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Synthesis of the Bicyclic Core of Pyrrolizidine and Indolizidine Alkaloids

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Abstract
Indolizidine and pyrrolizidine alkaloids are large classes of natural products whose members have a variety of interesting biological activities. In order to access a number of these compounds, we have developed a synthetic strategy that which allows for variation of structural features including size of the bicyclic core (indolizidine vs. pyrrolizidine), oxidation at C6 and/or C7, and saturation versus unsaturation at C1-C2. To that end, our recent efforts have focused on a method to assemble the indolizidine or pyrrolizidine alkaloid skeleton in a manner that will allow for further functionalization. The key step in this process is a novel intramolecular reductive coupling reaction to form the B ring.

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Synthesis of the Bicyclic Core of Pyrrolizidine and Indolizidine Alkaloids

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Abstract

Indolizidine and pyrrolizidine alkaloids are large classes of natural products whose members have a variety of interesting biological activities. In order to access a number of these compounds, we have developed a synthetic strategy that which allows for variation of structural features including size of the bicyclic core (indolizidine vs. pyrrolizidine), oxidation at C6 and/or C7, and saturation versus unsaturation at C1-C2. To that end, our recent efforts have focused on a method to assemble the indolizidine or pyrrolizidine alkaloid skeleton in a manner that will allow for further functionalization. The key step in this process is a novel intramolecular reductive coupling reaction to form the B ring.

Introduction

A. Compound Background

Pyrrolizidine and indolizidine alkaloids are vast categories of compounds that have many known biological functions. One common characteristic of these compounds is that they are bicyclic rings with a shared nitrogen. There are, however, parts of the structure that can be variable (**Figure 1**). If the A ring is five members then the B ring can be five- or six-membered. Pyrrolizidines feature two five membered rings whereas indolizidines feature a five and six membered ring. In addition, there may be saturation or unsaturation between C1 and C2, and the presence or absence of oxidation at C6 and or C7.

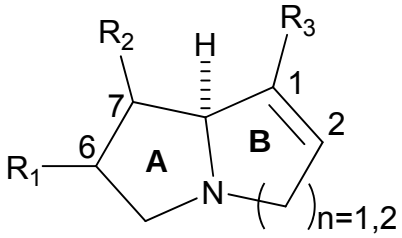


Figure 1. Pyrollizidine and indolizidine structural variables.

Many of these compounds found in nature have known biological activities. Representative examples of pyrrolizidines and indolizidine alkaloids include lycopsamine, alexine, castanospermine and swainsonine (**Figure 2**).

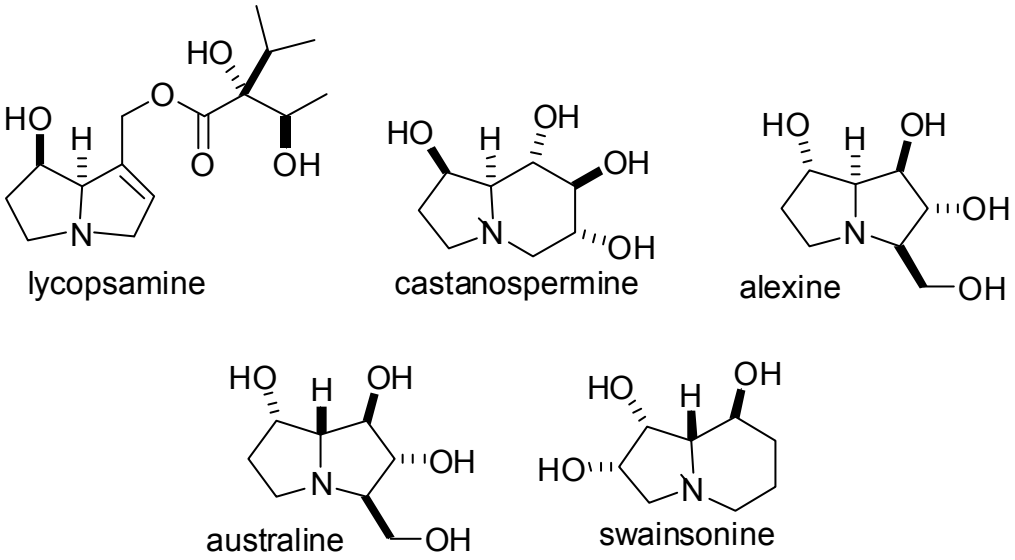


Figure 2. Representative examples of pyrrolizidine and indolizidines alkaloids

Lycopsamine is an example of a pyrrolizidine alkaloid that features unsaturation in the B ring between C1 and C2. Lycopsamine has shown anti-feedant activity against several insects, one of which is the Colorado potato beetle.[1] The Colorado potato beetle (**Figure 3**) has become the most significant and destructive pest of the potato.[2] It is so destructive that uncontrolled populations can completely defoliate potato, so finding new natural deterrents is highly desirable.[2] Consequently, lycopsamine and related molecules are under investigation for this purpose.

Figure 3. Image of the Colorado potato beetle.[3]

Castanospermine, an indolizidine alkaloid, is the major alkaloidal component of the plant organisms *Castanospermum australe* and *Alexa leiopetala*.[4] This compound is a powerful inhibitor of several glucosidases including several found in mammals. Another alkaloid found in the same species of plants is alexine (**Figure 2**), which is a pyrrolizidine alkaloid. Alexine has also shown activity as a glycosidase inhibitor.[4] Another pyrrolizidine alkaloid from these species is australine which has been shown to inhibit HIV-induced synostia formation in JM cells.[4]

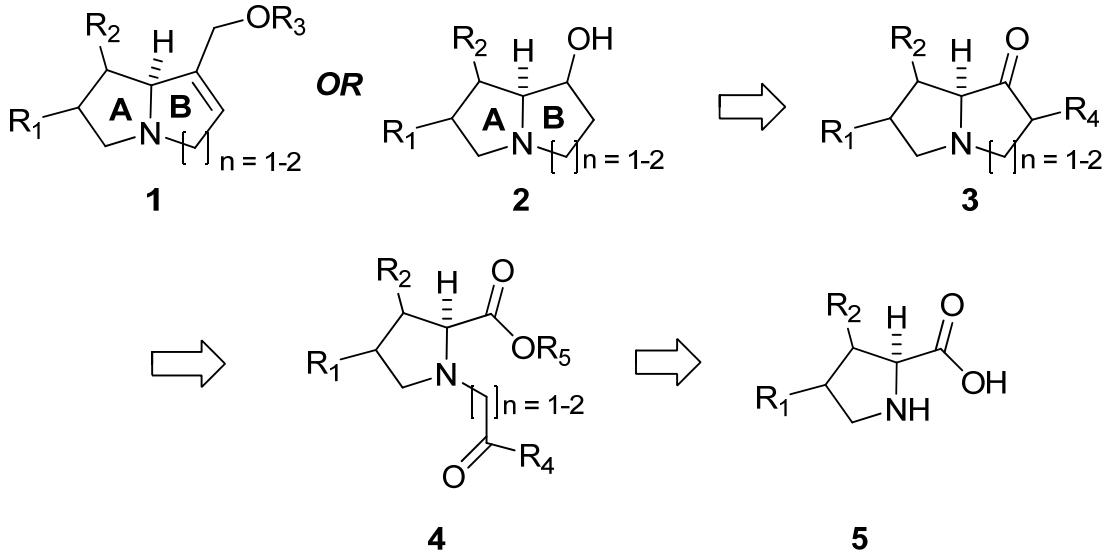
Swainsonine (**Figure 2**) is another example of an indolizidine. Swainsonine has long been known for its activity as a glycosidase inhibitor,[5] but has also demonstrated anti-tumor properties and use as a haematopoietic system protectant.[6]

The examples of lycopsamine, castanospermine, alexine, australine, and swainsonine illustrate the structural variability that can be seen in pyrrolizidine and indolizidine alkaloids. There has been a great deal of interest in these compounds and their derivatives because of the biological activities described above. However, extraction of these compounds from plant sources is costly, time consuming, and low-yielding. Consequently a versatile laboratory synthesis that would provide access to a number of these compounds is desirable. The goal of this research is to develop such a synthesis.

B. Synthetic Approaches

There were two different strategic approaches to this project which are described by retrosynthetic analyses (**Scheme 1** and **2**). Functionalized pyrrolizidine **1** or indolizidine **2** could be obtained from a pyrrolizidinone or indolizidinone **3**. The pyrrolizidinone or indolizidinone **3** could be obtained via an intramolecular reductive coupling reaction involving keto-ester **4**. The keto-ester would be obtained by alkylation and oxidation of a commercially available amino acid or its derivative **5**.

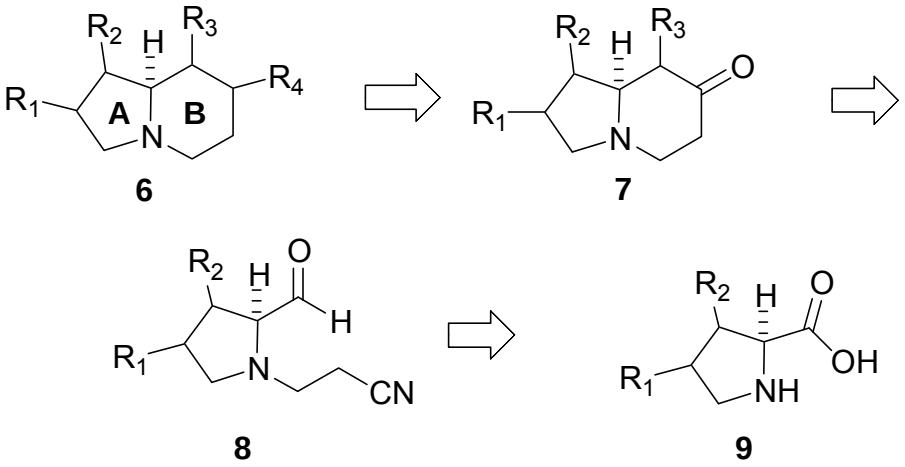
Scheme 1



1 **2** **3** **4** **5**

The second approach involves the cyclization of the B ring by an intramolecular reductive coupling of a nitrile and aldehyde (**Scheme 2**). Again the functionalized pyrrolizidine or indolizidine **6** would be obtained from its respective pyrrolizidinone or indolizidinone **7**. This would be obtained via a reductive coupling between cyano-aldehyde **8**. The cyano-aldehyde would be obtained in several steps from a commercially available amino acid **9**.

Scheme 2



C. Reductive Coupling

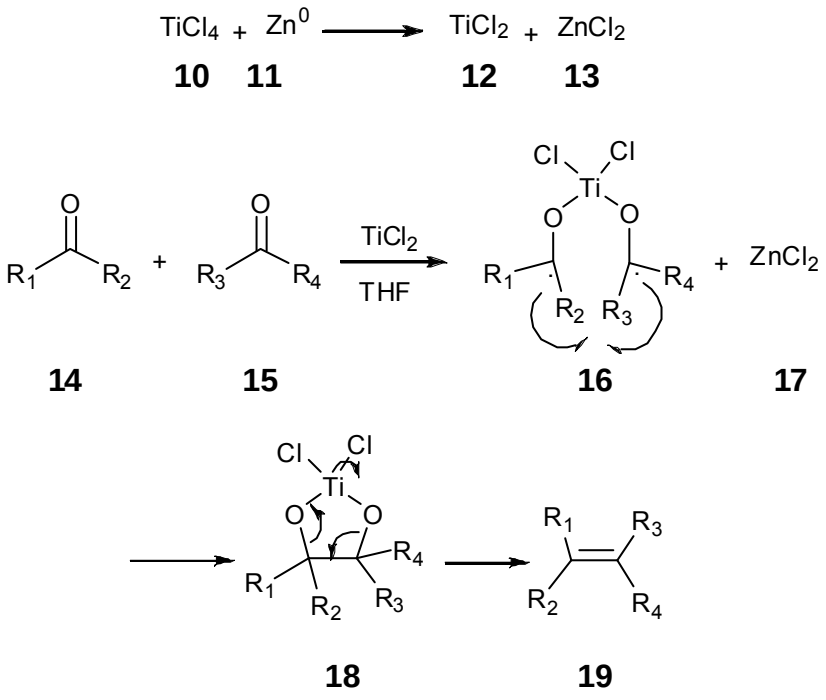
1. McMurry Reaction

An important aspect of the project is the development of new reaction methodology. Although reductive coupling reactions are not new,[7] intramolecular coupling reactions are largely limited to reactions of ketones and aldehydes. Few examples of couplings involving higher oxidation state carbonyl compounds such as the ones we proposed (**Scheme 1** and **2**) have been reported. Furthermore, there are few examples of coupling reactions being performed in the presence of Lewis basic amines. We propose to expand the scope of these coupling reactions by developing an intramolecular reductive coupling reaction of a keto-ester or cyano-aldehyde in the presence of a Lewis basic amine. Relevant representative examples of two different coupling methods here are the McMurry reaction and pinacol coupling.[7]

One of the reductive coupling methods being used is known as the McMurry reaction. According to McMurry, this reaction uses $TiCl_4$ or $TiCl_3$ and involves the formation and coupling of radicals.[7] A Ti(III) or Ti(IV) reagent is

reduced to Ti(II) by an appropriate reducing agent. Several reducing reagents can be used such as $LiAlH_4$, Zn, Li, and K. For the purposes of experiments in this paper, Zn was the reducing agent. **Scheme 3** shows an example of the McMurry reaction between two ketones. The reduced Ti species produces two carbon radicals **16** with the oxygen moieties coordinated by the Ti. A carbon-carbon single bond then forms between the radicals to give the cyclic intermediate **18**. In the final step, the Ti (IV) is eliminated and an alkene is formed.

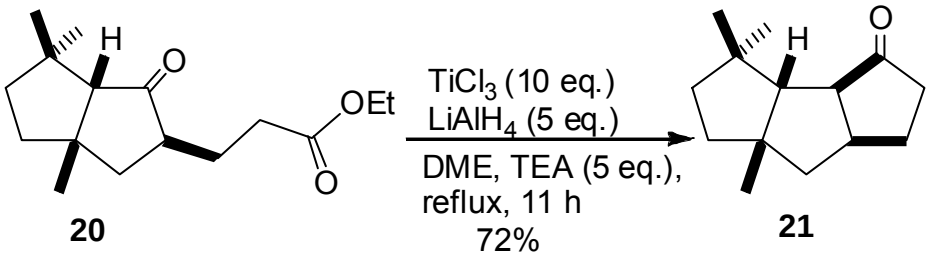
Scheme 3



Following are some representative examples of intramolecular cyclizations between keto-esters using the McMurry reaction. Iyoda used $TiCl_3$ which was reduced with $LiAlH_4$ (**Scheme 4**).[8] The keto-ester **20** was then added and yielded the McMurry product ketone **21** in 72%. Another example comes from Pederson

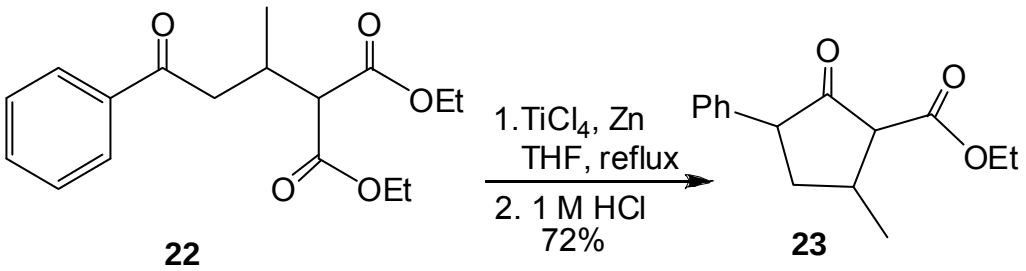
(**Scheme 5**).[9] This procedure used $TiCl_4$ which was reduced in THF using activated zinc. After an acidic work-up of the reaction mixture the desired ketone **23** was obtained in a 72% yield.

Scheme 4



20 **21**

Scheme 5



22 **23**

Other examples of keto-ester couplings have been described by Chattopaday[10] and Banjeri[11] (**Scheme 6**). In these cases, naphthalene was used to increase the solubility of the $TiCl_3$-Li in the organic solvent and iodine was used to increase the reactivity of the low-valent titanium species. The $TiCl_3$ was reduced with Li in THF and then iodine or naphthalene was added at room temperature. Keto-esters **24a-d** were then added and afforded the cyclized products **25a-d** in moderate yields (**Scheme 6, Table 1**).

Scheme 6

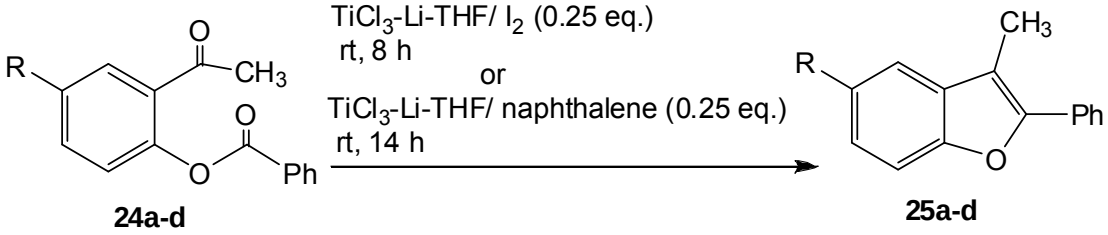


Table 1. McMurry reaction of keto-ester **24**

Keto-ester	R	Ti sources	Yield
24a	H	$TiCl_3$-Li- naphthalene –THF	**25a**, 55%
24b	OMe	$TiCl_3$-Li- naphthalene –THF	**25b**, 52%
24c	H	$TiCl_3$-Li-THF-I_2	**25c**, 62%
24d	OMe	$TiCl_3$-Li-THF-I_2	**25d**, 55%

Finally Chen has performed a similar cyclization of a keto-diester (**Scheme 7**).[12] In this procedure, $TiCl_4$ was reduced with Zn in THF. He subjected keto-diethyl ester **26a-c** to the McMurry reaction followed by an acidic work-up to yield the cyclic keto-esters **27a-c** in good yield (**Scheme 7, Table 2**).

Scheme 7

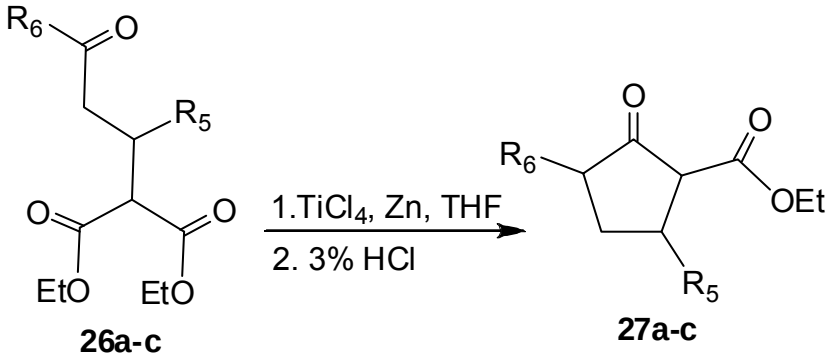
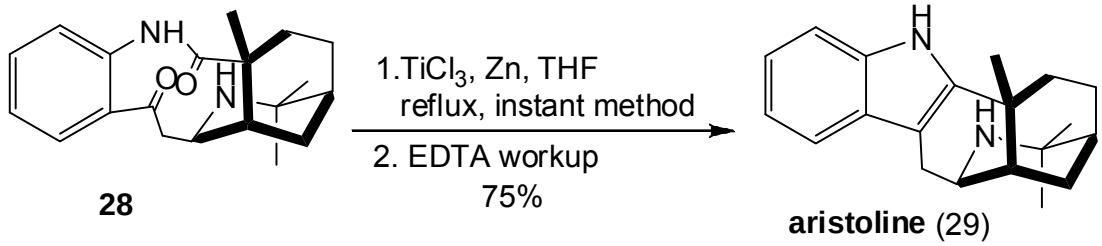


Table 2. McMurry reaction of keto-ester **26**

Keto-ester	R_5	R_6	Yield
26a	C_6H_5	C_6H_5	**27a**, 81%
26b	C_6H_5	4-$CH_3C_6H_4$	**27b**, 87%
26c	3,4-$Cl_2C_6H_3$	4-$CH_3C_6H_4$	**27c**, 78%

The examples discussed thus far demonstrate that McMurry cyclizations of keto-esters may be accomplished. In addition, there are examples of McMurry reactions in the presence of free amines. These examples are important because they demonstrate that the Lewis basic nitrogen does not out-compete the carbonyl oxygens for coordination sites on the Ti(II). An example of this type of reaction comes from Furstner who used the instant method to synthesize aristoline (**29**) (**Scheme 8**).[13] In the instant method, all reagents are added at the beginning of the reaction. The Ti species is not reduced prior to addition of the carbonyl compound. Using this procedure, they treated keto-amide **28** with $TiCl_3$ and Zn in refluxing THF to achieve the desired product **29** in good yield.

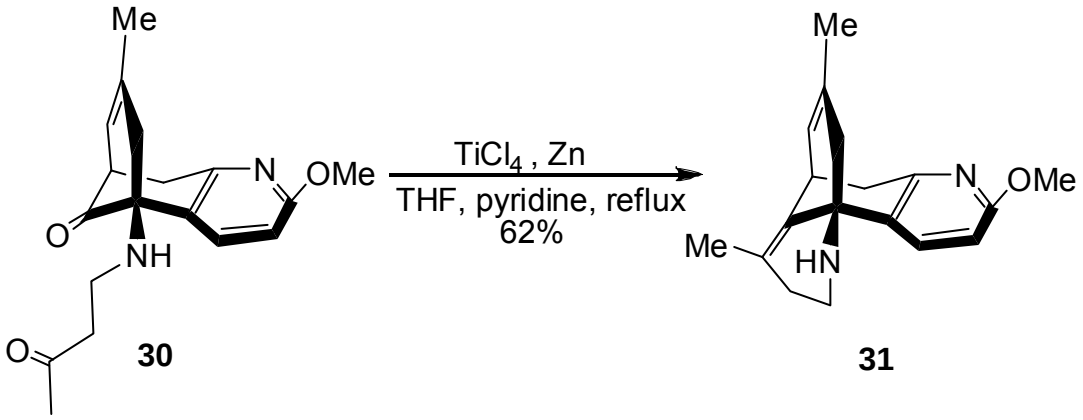
Scheme 8



28 **aristoline** (29)

Another similar example comes from Kozikowski (**Scheme 9**).[13] In this case, a pre-reduction of $TiCl_4$ with Zn was performed followed by the addition of pyridine as an activating Ti ligand. Diketone **30** was then added to give amino alkene **31** in 62% yield.

Scheme 9



The above examples illustrate that the intramolecular McMurry reaction may be accomplished between a ketone and ester (**Schemes 4-7**) and for a ketone and an amide (**Scheme 8**) or a diketone (**Scheme 9**) in the presence of a Lewis basic amine. Although there are many examples of McMurry reactions being done on many different kinds of substrates, the reactions described in this work are unique. The keto-ester (**Figure 3**) in our examples has an amine present in the ring, and this is what makes the substrate unique. In the case of the cyano-aldehyde (**Figure 3**), no McMurry reaction has been performed using a nitrile. Even though both of these substrates are unique they do have similarities to representative McMurry reactions that have been done before and so it is hypothesized that they are reasonable candidates for this reaction.

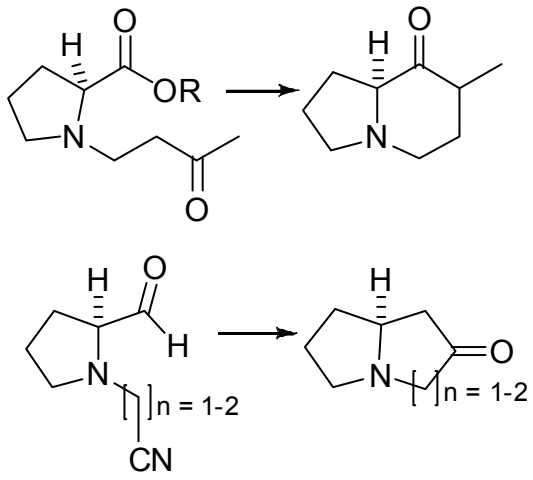


Figure 3. Subtrates for intramolecular McMurry Reactions.

2. Pinacol Coupling

Another coupling method that was used for the cyclization of substrates in **Figure 3** was pinacol coupling. It, like the McMurry reaction, is a reductive coupling reaction involving radicals. Pinacol coupling uses SmI_2 in THF with an alcohol present. An appealing feature of this reaction is that it is reported to have good stereoselectivity.[15] In addition, **Figure 4** shows the differences in the McMurry and pinacol cyclization products. The pinacol coupling offers a different functionalization pattern that would serve as a complement to the McMurry approach.

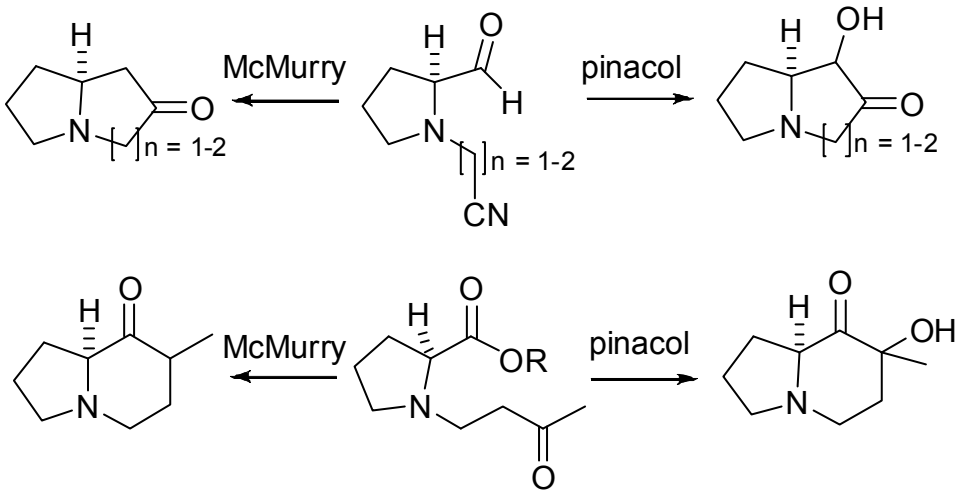
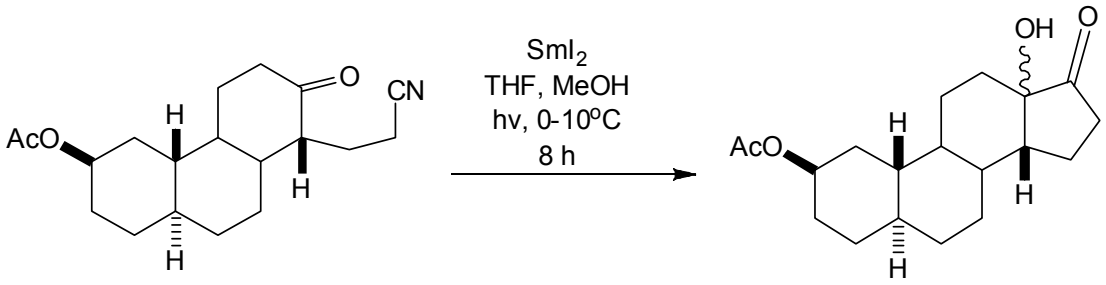


Figure 4. Differences in McMurry and pinacol approaches.

There are several examples of intramolecular pinacol couplings using keto-nitriles. Wang illustrated the coupling between a ketone and nitrile to afford a five-membered ring (**Scheme 9a**).[16] Cyano-ketone **32** was treated with SmI_2 in THF for 8 hours at 0°C while being irradiated by a 500W lamp. For this reaction no purified yield was reported and the product **33** was used without characterization or purification.

Scheme 9a

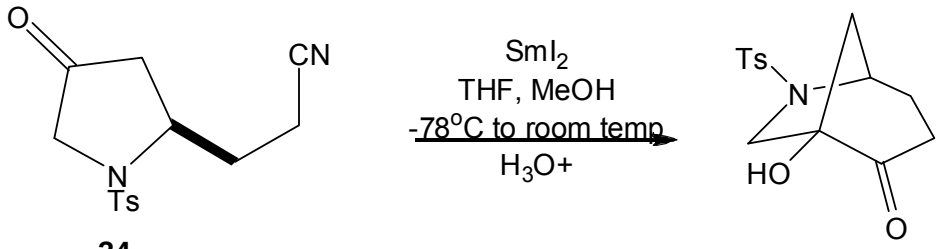


32 **33**

A similar reaction was illustrated by Weinreb which also involved the coupling of a ketone and nitrile (**Scheme 10**).[17] The substrate **34** used by

Weinreb was much closer to the substrates used in this work. They were able to obtain the desired azabicyclic α-hydroxyketone **35** in 78% yield.

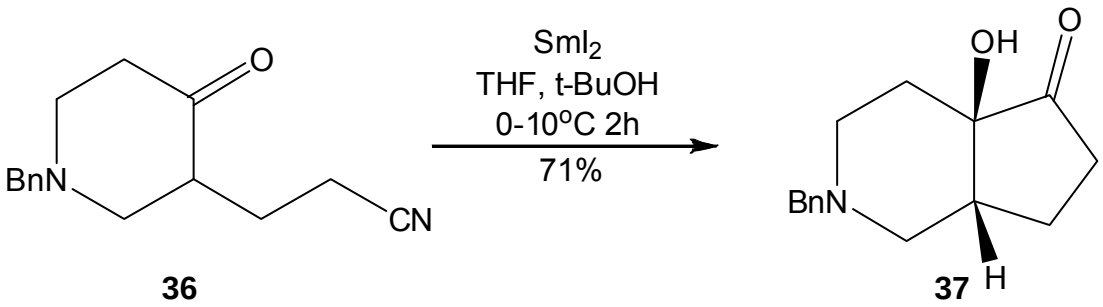
Scheme 10



34 **35**

The final example presented here represents the closest precedent to our investigation (**Scheme 11**).[15] Molander accomplished pinacol coupling of keto-nitrile **36** in the presence of a Lewis basic amine by treating the substrate with SmI_2 and irradiating with a 250 watt bulb. They were able to obtain the α-hydroxy ketone **37** in 71% yield and as a single diastereomer.

Scheme 11



36 **37**

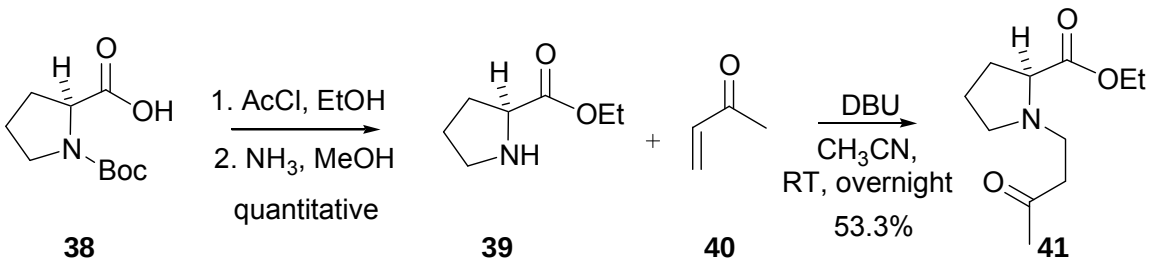
These examples demonstrate that pinacol coupling is a reasonable cyclization procedure for the substrates in this work (**Figure 3**), and should allow us to generate pyrrolizidines and indolizidines with high diastereoselectivity.

Results and Discussion

1. Keto-esters

As discussed earlier (**Scheme 1**), our first synthetic approach involved McMurry reductive cyclization of a keto-ester as the key step. Generating the keto-ester required a two-step synthesis. In the first step, proline-derived ester **39** was obtained from commercially available boc-proline **38** by one-pot deprotection and esterification in quantitative yield.[18] The next step was alkylation in order to obtain the carbon skeleton for cyclization of the B ring (**Scheme 12**). Ester **39** was alkylated with methyl vinyl ketone **40** according to an aza-Micheal mechanism to give keto-ester **41** in a 53.3% yield after purification.[19]

Scheme 12



38 **39** **40** **41**

With the carbon skeleton in place, the next step was the key cyclization. Both McMurry[20] and pinacol[21] coupling methods were attempted on this substrate. **Tables 3** and **4** summarize these attempts.

Two approaches to the McMurry reaction were attempted on keto-ester **41**. One method was the instant method where the $TiCl_4$, Zn, and keto-ester were added all at once and subjected to microwave irradiation (entry1, **Table 3**).[20b] In the other trail, the $TiCl_4$ was reduced with Zn first and then the starting material was added (entry 2). With both procedures, the product isolation efforts were

complicated by the formation of a Ti-THF complex that could not be removed from the crude reaction mixture.

Scheme 13

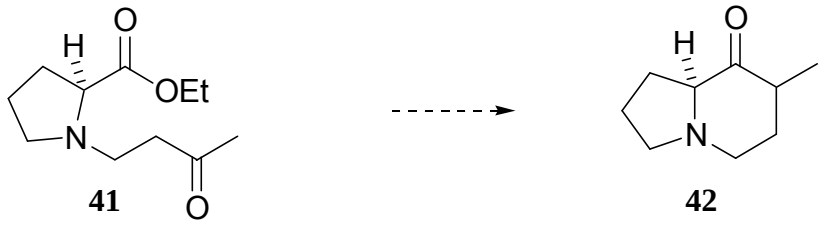


Table 3. Summary of McMurry reductive couplings of keto-ester **41**.

entry	eq. Zn, $TiCl_4$	pre-reduction	reaction conditions
1	4.0, 2.0	none	microwaves: 300W, 110^{o}C,175psi, 30 min
2	4.0, 2.0	2 hr reflux	room temp overnight

For the pinacol couplings, two procedures were also attempted. In the first procedure, SmI_2 solution and t-BuOH were added to keto-ester 41 and stirred for one hour at room temperature (entry 1, **Table 4**). The second method was the same except no alcohol was added (entry 2). Both procedures resulted in decomposition.

Scheme 14

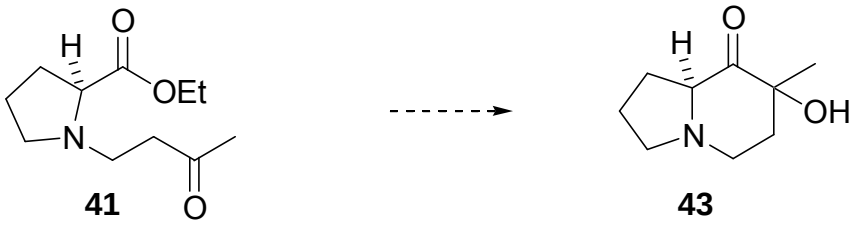
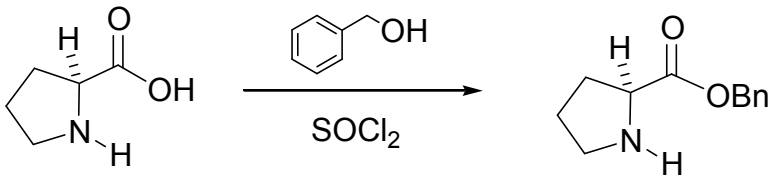


Table 4. Summary of pinacol couplings of keto-ester **41**.

entry	reaction conditions
1	2.2 eq SmI_2, 2 eq t-BuOH, 1 hour, room temp
2	same as entry 2 but no alcohol

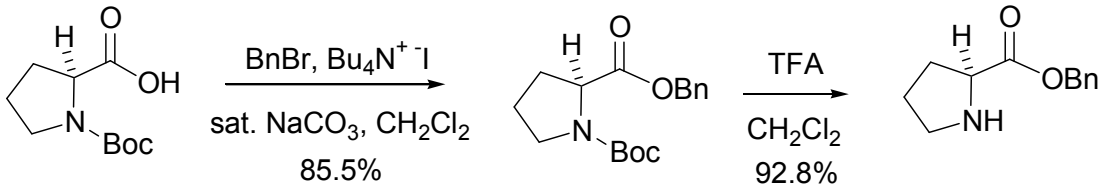
Both the ^{1}HNMR spectra of the crude reaction mixtures and the low mass recoveries suggested that either the starting materials or products were decomposing during the reaction or during product isolation. A test of the ethyl ester revealed that it was hydrolyzing under the work-up conditions used for product isolation. Accordingly it was hypothesized that a more robust ester was needed. The proposed ester was a benzyl ester which would be alkylated in the same way as the ethyl ester. Initially we attempted to form the ester directly from proline using benzyl alcohol and $SOCl_2$ (**Scheme 15**).[22] However this procedure required an excess of benzyl alcohol that was problematic to remove. In light of these results, we elected to use a two-step alkylation-deprotection procedure beginning with boc-proline **38** (**Scheme 16**).[23] Both steps were high yielding; ester **46** was formed in 85.5% yield using benzyl bromide, saturated $NaHCO_3$ solution and a phase transfer catalyst. Boc-deprotection using trifluoroacetic acid (TFA) provided the desired ester **45** in 92.8% yield.

Scheme 15



44 **45**

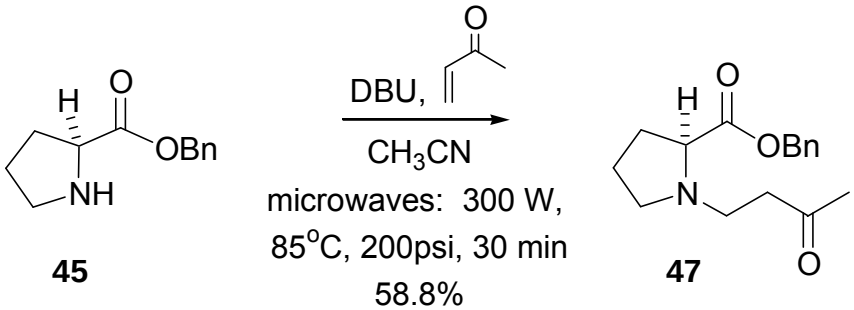
Scheme 16



38 **46** **45**

The alkylation of ester **45** was performed using methyl vinyl ketone and DBU (**Scheme 17)**.[19] The reaction was attempted by either stirring at room temperature orunder microwave-assisted heating. The microwave-assisted heating conditions proved to be the most effective, giving keto-ester **47** in 58.8% yield after purification. The room temperature reaction resulted in poor conversion.

Scheme 17

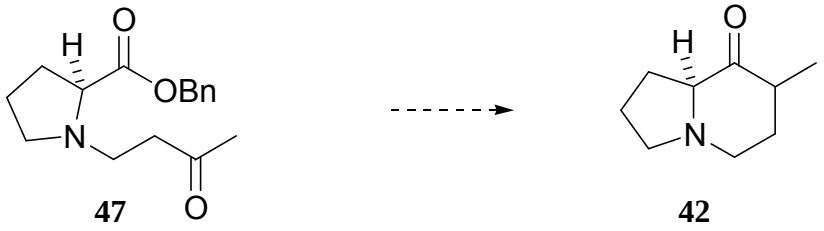


45 **47**

The cyclization of keto-ester **47** via the McMurry[20] reaction was attempted three times without success (**Scheme 18, Table 5**). One procedure involved pre-

reduction, and then addition of keto-ester **47** and refluxing overnight (entry 1). A second procedure involved the instant method and use of microwave heating (entry 2). The third method also involved no pre-reduction microwave heating, but with the addition of one molar equivalent of triethylamine (TEA) to neutralize HCl formed during the reaction (entry 3). The substrate was extremely sensitive to hydrolysis; consequently only complex mixtures and Ti-THF were present in the ^{1}H NMR spectrum of the crude reaction mixture. Because of these results, the second synthetic strategy outlined in **Scheme 2** was then pursued.

Scheme 18



47 **42**

Table 5. Summary of McMurry reactions of keto-benzyl ester **42**.

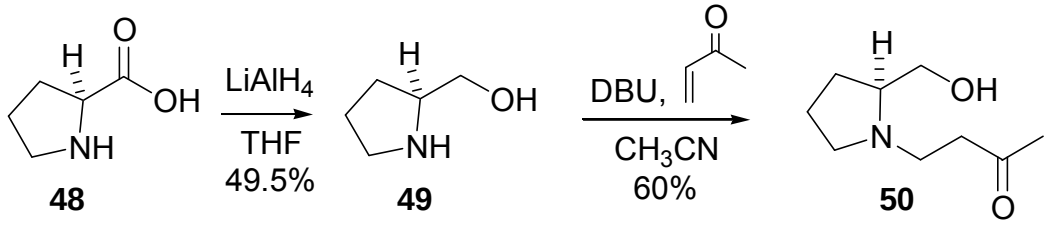
entry	eq. Zn, $TiCl_4$	pre-reduction	reaction conditions
1	6.0, 3.0	2 hr reflux	overnight reflux
2	4.8, 2.4	none	microwaves: 300W, 110^{o}C, 175 psi, 10 min
3	4.8, 2.4	none	same as entry 2 with 1 eq TEA

2. Keto-aldehyde

The synthesis of prolinol **49** from proline **48** was accomplished according to a known procedure[24] and purified by Kugelrohr distillation to give 49.5% yield (**Scheme 19**). Next prolinol **49** was alkylated with methyl vinyl ketone to give

hydroxyketone **50** in 60% purified yield.[19] In order to perform the reductive cyclization between an aldehyde and ketone, we required oxidation of the primary alcohol. Oxidation under a variety of conditions was attempted (**Scheme 20, Table 6**). Unfortunately oxidations using pyridinium chlorochromate (PCC)(entry 1), Parikh-Doering conditions (entries 2-5) and Swern oxidations (entry 6) all failed.[25a-c] In light of these results, we decided to pursue a different functional group combination for the reductive coupling.

Scheme 19



Scheme 20

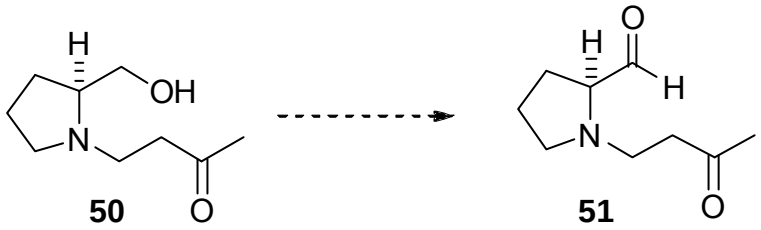


Table 6. Summary of oxidations attempted on hydroxyl ketone **50**.

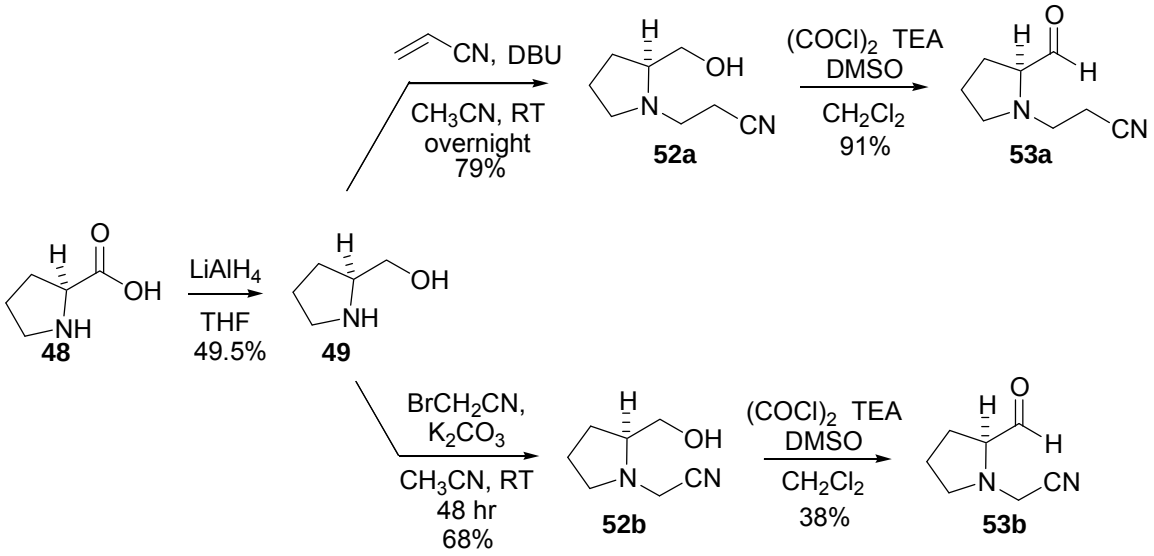
entry	reaction conditions
1	PCC(1.6eq), molecular seives, CH_2Cl_2, 2hrs, room temp
2	SO_3-pyr(4eq), TEA(4eq), DMSO(21eq), overnight, room temp
3	SO_3-pyr(4eq), TEA(4eq), DMSO(21eq), 2hrs, room temp
4	SO_3-pyr(4eq), TEA(4eq), DMSO(21eq),1 hr, room temp
5	SO_3-pyr(4eq), TEA(4eq), DMSO(21eq),3.5 hrs, 0^oC
6	oxalyl chloride(3.07eq), TEA(7.75eq), DMSO(3.86eq),1 hr, room temp

3. Cyano-aldehydes

The synthesis of cyano-aldehydes **53a-b** starts with the alkylation of prolinol **49** (**Scheme 21**). Acrylonitrile was the alkylating agent used to synthesize the six-membered B-ring skeleton **52a**.[19] Bromoacetonitrile was used in the alkylation to form the skeleton for the five-membered B-ring **52b**.[26] Cyano-alcohol **52a** did require purification after the alkylation and was produced in 79% purified yield. Cyano-alcohol **52b** was formed in 68% yield and was used without purification. The cyano-alcohols **52a-b** were then oxidized to their respective aldehydes **53a-b**. For cyano-alcohol **53a,** the Parikh-Doering[25b] method was attempted along with various Swern[25c,27] oxidations. The final optimized reaction utilized the Swern oxidation conditions. It was found that this reaction was very

temperature, time and moisture sensitive. For complete experimental details see the experimental section. The only purification involved Kugelrohr distillation to remove excess DMSO. Following this, the cyano-aldehyde **53a** was isolated in 91% yield. For cyano-alcohol **53b**, the same Swern oxidation was used. However cyano-aldehyde **53b** did require purification by column chromatography, and was produced in 38% purified yield.

Scheme 21

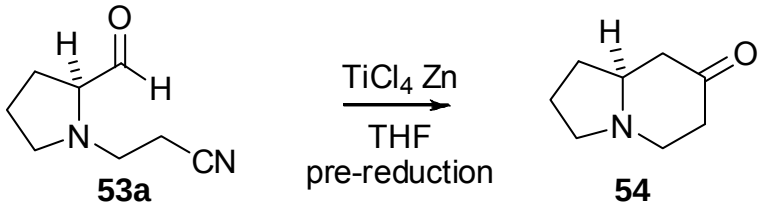


After the oxidation cyano-aldehydes **53a-b** had both the proper skeleton and oxidation states for the cyclization of the B ring. Cyano-aldehyde **53a** was used in both the McMurry[20a-d] and pinacol[21] couplings. Cyano aldehyde **53b** was used in the McMurry reaction once and three times in the pinacol reaction. The results of these reactions are summarized below.

For the cyclizations of cyano-aldehyde **53a** (**Scheme 22**), the instant procedure was used first with microwave-assisted heating (entry 1, **Table 7**). The other procedures all involved a pre-reduction of the $TiCl_4$. The reaction times and

temperatures were varied with no real improvement. In one case (entry 5) the reaction resulted in a 22% conversion to the desired indolizidinone **54**. However, this result was not reproducible. In addition, one significant disadvantage of this procedure was the difficulty removing Ti-THF complex that was formed under the reaction conditions.

Scheme 22



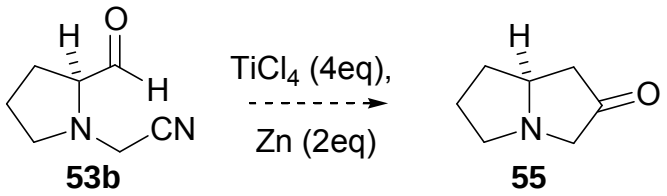
53a **54**

Table 7. Summary of McMurry coupling on cyano-aldehyde **53a**.

entry	eq. Zn, $TiCl_4$	pre-reduction	reaction conditions	comment
1	4.8, 2.4	none	microwaves: 300W, 110°C,175psi, 30 min	complex mixture
2	12.0, 6.0	2 hr reflux	16 hr reflux	complex mixture
3	6.0, 3.0	2 hr reflux	16 hr reflux	complex mixture
4	6.0, 3.0	2 hr reflux	16 hr rt	complex mixture
5	6.0, 3.0	2 hr reflux	1 hr rt	22 % conversion

For cyano-aldehyde **53b** the McMurry reaction was only attempted once. The microwave-assisted instant method was used, and unfortunately failed. (**Scheme 23, Table 8**)

Scheme 23



53b **55**

Table 8. McMurry reaction on cyano-aldehyde **53b**.

entry	conditions
1	microwaves - no pre-reduction 110^{o}C, 300W, 175psi, 10 min

There were many problems encountered with the McMurry reaction (**Scheme 22** and **23, Tables 7** and **8**). The reaction always resulted in a complex mixture and a significant amount of Ti-THF complex was always present and difficult to remove. In addition, the cyclization of cyano-aldehyde **53a** did provide the desired indolizidinone **54** once in 22% conversion, but this was never reproducible. Although the McMurry reaction was only attempted once on cyano-aldehyde **53b**, a similar complex mixture was obtained. Because of these results, we turned our attention to the pinacol coupling of cyano-aldehyde **53a-b**.

The pinacol coupling of cyano-aldehyde **53a** yielded promising results (**Scheme 24, Table 9**). When the reaction was performed using a commercially available SmI_2 solution, hydroxy indolizidinone **56** was formed as the major product along with 30% of a by-product presumed to be dimer **58** (entry 1). When we made the required SmI_2 solution ourselves, we generated only about 33-34% of the desired indolizidines **56** (entries 2 and 3). In addition to approximately 20% dimer, a second by-product, alcohol **57** was generated. Both by-products could result from an insufficient amount of SmI_2 in the reaction mixture, so the reaction

might be optimized by simply increasing the amount of SmI_2. These investigations are on-going.

Scheme 24

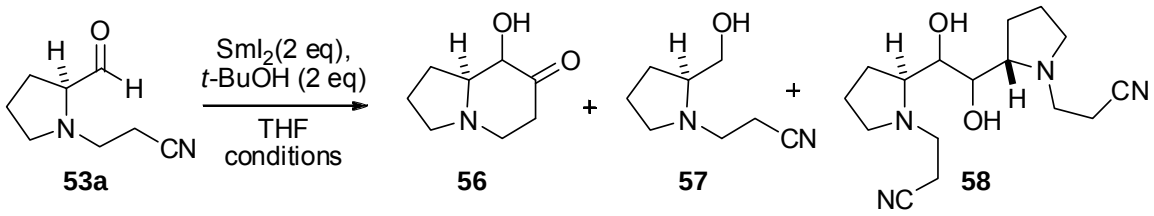


Table 9. Summary of pinacol coupling reactions performed on cyano-aldehyde **53a**.

entry	conditions	ratio[a] indolizidine : alcohol : dimer
1	0 °C, 2 hr	67:0:33
2[b]	0 °C, 2 hr	34:45:21
3[b]	0 °C to rt, 16 hr	33:46:21

[a]Based on ^1H NMR integration of crude reaction mixture

[b]SmI_2 solution was freshly prepared from Sm and EtI_2

By contrast, pinacol coupling of cyano-aldehyde **53b** was less successful, giving a complex mixture in all trials (**Scheme 25, Table 10**). After optimizing the pinacol coupling for cyano-aldehyde **53a**, we will apply those conditions in hopes of obtaining a useful result.

Scheme 25

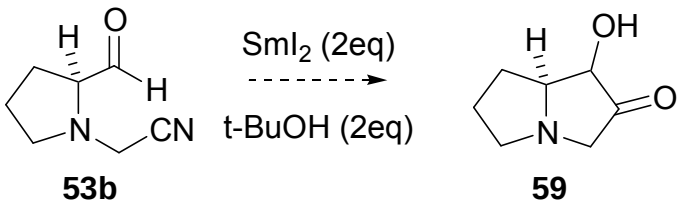


Table 10. Pinacol couplings of cyano-aldehyde **53b**.

entry	conditions
1	2 hr, 0°C
2*	2 hr, 0°C
3*	16 hr, 0°C to rt

*SmI_2 solution was freshly prepared from Sm and EtI_2

At this point in the project there has been much progress made but still there is much work to be done. The first synthetic method involving keto-ester cyclization was unsuccessful. The second method involving the nitrile and aldehyde looked much more promising. While the original strategy was to use the McMurry reaction it would appear based on the work done here that the pinacol coupling may be more successful. In addition, the pinacol coupling is likely to have better stereoselectivity than the McMurry reaction and provides more handles for further functionalization of the ring.

Future work to be done includes further optimization of the pinacol coupling of the two cyano-aldehydes. Upon optimization of the cyclization, the ring functionalization will be the next part of the project. Another aspect of the project will be to begin the synthesis with a more substituted A ring. Once this is accomplished several variations of the natural products will be attainable.

Experimental

General Information

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 ^{TM} 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 hydroxide 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.

Ethyl Ester 39

Boc-proline **38** (3 g, 13.935 mmol) was dissolved in ethanol (60 mL) in a round bottom flask and placed in an ice bath. Once dissolved, acetyl chloride (3.0 mL, 41.81 mmol) was added slowly while venting. The mixture was then stirred at room temperature for 48 hours. After 48 hours the flask was placed in an ice bath and was quenched slowly while venting with 7M ammonia in methanol (15 mL). Solvent was then evaporated and the residue was redissolved in CH_2Cl_2. The slurry was filtered using a fritted filter with cotton and the filtrate evaporated to yield ethyl ester **39** (1.874 g, 13.09 mmol, 93.6%) as a light yellow oil.

Keto-Ester 41

To a solution of the proline ethyl ester **39** (0.3022 g, 2.11 mmol) in acetonitrile (1.2 mL) was added DBU (0.16 mL, 1.1 mmol) and methyl vinyl ketone (0.26 mL, 3.2 mmol). The reaction mixture stirred under nitrogen at room temperature overnight. The mixture was concentrated and then purified over silica gel using 5:95 MeOH:CH_2Cl_2 to afford keto-ester **41** (0.1789 g, 1.25 mmol, 59.2%)

Benzyl Ester 45

To a solution of boc-proline **38** (0.5091 g, 2.37 mmols) in dichloromethane (10 mL) was added saturated sodium bicarbonate (7 mL), tetrabutyl ammonium iodide (0.8550 g, 2.31 mmol), and benzyl bromide (0.42 mL, 1.71 mmol). The mixture was allowed to stir overnight at room temperature. The mixture was concentrated and purified over silica gel using 1:15 EtOAc:hexane to afford the boc-protected benzyl ester **46** (0.7473 g, 1.98 mmol, 83.7%). The ester was then dissolved in dichloromethane (29 mL) and TFA (11 mL) was added. The reaction was allowed to stir for 60 minutes. Then the mixture was slowly poured into ice cold bicarbonate solution and extracted three times with dichloromethane, dried over $MgSO_4$ and concentrated to give keto-ester **45** (0.4608 g, 2.24 mmol, 94.5%-from boc-proline).

Prolinol 49

In a round-bottom flask, $LiAlH_4$ (1.4523 g, 38.27 mmol) was dissolved in THF (35 mL) that was made under inert conditions. The mixture was cooled to 0^oC and then solid L-proline **48** (3.0045 g, 26.1 mmol) was added. The mixture refluxed for two hours. The reaction mixture was then cooled and any excess $LiAlH_4$ was

quenched with 20% KOH (4 mL) which was added slowly. The reaction mixture, which was then very chunky, was filtered and rinsed thoroughly with THF (40-60 mL). The reaction mixture (liquid portion) was then refluxed for another 30 minutes. The reaction mixture was then cooled and dried using magnesium sulfate. It was then filtered through cotton and celite (rinsed with EtOAc) and concentrated to afford prolinol **49** (2.0253 g, 22.02 mmol, 76.9%) as a yellowish clear oil. The prolinol **49** was purified by kugelrohr distillation under vacuum at 210^{o}C (1.4586 g, 14.42 mmol, 55.2%).

Keto-alcohol 50

To a solution of prolinol **49** (0.4069 g, 4.05 mmol) in acetonitrile (2 mL) was added DBU (0.3 mL, 2 mmol) and methyl vinyl ketone (0.5 mL, 6 mmol). The reaction stirred overnight at room temperature and was then concentrated. The keto-alcohol **50** was purified over silica using 5:95 then 10:90 then 15:85 MeOH:CH_2Cl_2 to afford the keto-alcohol **50** as a brown oil (0.3831 g, 2.24 mmol, 55.9%).

Cyano-alcohol 52b

To a solution of prolinol **49** (1.4586 g,14.42 mmol) in acetonitrile (22.8 mL) was added potassium carbonate (2.7989 g, 20.25 mmol) and bromoacetonitrile (1.2 mL, 17.2 mmol). The reaction mixture stirred for 36 hours. The reaction mixture was concentrated and then repartitioned between water and dichloromethane. After extraction (3 x CH_2Cl_2), drying over $MgSO_4$ and concentrating, the material was able to be used without purification. The cyano-alcohol **52b** must be stored

at 0^{o}C in solution and used promptly. Cyano-alcohol **52b** was afforded as a brown oil (1.4793 g, 10.55 mmol, 73.2%).

Cyano-alcohol 52a

To a solution of prolinol **49** (1.4295 g, 14.13 mmol) in acetonitrile (20 mL) was added DBU (1.0 mL, 6.69 mmol) and acrylonitrile (1.3 mL, 19.7 mmol). The reaction stirred overnight at room temperature and then was concentrated. The cyano-alcohol **52a** was purified over silica using 10:90 MeOH:CH_2Cl_2. Following purification the cyano-alcohol **52a** was isolated as a brown oil (1.9677 g, 12.75 mmol, 90.23%).

Aldehyde 53b

Methylene chloride, DMSO, and TEA were all freshly distilled. A round bottom flask containing cyano alcohol **52b** (0.5000 g, 3.57 mmol) was purged and filled three times with nitrogen, and two more empty round bottom flasks were prepared in the same way. The appropriate amount of dichloromethane was added to each flask (23 mL for oxalyl chloride, 11.5 mL for alcohol, 11.5 mL for DMSO). Oxalyl chloride (0.45 mL, 5.16 mmol) was added to one and DMSO (0.73 mL, 10.28 mmol) to the other. The oxalyl chloride and DMSO flasks were cooled to -78^{o}C and then combined using a syringe for transfer. This mixture stirred for 10 minutes. The solution of alcohol was then added and allowed to stir for 45 minutes at -65^{o}C ($CHCl_3$-dry ice bath). Then TEA (1.4 mL, 10.05 mmol) was added and the reaction mixture was warmed to room temperature and stirred for one hour. The reaction mixture was purified on a florosil column using

EtOAc and then on a second florosil column using 50:50 EtOAc:Hex to afford the aldehyde **53b** as a brown oil (0.1542 g, 1.12 mmol, 31.4%).

Aldehyde 53a

Methylene chloride, DMSO, and TEA were all freshly distilled. A round bottom flask containing cyano-alcohol **52a** (0.2108 g, 1.37 mmol) was purged and filled three times with nitrogen, and two more empty round bottom flasks were prepared in the same way. The appropriate amount of dichloromethane was added to each flask (8.8 mL for oxalyl chloride, 4.4 mL for alcohol, 4.4 mL for DMSO). Oxalyl chloride (0.16 mL, 1.83 mmol) was added to one and DMSO (0.27 mL, 3.8 mmol) to the other. The oxalyl chloride and DMSO flasks were cooled to -78^{o}C and then combined using a syringe for transfer. This mixture stirred for 10 minutes. The solution of alcohol was then added and allowed to stir for 45 minutes at -65^{o}C. Then TEA (0.56 mL, 4.02 mmol) was added and the reaction mixture was warmed to room temperature and stirred for one hour. The aldehyde **53a** was obtained with an excess of DMSO. To get rid of the DMSO the compound was put on the kugelrohr under vacuum at 50^{o}C to afford aldehyde **53a** as a brown oil (0.1705 g, 1.12 mmol, 81.8%).

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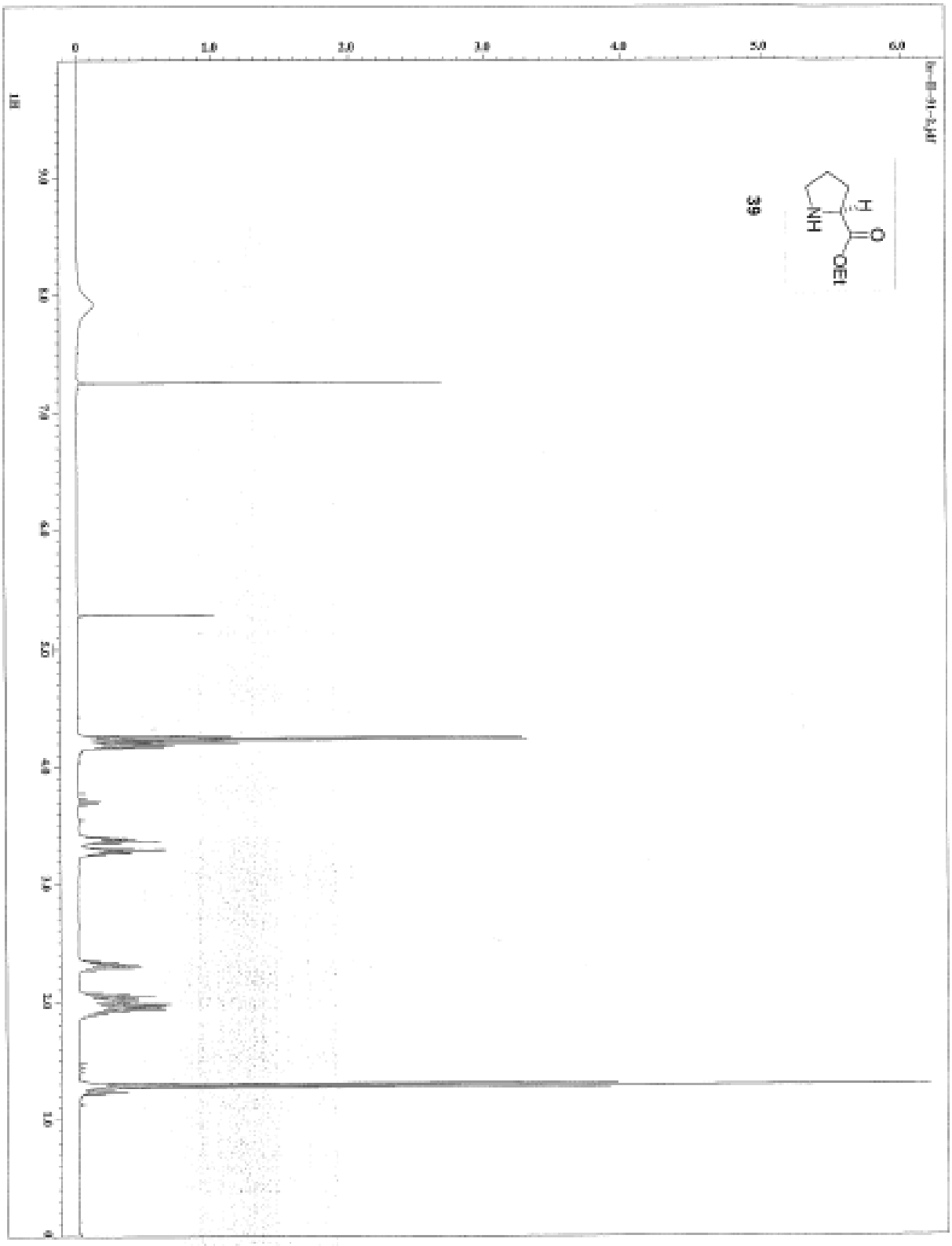
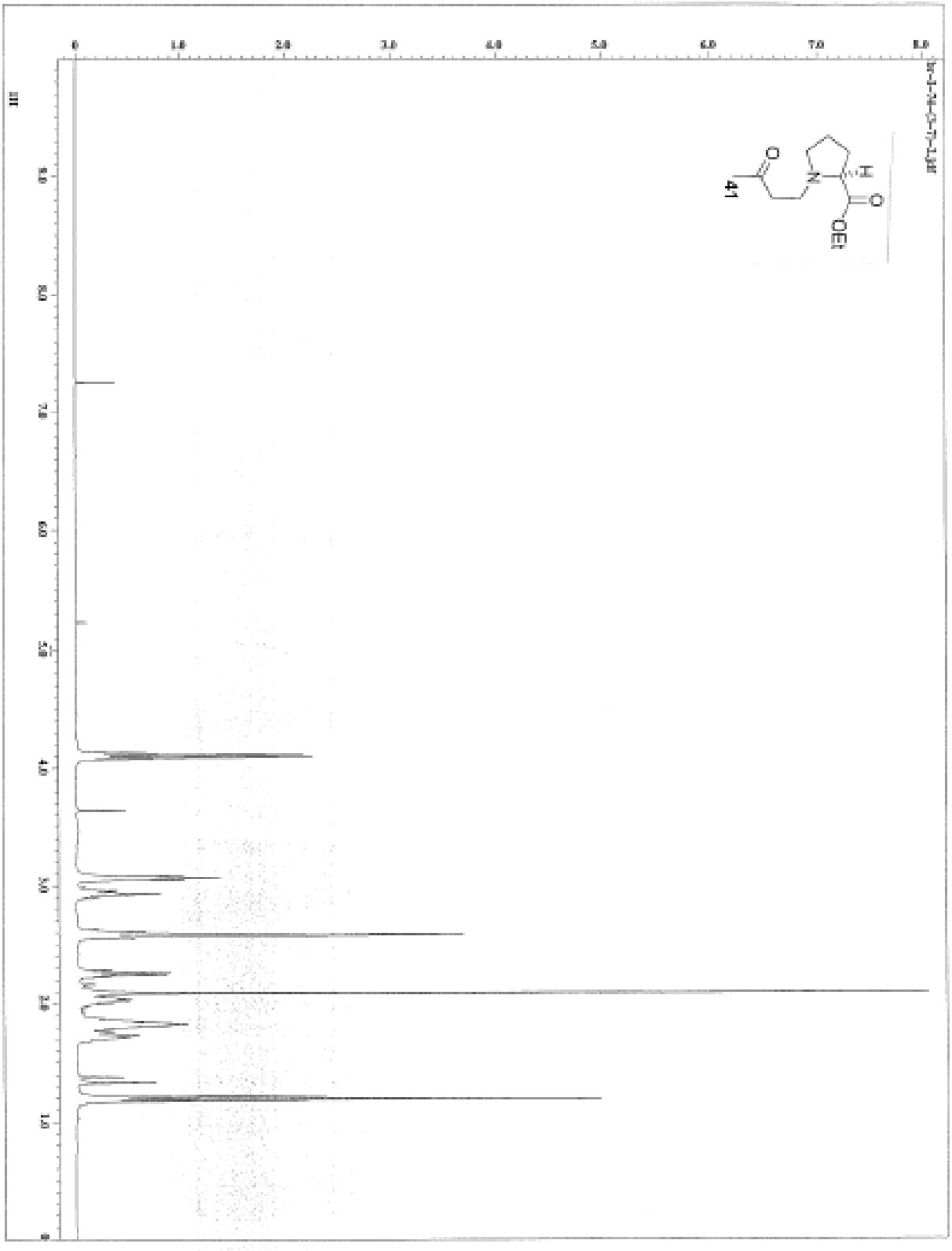
Appendix

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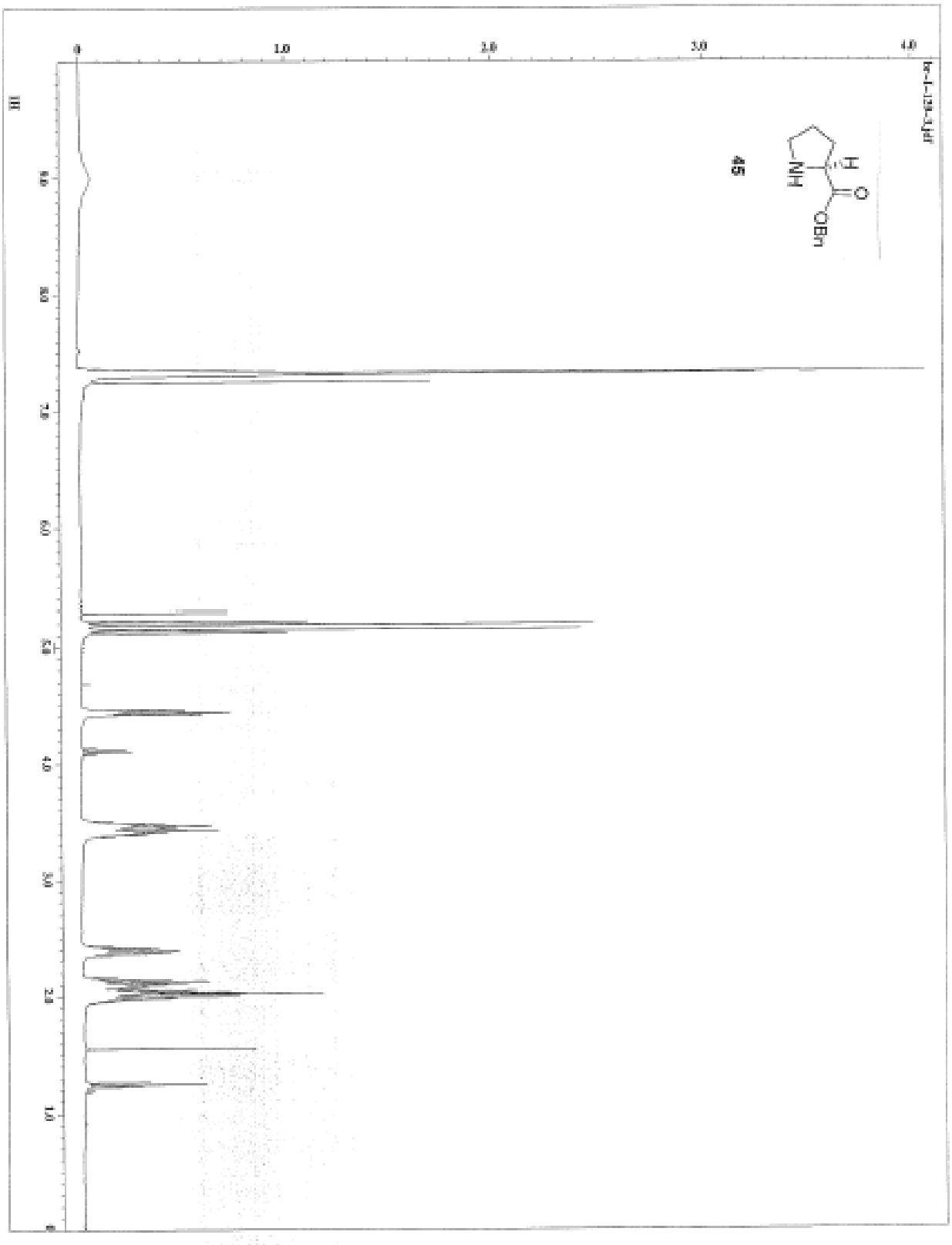
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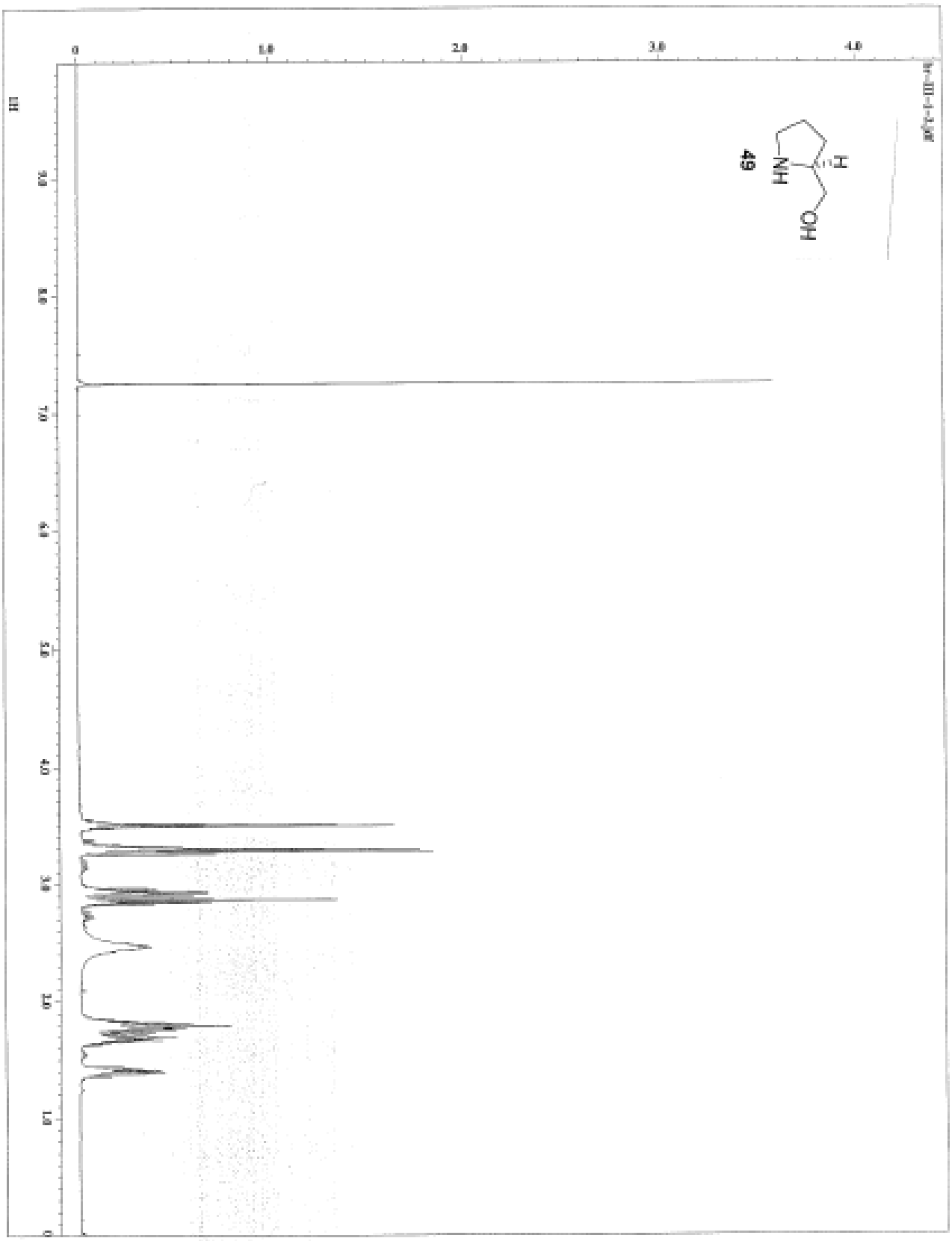
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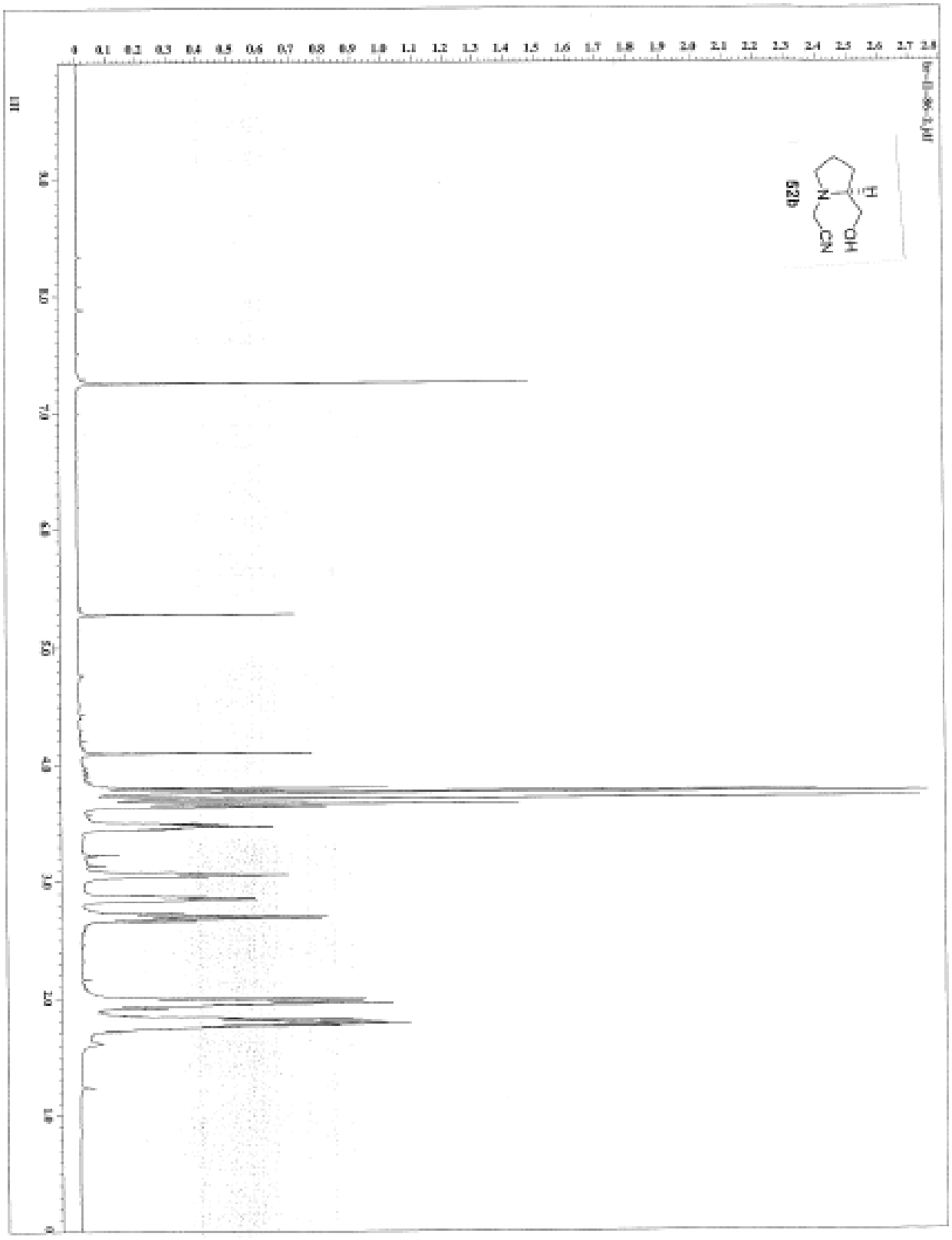
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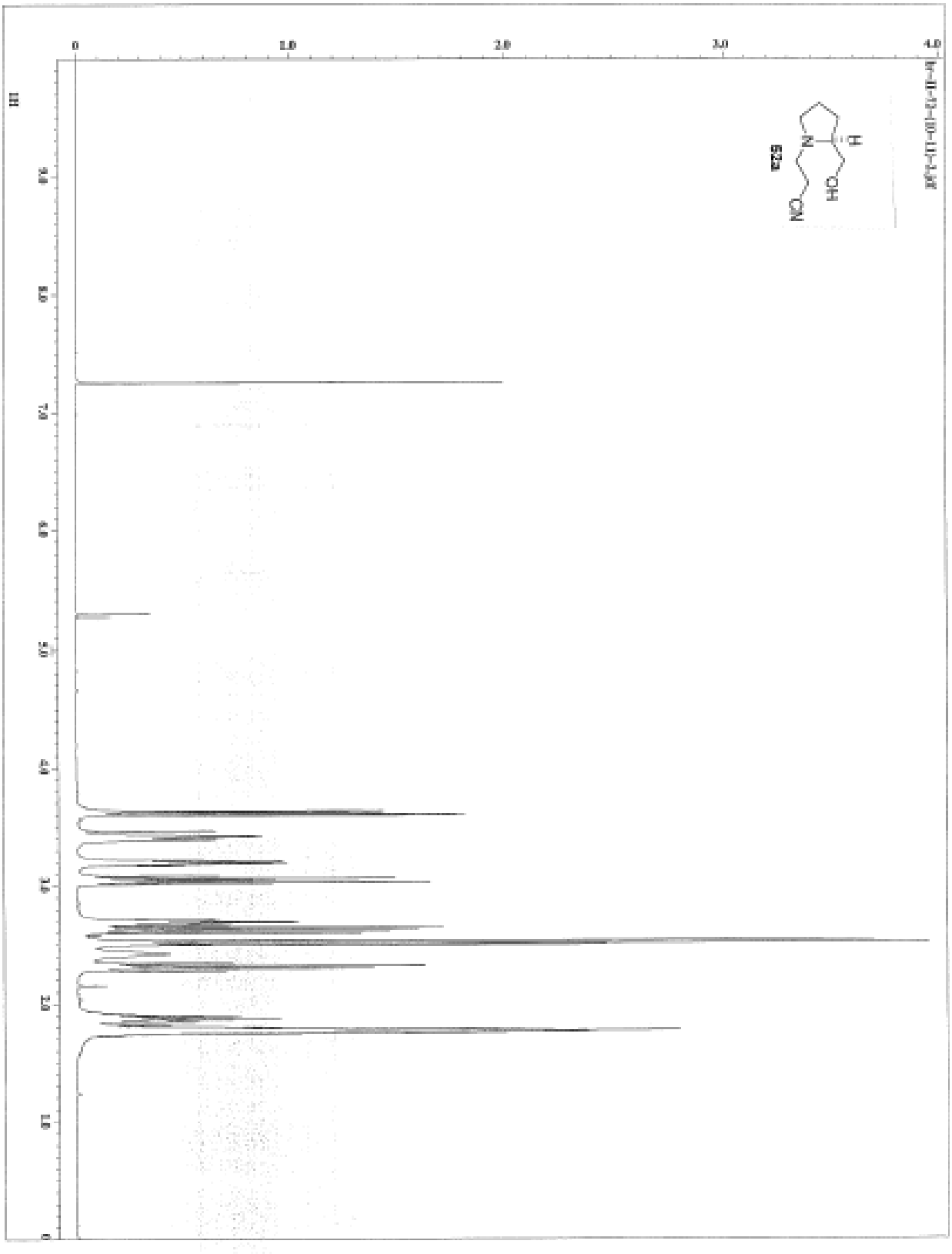

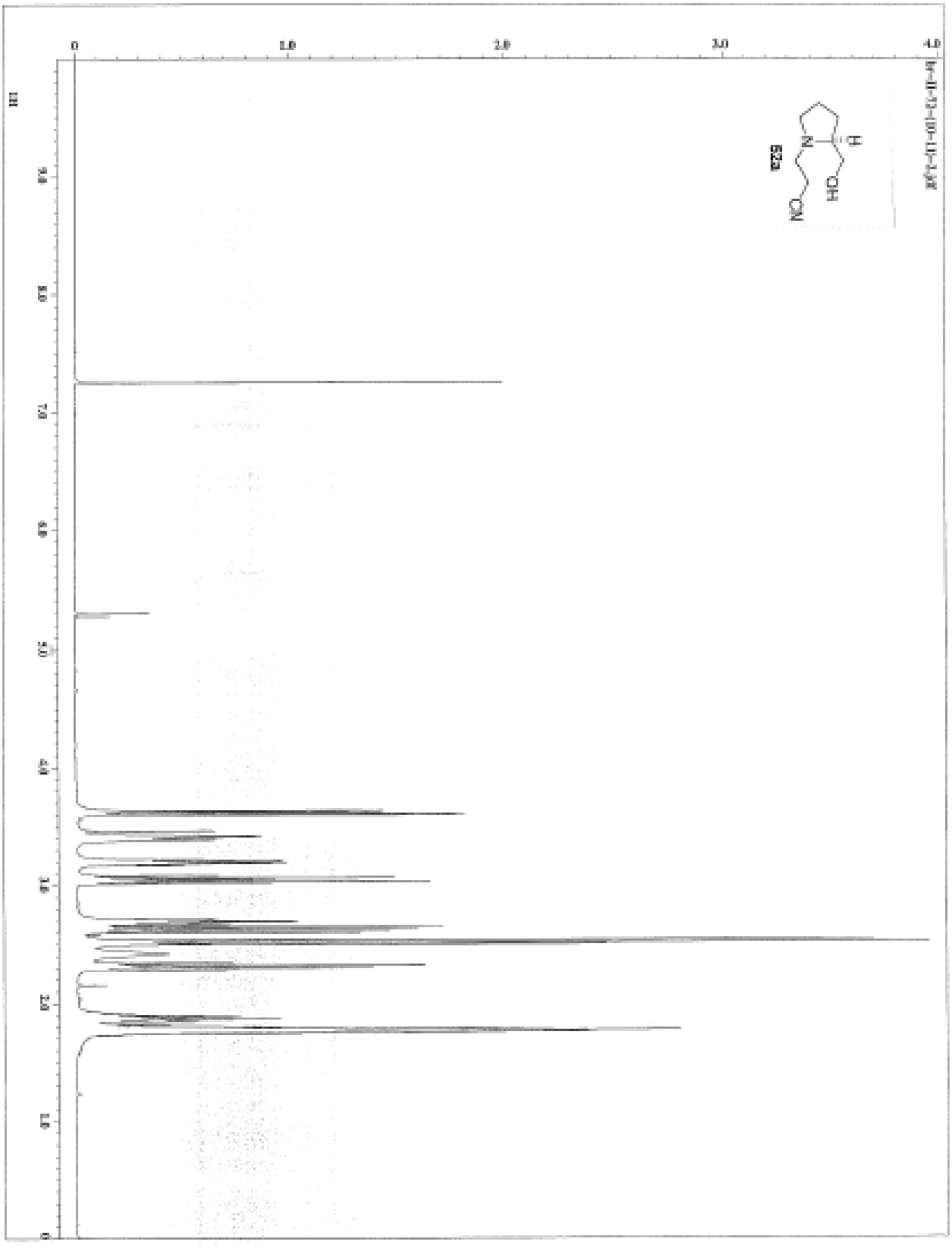
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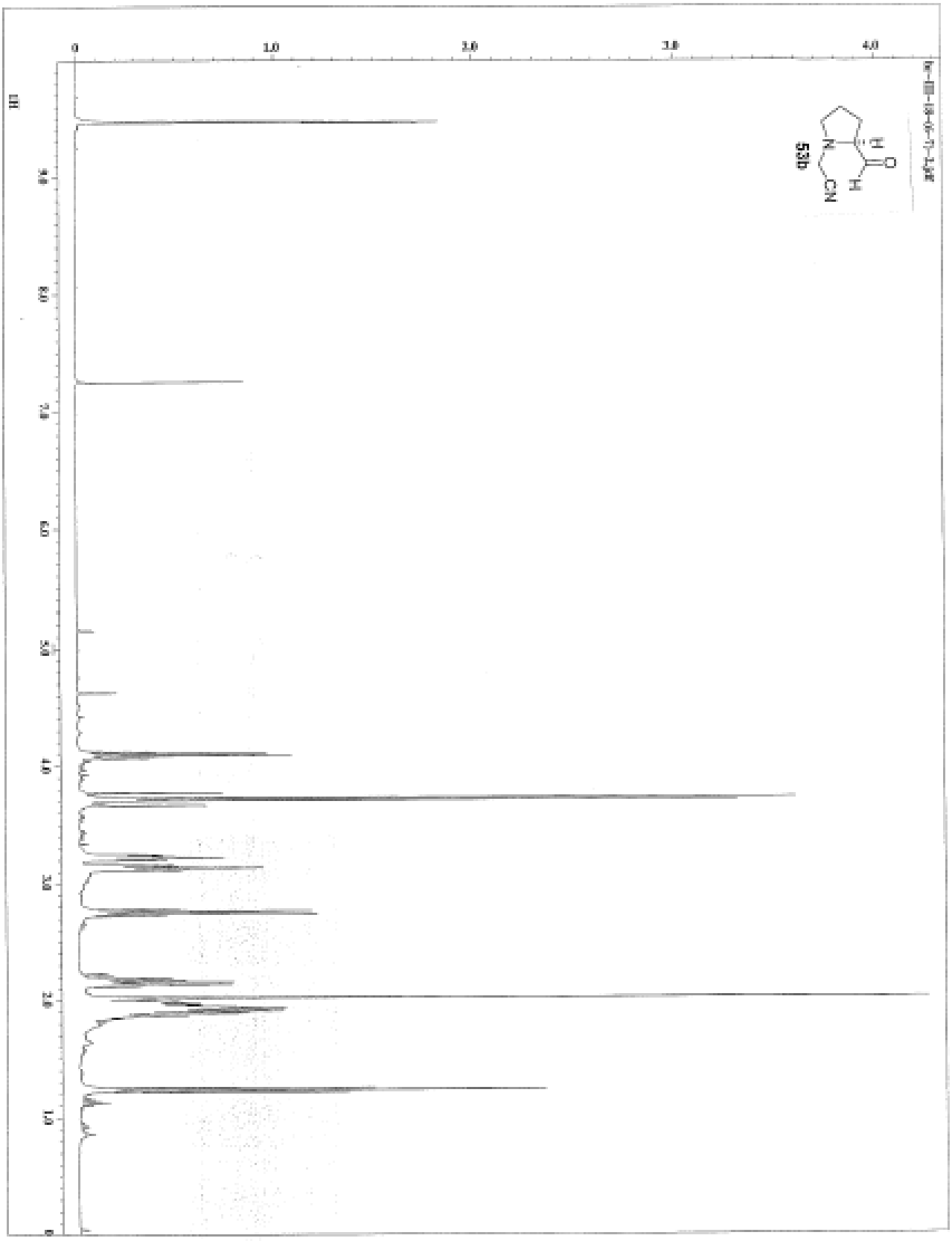
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