1-1-2016

Modified Synthesis Of Ligands For Lanthanide Ions

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MODIFIED SYNTHESIS OF LIGANDS FOR LANTHANIDE IONS

By

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DISSERTATION

Submitted to the Graduate School

of Wayne State University,

Detroit, Michigan

in partial fulfillment of the requirements

for the degree of

MASTER OF SCIENCE

2016

Major: Chemistry

Approved By:

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Advisor Date

DEDICATION

This thesis is dedicated to my family.
I could not have done this without your love, encouragement, and prayers.

ACKNOWLEDGMENTS

First and foremost, I am thankful to my Lord and Savior, Jesus Christ. His death on the cross, saving me from the penalty of my sins, enables me to now live a life inside the context of His will for me. Knowing this, I am confident that whatever He has planned for my life will come to fruition, and that He will be there every step of the way guiding me and paving the pathway for me to walk, even when that pathway may seem unclear. This masters degree may not have been my plan for my life, but it was His, and I can now say with absolute confidence that I can "consider it all joy" (James 1:2–4)

I am also beyond thankful for my family. Their love, support, and prayer for my life have enabled me to make it through this process of graduate school, daily reminding me to seek out God's will for my life and to be in His Word.

I am thankful that God placed me in Dr. Matthew Allen's lab. I remember praying that God would direct my decision when I had to choose an advisor and being confident that this was the lab that I was supposed to join. I am thankful for Dr. Allen's training in my life, pushing me to become an independent scientist who critically thinks about every aspect of their project. He has helped me define in my mind what it means to be an advisor and a mentor, and I will be able to take with me the lessons he has taught me, using them with my own students in the near future.

Part of the joy of being in the Allen lab was the interaction that I was able to have between both the original members of the lab and the now current members of the lab. The lessons that I have learned from members in both groups has helped define who I am as a person and a scientist, and I am thankful for the discussions, whether scientific, personal, or professional, that we have had. I am also thankful for the lasting friendships that have been formed inside and outside of my lab group at Wayne State, especially that of Joseph P. Klesko, those friendships helped me to be able to push forward in this program.

I am also extremely thankful for all of the staff in the Chemistry Department at Wayne State University. The Lumigen Instrument Center staff has always been there when needed to help with experiments, and have graciously answered any questions that I have had regarding the instruments. The science stores staff has been a source not only of help regarding purchases, but a source of friendship, laughter, and encouragement. In regards to the business office ladies, including Melissa, I will miss being able to see them on a daily basis and talk with them regarding all aspects of life.

Additionally, I would like to thank the National Institutes of Health EB013663 and GM058905 for support, as well as the IMSD program at Wayne State University. The opportunities presented to me through the IMSD program and the degree of mentoring there has greatly impacted my career choices, and I am extremely thankful for that experience.

Regarding my church family and friends, some of which have prayed for me since I was a child, and some of which have already passed on, I could not have done this without their support and upholding of me in prayer. God is good, and He is Sovereign. I am thankful for the constant encouragement, rebuke, and reminders of God's goodness that have been shown to me through my church family.

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1.1 Introduction and Background

Microwave-assisted heating is common in the field of lanthanide chemistry to aid in the formation of ceramics and nanoparticles. However, in comparison to ceramics and nanoparticles, the use of microwave-assisted heating in solution-phase lanthanide chemistry is less common. Microwave-assisted heating has been used in reactions such as the synthesis of Ln(II) salts, single-electron-transfer reactions, catalysis, and synthesis of ligands for lanthanide ions, which is the focal point of this document.

Regarding ligands for lanthanide ions, there are generally two classes of ligands, cyclic and acyclic. In this document, a discussion of microwave-assisted ligand synthesis is separated into ligands based upon a tetraazacyclododecane (cyclen)-based structure (Section 1.2.1) and ligands that are not based upon a cyclen-type structure (Section 1.2.2). This separation was included because until recently,[1–2] cyclen-based structures have been used primarily for lanthanides in the trivalent state. Consequently, this document draws attention to the potential use of microwaves in relation to the facile synthesis of ligands for trivalent lanthanide ions. In the second section, non-cyclen based ligands, there is some attention brought to ligands for divalent lanthanides, but the primary focus is on ligands for ions in the trivalent state. For the reactions described in this chapter, microwave-specific parameters used in each reaction (time, temperature, and in some cases power) are emphasized to enable comparisons between different microwave reactors. Because of the variability among different microwave reactors, the power of the microwave reactor is noted in cases where temperature is not directly controlled by a temperature probe. For these cases, power and reaction time are reported, and reaction temperature is reported as a

temperature maximum (max) instead of a specific temperature. In cases where the temperature was monitored with a temperature probe, the exact temperature is listed.

Before addressing specific microwave reactions related to lanthanides, it should be pointed out that microwave reactors use a combination of dipolar polarization and ionic conduction caused by microwave irradiation to enable rapid heating of reaction components.[3–4] These heating mechanisms are sometimes touted as enabling "special microwave effects", and one such example is described in this chapter.[5] The topic of special microwave effects versus thermal effects is a highly debated topic, and many chemists think that rate enhancement due to microwave heating is merely a thermal effect, following the Arrhenius equation, shown in **eq 1** where A is the preexponential factor, E_a is the activation energy, R is the gas constant, and T is temperature.[6–8] Regardless of the cause of rate enhancement, the effectiveness of using microwave irradiation to enhance reaction rates provides chemists with a useful tool to enable fast reaction rates and, therefore, rapid investigation of reactions and syntheses.

$$k = Ae^{\frac{-E_a}{RT}} \quad (1)$$

1.2 Lanthanide-related microwave-assisted ligand and complex synthesis

Ln(III) ions are critical to a diverse set of applications including luminescence imaging,[9–12] magnetic resonance imaging (MRI),[13–20] and catalysis;[21–26] and the separation of these ions from actinide ions is an important issue in nuclear waste separation.[27] Ligand synthesis is central to each of these areas, and microwave-assisted synthesis of ligands for Ln(III) ions is the focus of sections 1.2.1 and 1.2.2.

1.2.1. Reactions related to cyclen derivatives for Ln(III) ions

Many ligands for Ln(III) ions incorporate macrocycles based upon derivatives of 1,4,7,10-tetraazacyclododecane (cyclen, **1.1**, **Figure 1.1**).[28] Syntheses of cyclen-based ligands often require reaction times on the order of days; however, microwave-assisted heating has been used in some of these reactions to greatly decrease reaction times as detailed in this section.

Cyclen, **1.1**, is of great importance as a starting material for 1,4,7,10-tetraazacyclododecane-1,7-diacetic acid (DO2A, **1.2**), 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid (DO3A, **1.3**), 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA, **1.4**) and derivatives of these ligands (**Figure 1.1**). Consequently, facile syntheses of cyclen are useful. While there are many synthetic routes to form cyclen,[29-32] this chapter focuses on ones in which microwave irradiation has been used to improve the rate of reaction.

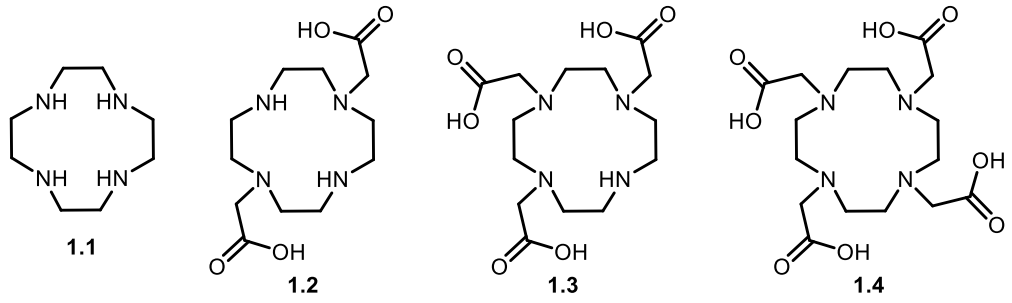
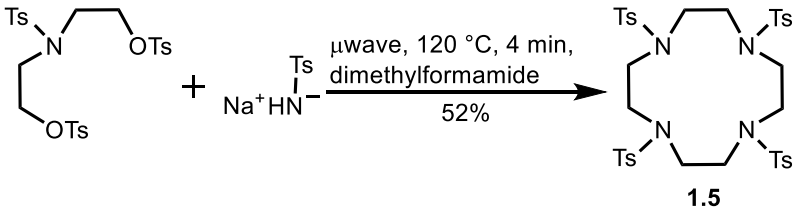


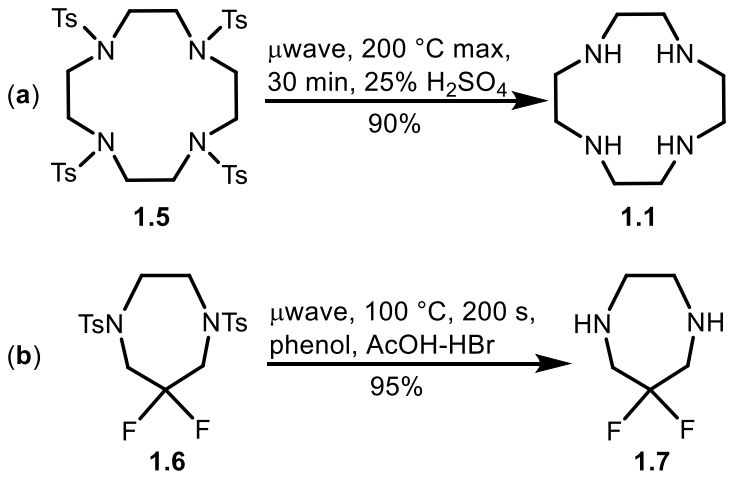
Figure 1.1. Cyclen (**1.1**) and cyclen derivatives DO2A (**1.2**), DO3A (**1.3**), and DOTA (**1.4**).

Synthesis of cyclen with conventional heating requires a day at minimum.[29] In contrast, microwave-assisted synthesis has been used to rapidly synthesize tetra-tosylated cyclen (**Scheme 1**), where tosyl stands for the *p*-toluenesulfonyl protecting group, denoted hereafter as Ts. Jebasingh and Alexander determined that microwave-assisted heating at 120 °C for 4 min leads

to the formation of the tetra-tosylated cyclen, **1.5,** in 52% yield. However, to remove the tosyl groups from **1.5**, a 65 h reflux in 48% HBr was required.[32] Alternatively, deprotection of the tosylated amines on **1.5** has been carried out using microwave-assisted heating by Mikhura and coworkers.[33] They developed a detosylation reaction promoted by 25% H_2SO_4 under microwave irradiation for 30 min with a maximum temperature of 200 °C (**Scheme 1.2a**). This detosylation reaction resulted in a 90% yield of cyclen. Mikhura and coworkers used 25% H_2SO_4 instead of HBr/acetic acid (AcOH) to demonstrate the ability to selectively deprotect Ts-protected amines over benzyl-protected amines because HBr/AcOH has been reported to remove both benzyl and Ts groups.[33] Using HBr/AcOH instead of 25% H_2SO_4, Pääkkönen and coworkers performed a detosylation of amine **1.6** and found that microwave irradiation at 100 °C for 200 s resulted in a 95% yield of detosylated product **1.7** (**Scheme 1.2b**).[34] However, because HBr/AcOH also removes benzyl protecting groups,[33] this faster reaction by Pääkkönen and coworkers is only useful for the deprotection of Ts-protected amines in the absence of benzyl-protected amines.

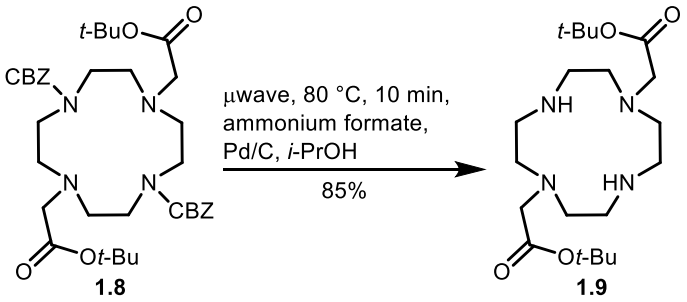


Scheme 1.1. Microwave-assisted synthesis of tetratosylated cyclen, **5**.[32]



Scheme 1.2. Microwave-assisted deprotection of tosylated amines on (**a**) cyclen derivative **1.5**[33] and (**b**) diamine **1.6**.[34]

In addition to rapid detoslyation of amines, another reaction of note in the synthesis of macrocyclic ligands is deprotection of benzyloxycarbamate (CBZ)-protected amines. Varchi and coworkers examined the deprotection of CBZ-protected amines under microwave conditions. In their reactions, ammonium formate was used as the hydrogen source, isopropanol was used as the solvent, and Pd/C (10%) was used as the hydrogenation catalyst. They found that microwave irradiation at 600 W allowed the solvent to reach its boiling point, and the reactions were complete in approximately 5 min with yields of 90% or higher.[35] As will be discussed in Chapter 2, a similar method as Varchi and coworkers was applied to the deprotection of bis-CBZ-DO2A-*t*-bu ester, **1.8** (**Scheme 1.3**), to afford the *t*-butyl-ester-protected analog of DO2A **1.9** in 85% yield in only 10 min at 400 W.[36] Reported hydrogenations for the deprotection of the CBZ-protected amines on **1.8** under conventional conditions require reaction times of 24–48 h at ambient temperature[37–39] as opposed to the 5–10 min reaction times reported for similar deprotections using microwave-assisted syntheses.[35–36]



Scheme 1.3. Deprotection of bis-CBZ-DO2A-*t*-Bu ester using microwave irradiation.[36]

DO2A and DO3A moieties are important ligands in the field of lanthanide chemistry for complexation to Ln(III) ions. Both DO2A- and DO3A-containing complexes have been used as precursors to Cu(I)-catalyzed azide–alkyne cycloaddition reactions for the synthesis of antenna-functionalized lanthanide-containing complexes. In the cycloaddition syntheses performed by Borbas and coworkers,[40] macrocycles containing an amine functionalized with either an alkyne or an azide were reacted with a corresponding antenna or macrocycle via microwave-assisted heating in acetonitrile with CuI as the catalyst and either di-isopropyl amine or piperidine as a base. Reaction conditions for the coordination of the various antennas to macrocycles under microwave irradiation were set at 100 °C for 15–60 min and resulted in complexes **1.10–1.26** in yields of 37–96% (**Figure 1.2**).[40] An exciting advantage of this microwave-assisted cycloaddition chemistry is the facile synthesis of multilanthanide-containing complexes such as **1.27–1.29** which were synthesized by linking two and three macrocycles together using DO3A or DO2A analogs, respectively.[40] Similar multi-lanthanide cycloaddition reactions require 48–72 h at ambient temperature,[41–42] demonstrating the usefulness of heating to shorten the reaction times for these lanthanide-containing cycloaddition reactions.

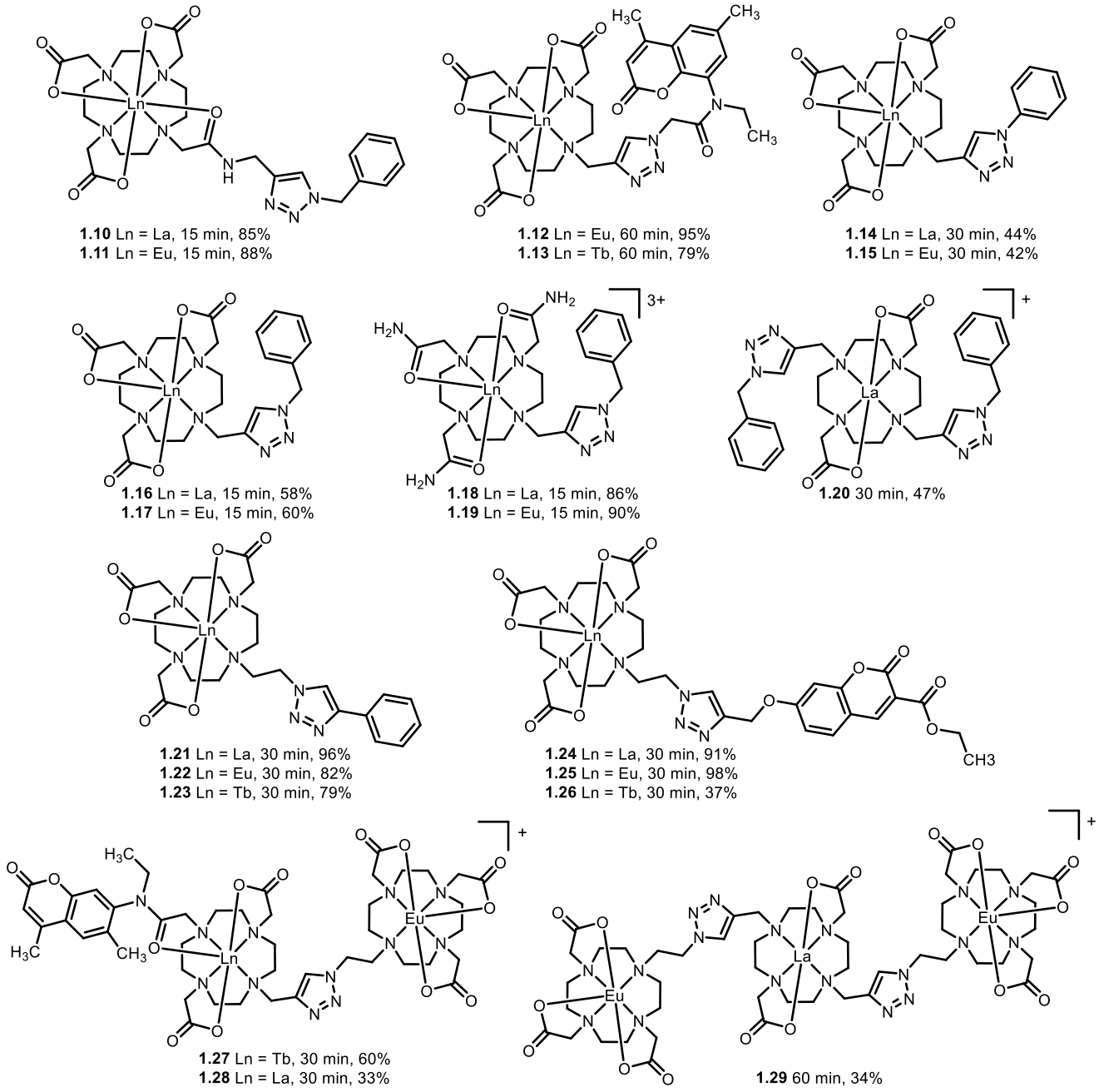


Figure 1.2. Products generated by Cu(I)-catalyzed cycloaddition under microwave irradiation at 100 °C. Reaction times and yields are included under structures.[40]

Another cycloaddition reaction used to couple a DOTA derivative to azide-functionalized molecules has been performed by Meade and coworkers via Cu(II)-assisted coupling under

microwave irradiation.[43] Meade and coworkers explored the relationship between rotational correlation time and multi-lanthanide-containing MRI contrast agents for three different multi-lanthanide-containing complexes (**Figure 1.3**).[43] To synthesize complexes **1.30–1.32** they reacted an alkyne-functionalized Gd(III)–DOTA derivative with three different molecules: trismethylazido benzene, hexakis(azidomethyl) benzene, and heptakis-6-azido-6-deoxy-β-cyclodextrin containing three, six, and seven azide functionalities, respectively. These reactions were performed under microwave irradiation for 5–20 min at 130 °C with sodium ascorbate in dimethylformamide/H_2O with Cu(II) sulfate. The reaction was also performed with similar yield in an oil bath at 70 °C for 18 h,[43] suggesting that the microwave rate enhancement effect for this reaction is merely a thermal effect following the Arrhenius equation.

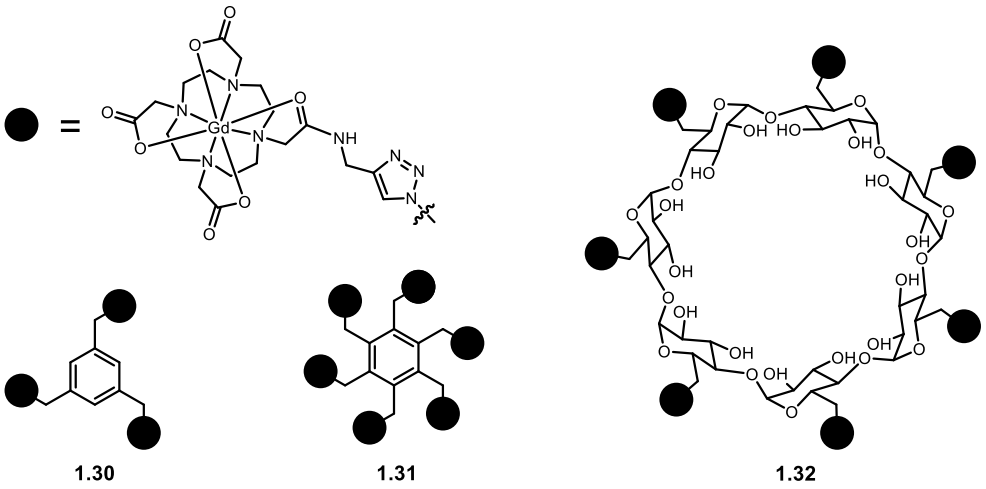
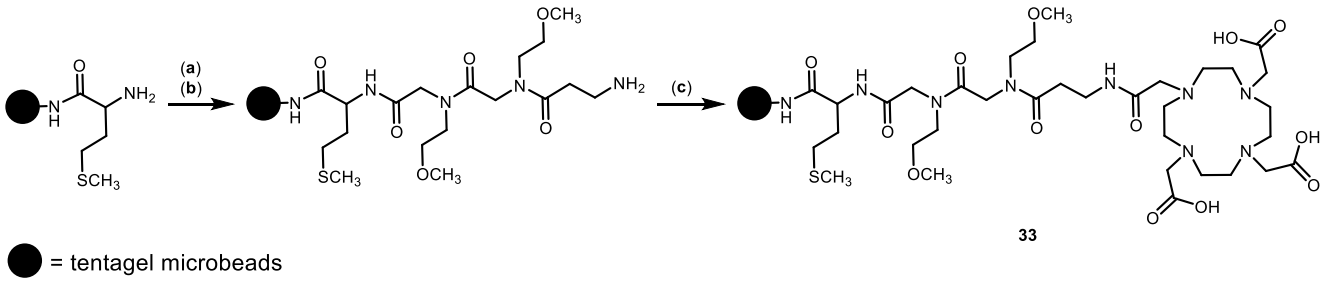


Figure 1.3. Multi-lanthanide-containing complexes synthesized by microwave-assisted Cu(II)-cycloaddition reactions. Adapted with permission from Song, Y.; Kohlmeir, E. K.; Meade, T. J. *J. Am. Chem. Soc.* **2008**, *130*, 6662–6663.

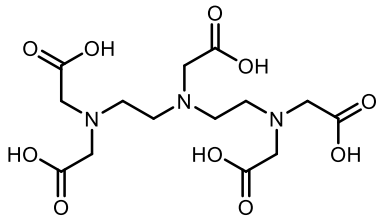
Udugamasooriya and coworkers performed microwave-assisted heating to facilitate a facile library synthesis of DOTA derivatives.[44] This library focused on functionalization of DOTA for optimized use with Eu(III) in chemical exchange saturation transfer imaging. For the library synthesis, a derivative of DOTA was first linked to the prepared tentagel resin and then further functionalized with a series of peptoid residues. Conventional synthesis to functionalize resin usually requires several hours; however, Udugamasooriya and coworkers used two 15 s microwave heating pulses at 10% power to add the first two peptoids to the functionalized resin following a synthesis reported by Kodadek and coworkers.[45] Then, they performed addition of the DO3A moiety under the same conditions but with one additional 15 s pulse to form **1.33** (**Scheme 1.4**).[44] Udugamasooriya and coworkers have demonstrated through this work that functionalization of DOTA-derivatives can be performed in a rapid, facile manner using a combination of solid-phase and microwave-assisted techniques.



Scheme 1.4. Example of DOTA-derivative synthesis on solid-phase using microwave-assisted heating, synthetic steps (**a**), (**b**), and (**c**) are as follows: (**a**) microwave-assisted addition of two peptoids, heating at 10% power for two 15 s pulses; (**b**) non-microwave-assisted coupling of Fmoc-β-Ala-OH and subsequent cleavage of Fmoc group; and (**c**) microwave-assisted addition of DO3A-*t*-butyl ester at 10% power for three 15 s pulses and subsequent removal of *t*-butyl groups.

1.2.2. Reactions related to non-cyclen derivatives for lanthanide ions

As noted with cyclen-based ligands in Section 1.2.1, synthesis of cyclen-based derivatives often requires the use of protecting groups; likewise, synthesis of many non-cyclen-based derivatives also requires the use of protecting groups. Protecting groups such as *tert*-butoxycarbamate (Boc), 9-fluorenylmethoxycarbamate (Fmoc), benzyloxycarbamate (CBZ), and *p*-toluenesulfonyl (Ts) are commonly used for protection of amines in multi-step syntheses. Consequently, these protecting groups are useful in the synthesis of both cyclen derivatives and non-cyclic polyaminopolycarboxylate derivatives such as diethylenetetraamine pentaacetic acid, **1.34** (**Figure 1.4**). The deprotection of CBZ and Ts groups via microwave-irradiation has been described in section 1.2.1. Here, focus is drawn to protection and deprotection of amines with Boc and Fmoc for use in ligand synthesis.

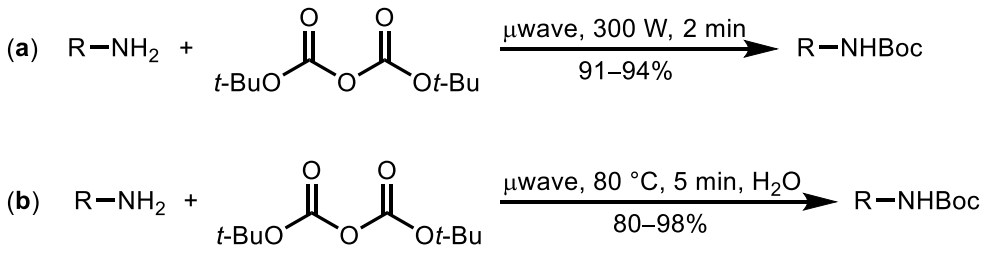


1.34

Figure 1.4. Diethylenetetraamine pentaacetic acid, a common acylic lanthanide chelate

The synthesis of acyclic ligands similar to diethylenetetraamine pentaacetic acid requires protection and deprotection of amines. Boc is often used as a protecting group for amines[46] and conventional Boc-protection of amines requires the reaction of the amine with Boc anhydride and either 4-(*N*,*N*-dimethylamino)pyridine or an inorganic base.[47–52] These reactions require several hours to complete;[47–52] however, microwave-irradiation has been reported to enable Boc-

protection of amines in 2 min.[53] Dighe and Jadhav developed a microwave-assisted synthesis wherein aliphatic amines have been protected by reaction of the amine with Boc anhydride under neat conditions using microwave irradiation at 300 W for 2 min with greater than 90% yields (**Scheme 1.5a**, temperature not reported).[53] Procopio and coworkers also developed a microwave-assisted synthesis for the Boc-protection of amines. In their synthesis, Boc anhydride is reacted with the amine at 80 °C in water for 5 min producing product in 80–98% yield (**Scheme 1.5b**).[54] Compared with the long reaction times and other reagents needed for conventional Boc-protection of amines, microwave-assisted synthesis enables a much more facile route using either neat or aqueous conditions in under 5 min. Dighe and Jadhav also reported in the same manuscript the amine protection with Fmoc and Ts groups under aqueous conditions.[53] They determined that a reaction temperature of 110 °C was needed to complete the reaction in 5 min for Fmoc- and Ts-protection of amines as opposed to the 80 °C needed for Boc-protection of amines.[53] All of these reactions would greatly aid in the synthesis of acyclic ligands for lanthanides by reducing the necessary reaction time for protection of amines in multi-step syntheses.

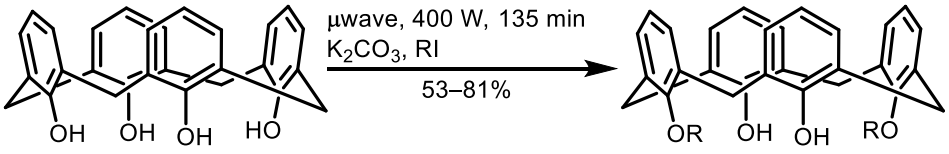


Scheme 1.5. Microwave-assisted Boc-protection of amines (**a**) under neat conditions and (**b**) under aqueous conditions

Deprotection of protected amines is also necessary for multi-step synthesis of acyclic ligands. In section 1.2.1, microwave-assisted deprotection of Ts- and Cbz-protected amines was described, likewise deprotection of Boc-protected amines has been reported by several methods using microwave-irradiation.[54–57] Two microwave-assisted reactions are noted here because of their use of either solvent-free conditions or of aqueous conditions. Park and Park developed a solvent-free microwave-assisted deprotection of Boc-protected amines by loading the Boc-protected amine onto silica gel. Once the silica gel is impregnated with the Boc-protected amine, the powder is subjected to a temperature of 120 °C under microwave irradiation at 30 W for 3 min or 600 W for 5 min (using a single-mode or multi-mode microwave reactor, respectively) to achieve near quantitative yields of deprotected amine.[55] Additionally, it was found that a reaction time of 180 min at an oil bath temperature of 120 °C was necessary to achieve comparable yields to the microwave reactions at 3 and 5 min, demonstrating that the addition of microwave-assisted heating facilitated this deprotection reaction.[55] While impregnation of silica gel allowed for reaction times of 5 min or less,[55] Nour-Eddine and coworkers determined that aqueous deprotection of Boc-amines could be performed in fewer than 12 min to afford 90–97% yields.[56] To deprotect Boc-protected amines, Nour-Eddine and coworkers combined the Boc-protected amine with water and heated in a microwave reactor to 100 °C for a maximum of 12 min;[56] in contrast, Jia and coworkers combined Boc-protected amines with water using non-microwave conditions at 150 °C under pressure and found that reaction times between 1 to 6 h were needed for reaction completion.[59] Therefore, for both the solvent-free and aqueous deprotection reactions, microwave-assisted heating greatly aided the deprotection of Boc-protected amines.

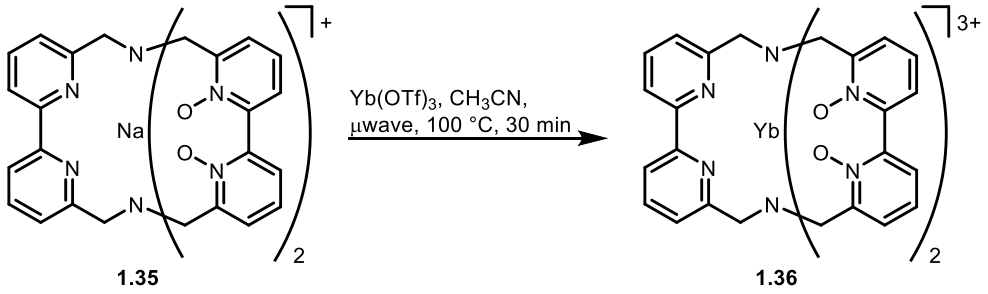
Non-cyclen ligands, based upon calixarene derivatives, have been used for separation of Ln(III) ions from actinide ions in nuclear waste. Studies with calixarene derivatives have

demonstrated the ability of these ligands to bind selectively with Ln(III) ions and, therefore, the ability to separate Ln(III) ions from actinide ions in solution, making the synthesis of calixarene derivatives of importance for nuclear waste related applications.[60] Nayak and Choudhary report a synthesis of a series of 1,3-dialkyl ether calix[4]arene derivatives using microwave-assisted synthetic techniques (**Scheme 1.6**). Microwave time was varied from 30 to 150 min as needed depending on the reactivity of the alkyl halide (the more electrophilic the less time required); the power was set at 400 W; and the temperature was not regulated for the series of reactions.[60] The 53–81% yields obtained with these conditions are comparable to similar reactions of complete esterification of the alcohol groups under conventional heating techniques that require 6 h to 4 days for reaction completion.[60]



Scheme 1.6. Synthesis of a 1,3-dialkyl ether calix[4]arene derivatives under microwave irradiation.

Other non-cyclen based cyclic ligands have also been synthesized and used for Ln(III) chelation. Synthesis of cryptands and crown ethers via microwave irradiation holds importance for the stabilization of lanthanides in their divalent state in addition to their trivalent state; however, a reaction with cryptate **1.36** (**Scheme 1.7**) demonstrated transmetallation via microwave irradiation related specifically to the trivalent state.[61] The final step in the synthesis of cryptate **1.36** was a transmetallation of Yb(III) to replace the Na^+ ion in cryptate **1.35**.

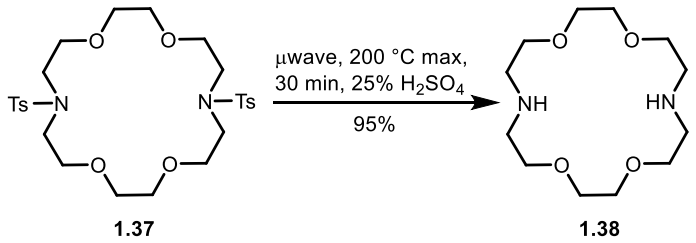


Scheme 1.7. Transmetallation of cryptate **1.35** under microwave-assisted conditions to yield cryptate **1.36.**[61]

Ln(II) ions are effective single-electron-donating reagents because of their propensity to oxide to Ln(III) ions, and consequently, the use of Ln(II) ions in other solution-state reactions is limited by this propensity to oxidize. This limitation can be addressed through the synthesis of ligands that chelate with Ln(II) ions to stabilize the divalent state.[62] Synthesis of ligands to stabilize the divalent state of Eu are important because Eu(II) has been studied as a potential substitute for Gd(III) ions in magnetic resonance imaging at high field strengths,[63] and as an additive in phosphors.[64] Crown ethers and cryptands based on a diazacrown ether motif have been used to stabilize Eu in its divalent state in aqueous solution.[65] More recently, a Eu(II)-contaning aza-222 cryptate was synthesized that exhibits oxidative stability in aqueous solution and displays bright yellow emission in solution.[66] The observations made in the studies of oxidatively stabilized Eu(II) in aqueous solution demonstrate the potential use and need for multidentate ligands such as cryptands and crown ethers for stabilizing the electron-rich oxidation state of lanthanides. Recently, a study by Richardson and coworkers demonstrated Yb(II) complexation with derivatives of 18-crown-6, including donor atoms of sulfur and selenium.[67] Likewise, Desreux and coworkers studied the complexation of Ln(III) and Ln(II)

ions with a series of crown ethers and noted that all of the crown ethers they studied had stabilizing effects on the Ln(II) oxidation state.[68]

An exhaustive seach of the literature indicates that no complexation studies with Ln(II) ions have examined the use of microwave irradiation, but there have been various reports on the synthesis of crown ethers via microwave irradiation. In **Scheme 1.2**, attention was drawn to Mikhura's detosylation of protected amines on cyclen; likewise, Mikhura and coworkers demonstrated a detosylation of the protected amines on a diazacrown ether, **1.37**, via microwave irradiation for 30 min with a maximum temperature of 200 °C using 25% H_2SO_4 to produce detosylated product **1.38** (**Scheme 1.8**).[33] Commonly used procedures for the detoslyation of **1.37** require reaction times of 48 h at 100 °C in a 33% HBr/AcOH mixture.[33] Microwave-assisted heating reduces the reaction time to only 30 min, making this reaction worth noting for the detosylation of amines on crown ethers; furthermore, detosylation of amines on crown ethers should be able to be performed in as little as 200 s using conditions as described in Section 1.2.1 of this thesis for the detosylation reaction performed by Pääkkönen and coworkers.[34]



Scheme 1.8. Detosylation of amines via microwave irradiation

Furthermore, a variety of crown ethers that have been synthesized using microwave-irradiation are shown in **Figure 1.5**, and the yields of the reactions assisted by microwave and conventional syntheses are compared in **Table 1.1**. Crown ethers **1.39**–**1.42** were synthesized by Sabzevari

and coworkers using microwave-irradiation of 700 W for 8 min with maximum temperatures of 95 °C in yields of 65–72% ,[69] and diazacrown thioethers **1.43**–**1.47** were synthesized in high yields (74–91%) using microwave-assisted heating at 100 °C for 9 min by Rostami and coworkers.[70] In another study by Rostami, crown ethers **1.48**–**1.68** were synthesized via microwave-assisted heating at 100 °C for 6 min.[5] Interestingly, the increased yields vs conventional heating were attributed to special microwave effects. As mentioned in the introduction, there is debate regarding whether or not the high yields and shortened reaction times in microwave-assisted synthesis is merely caused by thermal effects. This case by Rostami appears to give credence to the existence of special microwave effects. In his work, a decrease in acyclic byproducts due to oligomerization of the starting material was observed. This observation led him to hypothesize that the decrease in acyclic byproducts is due to the ratio of the diester starting material being in either the *syn* or *anti* conformation. His claim was that diesters in the *syn* position have a greater dipole moment and therefore interact with microwave irradiation more efficiently due to the microwave heating mechanism of dipolar polarization. This interaction leads to a more rapid rate of reaction of the desired macrocyclic complex, whereas the *anti* isomer has a weaker dipole moment and does not interact with the microwave irradiation as well, leading to less formation of the undesired acyclic byproducts. This increase in macrocycle formation due to the interaction of the *syn* isomer over the *anti* isomer appears to be a clear example of increased yields due to special microwave effects.

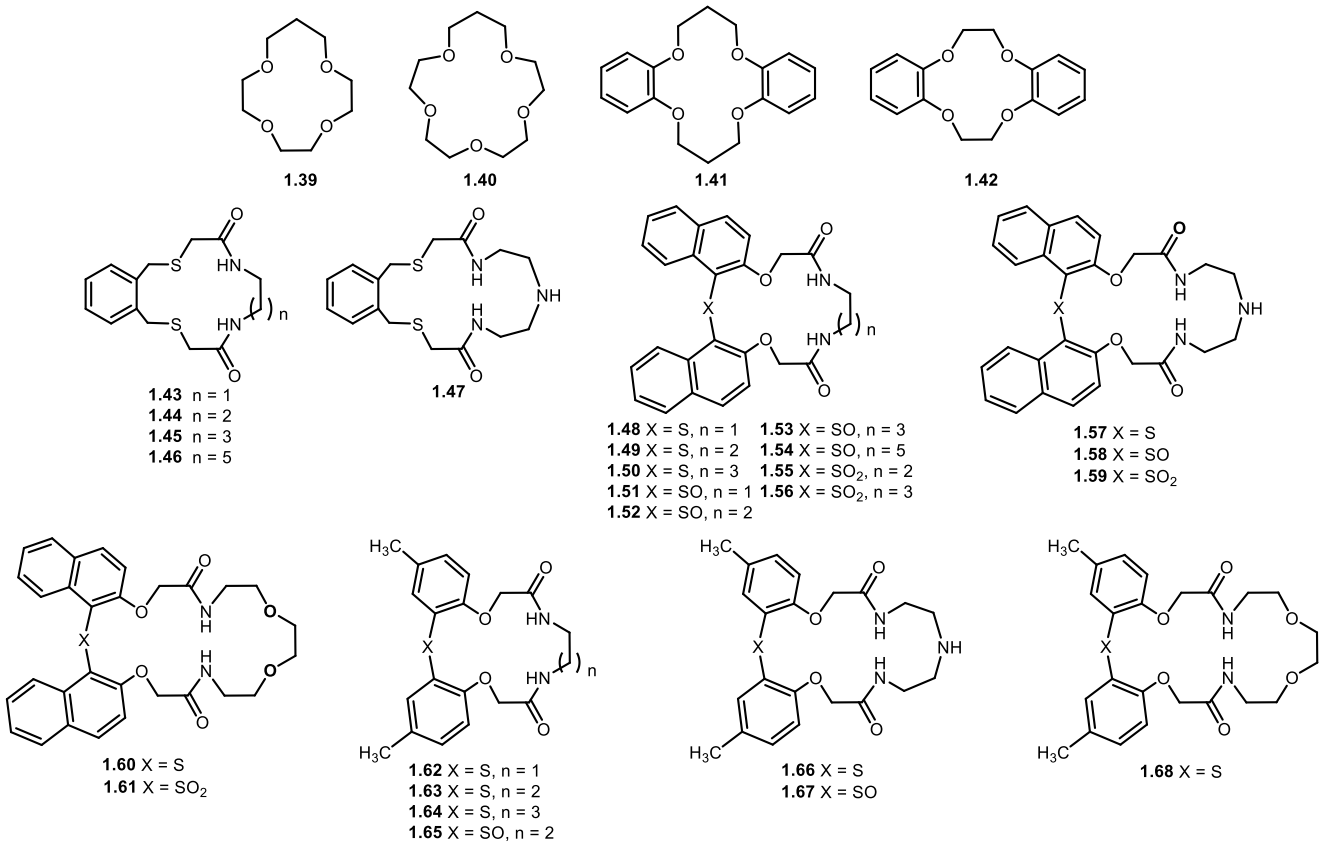


Figure 1.5. Crown ethers synthesized using microwave irradiation.

Table 1.1. Comparison of conventional and μwave yields for the crown ethers in **Figure 1.5**.

Crown ether	μwave yield (%)	Conventional yield (%)	Crown ether	μwave yield (%)	Conventional yield (%)
1.39	72	not reported	**1.54**	74	29
1.40	68	29	**1.55**	79	28
1.41	70	50	**1.56**	77	23
1.42	65	not reported	**1.57**	87	71
1.43	91	14	**1.58**	86	47
1.44	86	16	**1.59**	73	33
1.45	83	13	**1.60**	83	64
1.46	74	9	**1.61**	71	29
1.47	88	19	**1.62**	93	42
1.48	91	66	**1.63**	91	46
1.49	89	62	**1.64**	84	48
1.50	85	58	**1.65**	78	32
1.51	85	41	**1.66**	89	45
1.52	78	45	**1.67**	74	36
1.53	75	38	**1.68**	87	58

1.3 Summary

A variety of microwave-assisted reactions relevant to lanthanide ions have been reviewed in relation to their conventional heating counterparts when available. With the exception of the work by Rostami and coworkers,[5] the majority of the work performed with Ln ions under microwave irradiation appears to be the result of thermal effects. However, this does not discredit the use of microwave irradiation. The compilation of microwave-assisted work described above lends credence to the use of microwave irradiation as an effective tool for the field of lanthanide chemistry.

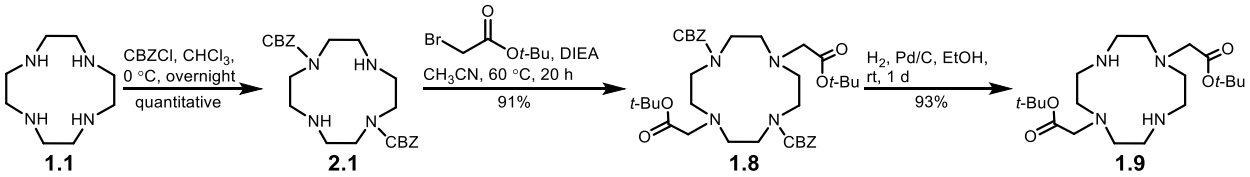
The use of microwaves in solution-state lanthanide chemistry is still a relatively new area, with much room to explore; however, in this chapter, a background of microwave-assisted syntheses that have been or could be applied to the synthesis of ligands for lanthanide ions has been presented. Similar to research described in Chapter 1, a modification of a common synthesis for intermediates for lanthanide ions is described in Chapter 2 that focuses on pK_a and the thermal components of the system. In Chapter 3, two potential areas where modification via microwave-assisted or solid-phase synthesis could be of interested are described.

Chapter 2 Synthesis of 1,7-Bis(*t*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane

This chapter was adapted with permission from Hopper, L. E.; Allen, M. J. *Tetrahedron Lett*. **2014**, *55*, 5560–5561.

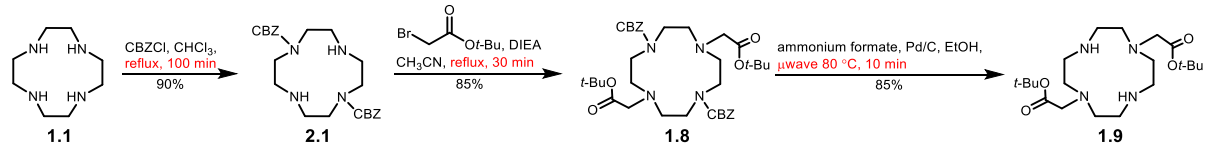
Derivatives of 1,4,7,10-tetraazacyclododecane (cyclen), including 1,7-bis(*t*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (DO2A-*t*-Bu ester, **1.9**), are commonly used intermediates when synthesizing metal complexes for biomedical-related studies.[71–90] However, reported routes to synthesize and purify this intermediate require multiple days to complete.[38–40] In accordance with the examples described in Chapter 1 of this thesis, it seemed reasonable that the reactions used to produce **1.9** could be accelerated by modification of the reaction conditions, leading to a shortened overall synthetic time while maintaining comparable yields to previously reported reactions.

The reported synthesis of DO2A-*t*-Bu ester, **1.9**, is described as the three steps depicted in **Scheme 2.1**.[38–40] First, two amines of commercially available cyclen are protected in the trans positions with a slow addition of benzyl chloroformate, CBZCl, at 0 °C and stirring overnight.[38] Second, *t*-Bu bromoacetate is reacted with CBZ-protected cyclen, **8**, at 60 °C in the presence of diisopropylethylamine (DIEA) to produce macrocycle **1.8** in 20 h.[39] Finally, hydrogenation for 1 day removes the CBZ groups yielding the desired product **1.9**.[39]



Scheme 2.1. Reported synthesis of DO2A-*t*-Bu ester, **1.9**, with shortest reported times shown.[38–40]

The reaction time necessary to convert **1.1** to **2.1** can be reduced with the application of heat, leading to a decrease in reaction time from 12 h to 30 min at reflux (**Scheme 2.2**). Temperatures below reflux led to either longer reaction times or lower yields, and heating in the microwave at reflux temperature (60 °C) resulted in a similar yield, suggesting that the application of microwave heating to this reaction would primarily be a thermal effect related to the Arrhenius equation. One concern related to heating is potential formation of the undesired cis-substituted product; but comparison of the NMR spectrum of product **1.9**, formed by heating at refux, with a reported NMR spectrum of 1,4-bis(*t*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane[91] reflux confirmed that the undesired product was not formed. Based upon these observations, heating the first step at reflux led to the exclusive formation of trans-substituted intermediate **2.1**.



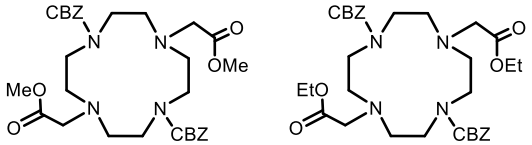
Scheme 2.2. Modified synthesis of **1.9** with modifications described in this thesis show in red.

The reported reaction of **2.1** to **1.8** requires heating at 60 °C with 2 equiv of base for 20 h to reach completion. Because of the similar pK_a values of DIEA and the amines on macrocycle **2.1** (all in the range of 9–10), the addition of excess base enabled a shorter overall reaction time by minimizing protonation of the amines on **2.1**, thereby allowing the desired reaction to occur. At 60 °C with a 20-fold excess of base per equivalent of **2.1**, this reaction took 50 min to reach completion compared to 20 h with 2 equiv of base, demonstrating that adjustment of the base is a key component of the reaction. To further accelerate the reaction, heating was performed at reflux instead of 60 °C, leading to a total reaction time of 30 min with 85% isolated yield

(**Scheme 2.2**). Again, use of microwave irradiation at 80 °C (reflux) led to similar yields, suggesting that microwave irradiation only benefits the reaction in terms of a thermal effect.

The final step from CBZ-protected **1.8** to product **1.9** was accelerated by transfer hydrogenation with ammonium formate and microwave irradiation. Ammonium formate is considered a user-friendly reagent relative to H_2 gas, and similar microwave-assisted transfer hydrogenation reactions have been performed to deprotect CBZ-protected amines.[92] With the addition of ammonium formate under microwave irradiation in a sealed vessel, the reaction was complete after 10 min at 80 °C. An excess of ammonium formate was used because some sublimation was observed during the reaction and heating above 80 °C increased the amount of sublimation that was observed. This third reaction was complete in 10 min, compared to the reported route that requires a reaction time of 1 day at room temperature with H_2 gas.

Due to the decreases in reaction times for all three steps, it is possible to synthesize DO2A-*t*-Bu ester, **1.9**, from commercially available cyclen in one day. The reactions leading to **1.9** starting from 5 g of cyclen with comparable yields to smaller scales, and larger batches would likely behave similarly. Furthermore, using the same synthetic protocol, similar yields were obtained for DO2A-methyl ester and DO2A-ethyl ester derivatives of **1.8**, **2.2** and **2.3**, respectively (**Figure 2.1**). The ability to rapidly synthesize methyl, ethyl, and *t*-Bu ester varients of DO2A has potential to greatly aid studies that use these molecules as intermediates.



2.2 **2.3**

Figure 2.1 DO2A-methyl ester, **2.2**, and DO2A-ethyl ester, **2.3**, derivatives of **1.8**

2.2 Experimental protocol

Commercially available chemicals were of reagent-grade purity and were used without further purification. Microwave irradiation was performed using a CEM MARS 5 microwave (400 W) with internal fiber-optic temperature probe. Water was purified using an Elga Purelab Ultra SC MK2 water purification system. Flash chromatography was performed using silica gel 60, 230–400 mesh. Analytical thin-layer chromatography (TLC) was carried out on TLC plates precoated with silica gel 60 F254 (250 μm layer thickness). Visualization of TLC plates was accomplished with a UV lamp and staining with I_2. ^{1}H- and ^{13}C-NMR spectra were obtained at 400 MHz for ^{1}H and 101 MHz for ^{13}C. Chemical shifts were referenced to residual $CHCl_3$ in $CDCl_3$: 7.27 ppm (δ) for ^{1}H and δ 77.0 for ^{13}C. ^{1}H-NMR multiplicities are reported as follows: “s” = singlet, “t” = triplet, “dt” = doublet of triplets, “m” = multiplet, and “br” = broad. Italicized elements are those that are responsible for the shift. Chemical shifts were assigned using distortionless enhancement by polarization transfer, correlation spectroscopy, and heteronuclear multiple quantum coherence spectra. High resolution electrospray ionization mass (HRESIMS) were obtained on an electrospray time-of-flight high-resolution mass spectrometer.

1,7-Bis(benzyloxycarbonyl)-1,4,7,10-tetraazacyclododecane (**2.1**). Benzyl chloroformate (2.05 equiv, 0.850 mL, 5.95 mmol) was added dropwise to a solution of cyclen, **1.1**, (0.4989 g, 2.902 mmol) in $CHCl_3$ (26 mL) under an atmosphere of argon. The resulting reaction mixture was stirred for 100 min at 60 °C and resulted in the formation of a white precipitate. Solvent was removed under reduced pressure, and the resulting white solid was washed with Et_2O (45 mL). The solid was dissolved in an aqueous solution of NaOH (3 M, 20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). Extracts were combined and dried over Na_2SO_4. Solvent was removed

under reduced pressure, and the resulting oil was purified using silica gel chromatography [5:2 MeOH/NH_4OH (30% aq)] to yield 1.15 g (90%) of **2.1** as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.42–7.28 (m, 10H, C_6H_5), 5.16 (s, 4H, OCH_2), 3.56–3.40 (m, 8H, NCH_2), 2.96 (t, J = 4.7 Hz, 2H, NCH_2), 2.87 (dt, J = 4.9 and 14.7 Hz, 4H, NCH_2), 2.77 (t, J = 4.7 Hz, 2H, NCH_2); ^{13}C NMR (101 MHz, $CDCl_3$, δ) 156.6, 136.5, 128.5 (*C*H), 127.8 (*C*H), 127.7 (*C*H), 67.4 (OCH_2), 51.0 (NCH_2), 50.6 (NCH_2), 50.1 (NCH_2), 49.8 (NCH_2), 49.3 (NCH_2), 48.6 (NCH_2), 48.3 (NCH_2); HRESIMS (*m*/*z*): $[M + H]^+$ calcd for $C_{24}H_{33}N_4O_4$, 441.2502; found, 441.2494; TLC R_f = 0.21 [5:2 MeOH/NH_4OH (30% aq)].

1,7-Bis(benzyloxycarbonyl)-4,10-bis(*t*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (**1.8**). To a solution of **2.1** (0.747 g, 1.70 mmol) dissolved in CH_3CN (12 mL) was added DIEA (20 equiv, 5.94 mL, 34.1 mmol) followed by *t*-Bu bromoacetate (2 equiv, 0.50 mL, 3.4 mmol). The reaction mixture was stirred for 30 min at reflux. Solvent was removed under reduced pressure, resulting in a light orange oil and a white precipitate. The oil was dissolved in Et_2O (15 mL) and washed with H_2O (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to yield 0.96 g (85%) of **1.8** as a light orange oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.42–7.28 (m, 10H, C_6H_5), 5.12 (s, 4H, CH_2), 3.56–3.05 (m, 12H, CH_2), 2.87 (brs, 8H, NCH_2), 1.42 (s, 18H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$, δ) 170.5, 156.4, 136.8 (*C*H), 128.4 (*C*H), 127.8 (*C*H), 80.9, 66.9 (CH_2), 56.0 (br, CH_2), 54.3 (br, NCH_2), 46.7 (br, NCH_2), 28.1 (CH_3); HRESIMS (*m*/*z*): $[M + H]^+$ calcd for $C_{36}H_{53}N_4O_8$, 669.3863; found, 669.3845.

1,7-Bis(*t*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (**1.9**). To a solution of **1.8** (0.2321 g, 0.3470 mmol) in *i*-PrOH (8 mL) was added 10% Pd/C (20 wt %, 0.0464 g, 0.0436 mmol) and ammonium formate (46 equiv, 0.9987 g, 15.81 mmol). The mixture was heated for 10 min at 80 °C in the microwave (ramp time of 1.5 min and cool down time of 5 min). Pd/C was removed by filtration, and the solvent was removed under reduced pressure. The resulting white solid was dissolved in NaOH (5 M, 5 mL) and extracted with $CHCl_3$ (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to yield 0.118 g (85%) of **1.9** as a light yellow oil that became an off-white solid upon exposure to air. ^{1}H NMR (400 MHz, $CDCl_3$, δ) 3.31 (s, 4H, OCC*H*$_2$), 2.82 (brs, 8H, CH_2CH_2), 2.63 (t, *J* = 4.9 Hz, 8H, CH_2CH_2), 1.45 (s, 18H, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$, δ) 171.0, 81.0, 57.2 (OC*C*H$_2$), 52.0 (CH_2CH_2), 46.0 (CH_2CH_2), 28.2 (*C*H$_3$); HRESIMS (*m*/*z*): $[M + H]^+$ calcd for $C_{20}H_{41}N_4O_4$, 401.3128; found, 401.3142.

1,7-Bis(benzyloxycarbonyl)-4,10-bis(methoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (**2.2**). To a solution of **2.1** (0.736 g, 1.67 mmol) dissolved in CH_3CN (12 mL) was added DIEA (20 equiv, 5.78 mL, 33.4 mmol) followed by methyl bromoacetate (2 equiv, 0.32 mL, 3.3 mmol). The reaction mixture was stirred for 30 min at reflux. Solvent was removed under reduced pressure, resulting in an off white/yellow solid. The solid was dissolved in Et_2O (15 mL) and washed with H_2O (3 × 15 mL). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to yield 0.67 g (69%) of **2.2** as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.41–7.27 (m, 10H, C$_6$*H*$_5$), 5.11 (s, 4H, C*H*$_2$), 3.62 (brs, 6H, C*H*$_3$), 3.54–3.21 (m, 12H, C*H*$_2$), 2.85(brs, 8H, NC*H*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$, δ) 171.5, 156.4, 136.7 (*C*H), 128.4 (*C*H), 127.8 (*C*H), 66.9 (*C*H$_2$), 54.9 (br, N*C*H$_2$), 54.5 (br, N*C*H$_2$), 51.2

(*C*H_3), 46.9 (br, N*C*H_2), 46.5 (br, N*C*H_2); HRESIMS (*m*/*z*): $[M + H]^+$ calcd for $C_{30}H_{41}N_4O_8$, 585.2924; found, 585.2921.

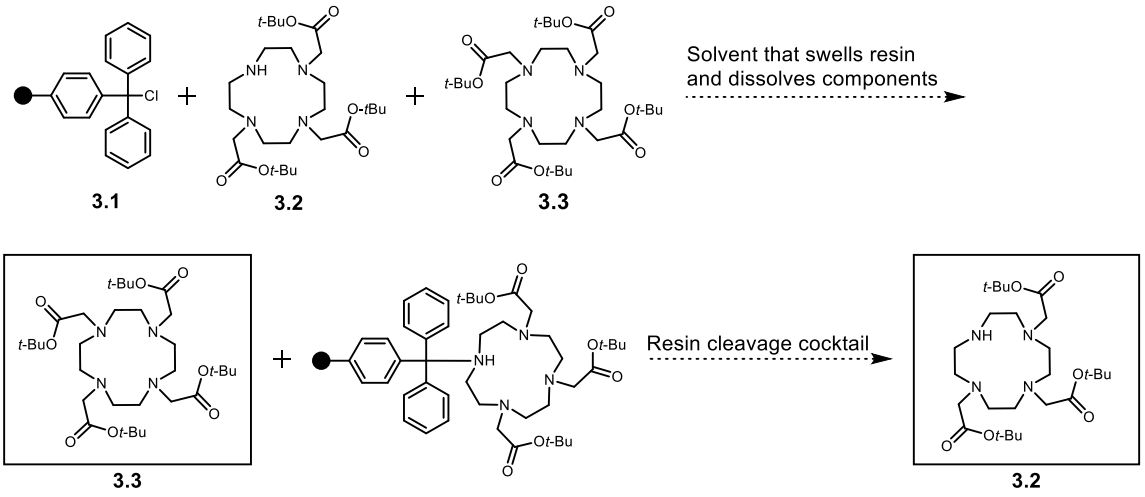
1,7-Bis(benzyloxycarbonyl)-4,10-bis(ethoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (**2.3**). To a solution of **2.1** (0.437 g, 0.992 mmol) dissolved in CH_3CN (5 mL) was added DIEA (20 equiv, 3.43 mL, 19.8 mmol) followed by ethyl bromoacetate (2 equiv, 0.22 mL, 1.98 mmol). The reaction mixture was stirred for 30 min at reflux. Solvent was removed under reduced pressure, resulting in an off white/yellow solid. The solid was dissolved in Et_2O (7 mL) and washed with H_2O (3 × 7 mL). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to yield 0.492 (81%) of **2.3** as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.42–7.27 (m, 10H, C_6*H*$_5$), 5.11 (s, 4H, C*H*$_2$), 4.11 (brs, 4H, C*H*$_2$), 3.55–3.19 (m, 12H, C*H*$_2$), 2.87 (m, 8H, NC*H*$_2$), 1.23 (t, *J* = 6.8 Hz 6H, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$, δ) 171.1, 156.4, 136.8 (*C*H), 128.4 (*C*H), 127.8 (*C*H), 66.9, 60.2 (*C*H_2), 55.1 (br, N*C*H_2), 54.5 (br, N*C*H_2), 47.0 (br, N*C*H_2), 46.5 (br, N*C*H_2), 14.2 (*C*H_3); HRESIMS (*m*/*z*): $[M + H]^+$ calcd for $C_{32}H_{45}N_4O_8$, 613.3237; found, 613.3223.

Chapter 3 Summary and Future Studies

Chapters 1 and 2 have described many ligand syntheses where microwave-assisted, or as seen in **Scheme 1.4**, solid-phase assisted techniques, were applied to both modify the current syntheses as well as pave the way for new syntheses of ligands for lanthanide ions. In this chapter, two areas are described where either application of microwave irradiation or application of solid-phase could be of interest for future studies.

In Chapter 1, cryptate **1.36** (**Scheme 1.7**) was synthesized by microwave-assisted transmetallation of Yb(III), replacing the Na^+ ion in cryptate **1.35**. This transmetallation proceeded using microwave-assisted heating at 100 °C for 30 min using 250 W irradiation.[61] This example of transmetallation with a trivalent lanthanide suggests that transmetallation of lanthanides in the divalent state should be possible using microwave-irradiation, if air-free conditions are maintained, and might be a study of interest to examine preference of a cryptand toward either Ln(II) or Ln(III) ions.

Looking forward toward other means of modifying ligand syntheses, separation of tertiary amines from secondary amines is an area where it is plausible that modification of the ligand synthesis by solid-phase could be of interest and use. Within the synthesis of ligands such as DO3A-*t*-Bu ester, **3.2**, and DOTA-*t*-Bu ester, **3.3**, purifications based on separations are needed. Separations can performed via column chromatography or recrystallization, or a mixture of both, as is the case for purifying DO3A-*t*-Bu ester.[92] Another technique that could be used for separation of secondary amines from tertiary amines is purification via binding of secondary amines to solid-phase resins such as trityl chloride, **3.1** (**Scheme 3.1)**. With DO3A-*t*-Bu ester and DOTA-*t*-Bu ester as examples, **Scheme 3.1** depicts how the separation of these two molecules could be performed.



Scheme 3.1 Proposed resin-mediated separation of secondary and tertiary amines using DO3A-*t*-Bu ester, **3.2**, and DOTA-*t*-Bu ester, **3.3**, as examples

The proposed resin-mediated separation could be useful in syntheses where separation by column chromatography is more complicated. As an example, recently, a former graduate student in the Allen Lab, Nikhil Barua, was attempting to separate compounds **3.4** and **3.5** (**Figure 3.1**). This separation could be performed by high performace liquid chromatography after metallation; however, purification of the unmetallated ligand should be able to be performed by using resin-mediate separation, similar to what is shown in **Scheme 3.1**, but by substituting **3.2** and **3.3** with **3.4** and **3.5**, respectively.

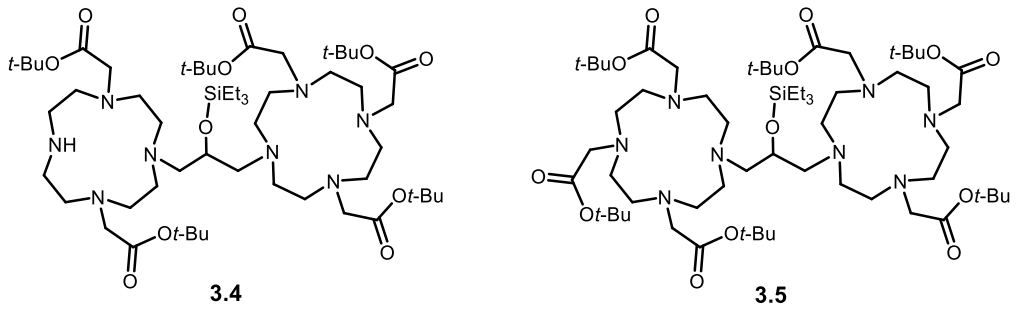


Figure 3.1 Example of two components that could be separated by resin-mediated separation

This resin-mediated separation was attempted for ligands **3.4** and **3.5**. To analyze the outcome of the separation, a colorimetric test that qualitatively demonstrates the presence of secondary amines was used.[93] This colorimetric test, named the chloranil test, uses a mixture of acetaldehyde and *p*-chloranil to produce either a blue color, indicative of the presence of secondary amines, or a yellow color, which is indicative of the absence of secondary amines. Following the proposed separation method in **Scheme 3.1**, a mixture of **3.4** and **3.5** dissolved in dichloromethane was added to trityl chloride resin that had been swollen in dichloromethane. After several hours of mixing, the dichloromethane solution was filtered from the resin and analyzed by the chloranil test. Colorimetric analysis of the solution before and after the resin purification is shown in **Figure 3.2**. Before application of the resin, the chloranil test produced a blue colored solution, indicative of the presence of secondary amines; after purification by resin, colorimetric testing of the resultant solution produced a yellow color, indicating that the amount of secondary amines has been reduced at least to below the limit of detection by the human eye. Analysis by NMR was also attempted, but was inconclusive. Further analysis of the final metallated complex should be pursued after complete deprotection and metallation of the ligand to demonstrate the effectiveness of this separation technique. Although this purification method

has been described here for a unique set of ligands, it is reasonable that it could be applied to any ligand synthesis where separation of compounds containing secondary amines from compounds containing purely tertiary amines is necessary, provided that the secondary amines are the only available nucleophiles on the compounds.

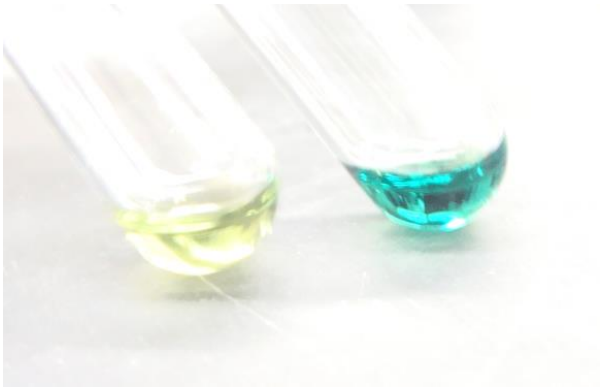
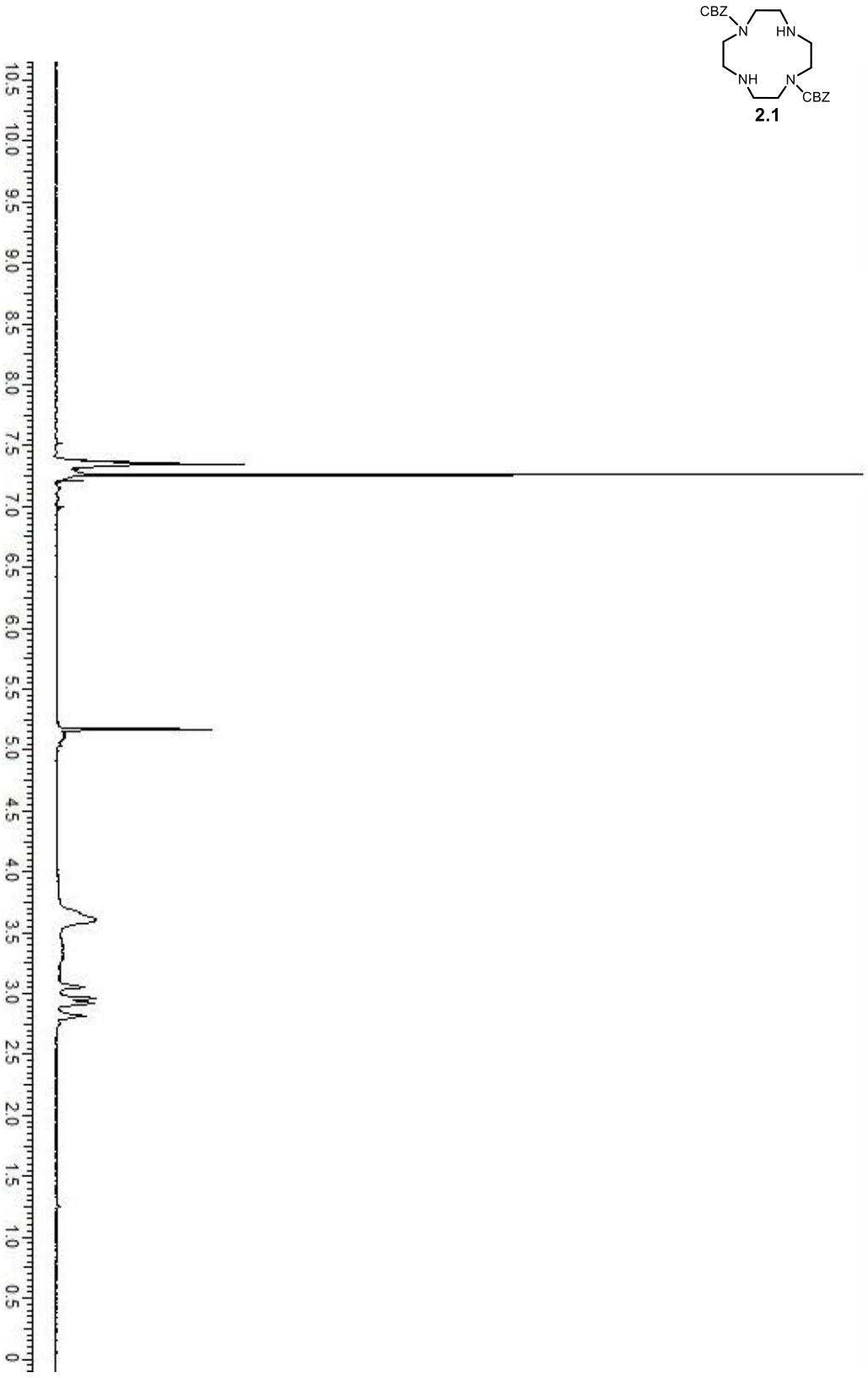


Figure 3.2 Analysis by chloranil test after resin-purification (left, yellow, absence of secondary amines) and before resin-purification (right, blue, presence of secondary amines)

In summary, this thesis describes several reactions in which syntheses related to ligands for lanthanide ions have been modified. This final chapter highlighted two areas in which modification by microwave-assisted or solid-phase assisted synthetic techniques could be of use in future studies related to lanthanide ions, namely, the examination of microwave-assisted transmetallation in the divalent state and the application of resin-mediated purification in ligand syntheses.

APPENDIX A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HN
NH
N
CBZ
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8.5
8.0
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6.5
6.0
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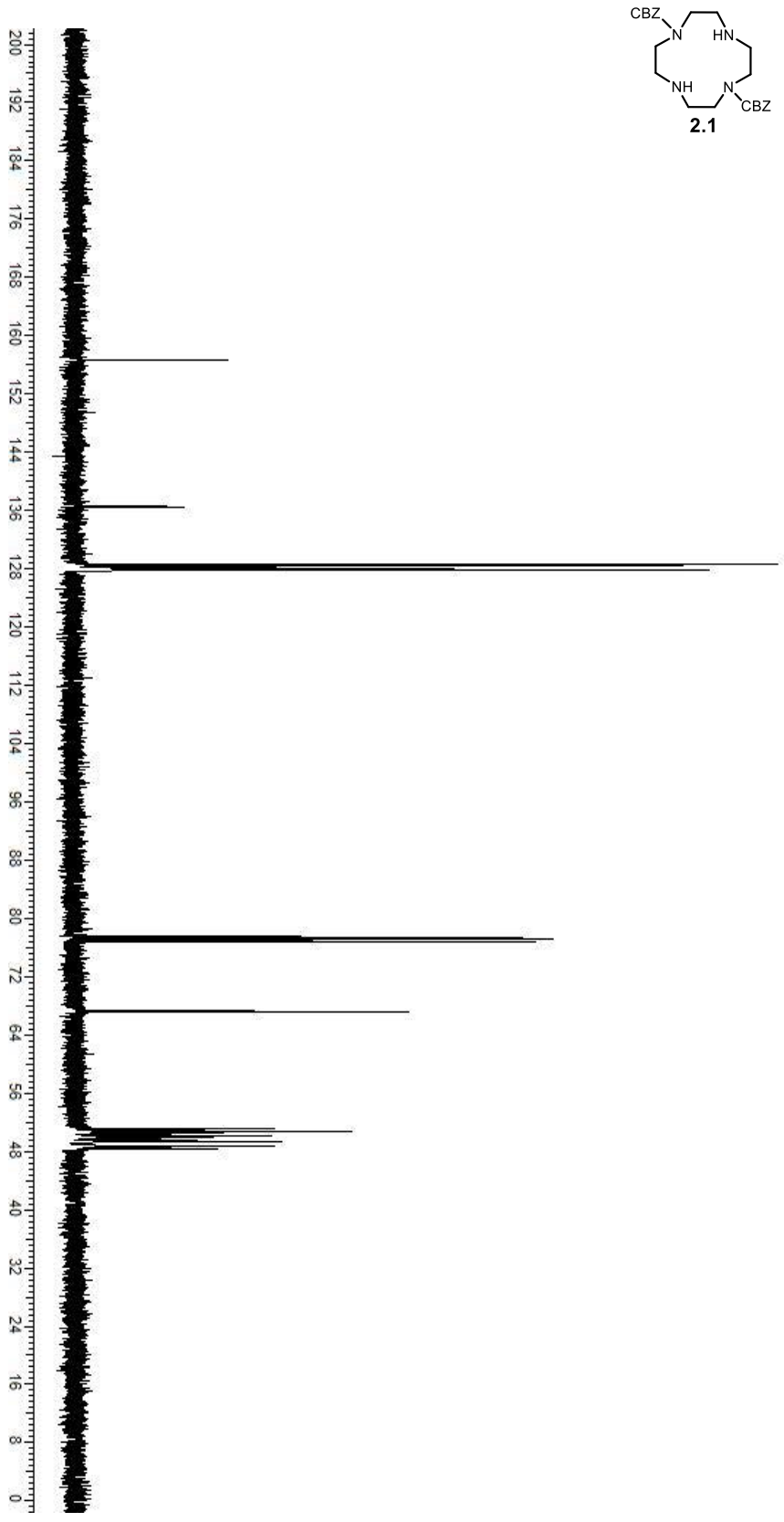
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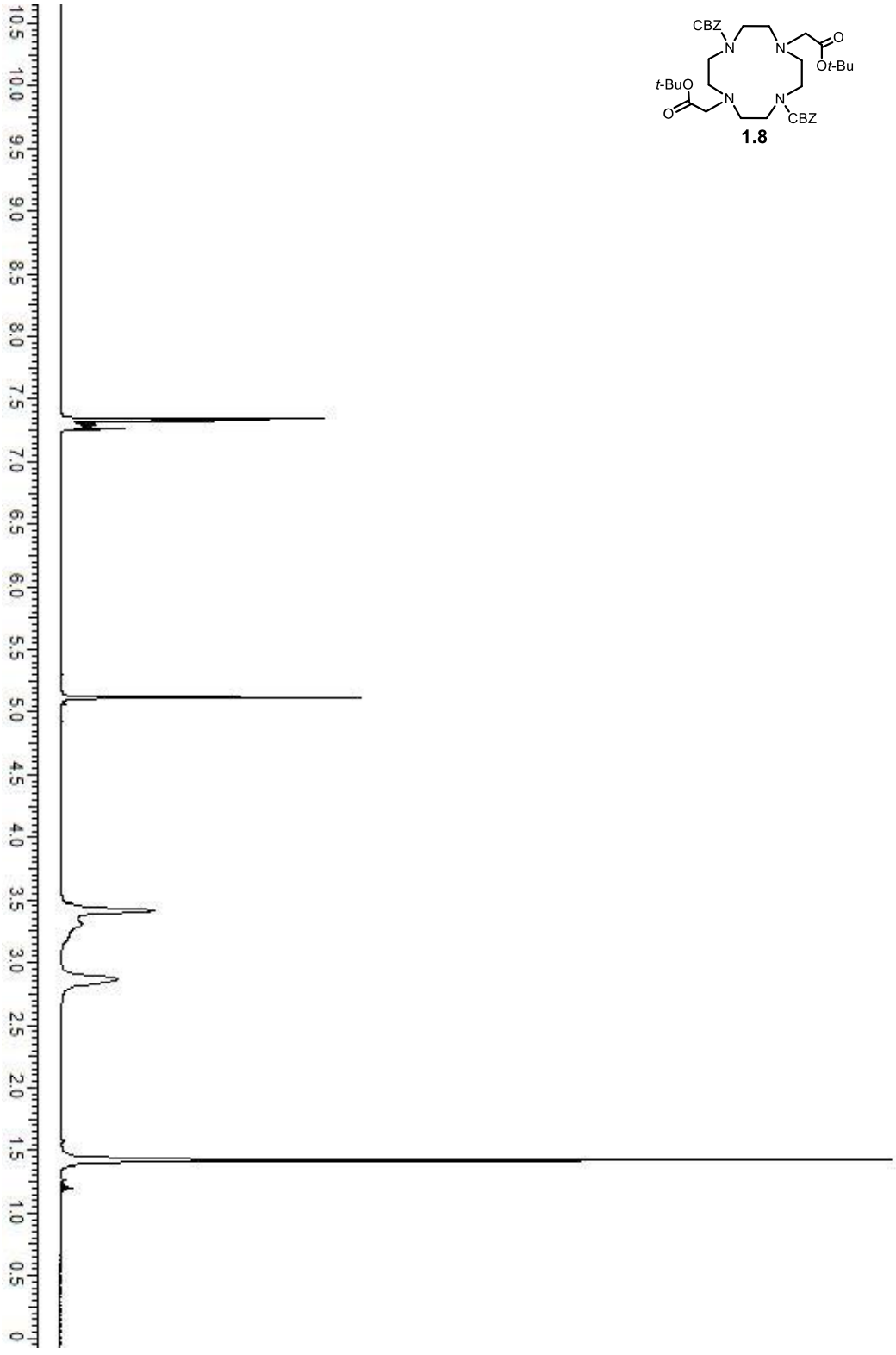
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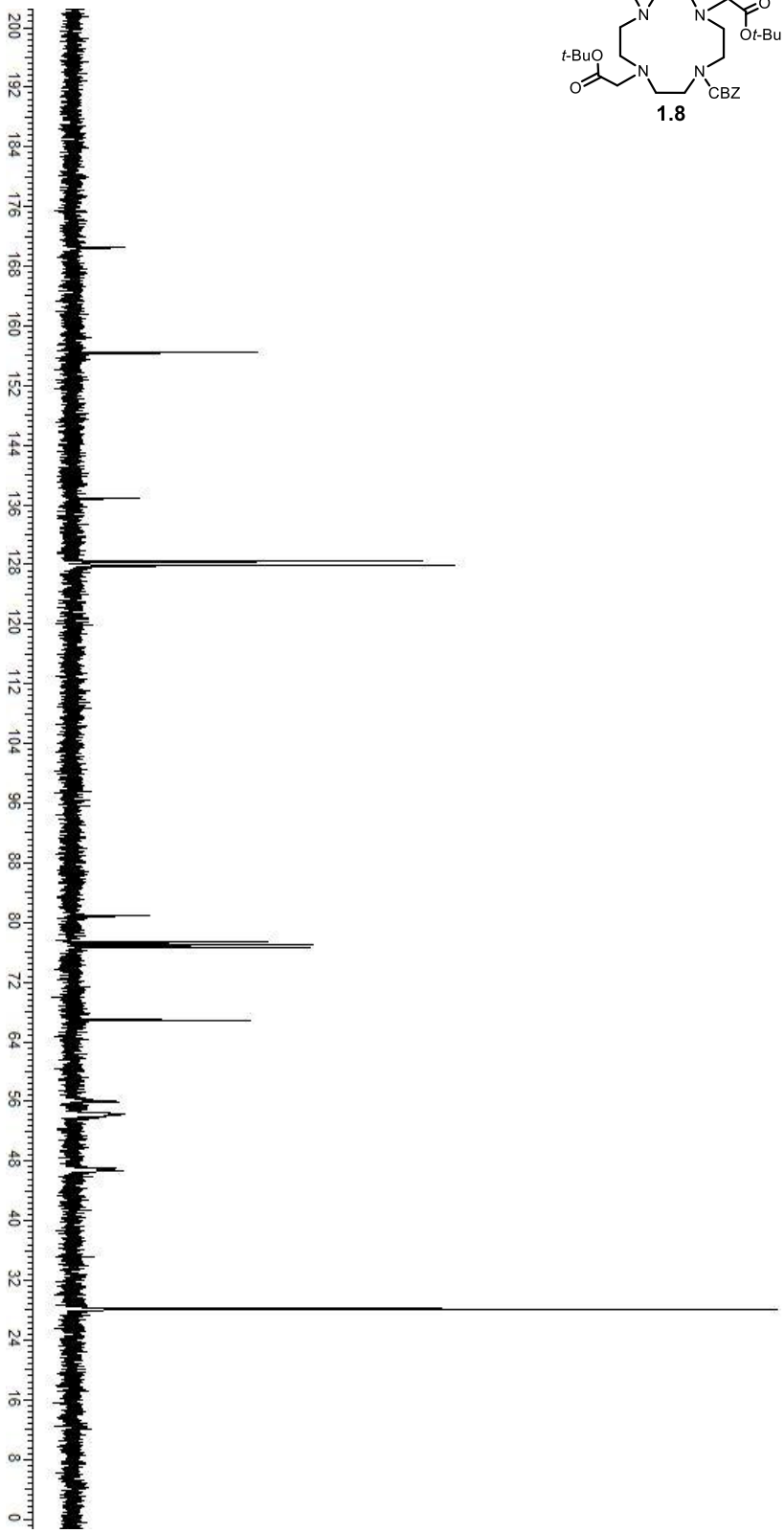
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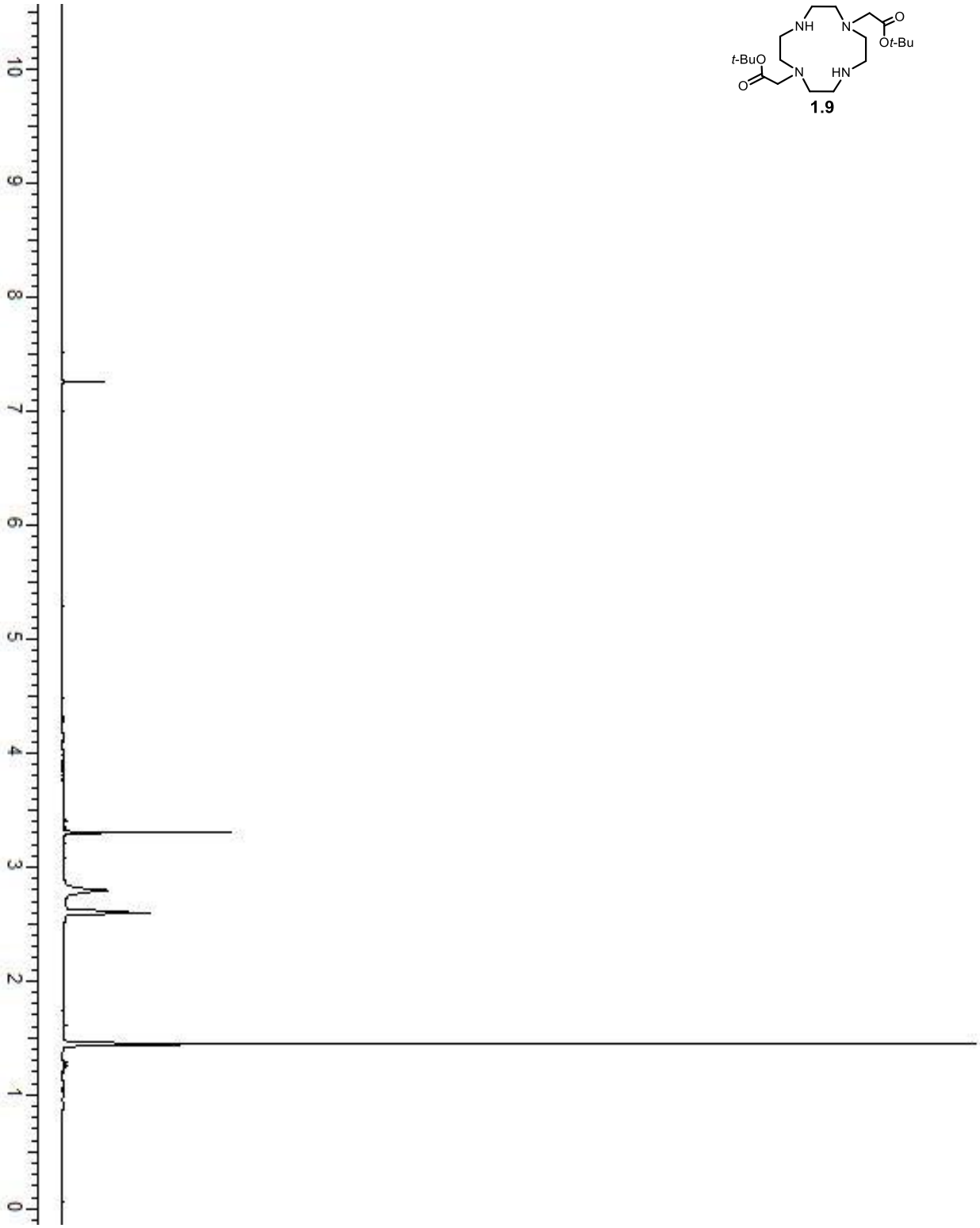
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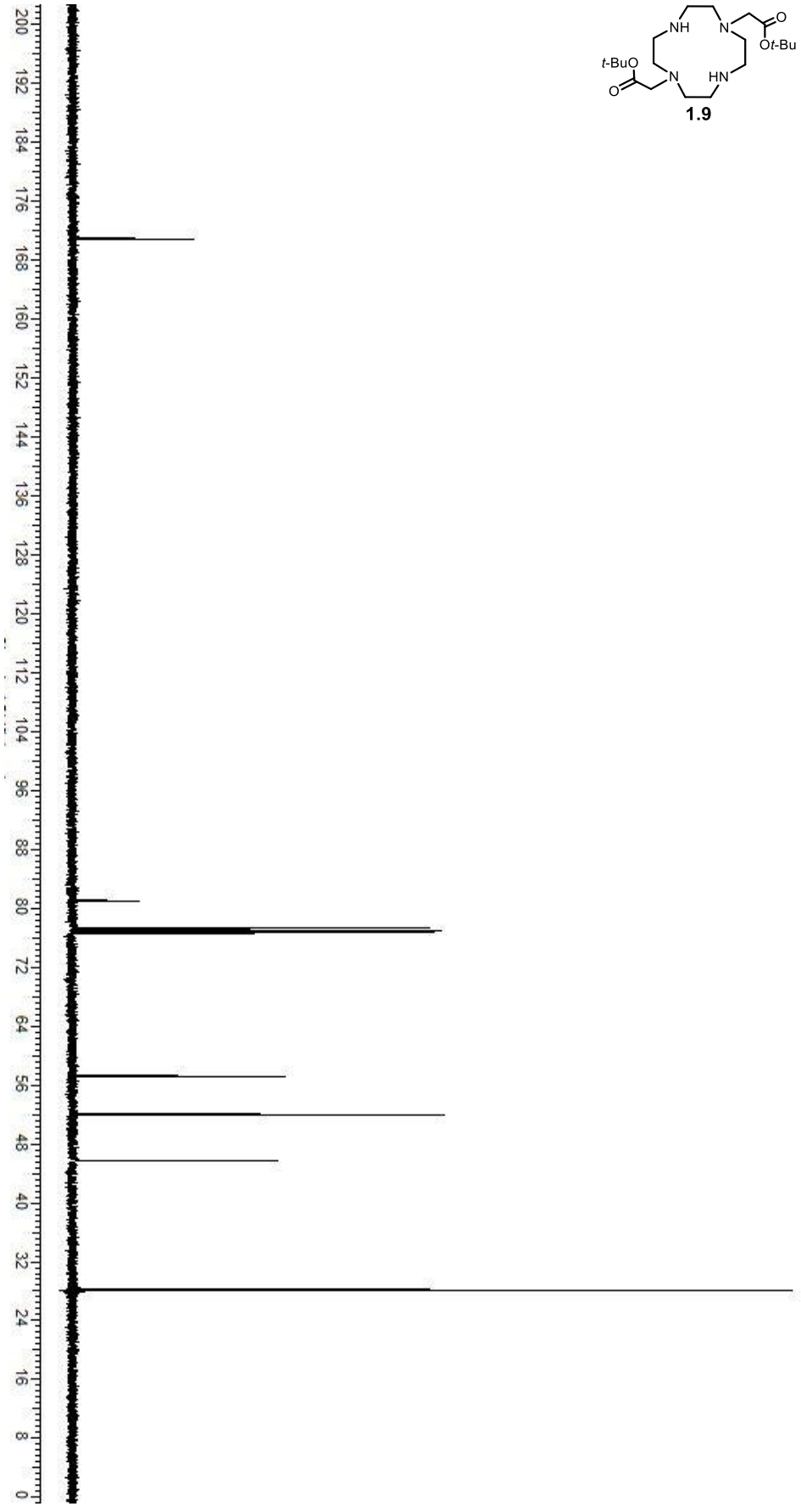
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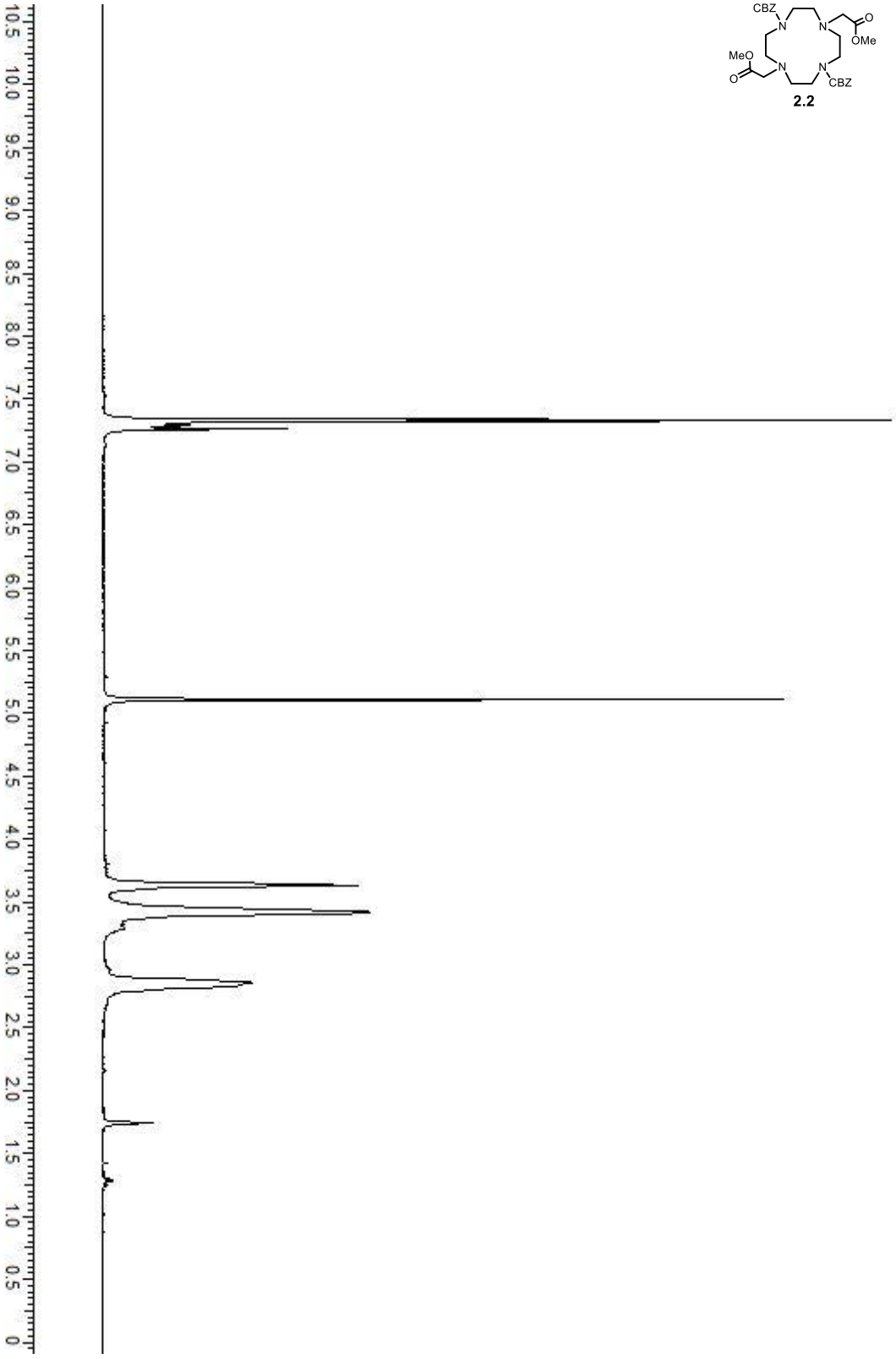
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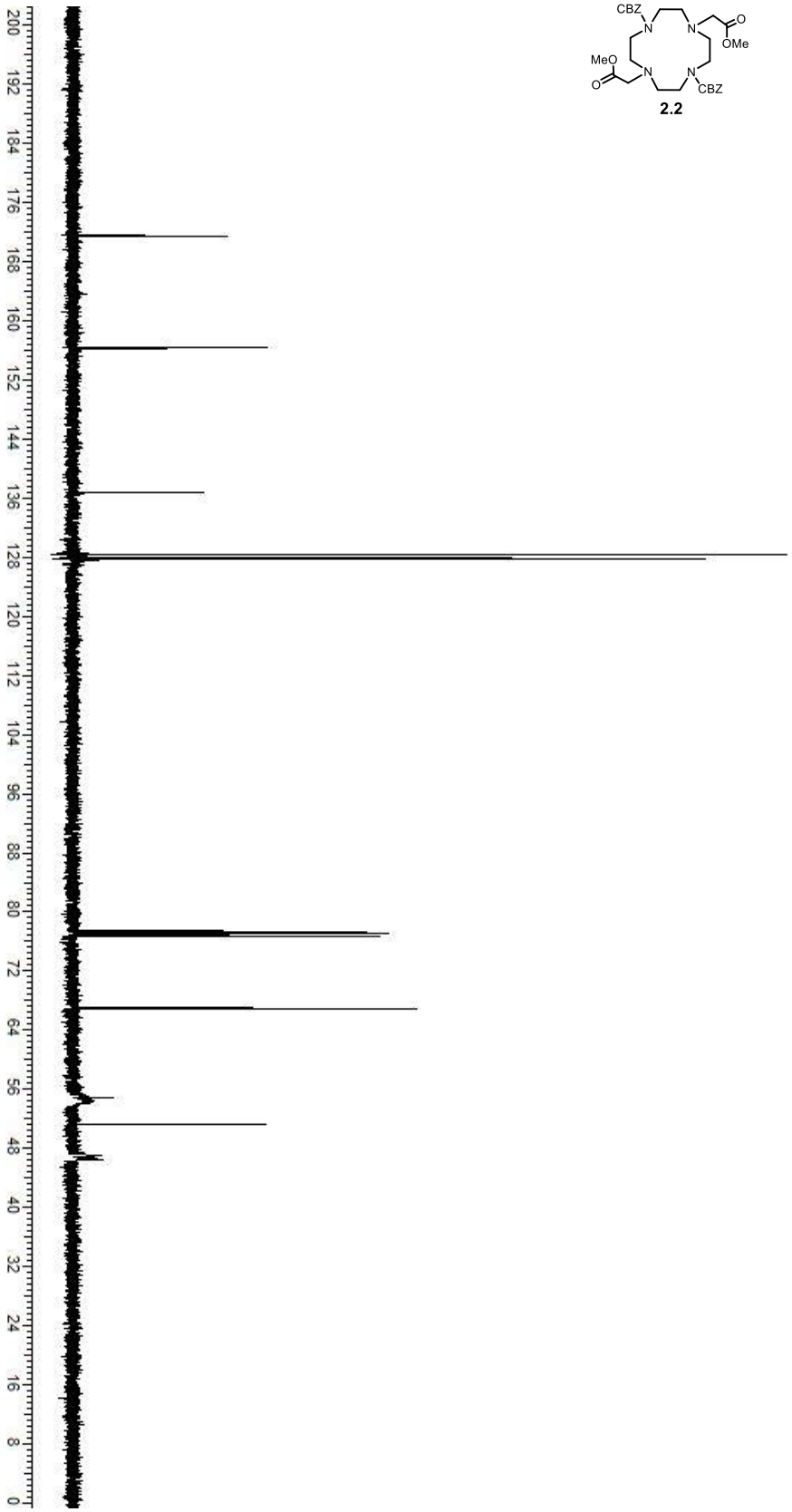
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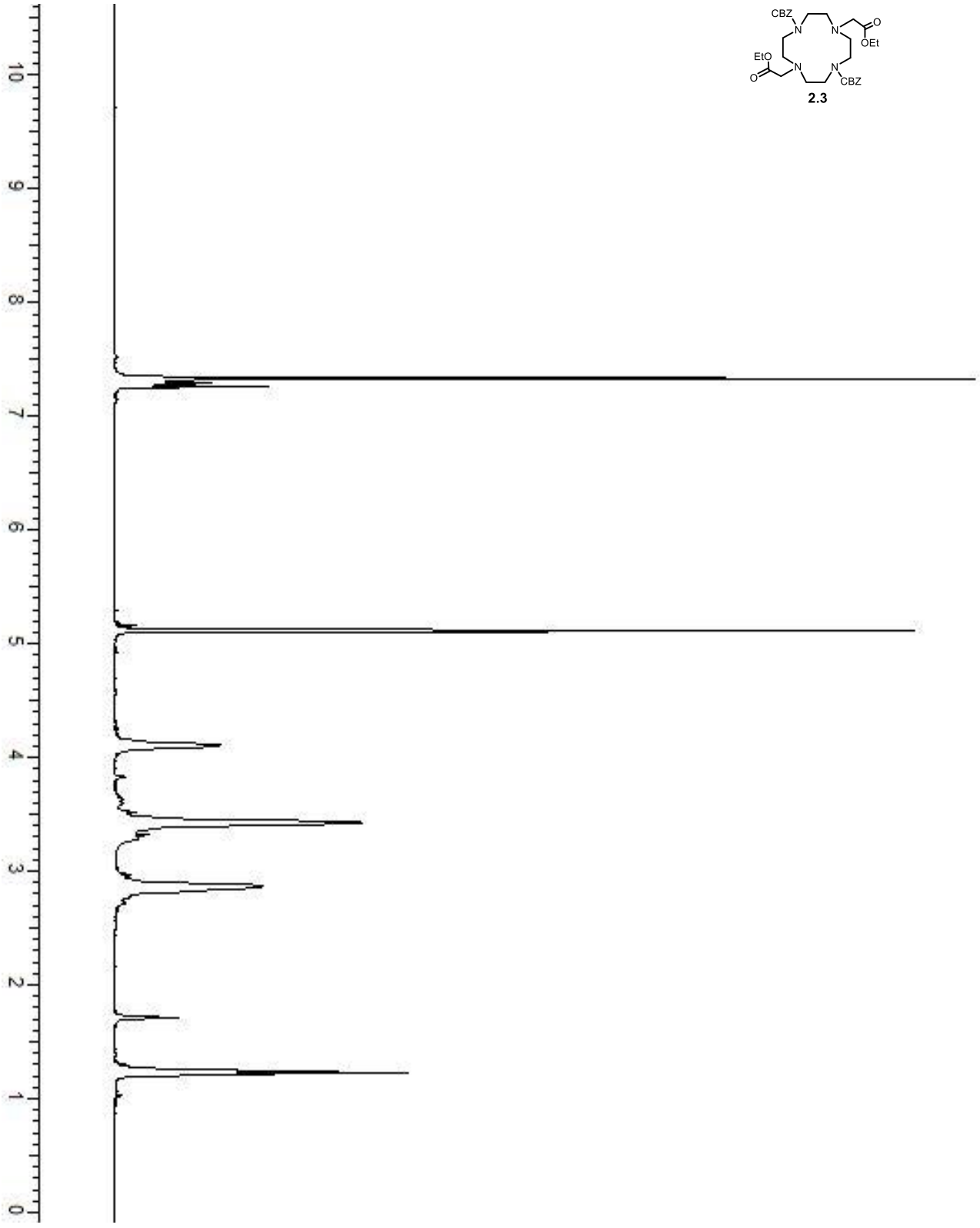
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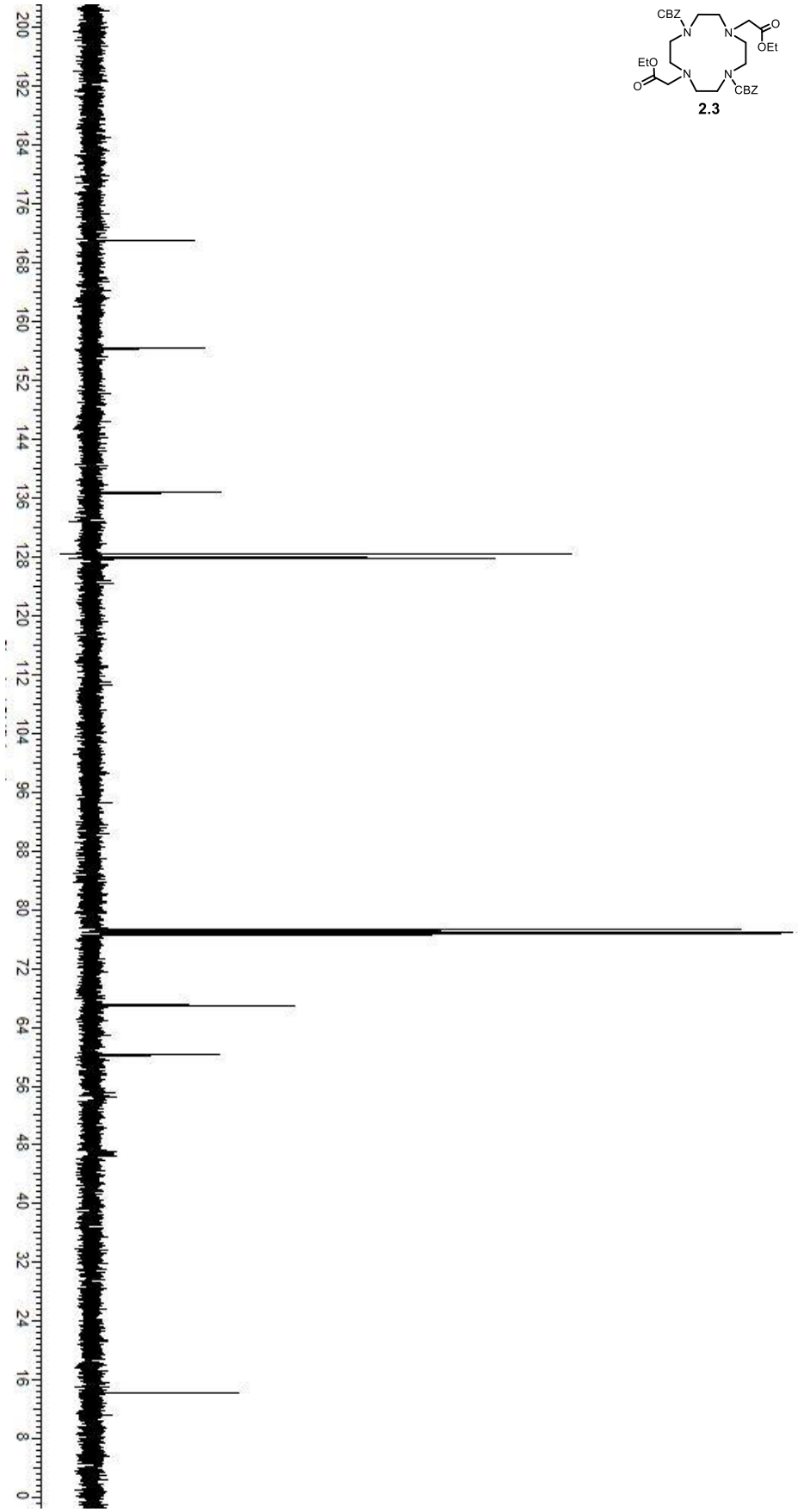
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APPENDIX B

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Title: Synthesis of Multimeric MR Contrast Agents for Cellular Imaging

Author: Ying Song, Ellen K. Kohlmeir, Thomas J. Meade

Publication: Journal of the American Chemical Society

Publisher: American Chemical Society

Date: May 1, 2008

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ABSTRACT

MODIFIED SYNTHESIS OF LIGANDS FOR LANTHANIDE IONS

by

LAUREN ELIZABETH HOPPER

December 2016

Advisor: Dr. Matthew J. Allen

Major: Chemistry

Degree: Master of Science

Ligands of relevance to lanthanide ions have been synthesized and modified with respect to pK_a and thermal conditions (both microwave and non-microwave). Microwave-assistance has been used previously to accelerate the rates of reactions of ligand syntheses, primarily as a thermal component in agreement with the Arrhenius equation. The modified syntheses of intermediates for lanthanide complexes presented in this thesis enable rapid synthesis of common intermediates—DO2A-methyl ester, DO2A-ethyl ester, and DO2A-*t*-butyl ester—that previously required days to synthesize. Additionally, this modified synthesis can be performed with or without microwave irradiation, suggesting that the thermal component of the rate acceleration is not due to special microwave effects. Modification of the syntheses of these intermediates is useful for studies where DO2A-methyl ester, DO2A-ethyl ester, or DO2A-*t*-butyl ester are used as precursors for the synthesis of ligands for lanthanide ions.

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