $CH_2Cl_2$ (3x25 mL). The combined organic layers were washed with distilled water (4x100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography on silica gel using EtOAc-hexanes (10:90) and 1% TEA afforded the title compound as a

reddish brown oil (1.088 g, 69%). $^{1}$H NMR: (400 MHz, $CDCl_3$): δ 7.97 (m, 2 H), 7.56 (m, 1 H), 7.44 (m, 2 H), 7.34 (m, 5 H), 5.16 (d, J= 2.75 Hz, 2 H), 4.32 (d, J= 16.94 Hz, 1 H), 4.03 (d, J= 16.94 Hz, 1 H), 3.67 (dd, J= 5.04 Hz, 5.50 Hz, 1 H), 3.16 (m, 1 H), 2.80 (dd, J= 7.36 Hz, 16.04 Hz, 1 H), 2.26 (m, 1 H), 2.03 (m, 3 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 197.2, 173.8, 135.9, 133.2, 128.6, 128.2, 66.3, 64.5, 59.2, 53.1, 29.5, 23.6.

**(S)-Ethyl pyrrolidine-2-carboxylate (14b)**

To a 50 mL round-bottom flask equipped with a magnetic stirring bar were added boc-L-proline **17** (0.5 g, 2.32 mmol) and EtOH (10 mL). The solution was cooled to 0 $^{o}$C, and acetyl chloride (0.5469 g, 6.97 mmol) was then added. The solution was allowed to stir at room temperature for 48 hours. The reaction mixture was cooled to 0 $^{o}$C and $NH_3$ (7M in MeOH, 2.5 mL) was added. The resulting white suspension was concentrated and filtered through cotton/celite using $CH_2Cl_2$. Concentration of the resulting solution afforded the title compound as a pale yellow oil (0.3433g, 103%), which was used without purification. $^{1}$H NMR: (400 MHz, $CDCl_3$): δ 4.28 (q, J= 7.33 Hz, 2H), 3.43 (m, 3 H), 2.33 (m, 1 H), 2.09 (m, 3 H), 1.32 (t, J= 7.33 Hz, 3 H).

**(S)-Benzyl pyrrolidine-2-carboxylate (14c)**[35b]

Esterification: To a 250 mL round-bottom flask equipped with a magnetic stirring bar were added boc-L-proline **17** (2.0 g, 9.30 mmol), tetrabutylammonium iodide (3.4 g, 9.30 mmol), saturated sodium bicarbonate solution (32 mL) and $CH_2Cl_2$ (32 mL). The solution was allowed to stir at room temperature for 16 hours. The reaction mixture then extracted three times with $CH_2Cl_2$, and the combined organic layers were dried over $MgSO_4$ and concentrated. The resulting residue was purified flash chromatography on silica gel using 5/95 EtOAc/hexanes to afford the boc-protected ester **118a** as a pale yellow oil (2.6 g, 91%).

$^1$H NMR: (400 MHz, $CDCl_3$, ca. 2:1 mixture of carbamate rotamers, major rotamer reported): δ 7.34 (m, 5 H), 5.18(d, J= 12.2 Hz, 1 H), 5.12 (d, J= 12.2 Hz, 1 H), 4.25 (dd, J= 8.72 Hz, 3.83 Hz, 1 H), 3.48 (m, 2 H), 2.21 (m, 1 H), 1.89 (m, 3 H), 1.34 (s, 9 H). Boc-deprotection: To a 50 mL round-bottom flask equipped with a magnetic stirring bar were added boc-L-proline benzyl ester **118** (2.6 g, 8.45 mmol) and $CH_2Cl_2$ (50 mL). The solution was cooled to room temperature, and trifluroacetic acid (20.0 mL) was added. The reaction was allowed to stir at 0 $^oC$ for 30 min. The reaction mixture was then slowly poured into an ice-cold, saturated sodium bicarbonate solution, extracted three times with $CH_2Cl_2$, dried over $MgSO_4$ and concentrated to afford a pale yellow oil that was used without purification (1.5 g, 7.26 mmol, 86%). $^1$H NMR: (400 MHz, $CDCl_3$): δ 7.35 (m, 5 H), 5.17 (s, 2 H), 3.93 (dd, J = 8.70 Hz, 5.95 Hz, 1 H), 3.14 (m, 1 H), 3.01 (m, 1 H), 2.20 (m, 1 H), 1.85 (m, 3 H). These values are consistent with the commercially available material.[35b]

**(S)-Ethyl 1-(2-hydroxyethyl) pyrrolidine-2-carboxylate (120a)**

To a 25 ml round-bottom flask equipped with a magnetic stirring bar and a nitrogen atmosphere were added proline ethyl ester **14b** (0.2957 g, 2.065 mmol), $CH_2Cl_2$ (13 mL), TEA (0.2178 g, 2.065 mmol), and 2-iodoethanol (0.4268 g, 2.478 mmol). The solution was stirred at room temperature for 72 hours. The reaction mixture was then diluted with $CH_2Cl_2$ (20 mL), poured into distilled water (25 mL), extracted with $CH_2Cl_2$ (3x25 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography on silica gel using MeOH-EtOAc (10:90) afforded the title compound as a pale yellow oil (0.09275 g, 24%). $^1$H NMR: (400 MHz, $CDCl_3$): δ 4.21 (q, J= 7.33 Hz, 2 H), 3.62 (m, 1 H), 3.52 (m, 1 H), 3.27 (m, 2 H), 3.11 (broad, 1 H), 2.77 (t, J= 5.50 Hz, 2 H), 2.47 (dd, J= 1.4 Hz, 8.72 Hz, 1 H), 2.16 (m, 1 H), 1.94 (m, 3 H), 1.28 (t, J= 7.33 Hz, 3 H).

**(2S)-Ethyl 1-(2, 3-dihydroxypropyl) pyrrolidine-2-carboxylate (120b)**

To a 10 ml microwave reactor vial equipped with a magnetic stirring bar were added proline ethyl ester **14b** (0.2864 g, 2 mmol)**,** $CH_3CN$ (0.5 ml), and glycidol (0.1450 g, 2 mmol). The vial was sealed with a cap and placed in the microwave reactor. The reaction was carried out with the following input parameters: temperature: 150 $^oC$, pressure: 150 psi, power: 300 W. After 5 minutes' hold time and a cooling period, the solution was concentrated in vacuo. Chromatography on silica gel using MeOH-EtOAc (20:80) afforded the title compound as a pale yellow oil (0.169 g, 39%). $^1H$ NMR (mixture of diastereomers, ca. 1:1 ratio) δ 4.18 (m, 4 H), 3.93 (m, 2 H), 3.65 (m, 8 H), 3.28 (m, 2 H), 2.79 (m, 2 H), 2.56 (m, 2 H), 2.17 (m, 2 H), 1.89 (m. 6 H), 1.27 (t, J= 6.88 Hz, 3 H).

**(S)-Ethyl 1-allylpyrrolidine-2-carboxylate (122)**

To a 10 ml round-bottom flask equipped with a magnetic stirring bar were added proline ethyl ester **14b** (0.1g, 0.6984 mmol), $CH_2Cl_2$ (3 mL), TEA (0.07 g, 0.6984 mmol), and allyl bromide (0.1 g, 0.8381 mmol). The solution was stirred under nitrogen for 48 hours. The mixture was quenched with distilled water (20 mL), extracted with $CH_2Cl_2$ (3x20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the title compound as a pale brown oil, which was used without purification (0.0483g, 38%). $^1H$ NMR: (400 MHz, $CDCl_3$): δ 5.95 (m, 1 H), 5.19 (m, 1 H), 5.09 (m, 1 H), 4.19 (q, J= 7.32 Hz, 2 H), 3.33 (m, 1 H), 3.14 (m, 3H), 2.40 (dd, J= 8.24 Hz, 1.69 Hz, 1 H), 2.23 (m, 1 H), 1.94 (m, 3 H), 1.27 (t, J= 7.33 Hz, 3 H).

**(2S)-Ethyl 1-(2-hydroxy-3-phenylpropyl) pyrrolidine-2-carboxylate (128)**

To a 10 ml microwave reactor vial equipped with a magnetic stirring bar were added proline ethyl ester **14b** (0.2864 g, 2 mmol)**,** toluene (0.5 mL), and (2,3-epoxypropyl)benzene

(0.2652 g, 2 mmol). The vial was sealed with a cap and placed in the microwave reactor. The reaction was carried out with the following input parameters: temperature: 100 $^{o}$C, pressure: 150 psi, power: 300 W. After 20 minutes' hold time and a cooling period, the solution was concentrated in vacuo. Chromatography on silica gel using EtOAc-hexanes (30:70) afforded the title compound as a pale brown oil (0.3882 g, 35%). $^{1}$H NMR: (400 MHz, $CDCl_3$, mixture of diastereomers, ca. 1:1 ratio): δ 7.26 (m, 10 H), 4.16 (m, 4 H), 3.87 (m, 2 H), 3.73 (m, 1 H), 3.60 (m, 1 H), 3.29 (dd, J= 9.16, 5.96 Hz, 1 H), 3.21 (m, 2 H), 3.10 (m, 1 H), 2.87 (m, 1 H), 2.59 (m, 6 H), 2.29 (dd, J= 7.80, 8.84 1 H), 2.11 (m, 2 H), 1.83 (m, 6 H), 1.24 (t, J= 6.88 Hz, 6 H).

**(2S)-Ethyl 1-(3-(tert-butyl diphenyl silyloxy)-2-hydroxypropyl) pyrrolidine-2 carboxylate (131)**

To a 10 mL microwave reactor vial equipped with a magnetic stirring bar were added proline ethyl ester **14b** (0.2864 g, 2 mmol)**,** $CH_3CN$ (0.8 mL), and silyl ether **130** (0.6250 g, 2 mmol). The vial was sealed with a cap and placed in the microwave reactor. The reaction was carried out with the following input parameters: temperature: 100 $^{o}$C, pressure: 150 psi, power: 300 W. After 30 minutes' hold time and a cooling period, the solution was concentrated in vacuo. Chromatography on silica gel using EtOAc-hexanes (30:70) afforded the title compound as a pale yellow oil (0.253 g, 29%). $^{1}$H NMR: (400 MHz, $CDCl_3$, mixture of diastereomers, ca. 1:1 ratio): δ 7.65 (m, 8 H), 7.36 (m, 12 H), 4.15 (m, 4 H), 3.78 (m, 1 H), 3.67 (broad m, 4 H), 3.59 (dd, J= 5.96, 10.08 Hz, 1 H), 3.27 (broad m, 3 H), 3.10 (m, 1 H), 2.72 (m, 4 H), 2.60 (dd, J= 7.32, 16.50 Hz, 1 H), 2.39 (dd, J= 7.80, 16.50 Hz, 1 H), 2.14 (m, 2 H), 1.86 (m, 6 H), 1.24 (t, J= 6.92 Hz, 1 H), 1.05 (s, 18 H)

**(2S)-Ethyl 1-(3-(benzyloxy)-2-hydroxypropyl) pyrrolidine-2-carboxylate (133)**

To a 10 mL microwave reactor vial equipped with a magnetic stirring bar were added proline ethyl ester **14b** (0.2864 g, 2 mmol)**,** $CH_3CN$ (0.8 mL), and epoxy benzyl ether **132** (0.3284 g, 2 mmol). The vial was sealed with a cap and placed in the microwave reactor. The reaction was carried out with the following input parameters: temperature: 100 $^oC$, pressure: 150 psi, power: 300 W. After 10 minutes' hold time and a cooling period, the solution was concentrated in vacuo. Chromatography on silica gel using EtOAc-MeOH-hexanes (20:10:70) afforded the title compound as a pale yellow oil (0.2356 g, 38%). $^1H$ NMR: (400 MHz, $CDCl_3$, mixture of diastereomers, ca. 1:1 ratio): δ 7.32 (m, 10 H), 4.56 (s, 4 H), 4.16 (m, 4 H), 4.01 (sextet, J= 5.04 Hz, 1 H), 3.88 (m, 1 H), 3.75 (m, 1 H), 3.63 (m, 3 H), 3.48 (m, 2 H), 3.28 (m, 1 H), 3.10 (m, 1 H), 2.90 (m, 1 H), 2.68 (m, 2 H), 2.39 (dd, J= 7.32, 8.24 Hz, 1 H), 2.15 (m, 2 H), 1.87 (m, 6 H), 1.25 (t, J= 7.36 Hz, 6 H).

**(2S)-Ethyl 1-(2-hydroxy-2-phenylethyl) pyrrolidine-2-carboxylate (137)**

To a 10 mL microwave reactor vial equipped with a magnetic stirring bar were added proline ethyl ester **14b** (0.2864g, 2mmol)**,** toluene (0.5 mL), and styrene oxide (0.2422 g, 2 mmol). The vial was sealed with a cap and placed in the microwave reactor. The reaction was carried out with the following input parameters: temperature: 100 $^oC$, pressure: 150 psi, power: 300 W. After 60 minutes' hold time and a cooling period, the solution was concentrated in vacuo. Chromatography on silica gel using EtOAc-hexanes (30:70) afforded the title compound as a pale yellow oil (0.1196 g, 23%). $^1H$ NMR: (400 MHz, $CDCl_3$, mixture of diastereomers, ca. 1:1 ratio): δ 7.32 (m, 10 H), 4.70 (dd, J= 3.68, 10.08 Hz, 1 H), 4.57 (dd, J= 5.04, 7.76 Hz, 1 H), 4.18 (m, 4 H), 3.40 (m, 2 H), 3.35 (dd, J= 5.96, 9.16 Hz,

1 H), 2.81 (m, 2 H), 2.71 (m, 3 H), 2.48 (dd, J= 7.32, 8.28 Hz, 1 H), 2.18 (m, 2 H), 1.91 (m, 6 H), 1.28 (t, J= 5.99 Hz, 6 H).

**(2S)-Benzyl 1-(2-hydroxy-3-phenylpropyl) pyrrolidine-2-carboxylate (139)**

To a 10 mL microwave reactor vial equipped with a magnetic stirring bar were added proline benzyl ester **14c** (0.4105 g, 2 mmol)**,** $CH_3CN$ (0.5 mL), and (2,3-epoxypropyl)benzene (0.2652 g, 2 mmol). The vial was sealed with a cap and placed in the microwave reactor. The reaction was carried out with the following input parameters: temperature: 100 $^oC$, pressure: 150 psi, power: 300 W. After 60 minutes' hold time and a cooling period, the solution was concentrated in vacuo. Chromatography on silica gel using EtOAc-hexanes (30:70) afforded the title compound as a pale yellow oil (0.0543 g, 8%). $^1H$ NMR: (400 MHz, $CDCl_3$, mixture of diastereomers, ca. 1:1 ratio): δ 7.27 (m, 20 H), 5.14 (m, 4 H), 3.88 (m, 1 H), 3.69 (m, 1 H), 3.34 (dd, J= 5.96, 9.16 Hz, 1 H), 3.29 (dd, J= 3.38, 9.16 Hz, 1 H), 3.20 (m, 1 H), 3.09 (m, 1 H), 2.80 (m, 2 H), 2.59 (m, 7 H), 2.30 (dd, J= 7.80, 8.56 Hz, 1 H), 2.12 (m, 2 H), 1.83 (m, 6 H)

**1-((S)-2-(hydroxymethyl) pyrrolidin-1-yl)-3-phenylpropan-2-ol (152)**

To a 10 mL microwave reactor vial equipped with a magnetic stirring bar were added pyrolidinol **151** (0.1968 g, 2 mmol)**,** $CH_3CN$ (0.5 mL), and (2,3-epoxypropyl)benzene (0.2652 g, 2 mmol). The vial was sealed with a cap and placed in the microwave reactor. The reaction was carried out with the following input parameters: temperature: 100 $^oC$, pressure: 150 psi, power: 300 W. After 30 minutes' hold time and a cooling period, concentration of the resulting solution afforded the title compound as a pale yellow liquid (0.4195 g, 89%). $^1H$ NMR: (400 MHz, $CDCl_3$, mixture of diastereomers, ca. 1:1 ratio): δ 3.91 (m, 2 H), 3.57

(m, 2 H) 3.43 (m, 2 H), 3.18 (m, 2 H), 2.80 (m, 3 H), 2.69 (m, 4 H), 2.51 (m, 4 H), 2.22 (dd, J= 8.72, 9.16 Hz, 1 H), 1.86 (m, 2 H), 1.73 (m, 6 H).

## References


1. El Nemr, A. *Tetrahedron* **2000**, *56*, 8579-8629.

2. Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213-7256.

3. Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645-1680.

4. Siciliano, T.; De Leo, M.; Bader, A.; De Tommosi, N.; Vrieling, K.; Braca, A.; Morelli, J. *Phytochemistry* **2005**, *66*, 1593-1600.

5. (a) Reina, M.; Mericli, A. H.; Cabrera, R.; Gonzalez-Coloma, A. *Phytochemistry* **1995**, *38*, 355-358; (b) Reina, M.; Gonzalez-Coloma, A.; Gutierrez, C.; Cabrera, R.; Rodriguez, M. L.; Fajardo, V.; Villaroel, C. *J. Nat. Prod.* **2001**, *64*, 6-11; (c) Reina, M.; Gonzalez-Coloma, A.; Gutierrez, C.; Cabrera, R.; Henriquez, J.; Villarroel, L. *Phytochemistry* **1997**, *46*, 845-853.

6. Sibi, M. P.; Christensen, J. W. *J. Org. Chem*. **1999**, *64*, 6434-6442.

7. Honda, T.; Namiki, H.; Nagase, H.; Mizutani, H. *Tetrahedron Lett.* **2003**, *44*, 3035, 3038.

8. Yoda, H.; Egawa, T.; Takabe, K. *Tetrahedron Lett.* **2003**, *44*, 1643–1646.

9. McMurry, J. E.; Fleming, M. P.; Lees, K. L.; Krepski, L. R. *J. Org. Chem.* **1978**, *43*, 3255-3266.

10. Furstner, A. Bogdanovic, B. *Angew. Chem.* **1996***, 108,* 2583-2609

11. McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513-1524.

12. Ladipo, F. T. *Curr. Org. Chem.* **2006**, *10*, 965-980.

13. (a) Furstner, A.; Hupperts, A.; Ptock, A.; Janssen, E. *J. Org. Chem.* **1994**, *59*, 5215-5229; (b) Furnster, A.; Hupperts, A.; Seidel, G. *Org. Synth., Coll.* **2004**, *10*, 382.

14. Furstner, A.; Bogdanovic, B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2442-2469.

15. Rajakumar, P.; Swaroop, M. G. *Tetrahedron Lett.* **2004**, *45*, 6165-6167.

16. Furstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B. *J. Org. Chem*. **2000**, *65*, 7990-7995.

17. Lhotak, P.; Zieba, R.; Hromadko, V.; Stibor, I.; Sykora, J. *Tetrahedron Lett.* **2003**, *44*, 4519-4522.

18. Pfeffer, M.; Gies, A. E. *J. Org. Chem.* **1999**, *64*, 3650-3654.

19. (a) Li, Y.; Liu, Z.; Li, W. Z. *Tetrahedron Lett.* **2001**, *12*, 95-100; (b) Li, Y.; Liu, Z.; Lan, J.; Li, Y.; Peng, L.; Li, W. Z.; Li, Y.; Chan, A. S. C. *Tetrahedron Lett.* **2000**, *41*, 7465-7469; (c) Li, Y.; Li, W.; Li, Y. *Tetrahedron Lett.* **1999**, *40*, 965-968; (d) Li, Y.; Liu, Z.; Zhang, T. *Tetrahedron Lett.* **2001**, *42*, 275-277.

20. Heissler, D.; Mouttet, M. P. M.; Gabriel, K. *Tetrahedron Lett.* **1999**, *40*, 843-846.

21. Bruckner, R.; Rank, E. *Eur. J. Org. Chem.* **1998**, 1045-1053.

22. Clive, D. L. J.; Murthy, K. K. S.; Wee, A. G. H.; Prasad, J. S.; Da Silva, G. V. J.; Majewski, M.; Anderson, P. C.; Evans, C. F.; Haugen, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 8, 3018-3028.

23. Hu, J.; Jiang, X.; He, T.; Zhou, J.; Hu, Y.; Hu, H. *J. Chem. Soc., Perkin Trans.* **2001**, *1*, 1820-1825.

24. Chen, Y.; Zeng, D. X.; Xie, N.; Dang, Y. Z. *J. Org. Chem.* **2005**, *70*, 5001-5005.

25. Shepelenko, E. N.; Rybalkin, V. P.; Karamov, D. G.; Makarova, N. I.; Metelitsa, A. V.; Popova, L. L.; Bren, V. A. *Russ. J. Org. Chem* **2006**, *42*, 1727-1729.

26. Kozikowski, A. P.; Rajendran, V.; Rong, S.; Saxena, A.; Doctor, B. P. *Tetrahedron Lett.* **2001**, *42*, 5359-5361.

27. Feng, J.; Chen, W.; Zhou, Z.; Zhang, J. *Synthesis* **1989**, 182-184.

28. (a) Chattopadhyay, S.; Rele, S.; Talukdar, S.; Banerji, A. *J. Org. Chem.* **2001**, *66*, 2990-2994; (b) Banerji, A.; Talukdar, S.; Nayak, S. K. *J. Org. Chem.* **1998**, *63*, 4925-4929.

29. Iyoda, M.; Kushida, T.; Kitami, S.; Oda, M. *J. Chem. Soc., Chem. Commun.* **1987**, 1607-1608.

30. Pedersen, E. B.; Therkelsen, F. D.; Hansen A. L.; Nielsen, C. *Org. Biomol. Chem.* **2003**, *1*, 2908-2918.

31. Chen, W.; Shi, D.; Chai, W.; Chen, J.; Kao, T. *Tetrahedron Lett.* **1993**, *34*, 2963-2964.

32. Nudelman, A.; Bechor, Y.; Falb, E.; Fischer, B.; Wexler, B. A.; Nudelman, A. *Synth. Commun.* **1998**, *28*, 471.

33. Microwave-assisted Laboratory Experiments; Leadbeater, N.; McGowan, C. CEM Publishing: Matthews, N.C., 2006

34. Smith, E. M.; Swiss, G. F.; Neustadt, B. R.; McNamara, P.; Gold, E. H. *J. Med. Chem.* **1989**, *32*, 1600-1606.

35. (a) Boger, D. L.; Chen, J. H.; Saionz, K. W. *J. Am. Chem. Soc.* **1996**, *118*, 1629-1644; (b) http://www.sigmaaldrich.com/catalog/ProductDetail.do?N4=364460|ALDRICH&N5=SEARCH_CONCAT_PNO|BRAND_KEY&F=SPEC, accessed May 18, 2009.

36. White, J. D.; Hansen, J. D. *J. Org. Chem.* **2005**, *70*, 1963-1977.

37. Murray, W. V.; Liu, Y.; Maden, A. *Tetrahedron* **2002**, *58*, 3159-3170.

38. Komatsu, K.; Tsuda, M.; Tanaka, Y.; Mikami, Y.; Kabayashi, J. *J. Org. Chem.* **2004**, *69*, 1535-1541.

39. Zhang, N.; Munch, W.; Nubbemeyer, U. *Adv. Synth. Catal.* **2004**, *346*, 1335.

40. Maring, C. J.; Stoll, V. S.; Zhao, C.; Sun, M.; Krueger, A. C.; Stewart, K. D.; Madigan, D. L.; Kati, W. M.; Carrick, R. J.; Montogomery, D. A.; Kempf- Grote, A.; Marsh, K. C.; Molla, A.; Steffy, K. R.; Sham, H. L.; Lover, W. G.; Gu, Y.; Kempf, D. J.; Kohlbrenner, W. E. *J. Med. Chem.* **2005**, *48*, 3980- 3990.

41. Zhu, J.; Jia, Y.; Choussy, M. B. *Org. Lett.* **2007**, *9*, 2401-2404.

42. Fuente, M. C.; Pullan, S. E.; Biesmans, I.; Dominguez, D. *J. Org. Chem.* **2006**, *71*, 3963-3966.

43. Desai, H.; D' Souza, B. R.; Foether, D.; Johnson, B. F.; Lindsay, H. A. *Synthesis* **2007**, 902-910.

44. Shing, T. K. M.; Zhong, Y. *J. Org. Chem.* **1997**, *62*, 2622-2624.

45. Barluenga, J.; FMrez, J.; Yus, M. *J. Chem. Soc. Perkin Trans. I* **1983**, 3019-3026.

46. Anastasia, M.; Allevi, P.; Cribiu, R.; Giannini, E. *J. Org. Chem.* **2007**, *72*, 3478-3483.

47. Crimmins, M. T.; Zuccarello, J. L.; Cleary, P. A.; Parrish, J. D. *Org. Lett.* **2006**, *8*, 159-162.

48. Hasserodt, J.; Barbe, R. *Tetrahedron* **2007**, *63*, 2199-2207.

49. Chen, Y. L.; Fang, K. C.; Sheu, J. Y.; Hsu, S. L.; Tzeng, C. C. *J. Med. Chem.* **2001**, *44*, 2374-2377.

50. Mathey, F.; Toullec, P.; Ricard, L. *Organometallics* **2002**, *21*, 2635-2638.

51. Stuhr-Hansen, N. *Tetrahedron Lett.* **2005**, *46*, 5491-5494.

52. Paguette, L. A.; Nakatani, S.; Zydowsky, T. M.; Edmondson, S. D.; Sun, L. Q.; Skerlj, R. *J. Org. Chem.* **1999**, *64*, 3244-3254.

53. Snider, B. B.; Gao, X. *Org. Lett.* **2005**, *7*, 4419- 4422.

54. Wallen, E. A. A.; Christiaans, J. A. M.; Saario, S. M.; Forsberg, M. M.; Venalainen, J. I.; Paso, H. M.; Mannisto, P. T.; Gynther, *J. Bioorg. Med. Chem.* **2002**, *10*, 2199-2206.

55. Leopold, E. *J. Org. Synth. Coll.* **1990**, *7*, 258.

56. Deng, W.; Overman, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 11241-11250.