I. [2 + 2] CYCLOADDITION AND BENZANNULATION OF 2-IODOYNAMIDES AND APPLICATIONS TO THE CONSTRUCTION OF HIGHLY SUBSTITUTED INDOLES
II. SYNTHESIS OF FURO[2,3-*g*]THIENO[2,3-*e*]INDOLE VIA A BENZANNULATION STRATEGY

By

Yu-Pu Wang
B.S., Chemistry
Rice University, 2009

SUBMITTED TO THE DEPARTMENT OF CHEMISTRY
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

at the

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

SEPTEMBER 2015

Signature of Author..... Signature redacted

Department of Chemistry
July 23, 2015

Certified by..... Signature redacted

Rick L. Danheiser
Thesis Supervisor

Accepted by..... Signature redacted

Robert W. Field
Departmental Committee on Graduate Studies

This doctoral thesis has been examined by a committee of the Department of Chemistry as follows:

Professor Timothy F. Jamison..... Signature redacted .....
Chairman

Professor Rick L. Danheiser..... Signature redacted .....
Thesis Supervisor

Professor Mohammad Movassaghi..... Signature redacted .....

Acknowledgments

I would first like to thank my thesis advisor, Rick Danheiser, for his generous guidance and support over the past five and a half years. His passion for both chemistry research and education has been an inspiration. I would also like to thank Tim Jamison, Mo Movassaghi, and Tim Swager for their advice for my research and professional goals during my time here at MIT.

I would like to acknowledge all of the former group members who studied the Danheiser benzannulation and the synthesis and chemistry of ynamides. My work would not be possible without the basis they established. In addition, I would like to thank Galina Mamaliga and Clarissa Forneris whose project I took over. Galina's initial work toward the synthesis of furo[2,3-*g*]thieno[2,3-*e*]indole provided foundations for my research and Clarissa worked with me collaboratively in the development of the final route to the synthesis of this compound.

I would have had a hard time without all of the people in the laboratory I have had the chance to work with during my graduate study at MIT. I would like to thank Shaun Fontaine for demonstrating excellent experimental skills when I first joined the lab. I would also like to thank Tom Willumstad for his guidance in the benzannulation project. I would like to acknowledge Lucy Aguirre, Phil Hamzik, Ilia Korboukh, Sami Tlais, and Steph Tumidajski for sharing valuable research experiences with me. I would like to thank all the undergraduates I had a chance to work with: James Deng, Clarissa Forneris, Thibault Guez, and John Read, for their enthusiasm in synthetic organic chemistry. I would like to wish the current group members Sam Bartko, James Deng, and René García Franceschini the best of luck with their research and future careers.

I would like to thank all my friends in MIT Asian Dance Team, Chinese Choral Society, OnStage Dance Company, Movements in Time Dance Company, Techiya, ROCSA, and Sidney-Pacific for keeping me sane and energized with music, dance, volunteering, and cultural activities. In addition, I would like to thank my best friend Vivian Lee for every moment we have been sharing in our endeavors in life and career goals. Also, I would like to acknowledge all my friends, allies, and supports from the Rainbow Lounge, MIT Medical, and the greater Boston area for standing up for my acts of discovering my gender identity, coming out as a queer individual, and fighting for equal rights in the LGBT community.

Last but not least, I would like to thank my family for their tremendous investments in my education, great care for my safety and health, and generous support for my undergraduate and graduate education in a foreign country.

For my parents, brother,

Kaitlyn, and Jillian

I. [2 + 2] CYCLOADDITION AND BENZANNULATION OF 2-IODOYNAMIDES AND APPLICATIONS TO THE CONSTRUCTION OF HIGHLY SUBSTITUTED INDOLES II. SYNTHESIS OF FURO[2,3-*g*]THIENO[2,3-*e*]INDOLE VIA A BENZANNULATION STRATEGY

By

Yu-Pu Wang

Submitted to the Department of Chemistry
on July 8, 2015 in partial fulfillment of the
requirements for the degree of Doctor of Philosophy

ABSTRACT

The synthesis and reactions of 2-iodoynamides were investigated. 2-Iodoynamides undergo efficient and regioselective [2 + 2] cycloaddition with ketene to produce cyclobutenones that are useful synthetic building blocks. Reaction of 2-iodoynamides and vinylketenes generated *in situ* from cyclobutenones proceeds via a pericyclic cascade mechanism to produce highly substituted 2-iodoanilines. Tandem strategies for the synthesis of highly substituted indoles involving this benzannulation reaction were investigated. In addition, the synthesis of furo[2,3-*g*]thieno[2,3-*e*]indole, a new tetracyclic aromatic compound, was achieved via a strategy based on benzannulation with ynamides.

Thesis Supervisor: Rick L. Danheiser

Title: Arthur C. Cope Professor of Chemistry

Table of Contents

Part I

[2 + 2] Cycloaddition and Benzannulation of 2-Iodoynamides and Applications to the Construction of Highly Substituted Indoles

Chapter 1
Introduction and Background

The synthesis of highly substituted benzene derivatives has long been a major subject of interest in synthetic organic chemistry. Traditional approaches typically involve successive functionalization of existing aromatic rings via electrophilic or nucleophilic aromatic substitution, cross-coupling reactions, and directed metallation. However, these linear approaches can suffer from regioselectivity and chemoselectivity problems and low overall atom economy especially as the complexity of the aromatic target molecules escalate. Consequently, the development of new strategies involving the rapid and efficient synthesis of highly substituted benzene derivatives continues to attract significant attention from synthetic chemists.

The formation of benzene rings bearing most if not all substituents in place from non-aromatic molecules provides an alternative to classical linear synthetic approaches. Specifically, benzannulation reactions[1] involving the formation of at least two bonds of the new ring are often the most convergent and potentially atom economical strategy for the construction of benzenoid aromatic compounds. Benzannulations can also be regioselective and chemoselective based on the specific reactivity of the starting materials. These features make benzannulation-based strategies especially useful in total syntheses.

The development of new benzannulation-based strategies for the synthesis of highly functionalized aromatic compounds has long been a primary focus in our laboratory. Aniline derivatives have been our primary targets in recent years due to their utility in the synthesis of benzofused nitrogen heterocycles, e.g., indoles, quinolines, and carbazoles, all of which have great biological and pharmaceutical importance.[2] The main focus of my graduate research has been the extension of the work on the development of new benzannulation strategies for the synthesis of highly substituted anilines and indoles in our laboratory.

---

[1] For reviews of benzannulation methods, see: (a) Kotha, S.; Misra, S.; Halder, S. *Tetrahedron* **2008**, *64*, 10775–10790. (b) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901–2915. (c) Bamfield, P.; Gordon, P. F. *Chem. Soc. Rev.* **1984**, *13*, 441–488.

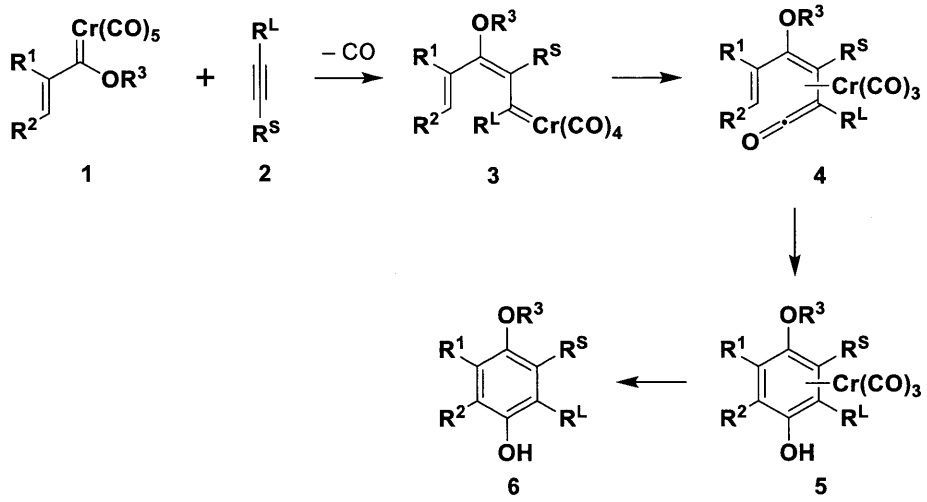
[2] Mak, X. Y.; Crombie, A. L.; Danheiser, R. L. *J. Org. Chem.* **2011**, *76*, 1852–1873.

To provide background to my research, this chapter presents a review of the benzannulation method developed in our laboratory as well as other important annulation methods for the synthesis of highly substituted anilines and indoles.

Benzannulation Methods for the Synthesis of Highly Substituted Anilines

The Dötz reaction [3] is arguably the most well-known transition metal-catalyzed benzannulation. [4] As outlined in Scheme 1, in the prototypical Dötz reaction an alkoxy pentacarbonyl chromium carbene complex **1** reacts with an alkyne **2** to produce chromium-complexed dienylketene **4** after insertion of CO. Electrocyclic ring closure and tautomerization afford chromium-complexed benzene derivative **5** and eventually the phenol product **6** is freed from chromium on mild oxidation.

Scheme 1



When the alkoxy group (OR^3 in **1**) is replaced with an amino group, however, cyclopentannulation dominates as the strong electron-donating amino substituent strengthens the metal–CO bond and retards CO insertion to form dienylketenes of type **4**. The yield of

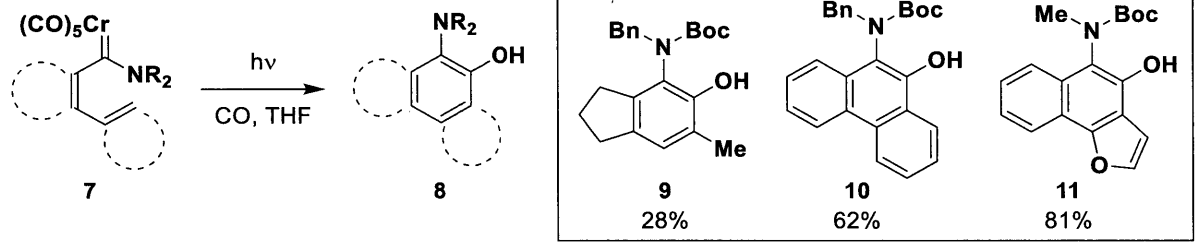
[3] Dötz, K. H. *Angew. Chem. Int. Ed.* **1975**, *14*, 644–645.

[4] For reviews on the Dötz benzannulation, see: (a) Dötz, K. H.; Stendel, J. *Chem. Rev.* **2009**, *109*, 3227-3274. (b) Waters, M. L.; Wulff, W. D. *Org. React.* **2008**, *70*, 121–623. (c) Dötz, K. H.; Stendel, J., Jr. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VHC: Weinheim, Germany, 2002; pp 250–296. (d) de Meijere, A.; Schirmer, H.; Duetsch, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 3964–4002. (e) Dötz, K. H.; Tomuschat, P. *Chem. Soc. Rev.* **1999**, *28*, 187–198.

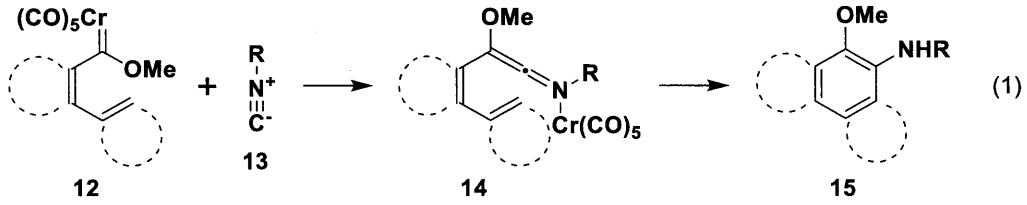
benzannulation product of type **6** can be improved by incorporation of an electron-withdrawing group on the nitrogen[5] or the terminal position of the alkene.[6]

Merlic and coworkers have developed variations of the original Dötz reaction that produce highly substituted anilines. As outlined in Scheme 2, irradiation of dienyl carbene complex **7** in the presence of CO afforded benzannulated product **8**.[7] This method enables the synthesis of polycyclic aniline derivatives such as **9**–**11**.

Scheme 2



Alternatively, dienyl alkoxycarbene complex **12** can be converted directly to aniline **15** by reaction with an isocyanide **13** as shown in eq 1.[8] This reaction proceeds via an electrocyclic closure of ketenimine complex **14** and gives *o*-aminophenols that differ in regiochemistry from the photochemical benzannulation products shown in Scheme 2.



Another useful method for the synthesis of anilines via benzannulation involves [4 + 2] cycloaddition. For example, Padwa and coworkers synthesized substituted anilines via a Diels-

---

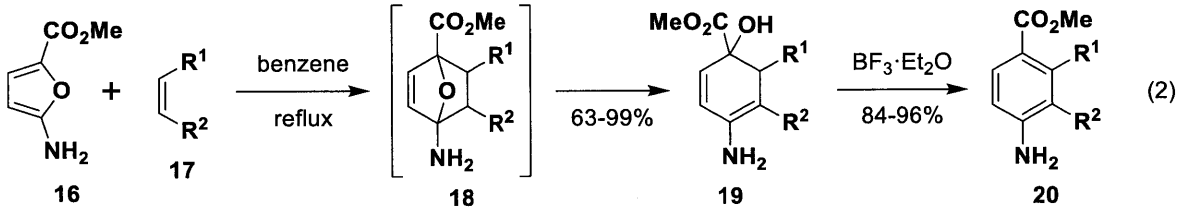
[5] (a) Dötz, K. H.; Grotjahn, D.; Harms, K. *Angew. Chem. Int. Ed.* **1989**, *28*, 1384–1386. (b) Grotjahn, D. B.; Dötz, K. H. *Synlett*, **1991**, 381–390.

[6] (a) Barluenga, J.; López, L. A.; Martínez, S.; Tomás, M. *J. Org. Chem.* **1998**, *63*, 7588–7589. (b) Barluenga, J.; López, L. A.; Martínez, S.; Tomás, M. *Tetrahedron* **2000**, *56*, 4967–4975.

[7] Merlic, C. A.; Xu, D.; Gladstone, B. G. *J. Org. Chem.* **1993**, *58*, 538–545.

[8] (a) Merlic, C. A.; Burns, E. E.; Xu, D.; Chen, S. Y. *J. Am. Chem. Soc.* **1992**, *114*, 8722–8724. (b) Merlic, C. A.; Xu, D.; Gladstone, B. G. *J. Org. Chem.* **1993**, *58*, 538–545. (c) Merlic, C. A.; Burns, E. E. *Tetrahedron Lett.* **1993**, *34*, 5401–5404.

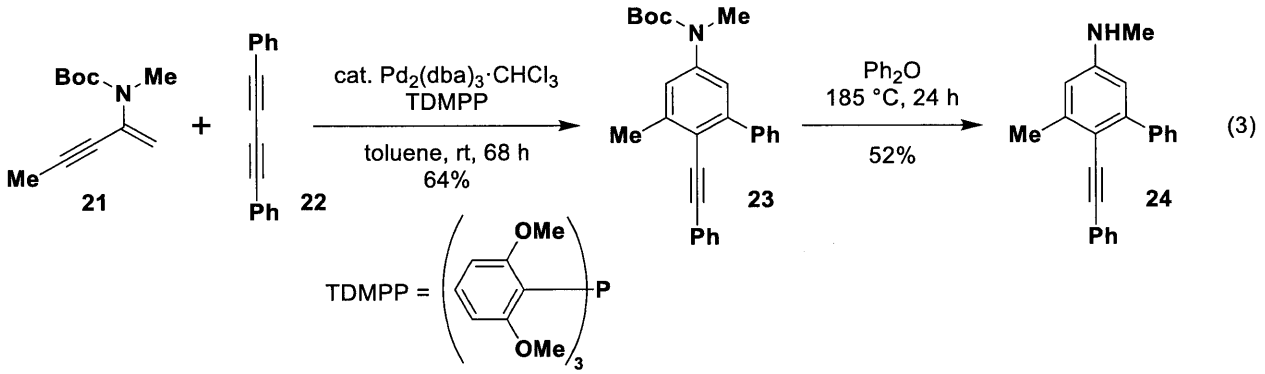
Alder reaction between 2-aminofuran **16** and various dienophiles (eq 2).[9] Under the typical reaction conditions, cleavage of the initially formed oxygen bridge ring gives cyclohexadiene **19**. Treatment with BF_3 etherate triggers a facile dehydration to form aniline **20** in high yield.



(2)

R^2 = H: R^1 = CO_2Me, COMe, CN, SO_2Ph
$R^2 \neq$ H: R^1 = R^2 = CO_2Me, *N*-phenylmaleimide

Y. Yamamoto prepared multiply-substituted anilines via a Pd-catalyzed [4 + 2] cycloaddition of aminoenynes with diynes.[10] One example is outlined in eq 3: tetrasubstituted aniline **23** was synthesized via a room temperature reaction between **21** and **22** in moderate yield. The Boc group can be removed by thermolysis at 185 °C if desired.



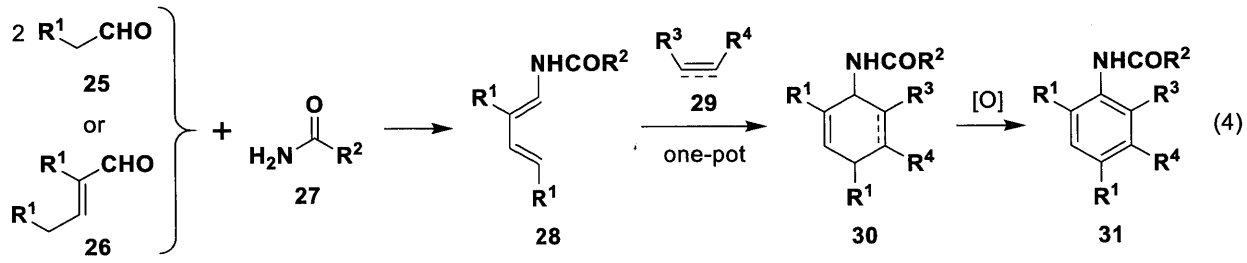
(3)

A tandem condensation-Diels-Alder strategy was developed by Beller and coworkers.[11] Eq 4 summarizes this three-component aniline synthesis. Aldehyde **25** or enal **26** condenses with amide **27** to form highly reactive amino diene **28** which is then trapped with a dienophile **29** to

---

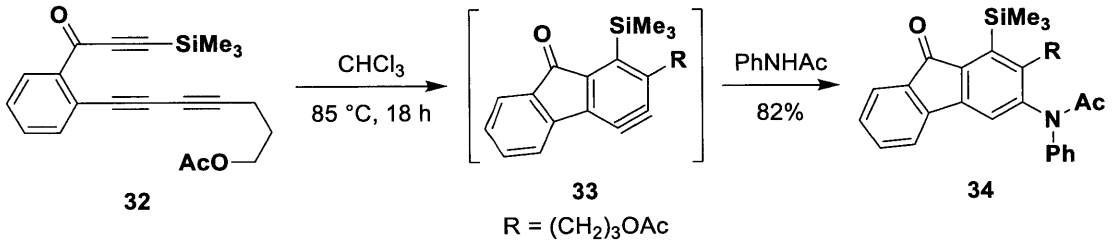
[9] (a) Padwa, A.; Dimitroff, M.; Waterson, A. G.; Wu, T. *J. Org. Chem.* **1997**, *62*, 4088–4096. See also: (b) Medimagh, R.; Marque, S.; Prim, D.; Chatti, S.; Zarrouk, H. *J. Org. Chem.* **2008**, *73*, 2191–2197.
[10] Saito, S.; Uchiyama, N.; Gevorgyan, V.; Yamamoto, Y. *J. Org. Chem.* **2000**, *65*, 4338–4341.
[11] (a) Neumann, H.; Jacobi von Wangelin, A.; Klaus, S.; Strübing, D.; Gördes, D.; Beller, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 4503–4507. (b) Fichtler, R.; Neudörfl, J.-M.; Jacobi von Wangelin, A. *Org. Biomol. Chem.* **2011**, *9*, 7224–7236.

form cyclohexene or cyclohexadiene derivative **30**. Dehydrogenation with palladium on carbon at 140 °C then yields the highly substituted aniline **31**.



(4)

A more recent example of the application of [4 + 2] benzannulation to produce anilines was reported by Hoye and coworkers.[12] As outlined in eq 5, an intramolecular "hexadehydro-Diels-Alder reaction" between the alkyne and 1,3-diyne in **32** yields benzyne **33** which can be trapped by nitrogen nucleophiles *in situ* to form highly substituted aromatic rings like aniline **34**.



(5)

In addition to these methods based on Dötz and [4 + 2] chemistry, numerous recent examples of benzannulation exist, most of which are based on condensation and related nucleophilic cyclization reactions.[13] In short, the development of new annulation strategies to synthesize highly substituted anilines remains a highly active field of synthetic organic chemistry. The next section describes in detail the benzannulation strategy based on vinylketenes developed in our laboratory.

---

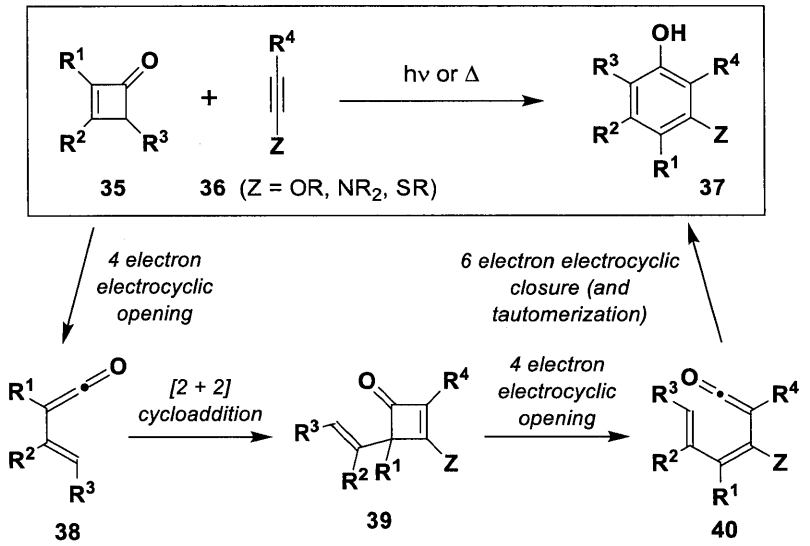
[12] Hoye, T. R.; Baire, B.; Niu, D.; Willoughby, P. H.; Woods, B. P. *Nature* **2012**, *490*, 208– 212.

[13] Representative examples: (a) Han, X.-D.; Zhao, Y.-L.; Meng, J.; Ren, C.-Q.; Liu, Q. *J. Org. Chem.* **2012**, *77*, 5173–5178. (b) Li, L.; Zhao, M.-N.; Ren, Z.-H.; Li, J.-L.; Guan, Z.-H. *Org. Lett.* **2012**, *14*, 3506–3509. (c) Jin, T.; Yang, F.; Yamamoto, Y. *Org. Lett.* **2010**, *12*, 388–390. (d) Kiren, S.; Padwa, A. *J. Org. Chem.* **2009**, *74*, 7781–7789. (e) Tiano, M.; Belmont, P. *J. Org. Chem.* **2008**, *73*, 4101–4109. (f) Lyaskovskyy, V.; Fröhlich, R.; Würthwein, E.-U. *Synthesis* **2007**, *14*, 2135–2144. (g) Sagar, P.; Fröhlich, R.; Würthwein, E.-U. *Angew. Chem. Int. Ed.* **2004**, *43*, 5694-5697.

The Danheiser Benzannulation

Our laboratory reported a benzannulation strategy based on the reaction of cyclobutenones with activated alkynes in 1984.[14] As shown in Scheme 3, this heat- or light-triggered reaction involves a cascade of four pericyclic reactions to produce a substituted phenol **37** as the final product.

Scheme 3



Thermal or photochemical electrocyclic opening of cyclobutenone **35** produces vinylketene **38**[15] which readily combines with activated alkyne **36** in a [2 + 2] cycloaddition[16] to form vinylcyclobutenone **39**. Electrocyclic opening furnishes dienylketene **40** and rapid six-electron electrocyclic closure and tautomerization leads to phenol **37** as the ultimate product. It is worth noting that our laboratory also developed a "second-generation" version of benzannulation which employs α-diazo ketones as vinylketene precursors. Details on this variant of the benzannulation are covered in Part 2, Chapter 1.

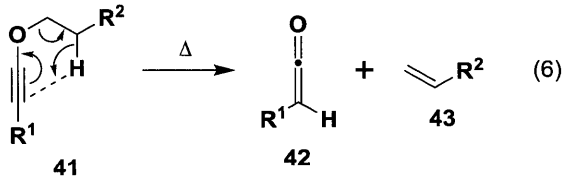
---

[14] Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1672–1674.

[15] For reviews of the chemistry of vinylketenes, see (a) Danheiser, R. L.; Dudley, G. B.; Austin, W. F. "Alkenylketenes", In *Science of Synthesis*; Danheiser, R. L., Ed.; Thieme: Stuttgart, 2006; Vol. 23; pp 493–568. (b) Tidwell, T. T. *Ketenes*, 2nd ed.; John Wiley & Sons: Hoboken, NJ, 2006; pp 206–214.

[16] For reviews of the [2 + 2] cycloaddition of ketenes, see: (a) Hyatt, J. A.; Reynolds, P. W. *Org. React.* **1994**, *45*, 159–646. (b) Snider, B. B. *Chem. Rev.* **1988**, *88*, 793–811. (c) Tidwell, T. T. "Ketene", In *Science of Synthesis*; Danheiser, R. L., Ed.; Thieme: Stuttgart, 2006; Vol. 23; pp 32–43 and related chapters. (d) See ref 15b, pp 460–528.

The alkyne partner **36** in this benzannulation typically requires heteroatom substitution. The benefit is twofold: first, activation of the alkyne facilitates the initial cycloaddition with vinylketene **38** and minimizes side reactions including dimerization of **38** and trapping of **38** by the product phenol **37**. Second, polarization of the alkyne induces regioselectivity of the [2 + 2] cycloaddition. The use of alkynyl alkyl ethers as the alkyne partner, however, is typically limited to those lacking β-hydrogens on the alkyl chain as otherwise the alkynyl ethers undergo retro-ene reactions at the temperature often required for the cleavage of cyclobutenones (eq 6).[17]

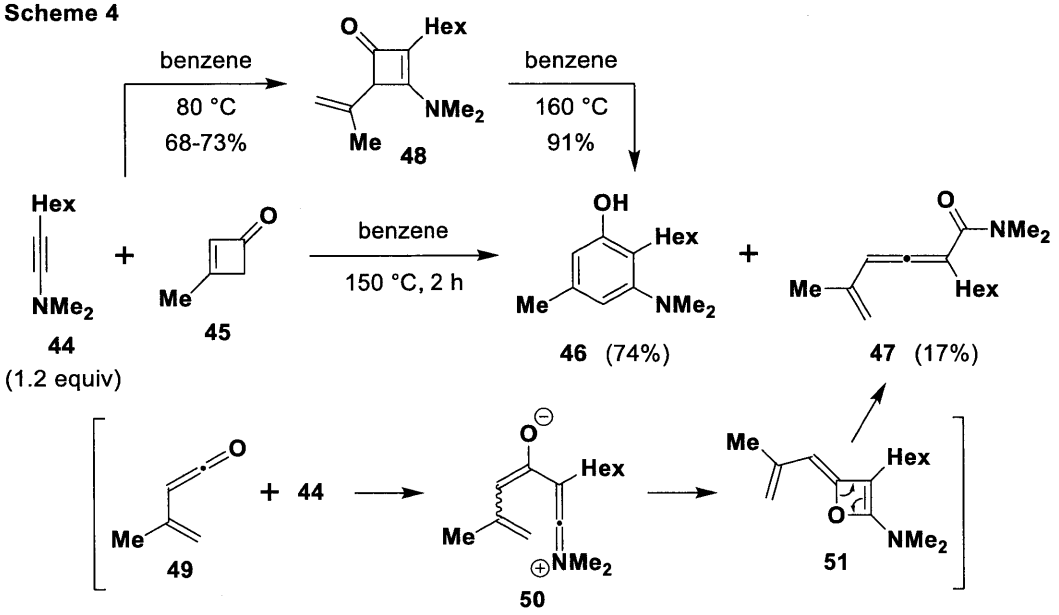


(6)

This problem can be circumvented by using methoxy or siloxy alkynes as the alkyne partner. Silyl groups have the advantage that they can be easily cleaved under mild conditions in the final product if needed. Alkynyl thioethers are also excellent substrates for the benzannulation reaction. In this case, the sulfur substituent in the final product can be removed with Raney nickel if desired. Ynamines also participate readily in the benzannulation; however, some undesired allene byproduct **47** is also produced as illustrated in Scheme 4. The highly nucleophilic nature of ynamines renders a polar stepwise pathway in the ketene addition step more favorable. Formation of the allene byproduct can be minimized by performing the reaction in a stepwise fashion as shown.

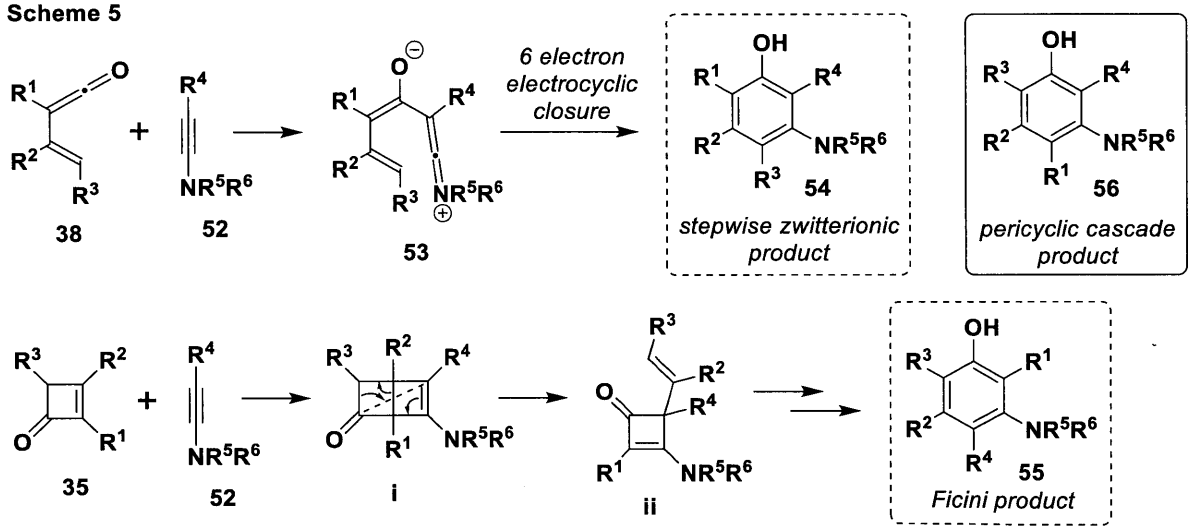
[17] Brandsma, L.; Bos, H. J. T.; Arens, J. F. In *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, 1969; pp 808–810.

Scheme 4



Another complication in the ynamine version of the benzannulation arises from the potential to form regioisomeric aromatic product **54** from a stepwise pathway proceeding via **53**, or from a Ficini rearrangement[18] to generate **55** as outlined in Scheme 5. Should these isomers form as a mixture along with the desired pericyclic cascade product, isolation of a single product can become a challenging task.

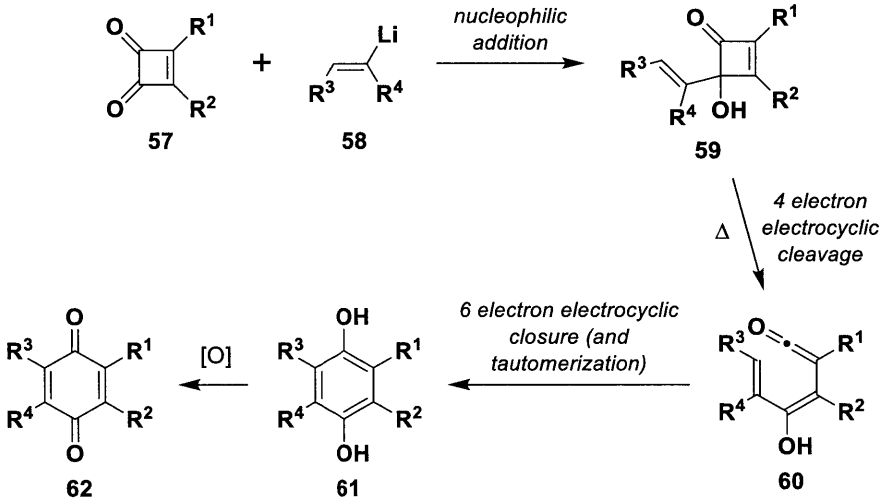
Scheme 5



[18] Ficini observed that some reactions of cyclobutenones with ynamines form bicyclo[2.2.0]hexenones which subsequently rearrange to vinylcyclobutenones. See: Ficini, J.; Falou, S.; d'Angelo, J. *Tetrahedron Lett.* **1977**, *18*, 1931–1934.

It is worth noting that Liebeskind [19] and Moore [20] have independently developed a benzannulation related to that described above. As depicted in Scheme 6, this benzannulation also involves electrocyclic opening and closure as the key steps. In the Liebeskind-Moore reaction, vinylcyclobutenone **59** is generated by nucleophilic addition of vinyl- or aryllithiums **58** to squaric acid derivatives **57**. The resulting highly substituted hydroquinones **61** are typically oxidized to benzoquinone **62** as the final product.

Scheme 6



Benzannulation with Ynamides

While ynamines are useful synthetic building blocks, they are difficult to store and handle due to their facile hydration caused by the high electron-donating tendency of the amino substituent. *Ynamides* with electron-withdrawing groups on the nitrogen atom possess markedly improved stability over ynamines and adequate reactivity in various polar and pericyclic

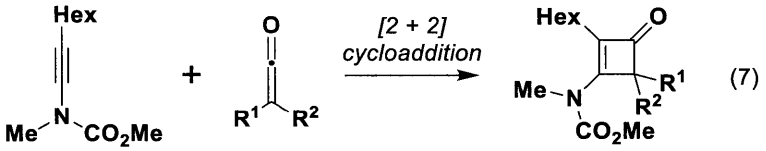
---

[19] For a seminal publication, see: (a) Liebeskind, L. S.; Iyer, S.; Jewell, C. F. Jr. *J. Org. Chem.* **1986**, *51*, 3065–3067. See also: (b) Zhang, D.; Llorente, I.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 4330–4338. (c) Pena Cabrara, E.; Liebeskind, L. S. *J. Org. Chem.* **2002**, 67, 1689–1691.

[20] For seminal publications, see: (a) Karlsson, J. O.; Nguyen, N. V.; Foland, L. D.; Moore, H. W. *J. Am. Chem. Soc.* **1985**, *107*, 3392–3393. (b) Perri, S. T.; Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1986**, *51*, 3067–3068. For a review, see: (c) Moore, H. W.; Yerxa, B. R. In *Advances in Strain in Organic Chemistry*; Halton, B. Ed.; Jai Press: London, 1995; Vol 4, pp 81–162. See also: (d) Tiedemann, R.; Turnbull, P.; Moore, H. W. *J. Org. Chem.* **1999**, *64*, 4030–4041.

reactions.[21] Our laboratory began to study the use of ynamides as benzannulation partners and since then ynamides have become an increasingly popular building block in organic synthesis due to their relative ease of synthesis, handling, and storage.

Ynamides were first tested for their reactivity with simple ketenes as this [2 + 2] cycloaddition is a key step in benzannulation.[22] As shown in eq 7, reaction of ynamide **63** with a variety of ketenes provided the desired cyclobutenone products regioselectively and in high yield. In all cases a single regioisomeric cycloadduct was isolated. In a competition experiment, ynamide **63** was shown to react with ketene at roughly the same rate as 1-ethoxy-1-octyne.



(7)

64 $R^1 = R^2 = H$ — **68:** 94%
65 $R^1 = R^2 = Me$ — **69:** 87%
66 $R^1 = R^2 = Cl$ — **70:** 88%
67 $R^1 = H$, $R^2 = SPh$ — **71:** 76%

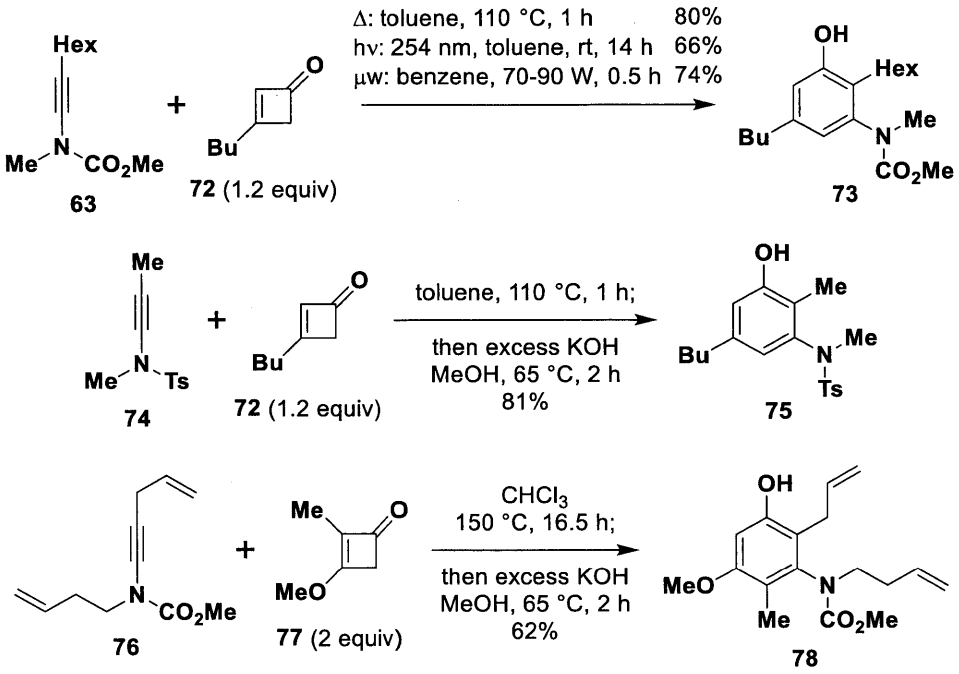
These promising initial results prompted our laboratory to investigate benzannulation based on ynamides. It was found that ynamides **63**, **74**, and **76** react with cyclobutenones **72** and **77** under thermal, photochemical, or microwave conditions to form the expected benzannulation products in moderate to good yield (Scheme 7).[2] It is worth noting that in some cases treatment of the crude product with KOH improved the yield of the desired phenolic product by hydrolysis of esters formed by the reaction of the product with ketene intermediates.

---

[21] For recent reviews on the synthesis and chemistry of ynamides, see: (a) Wang, X.-N.; Yeom, H.-S.; Fang, L.-C.; He, S.; Ma, Z.-X.; Kedrowski, B. L.; Hsung, R. P. *Acc. Chem. Res.* **2014**, *47*, 560–578. (b) Evano, G.; Jouvin, K.; Coste, A. *Synthesis* **2013**, *45*, 17–26. (c) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064−5106. (d) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 2840−2859.

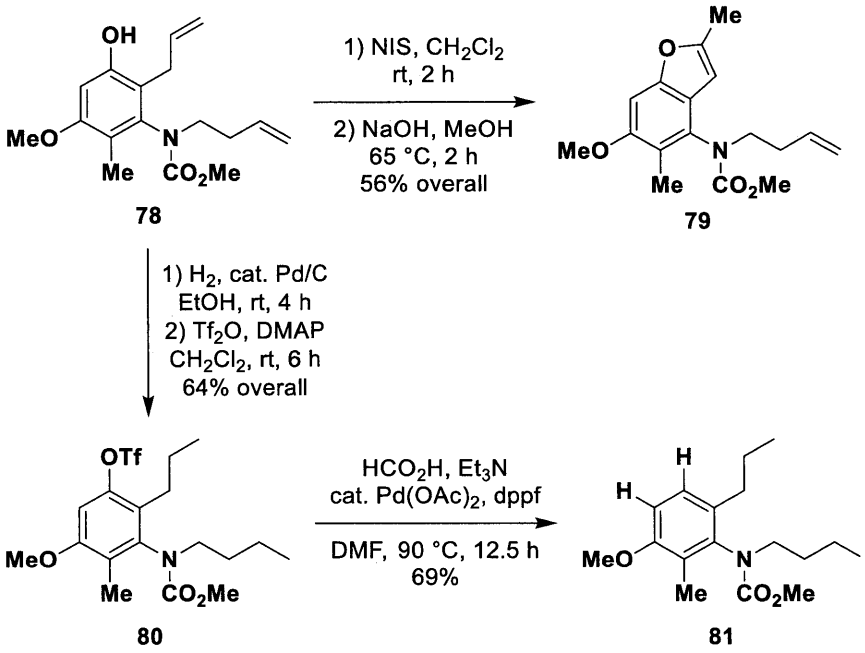
[22] Kohnen, A. L.; Mak, X. Y.; Lam, T. Y.; Dunetz, J. R.; Danheiser, R. L. *Tetrahedron* **2006**, *62*, 3815–3822.

Scheme 7

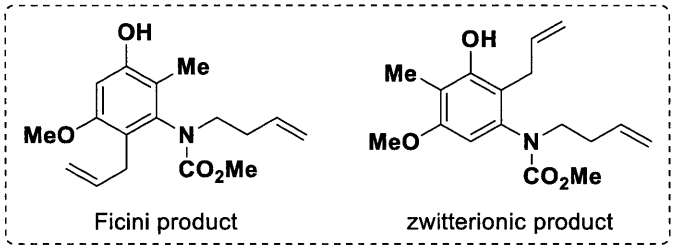


In all cases above a single aromatic product was isolated. However, as noted in the previous section, alternative reaction pathways could potentially be operative and give regioisomeric phenolic products. To confirm that the benzannulation indeed proceeded via the pericyclic cascade mechanism, the experiments outlined in Scheme 8 were conducted by Xiao Yin Mak to confirm the regiochemistry of benzannulation product **78**.

Scheme 8

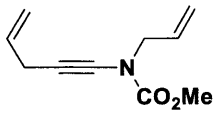
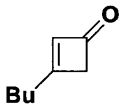
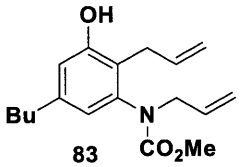
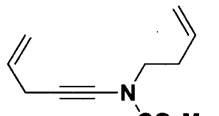
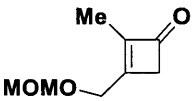
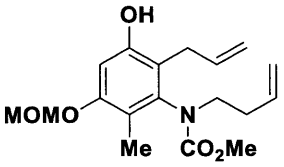
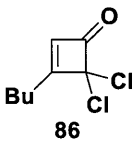
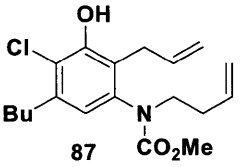
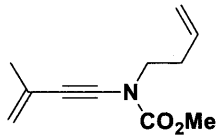
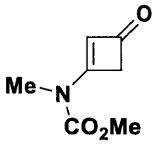
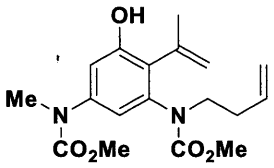
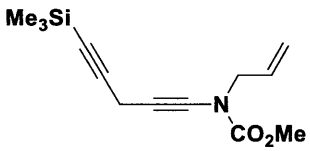
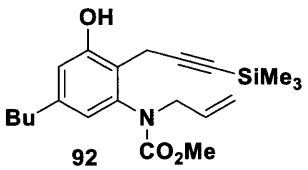


Treatment of **78** with NIS followed by base led to iodoetherification and elimination to form benzofuran **79.** This result indicated the *ortho* relationship between the allyl and hydroxyl groups, ruling out the Ficini product (i.e., **55** in Scheme 5). Hydrogenation of the side chains followed by deoxygenation via triflation and palladium-catalyzed reduction yielded aniline **81**. The coupling constant (J = 8.5 Hz) observed for the two aromatic protons confirmed that the hydroxyl group in **78** is adjacent to an unsubstituted aromatic carbon, ruling out the zwitterionic product (i.e., **54** in Scheme 5). The above results confirmed the benzannulation product was indeed **78** predicted by the pericyclic cascade pathway.



As shown in Table 1, a range of ynamides and cyclobutenones have been successfully used in the benzannulation to produce highly substituted anilines in moderate to good yield. Typical reaction conditions involve heating an ynamide with 1.2–2.0 equiv of a cyclobutenone at 80–150 °C followed by treatment of the crude product with KOH in certain cases (*vide supra*). It is worth noting that benzannulations that involve disubstituted ketene intermediates (i.e., entry 2) require higher temperatures due to the slower rate of the [2 + 2] cycloaddition step.

Table 1. Scope of Benzannulation Involving Ynamides and Cyclobutenones

entry	ynamide	cyclobutenone	conditions	product	yield(%)[a]
1	 **82**	 **72**	PhMe, 80 °C, 1.5 h; then 110 °C, 1.5 h	 **83**	84
2	 **76**	 **84**	$CHCl_3$, 150 °C, 16.5 h; then KOH, MeOH 65 °C, 2.5 h	 **85**	60
3	**76**	 **86**	PhMe, 135 °C, 4 h[b]	 **87**	45
4	 **88**	 **89**	PhMe, 110 °C, 10 h; then KOH, MeOH 65 °C, 3.5 h	 **90**	53
5	 **91**	**72**	PhMe, 80 °C, 1.5 h; then 110 °C, 1.5 h	 **92**	79

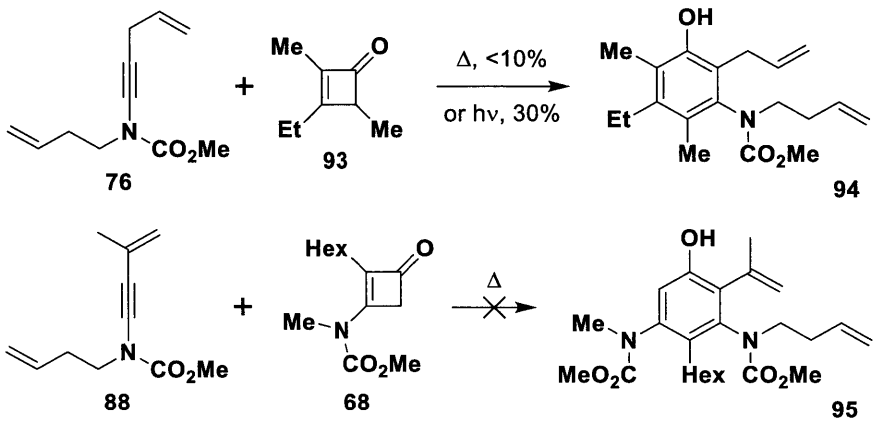
[a] Isolated yield of products purified by column chromatography on silica gel. Yields based on ynamide. [b] Reaction performed in the presence of 2.0 equiv of BHT using 1.0 equiv of cyclobutenone and 1.5 equiv of ynamide.

The benzannulation based on ynamides and cyclobutenones does have certain limitations. Mak found that trisubstituted and certain disubstituted cyclobutenones (e.g., **68**) are rather unreactive even under forcing conditions (Scheme 9).[23] The reaction of trisubstituted cyclobutenone **93** with ynamide **76** resulted in a low yield of the desired product and no product was observed when disubstituted cyclobutenone **68** was heated with ynamide **88**. We believe that

[23] Mak, X. Y. I. Tandem Benzannulation-Ring Closing Metathesis Strategy for the Synthesis of Benzo-Fused Nitrogen Heterocycles. Massachusetts Institute of Technology, Cambridge, MA, September 2008.

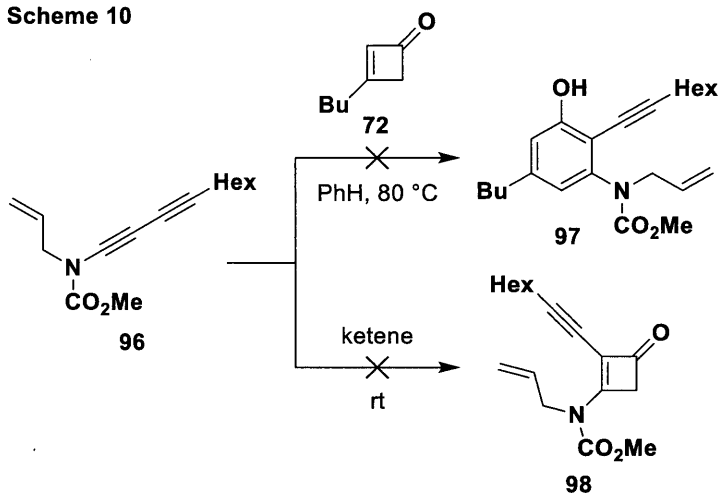
the poor reactivity of **93** is due to steric hindrance in the vinylketene produced from the initial electrocyclic cleavage.

Scheme 9



Diynamides were also found to be unreactive in the benzannulation. Ynamide **96** failed to participate in the benzannulation or in a simple [2 + 2] cycloaddition with excess ketene (Scheme 10).[23] Although **96** did react with dichloroketene, the reaction was not selective and gave a mixture of products. We believe the significant electron-withdrawing effect of the conjugated alkynyl substituent greatly reduces the ketenophilicity of ynamide **96**.

Scheme 10

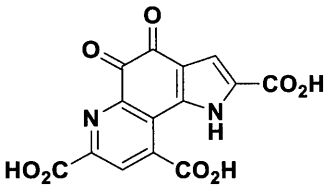


Despite the above limitations, this benzannulation remains a powerful method for the construction of highly substituted phenols and anilines. One of the goals of the work described in

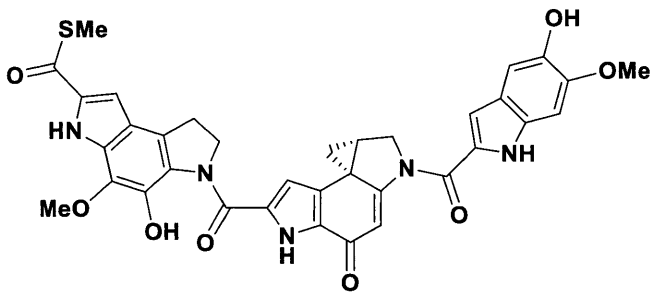
this thesis has been the application of the benzannulation to the synthesis of highly substituted indoles and indolines. The next section provides background on previous work in this area.

Annulation Approaches to Highly Substituted Indoles and Indolines

Indole is an extremely common heterocycle found as a substructure in numerous natural products, pharmaceutical compounds, and industrially important materials.[24] Consequently, the synthesis and derivatization of indoles remains an active field of synthetic organic chemistry.[25] However, the synthesis of indoles with certain substitution patterns is still often inefficient or challenging. In particular, the synthesis of indoles bearing multiple substituents on the benzenoid ring[26] is difficult and often complicated by low regioselectivity. Thus, the practical and efficient synthesis of many indole-containing natural products such as pyrroloquinoline quinone and yatakemycin continues to pose a challenge to synthetic chemists.



pyrroloquinoline quinone



yatakemycin

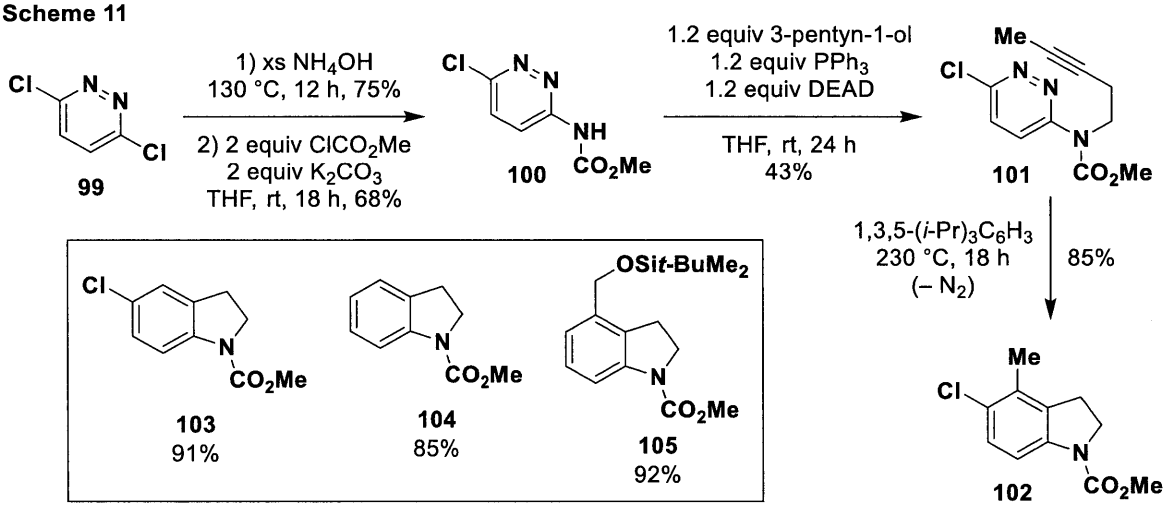
[24] (a) Wu, Y.-J. *Top. Heterocycl. Chem.* **2010**, *26*, 1–29. (b) Barden, T. C. *Top. Heterocycl. Chem.* **2010**, *26*, 31–46. (c) Gribble, G. W. "Pyrroles and their Benzo Derivatives: Applications." In *Comprehensive Heterocyclic Chemistry II*; A. R. Katritzky, C.W. Ress, E. F. V. Scriven, C. W. Bird, Ed. Pergamon Press, Oxford, 1996; Vol. 2, pp 207–257.

[25] For recent reviews on indole synthesis, see: (a) Joule, J. A. In *Science of Synthesis*; Thomas, E. J., Ed.; Thieme: Stuttgart, 2000; Vol. 10, pp 361-652. (b) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045–1075. (c) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875–2911. (d) Taber, D. F.; Tirunahari, P. K. *Tetrahedron* **2011**, *67*, 7195–7210. (e) Barluenga, J.; Valdés, C. Five-Membered Heterocycles: Indoles and Related Systems. In *Modern Heterocyclic Chemistry*; Alvarez-Builla, J.; Vaquero, J. J.; Barluenga, J., Eds.; Wiley-VCH: Weinheim, 2011; Vol. 1, pp 377-531. (f) Inman, M.; Moody, C. J. *Chem. Sci.* **2013**, *4*, 29–41.

[26] Selected recent examples of methods applicable to the synthesis of highly substituted indoles: (a) Katritzky, A. R.; Ledoux, S.; Nair, S. K. *J. Org. Chem.* **2003**, *68*, 5728–5730. (b) Dunetz, J. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 5776–5777. (c) Charrier, N.; Demont, E.; Dunsdon, R.; Maile, G.; Naylor, A.; O'Brien, A.; Redshaw, S.; Theobald, P.; Vesey, D.; Walter, D. *Synthesis* **2006**, *20*, 3467–3477. (d) Greshock, T. J.; Funk, R. L. *J. Am. Chem. Soc.* **2006**, *128*, 4946–4947. (e) Fang, Y.-Q.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 538–549. (f) Sapeta, K.; Lebold, T. P.; Kerr, M. A. *Synlett* **2011**, 1495–1514. (g) Ma, L.-J.; Li, X.-X.; Kusuyama, T.; El-Sayed, I. E.-T.; Inokuchi, T. *J. Org. Chem.* **2009**, *74*, 9218–9221.

An especially attractive approach to tackle the problem stated above involves assembly of the benzenoid ring using *benzannulation* strategies. As with the assembly of many six-membered ring-containing compounds, [4 + 2] cycloaddition is arguably the most commonly used reaction in these strategies. Some of the earliest work in this field was done by Boger and Coleman employing pyridazines with tethered alkynes as the cycloaddition substrate (Scheme 11).[27] While efficient, the reaction requires high temperatures and the scope and substitution patterns explored were fairly limited.

Scheme 11

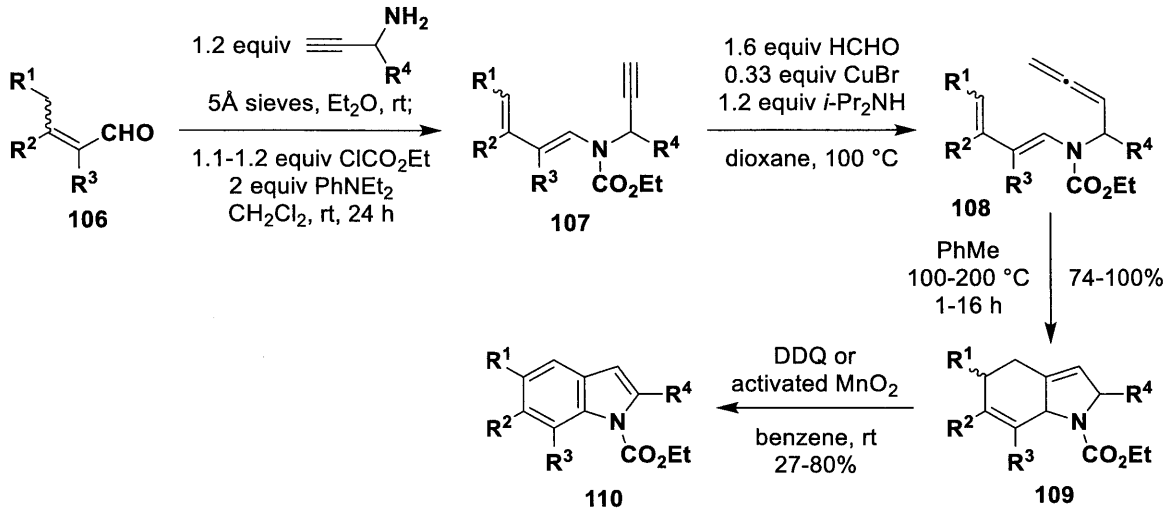


A related intramolecular Diels-Alder strategy was envisioned by Kanematsu et al.[28] As shown in Scheme 12, *N*-propargyl dienamides **107** were synthesized via *N*-acylation of corresponding α,β-unsaturated imines (generated *in situ* from aldehydes **106**) followed by treatment with base.[29] Homologation with formaldehyde[30] then provided the allenyl dienamide substrates for the key cycloaddition. Heating at 100–200 °C furnished tetrahydroindoles **109** in high yield which could be oxidized to indoles **110** by DDQ or activated MnO_2. However, the scope of this method may be somewhat limited as only singly substituted indoles were made.

---

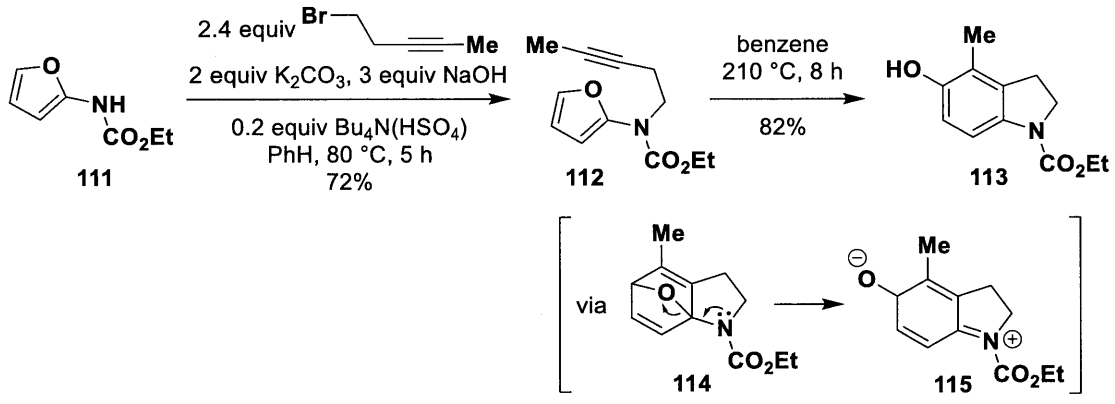
[27] Boger, D. L.; Coleman, R. S. *J. Org. Chem.* **1984**, *49*, 2240–2245.
[28] Hayakawa, K.; Yasukouchi, T.; Kanematsu, K. *Tetrahedron Lett.* **1986**, *27*, 1837–1840.
[29] This two-step synthetic sequence is based on: Oppolzer, W.; Bieber, L.; Francotte, E. *Tetrahedron Lett.* **1979**, *11*, 981–984.
[30] Based on: Crabbé, P.; Fillion, H.; André, D.; Luche, J.-L. *J. Chem. Soc. Chem. Commun.* **1979**, 859–860.

Scheme 12



Furans with tethered alkyne or alkene dienophiles represent another type of substrate capable of intramolecular Diels-Alder reactions to give indoline products. In work by Padwa et al., furan-2-yl carbamates, e.g., ethyl carbamate **111**, were *N*-alkylated with suitable dienophiles such as 5-bromo-2-pentyne and strongly heated to induce intramolecular [4 + 2] cycloaddition and ensuing ring opening-aromatization to form indoline-5-ols such as **113** (Scheme 13).[31] Alkenes were also found to be useful dienophiles in this reaction. In this case, the initially formed cyclohexadiene dehydrated during the reaction process to form the benzenoid ring.

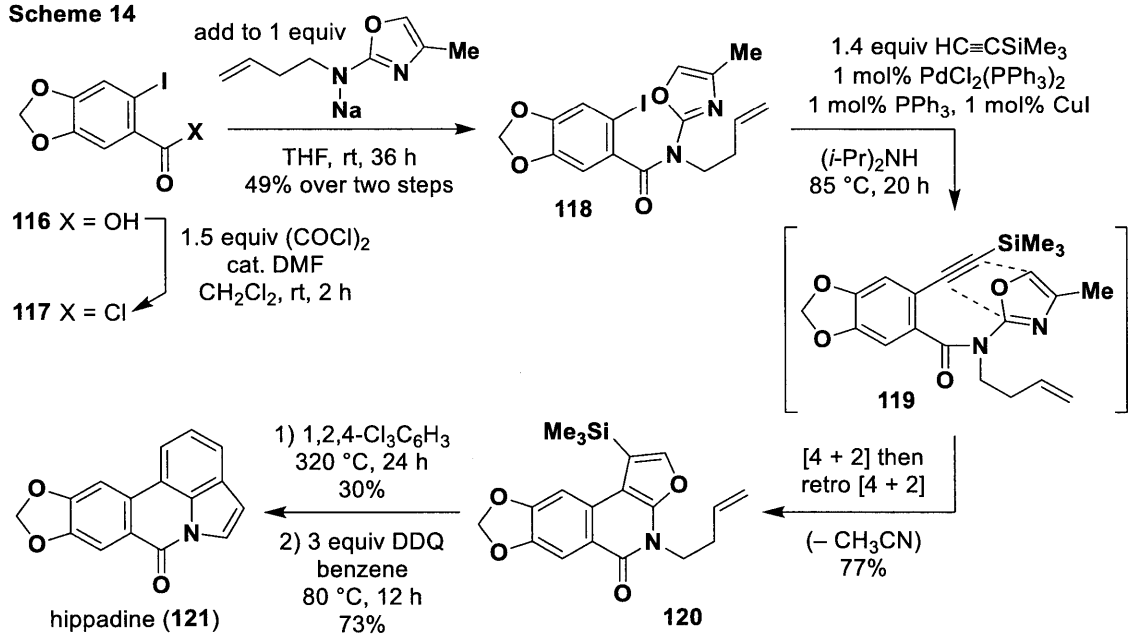
Scheme 13



[31] Padwa, A.; Brodney, M. A.; Liu, B.; Satake, K.; Wu, T. *J. Org. Chem.* **1999**, *64*, 3595–3607.

The Padwa group also completed a formal total synthesis of hippadine using this strategy. As shown in Scheme 14, oxazole and alkyne side chains were sequentially installed on the existing benzodioxole core via acylation and Sonogashira reaction. A cycloaddition cascade then furnished the requisite *N*-butenyl furan **120** and set the stage for the indoline-forming step. Unfortunately, the key Diels-Alder reaction required very high temperatures and the yield was low. The indoline product was then converted to hippadine (**121**) via a known oxidation step.[32] Overall, this total synthesis demonstrated the power of [4 + 2] cycloadditions in the synthesis of polycyclic natural products.

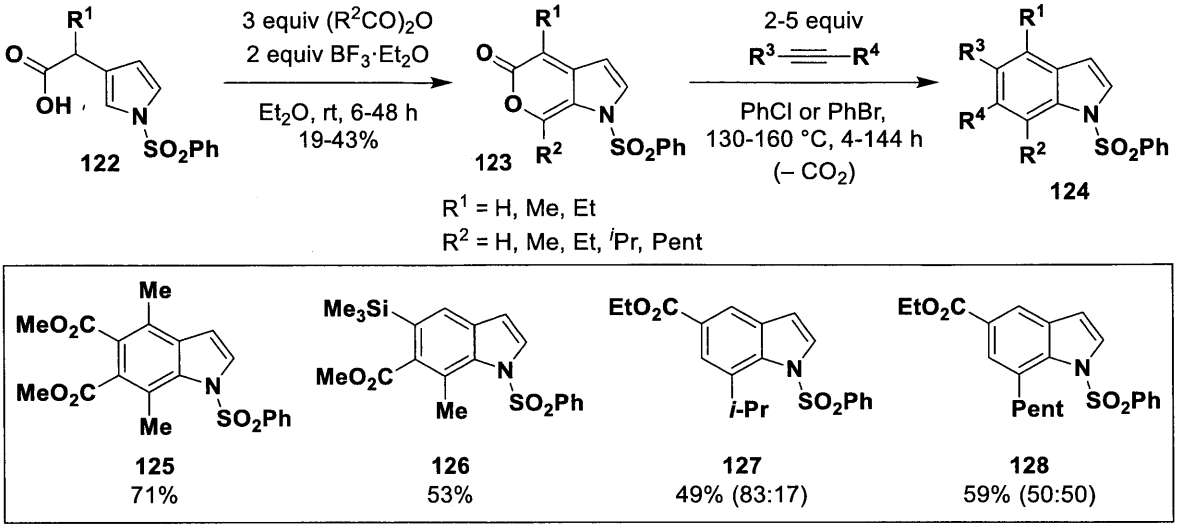
Scheme 14



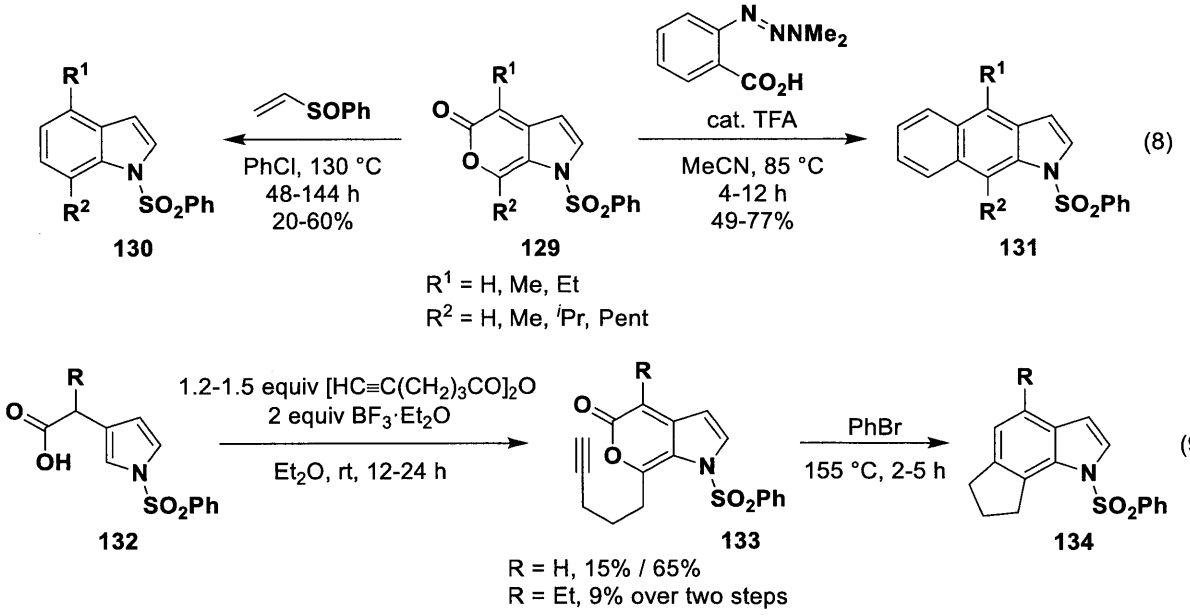
Moody et al. described an alternative approach to the synthesis of indoles based on Diels-Alder reactions of 1,5-dihydropyrano[3,4-*b*]pyrrol-5(1*H*)-ones.[33] As outlined in Scheme 15, the substrates were synthesized in one step (albeit in low yield) by treatment of 1-phenylsulfonylpyrrol-3-ylacetic acid (**122**) or its α-substituted derivatives with carboxylic anhydrides in the presence of $BF_3 \cdot Et_2O$. These highly reactive dienes react with a variety of electron-deficient alkynes to provide substituted indoles after extrusion of carbon dioxide.

[32] Ghosal, S.; Rao, P. H.; Jaiswal, D. K.; Kumar, Y.; Frahm, A. W. *Phytochem.* **1981**, *20*, 2003.
[33] Jackson, P. M.; Moody, C. J. *Tetrahedron* **1992**, *48*, 7447–7466.

Scheme 15



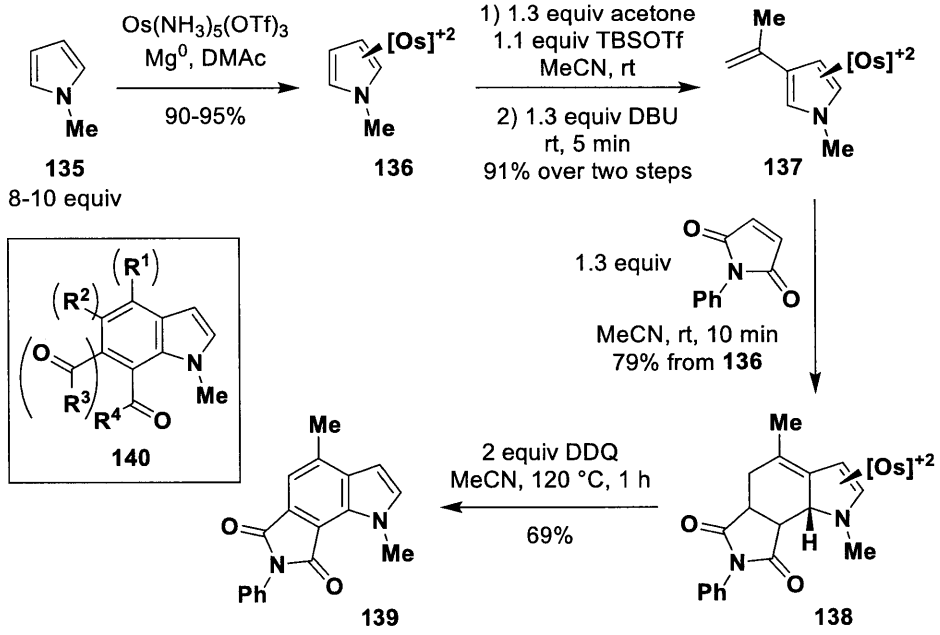
While the regioselectivity of this reaction is poor with unsymmetrical dienophiles, the method is applicable to the synthesis of C5,C6-unsubstituted indoles from phenyl vinyl sulfoxide and for the synthesis of benzo[*f*]indoles from benzyne (eq 8). Intramolecular Diels-Alder reaction also enabled the synthesis of tetrahydrocyclopenta[*g*]indoles (eq 9). This tricyclic system is found in a series of natural products from marine sponges including trikentrins and herbindoles.[34]



[34] For a review of syntheses of trikentrins and herbindoles, see: Silva, L. F., Jr.; Craveiro, M. V.; Tébéca, I. R. M. *Tetrahedron* **2010**, *66*, 3875–3895.

In a different approach by Harman et al., osmium(II) complexes of 3-vinylpyrroles were used as the diene component for Diels-Alder reactions to generate indole products after dehydrogenation.[35] As shown in Scheme 16, *N*-methylpyrrole was converted to an η^2-osmium complex **136** followed by installation of the 3-alkenyl side chain. To minimize migration of the osmium to the exocyclic alkene, compound **137** was immediately treated with dienophiles such as *N*-phenylmaleimide to afford tetrahydroindole derivative **138**. Oxidation with DDQ removed the osmium and produced indole **139**. A variety of indoles of type **140** were synthesized regioselectively using this approach.

Scheme 16



Our laboratory has also devoted significant effort to the development of syntheses of indoles via cycloaddition processes. Dunetz synthesized indoles using two types of ynamides as the intramolecular [4 + 2] cycloaddition substrates.[36]

In the first approach, ynamides with a tethered conjugated enyne were used as the substrate. As shown in Scheme 17, heating **142** at 180 °C led to indoline **144** directly in good yield. The

---

[35] (a) Hodges, L. M.; Moody, M. W.; Harman, W. D. *J. Am. Chem. Soc.* **1994**, *116*, 7931–7932. (b) Hodges, L. M.; Spera, M. L.; Moody, M. W.; Harman, W. D. *J. Am. Chem. Soc.* **1996**, *118*, 7117–7127.
[36] Dunetz, J. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 5776–5777.

initially formed highly strained cyclic allene **143** isomerizes to the benzene ring in the final isolated product **144**. Addition of BHT was found to result in improved yields presumably by suppressing radical-induced polymerization of the substrates at elevated temperatures.

Scheme 17

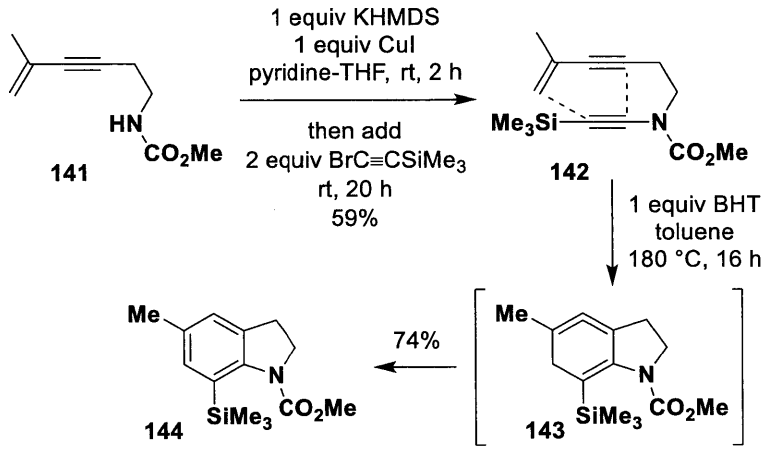
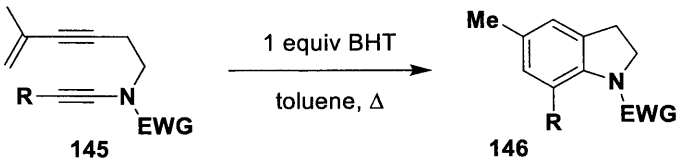


Table 2 lists the substrate scope of this indoline-forming cycloaddition. Both carbomethoxy and sulfonyl groups are tolerated as the protecting group for nitrogen. While the presence of alkyl groups on the ynamide resulted in poor yield possibly due to competing propargylic ene reactions (entries 8 and 9), an alkynyl R group worked great (entry 3) and the alkynyl group in the indoline product could be hydrogenated in case an alkyl group is needed in the final product. Although substitution of the ynamide with a bulky TIPS group (entry 10) or CO_2Me group (entry 11) gave unsatisfactory results,[37] a very wide range of substrates undergo the reaction in good yield making this a particularly useful synthesis of substituted indolines.

[37] Dunetz, J. R. Synthesis of Indolines and Indoles via Intramolecular [4 + 2] Cycloaddition of Ynamides and Conjugated Enynes. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, September, 2005.

Table 2. [4 + 2] Cycloadditions of Conjugated Enynes with Ynamides



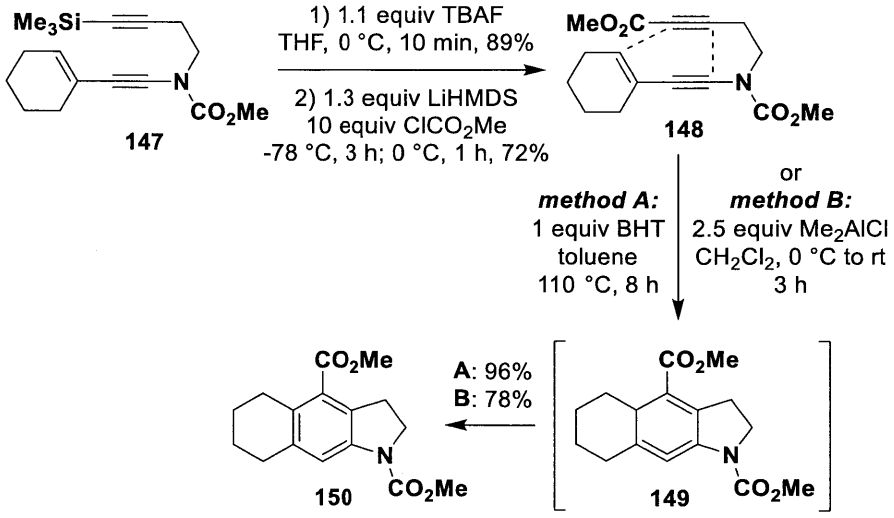
145 146

entry	R	EWG	conditions[a]	yield (%)[b]
1	H	CO_2Me	210 °C, 2 h	71
2	$SiMe_3$	CO_2Me	180 °C, 16 h	74
3	$C{\equiv}CSiMe_3$	CO_2Me	110 °C, 14 h	69
4	H	Ts	210 °C, 1.25 h	61
5	$SiMe_3$	Ts	210 °C, 1.25 h	56
6	H	Tf	180 °C, 5 h	56
7	$SiMe_3$	Tf	180 °C, 5 h	68
8	Hex	CO_2Me	150-180 °C	<5
9	CH_2OMe	CO_2Me	150-180 °C	5-20
10	Si(*i*-Pr)$_3$	CO_2Me	180 °C, 44 h	[c]
11	CO_2Me	Ts	120-180 °C	n.d.

[a] 3 equiv BHT for EWG = Ts and Tf. [b] Isolated yields of products purified by column chromatography. [c] A 60:40 mixture of unreacted ynamide and indoline was isolated in ~90-95% yield.

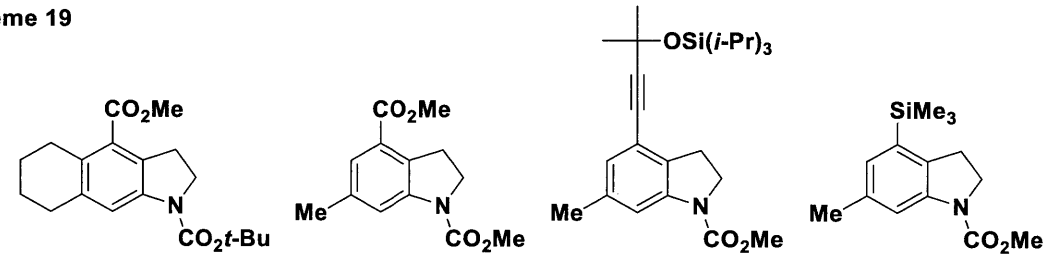
Conjugated enynamides with a tethered alkyne as the dienophile were used in the second variation (Scheme 18). This method is complementary to the first variation and particularly useful in the synthesis of C-4 substituted indolines. Like the previous case, the reaction is believed to proceed via a cyclic allene intermediate.

Scheme 18



It is worth noting that this cycloaddition can be promoted by either heat or Lewis acid. Scheme 19 shows several indolines made using this method. Just like the other variation, electron-withdrawing groups such as carbonyl and alkynyl substituents enabled cycloaddition at lower temperatures. The indoline products from both variations can be conveniently oxidized to indoles with *o*-chloranil or DDQ if desired.

Scheme 19



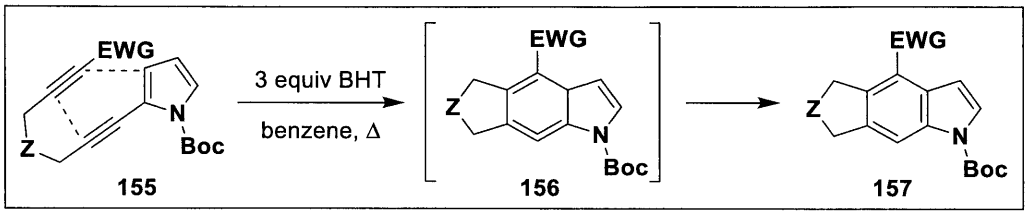
	151	**152**	**153**	**154**
Conditions	110 °C, 8 h	110 °C, 30 h	110 °C, 30 h	180 °C, 16 h
Yield	91%	95%	84%	86%

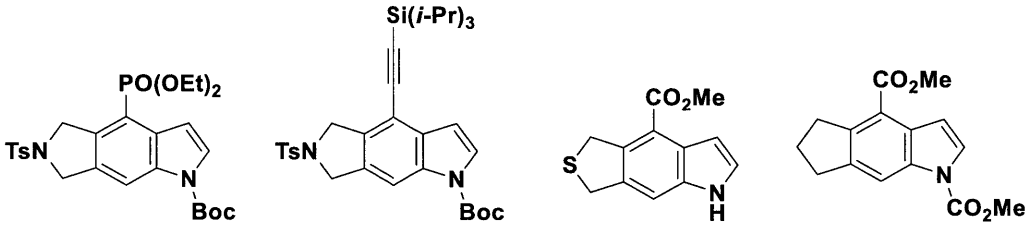
Horta studied yet another intramolecular [4 + 2] approach to indoles based on diynyl pyrroles.[38] As shown in Scheme 20, this reaction is similar to Dunetz's approach in that a strained cyclic allene **156** is produced as the intermediate. Although a tether between the two alkynes was

[38] Horta, J. E. Synthesis of Polycyclic Heteroaromatic Compounds via the Intramolecular [4 + 2] Cycloaddition of Conjugated Hetarenynes and Alkynes. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, May, 2006.

found necessary to drive the reaction, this method did provide a gateway to unique cyclopenta[*f*]indole skeletons. It is also worth noting that similar tricycles based on benzofuran and benzothiophene were also made using the same approach.

Scheme 20



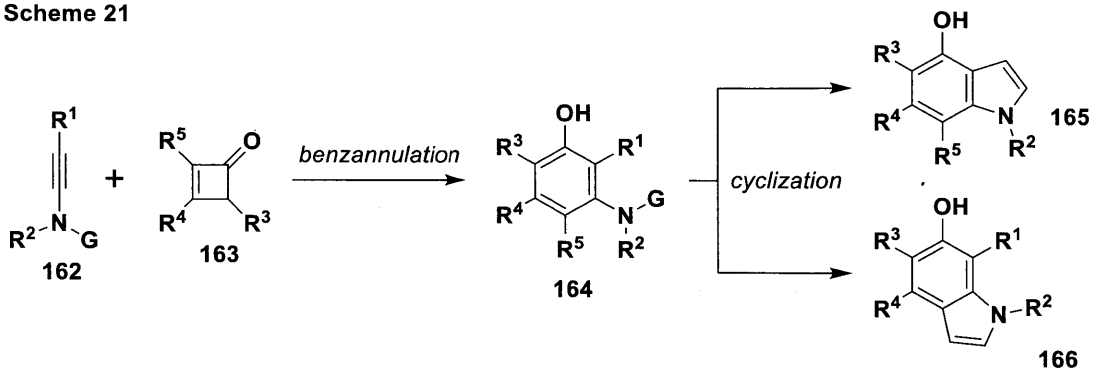


	158	159	160	161
Conditions	130 °C, 6 h	80 °C, 2 h	180 °C, 5 h	180 °C, 27 h
Yield	61%	48%	46% (with Boc cleavage)	67%

Synthesis of Indoles Based on Benzannulation of Ynamides and Cyclobutenones

While the various [4 + 2] cycloaddition strategies described above enable the rapid assembly of indole and indoline cores, the substrate scope and attainable substitution patterns are often limited. A different approach involves the use of the ynamide-based benzannulation to provide highly substituted anilines (*vide supra*). As shown in Scheme 21, if the resulting anilines bear appropriate *ortho* groups, they can then be converted to indoles in a second step. Although this tandem strategy requires two operations from the substrates to indoles, it is more convergent than [4 + 2]-based methods and can furnish indoles with very high degrees of substitution.

Scheme 21



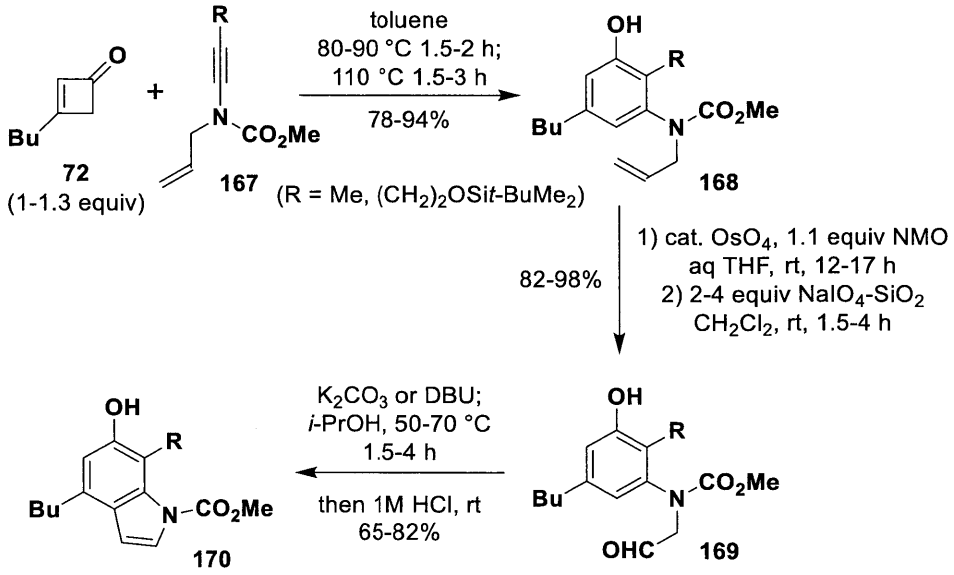
In our laboratory, Lam investigated three different and complementary approaches to the synthesis of highly substituted indoles based on benzannulation with ynamides.[39] It is well-known that anilines substituted on the nitrogen with a 2-carbonyl side chain can be converted to indoles by the action of Lewis and Brønsted acids[40] or, in certain cases, base.[41] This so-called Bischler indole synthesis proceeds via aromatic substitution followed by elimination.

As shown in Scheme 22, the requisite anilines **169** in this case were made by benzannulation of *N*-allyl ynamides **167** and cyclobutenone **72** followed by oxidative cleavage. While neither ozonolysis nor Lemieux-Johnson oxidation [42] gave satisfactory results, dihydroxylation followed by treatment of the crude diol with $NaIO_4$ on silica gel[43] provided aldehydes **169** in high yield. While initial attempts using Lewis acids were unpromising, Lam found that cyclization occurred readily by the action of bases such as K_2CO_3 and DBU. Complete dehydration to 6-hydroxy indoles **170** could be achieved by acidification of the reaction mixture with HCl.

---

[39] Lam, T. Y.; Wang, Y.-P.; Danheiser, R. L. *J. Org. Chem.* **2013**, *78*, 9396–9414.
[40] Joule, J. A. In *Science of Synthesis*; Thomas, E. J., Ed.; Thieme: Stuttgart, Germany, 2000; Vol. 10, pp 390–391 and 461–462.
[41] Pchalek, K.; Jones, A. W.; Wekking, M. M. T.; StC. Black, D. *Tetrahedron* **2005**, *61*, 77–82.
[42] Pappo, R.; Alen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478–479.
[43] Zhong, Y.-L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622–2624. See also: Daumas, M.; Vo-Quang, Y.; Vo-Quang, L.; Le Goffic, F. *Synthesis* **1989**, 64–65.

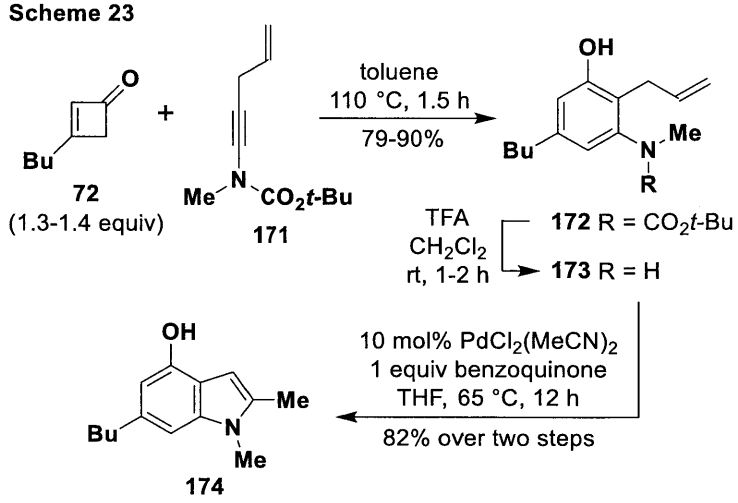
Scheme 22



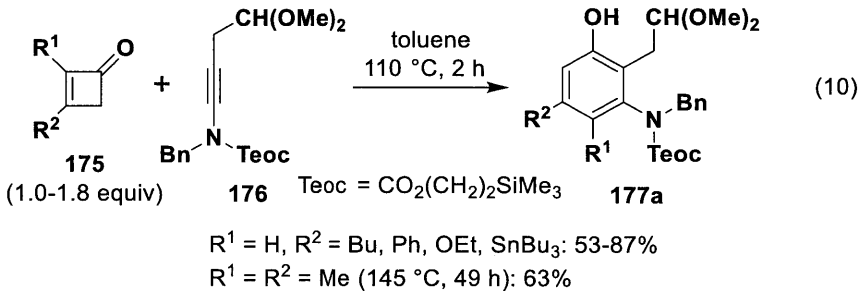
Another way of converting benzannulation products to indoles is via the Hegedus indole synthesis.[44] Scheme 23 illustrates the use of the Hegedus reaction in conjunction with ynamide-based benzannulation for the synthesis of indoles. Reaction of cyclobutenone **72** with ynamide **171** furnished *ortho*-allyl aniline **172**. Cleavage of the BOC group then set the stage for the Hegedus reaction. Treatment of **173** with catalytic Pd(II) in the presence of benzoquinone under typical conditions resulted in cyclization of the Pd-coordinated alkene onto the amino instead of the hydroxyl group, ultimately leading to the desired 4-hydroxy indole **174**.

[44] Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800–5807.

Scheme 23



Anilines bearing a $-CH_2C(O)R$ group (or its functional equivalent) adjacent to the amino group represent another type of indole precursor, most famously in the well-known Plieninger indole synthesis.[45] With the consideration that cyclization must be controlled to proceed via the amino instead of the hydroxyl group, ynamide **176** was chosen as the benzannulation substrate in which the carbonyl group was masked as an acetal and the nitrogen was protected as a (trimethylsilyl)ethyl carbamate (eq 10).

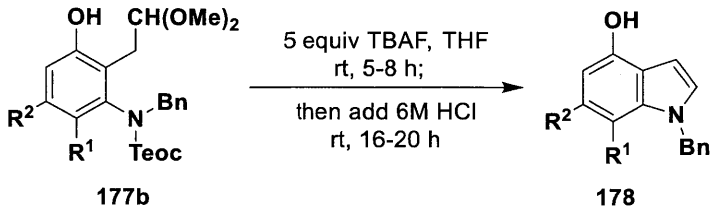


(10)

After benzannulation, as outlined in eq 11, anilines **177** were then treated with TBAF to reveal the nucleophilic nitrogen. Acidification with HCl then led to desired indole products **178** in good yield. While tributylstannyl benzannulation product is incompatible with the acidic

[45] (a) For the seminal publication, see: Plieninger, H.; Suhr, K. *Chem. Ber.* **1956**, *89*, 270–278. (b) For some notable recent applications of this methodology, see: Banfield, S. C.; England, D. B.; Kerr, M. A. *Org. Lett.* **2001**, *3*, 3325–3327. (c) Zawada, P. V.; Banfield, S. C.; Kerr, M. A. *Synlett* **2003**, 971–974. (d) England, D. B.; Kerr, M. A. *J. Org. Chem.* **2005**, *70*, 6519–6522.

cyclization conditions, the stannyl functional handle can be easily converted to various groups (e.g., iodo or benzoyl) before the indole formation step.



177b 178 (11)

R^1 = H, R^2 = Bu, Ph, OEt, I, COPh: 53-87%

R^1 = R^2 = Me: 74-80%

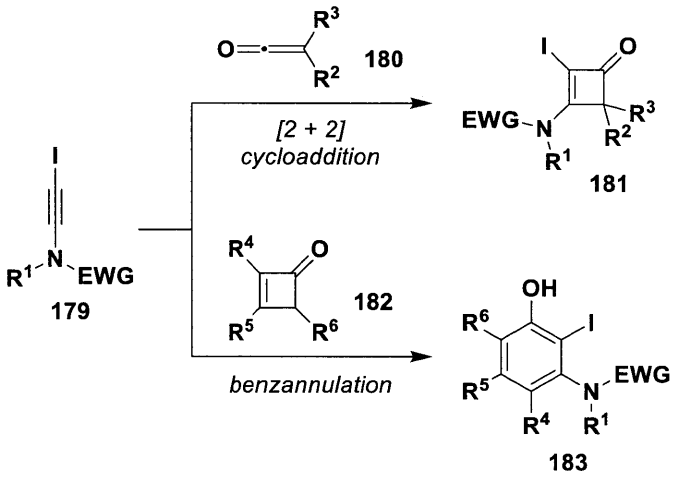
Inspired by the versatility of the ynamide-based benzannulation in the synthesis of indoles, my research has been primarily revolving around the use of a new type of ynamide, namely 2-iodoynamides, in the synthesis of highly substituted anilines, indoles, and polycyclic aromatic compounds. The next chapter details the synthesis and [2 + 2] cycloadditions of 2-iodoynamides.

Chapter 2

[2 + 2] Cycloaddition of 2-Iodoynamides with Ketene

Ynamides have been shown in our laboratory to be very useful substrates in the efficient synthesis of highly substituted aromatic compounds via benzannulation. The success of this type of benzannulation relies on the efficiency of the initial [2 + 2] cycloaddition of ynamides with vinylketenes (*vide supra*). We became interested in the synthesis of 2-iodoynamides (**179**) and the investigation of this new type of ynamide in [2 + 2] cycloadditions and benzannulations as no successful previous example of the cycloaddition of an alkynyl halide and any ketene had been reported to our knowledge.[46] In addition, the alkenyl or aryl iodide products (i.e., **181** and **183**) from [2 + 2] cycloadditions and benzannulations of 2-iodoynamides were expected to be highly useful substrates for reactions such as cross-coupling and cyclization to form benzofused heterocycles.

Scheme 24



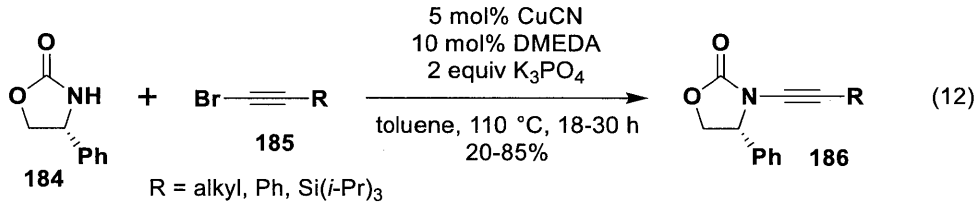
Synthesis of Ynamides

Several methods have been developed to synthesize ynamides. The earlier general methods include elimination from haloenamides[47] and the alkynyliodonium salt-based method developed

[46] For the single example of [2 + 2] cycloaddition of an *alkenyl* halide and a ketene, the reaction of bis(trifluoromethyl)ketene with methyl trifluorovinyl ether, see: England, D. C.; Krespan, C. G. *J. Org. Chem.* **1970**, 35, 3312–3322.

[47] See pp. 18–20 in ref 21b, pp. 5069–5070 in ref 21c, and pp. 2841–2842 in ref 21d.

by Stang.[48,49] However, these methods have limited substrate scope and involve lengthy synthetic sequences. The situation changed in 2003 when the groups of Hsung[50] and Danheiser[51] independently reported the first examples of ynamide synthesis by copper-mediated *N*-alkynylation of amides with alkynyl halides. As shown in eq 12, the original protocol developed by Hsung is an adaptation of the *N*-arylation of amides reported by Buchwald.[52] This method involves the use of catalytic CuCN, *N,N'*-dimethylethylenediamine (DMEDA) as ligand, and K_3PO_4 in refluxing toluene. While this method is useful for oxazolidinone-based ynamides, the yields were variable and the procedure worked poorly with ynamides based on cyclic ureas and acyclic carbamates.



(12)

Hsung subsequently reported an improved version of this ynamide synthesis using catalytic $CuSO_4 \cdot 5H_2O$, 1,10-phenanthroline as ligand, and either K_3PO_4 or K_2CO_3 as the base (depending on the amide substrates) (Scheme 25).[53] While this method also requires elevated temperatures, lower temperatures compared to the original protocol can be used. In addition to oxazolidinone derivatives, carbamate, sulfonamide, and some simple amide-based ynamides can be synthesized in good to excellent yields.

---

[48] (a) Williamson, B. L.; Stang, P. J.; Arif, A. M. *J. Am. Chem. Soc.* **1993,** *115,* 2590–2597. (b) Murch, P.; Williamson, B. L.; Stang, P. J. *Synthesis* **1994**, 1255–1256. (c) Zhdankin, V. V.; Stang, P. J. *Tetrahedron* **1998**, *54*, 10927–10966.

[49] For reviews regarding alkynyliodonium salts, see: (a) Zhdankin, V. V.; Stang, P. J. *Tetrahedron* **1998**, *54*, 10927–10966. (b) Brand, J. P.; Waser, J. *Chem. Soc. Rev.* **2012**, *41*, 4165–4179.

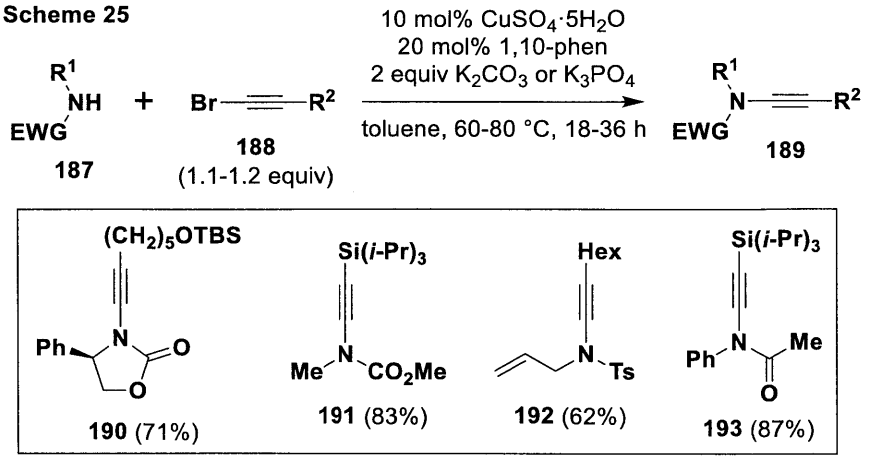
[50] Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368–2369.

[51] Dunetz, J. R.; Danheiser, R. L. *Org. Lett.* **2003**, *5*, 4011–4014.

[52] Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421-7428.

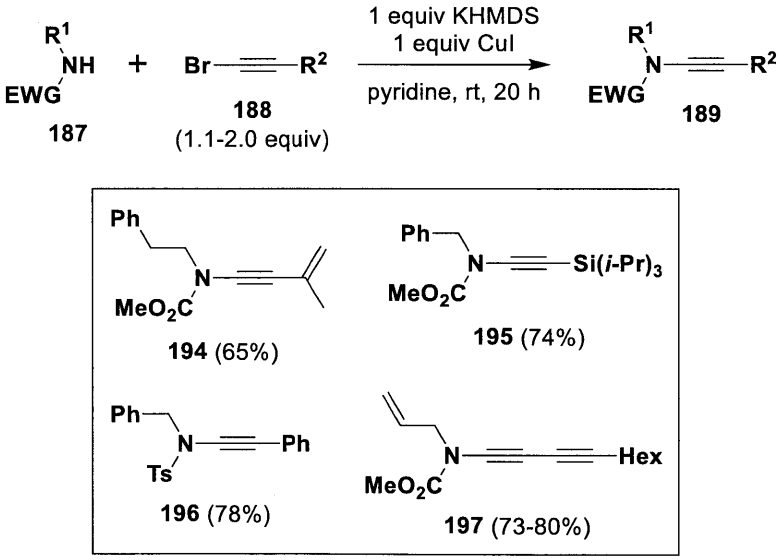
[53] (a) Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151-1154. (b) Zhang, X.; Zhang, Y.; Huang, J.; Hsung, R. P.; Kurtz, K. C. M.; Oppenheimer, J.; Petersen, M. E.; Sagamanova, I. K.; Shen, L.; Tracey, M. R. *J. Org. Chem.* **2006**, *71*, 4170-4177. (c) Sagamanova, I. K.; Kurtz, K. C. M.; Hsung, R. P. *Org. Synth.* **2007**, *84*, 359-367.

Scheme 25



As outlined in Scheme 26, the procedure developed in our laboratory utilizes CuI, pyridine as the ligand, and KHMDS as the base. While this procedure requires the use of stoichiometric amounts of CuI, and slow addition of the alkynyl halide to minimize the formation of alkyne dimers, the reaction takes place at room temperature and can thus tolerate thermally unstable substrates. For instance, diynamide **197** can be synthesized in good yield using this protocol[54] while it is formed in only 34-38% yield using the method of Hsung.

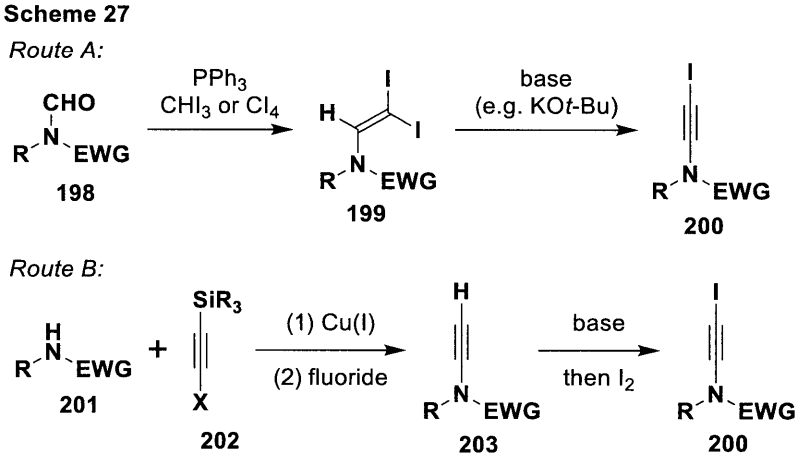
Scheme 26



[54] Kohnen, A. L.; Dunetz, J. R.; Danheiser, R. L. *Org. Synth.* **2007**, *84*, 88–101.

We envisioned two possible routes for the synthesis of 2-iodoynamides as shown in Scheme 27. Route A is based on the method of Brückner for the synthesis of ynamides from formamides.[55] Corey-Fuchs reaction of formamide **198** would generate diiodoenamide **199** which would then be treated with base to trigger the formation of iodoynamide **200** by elimination. Route B involves an alkynylation of amide **201** with 1-halo-2-silyl alkyne **202**, desilylation to expose the terminal ynamide **203**, treatment with base to deprotonate the alkyne, and iodination with I_2 or other iodinating agents.[56,57] As both the Danheiser and improved Hsung alkynylation methods have been routinely and extensively used in our laboratory for the construction of ynamides, we decided to proceed with the latter route for the synthesis of 2-iodoynamides.

Scheme 27



Eq 13 outlines the synthesis of carbamate-based terminal ynamide **207**[58] via alkynylation of methyl benzyl carbamate[59] with (iodoethynyl)trimethylsilane[60] and subsequent desilylation with TBAF. Silyl ynamide **206** has previously been synthesized by Tanaka from the

---

[55] (a) Brückner, D. *Synlett* **2000**, *10*, 1402–1404. (b) Brückner, D. *Tetrahedron* **2006**, *62*, 3809–3814.

[56] Frequently used protocols for the synthesis of alkynyl iodides from terminal alkynes include n-BuLi/I_2, morpholine/I_2, and NIS/$AgNO_3$. See: Stang, P. J.; Zhdankin, V. V. "Alkynyl Halides and Chalcogenides", In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R.; Meth-Cohn, O.; Rees, C. W.; Ley, S. V., Ed.; Pergamon: Cambridge, UK, 1995; Vol. 2; Ch. 21; pp 1082–1088.

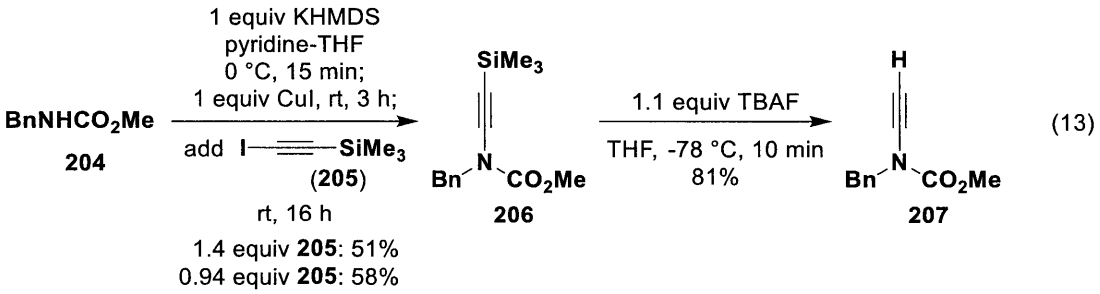
[57] Previous attempts to produce 2-iodoynamides by treatment of terminal or 2-trimethylsilyl ynamides with NIS/$AgNO_3$ by Olesya Haze in our laboratory were not successful.

[58] This compound has also been synthesized by treatment of **206** with Na_2CO_3 in methanol. See: Yamasaki, R.; Terashima, N.; Sotome, I.; Komagawa, S.; Saito, S. *J. Org. Chem.* **2010**, *75*, 480–483.

[59] Kost, D.; Zeichner, A.; Sprecher, M. S. *J. Chem. Soc., Perkin. Trans. 2* **1980**, 317–325.

[60] Amatore, C.; Blart, E.; Genet, J. P.; Jutand, A.; Lemaire-Audoire, S.; Savignac, M. *J. Org. Chem.* **1995**, *60*, 6829–6839.

alkynyliodonium salt.[61] We found the use of alkynyl iodide **205** more convenient due to the volatile and pungent nature of the corresponding bromide. However, iodide **205** was also found to form insoluble brown polymers under the conditions of the alkynylation step despite slow addition (dropwise over 1 h using a syringe pump). These polymers complicate the workup process but this problem can be mitigated by using an excess of carbamate **204** without a significant reduction in the yield.



(13)

Terminal ynamides with a more robust tosyl group on the nitrogen were also synthesized. As shown in eq 14, ethynyltrimethylsilane was brominated using the general procedure of Hofmeister.[62] The crude bromoalkyne was immediately used in the alkynylation step following the method of Hsung to afford ynamide **209**[63] in 40% yield over two steps. The moderate yield was attributed to cleavage of the labile TMS group and the subsequent side reactions (e.g., homocoupling) of the prematurely formed terminal ynamide **210** during the alkynylation step in the presence of K_2CO_3 and water. In the next step, the TMS group was cleaved with K_2CO_3 instead of TBAF.[64] However, the yield of this desilylation step was modest due to the facile hydration of terminal ynamide **210** to form acetamide **211** under the reaction conditions.

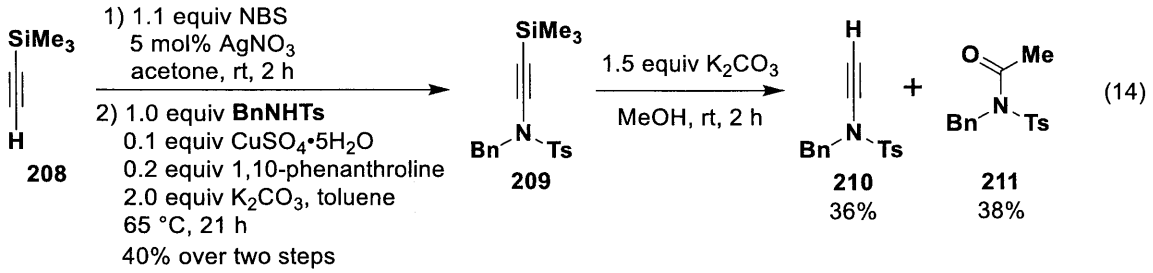
---

[61] (a) Tanaka, K.; Takeishi, K.; Noguchi, K. *J. Am. Chem. Soc.* **2006**, *128*, 4586–4587. (b) Tanaka, K.; Takeishi, K. *Synthesis* **2007**, *18*, 2920–2923.

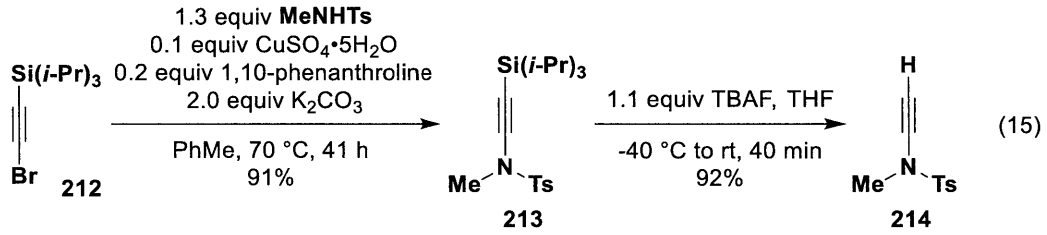
[62] Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R. *Angew. Chem., Int. Ed.* **1984**, *23*, 727–729.

[63] Previously synthesized using the original Hsung protocol in: Hirano, S.; Tanaka, R.; Urabe, H.; Sato, F. *Org. Lett.* **2004**, *6*, 727–729.

[64] For desilylation of **209** with TBAF, see: (a) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 489–492. (b) Witulski, B.; Buschmann, N.; Bergsträßer, U. *Tetrahedron* **2000**, *56*, 8473–8480.



N-Methyl terminal ynamide **214** was also synthesized as a simpler analog of **210**. To avoid the problems associated with the synthesis of ynamide **210**, the yield of ynamide **213**[65] was greatly improved by employing (bromoethynyl)*triisopropyl*silane (**212**)[66] as the alkynylating agent. The more robust TIPS group ensures desilylation is minimized during the alkynylation process. As outlined in eq 15, desilylation with TBAF[67] afforded the desired ynamide **214** in excellent yield.



Iodination of Ynamides

With terminal ynamides in hand, the next step was to optimize conditions for the deprotonation of the ynamide. Methyl iodide was employed as the trapping agent for the acetylide in these exploratory studies since this provided crude reaction products easily analyzed by ^{1}H NMR by comparing the acetylenic proton signal at 2.68 ppm for terminal ynamide **214**[68] and the propargylic CH_3 signal at 1.87 ppm for propynyl ynamide **215**,[69] both of which are known compounds. As shown in Table 3, KHMDS proved less effective than *n*-BuLi as the base and deprotonation was most complete when conducted at higher temperatures (e.g., -15 °C).

---

[65] Previously synthesized by Cu-catalyzed oxidative amidation of TIPS-acetylene in 87% yield. See: Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833–835.

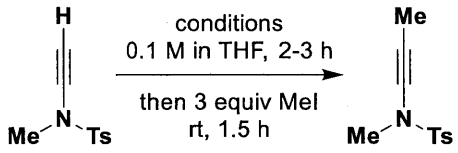
[66] Rubin, Y.; Lin, S. S.; Knobler, C. B.; Anthony, J.; Boldi, A. M.; Diederich, F. *J. Am. Chem. Soc.* **1991**, *113*, 6943–6949.

[67] Exact reaction was reported in ref 2.

[68] Kanemura, S.; Kondoh, A.; Yasui, H.; Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 506–514.

[69] Yasui, H.; Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 373–379.

Table 3. Optimization of Conditions for Deprotonation of 214



214 **215**

entry	conditions	conversion (%)[a]
1	1.0 equiv KHMDS, -78 °C	79
2	1.3 equiv KHMDS, -78 °C	83
3	1.0 equiv *n*-BuLi, -78 °C	85
4	1.0 equiv *n*-BuLi, -42 °C	83
5	1.0 equiv *n*-BuLi, -15 °C	93[b]

[a] Determined by ^{1}H NMR analysis. In each case the crude product was a clean mixture of **214** and **215**. [b] 92% isolated yield by column chromatography.

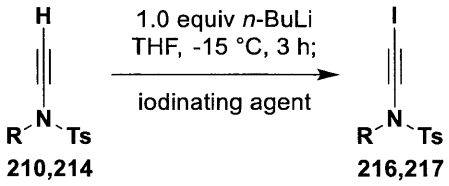
Several reagents including I_2, ICN, 1,2-diiodoethane, 1-chloro-2-iodoethane, and CF_3CH_2I have previously been used in the iodination of aryllithium compounds.[70] Among these iodinating agents, I_2 and 1,2-diiodoethane were chosen for our studies due to their ease of handling. Iodination of tosyl ynamide **214** with I_2 using the optimized deprotonation conditions of Table 3, entry 5 afforded 2-iodoynamide **216** in moderate yield after purification by column chromatography. Significant losses resulted when recrystallization was attempted.

As shown in Table 4, *N*-benzyl 2-iodoynamide **217** can be made in similar yield by using 1,2-diiodoethane in place of I_2 as the iodinating agent. Surprisingly, these 2-iodoynamides were observed to have the same R_f values as their precursor terminal ynamides on TLC analysis. This observation made reaction monitoring especially challenging. In the case of using I_2 as the iodinating agent for the synthesis of **216**, the reaction was believed to proceed rapidly as the color of I_2 faded immediately while the iodine crystals slowly dissolved. The formation of 2-iodoynamides could nevertheless be confirmed by their characteristic C2 alkyne carbon signals upfield of $SiMe_4$ (0 ppm) in ^{13}C NMR due to the combination of electron donation by the nitrogen

[70] For a review, see: Slocum, D. W.; Shelton, P.; Moran, K. M. *Synthesis* **2005**, *20*, 3477–3498.

atom and diamagnetic shielding by the iodine atom (the so-called "heavy atom effect").[71] To our knowledge, **216** and **217** are the first examples of 2-iodoynamides successfully synthesized.

Table 4. Iodination of *N*-Tosyl Ynamides



210,214 **216,217**

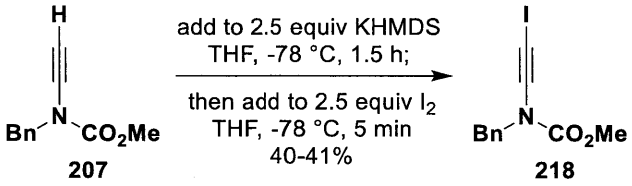
entry	R	iodination conditions	product	yield(%)[a]
1	Me	1 equiv I_2, -78 °C to rt, 2 h	**216**	58
2	Bn	1.05 equiv $I(CH_2)_2I$, rt, 48 h	**217**	60

[a] Isolated yields of products purified by column chromatography.

Iodination of carbamate-based ynamide **207** was much more challenging due to the presence of a carbonyl group susceptible to nucleophilic attack. Thus, KHMDS rather than *n*-BuLi was chosen as the base for the deprotonation step. When **207** was treated sequentially with stoichiometric KHMDS and I_2 in THF, however, only polymeric materials were observed and none of the desired 2-iodoynamide product was formed. The likely explanation is that the carbonyl group in the starting ynamide is also susceptible to nucleophilic attack by the acetylide generated during the deprotonation step. Addition of I_2 before KHMDS did not work either, because the reaction of KHMDS with I_2 appears to be much faster than its reaction with ynamide **207**.

These problems were circumvented by a double inverse addition procedure. First, ynamide **207** was added to excess (2.5 equiv) KHMDS to minimize the concentration of unreacted ynamide in the reaction mixture. Then the resulting solution was added to a solution of I_2 to furnish the desired 2-iodoynamide **218** as a new compound. The second inverse addition ensures low concentration of the acetylide which can potentially attack the 2-iodoynamide product which has already formed. As shown in eq 16, 2-iodoynamide **218** was synthesized in modest but reproducible yield using this protocol.

[71] Iodoynamides **216** and **217** show a ^{13}C signal at -14.5 and -12.5 ppm, respectively. For full spectral data, see Experimental Procedures.



(16)

Iodoynamides **216-218** are all colorless to yellow crystalline solids that are reasonably stable. They can be handled in air and no decomposition was observed on storage as dichloromethane solutions at -20 °C over several months to a year. While sensitive to acid, they can be purified by column chromatography on triethylamine-deactivated silica gel.

[2 + 2] Cycloaddition of 2-Iodoynamides with Ketene

Before investigating the utility of 2-iodoynamindes in the benzannulation, it was imperative that we study the reactivity of this new type of ynamides in [2 + 2] cycloadditions with ketenes. Treatment of these 2-iodoynamides with ketene (the parent compound, $H_2C{=}C{=}O$) would provide the most convenient assessment of their reactivity in [2 + 2] cycloadditions without complications from competing processes that might take place if ketenes substituted with extra functional groups were used.

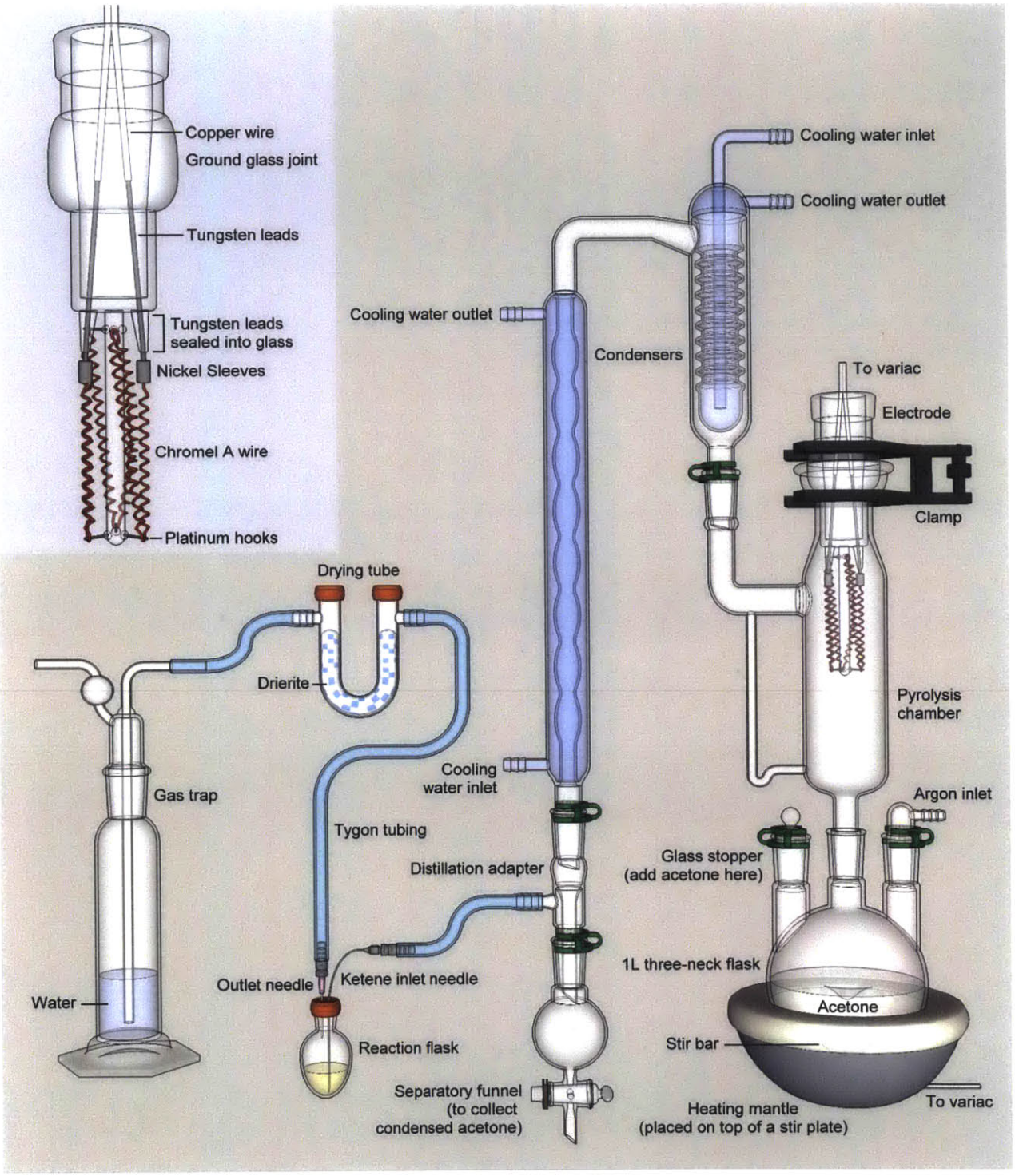
Ketene was conveniently generated by pyrolysis of acetone vapor at ca. 700–800 °C in the absence of air in a Hurd "ketene lamp"[72] (Figure 1) and bubbled into a 0.05–0.1 M solution of the ynamide in THF. As shown in Table 5, all three 2-iodoynamides afforded the expected cyclobutenone products in high yield as a single regioisomer. These reactions represent the first known examples of [2 + 2] cycloadditions of alkynyl halides with ketene. In contrast, reactions of 1-iodo-1-octyne (**222**) and 1-ethoxy-2-iodoacetylene (**223**)[73] with ketene were unsuccessful. Iodooctyne was completely unreactive and could be recovered in 78% yield after treatment with ketene for 39 h. Alkynyl ether **223** was gradually consumed over 3 h but a complex mixture resulted. The markedly higher reactivity of 2-iodoynamides relative to iodooctyne is attributed to activation of the alkyne by the electron-donating nitrogen substituents. The failure of alkynyl ether **223** to yield cyclobutenone is attributed to the instability of the alkyne.

---

[72] (a) Williams, J. W.; Hurd, C. D. *J. Org. Chem.* **1940**, *5*, 122–125. (b) Hanford, W. E.; Sauer, J. C. In *Organic Reactions*; Adams, R., Ed.; Wiley: New York, 1946, Vol 3, pp 108–140.

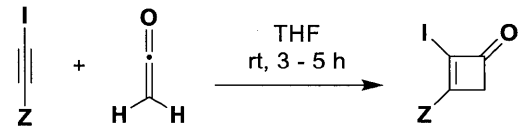
[73] Synthesized by treatment of ethoxyacetylene with *n*-BuLi followed by I_2. See: Verboom, W.; Westmijze, H.; Bos, H. J. T.; Vermeer, P. *Tetrahedron Lett.* **1978**, *19*, 1441–1442.

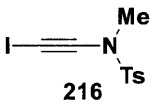
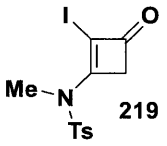
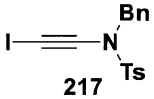
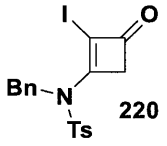
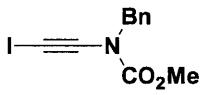
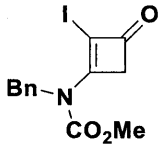
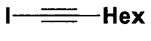
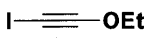
Figure 1. Ketene Lamp Setup



The regiochemistry of cycloadduct **219** was determined using a heteronuclear multiple bond correlation (HMBC) experiment. Strong *J*-coupling was observed between the alkene carbon bearing the nitrogen substituent and the C4 methylene protons. Strong coupling was also observed between the C1 carbonyl carbon and these protons. Only weak coupling of the alkene carbon bearing iodine to the methylene protons was noted. The observations confirmed the structure of **219** as shown in Table 5, which was expected as a result of the highly polarized nature of the reactive π bonds of the 2-iodoynamides and ketene.

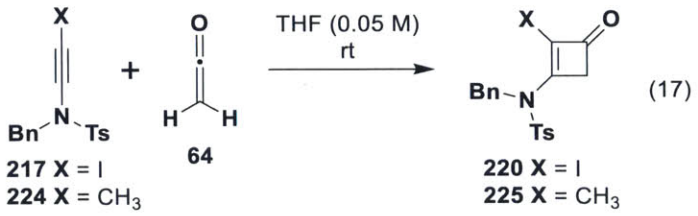
Table 5. [2 + 2] Cycloadditions of Iodoalkynes with Ketene



entry	alkyne	cycloadduct	yield(%)[a]
1	 **216**	 **219**	86-95
2	 **217**	 **220**	81
3	 **218**	 **221**	99
4	 **222**		0[b]
5	 **223**		0

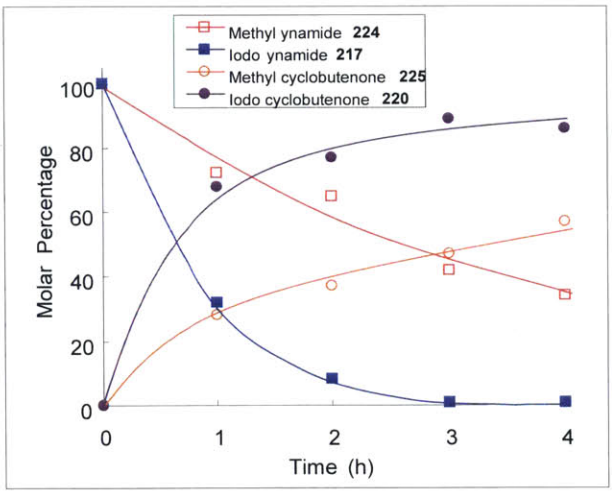
[a] Isolated yields of products purified by column chromatography.
[b] Reaction was run for 39 h. Unreacted iodooctyne was isolated in 78% yield after column chromatography.

As shown in eq 17, a comparison of the rate of the reactions of 2-iodoynamide **217** and propynyl ynamide **224**[74] with ketene was also carried out as separate parallel reactions using the same ketene source. Interestingly, 2-iodoynamide **217** was found to react much faster than propynyl ynamide **224** (Figure 2). While more than half of **217** was consumed within 1 h, the reaction of **224** required ca. 3 h to reach 50% conversion.



(17)

Figure 2. Comparison of Rate of [2+2] Cycloaddition of Ketene with 217 and 224

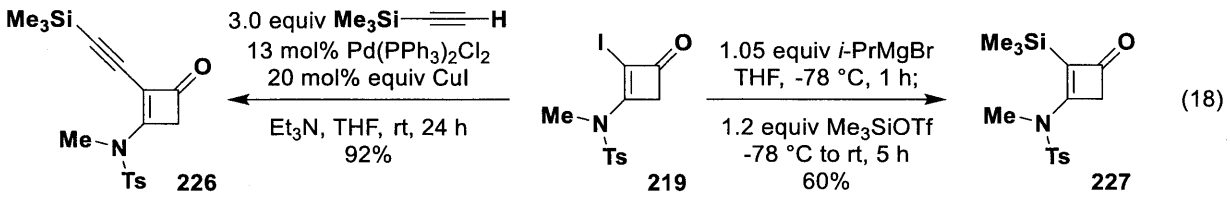


Synthetic Utility of 2-Iodocyclobutenones

The 2-iodocyclobutenone products are potentially useful synthetic intermediates. As shown in eq 18, Sonogashira coupling of cyclobutenone **219** with trimethylsilyl acetylene afforded the expected 2-alkynylcyclobutenone **226** in excellent yield. Halogen-metal exchange with Grignard reagents was found to be highly facile and quenching of the cyclobutenylmagnesium intermediate with trimethylsilyl triflate afforded the expected 2-silylcyclobutenone **227**. This

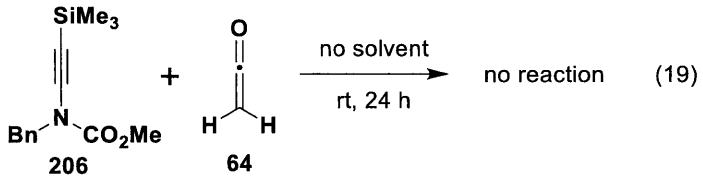
[74] Coste, A.; Karthikeyan, G.; Couty, F.; Evano, G. *Angew. Chem, Int. Ed.* **2009**, *48*, 4381–4385.

latter reaction was found to have a limited scope as weaker electrophiles such as trimethylsilyl chloride and dimethyl disulfide were totally unreactive under the reaction conditions.



(18)

These results are significant because cyclobutenones **226** and **227** cannot be made directly from reactions of the corresponding ynamides with ketene. Diynamides do not react with ketene (*vide supra*, Chapter 1) due to the electron-withdrawing conjugated alkynyl groups present. Silyl ynamides are also unreactive in [2 + 2] cycloadditions with ketene due to steric hindrance. For example, no reaction was observed when ynamide **206** was treated with ketene in the absence of solvent for 24 h (eq 19). While a reaction did occur when **206** was treated with dichloroketene,[75] a complex mixture resulted.



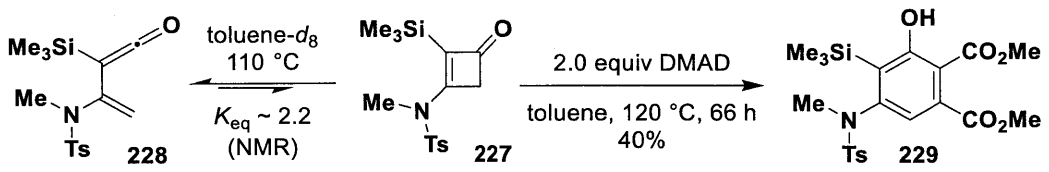
(19)

As shown in eq 20, silyl cyclobutenone **227** undergoes a reversible 4-electron electrocyclic ring opening to afford an equilibrium concentration of vinylketene **228** when refluxed in toluene ($K_{eq} \sim 2.2$ favoring vinylketene **228**). This type of silylketene has been previously demonstrated in our group to behave as a reactive diene in Diels-Alder reactions.[76] Indeed, reaction of **227** with dimethyl acetylenedicarboxylate (DMAD) as the dienophile furnished pentasubstituted phenol **229** in 40% yield as expected from the [4 + 2] reaction between vinylketene **228** and DMAD followed

[75] Generated by dehalogenation of trichloroacetyl chloride with Zn-Cu couple. See: Danheiser, R. L.; Sard, H. *Tetrahedron Lett.* **1983**, *24*, 23–26.

[76] (a) Loebach, J. L.; Bennett, D. M.; Danheiser, R. L. *J. Org. Chem.* **1998**, *63*, 8380–8389. (b) Bennett, D. M.; Okamoto, I.; Danheiser, R. L. *Org. Lett.* **1999**, *1*, 641–644.

by tautomerization. The modest yield is attributed to steric repulsion between the TMS and amino groups preventing the diene moiety from adopting the s-*cis* geometry.



(20)

In conclusion, 2-iodoynamides have been synthesized efficiently in two steps from 2-silyl ynamides. These iodoynamides readily participate in [2 + 2] reactions with ketene to provide 2-iodocyclobutenones in high yield and regioselectivity. The next chapter describes the use of 2-iodoynamides in benzannulation and tandem strategies for the synthesis of highly substituted indoles.

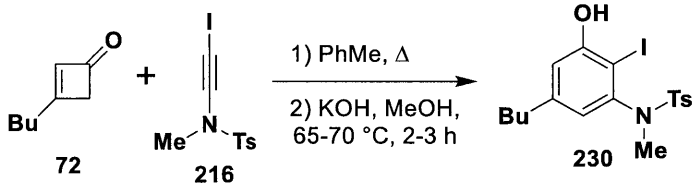
Chapter 3

Synthesis of Highly Substituted Anilines and Indoles via Benzannulation with 2-Iodoynamides

Benzannulation with 2-Iodoynamides

Having demonstrated that 2-iodoynamides react with ketene regioselectively and produce cyclobutenones in high yield, we held high hopes for these ynamides as benzannulation substrates. Initial results with 2-iodoynamide **216** and 3-butylcyclobutenone (**72**)[77] are shown in Table 6. Complete consumption of 2-iodoynamide was observed within 2 h when heated with 1.3 equiv of cyclobutenone in toluene at 80 °C (entry 2). The crude reaction mixture at this point, however, was found based on IR and ^{13}C NMR analysis to consist of mainly phenolic esters presumably formed from reactions of the expected phenol product **230** with ketene intermediates. Thus, a saponification step was carried out before purification of the final product. Interestingly, it was possible to effect the benzannulation at temperatures as low as 55 °C (entry 1) though in this case it took significantly longer for the 2-iodoynamide to be fully consumed. We attribute this observation to the high reactivity of 2-iodoynamides toward the vinylketene generated from the initial reversible 4 electron electrocyclic opening of cyclobutenone **72**. The yield, while modest, could be improved by increasing the amount of cyclobutenone used (entry 3). In all runs a single phenolic product was isolated.

Table 6. Benzannulation with 2-Iodoynamide 216



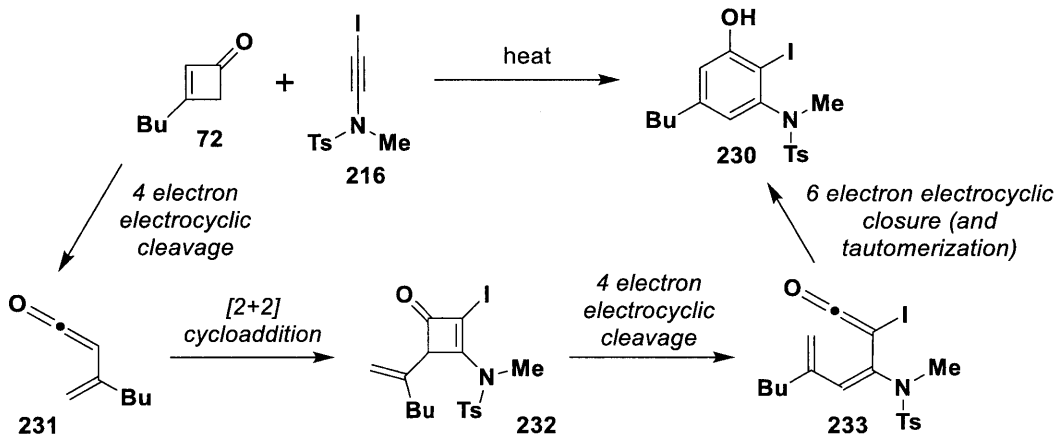
entry	equiv. of **72**	conditions for the first step	yield (%)[a]
1	1.3	55 °C, 23 h	36
2	1.3	80 °C, 2 h	42
3	2.0	80 °C, 2 h	64-72

[a] Isolated yields of products purified by column chromatography.

[77] Danheiser, R. L.; Savariar, S. *Tetrahedron Lett.* **1987**, *28*, 3299–3302.

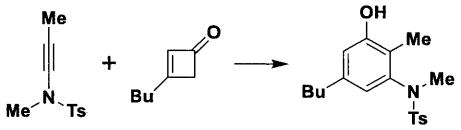
The relatively low yields of the 2-iodoaniline product[78] despite the higher reactivity of 2-iodoynamides in [2 + 2] reactions was worth some investigation. Slow decomposition of 2-iodoynamide **216** with a half-life of 40 h was observed when heated alone at 80 °C in toluene. In addition, the product phenol **230** and 2-iodoynamide **216** were not found to react with each other under these conditions. Thus, the 2-iodoynamide is believed to be consumed primarily by [2 + 2] cycloaddition. No reaction was observed when phenol **230** was heated with cyclobutenone **72** at either 80 °C or 110 °C in toluene overnight. Based on the reasonable assumption that benzannulation involving 2-iodoynamides proceeds via the same pericyclic cascade as previous benzannulations we studied (Scheme 28), this result suggested that the initially formed vinylketene **231** was not the main source of ester formation observed in the benzannulation. Based on the above observations, the lowered yield is attributed to the instability of the iodoketene intermediate **233** and the significant formation of esters is likely due to the high reactivity of ketene **233** toward nucleophiles.

Scheme 28



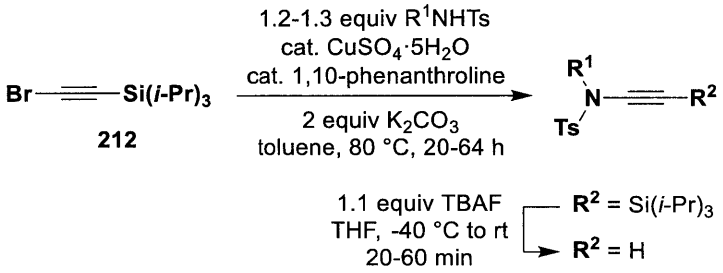
Encouraged by the positive results of the benzannulation based on 2-iodoynamide **216**, we next synthesized 2-iodoynamides bearing different groups on the nitrogen that are either easily cleaved (e.g., PMB) or would be useful in several indole-forming reactions (*vide infra*). As shown

[78] Compared to 81% yield of a similar phenolic product from benzannulation of propynyl ynamide **215** with 1.2 equiv of 3-butylcyclobutenone under similar conditions (see ref 2):



in Table 7, the terminal ynamides were prepared via the *N*-alkynylation protocol of Hsung followed by deprotection with TBAF. Both steps afforded the desired ynamide products in good to excellent yield.

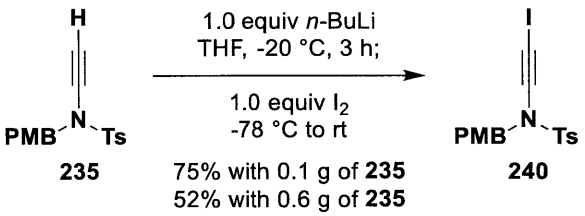
Table 7. Synthesis of Terminal Ynamides from Sulfonamides



entry	R^1	silyl ynamide	yield (%)[a]	terminal ynamide	yield (%)[a]
1	PMB[b]	**234**	87-90	**235**	93-96
2	allyl	**236**	90-93	**237**	87-91
3	2-furfuryl	**238**	61-64[c]	**239**	94-98

[a] Isolated yield of products purified by column chromatography. [b] PMB = 4-methoxybenzyl. [c] Reaction performed in toluene-DMF.

Iodination of ynamide **235** under our previously established conditions afforded 2-iodoynamide **240** after column chromatography on triethylamine-deactivated silica gel (eq 21). However, the yield was not reproducible and dropped significantly when the reaction was scaled up. In a separate run of the same reaction, the crude product was isolated in nearly quantitative yield and found to possess high (~95%) purity by ^{1}H NMR analysis. These results suggested that significant losses were occurring during column chromatography.

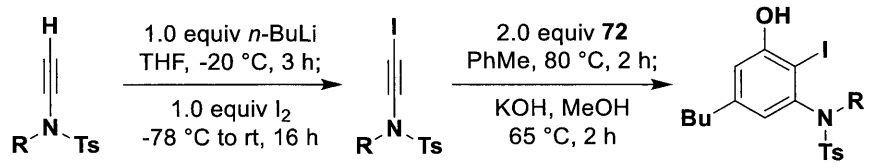


(21)

Due to complications associated with the purification of 2-iodoynamides, we decided to employ the ynamides in the benzannulation step without prior purification. As shown in Table 8,

heating the crude 2-iodoynamides with 2 equiv of 3-butylcyclobutenone (**72**) at 80 °C for 2 h (at which point TLC analysis showed that all of the ynamide had been consumed) followed by saponification of phenolic esters with KOH in methanol afforded the expected 2-iodoaniline products in moderate to good overall yield. In the case of furfuryl ynamide **239**, KHMDS was used instead of *n*-BuLi to avoid possible metalation of the furan ring.

Table 8. Iodination and Benzannulation of Terminal Ynamides



entry	R	ynamide	aniline	yield (%)[a]
1	PMB	**235**	**241**	59-77
2	allyl	**237**	**242**	41-49
3[b]	2-furfuryl	**239**	**243**	49

[a] Overall isolated yield of products purified by column chromatography.
[b] KHMDS was used in place of *n*-BuLi in the first step.

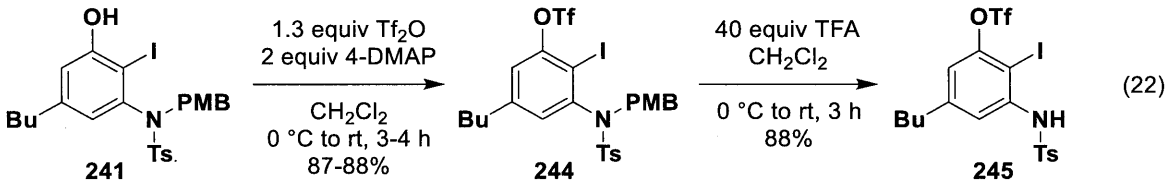
Synthesis of Indoles via Palladium Catalysis

With 2-iodoanilines in hand, we next investigated various methods for indole synthesis using these anilines as the substrates. Transition metal catalysis has proved to be one of the most powerful means of indole synthesis in recent years.[79] Discovered in 1991, the Larock indole synthesis provides an extremely useful way of construction of 2,3-disubstituted indoles.[80] This method is based on a palladium-catalyzed heteroannulation involving 2-haloanilines and internal alkynes. While the substitution patterns on the five-membered ring can be easily controlled by the choice of the alkyne partner, the synthesis of highly substituted haloaniline partners is generally

[79] For reviews on the synthesis of indoles via transition-metal mediated reactions, see (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873–2920. (b) Li, J. J.; Gribble, G. W. *Top. Heterocycl. Chem.* **2010**, *26*, 193–234. (c) Song, J. J.; Reeves, J. T.; Fandrick, D. R.; Tan, Z.; Yee, N. K.; Senanayake, C. H. *ARKIVOC (Gainesville, FL, U.S.A.)* **2010**, *1*, 390–449. (d) Platon, M.; Amardeil, R.; Djakovitch, L.; Hierso, J.-C. *Chem. Soc. Rev.* **2012**, *41*, 3929–3968. (e) Majumdar, K. C.; Samanta, S.; Sinha, B. *Synthesis* **2012**, *44*, 817–847.
[80] (a) Larock, R. C.; Yum. E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689–6690. (b) Larock, R. C.; Yum. E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652–7662. (c) Chen, Y.; Markina, N. A.; Yao, T.; Larock, R. C. *Org. Synth.* **2011**, *88*, 377–387.

challenging. The iodoynamide-based benzannulation proved to be an efficient means to access substituted 2-iodoanilines as substrates for the Larock reaction.

To avoid possible complications resulting from competing heteroannulation with the phenolic oxygen,[81] phenol **241** was first protected as a triflate. This would also provide a functional handle to further elaborate the indole product if desired. The PMB group was next cleaved to reveal the nucleophilic amino group (eq 22). Attempted oxidative cleavage with CAN required 4 equiv of the reagent for complete consumption of the starting material, [82] and while the PMB group was cleaved none of the desired product was found. This result is attributed to the highly electron-rich nature of the aromatic ring and the fact that both aromatic carbon atoms *para* to the heteroatoms are unsubstituted. On the other hand, treatment with TFA provided the desired deprotected aniline **245** in high yield.



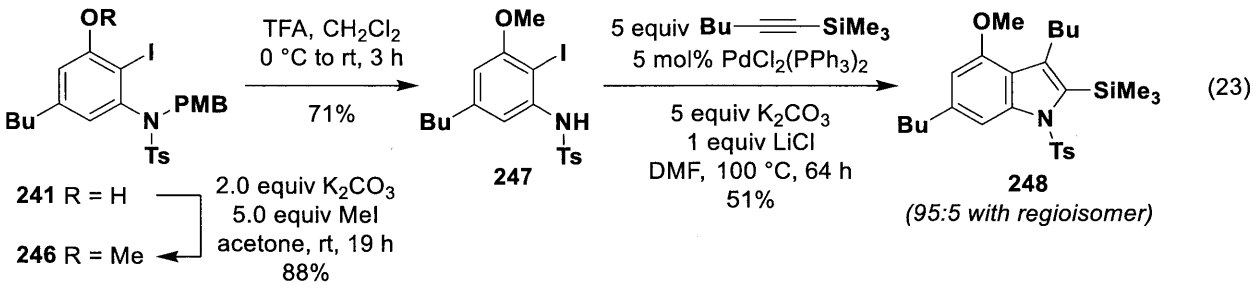
(22)

Unfortunately, all attempts to convert **245** to indole using 1-trimethylsilyl-1-hexyne as the alkyne partner under palladium catalysis resulted in complex mixtures. This failure is attributed to competing coupling reactions with the triflate group at the high temperatures (>100 °C) typically required for Larock heteroannulation. Protecting the phenolic oxygen as silyl ethers was not fruitful either due to the lability of these functional groups to basic conditions. Finally, protection as a robust methyl ether allowed successful synthesis of indole **248** in 51% yield and 95:5 regioselectivity under standard Larock conditions (eq 23).

---

[81] For the formation of benzofurans from 2-iodophenols and alkynes under similar conditions, see Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270–3271.

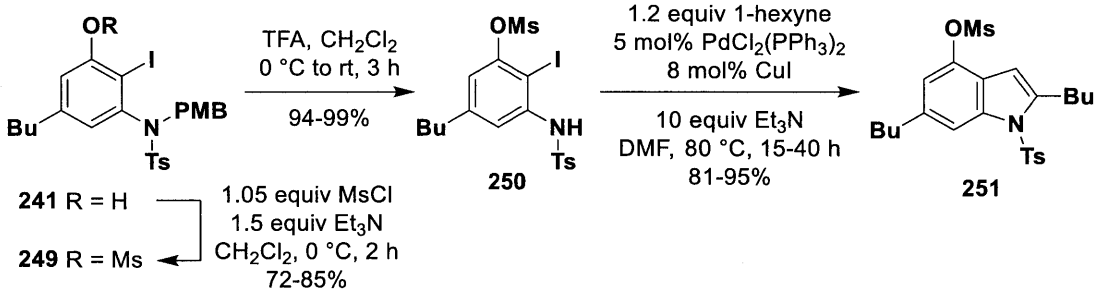
[82] Reaction conditions: 2 equiv CAN, aq MeCN, rt, 6.5 h. As TLC showed incomplete conversion, an extra 2 equiv of CAN was added and the reaction mixture was stirred for an additional 3.5 h.



(23)

The Castro-Stephens reaction and its variants provide convenient access to indoles substituted on C2 but not C3.[83] This palladium-catalyzed process involves initial Sonogashira reaction of a 2-haloaniline with a terminal alkyne. The resulting 2-alkynylaniline can then be cyclized *in situ* or in a separate step to yield a 2-substituted indole. It is worth noting that attempts to synthesize 2-alkynylanilines via direct benzannulation of conjugated diynamides have not been successful due to the diminished reactivity of these ynamides.

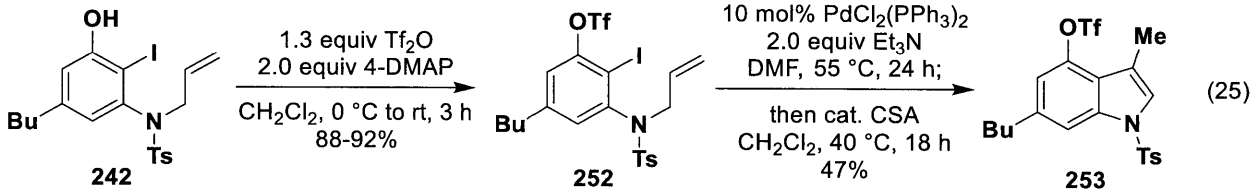
Attempts to employ 2-iodoanilines with the phenolic oxygen protected as a triflate in the Castro-Stephens reaction resulted in over-alkynylation and formation of the desired indoles in poor yield. Consequently, the phenol was instead protected as a mesylate to create enough differential reactivity to allow for selective Sonogashira reactions. The mesylate also provides a potential functional handle for elaboration of the product. As illustrated in eq 24, phenol **241** was converted to a mesylate and the PMB group was cleaved under the previously established conditions. One-pot heteroannulation with 1-hexyne then provided indole **251** in high yield.



(24)

[83] (a) Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313–3315. (b) Castro, C. E.; Gaughan, E. J.; Owsley, D. C. *J. Org. Chem.* **1966**, *31*, 4071–4078. (c) Castro, C. E.; Havlin, R.; Honwad, V. K.; Malte, A.; Moje, S. *J. Am. Chem. Soc.* **1969**, *91*, 6464-6470. (d) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1984**, *22*, 1347–1350. (e) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1986**, *34*, 2362–2368.

Intramolecular Heck reactions provide a powerful method for the synthesis of nitrogen heterocycles. In particular, 2-haloanilines bearing an *N*-allyl group serve as useful substrates for the synthesis of 3-methyl indoles in a method established by Mori and Ban.[84] As this type of cyclization can be performed under mild conditions at low temperatures due to its intramolecular nature, we found it possible to employ the triflate derivative of phenol **242** in the Mori-Ban reaction. Triflation of phenol **242** followed by palladium-catalyzed cyclization under the indicated conditions furnished a mixture of indole **253** and the corresponding 3-methyleneindoline isomer. The latter isomerized to the desired indole on exposure to catalytic camphorsulfonic acid (CSA). The 3-methyl indole **253** was obtained in moderate yield after column chromatography (eq 25).



(25)

Attempts to obtain cross-coupling products from indole mesylate **251** using either phenylboronic acid or triethylborane under either palladium or nickel catalysis[85] have not been fruitful. Heck reaction with ethyl acrylate also failed to give any of the desired product. In all cases little to no reaction was observed when typical conditions were employed and prolonged heating led to slow decomposition of the starting material. We attribute this lack of reactivity to the high electron density of the aromatic system. In an attempt to render cross-coupling reactions possible by reducing the electron density of the indole core, **251** was acetylated with $Ac_2O/AlCl_3$ to obtain the 3-acetyl indole **254** in 76% yield (Scheme 29). However, this indole still failed to participate in Suzuki-Miyaura couplings.

Interestingly, when indole **254** was treated with triethylborane under the indicated conditions in Scheme 29, isopropenyl indole **255** was isolated in 22% yield. Another product **256**

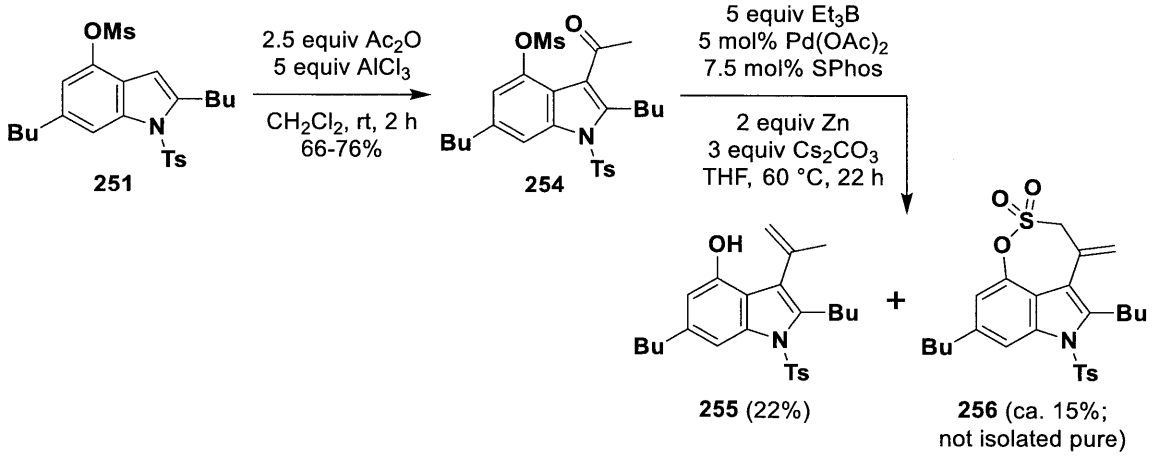
---

[84] (a) Mori, M.; Chiba, K.; Ban, Y. *Tetrahedron Lett.* **1977**, *18*, 1037–1040. (b) Ban, Y.; Wakamatsu, T.; Mori, M. *Heterocycles* **1977**, *6*, 1711–1715. (c) Larock, R. C.; Babu, S. *Tetrahedron Lett.* **1987**, *28*, 5291–5294.

[85] For selected recent Suzuki-Miyaura coupling methods with mesylates, see: (a) Bhayana, B.; Fors, B. P.; Buchwald, S. L. *Org. Lett.* **2009**, *11*, 3954–3957. (b) Xing, C.-H.; Lee, J.-R.; Tang, Z.-Y.; Zheng, J. R.; Hu, Q.-S. *Adv. Synth. Catal.* **2011**, *353*, 2051–2059. (c) Gao, H.; Li, Y.; Zhou, Y.-G.; Han, F.-S.; Lin, Y.-J. *Adv. Synth. Catal.* **2011**, *353*, 309–314. (d) So, C. M.; Lau, C. P.; Kwong, F. Y. *Angew. Chem. Int. Ed.* **2008**, *47*, 8059–8063. (e) Molander, G. A.; Beaumard, F. *Org. Lett.* **2010**, *12*, 4022–4025.

was also isolated in ca. 15% yield in an impure state. The inclusion of metallic zinc was found unnecessary for the success of this reaction, which likely proceeded via deprotonation of the mesyl group and intramolecular addition of the carbanion to the carbonyl group followed by elimination of water to form **256**. Oxidative addition of palladium into the C–S bond followed by protodemetallation and subsequent hydrolysis of the resulting sulfinate then furnished the main product **255**.

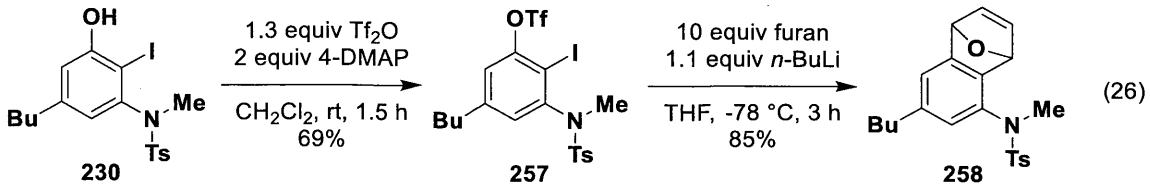
Scheme 29



Synthesis of Indoles via Aryne Cycloaddition

Another strategy to synthesize indoles via benzannulation of 2-iodoynamides that we examined employs the *ortho* relationship of the iodo and hydroxyl groups in the benzannulation products. In our plan, the triflate derivatives of these phenols would produce arynes via elimination[86] and heterocyclization would occur with appropriate reactive functional groups tethered to the nitrogen atom. To test the feasibility of this aryne cyclization strategy, benzannulation product **230** was converted to a triflate and treated with *n*-BuLi in THF in the presence of excess furan (eq 26). The expected [4 + 2] product **258** was isolated in good yield suggesting efficient formation and trapping of the aryne.

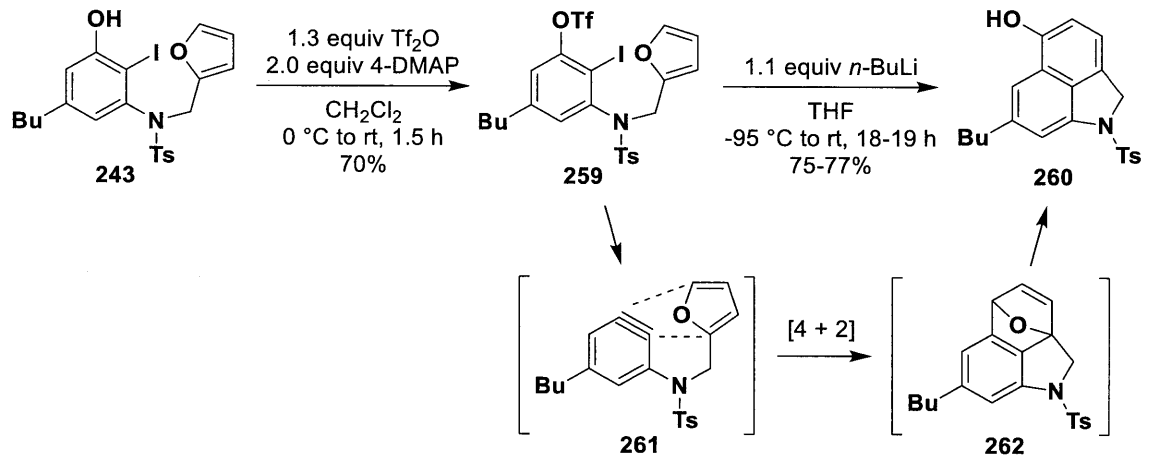
[86] Matsumoto, T.; Hosoya, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1991**, *32*, 6735–6736.



(26)

Next, the *N*-furfuryl benzannulation product **243** was subjected to the same reaction sequence. After conversion to a triflate, treatment with *n*-BuLi in THF furnished naphthol **260** as the product after purification (Scheme 30). The latter reaction was found to proceed in higher yield and give a cleaner product when conducted at -95 °C instead of -78 °C. Presumably, naphthol **260** forms via initial [4 + 2] cycloaddition of aryne **261** followed by ring opening of the highly strained bridged ring intermediate **262** under the reaction or workup conditions.

Scheme 30

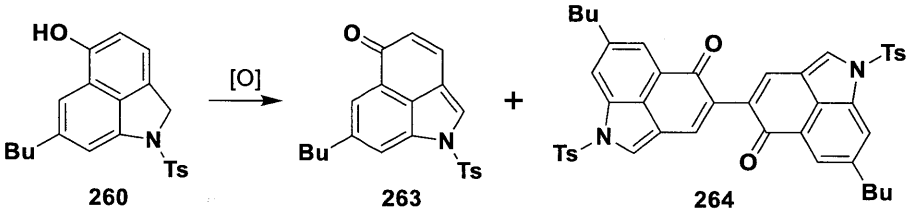


Naphthol **260** is prone to oxidation. As shown in Table 9, treatment of **260** with either CAN, DDQ, or $PhI(OAc)_2$ as the oxidant readily converted the phenol into benz[*cd*]indolone **263** in moderate to good yield.[87] Interestingly, dimer **264** was isolated in 14% yield as a bright yellow solid when $PhI(OAc)_2$ was used as the oxidant presumably via oxidative coupling. The

[87] For some previous synthetic approaches to benz[*cd*]indolones, see (a) Grob, C. A.; Voltz, J. *Helv. Chim. Acta* **1950**, *33*, 1796–1806. (b) Grob, C. A.; Schmid, Hj. U. *Helv. Chim. Acta* **1950**, *33*, 1955–1959. (c) Uhle, F. C.; Robinson, S. H. *J. Am. Chem. Soc.* **1955**, *77*, 3544–3546. (d) Kornfeld, E. C.; Fornefeld, E. J.; Kline, G. B.; Mann, M. J.; Morrison, D. E.; Jones, R. G.; Woodward, R. B. *J. Am. Chem. Soc.* **1956**, *78*, 3087–3114. (e) Neidlein, R.; Moller, F. *Liebigs Ann. Chem.* **1980**, *6*, 971–979. (f) Benzies, D. W. M.; Fresneda, P. M.; Jones, R. A.; McNab, H. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1651–1654.

benz[*cd*]indolone product **263** incorporates the tricyclic system reminiscent to ergoline alkaloids and the above-mentioned benzannulation-aryne cyclization strategy suggests the potential utility of this chemistry for the synthesis of natural products and pharmaceutical agents.

Table 9. Oxidation of Naphthol 260



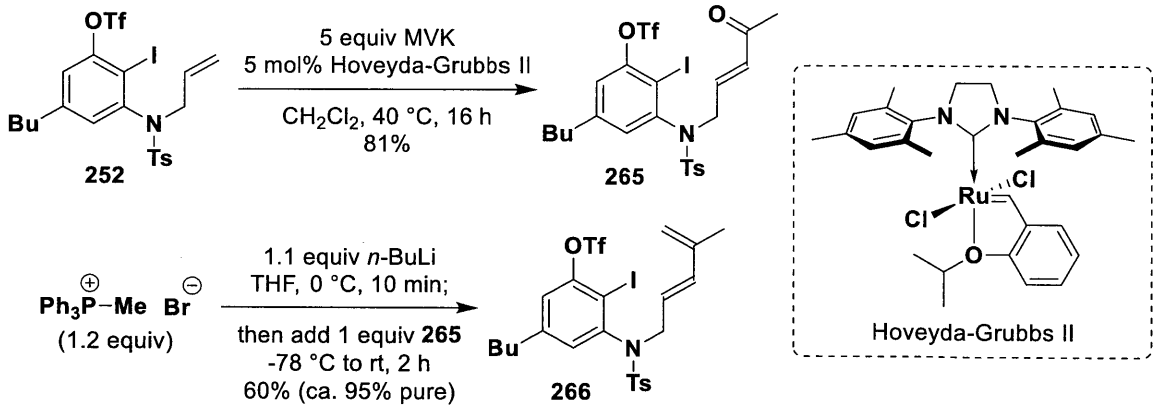
260 263 264

entry	conditions	yield of **263** (%)[a]	yield of **264** (%)[a]
1	2.2 equiv CAN, aq. MeCN, rt, 15 min	64	-
2	1 equiv DDQ, PhMe, rt, 20 h	71	-
3	1 equiv $PhI(OAc)_2$, CH_2Cl_2, 0 °C, 1 h	65	14

[a] Isolated yields of products purified by column chromatography.

An aryne precursor bearing a pentadienyl side chain on the nitrogen was also synthesized from the triflate derivative (**252**) of the *N*-allyl benzannulation product. As outlined in Scheme 31, cross metathesis with methyl vinyl ketone was found to give optimal results by using the "second generation" Hoveyda-Grubbs' catalyst[88] in refluxing dichloromethane. Wittig reaction with $Ph_3P{=}CH_2$ then furnished compound **266** ready for aryne cyclization.

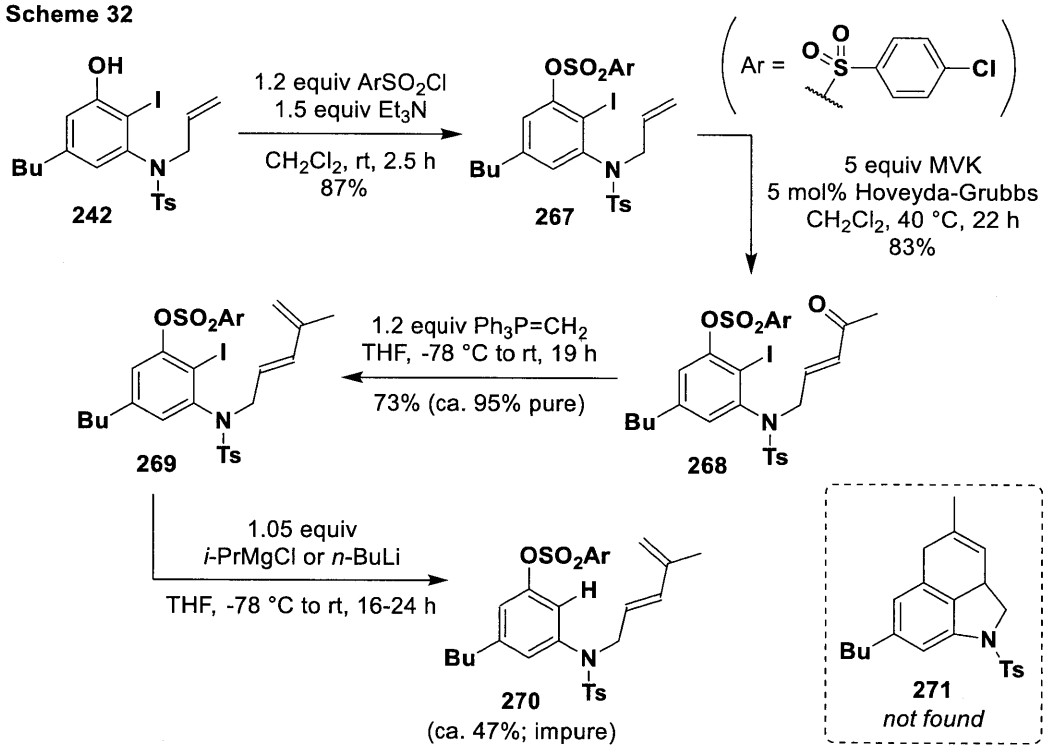
Scheme 31



[88] (a) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973–9976. (b) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

To our dismay, treatment of diene **266** with either *n*-BuLi or *i*-PrMgCl under high dilution conditions (0.005 M) at -78 °C resulted in an unidentifiable complex mixture. Based on Knochel's work, the leaving group ability of the sulfonate group plays an important role in the rate of aryne generation and yield of [4 + 2] cycloaddition products.[89] When *i*-PrMgCl was used for halogen-metal exchange and furan as the aryne trap, Knochel found that 4-chlorobenzenesulfonates gave the best results in terms of reaction time and isolated yield. However, these results did not translate well to our case. When compound **269**, synthesized from *N*-allyl aniline **242**, was treated with either *i*-PrMgCl or *n*-BuLi, a complex mixture still resulted. The only isolable product was deiodinated aniline **270** and no desired aryne Diels-Alder product **271** was found (Scheme 32).

Scheme 32



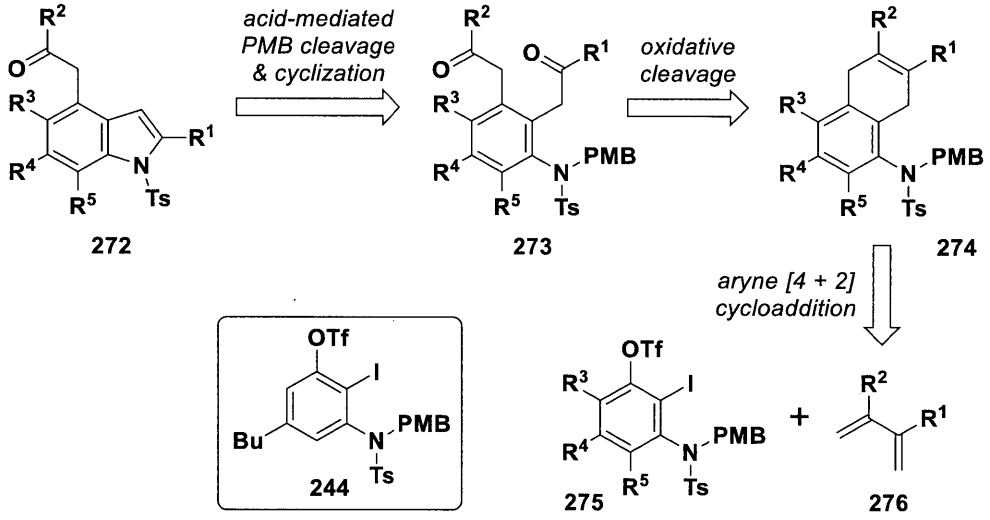
The failure of this cyclization is attributed to competing processes including possible ene reactions and metalation on the alkenyl side chain. The high reactivity and instability of the aryne intermediate and the conformational flexibility of the pentadienyl side chain may have encouraged

[89] Sapountzis, I.; Lin, W.; Fischer, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 4364–4366.

these unwanted reactions and examples of successful aryne [4 + 2] cycloadditions with acyclic dienes are scarce in the literature.[90]

An alternative route to indole involving aryne [4 + 2] cycloaddition would be via the Plieninger indole synthesis.[45] In this approach, the double bond in the cycloaddition product would be oxidatively cleaved and the resulting aldehyde or ketone then treated with acid to induce cyclization onto the nucleophilic aniline nitrogen. As outlined in Scheme 33, triflate **244** was considered ideal for this benzannulation-Plieninger strategy. Should the desired aryne [4 + 2] cycloaddition proceed as desired, the cycloadduct **274** could be oxidatively cleaved and treatment of the resulting carbonyl compound **273** with strong acid would ideally induce both cleavage of the PMB group and cyclization to indole **272** in one operation.

Scheme 33

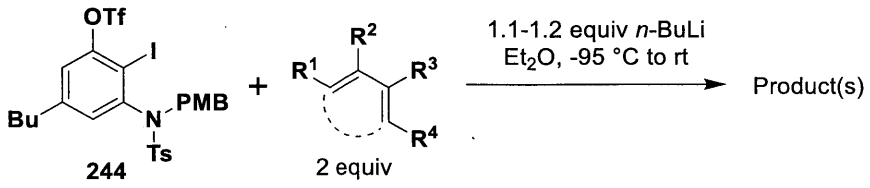


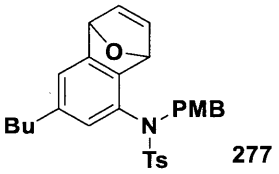
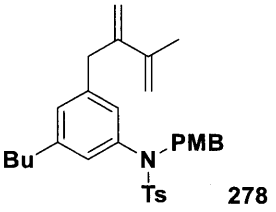
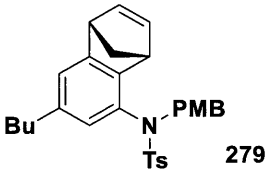
Results of aryne reactions with various dienes are listed in Table 10. While furan gave the cycloadduct **277** in quantitative yield, reaction with 2,3-dimethylbuta-1,3-diene furnished a complex mixture from which the ene reaction product **278** was isolated in low yield and purity (entry 2). Reaction with 1,3-cyclohexadiene was also unsuccessful, giving an unidentifiable

[90] (a) Hayes, M. E.; Shinokubo, H.; Danheiser, R. L. *Org. Lett.* **2005**, *7*, 3917–3920. (b) Buszek, K. R. *Tetrahedron Lett.* **1995**, *36*, 9125–9128.

complex mixture.[91] Finally, reaction with freshly prepared cyclopentadiene under modified conditions[92] afforded the expected Diels-Alder cycloadduct **279** in excellent yield.

Table 10. Intermolecular Aryne Cycloadditions from Aniline 244



entry	diene	product	yield (%)[a]
1		 **277**	99
2		 **278**	24[b]
3		complex mixture	n/a
4[c]		 **279**	91-93

[a] Isolated yields of products purified by column chromatography. [b] ca. 85% pure by ^{1}H NMR. [c] Reaction performed with 10 equiv of cyclopentadiene in toluene at -78 °C.

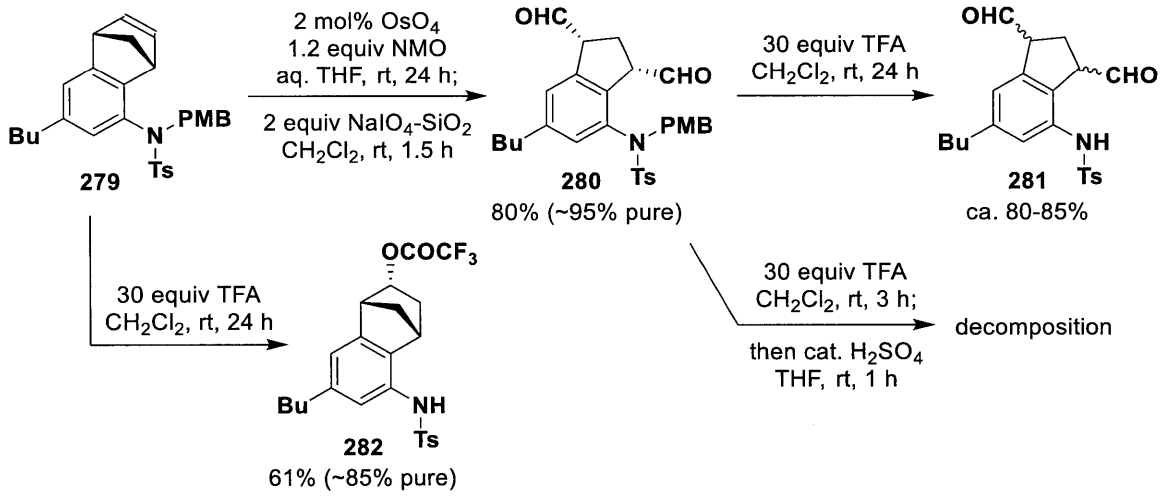
Attempts to oxidatively cleave furan cycloadduct **277** have been met with failure. On the other hand, cycloadduct **279** proved slightly more promising in this strategy. As outlined in

[91] Reaction of benzyne with 1,3-cyclohexadiene results in a mixture of [4 + 2], [2 + 2], and ene reaction products. See: Braun, A. M. *J. Org. Chem.* **1970**, *35*, 1208–1210.

[92] Butyllithium deprotonates cyclopentadiene in Et_2O rendering it unreactive in Diels-Alder reactions. This deprotonation can be suppressed by conducting the reaction in toluene. See: Coe, J. W.; Wirtz, M. C.; Bashore, C. G.; Candler, J. *Org. Lett.* **2004**, *6*, 1589–1592.

Scheme 34, **279** was efficiently dihydroxylated and oxidatively cleaved by the action of OsO_4-NMO followed by $NaIO_4$ supported on silica gel.[43] Dialdehyde **280** was isolated in 80% yield and 95% purity after column chromatography. However, treatment of **280** with TFA only led to cleavage of the PMB moiety and epimerization of the two formyl groups and no indole products were found. Treatment of **280** with TFA followed by catalytic sulfuric acid in THF only led to decomposition. Attempts to remove the PMB group before oxidative cleavage of the alkene were also unsuccessful as exposure of **279** to TFA led not only to cleavage of the PMB group but also nucleophilic addition of the alkene π bond to TFA.

Scheme 34



The failure of this cyclization is attributed to the significant ring strain of the resulting cyclopenta[*cd*]indole system. Overall, this benzannulation-aryne cycloaddition-Plieninger strategy seems impractical for the synthesis of substituted indoles due primarily to the limited scope in aryne cycloaddition reactions.

Summary

We have synthesized 2-iodoynamides and demonstrated their regioselective [2 + 2] cycloaddition with ketene to form cyclobutenones. In addition, 2-iodoynamides were also found to participate in our benzannulation with cyclobutenones. This 2-iodoynamide-based benzannulation proved highly useful for the synthesis of substituted anilines. Coupled with aryne [4 + 2] cycloadditions or palladium-catalyzed coupling reactions, indoles with different

substitution patterns on the five-membered ring can also be constructed efficiently from these benzannulation products. The next chapter describes a total synthesis of a tetracyclic unnatural product, furo[2,3-*g*]thieno[2,3-*e*]indole, using a benzannulation-based strategy.

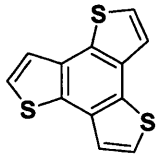
Part II

Synthesis of Furo[2,3-*g*]thieno[2,3-*e*]indole via a Benzannulation Strategy

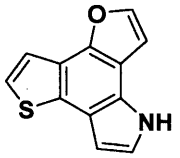
Chapter 1
Introduction and Background

Conjugated organic molecules have been the subject of great interest as the primary materials in the field of organic electronics. Compared to traditional inorganic electronic materials, organic electronic materials have electronic properties that can be fine-tuned by variations of molecular structures and functional groups. The vast majority of organic electronic materials involve polycyclic aromatic compounds either as individual small molecules or as repeating units within polymer frameworks with conductivity due to extensive π electron conjugation.

Polycyclic aromatic compounds with a central benzenoid core have been the subject of significant attention due to their discotic nature which facilitates molecular packing, ease of functionalization into star-shaped polymers, and improved conjugation between the core and side chains.[93] For example, benzotrithiophene (**283**), first synthesized in 1972,[94] and its derivatives have been the subject of significant research for applications in photovoltaic cells,[95] supramolecular networks with fullerene,[96] liquid crystals,[97] and field-effect transistors.[98]



283



284

We became interested in the synthesis of furo[2,3-*g*]thieno[2,3-*e*]indole (FTI, **284**) which we anticipate might possess interesting electronic properties. A survey of literature on similar tetracyclic compounds reveals that in addition to benzotrithiophenes, benzotrifurans,[99] benzotriselenophenes,[100] and dithienoindoles[101] have been made previously. In addition, tricycles with two different heterocycles fused to the central benzenoid ring have been shown to possess

---

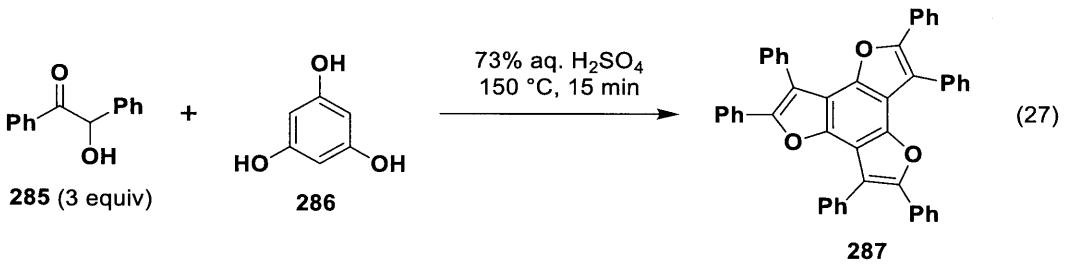
[93] Nicolas, Y.; Blanchard, P.; Levillain, E.; Allain, M.; Mercier, N.; Roncali, J. *Org. Lett.* **2004**, *6*, 273–276.
[94] Proetzsch, R.; Bieniek, D.; Korte, F. *Tetrahedron Lett.* **1972**, *13*, 543–544.
[95] Bettignies, R. d.; Nicolas, Y.; Blanchard, P.; Levillain, E.; Nunzi, J.-M.; Roncali, J. *Adv. Mater.* **2003**, *15*, 1939–1943.
[96] Piot, L.; Silly, F.; Tortech, L.; Nicolas, Y.; Blanchard, P.; Roncali, J.; Fichou, D. *J. Am. Chem. Soc.* **2009**, *131*, 12864–12865.
[97] Demenev, A.; Eichhorn, S. H.; Taerum, T.; Perepichka, D. F.; Patwardhan, S.; Grozema, F. C.; Siebbeles, L. D. A.; Klenkler, R. *Chem. Mater.* **2010**, *22*, 1420–1428.
[98] Kashiki, T.; Kohara, M.; Osaka, I.; Miyazaki, E.; Takimiya, K. *J. Org. Chem.* **2011**, *76*, 4061–4070.
[99] For the first synthesis of benzotrifuran derivatives, see: Japp, F. R.; Meldrum, A. N. *J. Chem. Soc., Trans.* **1899**, *75*, 1035–1043.
[100] For the first synthesis of benzotriselenophene, see: Kashiki, T.; Shinamura, S.; Kohara, M.; Miyazaki, E.; Takimiya, K.; Ikeda, M.; Kuwabara, H. *Org. Lett.* **2009**, *11*, 2473–2475.
[101] Perrine, D. M.; Kagan, J.; Huang, D.-B.; Zeng, K.; Teo, B.-K. *J. Org. Chem.* **1987**, *52*, 2213–2216.

biological activities and have been investigated for pharmaceutical applications.[102] However, the successful synthesis of a tetracycle with three different heterocycles joined by a central benzenoid ring has not been reported to date. We envisioned that **284** would be an interesting polycyclic aromatic compound in terms of its properties and would also provide an opportunity for the comparison of the chemical and electronic properties of furan, pyrrole, and thiophene systems.

Syntheses of Related Tetracyclic Aromatic Systems

Two general strategies have been used in the synthesis of tetracycles related to **284**. One approach starts from 1,3,5-triheterosubstituted benzenes and employs functionalization and cyclization reactions to conveniently afford the desired tetracycles.

Japp and Meldrum reported the first synthesis of benzotrifuran **287** via condensation of phloroglucinol and benzoin in one step with no yield reported (eq 27).[99] Benzotrifuran **289** was synthesized by Chen and coworkers via a reaction between phloroglucinol and nitroallylic acetate **288** (eq 28).[103] Another benzotrifuran (**292**) was synthesized via lactonization and *O*-acylation[104] of the known phloroglucinol derivative **290** which was prepared in four steps from phloroglucinol trimethyl ether (eq 29).[105]



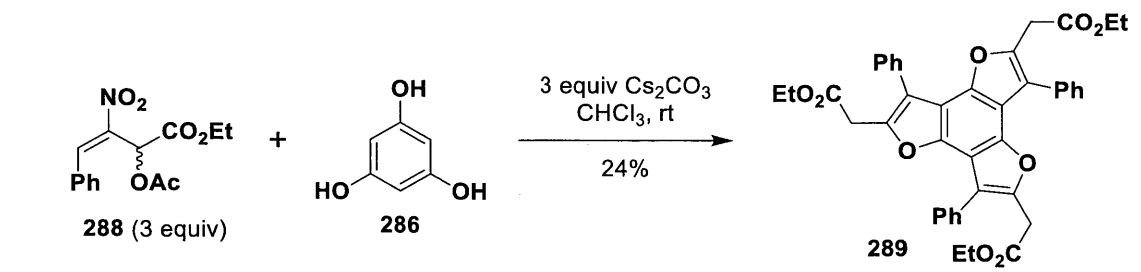
(27)

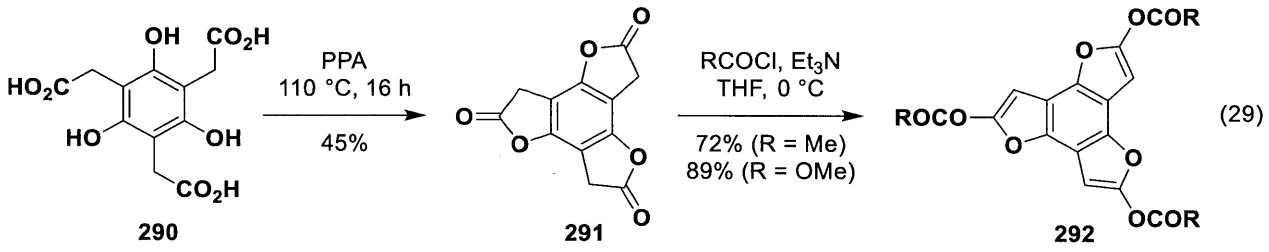
[102] (a) Abreu, A. S.; Silva, N. O.; Ferreira, P. M. T.; Queiroz, M.-J. R. P.; Venanzi, M. *Eur. J. Org. Chem.* **2003**, 4792–4796. (b) Abreu, A. S.; Silva, N. O.; Ferreira, P. M. T.; Queiroz, M.-J. R. P. *Tetrahedron Lett.* **2003**, *44*, 3377–3379. (c) Venkatraman, S.; Velazquez, F.; Gavalas, S.; Wu, W.; Chen, K. X.; Nair, A. G.; Bennett, F.; Huang, Y.; Pinto, P.; Jiang, Y.; Selyutin, O.; Vibulbhan, B.; Zeng, Q.; Lesburg, C.; Duca, J.; Huang, H.-C.; Agrawal, S.; Jiang, C.-K.; Ferrari, E.; Li, C.; Kozlowski, J.; Rosenblum, S.; Shih, N.-Y.; Njoroge, F. G. *Bioorg. Med. Chem.* **2013**, *21*, 2007–2017.

[103] Anwar, S.; Huang, W.-Y.; Chen, C.-H.; Cheng, Y.-S.; Chen, K. *Chem. Eur. J.* **2013**, *19*, 4344–4351.

[104] Li, Y.; Lampkins, A. J.; Baker, M. B.; Sumpter, B. G.; Huang, J.; Abboud, K. A.; Castellano, R. K. *Org. Lett.* **2009**, *11*, 4314–4317.

[105] (a) Li, H.; Homan, E. A.; Lampkins, A. J.; Chiviriga, I.; Castellano, R. K. *Org. Lett.* **2005**, *7*, 443–446. (b) Lampkins, A. J.; Abdul-Rahim, O.; Li, H.; Castellano, R. K. *Org. Lett.* **2005**, *7*, 4471–4474.

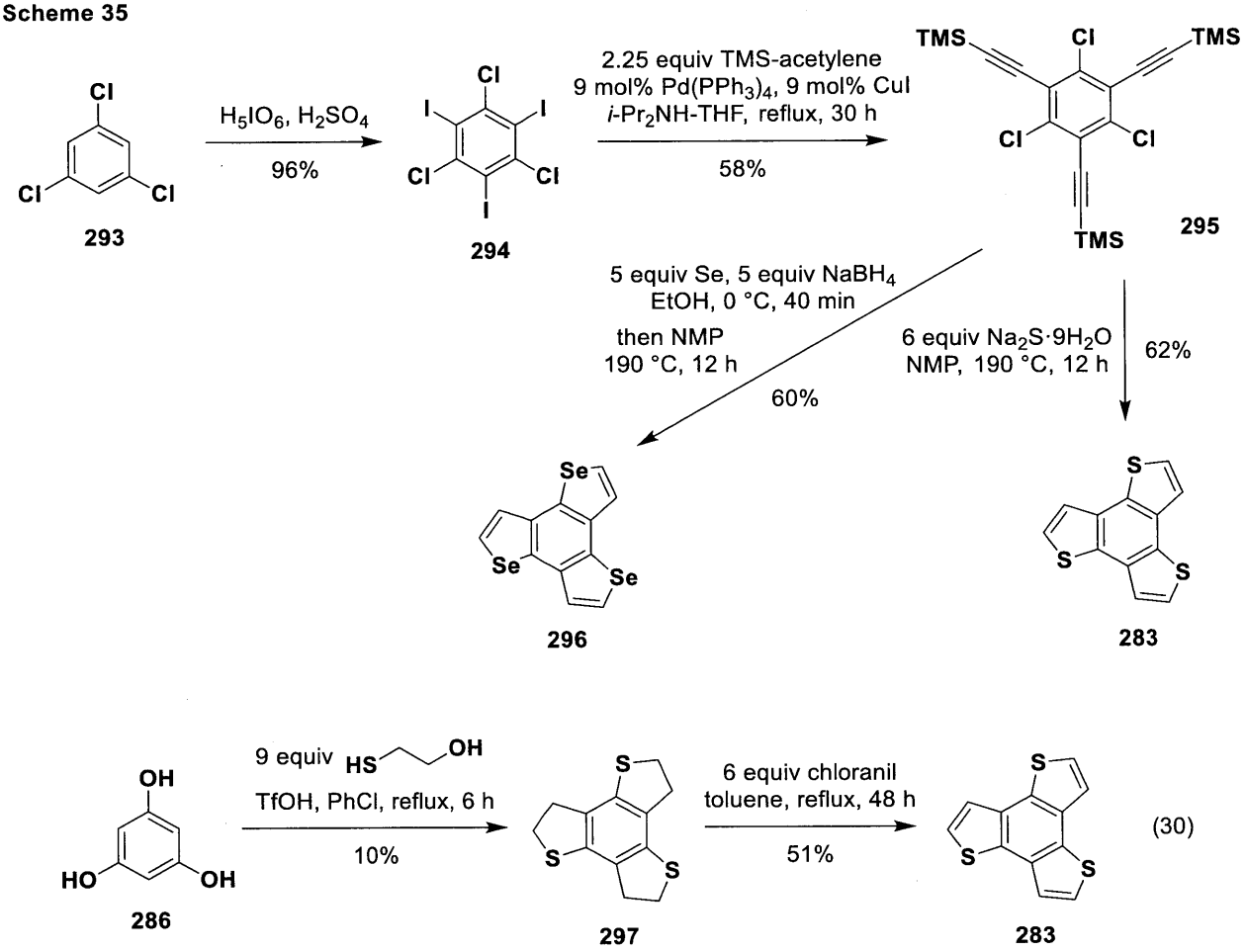




This general substitution strategy beginning with 1,3,5-trisubstituted benzene derivatives has also been used to synthesize benzotrithiophenes. As shown in Scheme 35, starting from 1,3,5-trichlorobenzene, exhaustive iodination, Sonogashira coupling, and addition of sodium sulfide or selenide provides benzotrithiophene and benzotriselenophene in moderate yield.[100] More recently, benzotrithiophene has been made in two steps, albeit in low yield, from phloroglucinol and 2-mercaptoethanol (eq 30).[106]

[106] Rungtaweevoranit, B.; Butsuri, A.; Wongma, K.; Sadorn, K.; Neranon, K.; Nerungsi, C.; Thongpanchang, T. *Tetrahedron Lett.* **2012**, *53*, 1816–1818.

Scheme 35



The second general strategy for the synthesis of these tetracycles first assembles linear trimers of five-membered heterocycles via condensation or cross-coupling reactions and then employs them as key substrates in a subsequent oxidative 6-electron photochemical cyclization that creates the central benzenoid core. The latter reaction is extremely similar to the well-known cyclization of stilbenes[107] and has been extensively used as a benzannulation strategy.[108]

Scheme 36 outlines Blanchard and Roncali's short synthesis of benzotrithiophene **283** from 2,3-dibromothiophene, tetrahydrothiophene-3-one, and 2-thienylmagnesium bromide, all of which are commercially available.[109] Trithiophene **300** was then cyclized to benzotrithiophene on

---

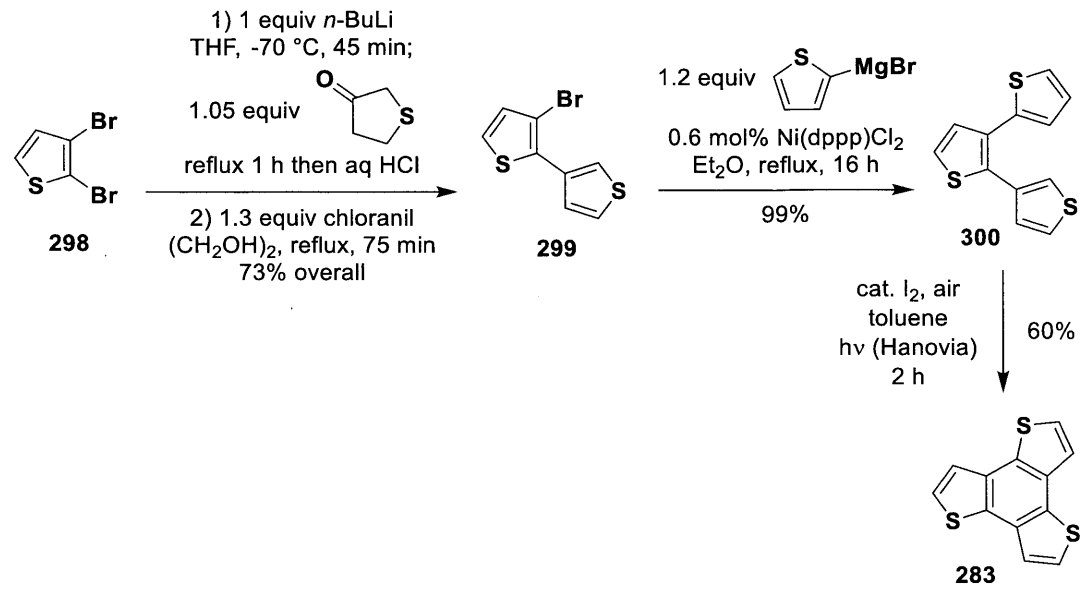
[107] Stará, I. G.; Starý, I. "Phenanthrenes, Helicenes, and Other Angular Acenes", In *Science of Synthesis*; Siegel, J.; Tobe, Y., Ed.; Thieme: Stuttgart, 2010; Vol. 45; pp 885–888, 911–915, and 918–921.

[108] Trauner, D.; Webster, R. "1,3-Cyclohexadiene Formation Reactions: 6π and Higher-Order Electrocyclizations." In *Comprehensive Organic Synthesis (Second Edition)*; Knochel, P.; Molander, G. A., Ed. Elsevier, Amsterdam, 2014; Vol. 5, pp 798–804.

[109] Nicolas, Y.; Blanchard, P.; Levillain, E.; Allain, M.; Mercier, N.; Roncali, J. *Org. Lett.* **2004**, *6*, 273–276.

irradiation under aerobic conditions in the presence of catalytic iodine following a general protocol described by Jayasuriya and Kagan.[110]

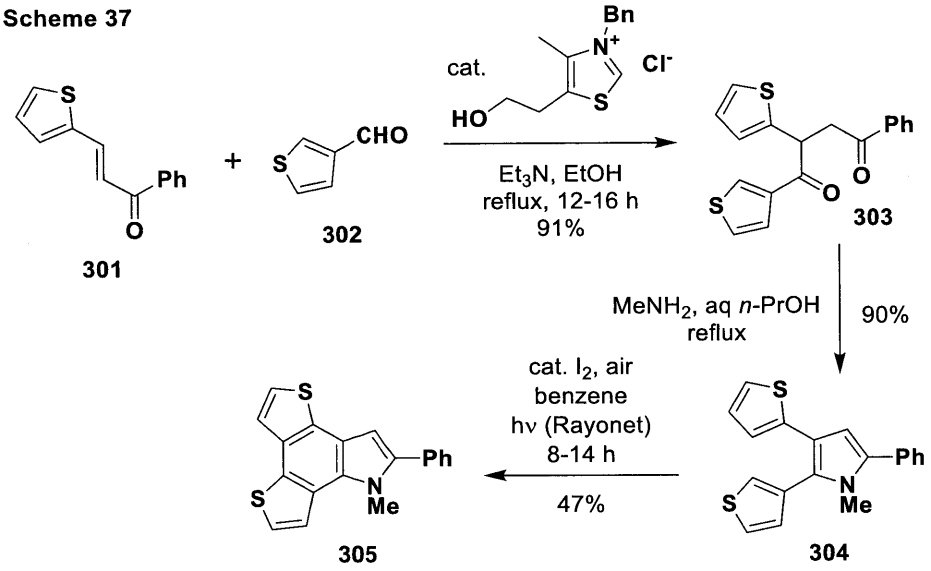
Scheme 36



Kagan and Teo's synthesis of dithienoindole **305** was also carried out using this approach. As shown in Scheme 37, Stetter reaction[111] of enone **301** and aldehyde **302** followed by condensation with methylamine afforded the requisite substrate **304** for photochemical cyclization to furnish **305**.[101]

[110] Jayasuriya, N.; Kagan, J. *J. Org. Chem.* **1989**, *54*, 4203–4205.
[111] (a) Stetter, H.; Krasselt, J. *J. Heterocycl. Chem.* **1977**, *14*, 573–581. (b) Stetter, H. *Chem. Ber.* **1985**, *118*, 3172–3187.

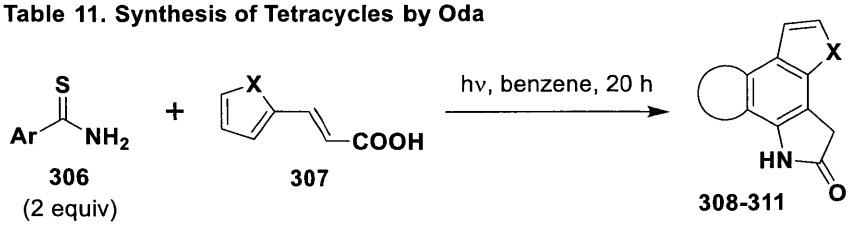
Scheme 37

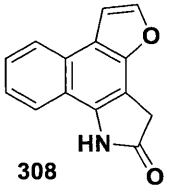
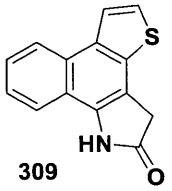
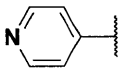
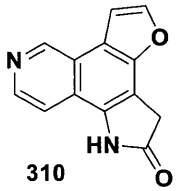
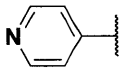
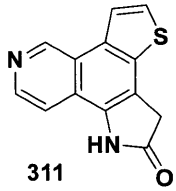
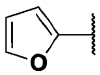
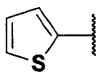


A variation of the photochemical cyclization strategy has also been used in the synthesis of similar tetracycles. In an attempt to synthesize tetracyclic furano- or thienoindoles, Oda and coworkers irradiated mixtures of aryl thioamides **306** and heteroaryl α,β-unsaturated carbonyl compounds such as **307** (Table 11).[112] Lactam **308** was subsequently reduced to benzofuroindole in 63% yield with $LiAlH_4$ in THF. However, tetracycles were isolated in low yield from phenyl and 4-pyridyl thioamides (entries 1–4) and neither furyl nor thienyl thioamide participated in this type of reaction (entries 5–8).

[112] Oda, K., Tsujita, H., Sakai M., Machida, M. *Chem. Pharm. Bull.* **1998**, *46*, 1522–1526.

Table 11. Synthesis of Tetracycles by Oda



entry	Ar	X	product	yield (%)[a]
1	Ph	O	 308	39
2	Ph	S	 309	32
3	4-pyridyl 	O	 310	31
4	4-pyridyl 	S	 311	28
5	2-furyl 	O		—
6		S		—
7	2-thienyl 	O		—
8		S		—

[a] Isolated yield of product purified by column chromatography.

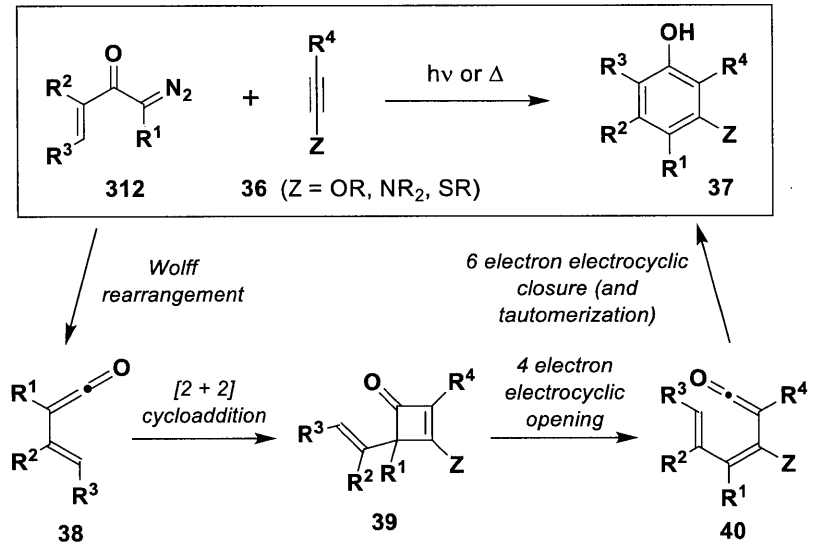
"Second-generation" Benzannulation

As mentioned in the previous section, the feasibility of the synthesis of tetracycles from 1,3,5-triheterosubstituted benzene derivatives relies on the availability of these types of trisubstituted aromatic compounds. We envisioned that the benzannulation strategy developed in our laboratory would be ideally suited for the efficient and regioselective synthesis of these

substituted benzenes and would make possible the construction of furo[2,3-*g*]thieno[2,3-*e*]indoles via subsequent cyclization reactions. For this purpose we proposed to employ the "second-generation" version of the benzannulation.

In 1990, our laboratory reported this variant of the vinylketene benzannulation in which α-diazo ketones now serve as the vinylketene precursor via a Wolff rearrangement[113] as shown in Scheme 38.[114] It is believed that this benzannulation proceeds via the same pericyclic cascade as the version with cyclobutenones. Though the process can be done entirely photochemically, it was also found that in certain cases the benzannulation can be made more efficient by irradiation of the reaction mixture followed by heating. In these cases, the reaction mixture after the initial irradiation typically contains significant amounts of vinylcyclobutenone **39**. The second part of the pericyclic cascade is then effected by heat instead of light.

Scheme 38

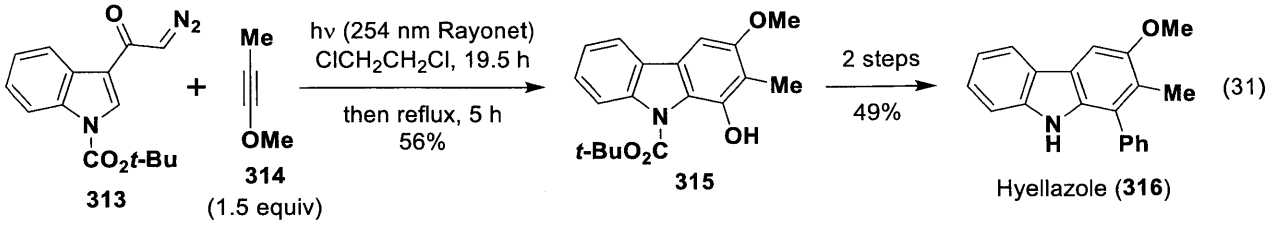


In the original paper the utility of this method was illustrated with a concise synthesis of hyellazole (**316**). As outlined in eq 31, benzannulation of diazo ketone **313** with methoxypropyne (**314**) afforded the highly substituted carbazole **315** which was subsequently converted to hyellazole in two steps.

---

[113] For reviews on the Wolff rearrangement, see: (a) Kirmse, W. *Eur. J. Org. Chem.* **2002**, 2193–2256. (b) Meier, H.; Zeller, K.-P. *Angew. Chem. Int. Ed.* **1975**, *14*, 32–43.

[114] Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc.* **1990**, *112*, 3093–3100.



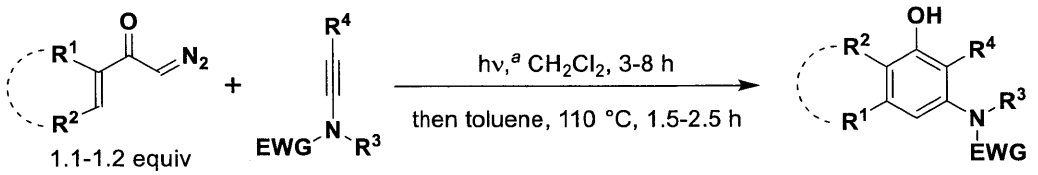
This "second-generation" benzannulation protocol has a marked advantage over the cyclobutenone-based "first-generation" benzannulation: the use of α-diazo ketones enables facile generation of cycloalkenyl- and arylketenes and subsequent formation of polycyclic benzannulation products. Hence, the "second-generation" strategy greatly expanded the scope of the method to include the synthesis of polycyclic aromatic and heteroaromatic products and has been used in a number of efficient syntheses of natural products.[115]

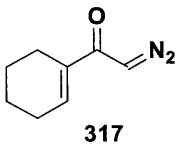
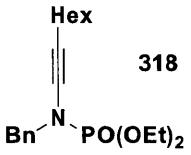
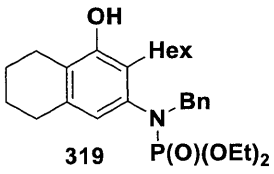
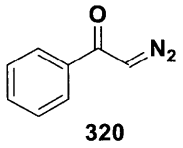
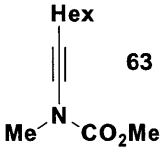
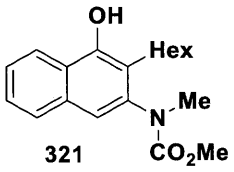
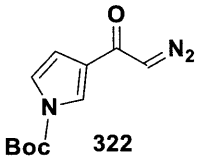
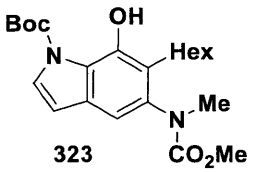
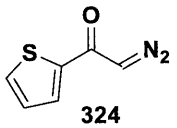
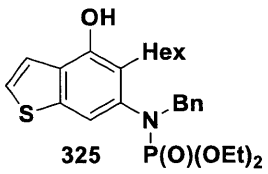
More recently, ynamides have been introduced as the alkyne partner in the "second-generation" benzannulation.[116] This extension has enabled the synthesis of a variety of fused anilines with high levels of substitution. As shown in Table 12, this benzannulation protocol proceeds with a variety of diazo ketones. Typical reaction conditions involve irradiation of a mixture of an ynamide with a slight excess (1.1–1.2 equiv) of a diazo ketone. After all diazo ketone is consumed, the reaction mixture is then refluxed in toluene briefly to complete the reaction.

[115] (a) Danheiser, R. L.; Cha, D. C. *Tetrahedron Lett.* **1990**, *31*, 1527–1530. (b) Danheiser, R. L.; Casebier, D. S.; Loebach, J. L. *Tetrahedron Lett.* **1992**, *33*, 1149–1152. (c) Danheiser, R. L.; Casebier, D. S.; Huboux, A. H. *J. Org. Chem.* **1994**, *59*, 4844–4848. (d) Danheiser, R. L.; Helgason, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 9471–9479. (e) Danheiser, R. L.; Trova, M. P. *Synlett* **1995**, 573–574. (f) Danheiser, R. L.; Casebier, D. S.; Firooznia, F. J. *J. Org. Chem.* **1995**, *60*, 8341–8350.

[116] Willumstad, T. P.; Haze, O.; Mak, X. Y.; Lam, T. Y.; Wang, Y.-P.; Danheiser, R. L. *J. Org. Chem.* **2013**, *78*, 11450–11469.

Table 12. Scope of Second-Generation Benzannulation with Ynamides

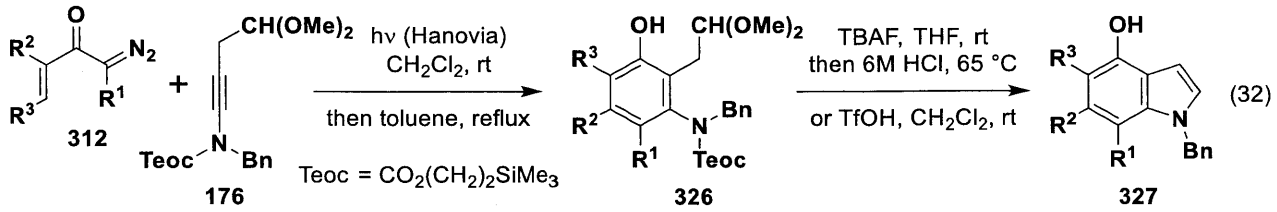


Entry	Diazo ketone	Ynamide	Product	Yield (%)[b]
1	 317	 318	 319	66
2	 320	 63	 321	64-76
3	 322	63	 323	40
4	 324	318	 325	78

[a] Irradiation with a Hanovia 450 W medium-pressure mercury lamp. [b] Isolated yield of products purified by column chromatography.

Coupled with subsequent cyclization to form nitrogen heterocycles, this tandem strategy is especially powerful in the synthesis of indoles and other benzofused nitrogen heterocycles. Two different cyclization strategies[117] to synthesize indoles are outlined below. As shown in eq 32, an ynamide derived from butynal acetal (**176**) was used in the benzannulation with diazo ketones. Deprotection of the aniline nitrogen in **326** with TBAF followed by treatment with acid affords indoles **327** via cyclization and dehydration.

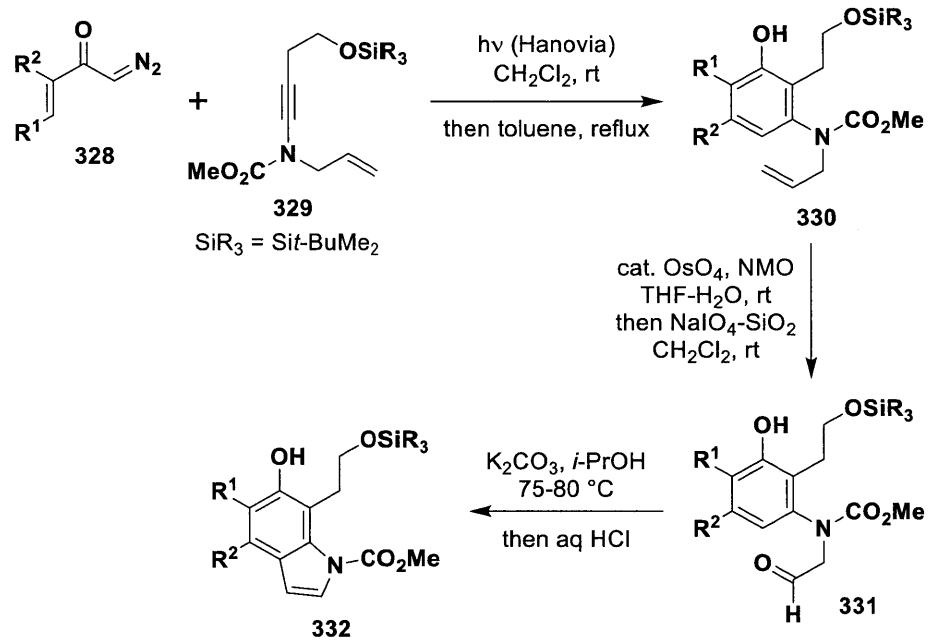
[117] Both approaches were described in our previous ynamide benzannulation paper. See ref 39.



(32)

Scheme 39 summarizes another route to indoles that employs *N*-allyl ynamides such as **329**. Oxidative cleavage of the alkene moiety in the benzannulation product **330** afforded aldehyde **331**. Treatment of **331** with base then triggers aromatic substitution on the highly electron-rich *m*-aminophenoxide system. Finally, dehydration to indole **332** proceeds on acidic workup.

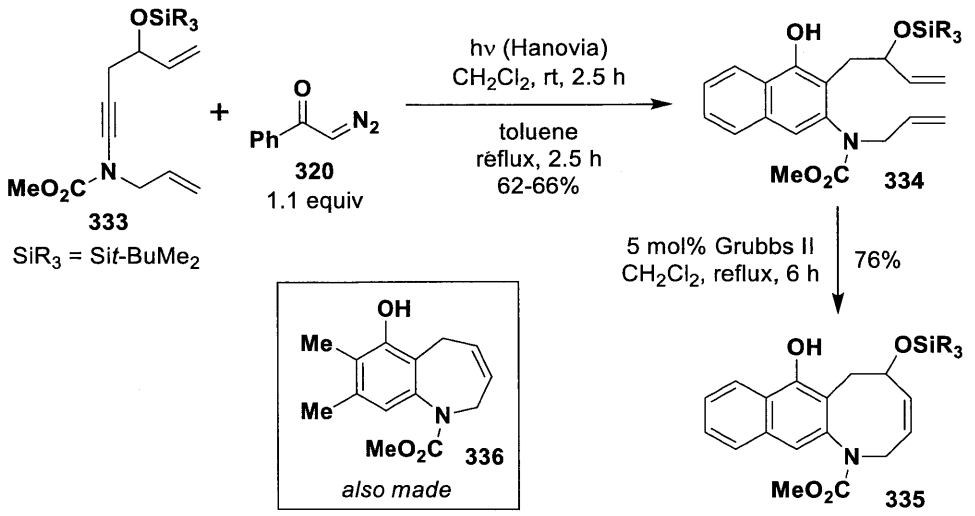
Scheme 39



Lastly, our lab demonstrated the utility of a tandem photochemical benzannulation-ring-closing metathesis (RCM) strategy[118] in the synthesis of benzofused nitrogen heterocycles such as naphthazocine **335** and benzazepine **336** (Scheme 40).

[118] For a related tandem strategy involving cyclobutenone-based benzannulation and RCM, see ref 2.

Scheme 40



Benzannulation in Continuous Flow

Our laboratory also examined this photochemical benzannulation where irradiation was conducted in continuous flow.[116] The advantages of such continuous flow photochemical reactors over traditional "batch" reactors are well-established.[119,120] Typical "batch" photochemical reactions are often inefficient due to low penetration depth of light. In contrast, flow reactors can be designed to have much larger surface-to-volume ratios by the use of narrow gauge tubing. In addition, decomposition of the desired products can be minimized by continuous removal of reaction mixture from the irradiation zone. Finally, reactions conducted in continuous flow reactors can be conveniently scaled up without the need for re-optimization of reaction parameters.

---

[119] For reviews of continuous flow photochemical reactions, see: (a) Gilmore, K.; Seeberger, P. H. *Chem. Rec.* **2014**, *14*, 410–418. (b) Schuster, E. M.; Wipf, P. *Isr. J. Chem.* **2014**, *54*, 361–370. (c) Knowles, J. P.; Elliott, L. D.; Booker-Milburn, K. I. *Beilstein J. Org. Chem.* **2012**, *8*, 2025–2052. (d) Oelgemöller, M.; Shvydkiv, O. *Molecules* **2011**, *16*, 7522–7550.

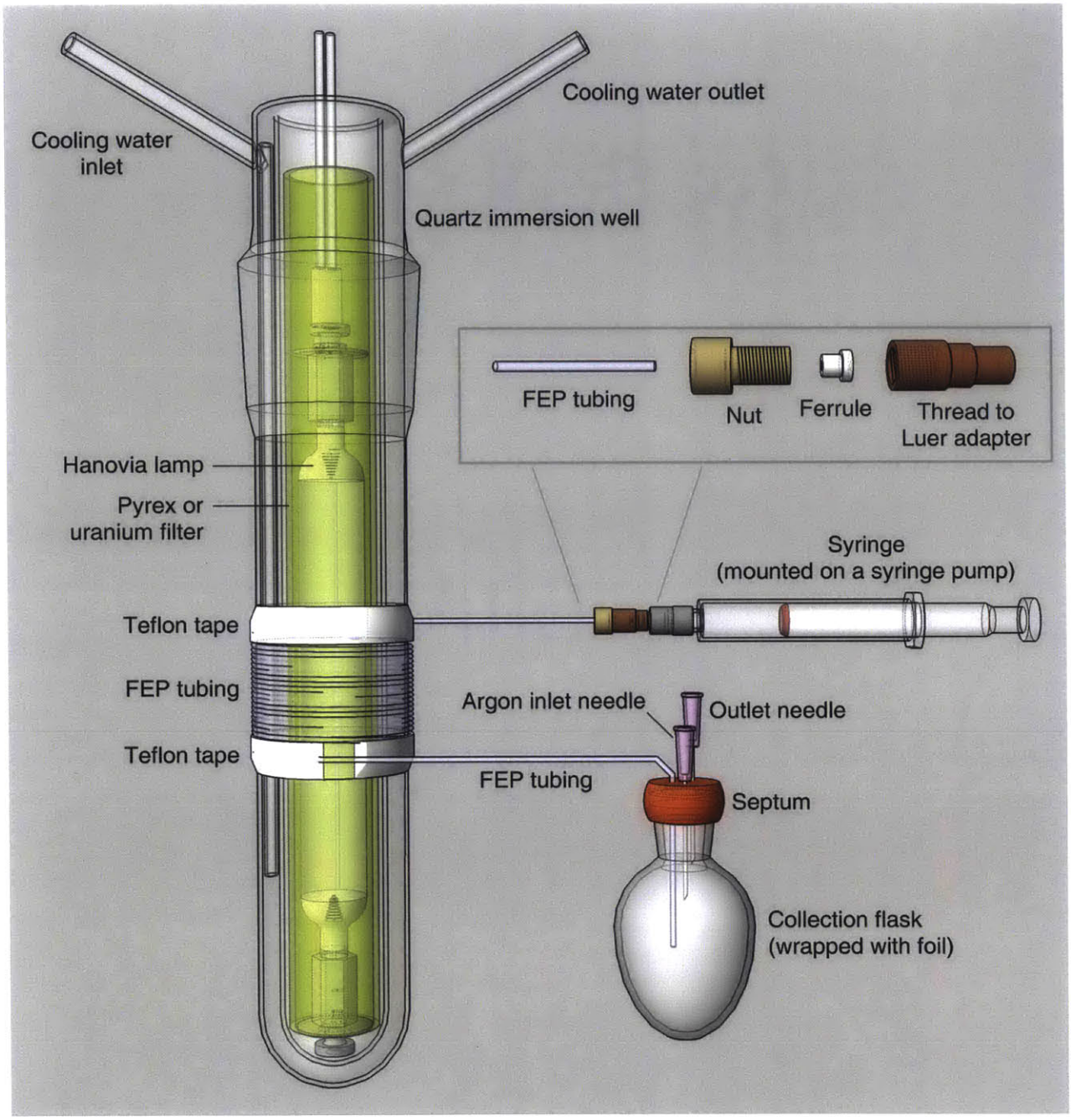
[120] For recent examples of continuous flow photochemical reactions, see: (a) Nguyen, J. D.; Reiss, B.; Dai, C.; Stephenson, C. R. J. *Chem. Commun.* **2013**, *49*, 4352–4354. (b) Zhang, Y.; Blackman, M. L.; Leduc, A. B.; Jamison, T. F. *Angew. Chem. Int. Ed.* **2013**, *52*, 4251–4255. (c) Maskill, K. G.; Knowles, J. P.; Elliott, L. D.; Alder, R. W.; Booker-Milburn, K. I. *Angew. Chem. Int. Ed.* **2013**, *52*, 1499–1502. (d) Šterk, D.; Jukič, M.; Časar, Z. *Org. Process. Res. Dev.* **2013**, *17*, 145–151. (e) Junkers, T.; Conradi, M. *J. Photochem. Photobiol., A* **2013**, *259*, 41–46. (f) Harrowven, D. C.; Mohamed, M.; Gonçalves, T. P.; Whitby, R. J.; Bolien, D.; Sneddon, H. F. *Angew. Chem. Int. Ed.* **2012**, *51*, 4405–4408. (g) Lévesque, F.; Seeberger, P. H. *Angew. Chem. Int. Ed.* **2012**, *51*, 1706–1709. (h) Anderson, B. G.; Bauta, W. E.; Cantrell, W. R., Jr. *Org. Process. Res. Dev.* **2012**, *16*, 967–975. (i) Terao, K.; Nishiyama, Y.; Tanimoto, H.; Morimoto, T.; Oelgemöller, M.; Kakiuchi, K. *J. Flow Chem.* **2012**, *2*, 73–76.

The continuous flow photochemical reactor employed in our laboratory is based on the easily-assembled design described by Booker-Milburn and coworkers.[121,122] As shown in Figure 3, UV-transparent fluorinated ethylene-propylene (FEP) tubing (0.76 mm i.d., 1.59 mm o.d.) was wound around a quartz immersion well cooled with circulating water. A 450-W medium pressure mercury lamp was placed inside the immersion well with a Pyrex filter sleeve to suppress polymer buildup inside the tubing. A syringe pump was used to drive the reaction mixture (ca. 0.25 M) through the tubing. With a typical residence time of 21 to 33 minutes in the irradiated section of tubing, the photochemical benzannulation can be achieved on preparative scales with yields comparable to batch reactions (Scheme 41).

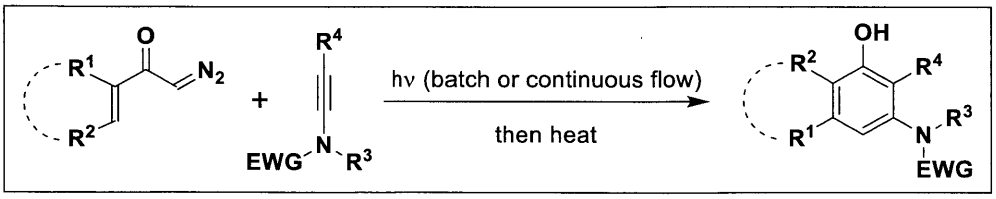
[121] Hook, B. D. A.; Dohle, W.; Hirst, P. R.; Pickworth, M.; Berry, M. B.; Booker-Milburn K. I. *J. Org. Chem.* **2005**, *70*, 7558–7564.

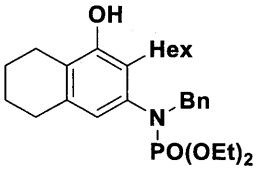
[122] For an early example of a similar photochemical flow reactor, see Birr, C.; Lochinger, W.; Stahnke, G.; Lang, P. *Liebigs Ann. Chem.* **1972**, *763*, 162–172.

Figure 3. Flow Reactor Setup



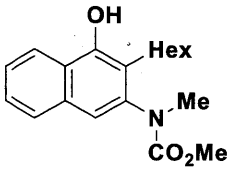
Scheme 41





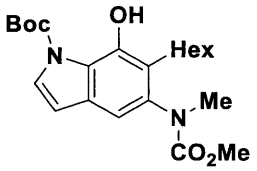
319

66% (batch)
53% (flow)



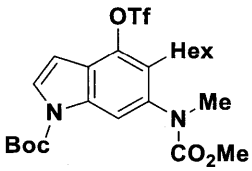
321

64-76% (batch)
66% (flow)



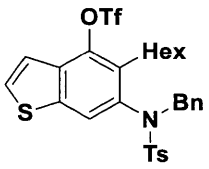
323

40% (batch)
37% (flow)



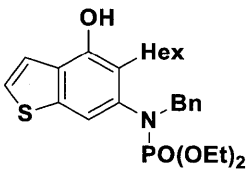
337

57%[a] (batch)
47-50%[a] (flow)



338

52%[a] (batch)
47%[a] (flow)



325

78% (batch)
79% (flow)

[a] Overall yield for 2 steps. Benzannulation product was treated with 1.2 equiv Tf_2O, 2 equiv 4-DMAP, CH_2Cl_2, 0 °C to rt, 2-4 h.

Overall, this "second-generation" benzannulation employing α-diazo ketones as the ketene precursor enables rapid and regioselective synthesis of a wide variety of highly substituted polycyclic aromatic molecules. The next chapter describes our investigation in the synthesis of furo[2,3-*g*]thieno[2,3-*e*]indole via the tandem "second-generation" benzannulation-cyclization strategy outlined above.

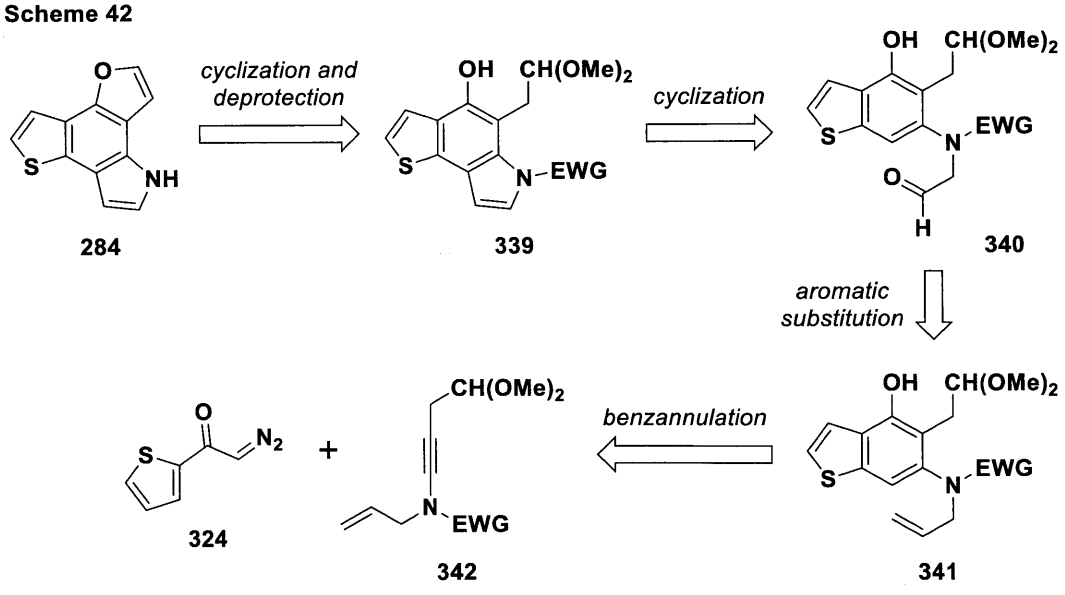
Chapter 2

Synthesis of Furo[2,3-*g*]thieno[2,3-*e*]indole

Retrosynthetic Analysis

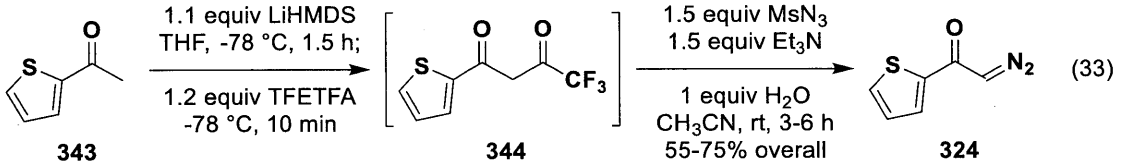
Scheme 42 outlines our retrosynthetic plan for the synthesis of furo[2,3-*g*]thieno[2,3-*e*]indole. Since our benzannulation with ynamides produces benzene derivatives featuring a *meta* relationship of oxygen and nitrogen substituents, the two heteroatoms are ideally poised for subsequent cyclization reactions to form the furan and pyrrole rings in furo[2,3-*g*]thieno[2,3-*e*]indole. We envisioned that the furan ring would be easily constructed via cyclization with the acetal in phenol **339** and subsequent elimination of methanol. The pyrrole ring would be formed by aromatic substitution with the tethered aldehyde in **340** following our previous work on the synthesis of indoles (*vide supra*).[39,116] The thiophene ring, being the least reactive of the three heterocycles, would be derived from the known diazo ketone **324** and we felt confident in carrying the thiophene through the entire synthetic sequence without significant complications. The key benzannulation step involving **324** and ynamide **342** decorated with two latent aldehyde groups would set in place all of the substituents needed for the two cyclization reactions.

Scheme 42



Previous Work in Our Laboratory

Galina Mamaliga and Clarissa Forneris conducted initial studies directed toward the synthesis of furo[2,3-*g*]thieno[2,3-*e*]indole. While diazo ketones are traditionally prepared by the reaction of carboxylic acid derivatives with diazomethane or related compounds, diazo transfer methods have become more popular in recent years. The thiophene-based diazo ketone **324** has previously been made by treatment of thiophene-2-carbonyl chloride with diazomethane in ether in 60-85% yield.[123] For our study, the detrifluoroacetylative diazo transfer method developed in our laboratory was employed (eq 33).[124] Commercially available ketone **343** was converted to an enolate with LiHMDS and treated with 2,2,2-trifluoroethyl trifluoroacetate (TFETFA). The crude Claisen condensation product, diketone **344**, was then treated with methanesulfonyl azide in the presence of triethylamine to afford diazo ketone **324** in moderate to good yield.



(33)

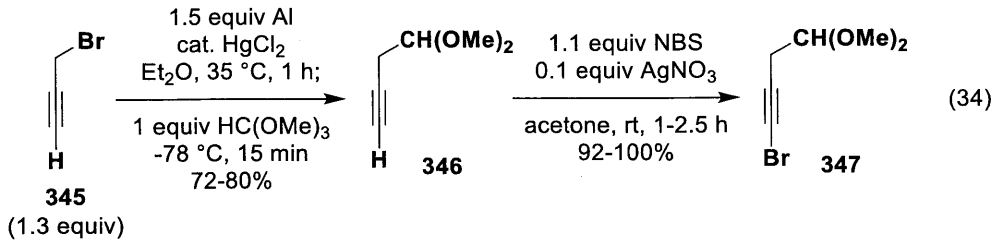
The ynamide component for the benzannulation was synthesized by copper-mediated alkynylation (*vide supra*, Part I, Chapter 2). The alkyne partner was made from addition of the organoaluminum species derived from propargyl bromide (**345**) to trimethyl orthoformate following a known procedure.[125] Bromination with NBS in the presence of catalytic $AgNO_3$[62] then furnished the desired bromoalkyne in excellent yield (eq 34).

---

[123] (a) Fu, N.; Allen, A. D.; Chan, W.; Kobayashi, S.; Tidwell, T. T.; Tahmassebi, D.; Aguilar, A.; Cabrera, E. P.; Godoy, J. *Can. J. Chem.* **2008**, *86*, 333–341. (b) Ihmels, H.; Maggini, M.; Prato, M.; Scorrano, G. *Tetrahedron Lett.* **1991**, *32*, 6215–6218.

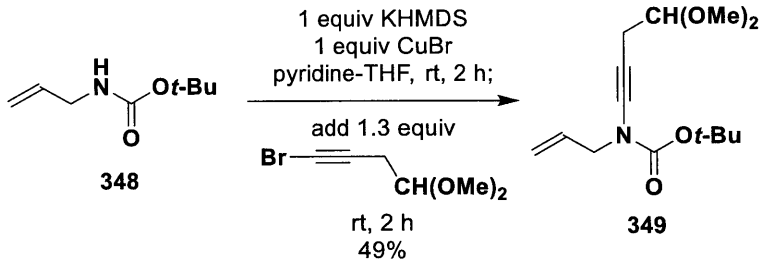
[124] (a) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959–1964. (b) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G. *Org. Synth.* **1996**, *73*, 134–140.

[125] (a) Picotin, G.; Miginiac, P. *Chem. Ber.* **1986**, *119*, 1725–1730. (b) See ref 39. (c) Deng, J.; Wang, Y.-P.; Danheiser, R. L. *Org. Synth.* **2015**, *92*, 13–25.



(34)

At the beginning of the project we decided to protect the nitrogen with a BOC group. Ynamide **349** was synthesized by reaction of commercially available *N*-allyl carbamate **348** with bromoalkyne **347** following the procedure developed in our laboratory using stoichiometric KHMDS and copper(I) bromide (eq 35). Purification of the desired ynamide was somewhat challenging as large amounts of alkyne homocoupling product were formed. In addition, ynamide **349** and unreacted carbamate **348** have similar R_f values on both silica gel and neutral alumina. Nevertheless, pure ynamide **349** could be obtained in 49% yield by evaporation of the unreacted carbamate **348** under reduced pressure (100 mmHg) from the crude product followed by column chromatography on silica gel.

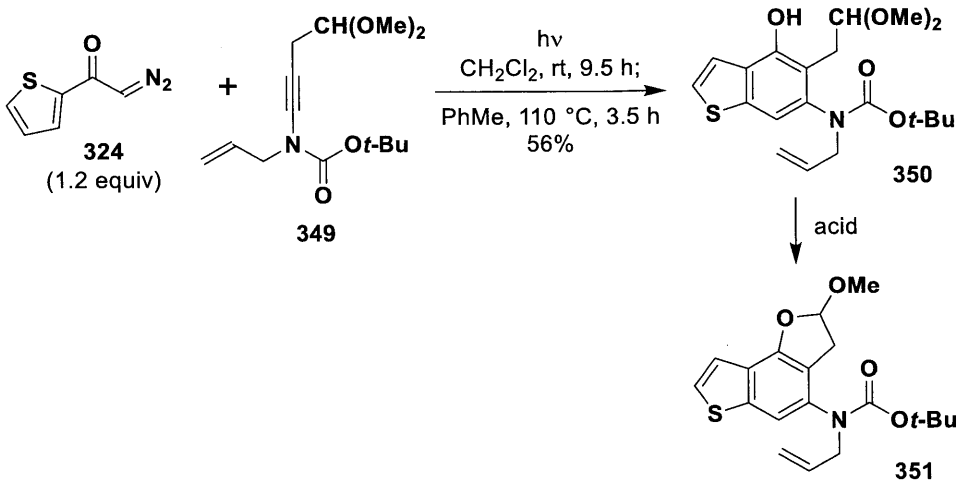


(35)

Scheme 43 outlines the key benzannulation step. Initial photochemical benzannulation attempts with 2.1 equiv of diazo ketone **324** in dichloromethane using a Hanovia medium-pressure mercury lamp resulted in formation of very large amounts of colored polymers which significantly reduced the efficiency of irradiation. An increase in polymer buildup was also observed when irradiation was conducted in acetonitrile. This problem could be mitigated by using 1.2 equiv of diazo ketone. Another complication was the formation of byproduct **351** from acid-catalyzed cyclization of the phenolic oxygen onto the acetal group. Although a furan ring is present in the final product, this byproduct is unwanted as the oxygen substituent cannot convert to a phenoxide required for the cyclization to form the nitrogen heterocycle. The formation of **351** could be

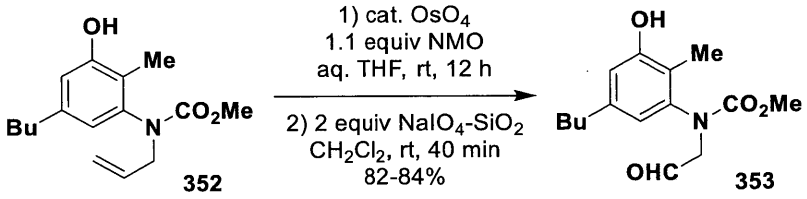
suppressed by azeotropic removal of moisture from the hygroscopic diazo ketone with benzene and washing the reaction vessels with alcoholic KOH prior to the reaction. These precautions presumably avoids the formation of carboxylic acids from the reaction of ketene intermediates with any water present in the reaction mixture.

Scheme 43



Oxidative cleavage of a phenol similar to **350** had previously been studied by Lam.[39] In that work ozonolysis of phenol **352** led to the formation of many undesired byproducts difficult to remove by column chromatography and the desired aldehyde could only be isolated in 80-85% purity. This result is presumably due to oxidative side reactions involving the very electron rich aromatic core. Lemieux-Johnson oxidation[126] with catalytic OsO_4 and excess $NaIO_4$ afforded the desired aldehyde **353** in 66% yield but the product was again difficult to separate from byproducts. The optimal conditions developed by Lam involve a two-step process outlined in eq 36: phenol **352** was dihydroxylated under classic conditions (cat. OsO_4 / NMO) and the crude diol was then treated with sodium metaperiodate on silica gel.[43]

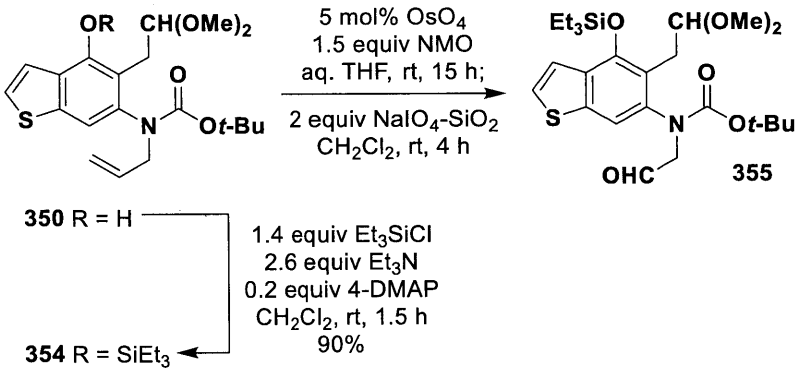
[126] Pappo, R.; Alen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478–479.



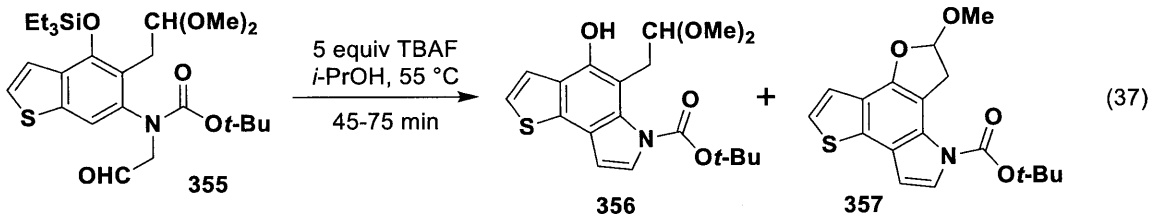
(36)

However, oxidative cleavage of benzannulation product **350** via direct dihydroxylation again resulted in the premature formation of the oxygen heterocycle due to the acidic reaction conditions (aq OsO_4). Consequently, the phenolic hydroxyl group was protected as a triethylsilyl (TES) ether before oxidative cleavage (Scheme 44). The basic conditions for the removal of the silyl group would ideally also initiate the desired aromatic substitution reaction to furnish the indole. While oxidative cleavage proceeded smoothly on the TES-protected substrate, aldehyde **355** was found to decompose on column chromatography so it was used directly in the next step without purification.

Scheme 44



Lam had previously found that the optimal conditions to produce indoles via aromatic substitution from substrates with an *N*-(2-oxoethyl) group involves treatment with K_2CO_3 or DBU in *i*-PrOH at 50-70 °C followed by acidification with HCl.[39] In the case of compound **355**, on the other hand, Mamaliga found that exposure of the triethylsilyl ether to TBAF alone in *i*-PrOH at 55 °C furnished a mixture of the desired indole **356** and tetracycle **357** (eq 37).

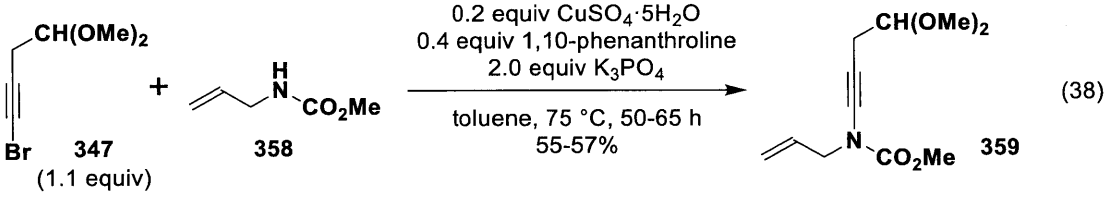


(37)

Unfortunately, this reaction was found to be difficult to reproduce and indole **356** was also unstable to column chromatography and storage. Attempts to construct the oxygen heterocycle from compound **356** by the action of Lewis acids such as $BF_3 \cdot Et_2O$ were unsuccessful. Elimination of methanol from tetracycle **357** under acidic conditions to furnish the desired furan ring also met with failure. These frustrating results are attributed to the acid sensitivity of the BOC protecting group and the expected electron rich nature of the tetracyclic system. Consequently, we decided to conduct the synthetic sequence starting with substrates protected with an acid-stable carbomethoxy group in place of BOC.

Benzannulation in Batch and Flow

The synthesis of the *N*-carbomethoxy ynamide required for the benzannulation was found to be more convenient using the protocol developed by Hsung.[53] Although the formation of the alkyne dimer was still a major side reaction, the desired ynamide (**359**) could be isolated in 55-57% yield (eq 38).

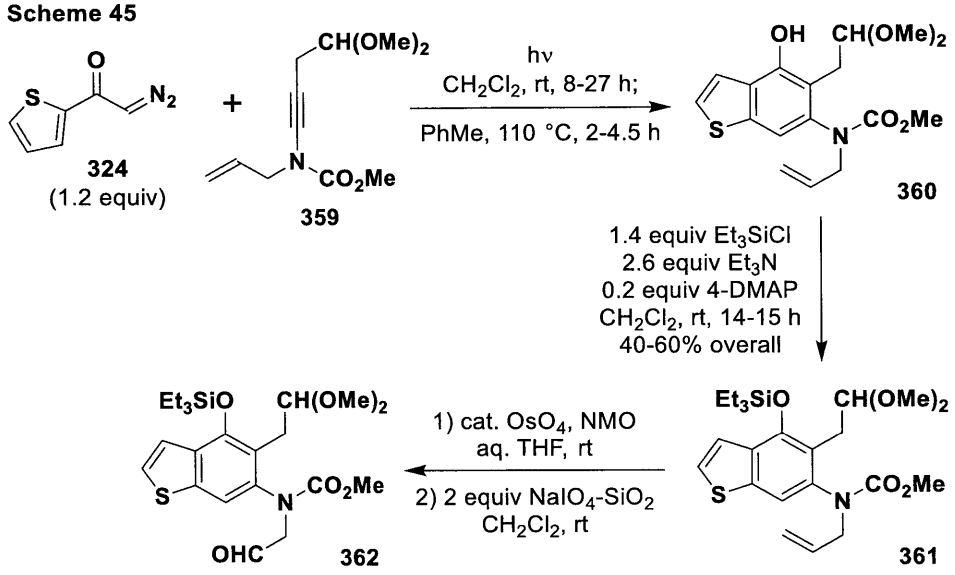


(38)

As shown in Scheme 45, Forneris conducted the benzannulation under the usual conditions by irradiation of a solution of ynamide **359** and 1.2 equiv of diazo ketone **324** in CH_2Cl_2 followed by refluxing in toluene to complete the pericyclic cascade. Phenol **360** could only be obtained in ca. 90% purity after column chromatography but is of sufficient quality to use in the next step. Protection of the hydroxyl group as a triethylsilyl ether afforded compound **361** in moderate and

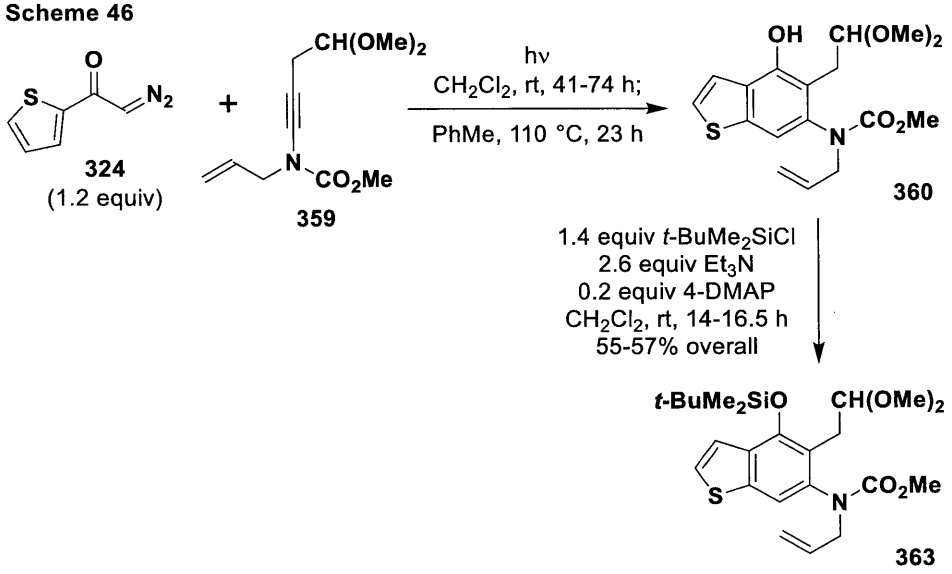
somewhat variable (40-60%) overall yield from ynamide **359**. Dihydroxylation and oxidative cleavage of the alkene moiety in **361** resulted in aldehyde **362** which was difficult to purify.

Scheme 45

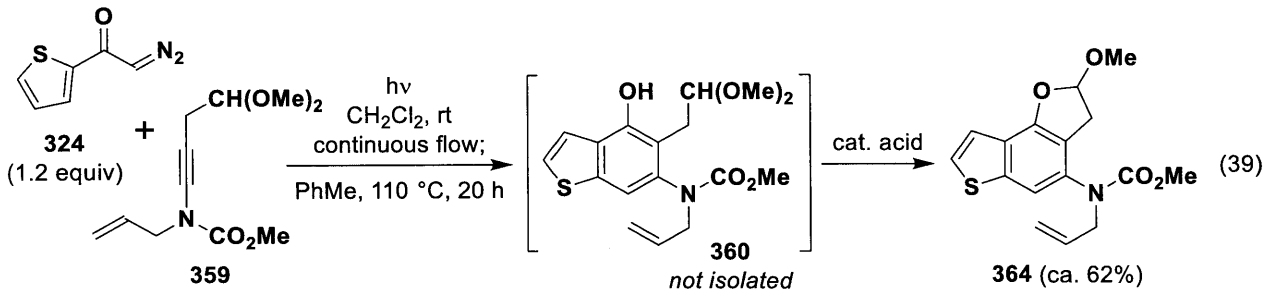


Due to the concerns about the lability of the triethylsilyl ether toward purification and storage, we decided to use more a robust *tert*-butyldimethylsilyl ether instead. The new benzannulation/protection sequence is outlined in Scheme 46. While the moderate yield was more reproducible, a significant concern arose with regards to the photochemical step. Scaling the reaction up to produce 1.9 g of phenol **360** lengthened the irradiation time to 74 h. This reveals an intrinsic problem associated with traditional "batch" photochemical reactions. Irradiation becomes increasingly inefficient when reactions are carried out in larger reaction vessels.

Scheme 46

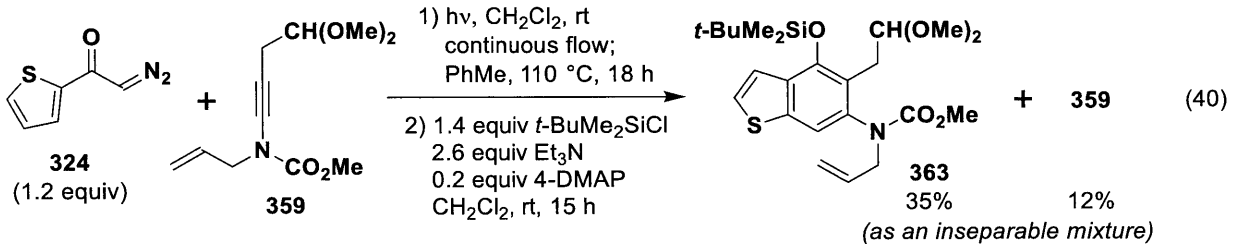


To improve the efficiency of the benzannulation, we decided to conduct the reaction in continuous flow. Initial attempts[127] resulted in complete cyclization of the oxygen heterocycle and yielded the unwanted product **364** (eq 39). This result highlights the large surface area of the flow reactor as a double-edged sword: it greatly improves the efficiency of irradiation, but on the other hand also encourages side reactions involving residual moisture or oxygen adsorbed on the wall of the tubing. In this case, the cyclization was likely caused by carboxylic acids formed by the reaction of moisture with ketene intermediates even though FEP is not particularly hygroscopic.



[127] Employing the setup described in Part II, Chapter 1 with 1340 cm of the tubing exposed to the full length of the Hanovia lamp.

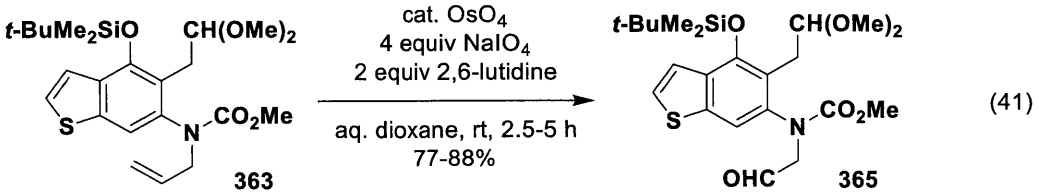
Drying the FEP tubing in a vacuum desiccator overnight and azeotropic removal of moisture from diazo ketone **324** with benzene prior to the flow photochemical reaction successfully suppressed the formation of cyclic acetal **364**. However, colored polymers were observed inside the tubing and incomplete reaction resulted. As shown in eq 40, silylated phenol **363** was isolated in only 35% yield as an inseparable mixture with 12% of the unreacted ynamide. Although the tubing was successfully cleaned by soaking in a base bath (KOH / aq *i*-PrOH) for a week and could be reused for further reactions, the formation of polymers is still highly problematic for this particular benzannulation case. While the problem of incomplete reaction can usually be solved by lowering the flow rate or using larger excess of diazo ketone (**324** in our case), both solutions only led to more severe polymer formation.



(40)

Double Cyclization

Despite discouraging results from benzannulation in continuous flow, the yield for the benzannulation in batch was reasonable and we decided to move on with oxidative cleavage to set the stage for the key cyclization reactions. The modified Lemieux-Johnson oxidation[128] with 2,6-lutidine as the additive was found to give aldehyde **365** in high yield without any need to isolate the diol intermediate (eq 41). The reaction mixtures had a very thick consistency and mechanical stirring must be used on larger scales. The aldehyde could be isolated in high purity and it is reasonably stable to storage.

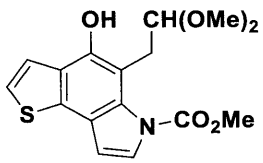


(41)

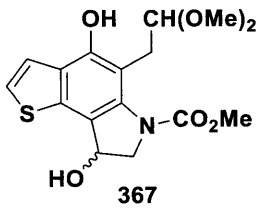
[128] Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217–3219.

With all requisite functional groups in place for the two cyclization reactions, we next investigated conditions for silyl ether cleavage and cyclization. Despite complete desilylation, incomplete formation of the indole was observed when triethylsilyl aldehyde **362** (cf. Scheme 45) was treated with TBAF alone and prolonged heating led to gradual decomposition. Treatment of **362** with excess (5 equiv) K_2CO_3 in *i*-PrOH also resulted in a low yield of the cyclized product. The problems we encountered in the former case are attributed to the water content in commercial TBAF, which is typically in the form of $TBAF \cdot 3H_2O$. This greatly reduces the basicity of the reaction media and the concentration of free phenoxide capable of undergoing efficient aromatic substitution with the tethered aldehyde moiety. In the latter case, the reason for the low yield may be simply due to the inefficiency of K_2CO_3 in desilylation reactions compared to fluoride. Prolonged heating is potentially detrimental as the electron-rich thienoindole product can react with the electrophilic aldehydic starting material and lead to polymerization.

Forneris found that cyclization could be achieved in much higher yield by combining the two basic reagents. Aldehyde **365** was first exposed to TBAF in *i*-PrOH at room temperature to ensure complete desilylation. K_2CO_3 was then added and the reaction mixture was warmed to 40-45 °C to encourage complete formation of the indole. The reaction mixture at this stage typically contained both indole **366** and its hydroxyindoline precursor **367**. Complete conversion to the indole was done by acidification of the reaction mixture with anhydrous HCl generated by the addition of acetyl chloride to methanol.

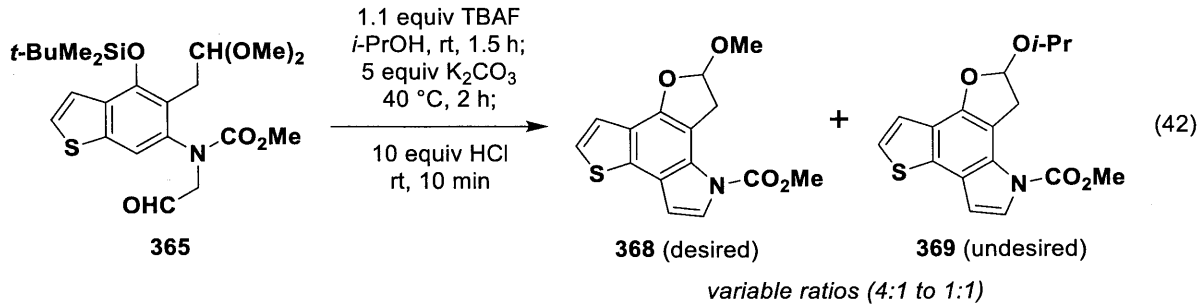


366



367

As we observed formation of the oxygen heterocycle during benzannulation catalyzed by traces of acid, it is not surprising that the conditions described above would also trigger the second cyclization to form tetracycle **368**. Indeed, we were able to accomplish both desired cyclization reactions in one pot and isolate tetracycle **368** as the major product. However, this reaction sequence also produced a byproduct which was difficult to remove. This byproduct was later identified as isopropyl acetal **369** resulting from acetal exchange with the solvent (eq 42).

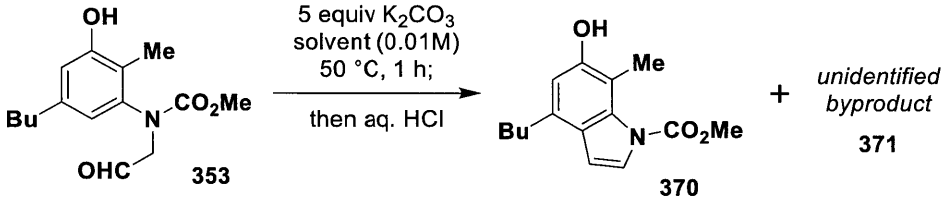


(42)

The ratios of methyl acetal **368** and isopropyl acetal **369** were quite variable across different runs. Isopropyl acetal **369** was later found to be inert to various elimination conditions and failed to produce any furan product. To minimize the formation of this byproduct, different solvents were screened for the cyclization reaction. Lam noticed the use of methanol led to cleavage of the *N*-carbomethoxy moiety in her previous work and the use of THF resulted in incomplete reaction and a mixture of unidentified products.[129] Consequently, we mainly focused our attention on the use of bulky alcoholic solvents to prevent deprotection of the indole nitrogen and minimize the undesired acetal exchange. Cyclization was conducted on small scale with model substrate **353**[39] in the presence of 5 equiv of K_2CO_3 in alcoholic solvents followed by acidification with 1 M aqueous HCl. As summarized in Table 13, both *sec*-butyl and neopentyl alcohols gave similar results comparable to that of the same reaction conducted in isopropyl alcohol by Lam (71% isolated yield of **370**). The use of *tert*-butyl alcohol, however, resulted in significantly reduced yield and formation of an unidentified byproduct (entry 2). This byproduct was likely formed by electrophilic substitution of indole **370** with aldehyde **353** judging by its molecular weight.

[129] Lam, T. L. Synthesis of Indoles via a Tandem Benzannulation-Cyclization Strategy. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, September, 2008.

Table 13. Solvent Screening for Indole Formation via Aromatic Substitution

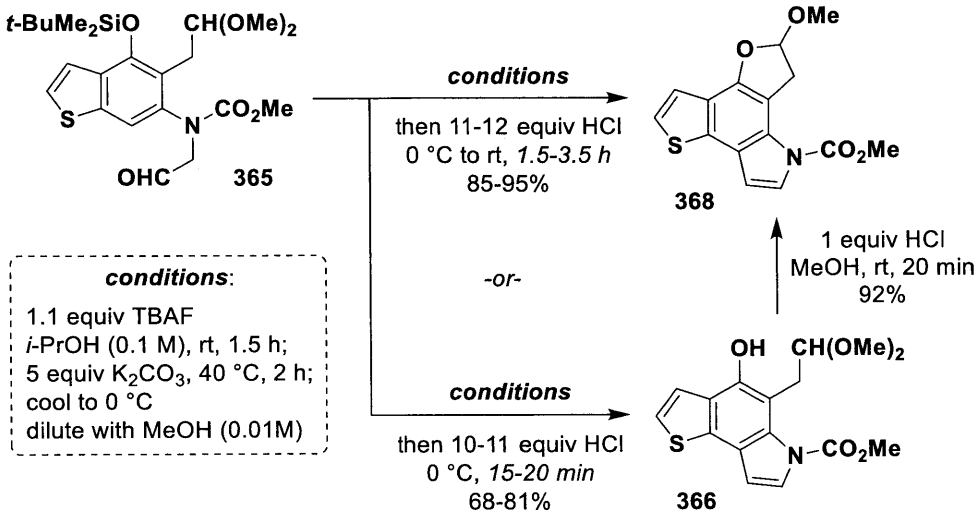


entry	solvent	approx. ratio of **370** : **371**[a]	conversion to **370** (%)[a]
1	*sec*-BuOH	92:8	73
2	*tert*-BuOH	74:26	45
3	*neo*-PentOH	91:9	67

[a] Determined by GC-MS.

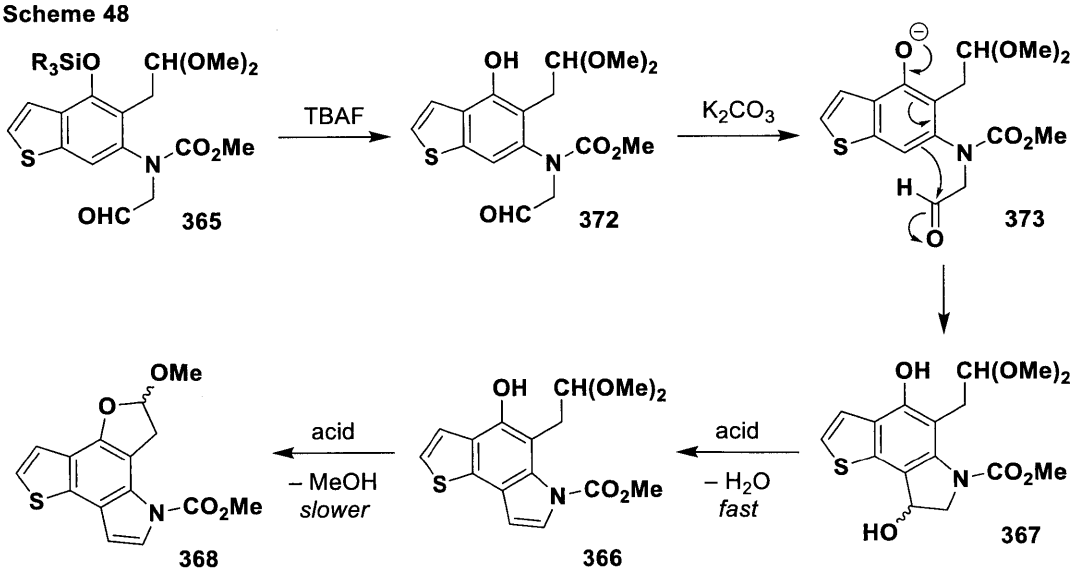
Though we were unable to find a solvent superior to *i*-PrOH for the cyclization reaction, the solution to the original problem was in fact quite straightforward. As outlined in Scheme 47, by conducting the desilylation and indole formation steps in *i*-PrOH and dilution of the reaction mixture tenfold with methanol before the addition of acid, the desired tetracycle **368** could be obtained in high yield with minimal contamination (< 2%) by the undesired isopropyl acetal **369**. Conducting double cyclization of aldehyde **365** in *sec*-butyl alcohol provided no practical advantages over *i*-PrOH. Due to the high dilution of the acidic step the formation of the oxygen heterocycle was significantly slower, enabling us to interrupt the reaction sequence and isolate tricycle **366** in good yield if the reaction was worked up in 15-20 min. Tricycle **366** could be converted to the desired tetracycle **368** in 92% yield by the action of acid in a separate step.

Scheme 47



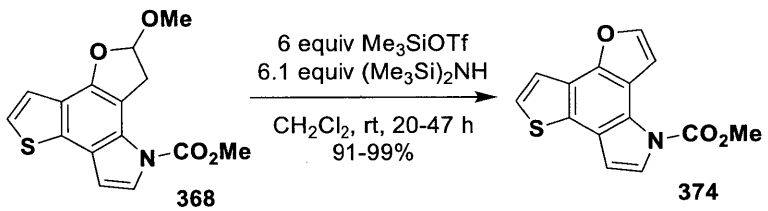
The results above provided valuable insights to the order of reactions taking place in this sequence. As outlined in Scheme 48, compound **365** is first desilylated by TBAF and deprotonated by K_2CO_3 to trigger the formation of the nitrogen heterocycle by aromatic substitution. Part of the initially formed hydroxyindoline **367** then dehydrates to form indole **366**. The process is especially rapid and complete in the presence of acid. Finally, the oxygen heterocycle forms under acidic conditions to furnish the desired tetracyclic product **368**. By careful choreography of reaction conditions, this double cyclization procedure enables direct synthesis of the tetracyclic core of the target from benzothiophene **365** in impressive efficiency and yield.

Scheme 48



The Endgame

In contrast to hydroxyindoline **367**, tetracycle **368** does not spontaneously eliminate methanol to form the furan ring on acidification of the reaction mixture. The ease of dehydration of **367** is attributed to the facile formation of a benzylic cation under acidic conditions. Forneris found that elimination proceeded on treatment of **368** with TFA in refluxing dichloromethane but the yield was only 36%. Elimination under basic conditions with KO*t*-Bu was also unsuccessful. A method reported by Miller and McKean involves the use of trimethylsilyl iodide and hexamethyldisilazane (HMDS) for the conversion of dimethyl acetals and ketals to methyl vinyl ethers.[130] We found this method applicable to our tetracyclic substrate in small scale test reactions although a large excess (7 equiv) of Me_3SiI was required to drive the reaction to completion. Due to concerns about the high cost and sensitivity of Me_3SiI, we replaced it with Me_3SiOTf and found the latter equally effective. Tetracycle **374** was generated in excellent yield under the indicated conditions (eq 43).



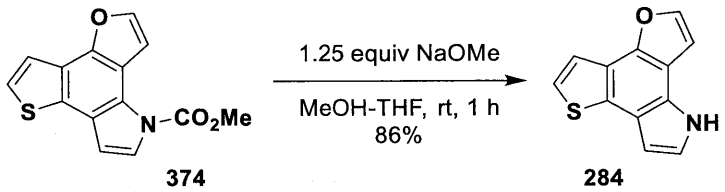
(43)

We believe the elimination proceeded via silylation of the methoxy group by Me_3SiOTf and subsequent deprotonation by HMDS.[131] The need of a large excess of Me_3SiOTf suggests that silylation also occurs on other parts of the molecule, e.g., the carbomethoxy group. However, the steric bulk of HMDS prevents its nucleophilic addition to the carbonyl group and subsequent cleavage of the carbomethoxy group from the aromatic core.

The carbomethoxy protecting group was easily cleaved by the action of sodium methoxide to furnish fully unsubstituted furo[2,3-*g*]thieno[2,3-*e*]indole (**284**) in high yield (eq 44). To our knowledge, this is the first reported successful synthesis of a fused tetracycle featuring three different types of five-membered aromatic heterocycles.

---

[130] Miller, R. D.; McKean, D. R. *Tetrahedron Lett.* **1982**, *23*, 323–326.
[131] The same observation with Me_3SiI was reported in: Miller, R. D.; McKean, D. R. *Synthesis* **1979**, 730–732.

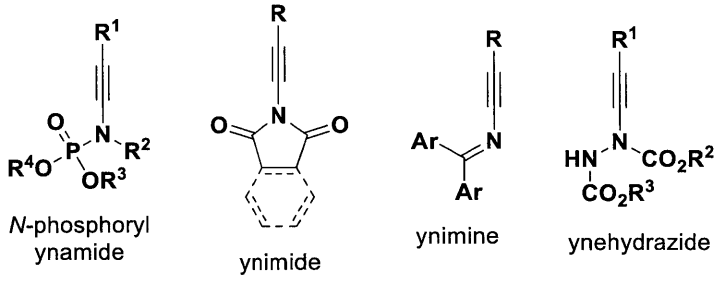


(44)

Both **374** and **284** are colorless and odorless solids which absorb strongly in the middle UV region.[132] They are sparingly soluble in most organic solvents while the parent furo[2,3-*g*]thieno[2,3-*e*]indole **284** is significantly soluble in hydroxylic solvents like ethanol possibly due to hydrogen bonding. While carbomethoxy-protected **374** is shelf-stable up to several months, the parent compound **284** slowly turns brown on storage at room temperature over a week or two. In addition, brown discoloration and decomposition were also observed when **284** was exposed to either ambient light or trifluoroacetic acid. The light and acid sensitivities are reminiscent of indole and attributed to the electron rich nature of the tetracyclic core.

Use of *N*-Phosphoryl Ynamides

As part of the active research on the synthesis and chemistry of ynamides in recent years, several new types of ynamides and closely related compounds have been reported including *N*-phosphoryl ynamides,[133] ynimides,[134] ynimines,[135] and ynehydrazides.[136] It was thus worthwhile to investigate the utility of these different classes of activated alkynes in our benzannulation.



[132] Maximum absorptions at 258 and 248 nm, respectively. See Experimental Procedures for full UV data.
[133] (a) DeKorver, K. A.; Walton, M. C.; North, T. D.; Hsung, R. P. *Org. Lett.* **2011**, *13*, 4862–4865. (b) DeKorver, K. A.; Johnson, W. L.; Zhang, Y.; Hsung, R. P.; Dai, H.; Deng, J.; Lohse, A. G.; Zhang, Y.-S. *J. Org. Chem.* **2011**, *76*, 5092–5103. (c) DeKorver, K. A.; Wang, X.-N.; Walton, M. C.; Hsung, R. P. *Org. Lett.* **2012**, *14*, 1768–1771.
[134] Sueda, T.; Oshima, A.; Teno, N. *Org. Lett.* **2011**, *13*, 3996–3999.
[135] Laouiti, A.; Rammah, M. M.; Rammah, M. B.; Marrot, J.; Couty, F.; Evano, G. *Org. Lett.* **2012**, *14*, 6–9.
[136] Beveridge, R. E.; Batey, R. A. *Org. Lett.* **2012**, *14*, 540–543.

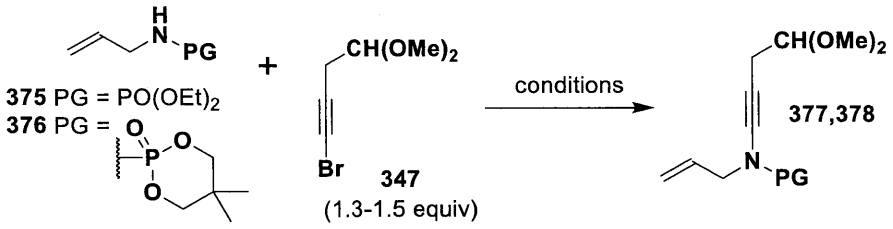
While preliminary results from our laboratory suggest that ynimines are inferior to regular *N*-carbonyl or sulfonyl ynamides in the benzannulation,[137] experiences with *N*-phosphoryl ynamides have been highly encouraging. Competition experiments indicated that *N*-phosphoryl ynamides undergo [2 + 2] cycloaddition with ketene at a rate 5 times faster than *N*-sulfonyl ynamides. The former is also around 8 times more reactive than *N*-carbomethoxy ynamides in the same reaction. This enhanced reactivity is attributed to the less electron-withdrawing nature of phosphoryl moieties. As a result, *N*-phosphoryl ynamides often gave superior yield of benzannulation products in shorter reaction times.[116]

In the synthetic sequence leading to furo[2,3-*g*]thieno[2,3-*e*]indole described previously, the photochemical benzannulation step was plagued by low reaction rates, polymer buildup, and moderate yield. Thus, we attempted to improve the synthesis by using *N*-phosphoryl ynamides in place of *N*-carbomethoxy derivatives. Two sets of conditions are described in the paper by Hsung for the synthesis of *N*-phosphoryl ynamides.[133a] First, "method A" involves the use of $CuSO_4 \cdot 5H_2O$ and 1,10-phenanthroline and requires 90-100 °C. Anhydrous conditions involving CuTC and DMEDA ("method B"), on the other hand, were reported to enable ynamide synthesis at temperatures as low as 50 °C.

Our attempts to synthesize *N*-phosphoryl ynamides are summarized in Table 14. As the *N*-allyl group in the ynamide product causes undesirable aza-Claisen arrangements to yield ketenimines at elevated temperatures (>75 °C), it is not surprising that the desired ynamide **377** was produced in low yield using method A (entry 1). However, conducting the alkynylation using method B still resulted in minimal conversion (entry 2). Hsung reported improved results with cyclic neopentyl glycol-derived phosphoramidates (e.g., **376**) and attributed this observation to the increased hydrolytic stability of these derivatives. Indeed, phosphoramidate **376** gave a somewhat better, though still modest and variable yield of ynamide **378** in our hands (entry 4). Attempts to obtain *N*-phosphoryl ynamides using the method developed by our laboratory (KHMDS/CuI/pyridine) resulted in no desired product and mainly dimerization of the bromoalkyne.

[137] Clément Chauvier. Unpublished work.

Table 14. Synthesis of *N*-Phosphoryl Ynamides

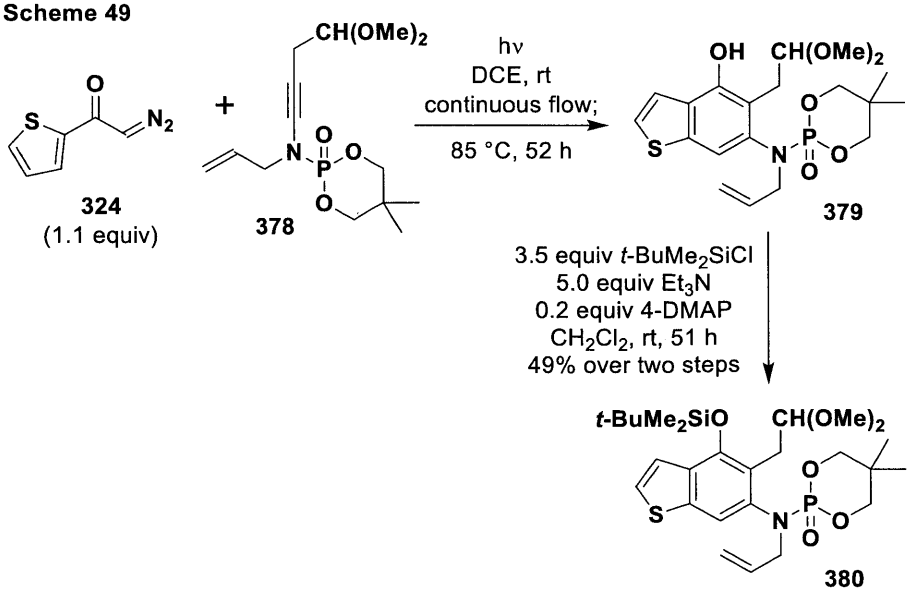


entry	phosphoramidate	conditions	ynamide	yield (%)[a]
1	**375**	cat. $CuSO_4 \cdot 5H_2O$, 1,10-phen 2 equiv K_3PO_4, PhMe, 90 °C, 72 h	**377**	10
2		cat. CuTC, DMEDA 2 equiv K_3PO_4, dioxane, 50 °C, 72 h		trace
3	**376**	cat. CuTC, DMEDA 3 equiv Cs_2CO_3, Et_3N-dioxane, 95 °C, 12 h	**378**	21
4		cat. CuTC, DMEDA 2 equiv K_3PO_4, dioxane, 50 °C, 72 h		18-56[b]
5		1 equiv KHMDS, 1 equiv CuI THF-pyridine, rt, 21 h		0[c]

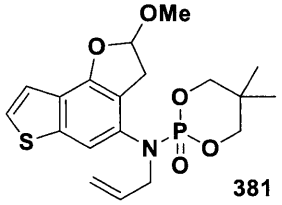
[a] Isolated yield of products purified by column chromatography. [b] 56% on 0.2 g scale; 39% on 0.9 g scale; 18% on 1.5 g scale (54% BRSM). [c] 75% of alkyne dimer was isolated.

With the desired *N*-phosphoryl ynamide in hand, we next investigated its photochemical benzannulation in continuous flow. Using tubing dried in a 160 °C oven overnight, glassware treated with a base bath (KOH/aq. *i*-PrOH), and azeotropically dried diazo ketone **324**, benzothiophene **380** was obtained in 49% overall yield after benzannulation and silylation (Scheme 49). Using 1,2-dichloroethane (DCE) instead of CH_2Cl_2 as the solvent for the irradiation step made it possible to conduct the subsequent heating step without solvent exchange. Complete consumption of the starting materials was observed with a residence time of 21 min typical of our previous benzannulations in flow.[116] In addition, there was no colored polymers observed inside the tubing at the end of irradiation. Both of these signs point to a significantly higher reaction rate for *N*-phosphoryl compared to *N*-carbomethoxy ynamides.

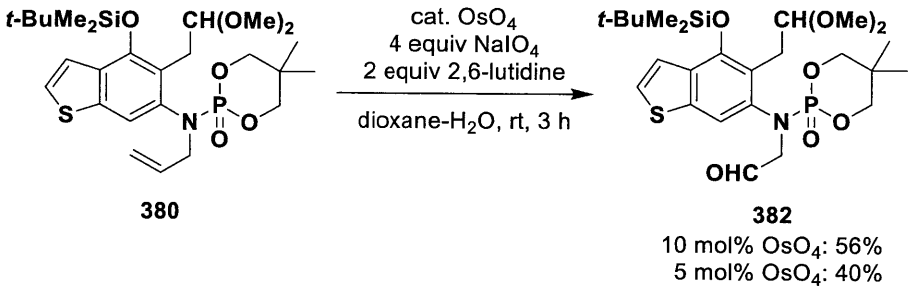
Scheme 49



The reduced yield of the benzannulation product compared to the *N*-carbomethoxy counterpart is attributed to the higher tendency for phenol **379** to undergo the unwanted cyclization to form tricycle **381**. Even with all precautions taken as described above, partial formation of **381** was still observed and this byproduct was difficult to separate from the desired phenol by column chromatography. In a separate experiment, even contact of phenol **379** with water in a workup step was found to be sufficient to partially cause cyclization. The ease of the cyclization is attributed the higher nucleophilicity of the phenol hydroxyl group due to the lower electron-withdrawing ability of the *N*-phosphoryl group compared to the *N*-carbomethoxy moiety.



Oxidative cleavage was carried out using the modified Lemieux-Johnson method (eq 45). While TLC analysis indicated complete reaction after 3 h, the isolated yield was less than ideal. The modest yield may be attributed to the instability of the substrate toward the strong oxidant $NaIO_4$ under aqueous conditions.



380

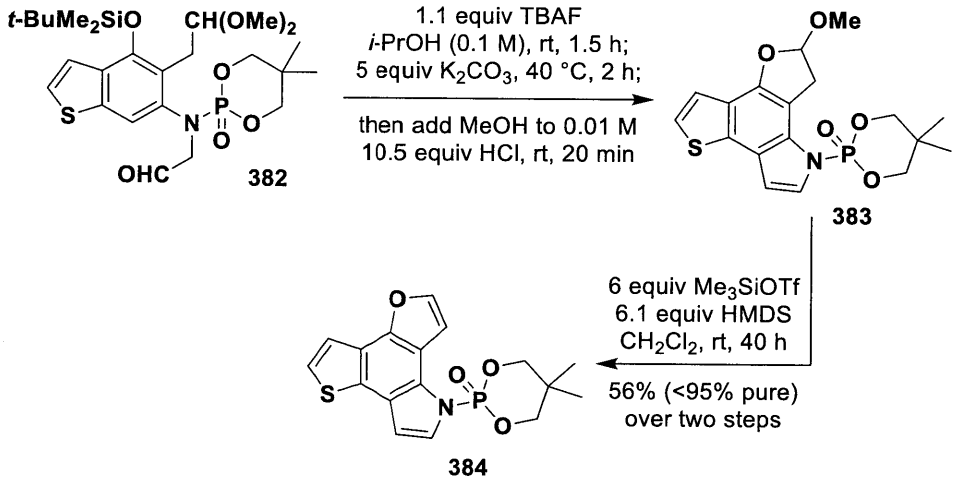
382

10 mol% OsO_4: 56%
5 mol% OsO_4: 40%

(45)

We then conducted the key double cyclization using the same conditions used in the *N*-carbomethoxy counterpart. While the cleavage of the silyl group and the first cyclization proceeded smoothly, the product partially decomposed during the acidic cyclization step. The decomposition is attributed to the acid-labile nature of the phosphoryl protecting group. This led to a reduced yield (ca. 70%) and difficulty in purification of the desired tetracyclic product. Elimination of methanol with Me_3SiOTf/HMDS finally furnished the slightly impure *N*-phosphoryl tetracycle **384** in 56% overall yield from aldehyde **382** (Scheme 50).

Scheme 50



382

383

384

While the use of *N*-phosphoryl ynamides enabled successful photochemical benzannulation in continuous flow, the subsequent steps gave markedly inferior results to those in the *N*-carbomethoxy ynamide route. Along with the reduced atom economy from the large phosphoryl group, the route was determined to be inefficient and we did not attempt to make further optimization.

Summary

Furo[2,3-*g*]thieno[2,3-*e*]indole was synthesized in 9 steps in the longest linear sequence from commercially available compounds. This total synthesis highlights the power of the "second-generation" benzannulation based on ynamides and diazo ketones in the synthesis of highly substituted aromatic compounds and unique polycyclic aromatic systems.

Chapter 3

Chemistry of Furo[2,3-*g*]thieno[2,3-*e*]indole

The first synthesis of furo[2,3-*g*]thieno[2,3-*e*]indole (FTI, **284**) was described in the previous chapter. We next focused our attention on investigating the properties of this unique tetracyclic system with three different types of heterocyclic ring fused to a central benzenoid ring. In addition, it was also of interest to investigate methods for the functionalization of the tetracyclic core that could enable the preparation of extended systems and oligomers with potential utility in organic electronic applications.

Bromination

Bearing three electron-donating heteroatoms, furo[2,3-*g*]thieno[2,3-*e*]indole is expected to be a highly electron-rich aromatic system. Like indole, benzofuran, and benzothiophene, facile electrophilic aromatic substitution is anticipated to be a prominent mode of reaction of FTI. The relative reactivity of five-membered aromatic heterocycles has been the subject of some research and it is well known that pyrrole is significantly more reactive than furan, which is much more reactive than thiophene (Table 15).[138] In all cases the most reactive site is C2 adjacent to the heteroatom due to greater delocalization of the positive charge in the resulting σ-complex.

Table 15. Relative Reaction Rates of Heterocycles (Thiophene = 1)

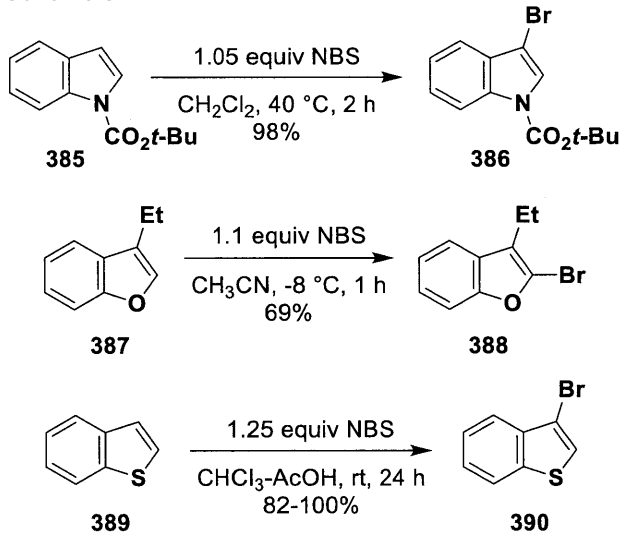
Reaction	Reagents	Thiophene	Furan	Pyrrole
Acetylation	Ac_2O, $SnCl_4$	1	11.9	
Trifluoroacetylation	$(CF_3CO)_2O$ in DCE	1	150	5×10^7
Formylation	DMF, $(COCl)_2$ in $CHCl_3$	1	100	
Bromination	Br_2	1	120	5.9×10^8

The relative reactivity of benzo-fused five-membered heterocycles follows the exact same trend. However, the regiochemistry of electrophilic substitution is somewhat different in the case of the bicyclic compounds. Ab initio calculations in a Gaussian orbital basis[139] showed that both benzofuran and benzothiophene have a dipole moment (1.56 and 0.56 D, respectively) pointing

[138] Marino, G. *J. Heterocycl. Chem.* **1972**, *9*, 817–819.
[139] Palmer, M. H.; Kennedy, S. M. F. *J. Chem. Soc., Perkin. Trans. 2* **1974**, 1893–1903.

toward the heteroatom. In contrast, indole has a large dipole moment (2.31 D) pointing away from the nitrogen in a roughly C2-to-C3 direction. Indeed, electrophilic substitution reactions of indole primarily occur at C3 as reactions at C2 create intermediates that cannot be stabilized by the heteroatom without disruption of the benzenoid aromatic systen. Substitution on benzothiophene and benzofuran has been found to occur at either C2 or C3 depending on reaction conditions. While studies that include comparisons of the reactivity of *N-protected* indoles vs. other heterocycles have been scarce, literature records of bromination with NBS suggest that *N*-acyl indoles are more reactive than benzofurans (Scheme 51).[140] Thus, it would be interesting to determine the regiochemistry of electrophilic aromatic substitution on the FTI tetracyclic system as it is the first example of a compound combining all three heterocycles in one molecule and would enable the comparison of the reactivity of the three heterocycles, as well as the perturbations within the system.

Scheme 51

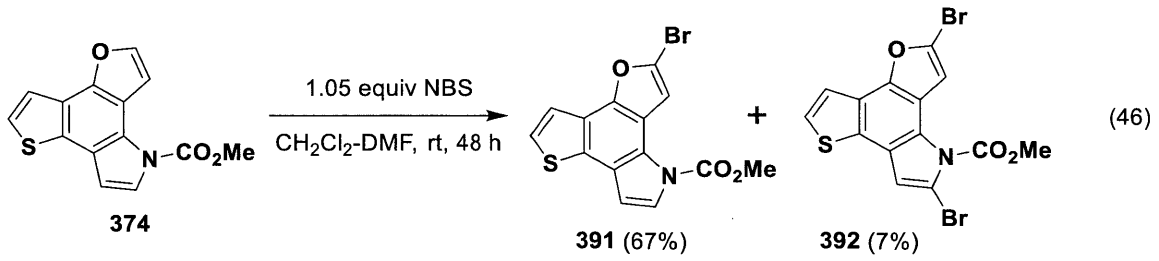


We decided to initially conduct bromination on the *N*-carbomethoxy protected FTI (**374**) as we felt that the free indole NH moiety might cause unwanted side reactions. Bromination would

[140] Bromination of *N*-Boc-indole (**385**), 3-ethylbenzofuran (**387**), and benzothiophene (**389**), in that order, required the use of increasingly polar solvents. For respective reactions, see: (a) James, C. A.; Coelho, A. L.; Gevaert, M.; Forgione, P.; Snieckus, V. *J. Org. Chem.* **2009**, *74*, 4094–4103. (b) Ando, K.; Kawamura, Y.; Akai, Y.; Kunitomo, J.; Yokomizo, T.; Yamashita, M.; Ohta, S.; Ohishi, T.; Ohishi, Y. *Org. Biomol. Chem.* **2008**, *6*, 296–307. (c) Dit Chabert, J. F.; Joucla, L.; David, E.; Lemaire, M. *Tetrahedron* **2004**, *60*, 3221–3230. (d) Qi, T.; Guo, Y.; Liu, Y.; Xi, H.; Zhang, H.; Gao, X.; Liu, Y.; Lu, K.; Du, C.; Yu, G.; Zhu, D. *Chem. Commun.* **2008**, 6227–6229.

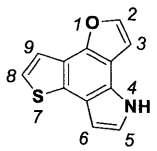
also provide the simplest NMR spectra and distinct isotope patterns in mass spectra, both of which could be used to our advantage to analyze the product distribution. We believe it was reasonable to use *N*-carbomethoxyindole as the model compound in our study. Preliminary model studies by Thibault Guez in our laboratory suggested that *N*-carbomethoxyindole can be brominated at C3 with NBS in DMF or THF while benzofuran is unreactive under the same conditions.

While **374** was found to be nearly unreactive toward purified NBS in dichloromethane, formation of a major product was observed when DMF was added to the reaction mixture. The product was isolated in 67% yield and identified as the 2-bromo compound **391**[141] based on ^{1}H NMR analysis (eq 46). FTI and its derivatives show characteristic coupling constants between the downfield H2 signals and upfield H3 signals typical for simple bicyclic compounds: J = 2.2 Hz for benzofuran,[142] 3.8 Hz for *N*-carbomethoxyindole,[143] and 5.5 Hz for benzothiophene.[144] A small amount (7%) of 2,5-dibromide **392** was also isolated as a minor overbromination product.

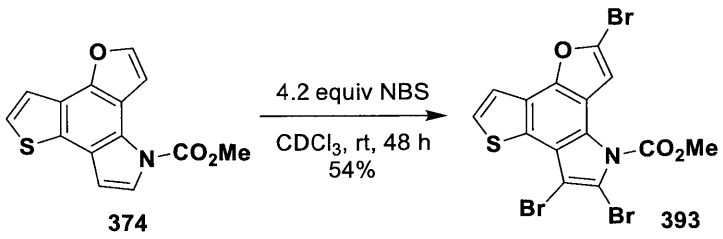


374 **391** (67%) **392** (7%) (46)

While attempts to obtain the dibromide **392** in higher yield were unsuccessful, treatment of **374** with 4.2 equiv of NBS in chloroform resulted in the clean formation of 2,5,6-tribromide **393** in moderate yield (eq 47). Copper(II) bromide,[145] on the other hand, was found too aggressive and caused mainly decomposition of the starting material.



[141] Numbering of the heavy atoms in the FTI system according to IUPAC nomenclature:
[142] Black, P. J.; Heffernan, M. L. *Aust. J. Chem.* **1965**, *18*, 353–361.
[143] Heller, S. T.; Schultz, E. E.; Sarpong, R. *Angew. Chem., Int. Ed.* **2012**, *51*, 8304–8308.
[144] Ewing, D. F.; Scrowston, R. M. *Org. Magn. Reson.* **1971**, *3*, 405.
[145] For recent examples of bromination of similar indole systems with $CuBr_2$, see: (a) Gallou, F.; Reeves, J. T.; Tan, Z.; Song, J. J.; Yee, N. K.; Campbell, S.; Jones, P.-J.; Senanayake, C. H. *Synlett* **2005**, 2400–2402. (b) Gallou, F.; Reeves, J. T.; Tan, Z.; Song, J. J.; Yee, N. K.; Harcken, C.; Liu, P.; Thomson, D.; Senanayake, C. H. *Synlett* **2007**, 211–214. (c) Tang, S.; Li, J.-H.; Xie, Y.-X.; Wang, N.-X. *Synthesis* **2007**, 1535–1541.



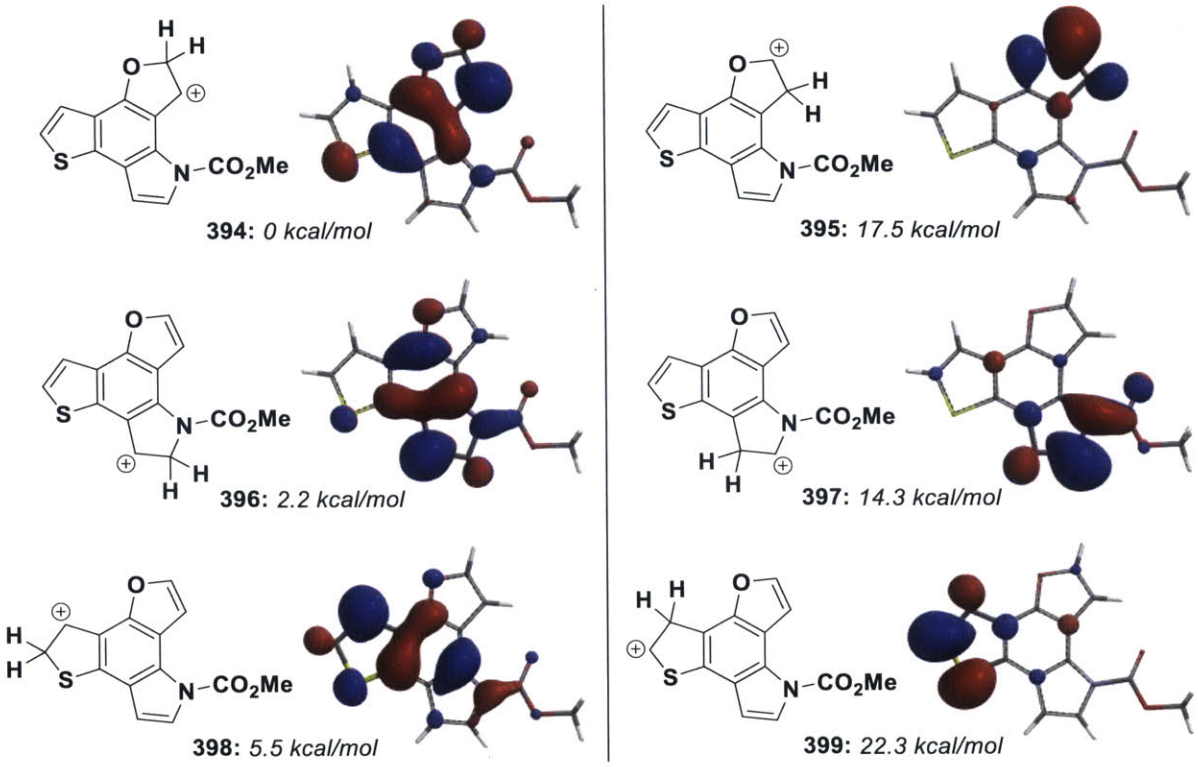
(47)

These results are surprising as the literature suggests that *N*-acyl indoles are more reactive than benzofurans toward bromination. In addition, electrophilic substitutions of indoles typically occur exclusively at C3 while dibromide **392** had the carbon adjacent to the nitrogen atom brominated. The observed regiochemistry of the bromination indicates significant perturbations of the electronic structure of FTI compared to indole, benzofuran, and benzothiophene.

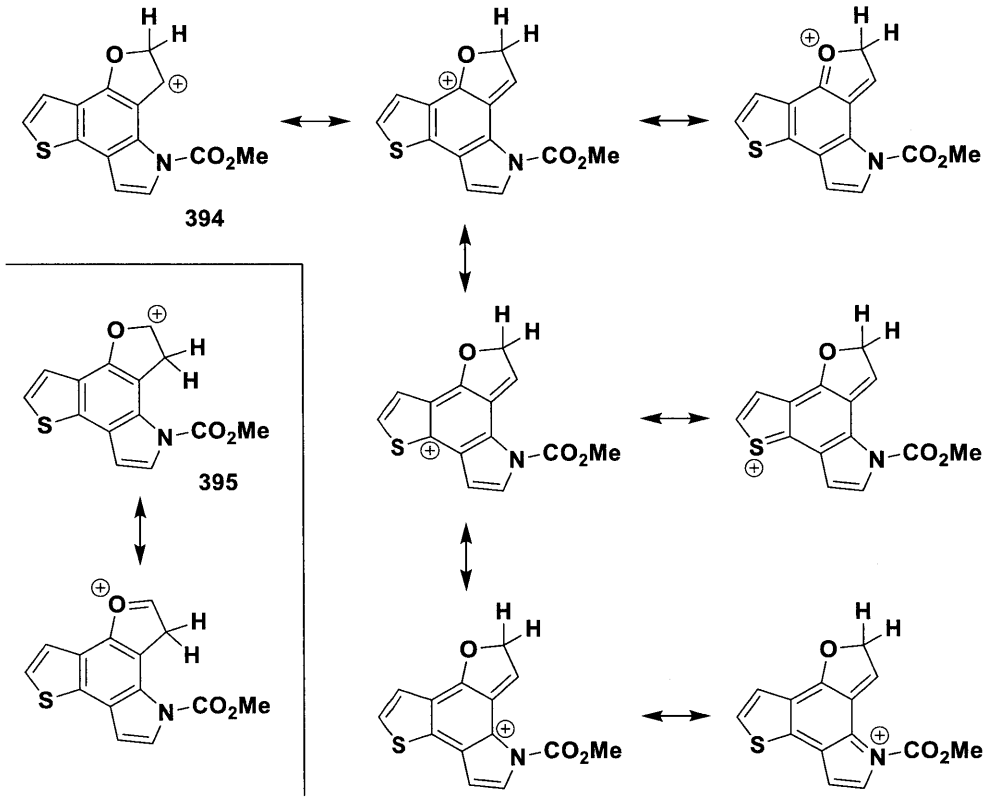
Some theoretical calculations were set up to gain insights to the experimental results.[146] The relative energies and LUMOs of **374** protonated at each of the six peripheral positions were obtained. As shown in Figure 4, protonation at each of the "C2" positions results in significantly more delocalization of the positive charge – and hence lower energies – than protonation at each of the "C3" positions. These results are in agreement with simple arguments based on resonance structures. As shown in Scheme 52, C2-protonated tetracycle **394** is capable of delocalizing the charge throughout the entire molecule while delocalization of the charge in C3-protonated species **395** is mainly limited to a single heterocycle.

[146] The Hartree–Fock 3-21G basis set was used to find the equilibrium conformer of **374** and its protonated derivatives. Hartree–Fock 6-311+G** was then employed to further optimize the geometries and obtain molecular orbitals and relative energies.

Figure 4. Relative Energies and LUMO Diagrams of Protonated FTI Derivatives



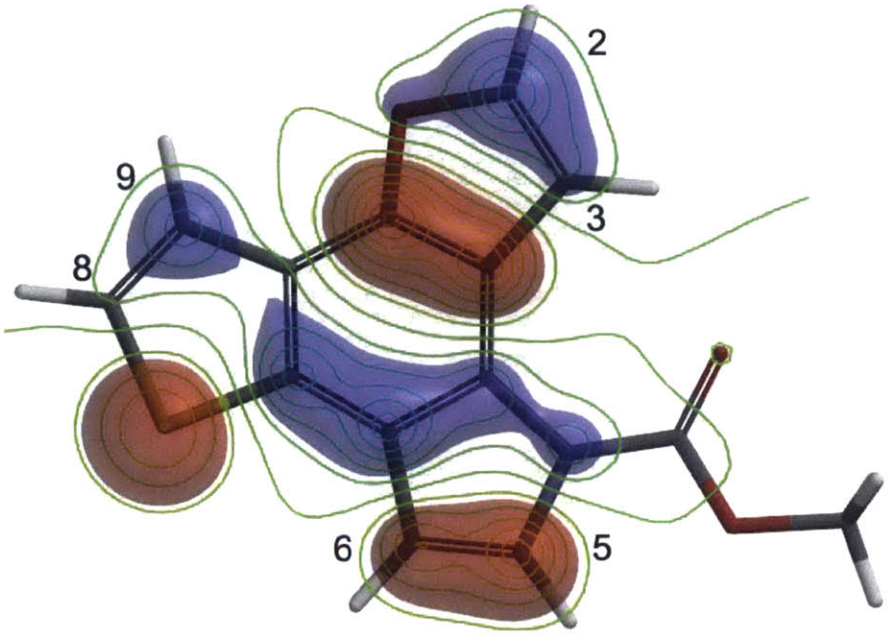
Scheme 52



The marked preferences of bromination at C2 over C3 of each heterocycle in **374** is attributed to the significantly enhanced stability of the carbocation intermediates involved in the former case. While calculated relative energies are in agreement with the preferred first and second sites of bromination based on Hammond's postulate, the third bromination did not occur on the thiophene ring in reality as would be expected from the calculations.

Analysis of the HOMO of **374** may provide a better picture of the regioselectivity of electrophilic substitutions as these reactions may have early transition states due to the reactive nature of the tetracycle. Indeed, as shown in Figure 5, the calculated HOMO has the highest coefficients on C2 and C5 followed by C6 among all peripheral heavy atoms. This is in good agreement with the observed pattern of bromination of **374** based on the assumption that bromination does not cause significant changes to the HOMO structure of the molecule. While the differences in C2 and C5 both in HOMO coefficients and carbocation energies are not significant, the preference of bromination on C2 over C5 may be attributed to steric reasons.

Figure 5. Calculated HOMO Diagram of 374[a]



[a] HOMO isosurface of ±0.032 and nineteen contours between values of -0.2 to 0.2 were plotted.

Lithiation

Another frequently conducted reaction in the derivatization of heterocycles is metallation, especially lithiation. While it is well-known that benzofuran, benzothiophene, and *N*-substituted indoles all lithiate at C2, direct comparison of their relative acidities is scarce in the literature. In addition, the carbomethoxy group is seldom used to protect indoles during metallation due to the possibility of addition to the carbonyl group. Nevertheless, a few reports of successful 2-lithiation of *N*-carbomethoxy indoles exist,[147] and we felt it might be possible to lithiate the *N*-carbomethoxy protected FTI (**374**) and investigate the regiochemistry by reaction of the lithiated species with electrophiles.

Treatment of *N*-carbomethoxyindole with *t*-BuLi in THF at -78 °C resulted in complete deprotection so this set of conditions was not used in the lithiation of **374**. Lithiation of **374** with LDA in THF at -78 °C followed by quenching with D_2O resulted in no deuteration of the aromatic core and an 83:17 mixture of unreacted starting material and deprotected FTI (**284**) was recovered. The deprotection was attributed to the formation of LiOD from quenching of the unreacted LDA

[147] (a) Daïri, K.; Yao, Y.; Faley, M.; Tripathy, S.; Rioux, E.; Billot, X.; Rabouin, D.; Gonzalez, G.; Lavallée, J.-F.; Attardo, G. *Org. Process Res. Dev.* **2007**, *11*, 1051–1054. (b) Nicolaou, K. C.; Dalby, S. M.; Li, S.; Suzuki, T.; Chen, D. Y.-K. *Angew. Chem. Int. Ed.* **2009**, *48*, 7616 –7620.

with D_2O. Reaction of **374** with bulky lithium tetramethylpiperidide (LiTMP) as the base in THF at -78 °C followed by addition of DMF and warming to rt overnight resulted in a mixture of the starting material, deprotected FTI (**284**), and a significantly more polar product separable from the first two by column chromatography. However, this polar product was found to contain an inseparable complex mixture of at least two different aldehydes among other impurities. The regiochemistry could not be determined.

The results above suggested that **374** is likely more difficult to lithiate than *N*-carbomethoxyindole due to its higher level of electron density. Lithiation also does not seem to be regioselective enough to be synthetically useful. It is conceivable that lithiation may be more selective with a stronger directing group on the nitrogen atom.

Conclusion

Benzannulation based on ynamides has proven to be a highly efficient means for the efficient and regioselective synthesis of multiply substituted anilines. Benzofused nitrogen heterocycles, especially indoles, can easily be derived from the benzannulation products. The use of 2-iodoynamides further expanded the toolbox for the synthesis of indoles based on the benzannulation-cyclization strategy. The "second-generation" benzannulation using diazo ketones as the vinylketene precursor further expanded the scope of benzannulation to enable the direct synthesis of fused bicyclic and polycyclic aromatic compounds. We have demonstrated a significant application of this diazo ketone-based benzannulation in the synthesis of an exotic unnatural product, furo[2,3-*g*]thieno[2,3-*e*]indole (FTI). Further work will continue in our laboratory to improve the synthesis of this compound and investigate its often unexpected chemical and electronic behaviors.

Part III

Experimental Procedures and NMR Data

General Procedures. All reactions were performed in flame-dried or oven-dried glassware under a positive pressure of argon and stirred magnetically unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred via gas-tight syringe or cannula and introduced into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated by using a rotary evaporator at 20 mmHg and then at 20 °C, 0.05 mmHg (vacuum pump) overnight unless otherwise indicated. Filtration was conducted through sintered-glass Büchner funnels with vacuum suction (20 mmHg) unless otherwise indicated. Column chromatography was performed on silica gel 60 (35-75 μm or 230-400 mesh) unless otherwise indicated. Slow addition from syringes were performed with an Orion M365 multi-range variable rate syringe pump.

Materials. Commercial grade reagents and solvents were used without further purification except as indicated below.

(a) Purified by pressure filtration through activated alumina: dichloromethane, diethyl ether, and tetrahydrofuran.

(b) Purified by pressure filtration through activated alumina and copper(II) oxide: toluene.

(c) Distilled under argon from calcium hydride: acetonitrile, benzene, dichloroethane (DCE) , hexamethyldisilazane (HMDS), 2,6-lutidine, pyridine, triethylamine, and trimethyl orthoformate.

(d) Distilled under argon from magnesium powder: methanol and isopropyl alcohol.[148]

(e) Dried at 110 °C, 0.05–0.1 mmHg for 18 h: cesium carbonate, lithium chloride, and potassium carbonate.

(f) Other:

Acetyl chloride was distilled from quinoline.

N-Bromosuccinimide was recrystallized from water.[149]

n-Butyllithium was titrated using menthol in THF with 1,10-phenanthroline as an indicator.[150]

Copper(I) iodide was purified by washing with refluxing THF in a Soxhlet extractor for 72 h followed by drying in a vacuum desiccator over P_2O_5 overnight.

---

[148] Burfield, D. R.; Smithers, R. H. *J. Org. Chem.* **1983**, *48*, 2420–2422.

[149] Dauben, H. J.; McCoy, L. L. *J. Am. Chem. Soc.* **1959**, *81*, 4863–4873.

[150] (a) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165–167. (b) Ellison, R. A.; Griffin, R. ; Kotsonis, F. N. *J. Organomet. Chem.* **1972**, *36*, 209–213.

Copper(I)-thiophene-2-carboxylate (CuTC) was washed successively with anhydrous methanol, diethyl ether, and pentane, and dried under vacuum.

Deuterochloroform ($CDCl_3$), when used in reactions, was allowed to stand over 4Å molecular sieves for at least 24 h prior to use.

1,2-Diiodoethane was washed with satd aqueous $Na_2S_2O_3$ solution and crystallized from diethyl ether.

N,N-Dimethylformamide (DMF) was stirred with CaH_2 overnight and distilled under vacuum (20 mmHg) onto 4Å molecular sieves.

1,4-Dioxane was distilled under argon from sodium-benzophenone ketyl.

Furan was washed with 5% aqueous KOH and distilled under argon from KOH pellets.

Iodomethane was passed through neutral alumina immediately prior to use.

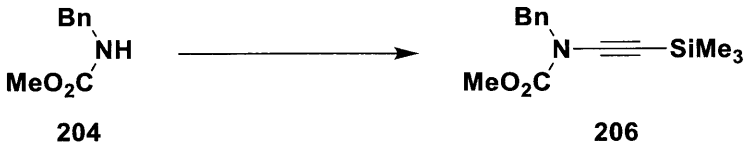
Sodium periodate supported on silica gel was prepared according to the procedure of Zhong and Shing.[43]

Instrumentation. Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained using a Perkin Elmer 2000 FT-IR spectrophotometer. ^{1}H NMR spectra were measured with a Varian Mercury 300 (300 MHz) and Varian Inova 500 (500 MHz) spectrometers. ^{1}H NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the $CHCl_3$ peak at 7.27 ppm used as a standard). ^{13}C NMR spectra were measured with a Varian Inova 500 (125 MHz) spectrometer. ^{13}C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the central peak of $CDCl_3$ at 77.23 ppm used as a standard). High resolution mass spectra (HRMS) were measured on a Bruker Daltonics APEXII 3 telsa Fourier transform mass spectrometer.

Construction of the Continuous Flow Reactor. The continuous flow reactor employed in our experiments was constructed based on the design of Booker-Milburn et al.[121] Fluorinated ethylene propylene (FEP) tubing, 1.59 mm o.d., 0.76 mm i.d., length = 440 cm, was wrapped around a quartz immersion well in tightly packed coils leaving 90 cm of tubing free at each end. The length of tubing wrapped around the well was 260 cm (internal volume ca. 1.2 mL). The ends of the tubing were secured to the well with Teflon tape. The top end of the tubing was fitted with a nut, ferrule, and a thread to a female Luer adapter for attachment of a syringe. The bottom end

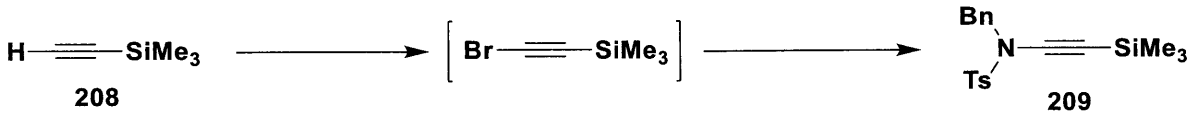
of the tubing was connected through a rubber septum to a 25-mL or 50-mL pear flask equipped with an argon inlet needle and a needle vent. The flask was wrapped in aluminium foil. The immersion well was connected to recirculating tap water via PVC tubing. A Pyrex or uranium filter and a 450 W Hanovia medium-pressure mercury lamp were placed inside the immersion well.[151]

[151] See Figure 3 (p. 80) for a diagram of the continuous flow reactor.

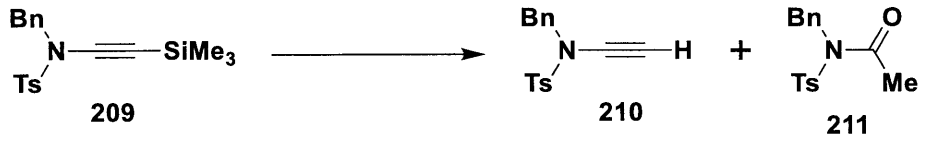


***N*-Benzyl-*N*-methoxycarbonyl-2-(trimethylsilyl)ethynylamine (206).** A 250-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and argon inlet adapter was charged with carbamate **204**[59] (1.50 g, 9.10 mmol, 1.0 equiv), 70 mL of THF, and 18.3 mL of pyridine. The colorless solution was cooled at 0 °C and a solution of KHMDS (0.91 M in THF, 10.0 mL, 9.10 mmol, 1.0 equiv) was added dropwise via syringe over 30 min. The resulting tan suspension was stirred for 15 min and CuI (1.73 g, 9.10 mmol, 1.0 equiv) was added in one portion. The resulting grass-green suspension was allowed to warm to rt and stirred for a total of 3 h. A solution of iodo(trimethylsilyl)acetylene[60] (1.92 g, 8.57 mmol, 0.94 equiv) in 8 mL of THF was added to the dark green reaction mixture dropwise over 1 h via syringe, and the reaction mixture was stirred at rt for 16 h. The resulting brown solution was diluted with 100 mL of Et_2O and washed with three 75-mL portions of a 2:1 mixture of brine and concentrated NH_4OH solution. The combined aqueous phases were extracted with two 80-mL portions of Et_2O, and the combined organic phases were washed with two 80-mL portions of 3 M aqueous HCl solution and 80 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 4.23 g of dark brown oil. Column chromatography on 55 g of silica gel (gradient elution with 0–5% EtOAc–hexanes) afforded 1.31 g (58%) of ynamide **206** as a yellow oil with spectral data consistent with that previously reported.[61]

***N*-Benzyl-*N*-(methoxycarbonyl)ethynylamine (207).** A 100-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with ynamide **206** (0.500 g, 1.91 mmol, 1.0 equiv) and 25 mL of THF. The yellow solution was cooled at -78 °C and TBAF (2.1 mL, 1.0 M in THF, 2.1 mmol, 1.1 equiv) was added dropwise via syringe over 5 min. The resulting brown suspension was stirred for 10 min and then diluted with 25 mL of Et_2O, 25 mL of water, and 5 mL of brine. The aqueous phase was extracted with two 20-mL portions of Et_2O, and the combined organic phases were washed with 30 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.441 g of orange oil. Column chromatography on 12 g of acetone-deactivated silica gel (elution with 4% EtOAc and 1% Et_3N in hexanes) afforded 0.294 g (81%) of ynamide **207** as a viscous pale yellow oil with spectral data consistent with that previously reported.[58]

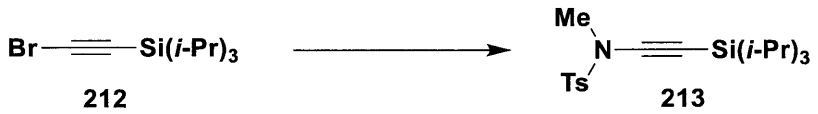


***N*-Benzyl-*N*-(*p*-toluenesulfonyl)-2-(trimethylsilyl)ethynylamine (209).** A 200-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with (trimethylsilyl)acetylene (2.80 mL, 1.95 g, 19.8 mmol, 1.0 equiv) and 100 mL of acetone. NBS (3.88 g, 21.8 mmol, 1.1 equiv) and $AgNO_3$ (0.168 g, 0.990 mmol, 0.05 equiv) were added, and the reaction flask was wrapped in aluminum foil. The reaction mixture was stirred at rt for 2 h, and the resulting white suspension was diluted with 100 mL of pentane and 100 mL of water. The organic phase was washed with two 100-mL portions of satd aqueous $Na_2S_2O_3$ solution and 100 mL of brine, dried over $MgSO_4$, filtered, and carefully concentrated by rotary evaporation (0 °C, 20 mmHg) to afford 3.48 g of colorless liquid. This material was dissolved in 30 mL of toluene and transferred into a 100-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle containing BnNHTs (5.18 g, 19.8 mmol, 1.0 equiv), $CuSO_4 \cdot 5H_2O$ (0.494 g, 1.98 mmol, 0.1 equiv), 1,10-phenanthroline (0.714 g, 3.96 mmol, 0.2 equiv), and K_2CO_3 (5.47 g, 39.6 mmol, 2.0 equiv). The resulting pale green suspension was heated at 65 °C with vigorous stirring for 21 h and then allowed to cool to rt. The resulting dark green suspension was filtered through a pad of Celite with the aid of 50 mL of EtOAc. The deep red filtrate was concentrated onto 25 g of silica gel and purified by column chromatography on 200 g of silica gel (gradient elution with 0–10 % EtOAc-hexanes) to give 2.85 g (40%) of ynamide **209** as an off-white solid: mp 72–73 °C with spectral data consistent with that previously reported.[64a]

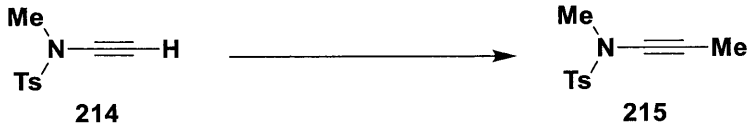


***N*-Benzyl-*N*-(*p*-toluenesulfonyl)ethynylamine (210) and *N*-benzyl-*N*-tosylacetamide (211).** A 300-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with ynamide **209** (1.43 g, 4.00 mmol, 1.0 equiv) and 50 mL of methanol. K_2CO_3 (0.829 g, 6.00 mmol, 1.5 equiv) was added in one portion and the mixture was stirred vigorously at rt for 2 h. The resulting white suspension was diluted with 50 mL of water and 50 mL of Et_2O. The aqueous phase was extracted with four 30-mL portions of Et_2O, and the combined organic phases were washed with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.789 g of an off-white solid. Column chromatography on 50 g of silica gel (elution with 10% EtOAc-hexanes) afforded 0.410 g of ynamide **210** as a colorless solid and 0.461 g of acetamide **211** as a colorless solid both with spectral data consistent with that previously reported.[64a,152]

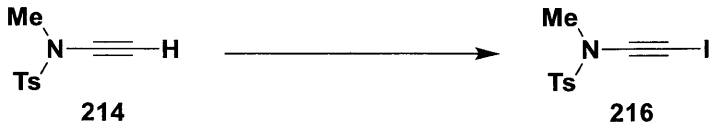
[152] Raji Reddy, C.; Mahipal, B.; Yaragorla, S. R. *Tetrahedron Lett.* **2007**, *48*, 7528–7532.



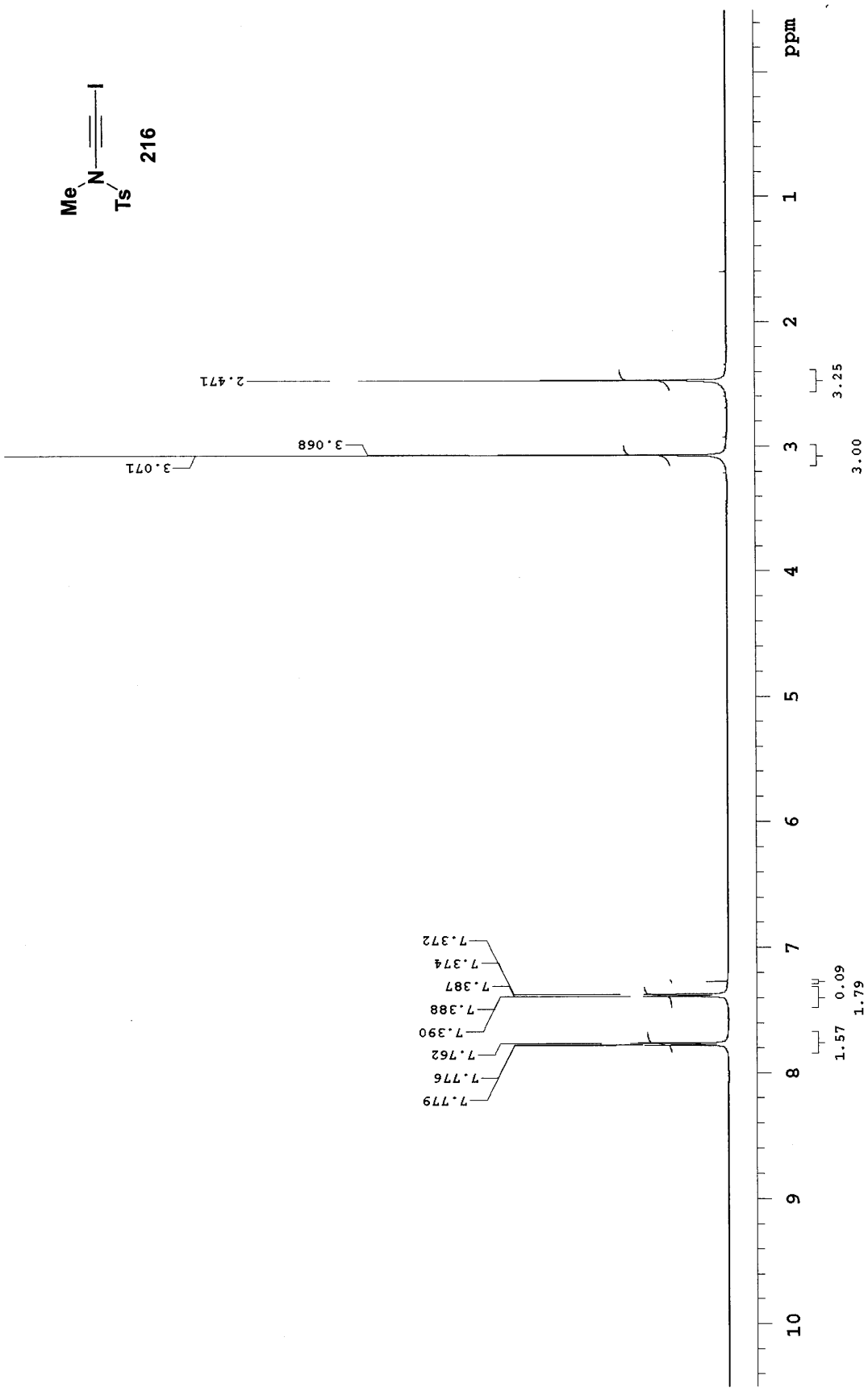
***N*-Methyl-*N*-(*p*-toluenesulfonyl)-2-(triisopropylsilyl)ethynylamine (213).** A 100-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with *N*-methyl-*p*-toluenesulfonamide (2.67 g, 14.4 mmol, 1.3 equiv), $CuSO_4 \cdot 5H_2O$ (0.277 g, 1.11 mmol, 0.1 equiv), 1,10-phenanthroline (0.400 g, 2.22 mmol, 0.2 equiv), and K_2CO_3 (3.07 g, 22.2 mmol, 2.0 equiv). A solution of bromo(triisopropylsilyl)acetylene[66] (2.91 g, 11.1 mmol, 1.0 equiv) in 20 mL of toluene was added, and argon was bubbled through the pale green reaction mixture with vigorous stirring for 5 min. The reaction mixture was heated at 70 °C with vigorous stirring for 41 h and then allowed to cool to rt. The resulting dark green suspension was filtered through a pad of Celite with the aid of 50 mL of dichloromethane. The deep red filtrate was concentrated onto 7 g of silica gel and purified by column chromatography on 60 g of silica gel (gradient elution with 0–7.5 % EtOAc-hexanes) to give 3.69 g (91%) of ynamide **10** as a white waxy crystalline solid: mp 47–49 °C with spectral data consistent with that previously reported.[65]



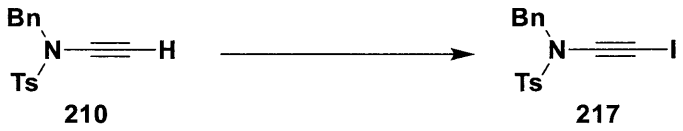
***N*-Methyl-*N*-(*p*-toluenesulfonyl)-prop-1-ynylamine (215).** A 25-mL pear flask equipped with a rubber septum and argon inlet needle was charged with ynamide **214** (0.200 g, 0.956 mmol, 1.0 equiv) and 10 mL of THF. The pale yellow solution was cooled at -20 °C and a solution of *n*-BuLi (2.44 M in hexanes, 0.430 mL, 1.05 mmol, 1.1 equiv) was added dropwise via syringe over 3 min. The resulting orange solution was stirred at -20 °C for 3 h and then iodomethane (0.178 mL, 2.87 mmol, 3.0 equiv) was added in one portion. The reaction mixture was allowed to warm to rt over 1.5 h and then diluted with 10 mL of Et_2O and 10 mL of satd aqueous NH_4Cl solution. The aqueous phase was extracted with two 10-mL portions of Et_2O, and the combined organic phases were washed with 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.198 g (93%) of ynamide **215** as an orange crystalline solid: mp 96–99 °C with spectral data consistent with that previously reported.[69]



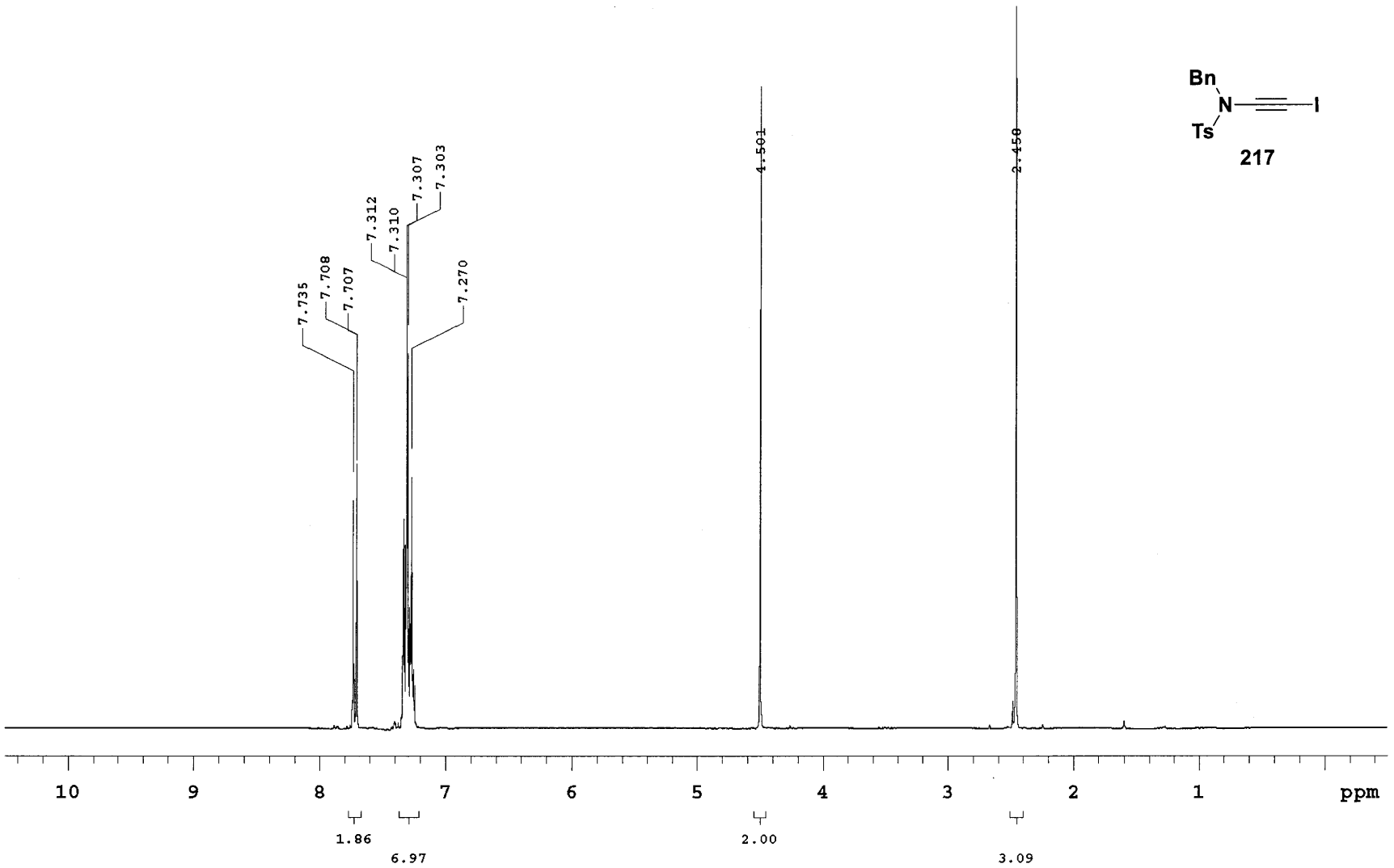
2-Iodo-*N*-methyl-*N*-(*p*-toluenesulfonyl)-ethynylamine (216). A 300-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with ynamide **214** (1.99 g, 9.52 mmol, 1.0 equiv) and 100 mL of THF. The pale yellow solution was cooled at -15 °C and a solution of *n*-BuLi (2.31 M in hexanes, 4.15 mL, 9.59 mmol, 1.0 equiv) was added dropwise via syringe over 25 min. The resulting red-brown solution was stirred at -15 °C for 3 h and then cooled to -78 °C. Powdered I_2 (2.46 g, 9.69 mmol, 1.1 equiv) was added in one portion and the resulting mixture was allowed to warm to rt and stirred for a total of 15 h. The resulting brown solution was diluted with 100 mL of Et_2O and washed with 100 mL of a 1:1 mixture of satd aqueous $Na_2S_2O_3$ and $NaHCO_3$ solutions. The aqueous phase was extracted with two 100-mL portions of Et_2O, and the combined organic phases were washed with 250 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 3.50 g of dark brown oil. Column chromatography on 100 g of acetone-deactivated silica gel (elution with 9% EtOAc and 1% Et_3N in hexanes) afforded 1.84 g (58%) of iodoynamide **216** as pale yellow crystals: mp 95–98 °C; IR (neat) 2936, 2186, 1363, 1170, 1088, 978, and 715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 3.07 (s, 3H), and 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.2, 133.3, 130.1, 128.0, 84.7, 38.9, 21.9, and –14.5; HRMS (DART) *m/z* $[M+H]^+$ calcd for $C_{10}H_{10}INO_2S$, 335.9550; found 335.9565.


Me
N
Ts
I
216
2.471
3.068
3.071
7.372
7.374
7.387
7.388
7.390
7.762
7.776
7.779
ppm
1
2
3
4
5
6
7
8
9
10
3.25
3.00
1.57
0.09
1.79

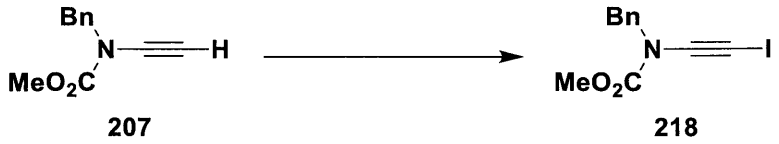
Me
N
Ts
I
216
145.219
133.312
130.094
127.975
84.678
77.486
77.230
76.978
38.859
21.880
14.481
180
160
140
120
100
80
60
40
20
0
ppm



***N*-Benzyl-2-iodo-*N*-(*p*-toluenesulfonyl)-ethynylamine (217).** A 30-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with ynamide **210** (0.200 g, 0.70 mmol, 1.0 equiv) and 7 mL of THF. The pale yellow solution was cooled at -15 °C and a solution of *n*-BuLi (2.44 M in hexanes, 0.29 mL, 0.70 mmol, 1.0 equiv) was added dropwise via syringe over 2 min. The resulting orange solution was stirred at -15 °C for 3 h and then cooled to -78 °C. 1,2-Diiodoethane (0.207 g, 0.74 mmol, 1.05 equiv) was added in one portion and the resulting red reaction mixture was allowed to warm to rt and stirred for a total of 48 h. The resulting red-brown solution was diluted with 15 mL of Et_2O and washed with 15 mL of saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with two 10-mL portions of Et_2O, and the combined organic phases were washed with 15 mL of a 1:1 mixture of saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$ solutions and 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.300 g of red oil. Column chromatography on 25 g of acetone-deactivated silica gel (elution with 5% EtOAc and 1% Et_3N in hexanes) afforded 0.201 g of a greasy yellow solid. Recrystallization from 15 mL of 1:1 Et_2O–pentane at -78 °C furnished 0.174 g (60%) of iodoynamide **217** as pale yellow crystals: mp 89–93 °C; IR (neat) 3032, 2188, 1597, 1496, 1455, 1363, 1169, 1088, and 601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 8.5 Hz, 2H), 7.24-7.35 (m, 7H), 4.50 (s, 2H), and 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.0, 134.8, 134.4, 130.0, 128.9, 128.7, 128.6, 127.9, 83.5, 55.4, 21.9, and –12.5; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{16}H_{14}INO_2S$, 433.9682; found 433.9672.

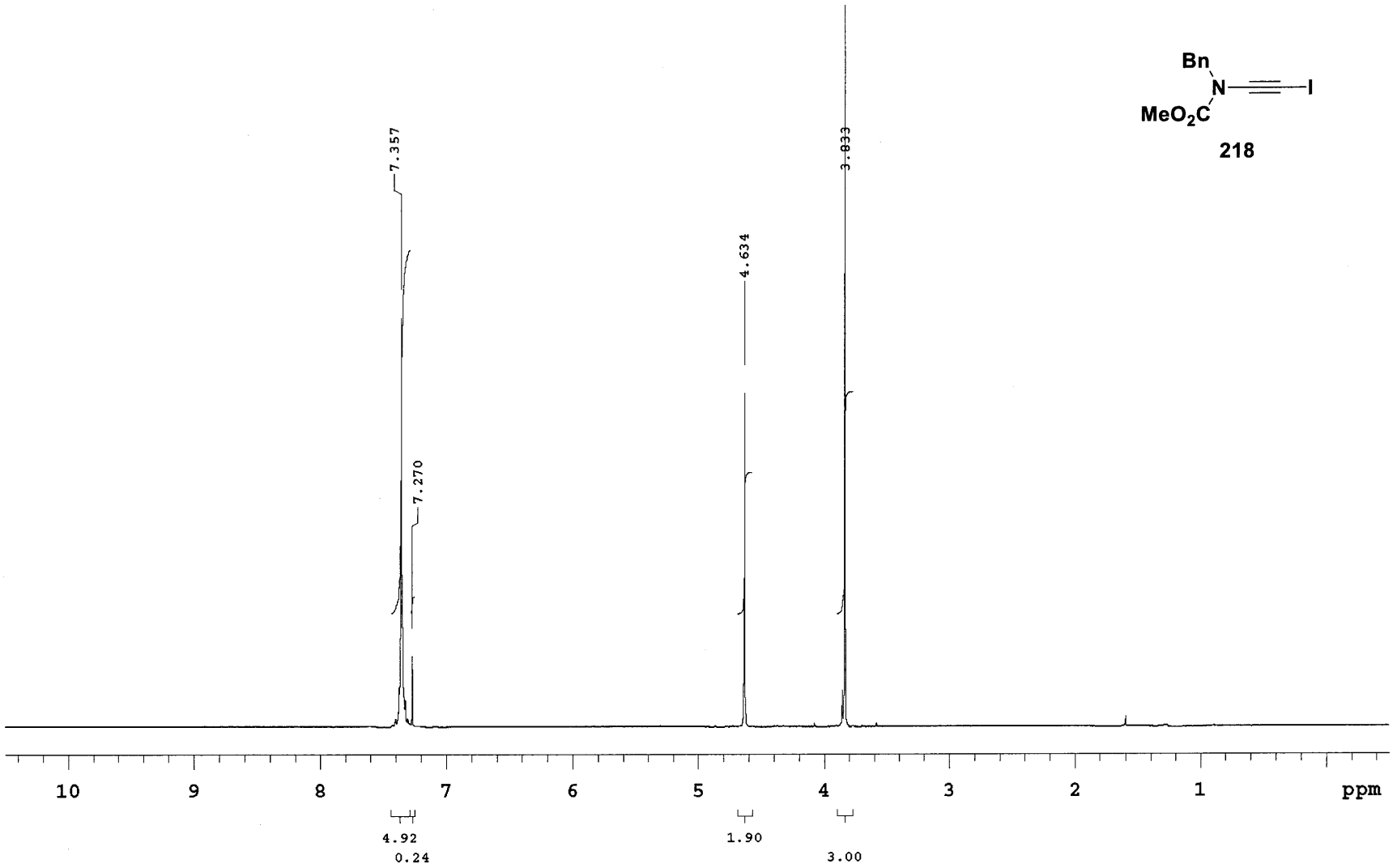

Bn
N
I
Ts
217
7.735
7.708
7.707
7.312
7.310
7.307
7.303
7.270
4.501
2.458
10
9
8
7
6
5
4
3
2
1
ppm
1.86
6.97
2.00
3.09

Bn
N
I
Ts
217
129.971
128.863
128.744
128.561
128.529
127.865
145.009
134.782
134.402
83.515
77.482
77.230
76.974
55.408
21.866
-12.540
180
160
140
120
100
80
60
40
20
0
ppm

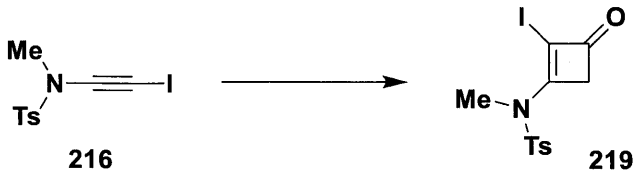


207 218

***N*-Benzyl-2-iodo-*N*-(methoxycarbonyl)ethynylamine (218).** A 25-mL pear flask equipped with a rubber septum and argon inlet needle was charged with ynamide **207** (0.194 g, 1.02 mmol, 1.0 equiv) and 5 mL of THF. The colorless solution was transferred via cannula over 1.5 h into a vigorously stirred solution of KHMDS (0.91 M in THF, 2.81 mL, 2.56 mmol, 2.5 equiv) in 10 mL of THF cooled at -78 °C in a 25-mL pear flask equipped with a rubber septum and argon inlet needle. The resulting yellow solution was immediately transferred via cannula over 20 min into a vigorously stirred solution of I_2 (0.649 g, 2.56 mmol, 2.5 equiv) in 5 mL of THF at -78 °C in a 50-mL round-bottomed flask equipped with a rubber septum. The resulting brown solution was stirred at -78 °C for 5 min, diluted with 40 mL of Et_2O, and quenched with 40 mL of a 1:1 mixture of saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$ solutions. The aqueous phase was extracted with two 20-mL portions of Et_2O, and the combined organic phases were washed with 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.350 g of orange oil. Column chromatography on 35 g of acetone-deactivated silica gel (elution with 2.5% EtOAc and 1% Et_3N in hexanes) afforded 0.129 g (40%) of iodoynamide **218** as a pale orange crystalline solid: mp 56–58 °C; IR (neat) 2955, 2200, 1712, 1446, 1367, 1261, 1116, 942, 759, and 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.41 (m, 5H), 4.63 (s, 2H), and 3.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 135.9, 128.8, 128.5, 128.4, 83.7, 54.5, 53.7, and –13.3; HRMS (DART) *m/z* $[M+H]^+$ calcd for $C_{11}H_{10}INO_2$, 315.9829; found 315.9835.

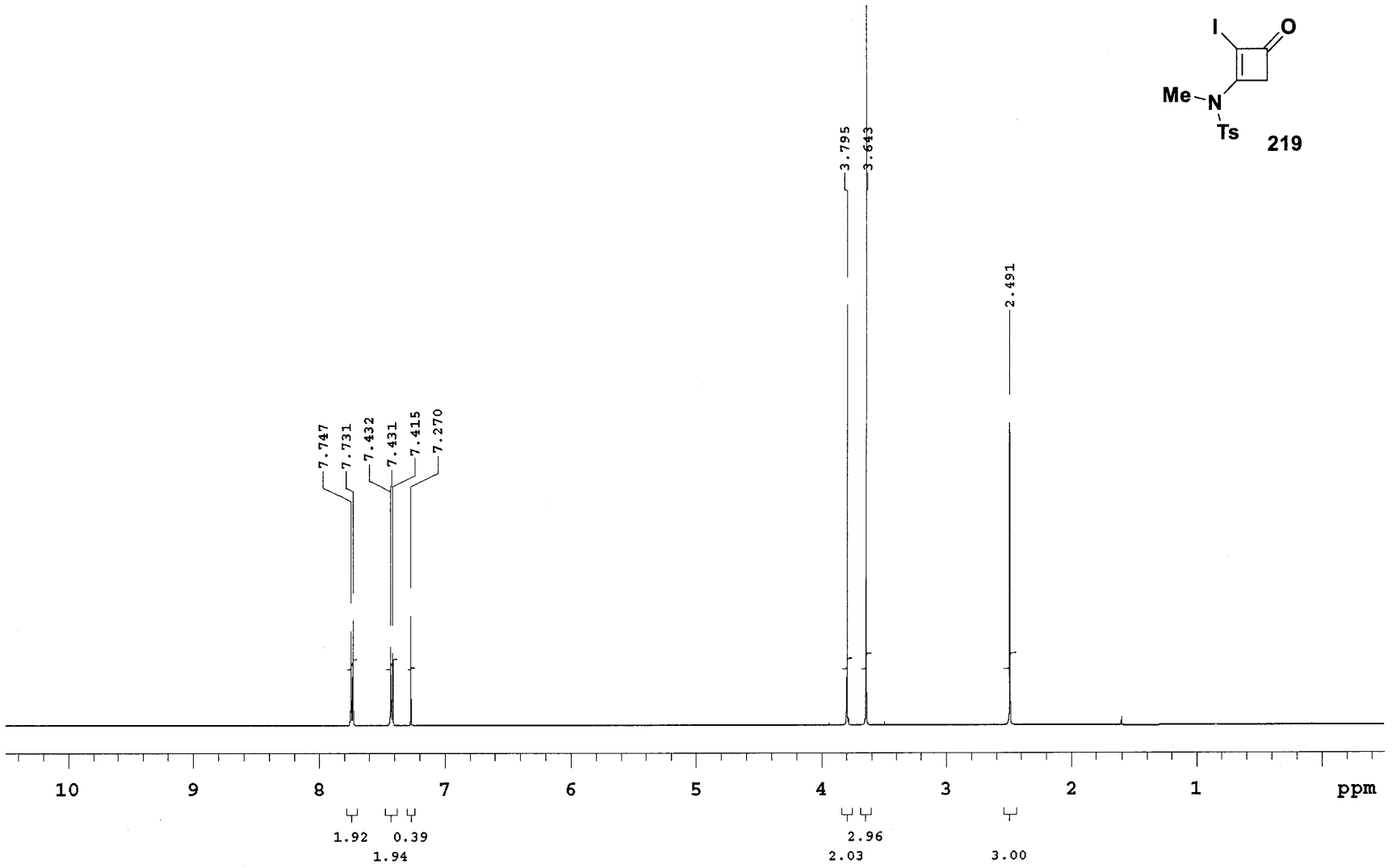

Bn
N
I
MeO2C
218
7.357
7.270
4.634
3.833
10
9
8
7
6
5
4
3
2
1
ppm
4.92
0.24
1.90
3.00

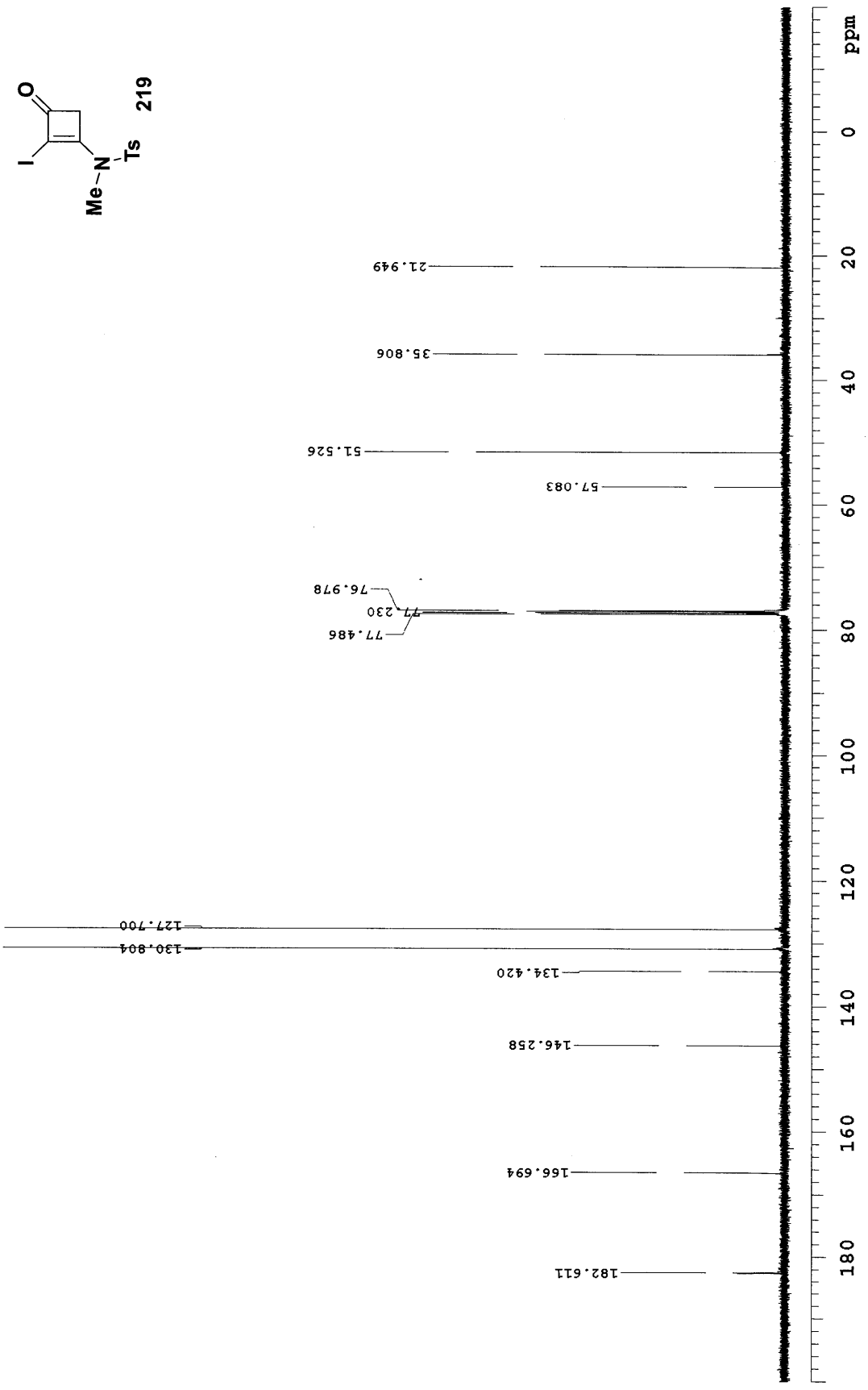
Bn
N
I
MeO2C
218
128.812
128.551
128.355
155.817
135.858
77.486
77.230
76.978
54.483
53.714
83.749
-13.314
180
160
140
120
100
80
60
40
20
0
ppm

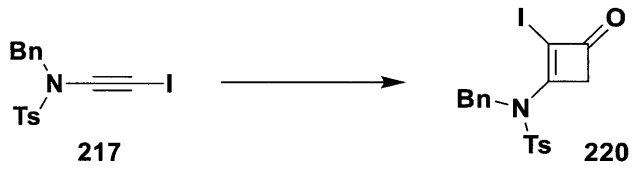


2-Iodo-3-(*N*-methyl-*N*-tosylamino)-2-cyclobuten-1-one (219). Ketene was generated by pyrolysis of acetone over an electrically heated metal filament using the apparatus described by Williams and Hurd.[153] A 100-mL round-bottomed flask equipped with a stir bar, rubber septum, and argon inlet needle was charged with iodoynamide **216** (0.451 g, 1.34 mmol, 1.0 equiv) and 35 mL of THF. The argon inlet needle was replaced with a 15-gauge needle connected via Tygon tubing to the ketene generator. The septum was fitted with an outlet needle connected via tubing to a column of $CaSO_4$ leading to a trap of H_2O. Ketene was bubbled into the pale yellow reaction mixture with vigorous stirring at rt over a period of 4.5 h. The resulting brown solution was then concentrated onto 2.5 g of silica gel to afford a brown powder. Elution through 30 g of silica gel using 1:1 EtOAc–hexanes afforded 0.515 g of an orange solid. Recrystallization from 4.5 mL of CH_3CN at -20 °C furnished 0.482 g (86%) of cyclobutenone **219** as white needles: mp 160 °C (dec.); IR (neat) 2924, 1781, 1757, 1563, 1405, 1371, 1162, 1003, and 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 3.80 (s, 2H), 3.64 (s, 3H), and 2.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.6, 166.7, 146.3, 134.4, 130.8, 127.7, 57.1, 51.5, 35.8, and 21.9; HRMS (DART) *m/z* $[M+H]^+$ calcd for $C_{12}H_{12}INO_3S$, 377.9655; found 377.9639.

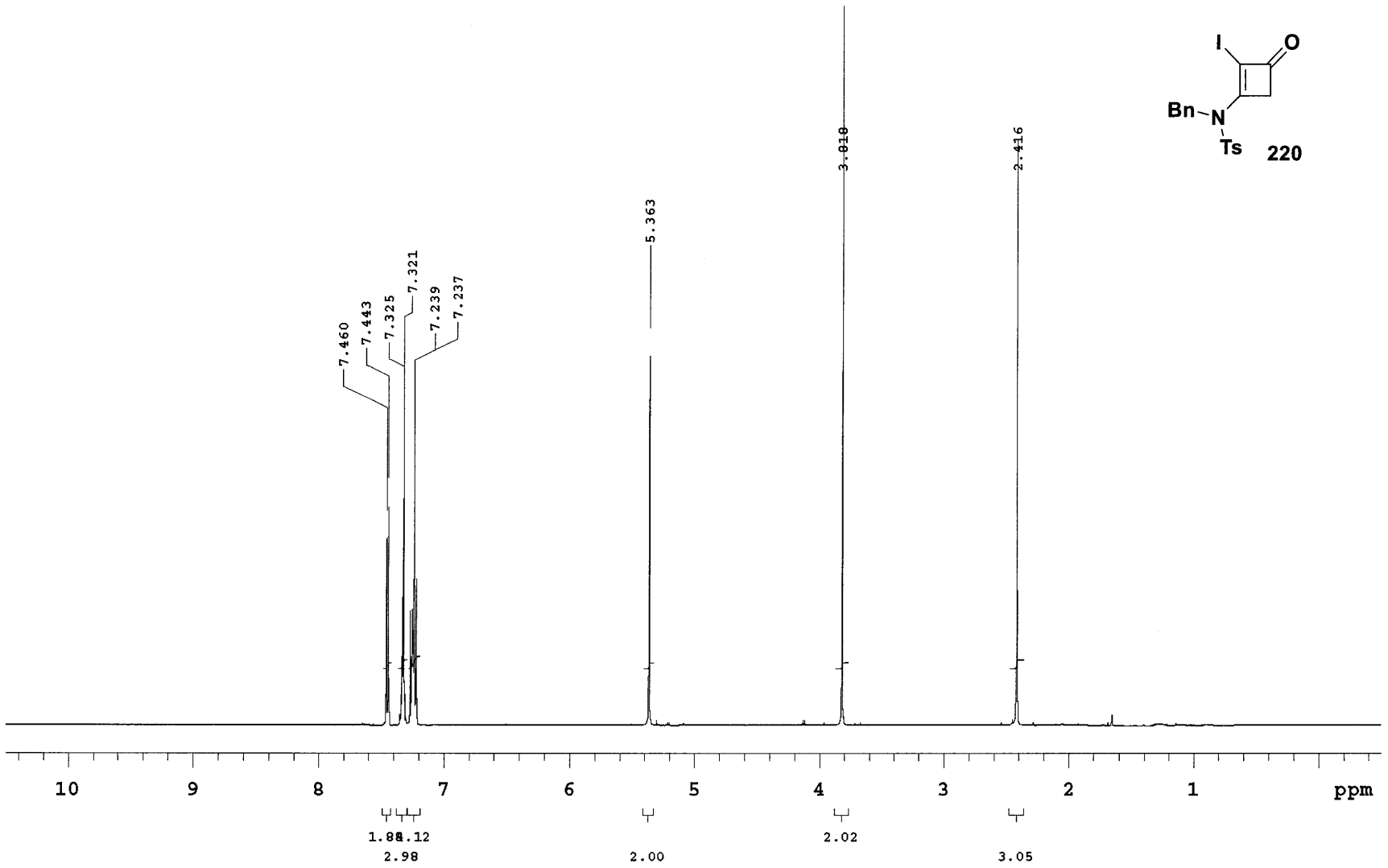
[153] See ref 72 and Figure 1 (p.46) for the setup.

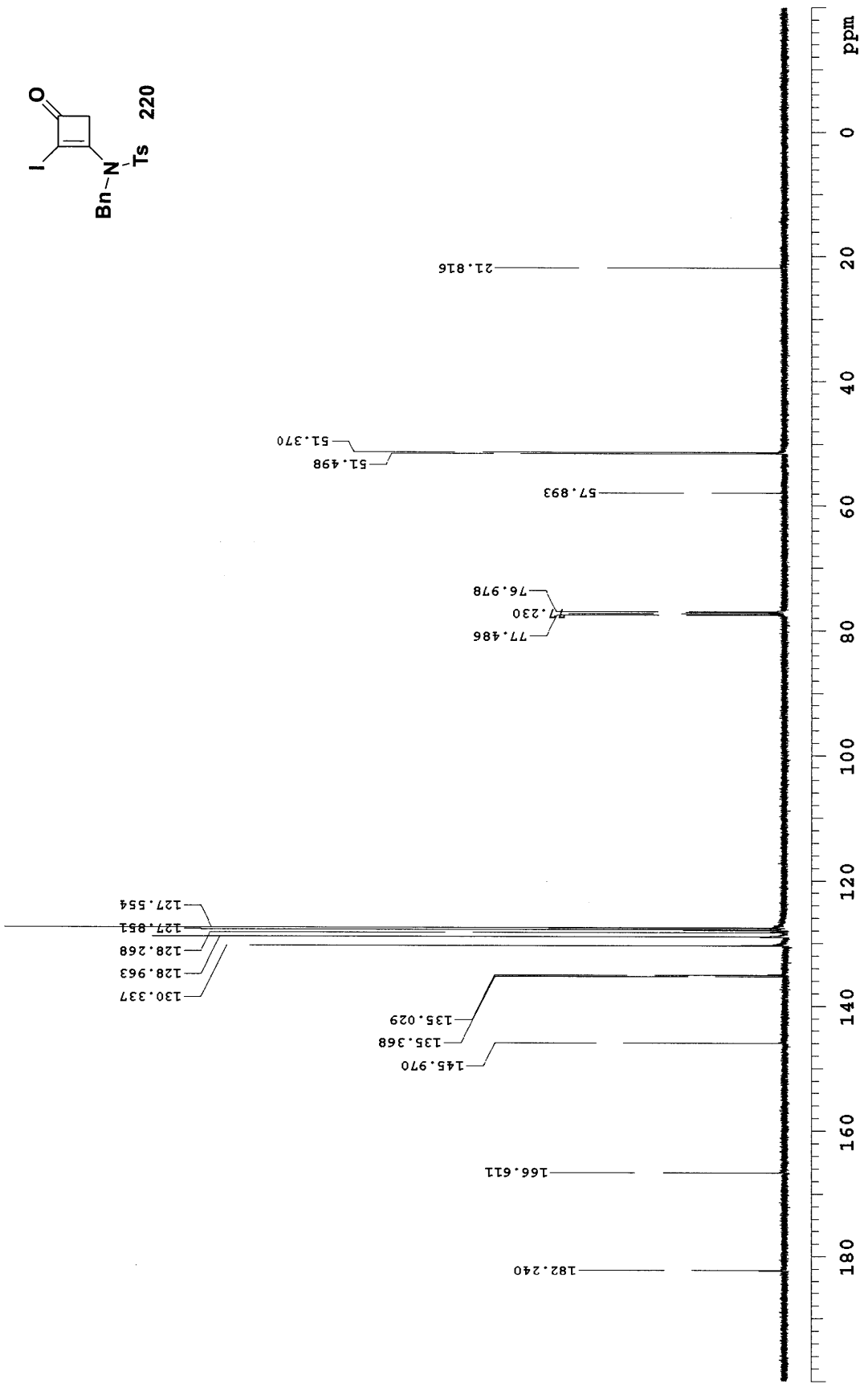

I
O
Me
N
Ts
219
7.747
7.731
7.432
7.431
7.415
7.270
3.795
3.643
2.491
10
9
8
7
6
5
4
3
2
1
ppm
1.92
0.39
1.94
2.96
2.03
3.00


O
I
Me
N
Ts
219
182.611
166.694
146.258
134.420
130.804
127.700
77.486
77.230
76.978
57.083
51.526
35.806
21.949
ppm
180
160
140
120
100
80
60
40
20
0

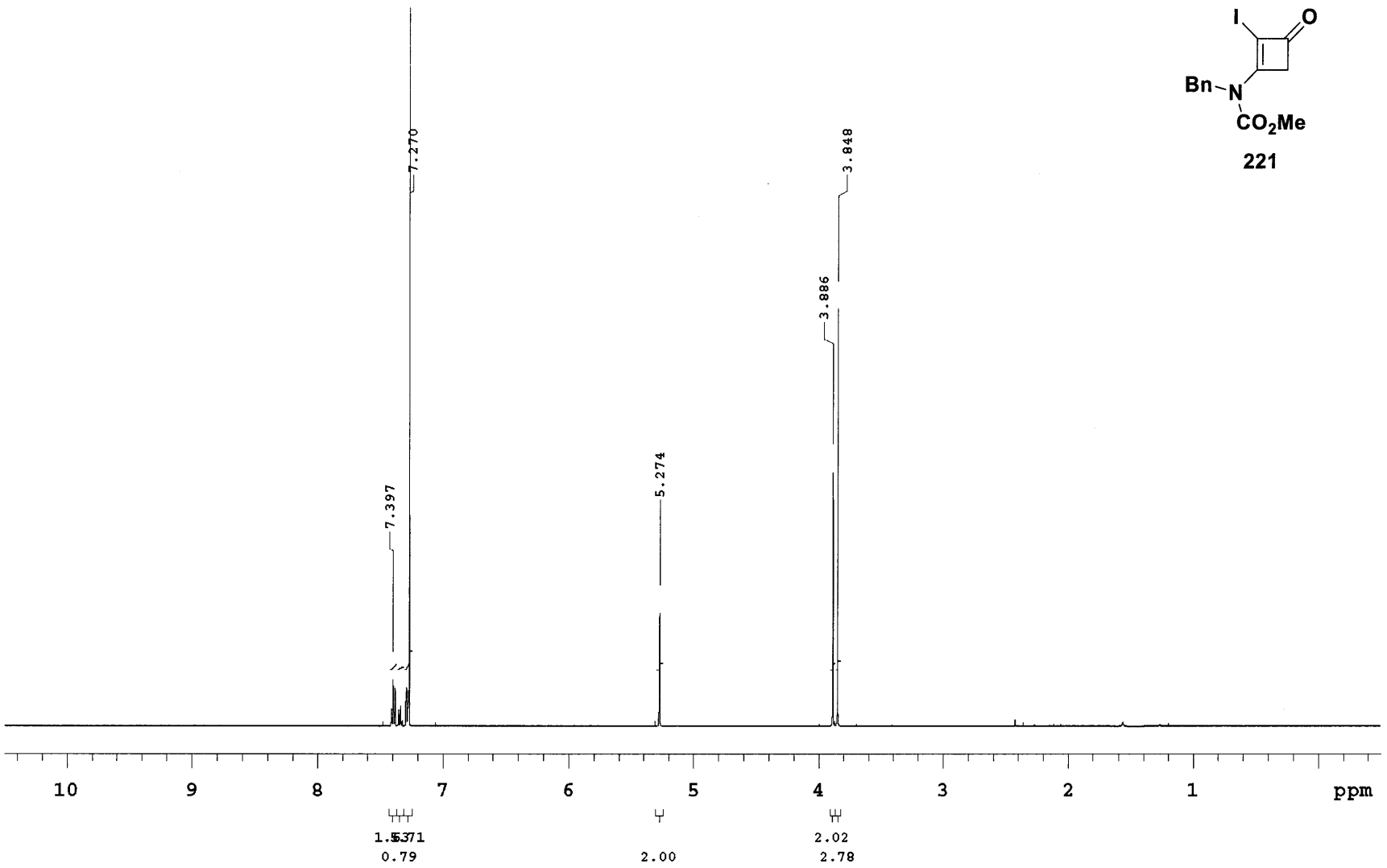


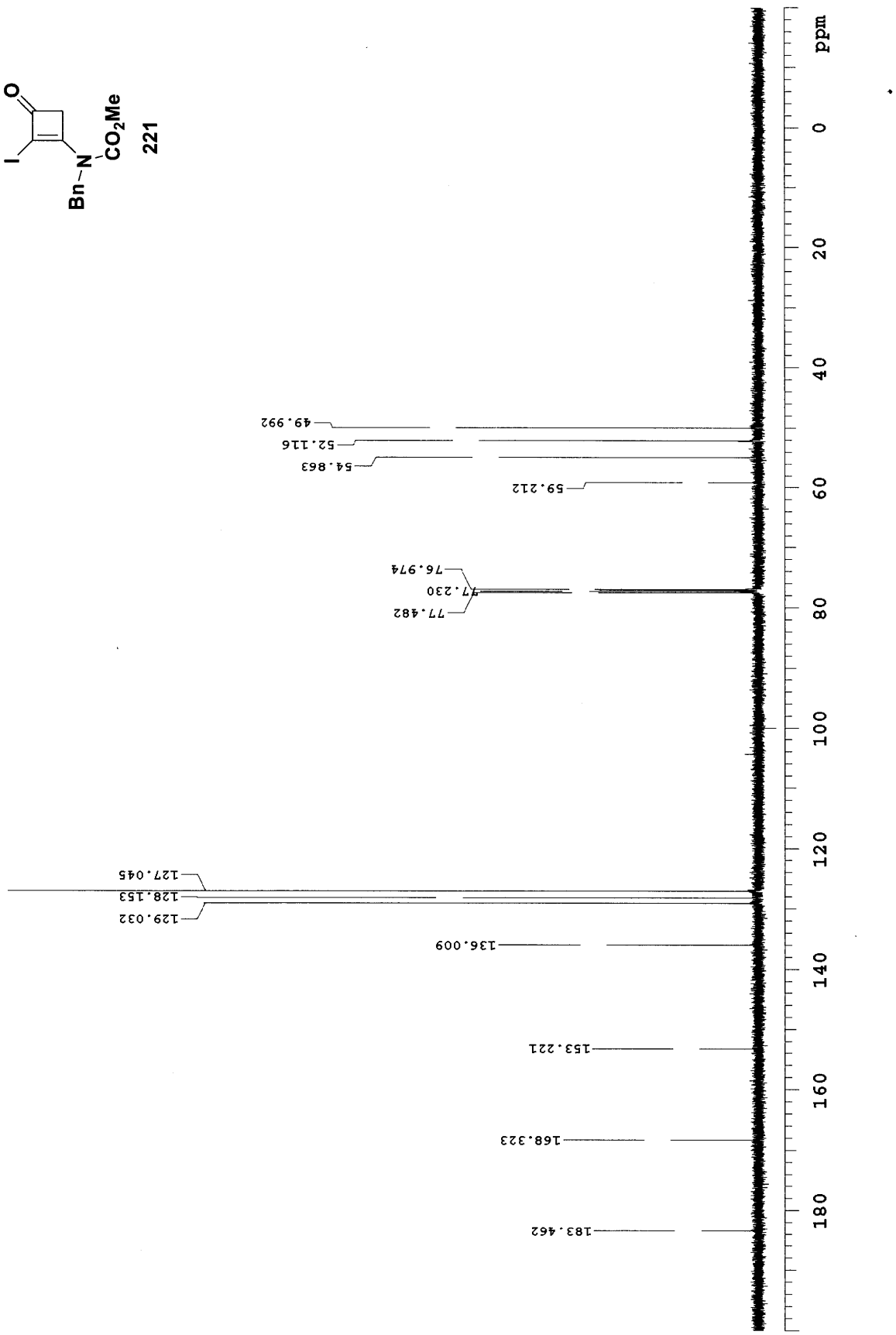
3-(*N*-Benzyl-*N*-tosylamino)-2-Iodo-2-cyclobuten-1-one (220). Ketene was generated by pyrolysis of acetone over an electrically heated metal filament using the apparatus described by Williams and Hurd. A 4-mL conical vial equipped with a rubber septum and argon inlet needle was charged with iodoynamide **217** (0.084 g, 0.20 mmol, 1.0 equiv) and 2 mL of THF. The argon inlet needle was replaced with a 20-gauge needle connected via Tygon tubing to the ketene generator. The septum was fitted with an outlet needle connected via tubing to a column of $CaSO_4$ leading to a trap of H_2O. Ketene was bubbled into the pale yellow reaction mixture with vigorous stirring at rt over a period of 5 h. The resulting brown solution was then concentrated to afford 0.135 g of viscous brown oil. Column chromatography on 10 g of silica gel (gradient elution with 10–30% EtOAc–hexanes) afforded 0.075 g (81%) of cyclobutenone **220** as an off-white greasy semisolid: IR (neat) 3064, 3033, 2928, 1763, 1557, 1373, 1319, 1172, and 1048 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, J = 8.5 Hz, 2H), 7.29-7.36 (m, 3H), 7.20-7.28 (m, 4H), 5.36 (s, 2H), 3.82 (s, 2H), and 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.2, 166.6, 146.0, 135.4, 135.0, 130.3, 129.0, 128.3, 127.9, 127.6, 57.9, 51.5, 51.4, and 21.8; HRMS (DART) *m/z* $[M+H]^+$ calcd for $C_{18}H_{16}INO_3S$, 453.9968; found 453.9959.

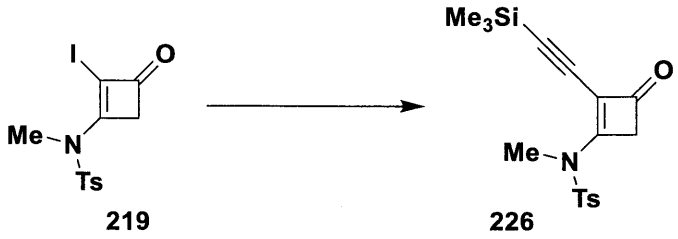

7.460
7.443
7.325
7.321
7.239
7.237
5.363
3.818
2.416
I
O
Bn
N
Ts
220
10
9
8
7
6
5
4
3
2
1
ppm
1.88
4.12
2.98
2.00
2.02
3.05


O
I
N
Bn
Ts
220
182.240
166.611
145.970
135.368
135.029
130.337
128.963
128.268
127.851
127.554
77.486
77.230
76.978
57.893
51.498
51.370
21.816
ppm
0
20
40
60
80
100
120
140
160
180

3-[*N*-Benzyl-*N*-(methoxycarbonyl)-amino]-2-iodo-2-cyclobuten-1-one (221). Ketene was generated by pyrolysis of acetone over an electrically heated metal filament using the apparatus described by Williams and Hurd. A 10-mL test tube equipped with a rubber septum and argon inlet needle was charged with iodoynamide **218** (0.058 g, 0.18 mmol, 1.0 equiv) and 2 mL of THF. The argon inlet needle was replaced with a 20-gauge needle connected via Tygon tubing to the ketene generator. The septum was fitted with an outlet needle connected via tubing to a column of $CaSO_4$ leading to a trap of H_2O. Ketene was bubbled into the pale yellow reaction mixture with vigorous stirring at rt over a period of 5 h. The resulting brown solution was then concentrated onto 1 g of silica gel to afford a free-flowing powder. Column chromatography on 10 g of silica gel (gradient elution with 10–45% EtOAc–hexanes) afforded 0.065 g (99%) of cyclobutenone **221** as a viscous orange oil: IR (neat) 3032, 2956, 1767, 1746, 1573, 1449, 1353, 1223, 1113, and 1040 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27-7.40 (m, 5H), 5.27 (s, 2H), 3.89 (s, 2H), and 3.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.5, 168.3, 153.2, 136.0, 129.0, 128.2, 127.0, 59.2, 54.9, 52.1, and 50.0; HRMS (DART) *m/z* $[M+H]^+$ calcd for $C_{13}H_{12}INO_3$, 357.9935; found 357.9922.

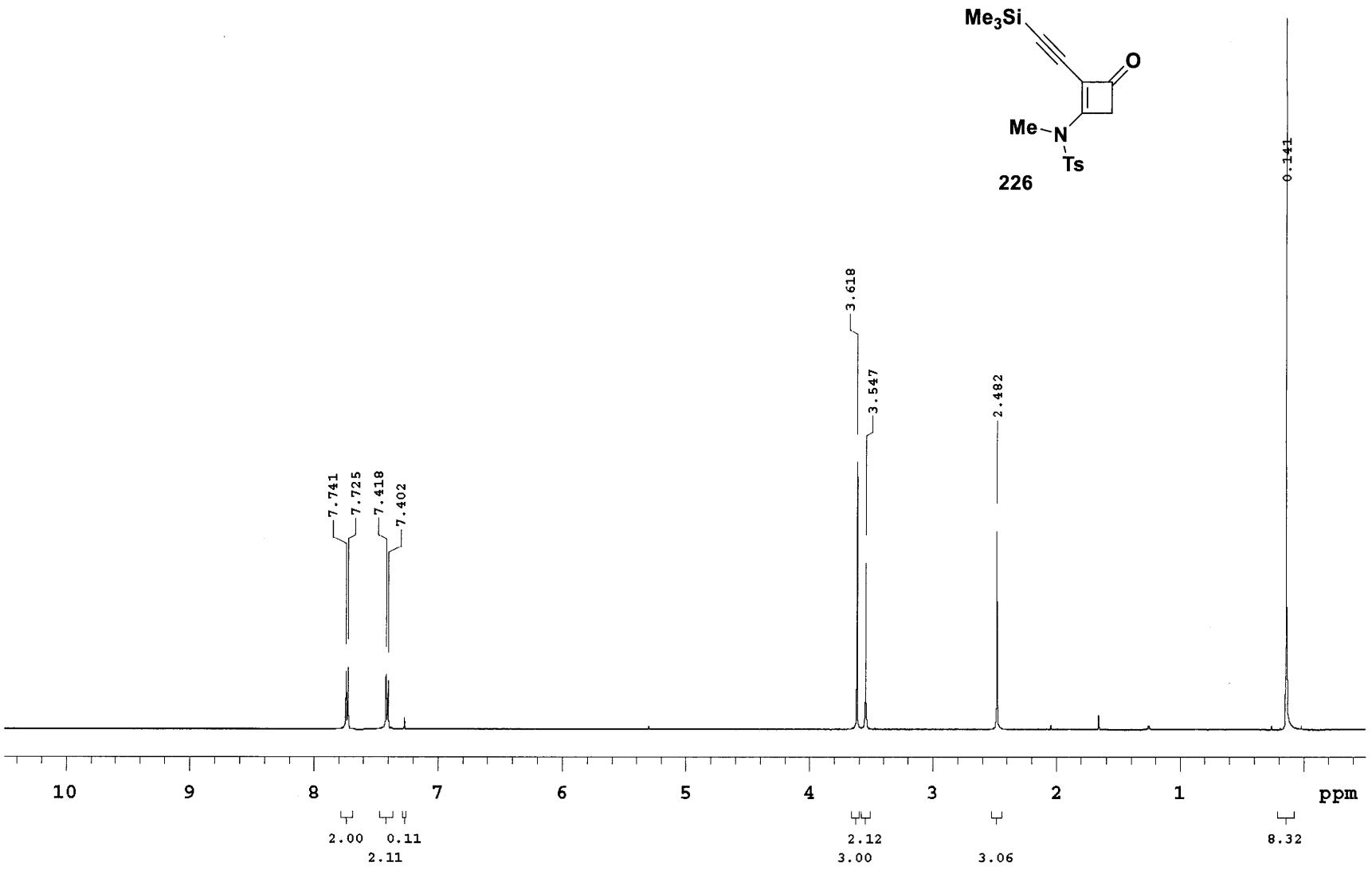

I
O
Bn
N
CO2Me
221
7.270
3.848
3.886
7.397
5.274
10
9
8
7
6
5
4
3
2
1
ppm
1.53
0.79
2.00
2.02
2.78


O
I
N
Bn
CO2Me
221
183.462
168.323
153.221
136.009
129.032
128.153
127.045
77.482
77.230
76.974
59.212
54.863
52.116
49.992
ppm
0
20
40
60
80
100
120
140
160
180



219 226

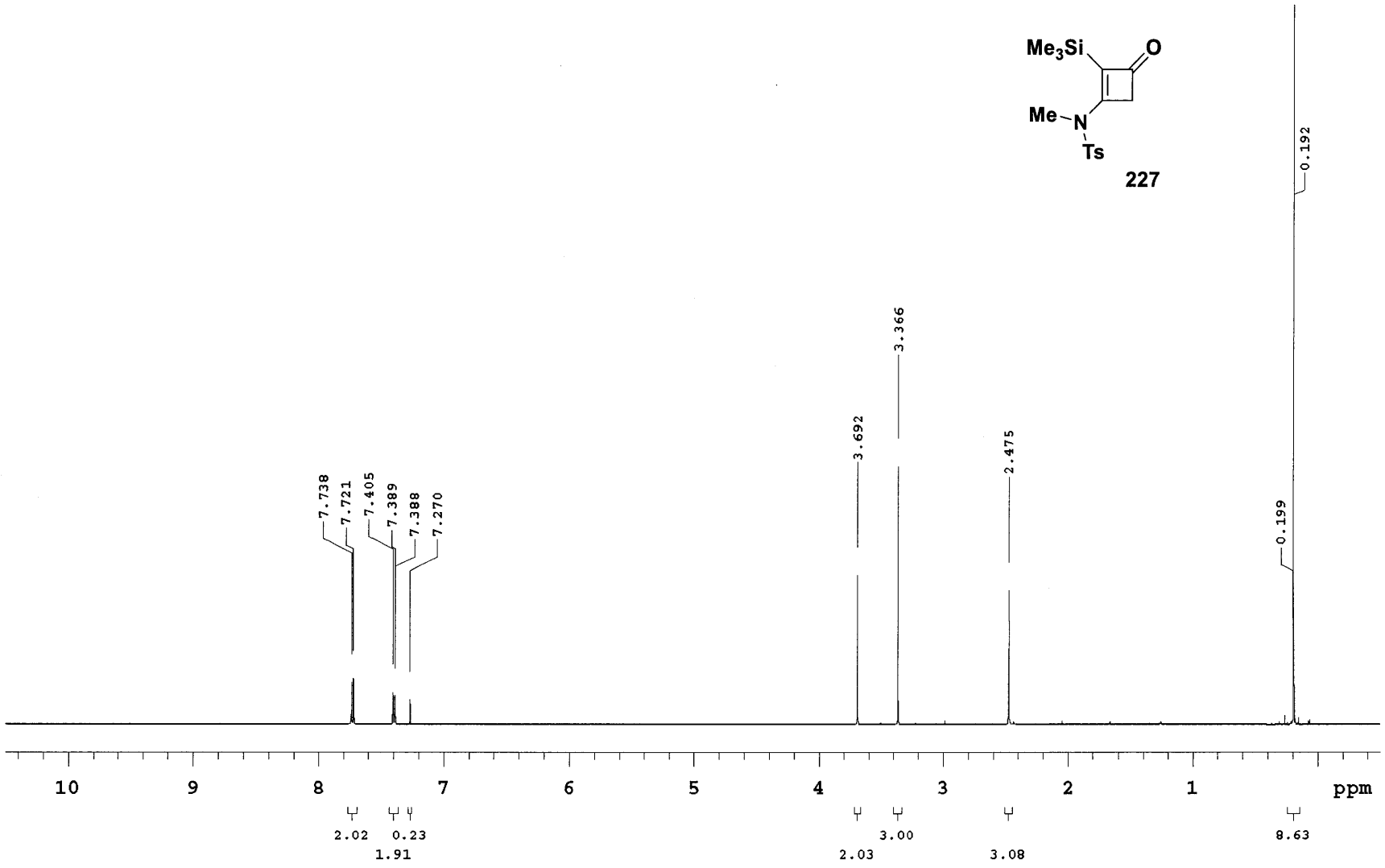
3-(*N*-Methyl-*N*-tosylamino)-2-(2-trimethylsilylethynyl)-2-cyclobuten-1-one (226). A 10-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with cyclobutenone **219** (0.060 g, 0.16 mmol, 1.0 equiv), $Pd(PPh_3)_2Cl_2$ (0.007 g, 0.01 mmol, 0.06 equiv), CuI (0.002 g, 0.01 mmol, 0.07 equiv), and 3 mL of THF. Trimethylsilylacetylene (0.034 mL, 0.024 g, 0.24 mmol, 1.5 equiv) was added in one portion, followed by Et_3N (0.220 mL, 0.160 g, 1.59 mmol, 10 equiv), and the resulting yellow mixture was stirred at rt for 10 h. Additional $Pd(PPh_3)_2Cl_2$ (0.007 g, 0.01 mmol, 0.06 equiv), CuI (0.004 g, 0.02 mmol, 0.1 equiv), and trimethylsilylacetylene (0.034 mL, 0.024 g, 0.24 mmol, 1.5 equiv) were added and the reaction mixture was stirred at rt for an additional 14 h. The resulting brown reaction mixture was diluted with 10 mL of Et_2O and extracted with 10 mL of saturated aqueous NH_4Cl solution. The aqueous phase was extracted with two 5-mL portions of Et_2O, and the combined organic phases were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.142 g of an orange solid. Column chromatography on 8 g of silica gel (gradient elution with 0–30% EtOAc-hexanes) afforded 0.051 g (92%) of cyclobutenone **226** as orange crystals: mp 153–155 °C (dec.); IR (neat) 2961, 2145, 1764, 1587, 1387, 1357, 1250, 1171, 1087, 1031, and 863 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 3.62 (s, 3H), 3.55 (s, 2H), 2.48 (s, 3H), and 0.14 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.0, 163.1, 146.2, 134.2, 130.7, 127.7, 106.7, 99.2, 92.0, 50.4, 35.9, 21.9, and -0.2; HRMS (DART) *m/z* $[M+H]^+$ calcd for $C_{17}H_{21}NO_3SSi$, 348.1084; found 348.1099.


Me3Si
O
Me
N
Ts
226
7.741
7.725
7.418
7.402
3.618
3.547
2.482
0.141
10
9
8
7
6
5
4
3
2
1
ppm
2.00
0.11
2.11
2.12
3.00
3.06
8.32

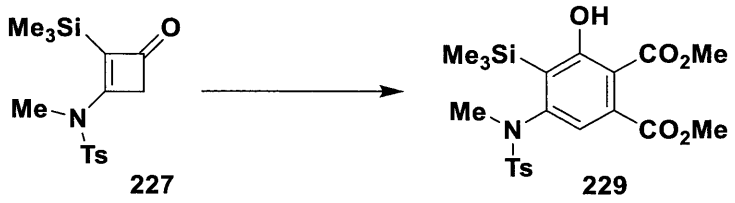
Me3Si
O
Me
N
Ts
226
183.045
163.095
146.194
134.237
130.717
127.746
106.674
99.153
92.035
77.482
77.230
76.974
50.390
35.879
21.912
0.199
200
180
160
140
120
100
80
60
40
20
ppm

219 227

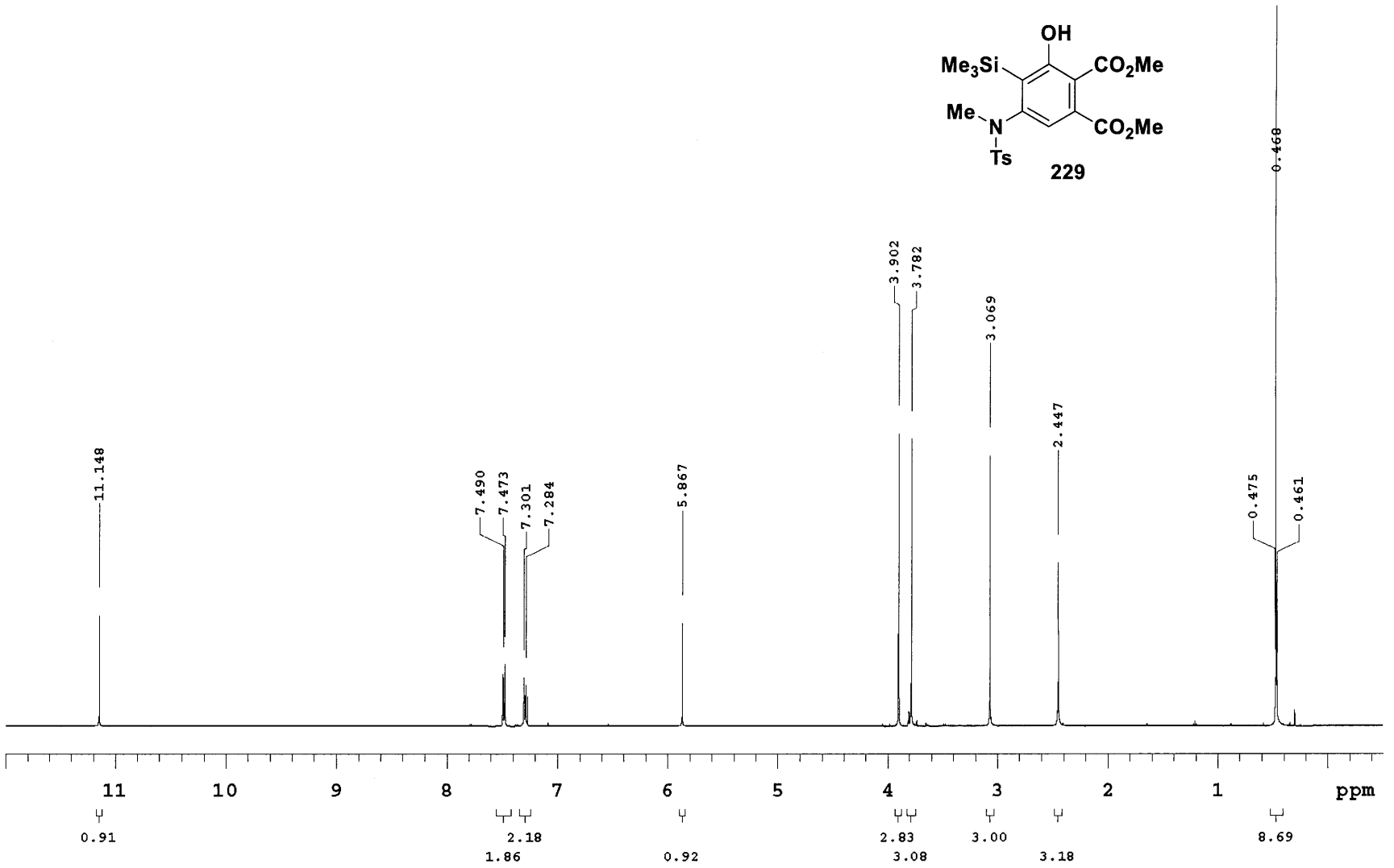
3-(*N*-Methyl-*N*-tosylamino)-2-(trimethylsilyl)-2-cyclobuten-1-one (227). A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with cyclobutenone **219** (0.151 g, 0.400 mmol, 1.0 equiv) and 8 mL of THF. The solution was cooled to -78 °C and *i*-PrMgBr (0.705 mL, 0.596 M in THF, 0.420 mmol, 1.05 equiv) was added dropwise over 4 min. The resulting bright yellow solution was stirred at -78 °C for 1 h and then Me_3SiOTf (0.087 mL, 0.107 g, 0.479 mmol, 1.2 equiv) was added dropwise over 1 min. The reaction mixture was allowed to warm to rt and stirred for a total of 5 h. The resulting orange solution was diluted with 15 mL of Et_2O and then quenched with 20 mL of saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with two 10-mL portions of Et_2O, and the combined organic phases were washed with 30 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.184 g of an orange solid. Column chromatography on 10 g of silica gel (elution with 15% EtOAc-hexanes) afforded 0.077 g (60%) of cyclobutenone **227** as a pale orange oil: IR (neat) 2956, 2098, 1740, 1540, 1375, 1251, 1167, 1085, and 841 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 8.5 Hz, 2H), 7.40 (d, J = 8.5 Hz, 2H), 3.69 (s, 2H), 3.37 (s, 3H), 2.48 (s, 3H), and 0.19 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.0, 169.4, 145.7, 135.2, 130.6, 128.1, 127.5, 53.3, 37.2, 21.9, and 0.7; HRMS (DART) *m/z* $[M+H]^+$ calcd for $C_{15}H_{21}NO_3SSi$, 324.1084; found 324.1099.


Me3Si
O
Me
N
Ts
227
7.738
7.721
7.405
7.389
7.388
7.270
3.692
3.366
2.475
0.199
0.192
10
9
8
7
6
5
4
3
2
1
ppm
2.02
0.23
1.91
2.03
3.00
3.08
8.63

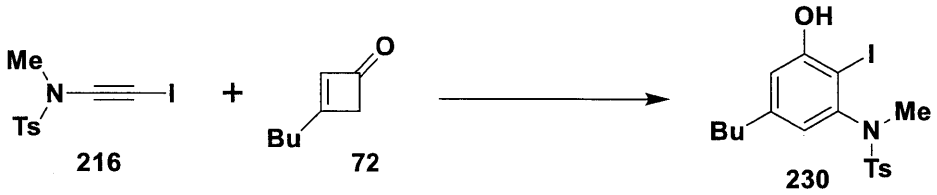
188.974
169.422
145.709
135.171
130.616
128.075
127.517
77.486
77.230
76.978
53.270
37.152
21.912
0.717
Me3Si
O
Me
N
Ts
227
200
180
160
140
120
100
80
60
40
20
ppm



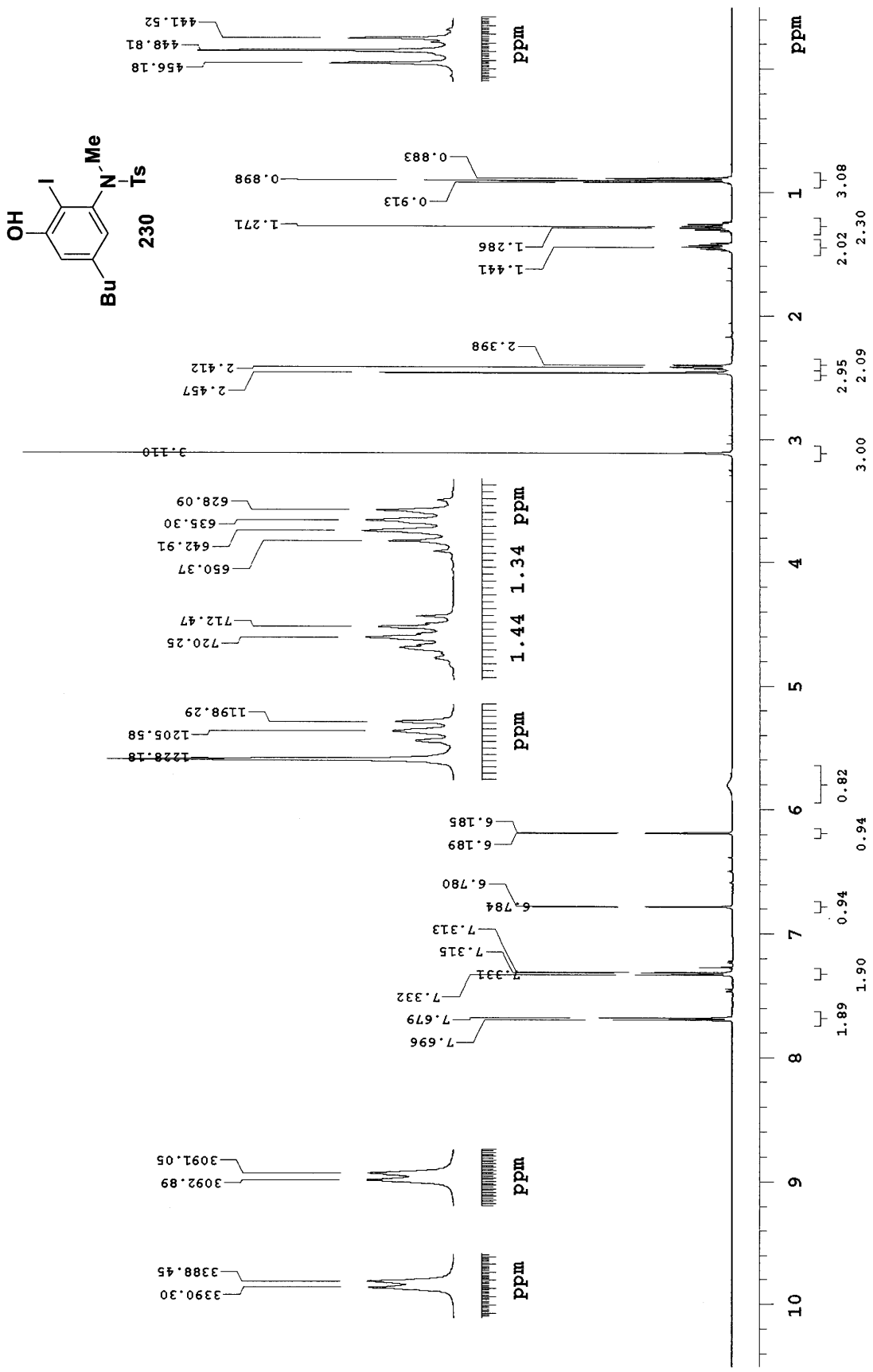
Dimethyl 3-hydroxy-5-(*N*-methyl-*p*-toluenesulfonamido)-4-(trimethylsilyl)phthalate (229). A 15-mL threaded Pyrex tube (20 mm o.d., 16 mm i.d.) equipped with a rubber septum and argon inlet needle was charged with cyclobutenone **227** (0.128 g, 0.396 mmol, 1.0 equiv), 2 mL of toluene, and dimethyl acetylenedicarboxylate (0.097 mL, 0.79 mmol, 2.0 equiv). The orange solution was degassed (three freeze-pump-thaw cycles at -196 °C, 0.2 mmHg), backfilled with argon, and the reaction tube was sealed with a threaded Teflon cap. The reaction mixture was heated at 120 °C for 66 h, cooled to rt, and concentrated to afford 0.266 g of a brown oil. This material was dissolved in ca. 3 mL of CH_2Cl_2 and concentrated onto 1.5 g of silica gel. The resulting free-flowing powder was added to the top of a column of 15 g of silica gel and eluted with a gradient of 10–40% EtOAc–hexane to afford 0.073 g (40%) of phthalate **229** as an off-white crystalline solid: mp 130–132 °C; IR (film) 2954, 2900, 1739, 1676, 1596, 1548, 1440, 1350, 1328, 1256, 1202, 1156, 1020, 846, and 665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 11.15 (s, 1H), 7.48 (app d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 5.87 (s, 1H), 3.90 (s, 3H), 3.78 (s, 3H), 3.07 (s, 3H), 2.45 (s, 3H), and 0.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 168.7, 167.2, 151.7, 144.1, 136.4, 133.7, 133.4, 129.6, 128.6, 117.3, 108.4, 53.2, 52.7, 39.2, 21.8, and 0.9; HRMS (DART) *m/z* $[M+H]^+$ calcd for $C_{21}H_{27}NO_7SSi$, 466.1350; found 466.1354.

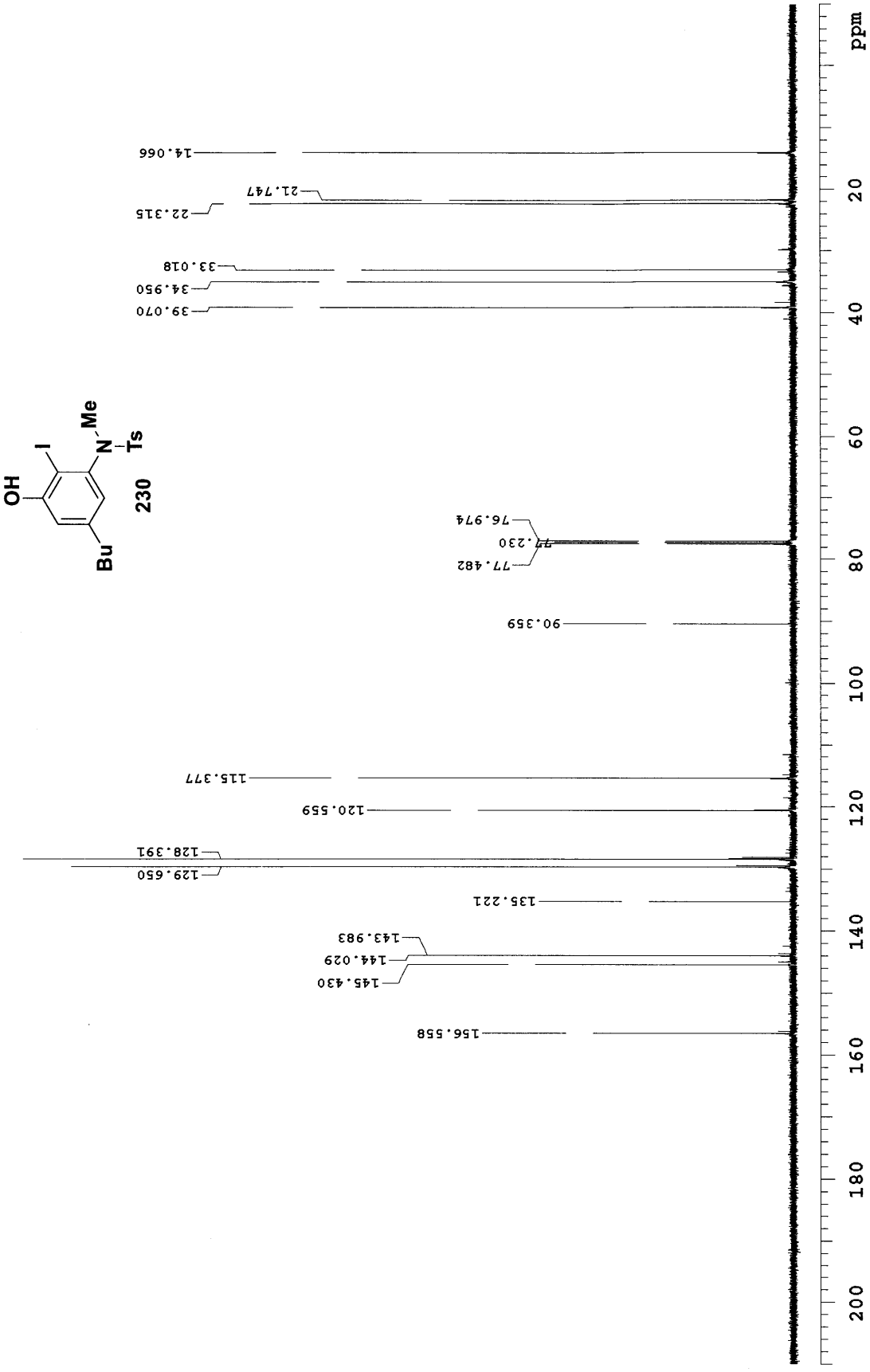

OH
Me3Si
CO2Me
Me
N
CO2Me
Ts
229
11.148
7.490
7.473
7.301
7.284
5.867
3.902
3.782
3.069
2.447
0.475
0.461
0.468
11
10
9
8
7
6
5
4
3
2
1
ppm
0.91
2.18
1.86
0.92
2.83
3.08
3.00
3.18
8.69

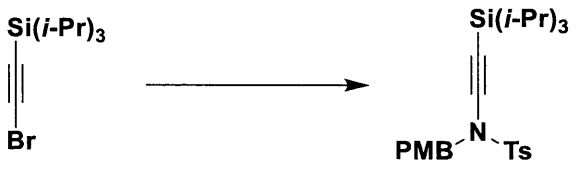
OH
Me3Si
CO2Me
Me
N
CO2Me
Ts
229
169.555
168.740
167.179
151.692
144.070
136.375
133.743
133.445
129.595
128.606
117.263
108.437
77.482
77.230
76.974
53.201
52.734
39.157
21.756
0.932
200
180
160
140
120
100
80
60
40
20
ppm



***N*-Methyl-*N*-(*p*-toluenesulfonyl)-(5-butyl-3-hydroxy-2-iodophenyl)amine (230).** A 25-mL pear flask equipped with a rubber septum and argon inlet needle was charged with ynamide **216** (0.234 g, 0.697 mmol, 1.0 equiv), 3-butylcyclobutenone **72**[77] (0.173 g, 1.39 mmol, 2.0 equiv), and 2.5 mL of toluene and the pale yellow reaction mixture was heated at 80 °C for 2 h. The resulting orange solution was cooled to rt and concentrated to afford 0.495 g of a brown oil. This material was diluted with 2 mL of MeOH and 2 mL of 5 M aqueous KOH solution, the same flask was equipped with a rubber septum and argon inlet needle, and the reaction mixture was heated at 70 °C for 2 h. The resulting red suspension was cooled to rt, diluted with 13 mL of 1 M aqueous HCl solution and 15 mL of Et_2O, and transferred to a 60-mL separatory funnel. The aqueous phase was separated and extracted with two 7-mL portions of Et_2O, and the combined organic phases were washed with 20 mL of water and 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.353 g of a brown oil. This material was dissolved in ca. 3 mL of CH_2Cl_2 and concentrated onto 1.5 g of silica gel. The resulting free-flowing powder was added to the top of a column of 30 g of silica gel and eluted with 15% EtOAc-hexane to afford 0.231 g (72%) of phenol **230** as a pale yellow solid: mp 118–121 °C; IR (film) 3411, 2956, 2929, 1597, 1582, 1426, 1348, 1156, 1087, and 987 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 6.78 (d, J = 1.9 Hz, 1H), 6.19 (d, J = 1.9 Hz, 1H), 5.80 (br s, 1H), 3.11 (s, 3H), 2.46 (s, 3H), 2.41 (t, J = 7.5 Hz, 2H), 1.44 (app quintet, J = 7.5 Hz, 2H), 1.28 (app sextet, J = 7.4 Hz, 2H), and 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6, 145.4, 144.03, 143.98, 135.2, 129.7, 128.4, 120.6, 115.4, 90.4, 39.1, 35.0, 33.0, 22.3, 21.7, and 14.1; HRMS (DART) *m/z* $[M–H]^-$ calcd for $C_{18}H_{22}INO_3S$, 458.0292; found 458.0286. A sample recrystallized from Et_2O-pentane had mp 120–122 °C.


OH
I
N
Me
Ts
Bu
230
ppm
1.44
1.34
3.00
2.09
2.30
0.82
0.94
1.90
0.94
1.89


OH
I
N
Me
Ts
Bu
230
14.066
21.747
22.315
33.018
34.950
39.070
76.974
77.230
77.482
90.359
115.377
120.559
128.391
129.650
135.221
143.983
144.029
145.430
156.558
ppm
20
40
60
80
100
120
140
160
180
200

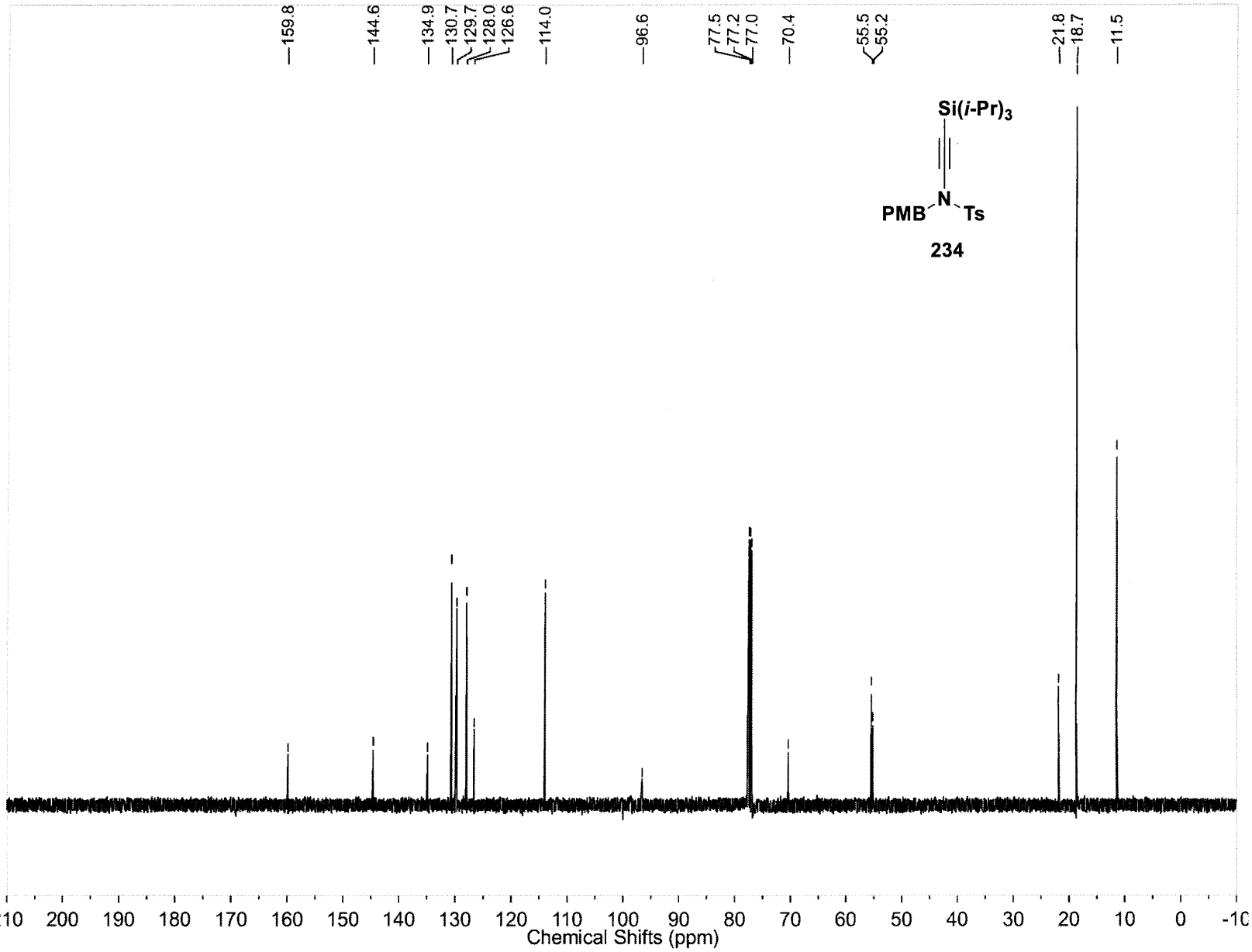


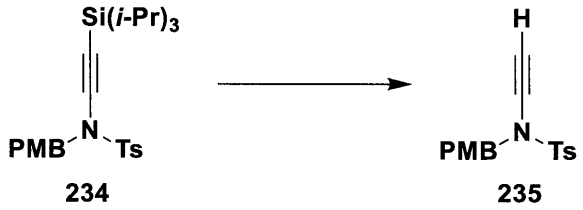
212 234

***N*-(4-Methoxybenzyl)-*N*-(*p*-toluenesulfonyl)-2-(triisopropylsilyl)ethynylamine (234).** A 50-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with PMBNHTs[154] (3.26 g, 11.2 mmol, 1.3 equiv), bromo(triisopropylsilyl)acetylene **212**[66] (2.25 g, 8.60 mmol, 1.0 equiv), $CuSO_4 \cdot 5H_2O$ (0.429 g, 1.72 mmol, 0.2 equiv), 1,10-phenanthroline (0.620 g, 3.44 mmol, 0.4 equiv), and K_2CO_3 (2.38 g, 17.2 mmol, 2.0 equiv), and 12 mL of toluene. The pale green suspension was heated at 80 °C with vigorous stirring for 64 h and then allowed to cool to rt. The resulting dark green reaction mixture was filtered through a pad of Celite with the aid of ca. 50 mL of ethyl acetate. The filtrate was concentrated to afford 6.17 g of a viscous green oil. This material was added to the top of a column of 75 g of silica gel with the aid of hexane and eluted with a gradient of 0–20 % EtOAc-hexane to afford 3.56 g (88%) of ynamide **234** as a viscous colorless oil: IR (film) 2942, 2865, 2165, 1613, 1515, 1464, 1370, 1251, 1169, 1035, 738, and 665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (app d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.6 Hz, 2H), 7.21 (app d, J = 8.7 Hz, 2H), 6.80 (app d, J = 8.8 Hz, 2H), 4.44 (s, 2H), 3.79 (s, 3H), 2.44 (s, 3H), and 0.96 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 144.6, 134.9, 130.7, 129.7, 128.0, 126.6, 114.0, 96.6, 70.4, 55.5, 55.2, 21.8, 18.7, and 11.5; HRMS (DART) *m/z* $[M–H]^-$ calcd for $C_{26}H_{37}NO_3SSi$, 470.2191; found 470.2208.

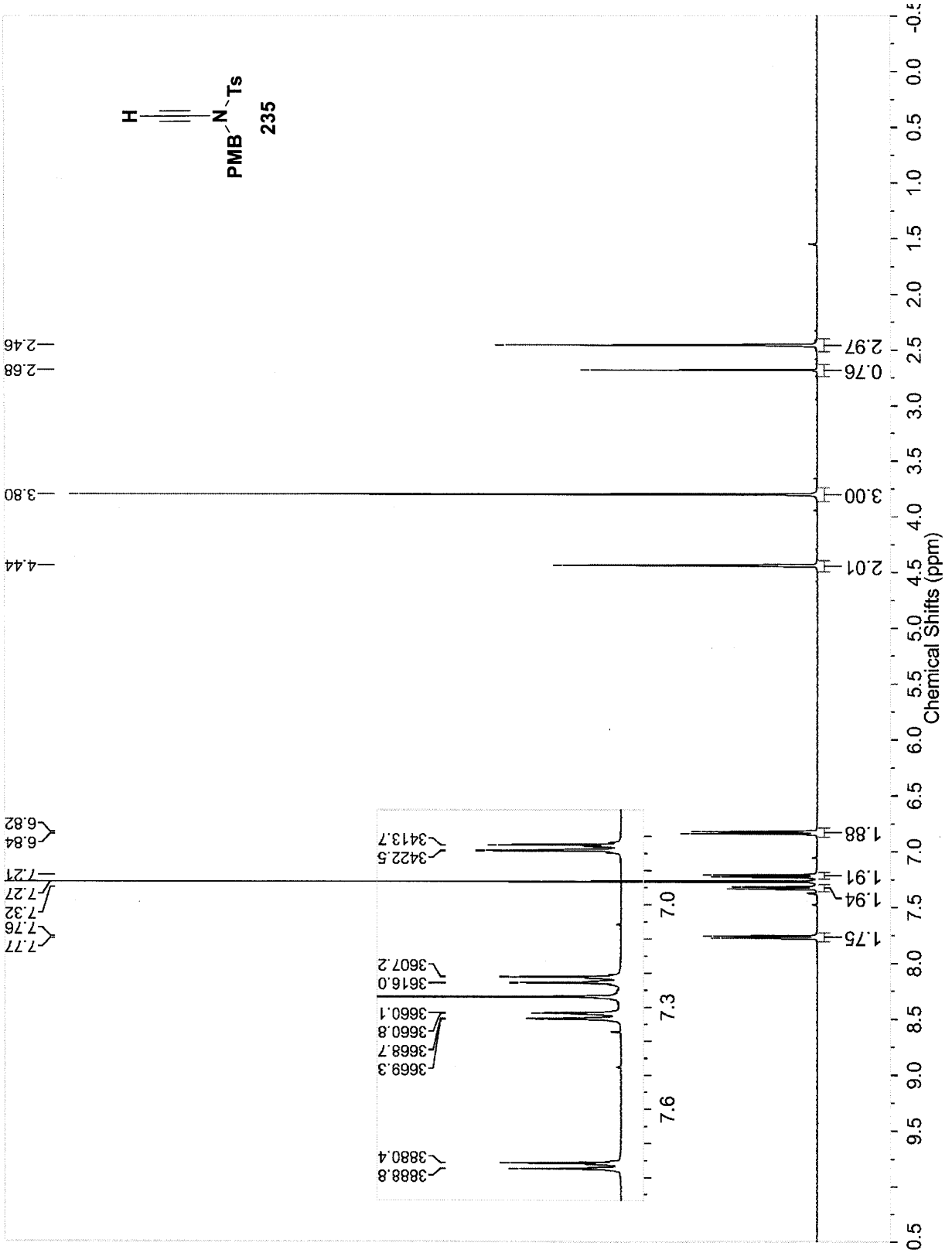
[154] Bendikov, M.; Duong, H. M.; Bolanos, E.; Wudl, F. *Org. Lett.* **2005**, *7*, 783–786.

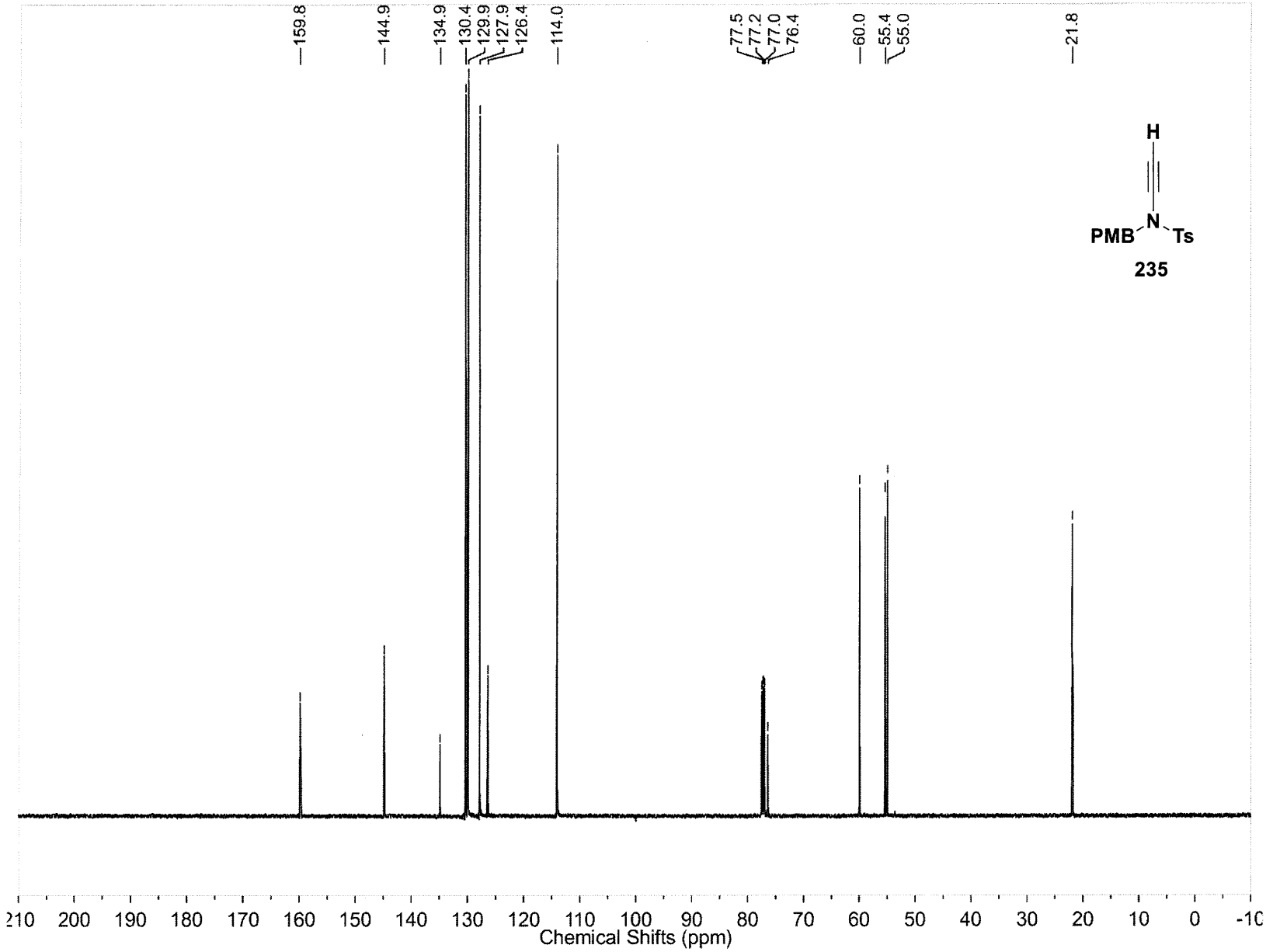
7.76
7.75
7.28
7.20
6.81
6.79
4.44
3.79
2.44
0.96
Si(i-Pr)3
PMB
N
Ts
234
3882.9
3874.6
3651.3
3650.7
3642.7
3642.1
3610.9
3602.1
3407.0
3398.2
7.6
7.3
7.0
1.83
2.13
1.84
1.86
2.03
3.00
3.00
21.29
Chemical Shifts (ppm)


159.8
144.6
134.9
130.7
129.7
128.0
126.6
114.0
96.6
77.5
77.2
77.0
70.4
55.5
55.2
21.8
18.7
11.5
Si(i-Pr)3
N
PMB
Ts
234
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shifts (ppm)



***N*-(4-Methoxybenzyl)-*N*-(*p*-toluenesulfonyl)ethynylamine (235).** A 50-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with ynamide **234** (1.00 g, 2.12 mmol, 1.0 equiv) and 21 mL of THF. The colorless solution was cooled at -40 °C and a solution of TBAF (1.0 M in THF, 2.33 mL, 2.33 mmol, 1.1 equiv) was added dropwise via syringe over 4 min. The resulting orange suspension was allowed to warm to rt over 20 min, diluted with 20 mL of satd aq NH_4Cl solution and 20 mL of Et_2O, and transferred to a 125-mL separatory funnel. The aqueous phase was separated and extracted with two 15-mL portions of Et_2O, and the combined organic phases were washed with 30 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 1.23 g of a wet off-white solid. This material was transferred to a 25-mL, round-bottomed flask, dissolved in 2 mL of hot benzene (70 °C), and 2 mL of hot hexane (70 °C) was added. The solution was allowed to slowly cool to rt and then -20 °C overnight. The resulting crystals were collected by removal of the mother liquor via cannula under argon, washed with two 2.5-mL portions of ice-cold hexane, and dried to afford 0.643 g (96%) of ynamide **235** as colorless crystals: mp 123–125 °C; IR (film) 3286, 2972, 2937, 2839, 2133, 1612, 1594, 1514, 1358, 1304, 1255, 1189, 1169, 1030, and 706 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (app d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 7.22 (app d, J = 8.8 Hz, 2H), 6.83 (app d, J = 8.8 Hz, 2H), 4.44 (s, 2H), 3.80 (s, 3H), 2.68 (s, 1H), and 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 144.9, 134.9, 130.4, 129.9, 127.9, 126.4, 114.0, 76.4, 60.0, 55.4, 55.0, and 21.8; HRMS (DART) *m/z* $[M+H]^+$ calcd for $C_{17}H_{17}NO_3S$, 316.1002; found 316.1004.

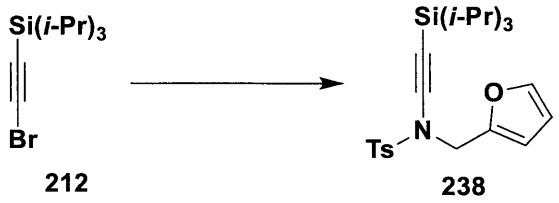

H
N
Ts
PMB
235
Chemical Shifts (ppm)


159.8
144.9
134.9
130.4
129.9
127.9
126.4
114.0
77.5
77.2
77.0
76.4
60.0
55.4
55.0
21.8
H
N
PMB
Ts
235
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shifts (ppm)

236 237

***N*-Allyl-*N*-(*p*-toluenesulfonyl)ethynylamine (237).** A 25-mL pear flask equipped with a rubber septum and argon inlet needle was charged with ynamide **236**[155] (0.465 g, 1.19 mmol, 1.0 equiv) and 6 mL of THF. The yellow solution was cooled at -40 °C and a solution of TBAF (1.0 M in THF, 1.3 mL, 1.3 mmol, 1.1 equiv) was added dropwise via syringe over 4 min. The resulting orange suspension was allowed to warm to rt over 1 h, diluted with 15 mL of satd aq NH_4Cl solution and 15 mL of Et_2O, and transferred to a 60-mL separatory funnel. The aqueous phase was separated and extracted with two 5-mL portions of Et_2O, and the combined organic phases were washed with 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.499 g of an orange oil. This material was added to the top of a column of 40 g of silica gel with the aid of a small amount of CH_2Cl_2 and eluted with 94:5:1 hexane-EtOAc-Et_3N to afford 0.254 g (91%) of ynamide **237** as colorless needles: mp 69–71 °C with spectral data consistent with that previously reported.[55b]

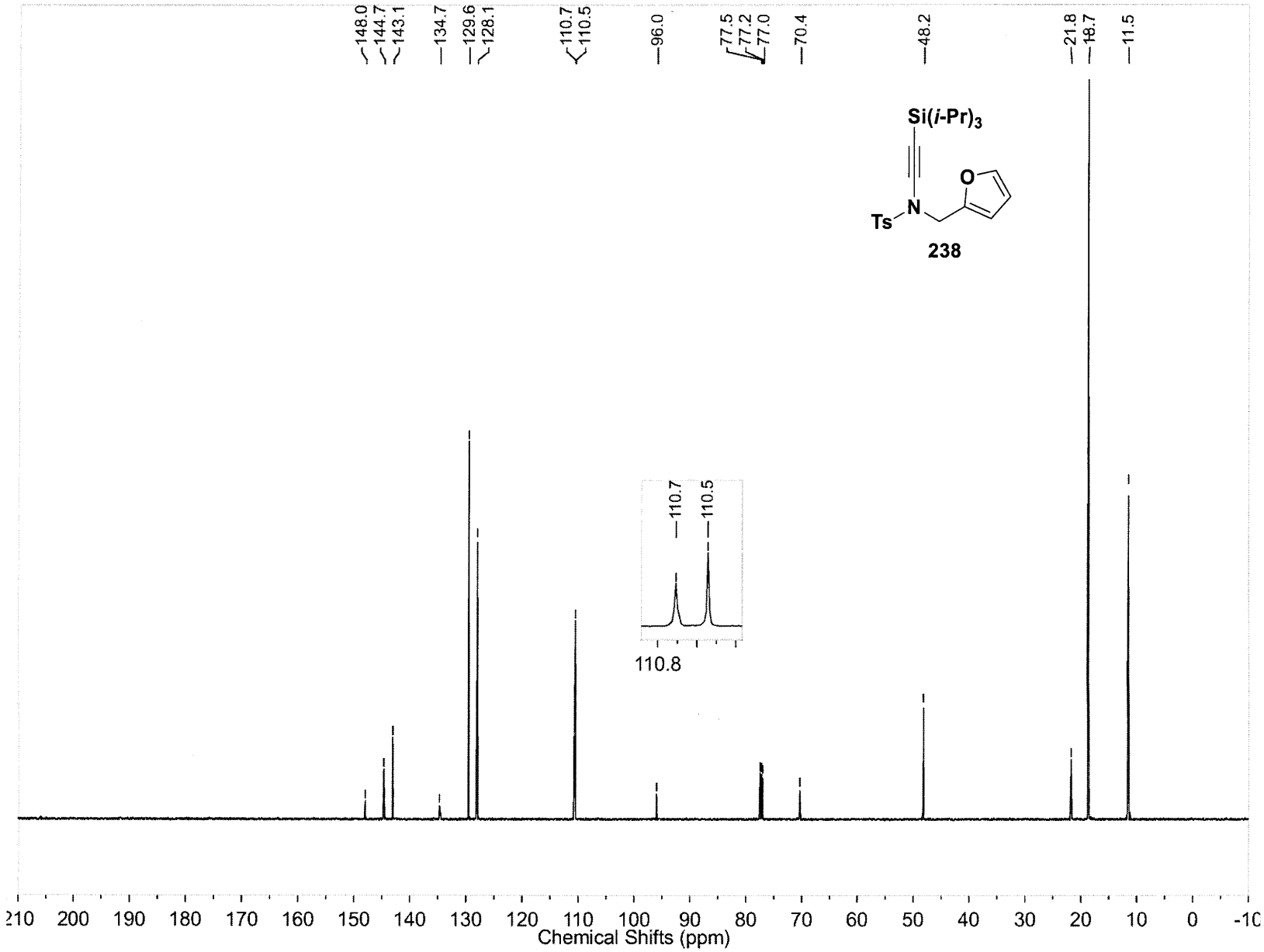
[155] Zhang, Y.; DeKorver, K. A.; Lohse, A. G.; Zhang, Y.-S.; Huang, J.; Hsung, R. P. *Org. Lett.* **2009**, *11*, 899–902.

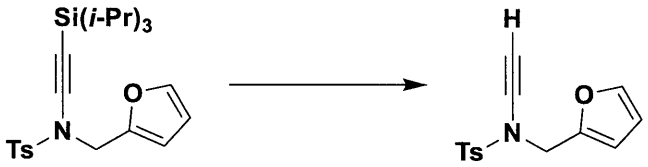


***N*-(Furan-2-ylmethyl)-*N*-(*p*-toluenesulfonyl)-2-(triisopropylsilyl)ethynylamine (238).** A 15-mL test tube equipped with a rubber septum and argon inlet needle was charged with *N*-(furan-2-ylmethyl)-*p*-toluenesulfonamide[156] (0.500 g, 1.99 mmol, 1.2 equiv), $CuSO_4 \cdot 5H_2O$ (0.041 g, 0.17 mmol, 0.1 equiv), 1,10-phenanthroline (0.060 g, 0.33 mmol, 0.2 equiv), and K_2CO_3 (0.458 g, 3.32 mmol, 2.0 equiv). Bromo(triisopropylsilyl)acetylene **212** (0.433 g, 1.66 mmol, 1.0 equiv) and 3.3 mL of toluene were added, and argon was bubbled through the pale green reaction mixture for ca. 5 min. The reaction mixture was heated at 80 °C with vigorous stirring for 30 min and 0.6 mL of DMF was added. The green suspension was heated at 80 °C with vigorous stirring for additional 20 h and then allowed to cool to rt. The resulting dark green suspension was diluted with 15 mL of EtOAc and 15 mL of water and transferred to a 60-mL separatory funnel. The aqueous phase was separated and extracted with two 5-mL portions of EtOAc, and the combined organic phases were washed with 15 mL of satd aq NH_4Cl solution, 15 mL of water, and 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 1.05 g of a wet green crystalline solid. This material was dissolved in ca. 5 mL of CH_2Cl_2 and concentrated onto 2.5 g of silica gel. The resulting free-flowing powder was added to the top of a column of 40 g of silica gel and eluted with 5 % EtOAc-hexane to afford 0.459 g (64%) of ynamide **238** as colorless crystals: mp 47–48 °C; IR (film) 2942, 2865, 2165, 1598, 1502, 1462, 1452, 1370, 1169, 1091, 1008, 883, and 665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (app d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.6 Hz, 2H), 7.27 (dd, J = 2.7, 1.4 Hz, 1H), 6.25 (m, 2H), 4.57 (s, 2H), 2.43 (s, 3H), and 0.99 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 144.7, 143.1, 134.7, 129.6, 128.1, 110.7, 110.5, 96.0, 70.4, 48.2, 21.8, 18.7, and 11.5; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{23}H_{33}NO_3SSi$, 454.1843; found 454.1853.

[156] Hashmi, A. S. K.; Weyrauch, J. P.; Kurpejovic, E.; Frost, T. M.; Miehlich, B.; Frey, W.; Bats, J. W. *Chem. Eur. J.* **2006**, *12*, 5806–5814.

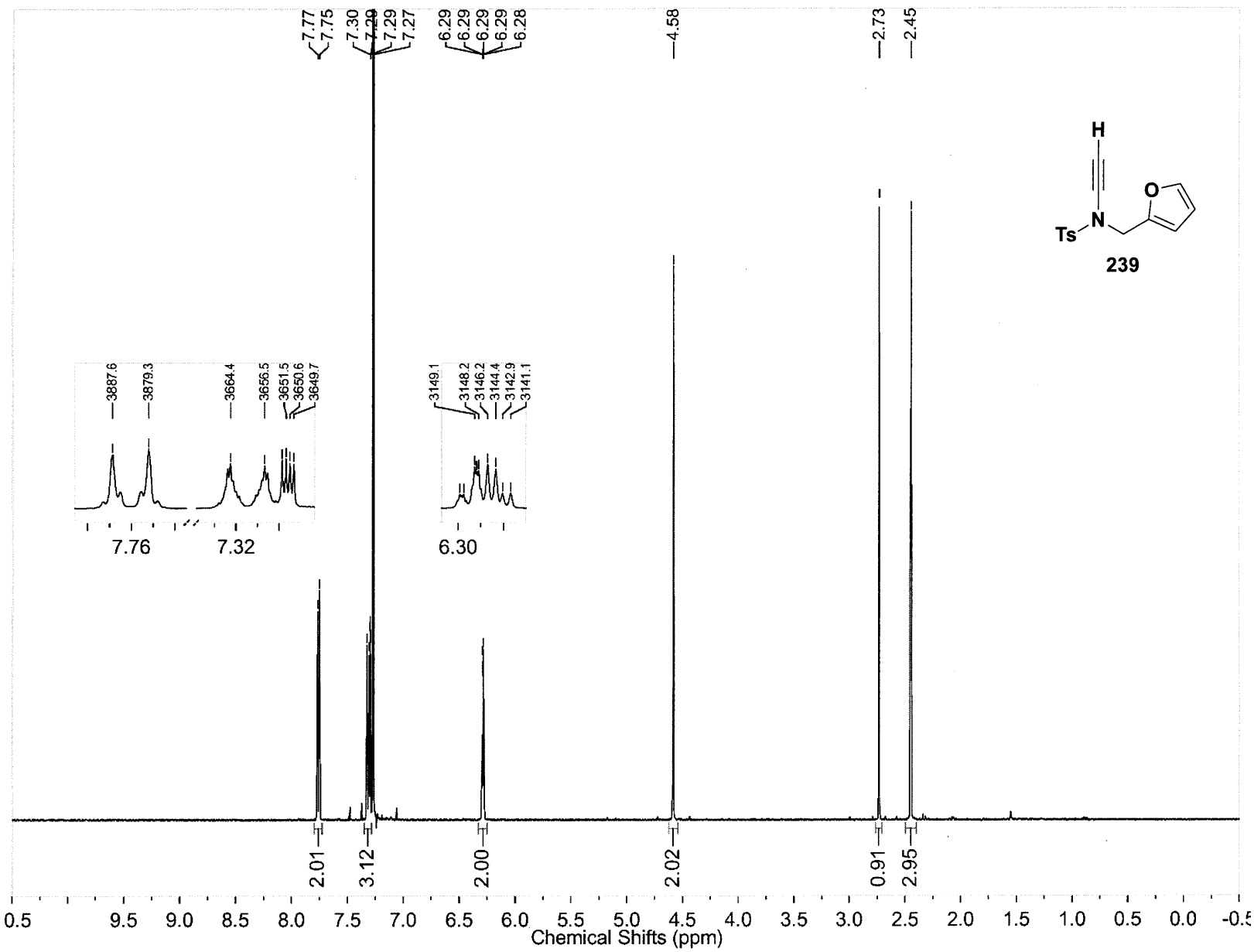
7.77
7.75
7.29
7.27
7.27
7.26
7.26
6.25
6.25
4.57
2.43
0.99
Si(i-Pr)3
O
N
Ts
238
3888.2
3879.9
3649.1
3648.5
3640.5
3638.0
3636.6
3635.3
3633.9
3128.4
3126.9
7.78
7.74
7.28
6.26
2.03
3.20
2.00
2.05
2.97
19.38
0.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
Chemical Shifts (ppm)

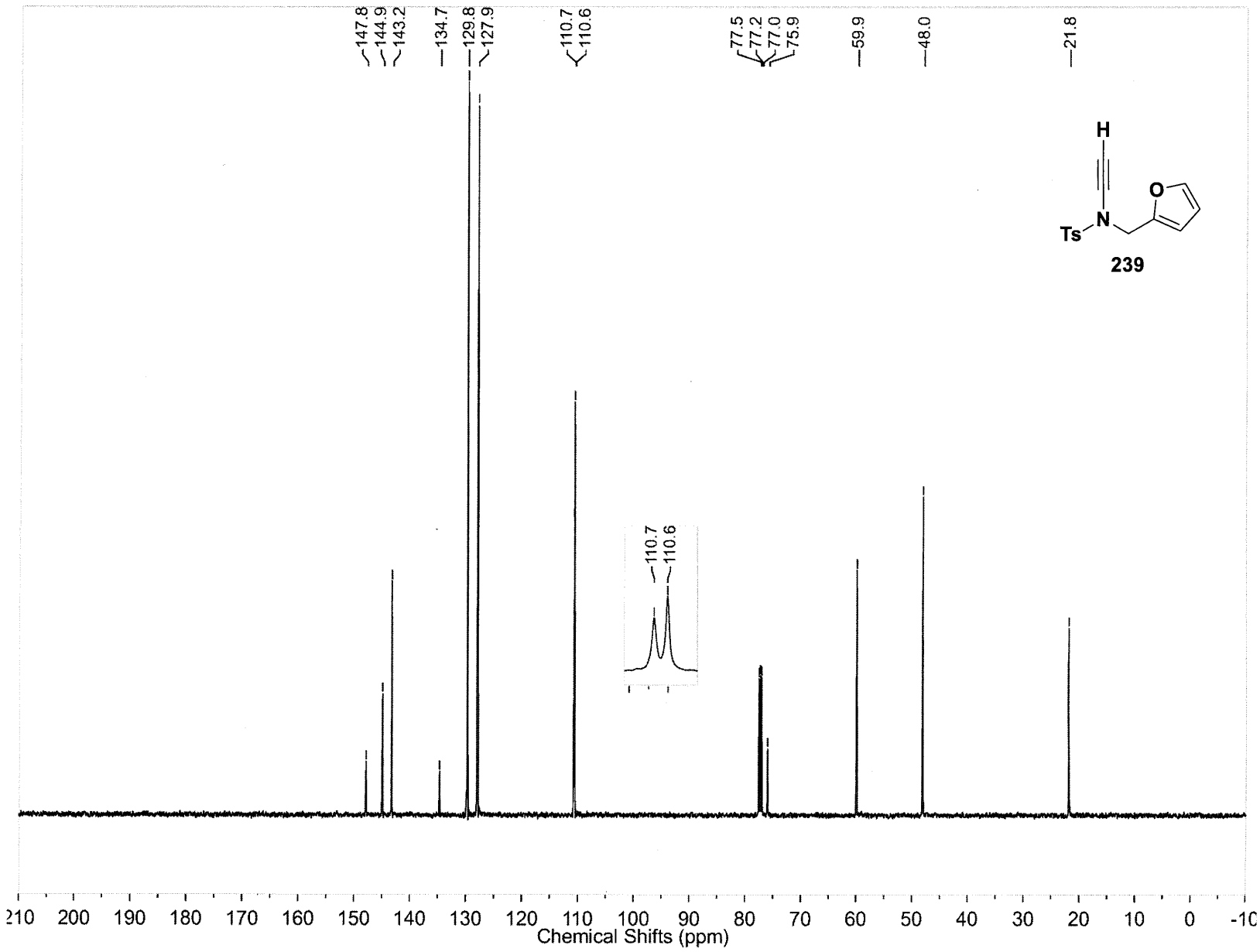

148.0
144.7
143.1
134.7
129.6
128.1
110.7
110.5
96.0
77.5
77.2
77.0
70.4
48.2
21.8
18.7
11.5
Si(i-Pr)3
O
N
Ts
238
110.7
110.5
110.8
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shifts (ppm)

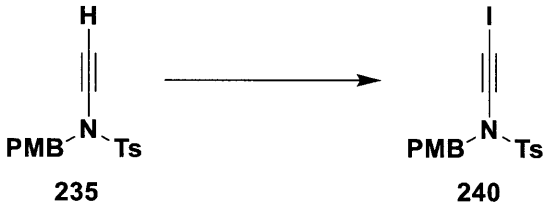


238 239

***N*-(Furan-2-ylmethyl)-*N*-(*p*-toluenesulfonyl)ethynylamine (239).** A 50-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with ynamide **238** (0.458 g, 1.06 mmol, 1.0 equiv) and 10 mL of THF. The colorless solution was cooled at -40 °C and a solution of TBAF (1.0 M in THF, 1.17 mL, 1.17 mmol, 1.1 equiv) was added dropwise via syringe over 2 min. The resulting orange suspension was allowed to warm to rt over 1 h with stirring and then diluted with 10 mL of satd aq NH_4Cl solution and 10 mL of Et_2O. The mixture was transferred to a 60-mL separatory funnel and the aqueous phase was separated and extracted with two 7.5-mL portions of Et_2O. The combined organic phases were washed with 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.542 g of a pale yellow solid. This material was transferred to a 25-mL, round-bottomed flask, dissolved in 0.5 mL of hot benzene (70 °C), and 1.5 mL of hot hexane (70 °C) was added. The solution was allowed to slowly cool to rt and then -20 °C overnight. The resulting crystals were collected by removal of the mother liquor via cannula under argon, washed with two 2-mL portions of ice-cold hexane, and dried to afford 0.287 g (98%) of ynamide **239** as pale yellow crystals: mp 103–104 °C; IR (film) 3279, 3113, 2136, 1597, 1503, 1359, 1307, 1289, 1171, 1152, 1089, 1008, 932, 750, 706, and 576 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (app d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 7.30 (dd, J = 1.8, 0.9 Hz, 1H), 6.27–6.30 (m, 2H), 4.58 (s, 2H), 2.73 (s, 1H), and 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 144.9, 143.2, 134.7, 129.8, 127.9, 110.7, 110.6, 75.9, 59.9, 48.0, and 21.8; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{14}H_{13}NO_3S$, 298.0508; found 298.0513.

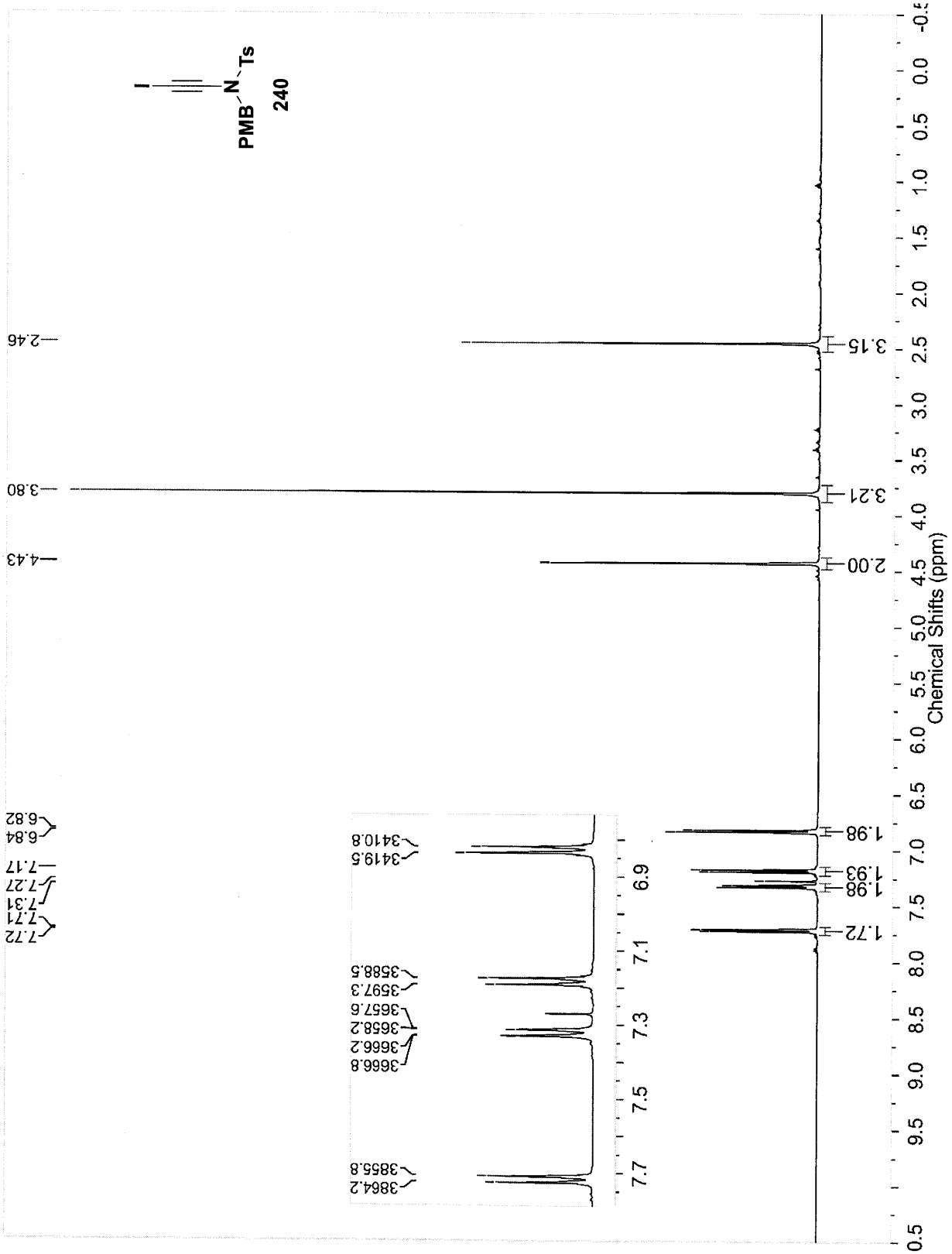

7.77
7.75
7.30
7.29
7.27
6.29
6.29
6.29
6.29
6.28
4.58
2.73
2.45
H
O
N
Ts
239
3887.6
3879.3
3664.4
3656.5
3651.5
3650.6
3649.7
3149.1
3148.2
3146.2
3144.4
3142.9
3141.1
7.76
7.32
6.30
2.01
3.12
2.00
2.02
0.91
2.95
Chemical Shifts (ppm)

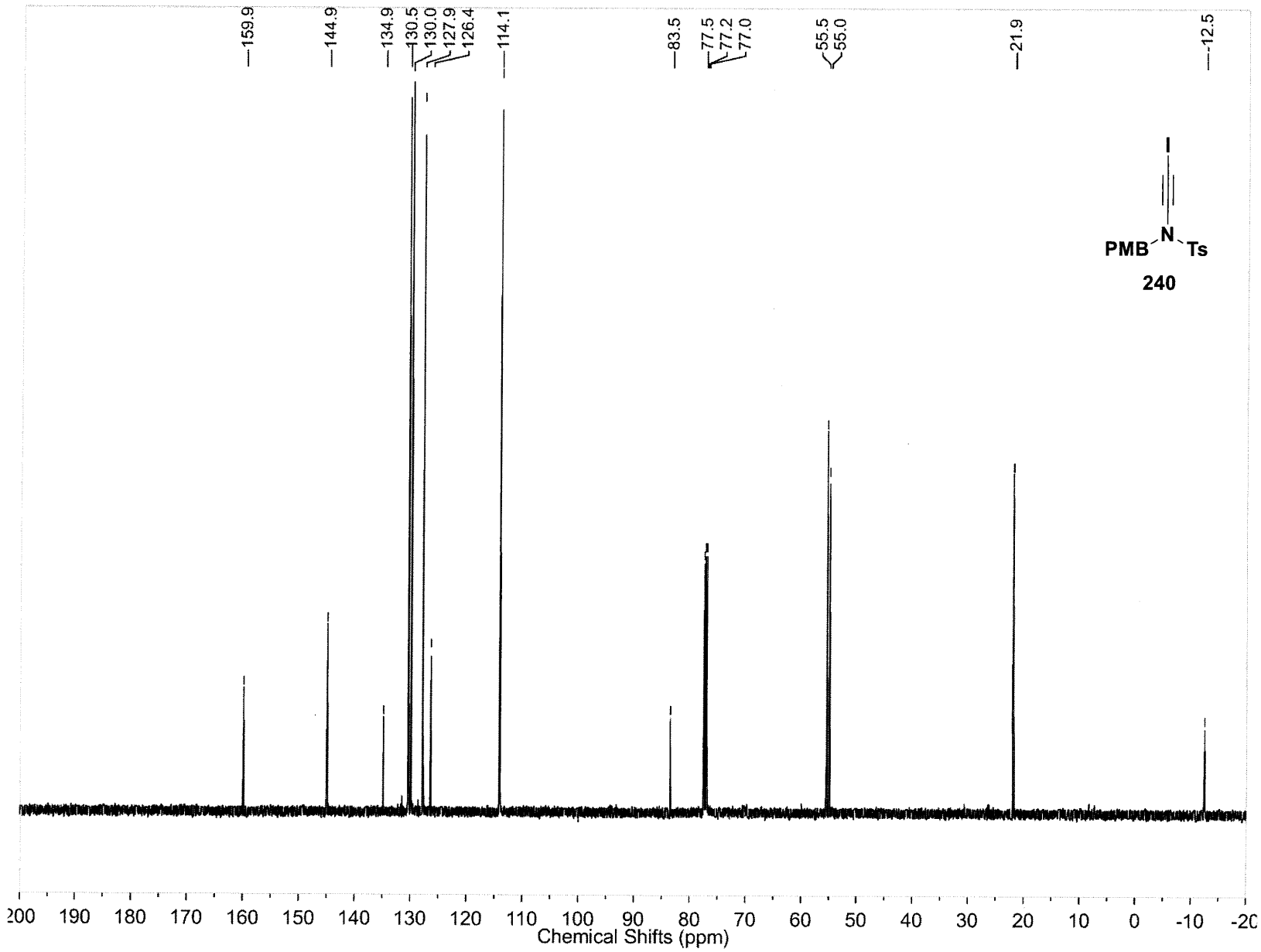

147.8
144.9
143.2
134.7
129.8
127.9
110.7
110.6
77.5
77.2
77.0
75.9
59.9
48.0
21.8
110.7
110.6
H
O
N
Ts
239
Chemical Shifts (ppm)

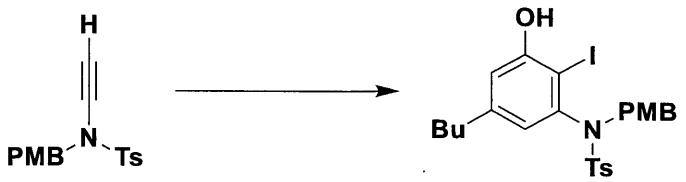


235 240

***N*-(4-Methoxybenzyl)-*N*-(*p*-toluenesulfonyl)-2-iodoethynylamine (240).** A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with ynamide **235** (0.100 g, 0.317 mmol, 1.0 equiv) and 3.2 mL of THF. The pale yellow solution was cooled at -20 °C and a solution of *n*-BuLi (2.45 M in hexane, 0.13 mL, 0.32 mmol, 1.0 equiv) was added dropwise via syringe over 2 min. The resulting orange-brown solution was stirred at -20 °C for 3 h and then cooled to -78 °C. Powdered iodine (0.081 g, 0.32 mmol, 1.0 equiv) was added in one portion, and the reaction mixture was allowed to slowly warm to rt and stirred for a total of 64 h. The resulting suspension was diluted with 10 mL of Et_2O and 10 mL of a 1:1 mixture of satd aq $Na_2S_2O_3$ and $NaHCO_3$ solutions and transferred to a 60-mL separatory funnel. The aqueous phase was separated and extracted with two 5-mL portions of Et_2O, and the combined organic phases were washed with 10 mL of water and 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.156 g of a brown oil. This material was added to the top of a column of 12 g of acetone-deactivated silica gel with the aid of a small amount of CH_2Cl_2 and eluted with 89:10:1 hexane-EtOAc-Et_3N to afford 0.105 g (75%) of iodoynamide **240** as a pale yellow solid: mp 79–81 °C; IR (film) 2934, 2837, 2186, 1612, 1597, 1514, 1364, 1250, 1168, 1089, 1032, 737, 657, and 592 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (app d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.6 Hz, 2H), 7.18 (app d, J = 8.8 Hz, 2H), 6.83 (app d, J = 8.7 Hz, 2H), 4.43 (s, 2H), 3.80 (s, 3H), and 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 144.9, 134.9, 130.5, 130.0, 127.9, 126.4, 114.1, 83.5, 55.5, 55.0, 21.9, and -12.5; HRMS (DART) *m/z* $[M+H]^+$ calcd for $C_{17}H_{16}INO_3S$, 441.9968; found 441.9956.


I
PMB
N
Ts
240
2.46
3.80
4.43
6.82
6.84
7.17
7.27
7.31
7.71
7.72
3864.2
3855.8
3666.8
3666.2
3658.2
3657.6
3597.3
3588.5
3419.5
3410.8
1.72
1.98
1.93
1.98
2.00
3.21
3.15
Chemical Shifts (ppm)


159.9
144.9
134.9
130.5
130.0
127.9
126.4
114.1
83.5
77.5
77.2
77.0
55.5
55.0
21.9
12.5
I
N
PMB
Ts
240
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
Chemical Shifts (ppm)

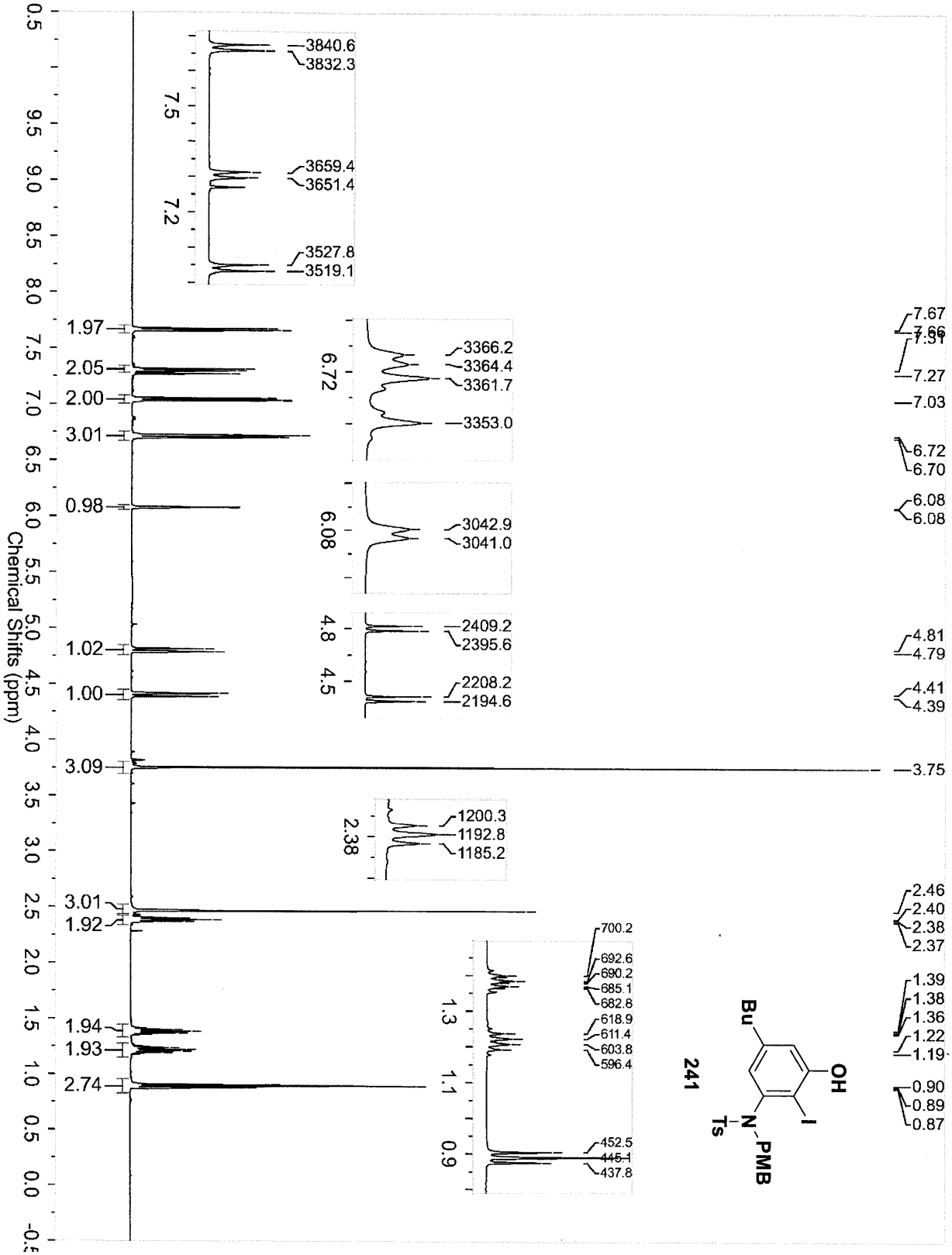


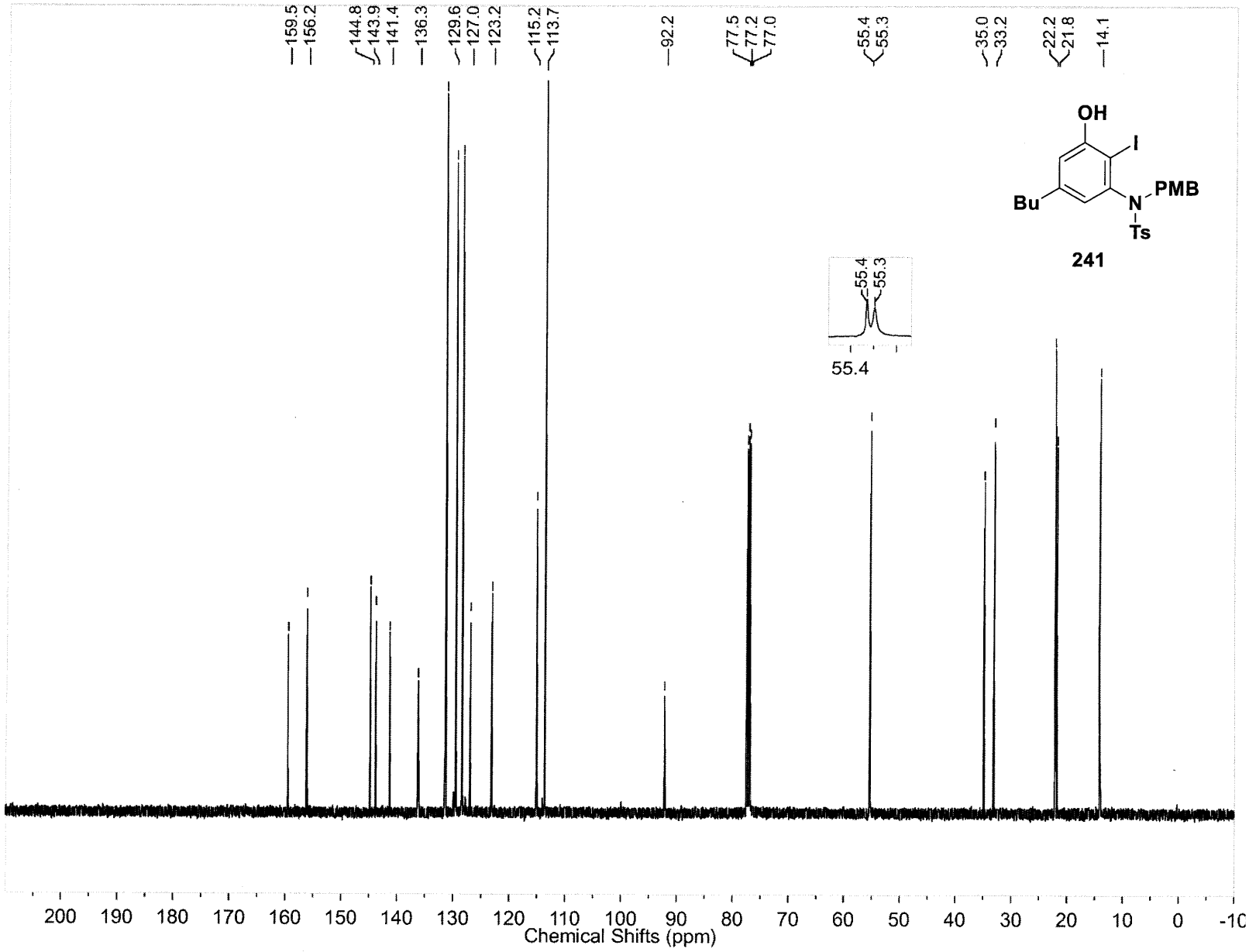
235 241

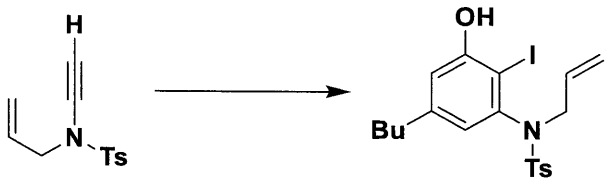
***N*-(4-Methoxybenzyl)-*N*-(*p*-toluenesulfonyl)-(5-butyl-3-hydroxy-2-iodophenyl)amine (241).** A 250-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with ynamide **235** (2.18 g, 6.92 mmol, 1.0 equiv) and 70 mL of THF. The solution was cooled at -15 °C and a solution of *n*-BuLi (2.26 M in hexane, 3.06 mL, 6.92 mmol, 1.0 equiv) was added dropwise via syringe over 7 min. The resulting brown solution was stirred at -15 °C for 3 h and then cooled to -78 °C. Powdered iodine (1.76 g, 6.92 mmol, 1.0 equiv) was added in one portion, and the reaction mixture was allowed to slowly warm to rt and stirred for a total of 17 h. The resulting red-brown mixture was diluted with 150 mL of Et_2O, transferred to a 500-mL separatory funnel, and washed with 150 mL of a 1:1 mixture of satd aq $Na_2S_2O_3$ and $NaHCO_3$ solutions. The organic phase was separated and washed with 150 mL of water, and the combined aqueous phases were extracted with two 75-mL portions of Et_2O. The combined organic phases were washed with 150 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 3.01 g of a brown solid. This material was found to contain ca. 95% iodoynamide **240** and no purification was attempted at this stage.

Crude iodoynamide **240** was transferred to a 100-mL pear flask equipped with a rubber septum and argon inlet needle, and 3-butylcyclobutenone **72** (1.71 g, 13.8 mmol, 2.0 equiv) and 20 mL of toluene were added. The brown reaction mixture was heated at 80 °C for 2 h, allowed to cool to rt and concentrated to afford 5.45 g of a dark brown oil. This material was diluted with 20 mL of MeOH and 20 mL of 5 M aqueous KOH solution, the same flask was equipped with a rubber septum and argon inlet needle, and the reaction mixture was heated at 70 °C for 2 h. The resulting brown suspension was cooled to rt, diluted with 125 mL of 1 M aqueous HCl solution and 125 mL of CH_2Cl_2, and transferred to a 500-mL separatory funnel. The aqueous phase was separated and extracted with two 60-mL portions of CH_2Cl_2, and the combined organic phases were washed with two 100-mL portions of water and 100 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 5.28 g of a dark red oil. This material was dissolved in ca. 30 mL of CH_2Cl_2 and concentrated onto 10 g of silica gel. The resulting free-flowing powder was added to the top of a

column of 200 g of silica gel and eluted with 50:40:10 benzene-hexane-EtOAc to afford 2.72 g (69%) of phenol **241** as a pale yellow solid: mp 150–153 °C; IR (film) 3415, 2955, 2930, 2860, 1612, 1586, 1514, 1423, 1347, 1304, 1249, 1159, 1090, 1035, and 815 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.04 (app d, J = 8.7 Hz, 2H), 6.72 (d, J = 1.8 Hz, 1H), 6.71 (app d, J = 8.7 Hz, 2H), 6.08 (d, J = 1.9 Hz, 1H), 4.80 (d, J = 13.6 Hz, 1H), 4.40 (d, J = 13.6 Hz, 1H), 3.75 (s, 3H), 2.46 (s, 3H), 2.38 (t, J = 7.6 Hz, 2H), 1.38 (app quint, J = 7.6 Hz, 2H), 1.21 (sext, J = 7.4 Hz, 2H), and 0.89 (t, J = 7.3 Hz, 3H), phenolic proton not observed; ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 156.2, 144.8, 143.9, 141.4, 136.3, 131.5, 129.6, 128.5, 127.0, 123.2, 115.2, 113.7, 92.2, 55.4, 55.3, 35.0, 33.2, 22.2, 21.8, and 14.1; HRMS (DART) *m/z* $[M+H]^+$ calcd for $C_{25}H_{28}INO_4S$, 566.0856; found 566.0864.


Chemical Shifts (ppm)
3840.6
3832.3
3659.4
3651.4
3527.8
3519.1
3366.2
3364.4
3361.7
3353.0
3042.9
3041.0
2409.2
2395.6
2208.2
2194.6
1200.3
1192.8
1185.2
700.2
692.6
690.2
685.1
682.8
618.9
611.4
603.8
596.4
452.5
445.1
437.8
1.97
2.05
2.00
3.01
0.98
1.02
1.00
3.09
3.01
1.92
1.94
1.93
2.74
7.67
7.66
7.31
7.27
7.03
6.72
6.70
6.08
6.08
4.81
4.79
4.41
4.39
3.75
2.46
2.40
2.38
2.37
1.39
1.38
1.36
1.22
1.19
0.90
0.89
0.87
241
Bu
OH
I
N
PMB
Ts


159.5
156.2
144.8
143.9
141.4
136.3
129.6
127.0
123.2
115.2
113.7
92.2
77.5
77.2
77.0
55.4
55.3
35.0
33.2
22.2
21.8
14.1
OH
I
Bu
N
PMB
Ts
241
55.4
55.3
55.4
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shifts (ppm)

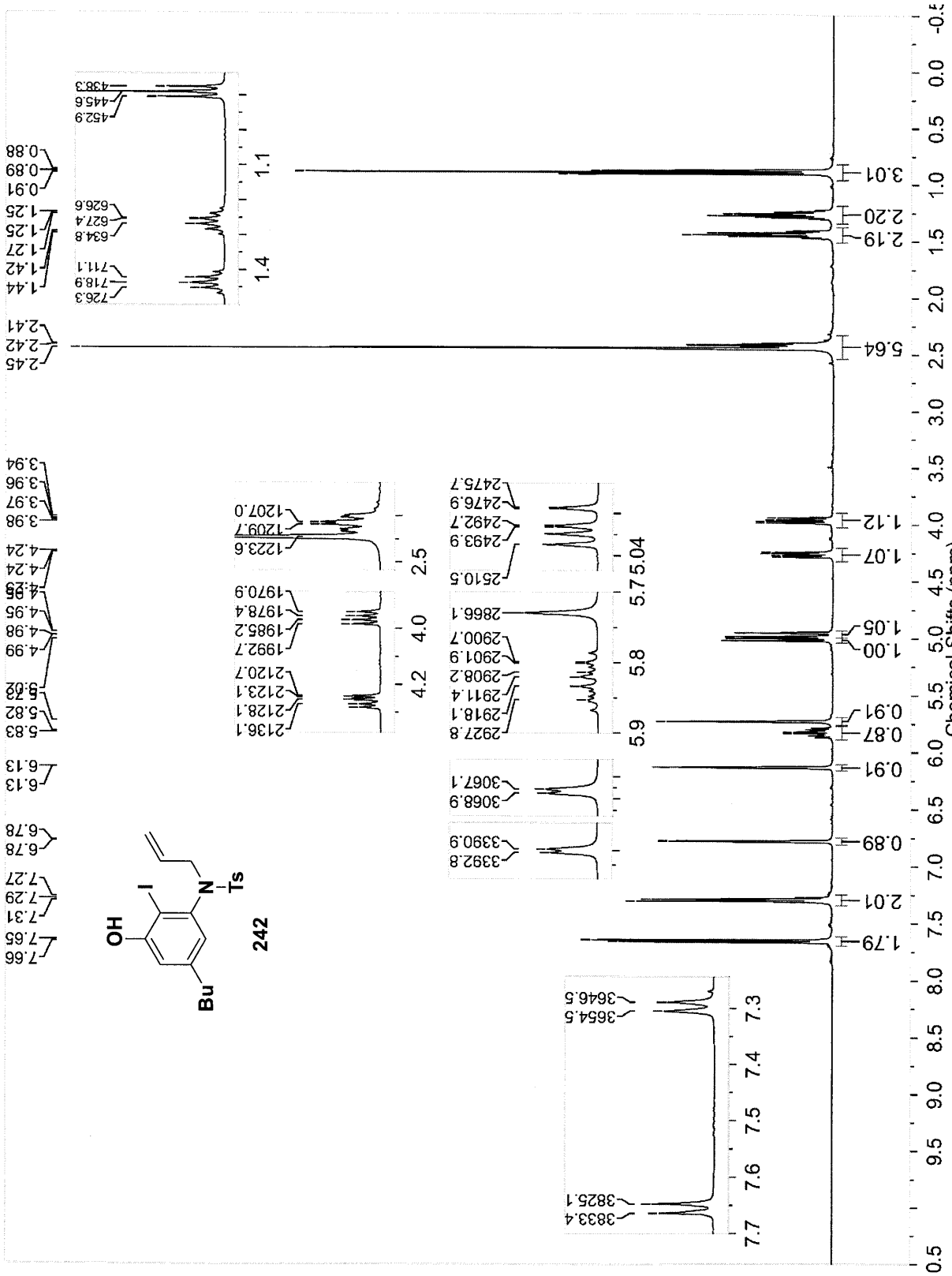


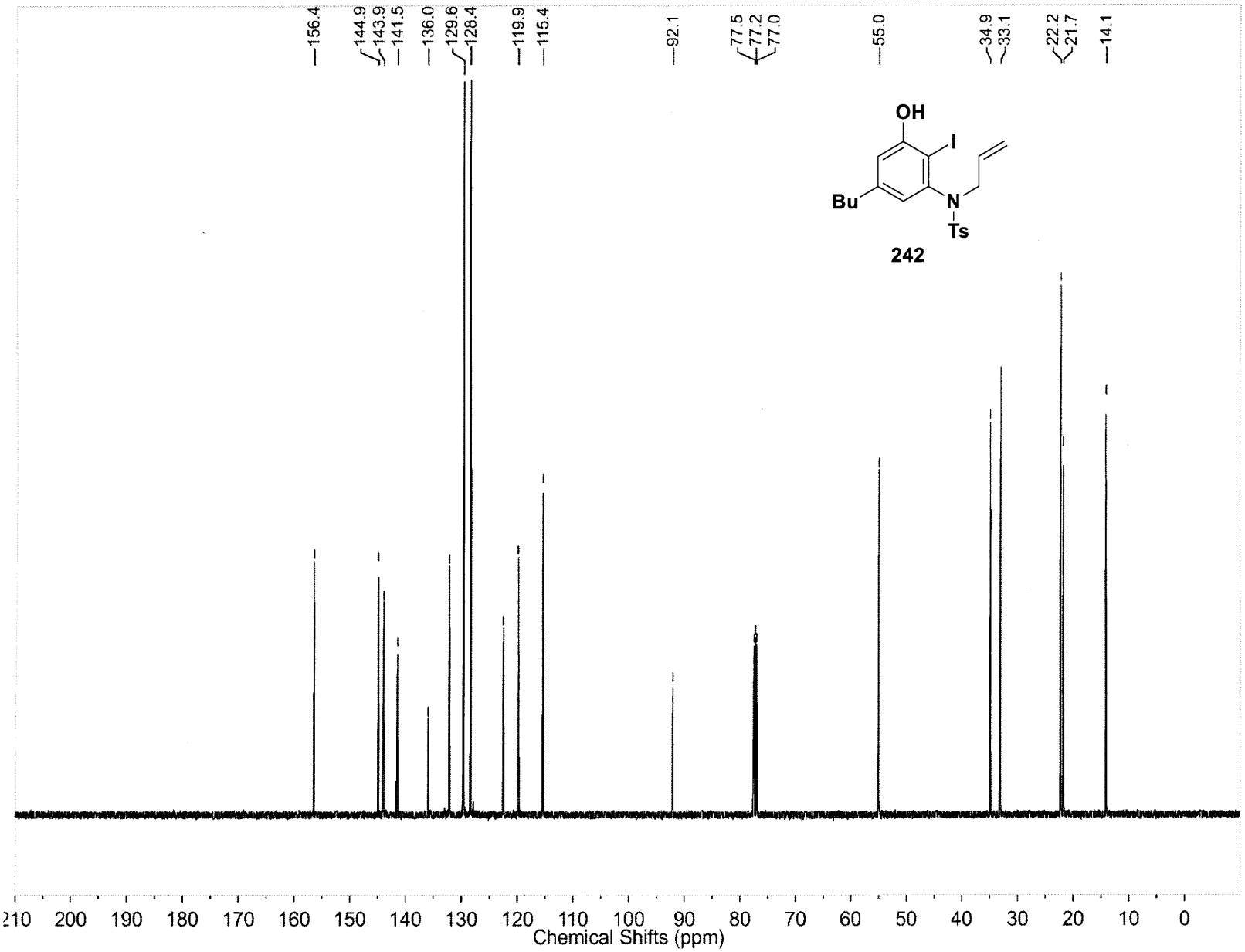
237 242

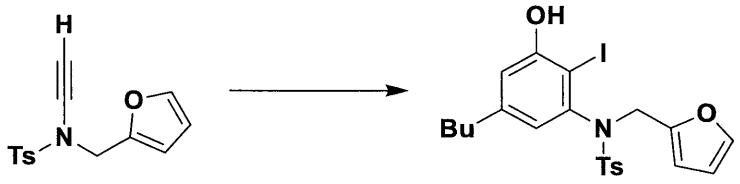
***N*-Allyl-*N*-(*p*-toluenesulfonyl)-(5-butyl-3-hydroxy-2-iodophenyl)amine (242).** A 50-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with ynamide **237** (0.466 g, 1.98 mmol, 1.0 equiv) and 20 mL of THF. The colorless solution was cooled at -15 °C and a solution of *n*-BuLi (2.34 M in hexane, 0.85 mL, 1.99 mmol, 1.0 equiv) was added dropwise via syringe over 7 min. The resulting brown solution was stirred at -15 °C for 3 h and then cooled to -78 °C. Powdered iodine (0.503 g, 1.98 mmol, 1.0 equiv) was added in one portion, and the reaction mixture was allowed to slowly warm to rt and stirred for a total of 16 h. The resulting red-brown mixture was diluted with 40 mL of Et_2O, transferred to a 125-mL separatory funnel, and washed with 40 mL of a 1:1 mixture of satd aq $Na_2S_2O_3$ and $NaHCO_3$ solutions. The aqueous phase was separated and extracted with two 20-mL portions of Et_2O, and the combined organic phases were washed with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.707 g of crude iodoynamide as a brown oil.

The crude iodoynamide was transferred to a 50-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle, and 3-butylcyclobutenone **72** (0.492 g, 3.96 mmol, 2.0 equiv) and 10 mL of toluene were added. The brown reaction mixture was heated at 80 °C for 2 h, allowed to cool to rt, and concentrated to afford 0.785 g of a dark brown oil. This material was diluted with 5 mL of MeOH and 5 mL of 5 M aqueous KOH solution, the same flask was equipped with a rubber septum and argon inlet needle, and the reaction mixture was heated at 70 °C for 2 h. The resulting brown suspension was cooled to rt, diluted with 30 mL of 1 M aqueous HCl solution and 30 mL of Et_2O, and transferred to a 125-mL separatory funnel. The aqueous phase was extracted with three 15-mL portions of Et_2O, and the combined organic phases were washed with 30 mL of water and 30 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 1.05 g of a red oil. This material was dissolved in ca. 15 mL of CH_2Cl_2 and concentrated onto 5 g of silica gel. The resulting free-flowing powder was added to the top of a column of 100 g of silica gel and eluted with 50:42.5:7.5 benzene-hexane-EtOAc to afford 0.392 g (41%) of phenol **17** as a viscous yellow oil: IR (film) 3416, 2955, 2929, 2860, 1597, 1581, 1423, 1345, 1305, 1161, 1089, 929, 813,

722, and 663 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (app d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 6.78 (d, J = 1.9 Hz, 1H), 6.13 (d, J = 1.8 Hz, 1H), 5.78–5.87 (m, 1H), 5.73 (br s, 1H), 5.01 (dd, J = 10.1, 1.0 Hz, 1H), 4.97 (dq, J = 17.0, 1.2 Hz, 1H), 4.26 (ddt, J = 14.3, 6.2, 1.3 Hz, 1H), 3.96 (dd, J = 14.3, 7.5 Hz, 1H), 2.45 (s, 3H), 2.42 (td, J = 7.6, 2.4 Hz, 2H), 1.44 (quint, J = 7.6 Hz, 2H), 1.26 (sext, J = 7.4 Hz, 2H), and 0.89 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.4, 144.9, 143.9, 141.5, 136.0, 132.2, 129.6, 128.4, 122.5, 119.9, 115.4, 92.1, 55.0, 34.9, 33.1, 22.2, 21.7, and 14.1; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{20}H_{24}INO_3S$, 508.0414; found 508.0418.


OH
I
N
Ts
Bu
242
Chemical Shifts (ppm)

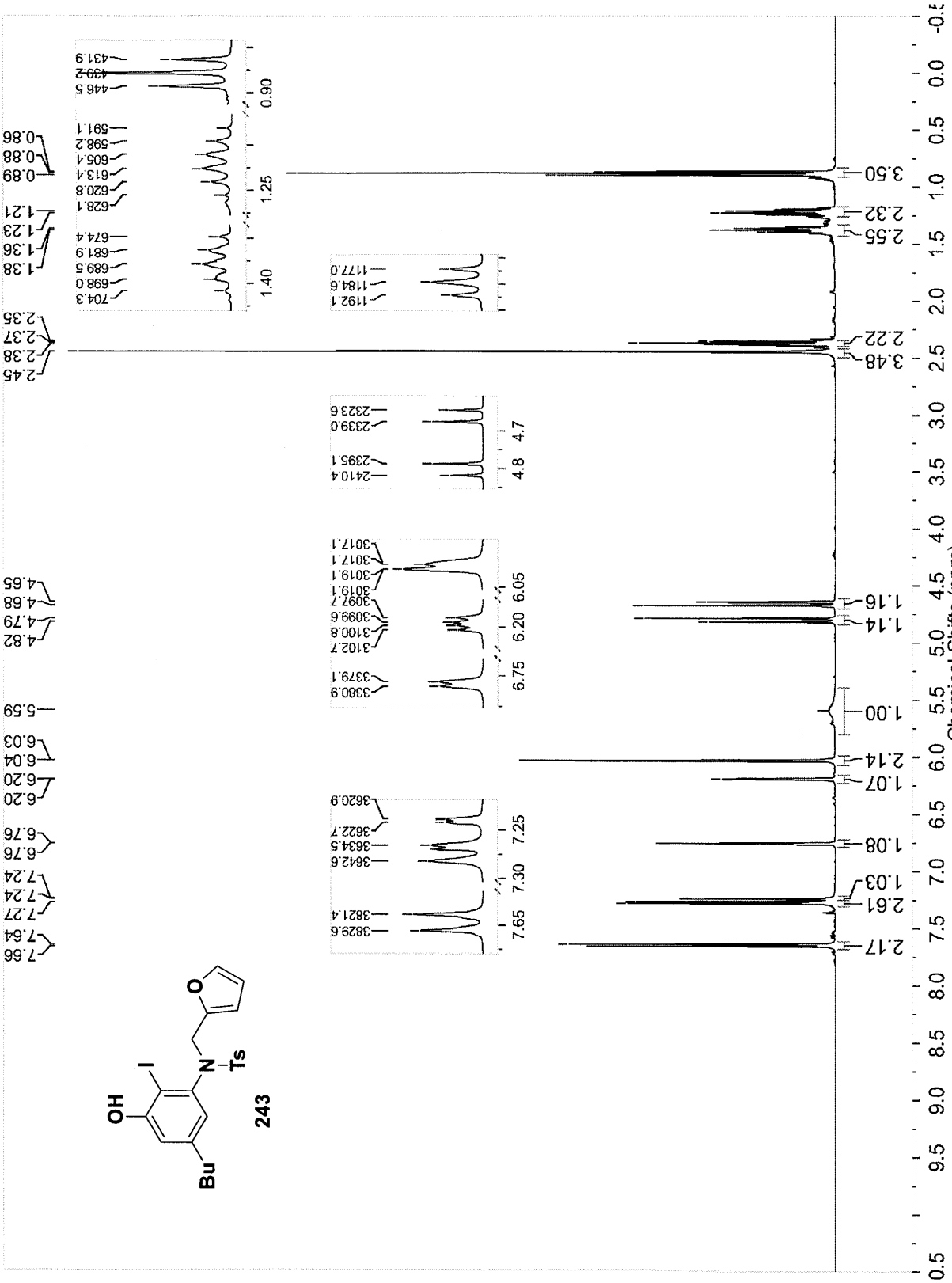

156.4
144.9
143.9
141.5
136.0
129.6
128.4
119.9
115.4
92.1
77.5
77.2
77.0
55.0
34.9
33.1
22.2
21.7
14.1
OH
I
Bu
N
Ts
242
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shifts (ppm)

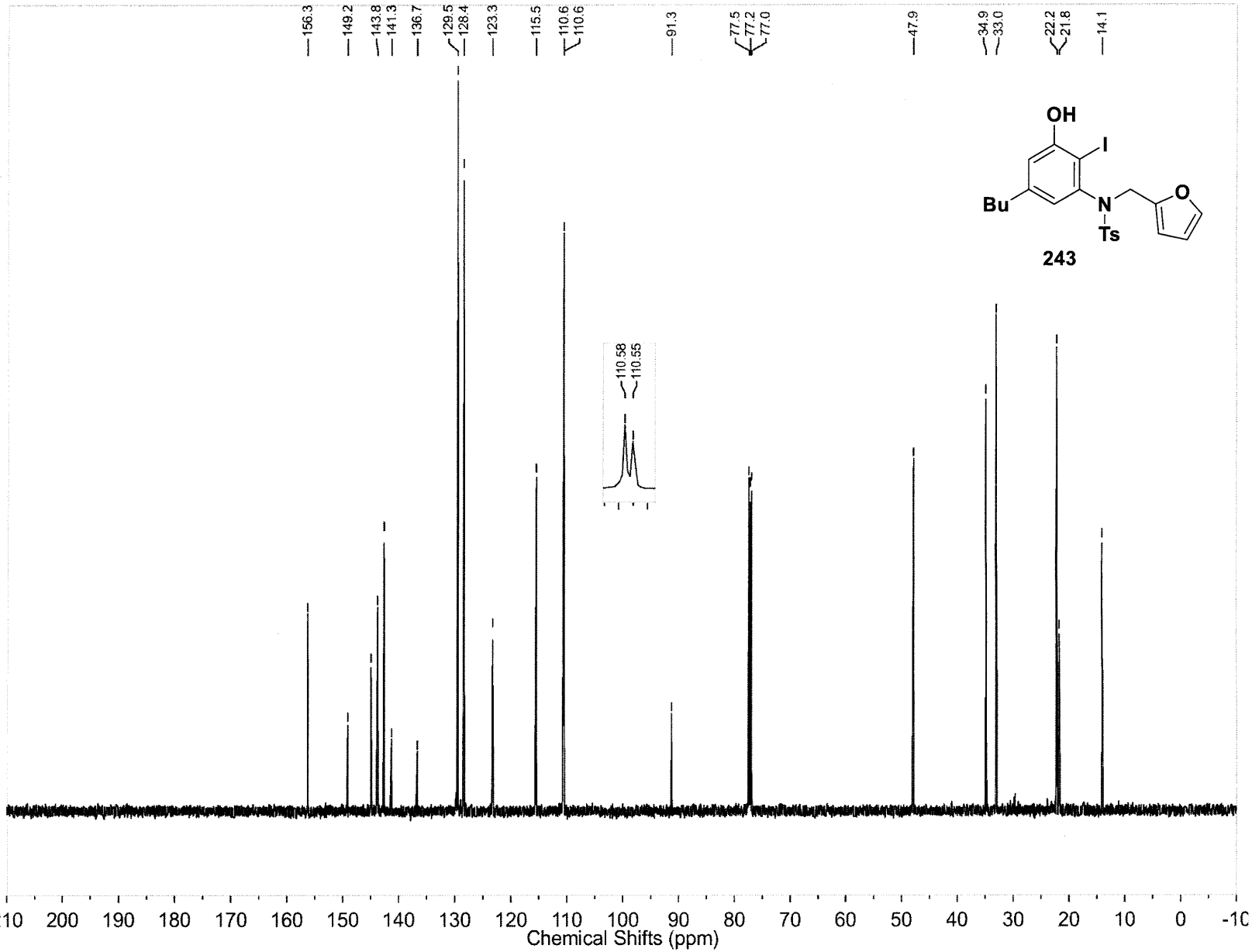


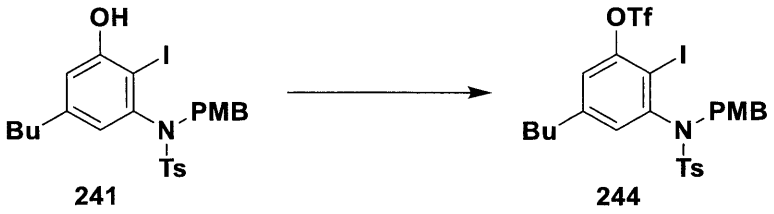
***N*-(Furan-2-ylmethyl)-*N*-(*p*-toluenesulfonyl)-(5-butyl-3-hydroxy-2-iodophenyl)amine (243).** A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with ynamide **239** (0.140 g, 0.508 mmol, 1.0 equiv) and 5 mL of THF. The nearly colorless reaction mixture was cooled at -25 °C and a solution of KHMDS (0.91 M in THF, 0.56 mL, 0.51 mmol, 1.0 equiv) was added dropwise via syringe over 2 min. The resulting dark red solution was stirred at -20 °C for 3 h and then cooled to -78 °C. Powdered iodine (0.129 g, 0.508 mmol, 1.0 equiv) was added in one portion, and the reaction mixture was allowed to slowly warm to rt and stirred for a total of 19 h. The resulting brown suspension was diluted with 10 mL of Et_2O, transferred to a 60-mL separatory funnel, and washed with 10 mL of satd aq $Na_2S_2O_3$ solution. The organic phase was separated and washed with 10 mL of water, and the combined aqueous phases were extracted with two 5-mL portions of Et_2O. The combined organic phases were washed with 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.258 g of a brown solid. This material was added to the top of a column of 20 g of acetone-deactivated silica gel and eluted with 91:8:1 hexane-EtOAc-Et_3N to afford 0.156 g of crude iodoynamide as a pale yellow waxy solid.

The crude iodoynamide was transferred to a 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle, and 3-butylcyclobutenone (0.097 g, 0.78 mmol, 1.5 equiv) and 2 mL of toluene were added. The pale yellow reaction mixture was heated at 80 °C for 2 h, allowed to cool to rt and concentrated to afford 0.315 g of an orange-brown oil. This material was diluted with 1 mL of MeOH and 1 mL of 5 M aqueous KOH solution, the same flask was equipped with a rubber septum and argon inlet needle, and the reaction mixture was heated at 70 °C for 2 h. The resulting brown suspension was cooled to rt, diluted with 6 mL of 1 M aqueous HCl solution and 10 mL of CH_2Cl_2, and transferred to a 60-mL separatory funnel. The aqueous phase was separated and extracted with two 5-mL portions of CH_2Cl_2, and the combined organic phases were washed with 15 mL of water and 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.289 g of a brown oil. This material was dissolved in ca. 3 mL of CH_2Cl_2 and concentrated onto

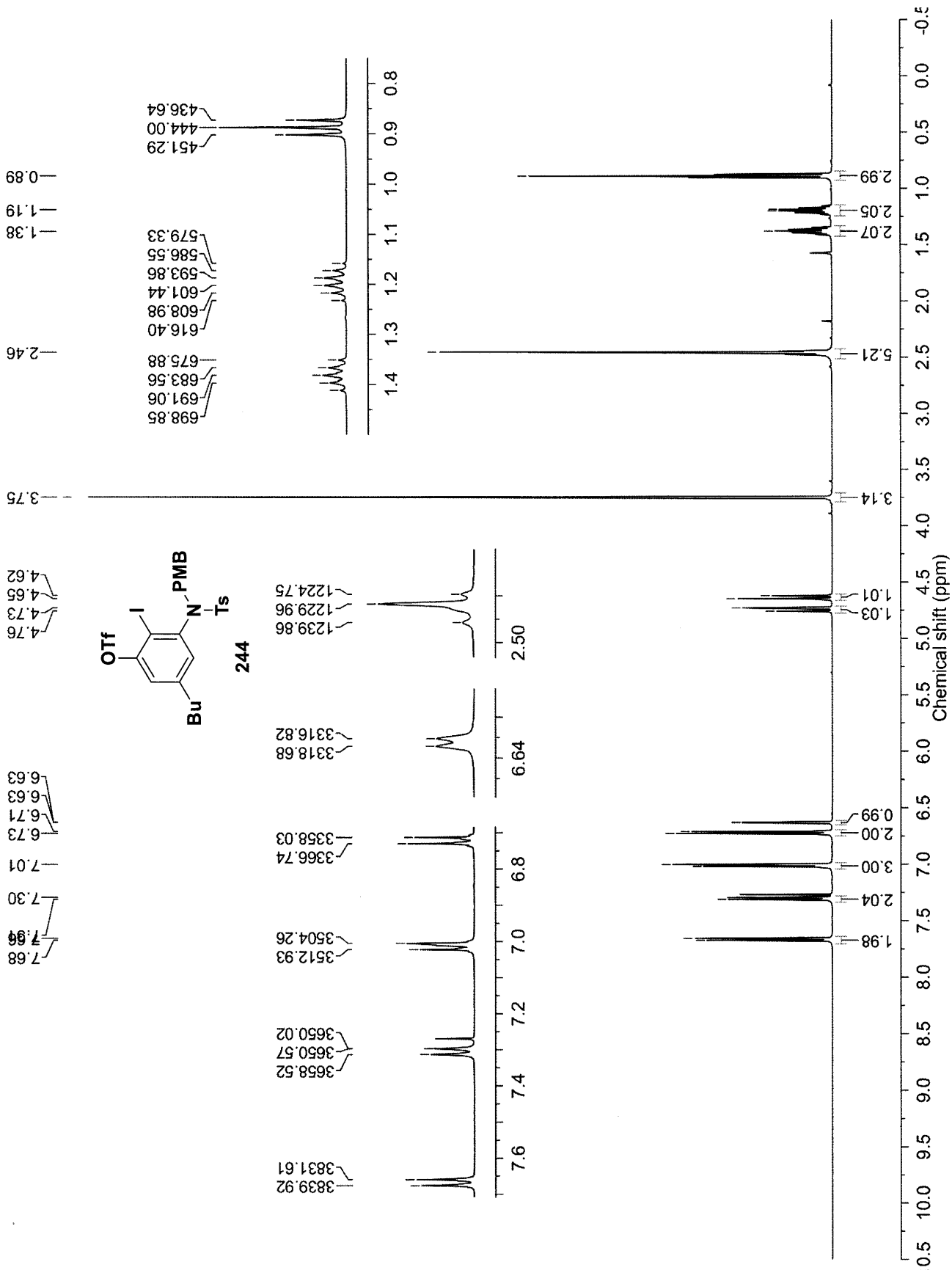
1 g of silica gel. The resulting free-flowing powder was added to the top of a column of 20 g of silica gel and eluted with 50:40:10 hexane-benzene-EtOAc. The mixed fractions were concentrated onto 1 g of silica gel, the resulting free-flowing powder was added to the top of a column of 20 g of silica gel, and eluted again with 50:40:10 hexane-benzene-EtOAc. The pure fractions from the two columns were combined, concentrated, and dried to afforded 0.129 g (49%) of phenol **243** as a viscous pale yellow oil: IR (film) 3419, 2955, 2929, 2859, 1597, 1581, 1423, 1348, 1289, 1159, 1091, 1010, 814, and 719 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.1 Hz, 2H), 7.23–7.24 (m, 1H), 6.76 (d, J = 1.8 Hz, 1H), 6.20 (dd, J = 3.1, 1.9 Hz, 1H), 6.03–6.04 (m, 2H), 5.59 (br s, 1H), 4.80 (d, J = 15.3 Hz, 1H), 4.66 (d, J = 15.4 Hz, 1H), 2.45 (s, 3H), 2.37 (t, J = 7.6 Hz, 2H), 1.37 (app quint, J = 7.5 Hz, 2H), 1.22 (sext, J = 7.4 Hz, 2H), and 0.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3, 149.2, 145.0, 143.8, 142.7, 141.3, 136.7, 129.5, 128.4, 123.3, 115.5, 110.58, 110.55, 91.3, 47.9, 34.9, 33.0, 22.2, 21.8, and 14.1; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{22}H_{24}INO_4S$, 548.0363; found 548.0375.

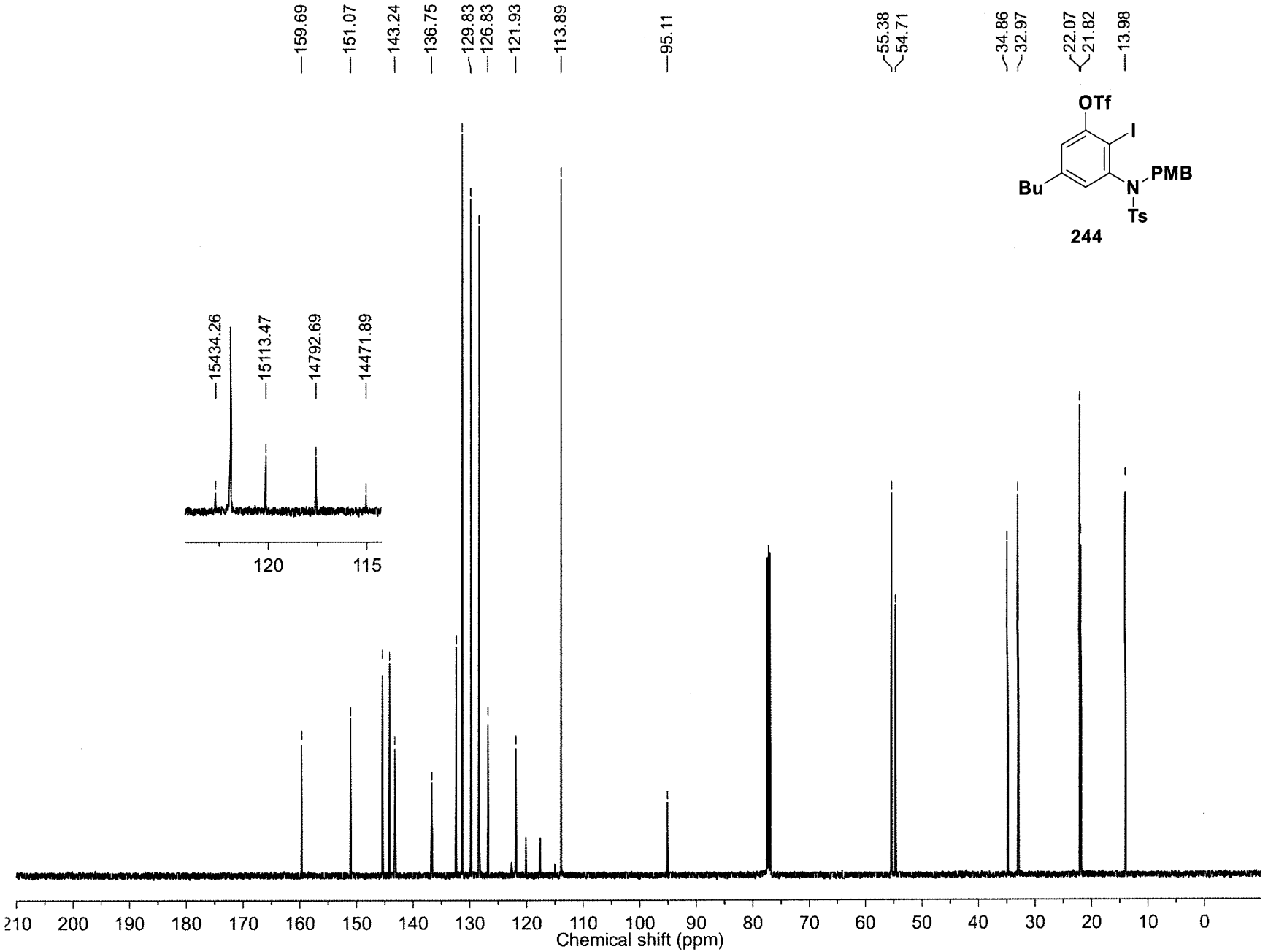

243
Chemical Shifts (ppm)

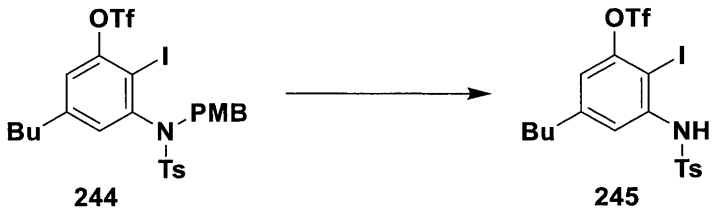

156.3
149.2
143.8
141.3
136.7
129.5
128.4
123.3
115.5
110.6
110.6
91.3
77.5
77.2
77.0
47.9
34.9
33.0
22.2
21.8
14.1
110.58
110.55
OH
I
Bu
N
Ts
O
243
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shifts (ppm)



5-Butyl-2-iodo-3-(*N*-(4-methoxybenzyl)-*N*-(*p*-toluenesulfonyl)amino)phenyl trifluoromethanesulfonate (244). A 50-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with **241** (0.655 g, 1.16 mmol, 1.0 equiv), 4-DMAP (0.283 g, 2.32 mmol, 2.0 equiv), and 12 mL of CH_2Cl_2. The yellow solution was cooled at 0 °C and Tf_2O (0.254 mL, 0.426 g, 1.51 mmol, 1.3 equiv) was added dropwise over 3 min. The resulting suspension was allowed to warm to rt over 4 h and diluted with 15 mL of CH_2Cl_2 and 20 mL of 1 M aq HCl solution. The aqueous phase was separated and extracted with two 10-mL portions of CH_2Cl_2, and the combined organic phases were washed with 30 mL of satd aq $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated to afford 2.26 g of an orange oil. This material was dissolved in ca. 5 mL of CH_2Cl_2 and concentrated onto 2.5 g of silica gel. The resulting free-flowing powder was added to the top of a column of 60 g of silica gel and eluted with 12% EtOAc-hexanes to afford 0.702 g (87%) of triflate **244** as a very viscous pale yellow oil: IR (film) 2958, 2932, 2872, 1612, 1514, 1426, 1412, 1353, 1248, 1216, 1163, 1139, 1091, and 1036 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (app d, J = 8.2 Hz, 2H), 7.31 (d, J = 7.9 Hz, 2H), 7.014 (app d, J = 8.7 Hz, 2H), 7.010 (d, J = 1.7 Hz, 1H), 6.72 (app d, J = 8.7 Hz, 2H), 6.63 (d, J = 1.8 Hz, 1H), 4.75 (d, J = 14.0 Hz, 1H), 4.64 (d, J = 14.0 Hz, 1H), 3.75 (s, 3H), 2.463 (t, J = 7.6 Hz, 2H), 2.459 (s, 3H), 1.38 (app quint, J = 7.6 Hz, 2H), 1.19 (sext, J = 7.4 Hz, 2H), and 0.89 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7, 151.1, 145.5, 144.2, 143.2, 136.8, 132.4, 131.3, 129.8, 128.3, 126.8, 121.9, 118.9 (q, J = 320.7 Hz), 113.9, 95.1, 55.4, 54.7, 34.9, 33.0, 22.1, 21.8, and 14.0; HRMS (DART) *m/z* $[M–H]^-$ calcd for $C_{26}H_{27}F_3NO_6S_2$, 696.0204; found 696.0215.

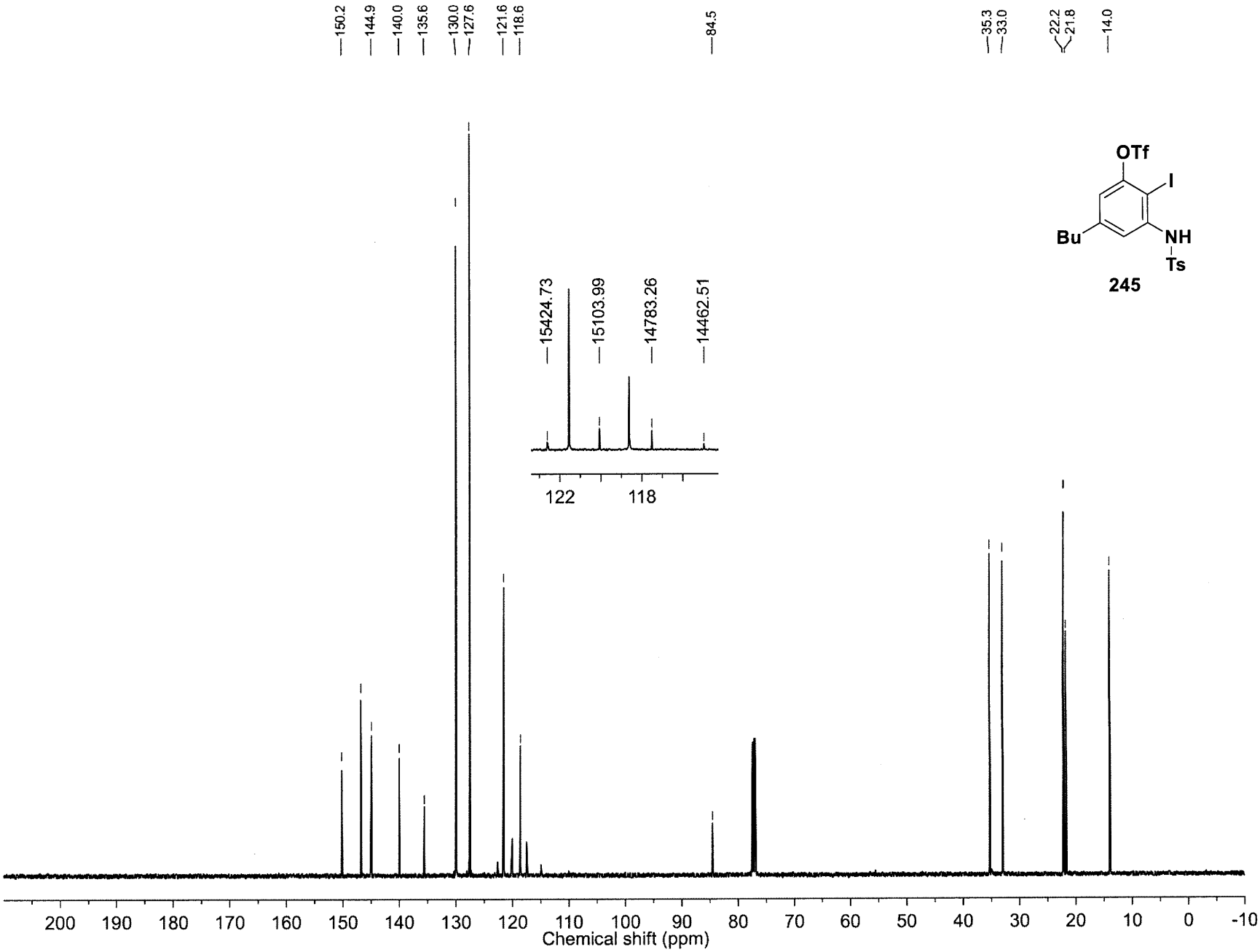

OTf
I
N
PMB
Ts
Bu
244
Chemical shift (ppm)

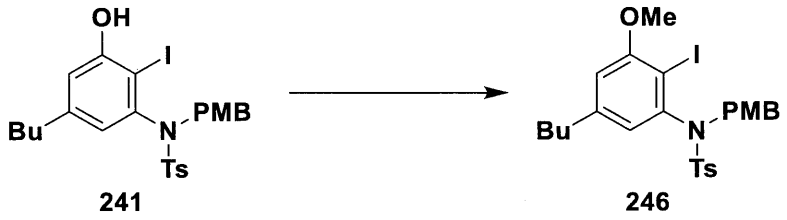

159.69
151.07
143.24
136.75
129.83
126.83
121.93
113.89
95.11
55.38
54.71
34.86
32.97
22.07
21.82
13.98
OTf
I
Bu
PMB
N
Ts
244
15434.26
15113.47
14792.69
14471.89
120
115
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical shift (ppm)



5-Butyl-2-iodo-3-(*N*-(*p*-toluenesulfonyl)amino)phenyl trifluoromethanesulfonate (245). A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with aniline **244** (0.096 g, 0.14 mmol, 1.0 equiv) and 1.4 mL of CH_2Cl_2. The pale yellow reaction mixture was cooled at 0 °C and TFA (0.42 mL, 5.5 mmol, 40 equiv) was added dropwise via syringe over 4 min. The resulting purple solution was allowed to warm to rt and stirred for a total of 3 h. The reaction mixture was then diluted with 10 mL of CH_2Cl_2 and 10 mL of satd aq $NaHCO_3$ solution was carefully added. The aqueous phase was separated and extracted with two 5-mL portions of CH_2Cl_2. The combined organic phases were washed with 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.139 g of a pale yellow oil. This material was dissolved in ca. 3 mL of CH_2Cl_2 and concentrated onto 1 g of silica gel. The resulting free-flowing powder was added to the top of a column of 7 g of silica gel and eluted with 10% EtOAc–hexane to afford 0.076 g of a pale yellow solid, Recrystallization from 1 mL of hexanes at -20 °C afforded 0.070 g (88%) of aniline **245** as a colorless crystalline solid: mp 93–95 °C; IR (film) 3312, 3268, 2959, 2932, 2864, 1599, 1563, 1468, 1426, 1403, 1336, 1221, 1169, 1139, 1091, 1028, 996, and 814 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 1.8 Hz, 1H), 7.23 (d, J = 8.5 Hz, 2H), 6.95 (s, 1H), 6.89 (d, J = 1.7 Hz, 1H), 2.63 (t, J = 7.6 Hz, 2H), 2.39 (s, 3H), 1.58 (app quint, J = 7.7 Hz, 2H), 1.32 (sext, J = 7.6 Hz, 2H), and 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.2, 146.8, 144.9, 140.0, 135.6, 130.0, 127.6, 121.6, 118.8 (q, J = 320.7 Hz), 118.6, 84.5, 35.3, 33.0, 22.2, 21.8, and 14.0; HRMS (DART) *m/z* $[M+NH_4]^+$ calcd for $C_{18}H_{19}F_3INO_5S_2$, 595.0040; found 595.0039.

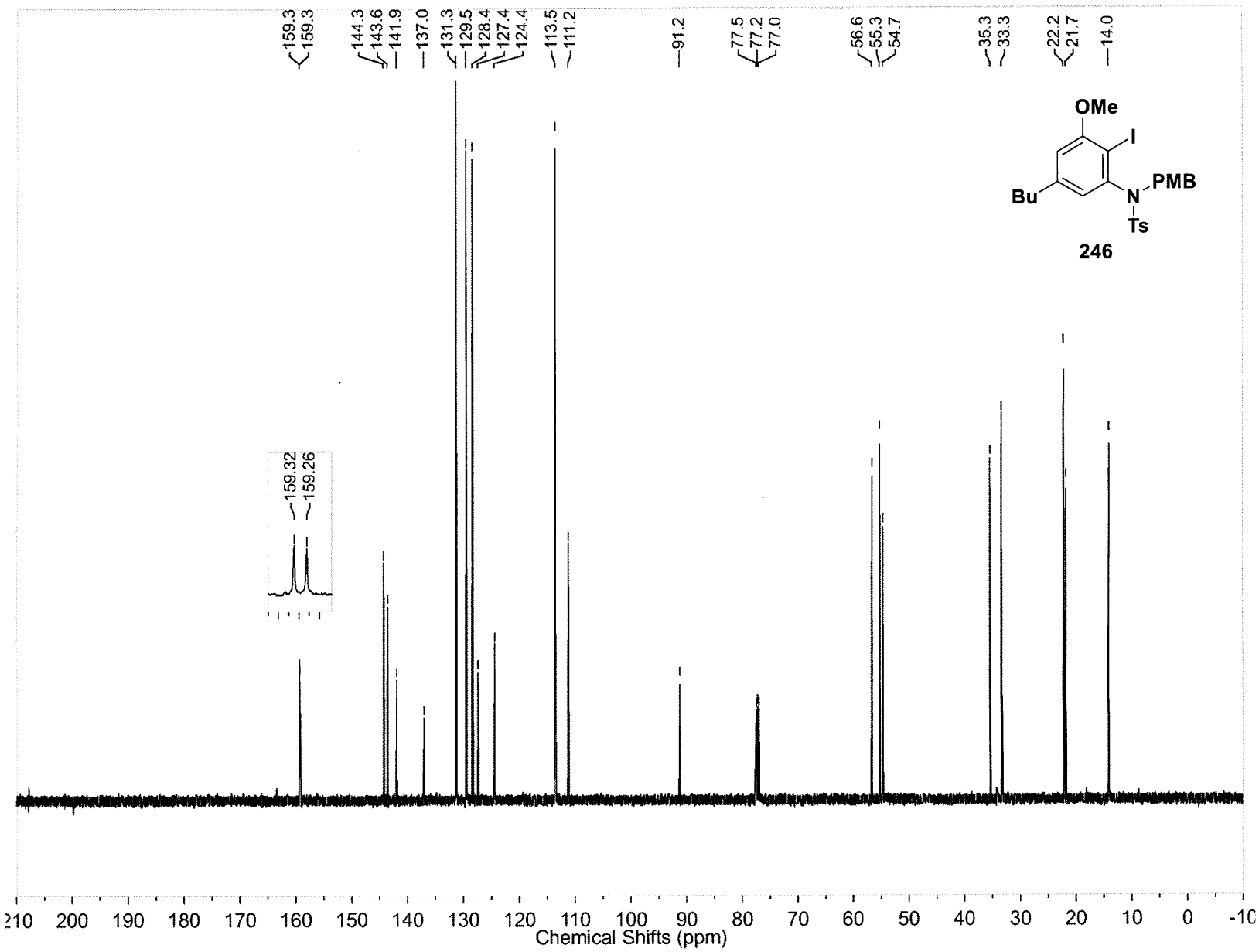
7.63
7.62
7.51
7.51
7.23
6.95
6.89
6.89
2.63
2.39
1.58
1.33
1.31
0.94
OTf
I
Bu
NH
Ts
245
3759.12
3757.32
3449.73
3447.99
1323.20
1315.60
1307.84
806.46
798.97
791.27
784.78
783.64
775.96
678.12
670.71
663.27
655.66
648.26
640.96
476.19
468.84
461.48
7.50
6.90
2.6
1.6
1.5
1.4
1.3
1.0
0.9
2.03
1.02
2.07
1.01
1.05
2.01
3.00
2.03
1.94
2.78
Chemical shift (ppm)

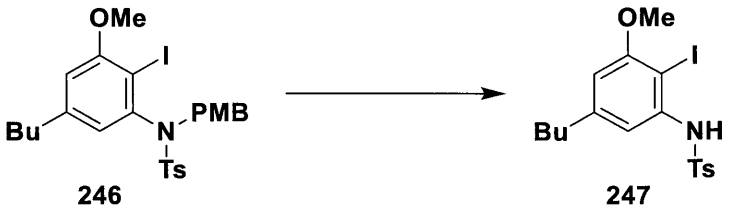

150.2
144.9
140.0
135.6
130.0
127.6
121.6
118.6
84.5
35.3
33.0
22.2
21.8
14.0
OTf
I
Bu
NH
Ts
245
15424.73
15103.99
14783.26
14462.51
122
118
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical shift (ppm)



***N*-(4-Methoxybenzyl)-*N*-(*p*-toluenesulfonyl)-(5-butyl-2-iodo-3-methoxyphenyl)amine (246).** A 25-mL pear flask equipped with a rubber septum and argon inlet needle was charged with phenol **241** (0.200 g, 0.354 mmol, 1.0 equiv), K_2CO_3 (0.098 g, 0.71 mmol, 2.0 equiv), 3.5 mL of acetone, and iodomethane (0.11 mL, 1.77 mmol, 5.0 equiv). The pale yellow reaction mixture was stirred at rt for 19 h, diluted with 10 mL of Et_2O and 10 mL of satd aq NH_4Cl solution, and transferred to a 60-mL separatory funnel. The aqueous phase was separated and extracted with two 5-mL portions of Et_2O, and the combined organic phases were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.232 g of a yellow oil. This material was dissolved in ca. 3 mL of CH_2Cl_2 and concentrated onto 1 g of silica gel. The resulting free-flowing powder was added to the top of a column of 10 g of silica gel and eluted with 15% EtOAc–hexane to afford 0.180 g (88%) of aniline **246** as a viscous pale yellow oil: IR (film) 2956, 2932, 2860, 1612, 1568, 1514, 1415, 1351, 1248, 1161, 1117, 1091, 1034, 816, and 724 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.06 (app d, J = 8.7 Hz, 2H), 6.70 (app d, J = 8.7 Hz, 2H), 6.51 (d, J = 1.7 Hz, 1H), 6.23 (d, J = 1.8 Hz, 1H), 4.69 (d, J = 14.0 Hz, 1H), 4.65 (d, J = 14.1 Hz, 1H), 3.82 (s, 3H), 3.73 (s, 3H), 2.44 (s, 3H), 2.42 (t, J = 7.7 Hz, 2H), 1.38 (app quint, J = 7.6 Hz, 2H), 1.20 (sext, J = 7.6 Hz, 2H), and 0.88 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.32, 159.26, 144.3, 143.6, 141.9, 137.0, 131.3, 129.5, 128.4, 127.4, 124.4, 113.5, 111.2, 91.2, 56.6, 55.3, 54.7, 35.3, 33.3, 22.2, 21.7, and 14.0; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{26}H_{30}INO_4S$, 602.0832; found 602.0828.

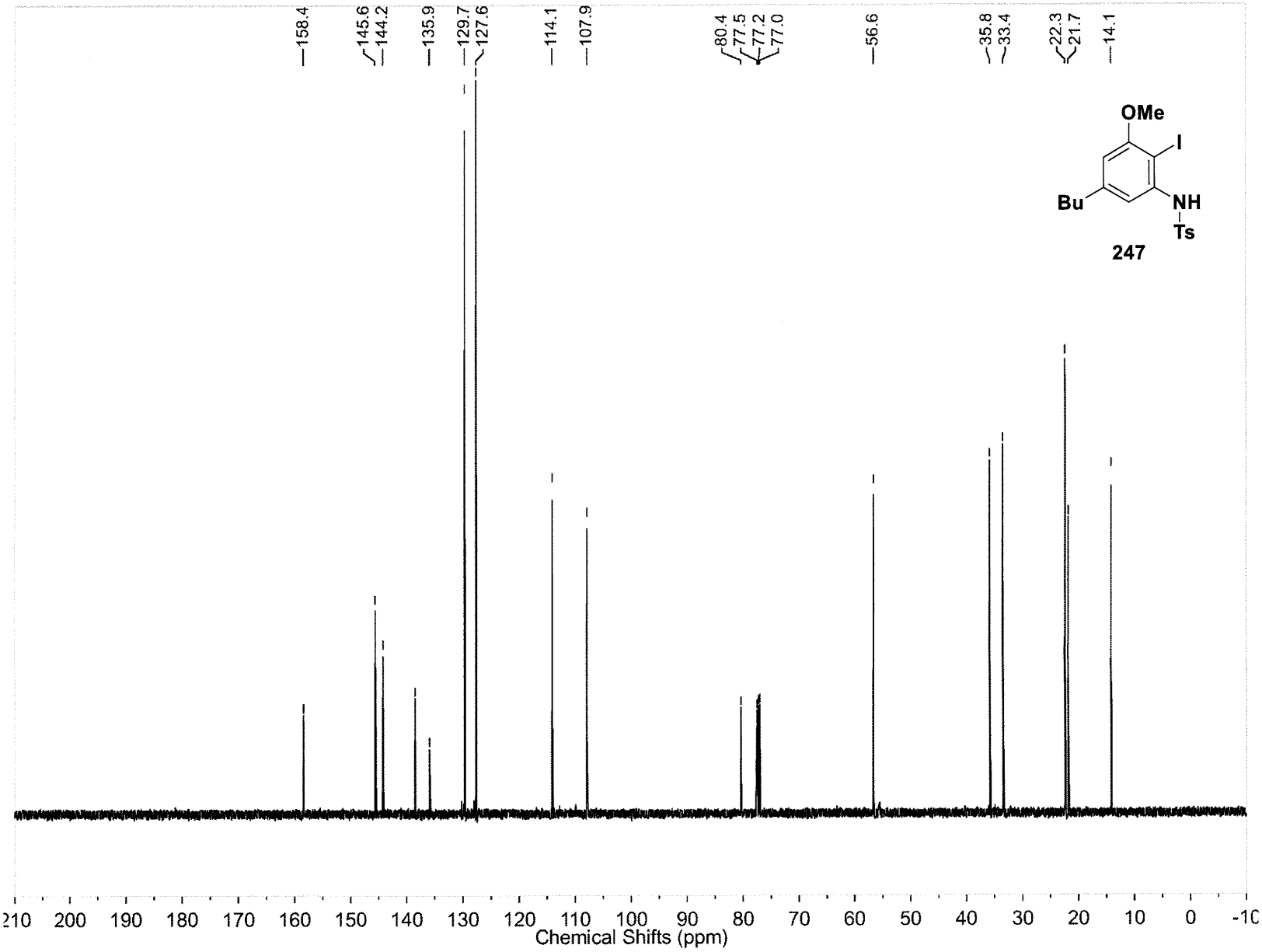
OMe
I
Bu
N
PMB
Ts
246
Chemical Shifts (ppm)

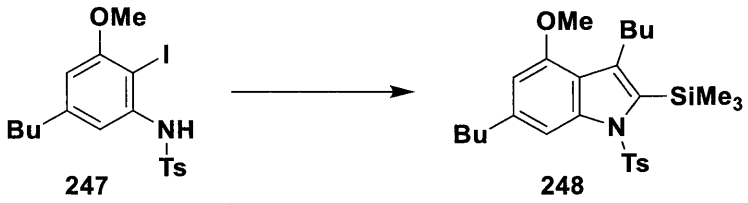

159.3
159.3
144.3
143.6
141.9
137.0
131.3
129.5
128.4
127.4
124.4
113.5
111.2
91.2
77.5
77.2
77.0
56.6
55.3
54.7
35.3
33.3
22.2
21.7
14.0
159.32
159.26
OMe
I
Bu
PMB
N
Ts
246
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shifts (ppm)



***N*-(*p*-Toluenesulfonyl)-(5-butyl-2-iodo-3-methoxyphenyl)amine (247).** A 25-mL pear flask equipped with a rubber septum and argon inlet needle was charged with aniline **246** (0.180 g, 0.310 mmol, 1.0 equiv) and 3 mL of CH_2Cl_2. The pale yellow reaction mixture was cooled at 0 °C and TFA (0.36 mL, 4.6 mmol, 15 equiv) was added dropwise via syringe over 2 min. The resulting purple solution was allowed to warm to rt and stirred for a total of 3 h. The reaction mixture was then diluted with 10 mL of CH_2Cl_2 and 15 mL of satd aq $NaHCO_3$ solution was carefully added. The mixture was then transferred to a 60-mL separatory funnel and the aqueous phase was separated and extracted with three 5-mL portions of CH_2Cl_2. The combined organic phases were washed with 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.216 g of an orange oil. This material was dissolved in ca. 3 mL of CH_2Cl_2 and concentrated onto 1 g of silica gel. The resulting free-flowing powder was added to the top of a column of 20 g of silica gel and eluted with 10% EtOAc–hexane to afford 0.101 g (71%) of aniline **247** as a colorless oil: IR (film) 3303, 2955, 2930, 2859, 1577, 1452, 1420, 1388, 1328, 1242, 1165, 1082, 813, and 666 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 8.3 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 1.7 Hz, 1H), 7.03 (s, 1H), 6.37 (d, J = 1.7 Hz, 1H), 3.80 (s, 3H), 2.57 (t, J = 7.7 Hz, 2H), 2.36 (s, 3H), 1.56 (app quint, J = 7.7 Hz, 2H), 1.30 (sext, J = 7.6 Hz, 2H), and 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4, 145.6, 144.2, 138.5, 135.9, 129.7, 127.6, 114.1, 107.9, 80.4, 56.6, 35.8, 33.4, 22.3, 21.7, and 14.1; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{22}INO_3S$, 460.0438; found 460.0427.

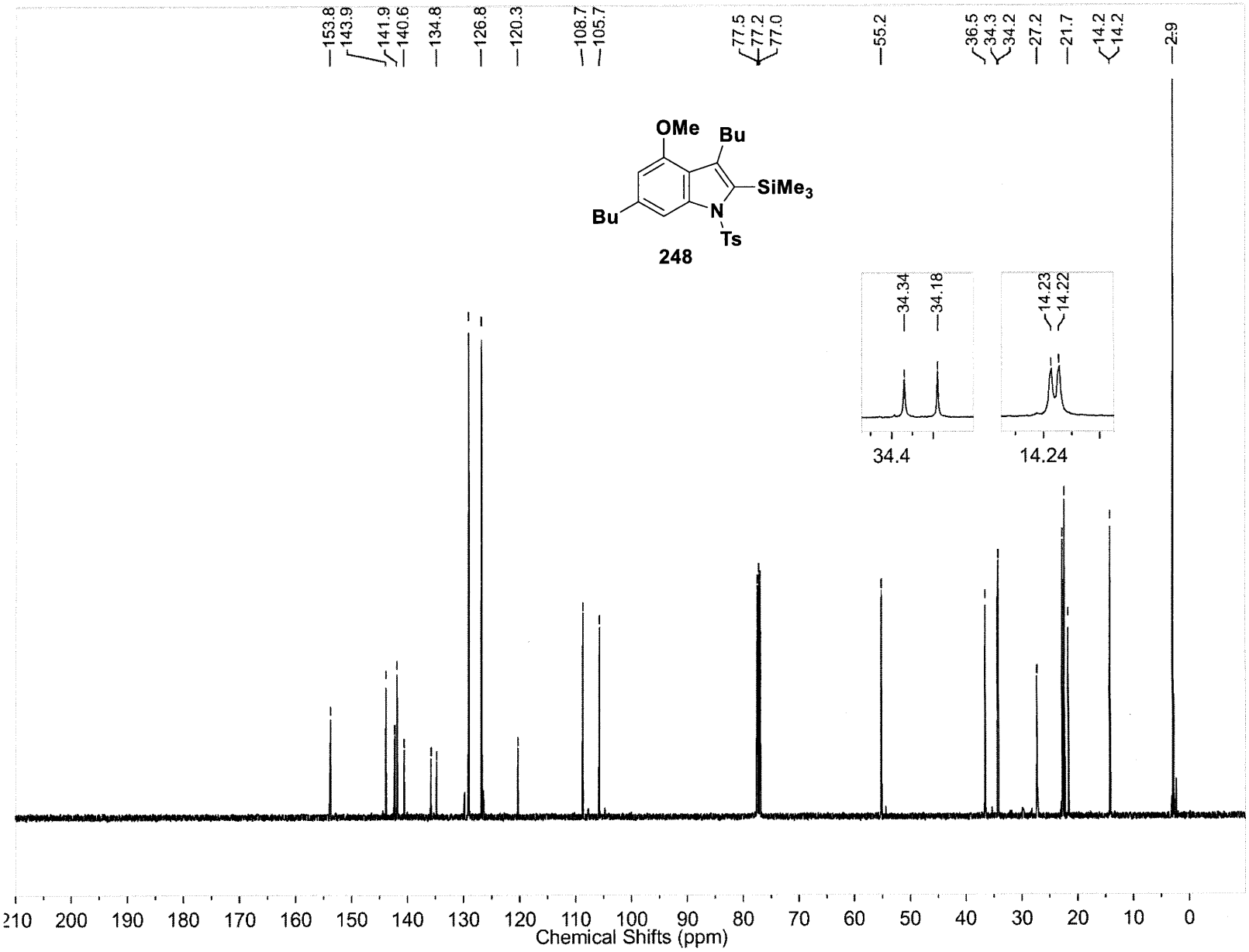
7.68
7.66
7.20
7.18
7.16
7.16
7.03
6.37
6.37
3.80
2.59
2.57
2.56
2.36
1.58
1.56
1.55
1.29
0.94
0.93
0.91
OMe
I
Bu
NH
Ts
247
1294.4
1286.8
1279.1
790.6
783.0
775.3
653.5
645.9
470.8
463.4
456.1
2.6
1.6
1.3
3841.4
3833.1
3603.1
3595.1
3582.8
3581.1
3189.2
3187.5
7.68
7.20
6.40
2.03
2.05
1.02
1.04
1.00
3.40
2.00
2.99
1.90
2.05
2.81
0.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Chemical Shifts (ppm)

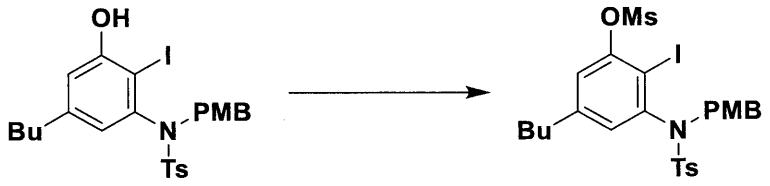

158.4
145.6
144.2
135.9
129.7
127.6
114.1
107.9
80.4
77.5
77.2
77.0
56.6
35.8
33.4
22.3
21.7
14.1
OMe
I
Bu
NH
Ts
247
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shifts (ppm)



3,6-Dibutyl-4-methoxy-1-(*p*-toluenesulfonyl)-2-(trimethylsilyl)indole (248). A 25-mL pear flask equipped with a rubber septum and argon inlet needle was charged with aniline **247** (0.101 g, 0.220 mmol, 1.0 equiv), $PdCl_2(PPh_3)_2$ (0.008 g, 0.01 mmol, 0.05 equiv), K_2CO_3 (0.152 g, 1.10 mmol, 5.0 equiv), LiCl (0.009 g, 0.2 mmol, 1.0 equiv), 1-trimethylsilyl-1-hexyne (0.088 mL, 0.44 mmol, 2.0 equiv), and 4.4 mL of DMF. The yellow suspension was heated at 100 °C for 40 h, cooled to rt, and additional 1-trimethylsilyl-1-hexyne (0.132 mL, 0.66 mmol, 3.0 equiv) was added. The reaction mixture was heated at 100 °C for an additional 24 h and allowed to cool to rt. The resulting brown suspension was diluted with 40 mL of Et_2O and 40 mL of satd aq NH_4Cl solution and transferred to a 250-mL separatory funnel. The aqueous phase was separated and extracted with two 20-mL portions of Et_2O, and the combined organic phases were washed with 40 mL of water and 40 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.139 g of a brown oil. This material was dissolved in ca. 3 mL of CH_2Cl_2 and concentrated onto 1 g of silica gel. The resulting free-flowing powder was added to the top of a column of 20 g of silica gel and eluted with 3.5% EtOAc–hexane to afford 0.055 g (51%) of a ca. 95:5 mixture of indole **248** and its 2,3-regioisomer as a pale yellow oil: IR (film) 2956, 2930, 2859, 1587, 1465, 1411, 1362, 1248, 1176, 1117, 1088, 843, and 593 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) for major regioisomer **248**: δ 7.41 (app d, J = 8.4 Hz, 2H), 7.41 (s, 1H), 7.04 (d, J = 8.4 Hz, 2H), 6.38 (s, 1H), 3.80 (s, 3H), 2.85–2.88 (m, 2H), 2.63 (t, J = 7.6 Hz, 2H), 2.27 (s, 3H), 1.57 (app quint, J = 7.6 Hz, 2H), 1.49 (app quint, J = 7.6 Hz, 2H), 1.24–1.35 (m, 4H), 0.93 (t, J = 7.4 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H), and 0.52 (s, 9H); ^1H NMR (500 MHz, $CDCl_3$) for minor regioisomer: δ 7.64 (s, 1H), 7.60 (d, J = 8.5 Hz, 2H), 7.18 (d, J = 7.9 Hz, 2H), 6.48 (s, 1H), 3.85 (s, 3H), 2.70 (t, J = 7.6 Hz, 2H), 2.35 (s, 3H), and 0.31 (s, 9H), all other aliphatic signals overlap with peaks from **248**; ^{13}C NMR (125 MHz, $CDCl_3$) for major regioisomer **248**: δ 153.8, 143.9, 142.3, 141.9, 140.6, 135.8, 134.8, 129.1, 126.8, 120.3, 108.7, 105.7, 55.2, 36.5, 34.3, 34.2, 27.2, 22.8, 22.4, 21.7, 14.23, 14.22, and 2.9; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{27}H_{39}NO_3SSi$, 508.2312; found 508.2345.

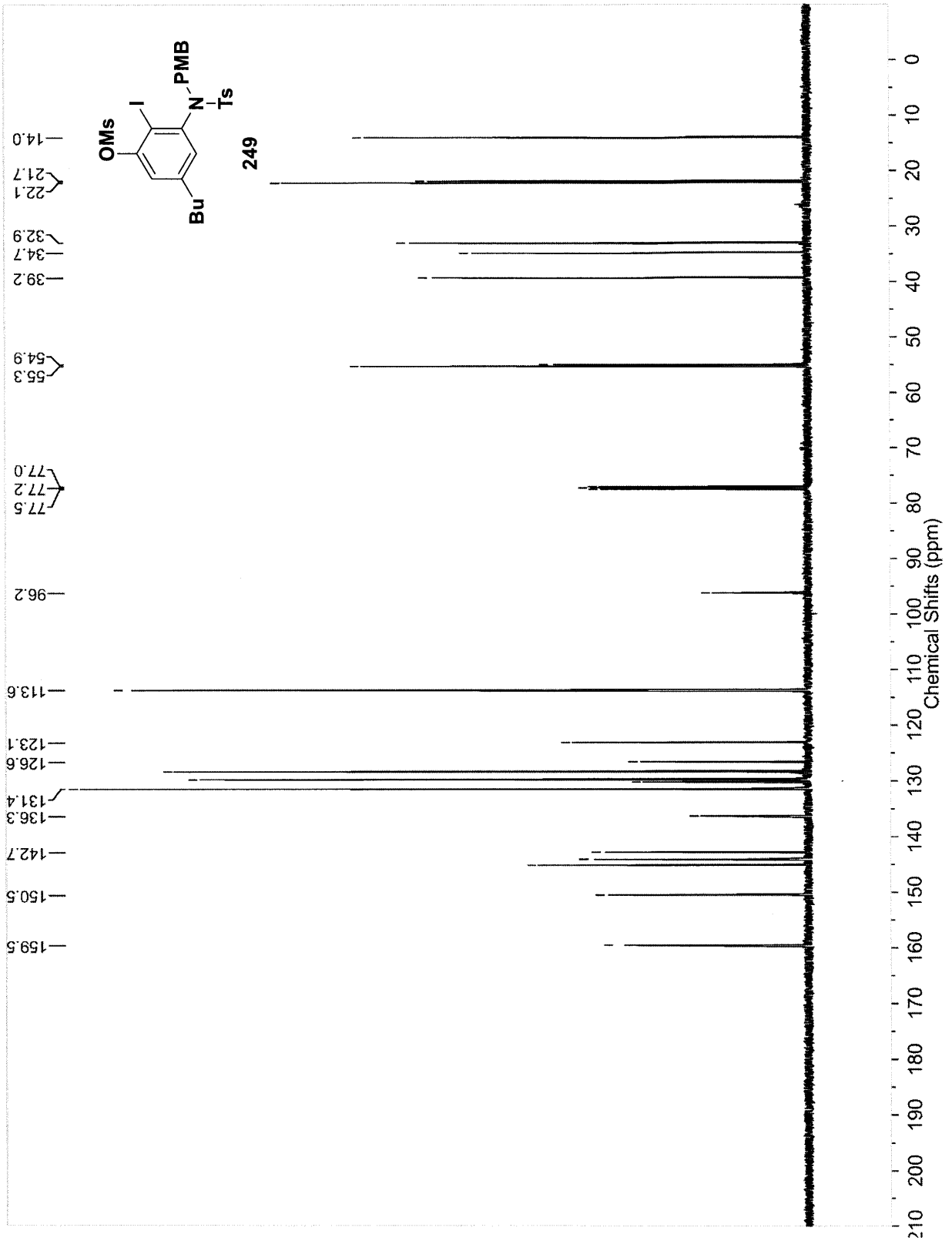
7.42
7.42
7.41
7.40
7.27
7.05
7.05
7.03
6.38
3.80
2.88
2.86
2.85
2.64
2.62
2.27
1.57
1.50
1.47
1.27
0.93
0.92
0.52
OMe
Bu
SiMe3
Bu
N
Ts
248
1439.7
1432.1
1424.3
1326.0
1318.4
1310.8
789.0
784.4
781.4
752.6
744.5
737.3
651.4
643.8
635.9
464.5
459.3
3711.9
3709.3
3708.9
3703.5
3524.8
3524.2
3516.2
2.96
2.00
1.00
3.03
2.01
2.03
3.00
2.47
2.13
4.77
6.55
8.68
Chemical Shifts (ppm)

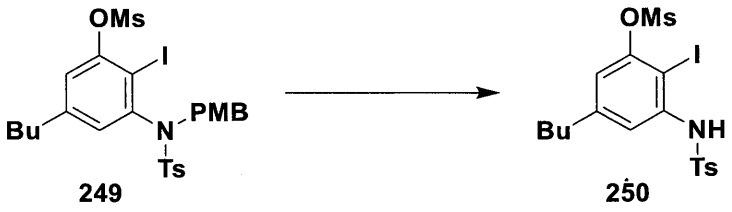

153.8
143.9
141.9
140.6
134.8
126.8
120.3
108.7
105.7
77.5
77.2
77.0
55.2
36.5
34.3
34.2
27.2
21.7
14.2
14.2
2.9
OMe
Bu
SiMe3
Bu
N
Ts
248
34.34
34.18
14.23
14.22
34.4
14.24
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shifts (ppm)



5-Butyl-2-iodo-3-(*N*-(4-methoxybenzyl)-*N*-(*p*-toluenesulfonyl)amino)phenyl methanesulfonate (249). A 50-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with phenol **241** (0.794 g, 1.40 mmol, 1.0 equiv), Et_3N (0.29 mL, 2.1 mmol, 1.5 equiv), and 14 mL of CH_2Cl_2. The yellow solution was cooled at 0 °C and MsCl (0.114 mL, 1.47 mmol, 1.05 equiv) was added dropwise via syringe over 1 min. The reaction mixture was stirred at 0 °C for 2 h, diluted with 15 mL of water, and transferred to a 60-mL separatory funnel. The aqueous phase was separated and extracted with two 7.5-mL portions of CH_2Cl_2, and the combined organic phases were washed with 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 1.73 g of an orange oil. This material was dissolved in ca. 10 mL of CH_2Cl_2 and concentrated onto 3 g of silica gel. The resulting free-flowing powder was added to the top of a column of 60 g of silica gel and eluted with 30% EtOAc–hexane to afford 0.772 g (85%) of aniline **249** as a yellow semisolid: IR (film) 2956, 2933, 2871, 1612, 1597, 1514, 1413, 1354, 1249, 1181, 1161, 1091, 1034, 962, 815, 800, 789, and 714 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (app d, J = 8.3 Hz, 2H), 7.30 (d, J = 7.9 Hz, 2H), 7.16 (d, J = 1.9 Hz, 1H), 7.00 (app d, J = 8.7 Hz, 2H), 6.69 (app d, J = 8.7 Hz, 2H), 6.50 (d, J = 1.9 Hz, 1H), 4.73 (d, J = 13.7 Hz, 1H), 4.54 (d, J = 13.8 Hz, 1H), 3.72 (s, 3H), 3.14 (s, 3H), 2.45 (s, 3H), 2.44 (t, J = 7.6 Hz, 2H), 1.38 (app quint, J = 7.6 Hz, 2H), 1.20 (sext, J = 7.4 Hz, 2H), and 0.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 150.5, 145.1, 144.0, 142.7, 136.3, 131.4, 130.2, 129.7, 128.3, 126.6, 123.1, 113.6, 96.2, 55.3, 54.9, 39.2, 34.7, 32.9, 22.1, 21.7, and 14.0; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{26}H_{30}INO_6S_2$, 666.0451; found 666.0437.

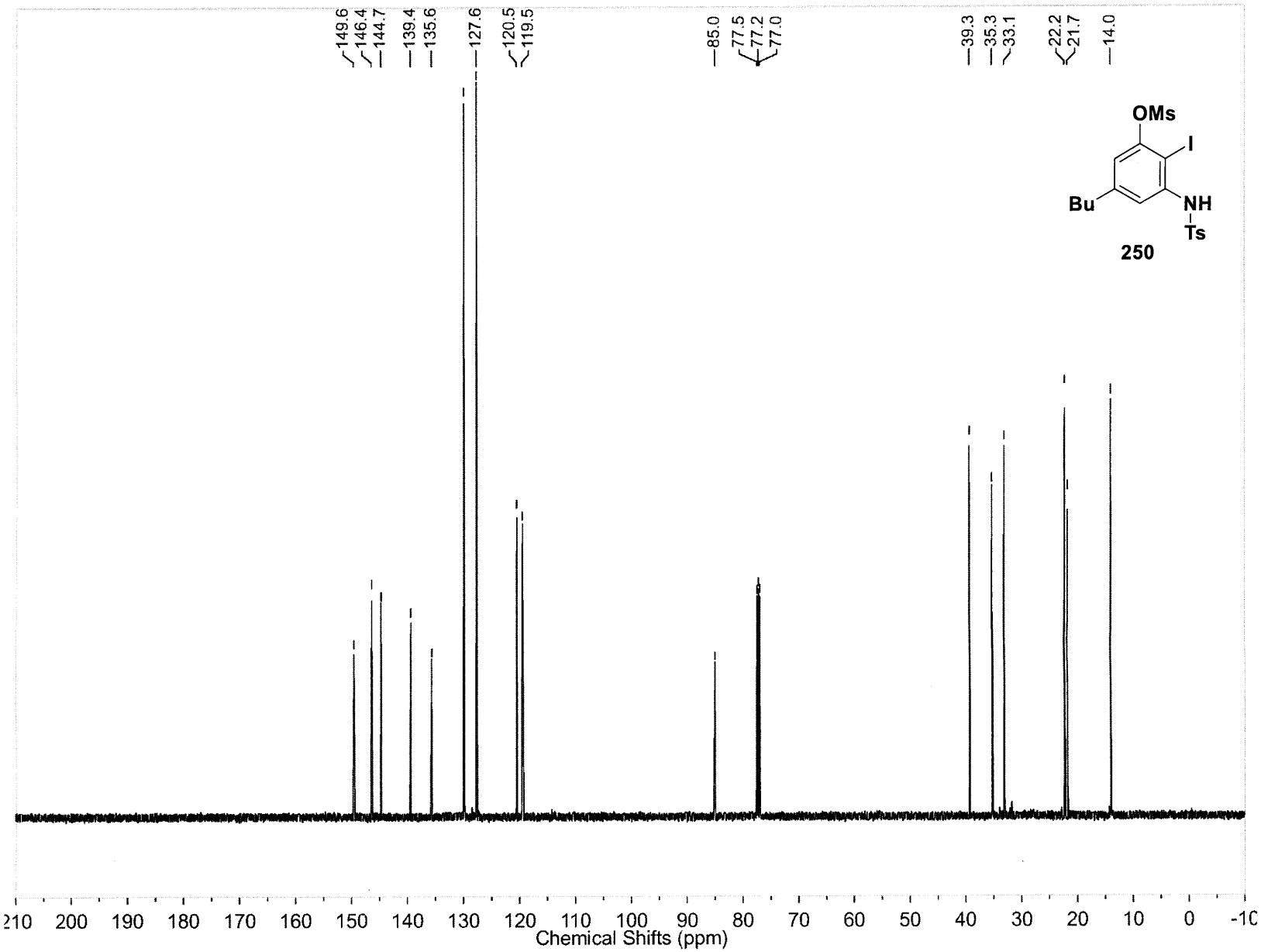
OMs
I
Bu
N
PMB
Ts
249
Chemical Shifts (ppm)

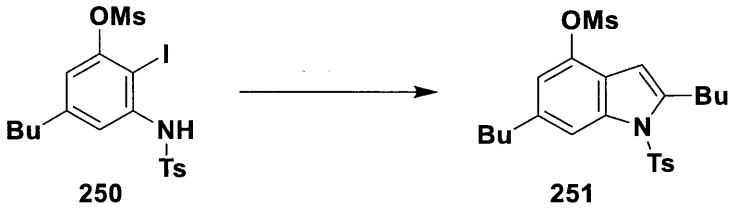

249
OMs
I
PMB
N
Ts
Bu
14.0
21.7
22.1
32.9
34.7
39.2
54.9
55.3
77.0
77.2
77.5
96.2
113.6
123.1
126.6
131.4
136.3
142.7
150.5
159.5
Chemical Shifts (ppm)



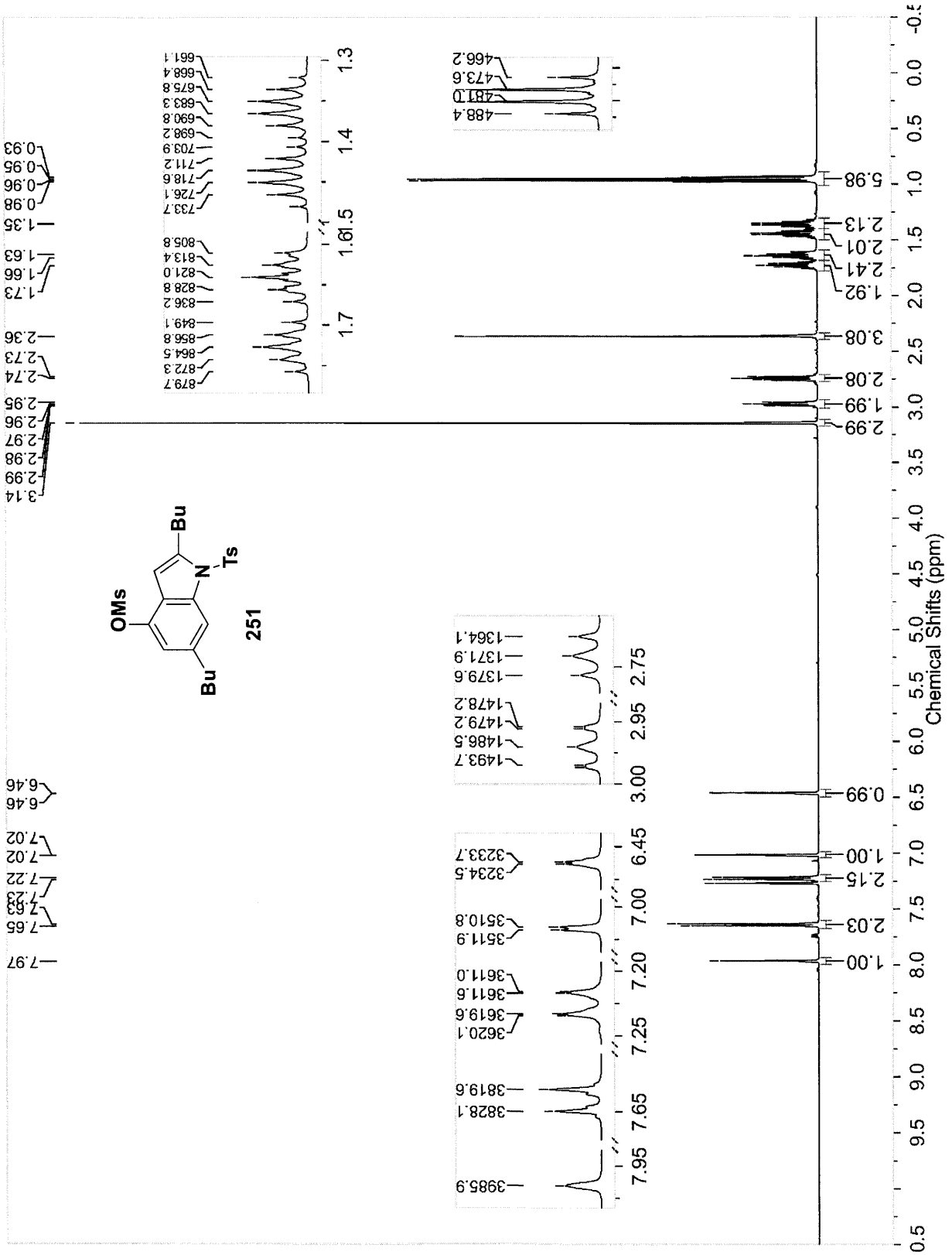
5-Butyl-2-iodo-3-(*N*-(*p*-toluenesulfonyl)amino)phenyl methanesulfonate (250). A 50-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with aniline **249** (0.772 g, 1.20 mmol, 1.0 equiv) and 12 mL of CH_2Cl_2. The yellow solution was cooled at 0 °C and TFA (2.75 mL, 36.0 mmol, 30 equiv) was added dropwise via syringe over 7 min. The resulting purple solution was allowed to warm to rt and stirred for a total of 3 h. The septum was removed and 40 mL of satd aq $NaHCO_3$ solution was carefully added to the reaction mixture. The mixture was then transferred to a 125-mL separatory funnel and the aqueous phase was separated and extracted with three 20-mL portions of CH_2Cl_2. The combined organic phases were washed with 60 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 1.25 g of an orange oil. This material was dissolved in ca. 15 mL of CH_2Cl_2 and concentrated onto 5 g of silica gel. The resulting free-flowing powder was added to the top of a column of 70 g of silica gel and eluted with 25% EtOAc–hexane to afford 0.619 g (99%) of aniline **250** as a pale yellow solid: mp 118–119 °C; IR (film) 3294, 2956, 2931, 2860, 1597, 1566, 1421, 1373, 1331, 1181, 1167, 1091, 1022, 966, 803, and 666 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.64 (app d, J = 8.3 Hz, 2H), 7.42 (d, J = 1.8 Hz, 1H), 7.22 (d, J = 8.6 Hz, 2H), 7.02 (d, J = 1.9 Hz, 1H), 6.96 (s, 1H), 3.19 (s, 3H), 2.60 (t, J = 7.7 Hz, 2H), 2.38 (s, 3H), 1.57 (app quint, J = 7.7 Hz, 2H), 1.30 (sext, J = 7.4 Hz, 2H), and 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.6, 146.4, 144.7, 139.4, 135.6, 129.9, 127.6, 120.5, 119.5, 85.0, 39.3, 35.3, 33.1, 22.2, 21.7, and 14.0; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{18}H_{22}INO_5S_2$, 545.9879; found 545.9876.

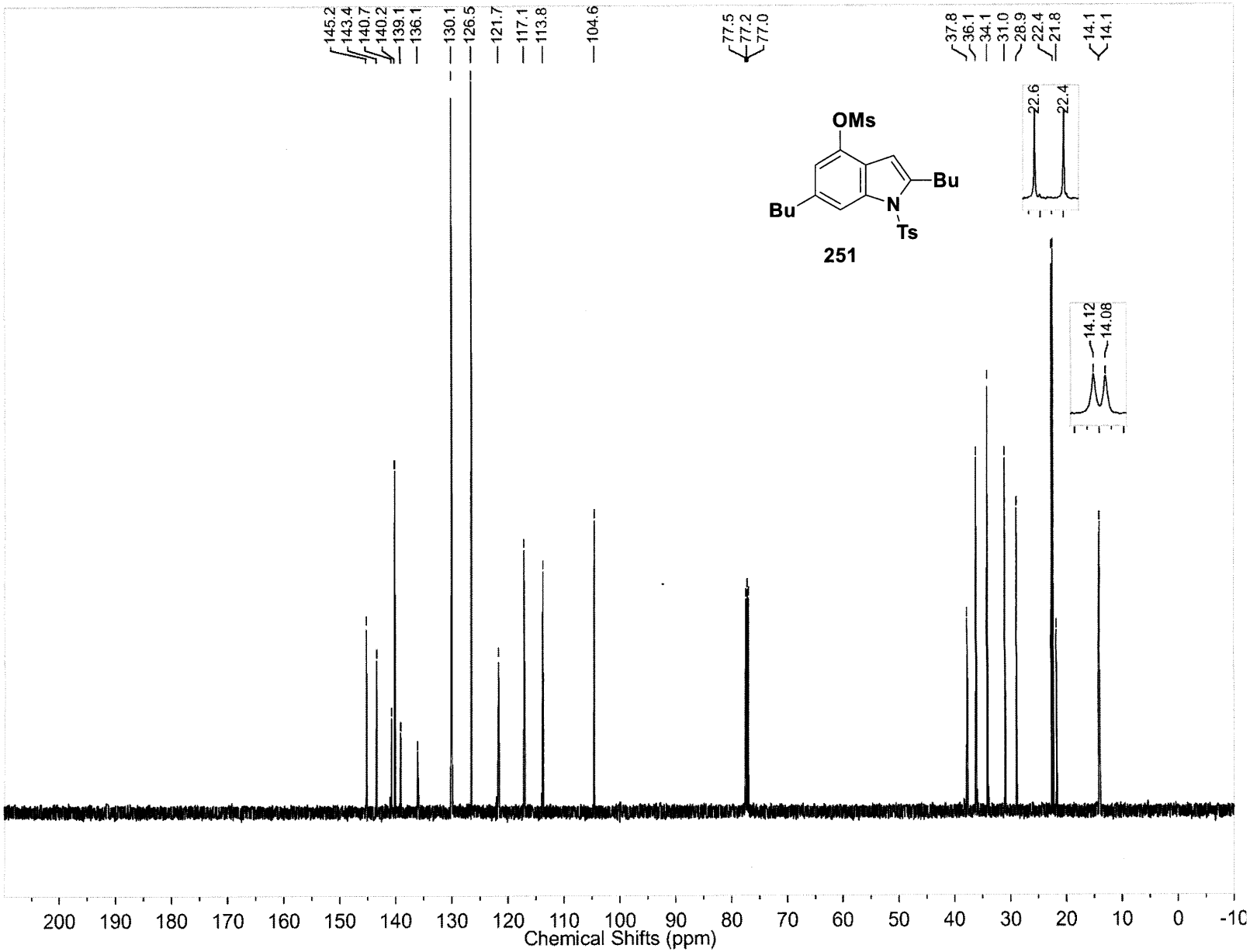
7.64
7.63
7.42
7.21
7.02
7.02
6.96
3.19
2.60
2.58
2.38
1.58
1.57
1.55
1.30
0.94
0.92
0.91
OMs
I
Bu
NH
Ts
250
1307.8
1300.1
1292.4
783.7
776.1
768.4
664.4
649.3
642.0
461.2
453.8
1.6
1.3
0.9
3825.6
3817.3
3713.9
3712.1
3619.5
3618.9
3610.9
3610.3
3513.9
3512.0
7.64
7.42
7.22
2.02
1.02
2.05
1.04
1.04
3.00
1.99
2.96
1.93
2.32
2.85
0.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Chemical Shifts (ppm)

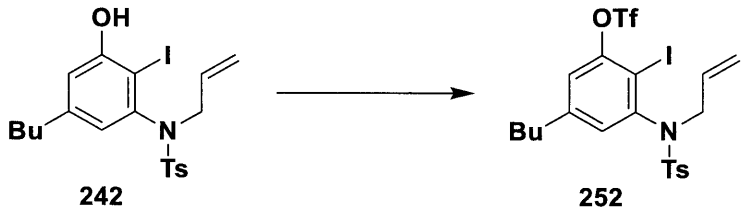

149.6
146.4
144.7
139.4
135.6
127.6
120.5
119.5
85.0
77.5
77.2
77.0
39.3
35.3
33.1
22.2
21.7
14.0
OMs
I
Bu
NH
Ts
250
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shifts (ppm)



2,6-Dibutyl-1-(*p*-toluenesulfonyl)-indol-4-yl methanesulfonate (251). A 15-mL threaded Pyrex tube (20 mm o.d., 16 mm i.d.) equipped with a rubber septum and argon inlet needle was charged with aryl iodide **250** (0.134 g, 0.256 mmol, 1.0 equiv), $PdCl_2(PPh_3)_2$ (0.009 g, 0.013 mmol, 0.05 equiv), CuI (0.004 g, 0.020 mmol, 0.08 equiv), Et_3N (0.36 mL, 2.6 mmol, 10 equiv), 2.6 mL of DMF, and 1-hexyne (0.035 mL, 0.31 mmol, 1.2 equiv). The yellow reaction mixture was purged with argon for ca. 5 min and the reaction tube was sealed with a threaded Teflon cap. The reaction mixture was heated at 80 °C for 17 h. The resulting orange solution was allowed to cool to rt, diluted with 25 mL of satd aq NH_4Cl solution and 25 mL of Et_2O, and transferred to a 125-mL separatory funnel. The aqueous phase was separated and extracted with two 12.5-mL portions of Et_2O, and the combined organic phases were washed with 50 mL of water and 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.183 g of a brown oil. This material was dissolved in ca. 3 mL of CH_2Cl_2 and concentrated onto 1.5 g of silica gel. The resulting free-flowing powder was added to the top of a column of 20 g of silica gel and eluted with 13% EtOAc–hexane to afford 0.116 g (95%) of indole **251** as a pale yellow oil: IR (film) 2957, 2932, 2872, 1621, 1596, 1563, 1423, 1371, 1173, 1155, 1141, 1095, 1071, 968, 812, 666, and 592 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.64 (app d, J = 8.5 Hz, 2H), 7.22 (d, J = 8.6 Hz, 2H), 7.02 (d, J = 1.1 Hz, 1H), 6.46 (d, J = 0.8 Hz, 1H), 3.14 (s, 3H), 2.97 (app t, J = 7.7 Hz, 2H), 2.74 (t, J = 7.8 Hz, 2H), 2.36 (s, 3H), 1.73 (app quint, J = 7.7 Hz, 2H), 1.64 (app quint, J = 7.6 Hz, 2H), 1.44 (sext, J = 7.4 Hz, 2H), 1.36 (sext, J = 7.4 Hz, 2H), 0.96 (t, J = 7.4 Hz, 3H), and 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.2, 143.4, 140.7, 140.2, 139.1, 136.1, 130.1, 126.5, 121.7, 117.1, 113.8, 104.6, 37.8, 36.1, 34.1, 31.0, 28.9, 22.6, 22.4, 21.8, 14.12, and 14.08; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{31}NO_5S_2$, 478.1716; found 478.1738.

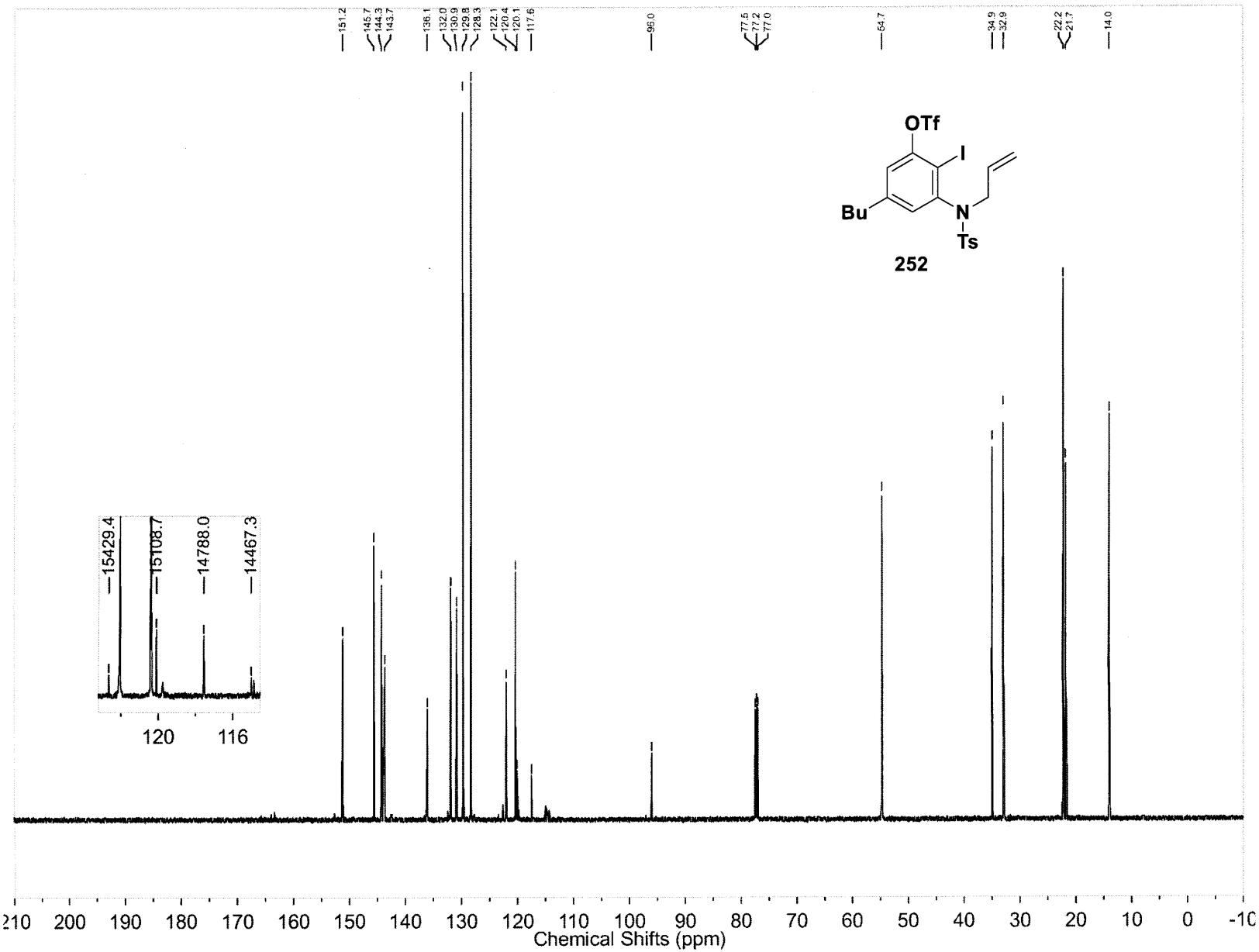

OMs
Bu
N
Ts
Bu
251
Chemical Shifts (ppm)

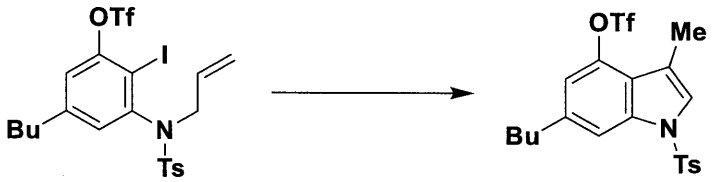

145.2
143.4
140.7
140.2
139.1
136.1
130.1
126.5
121.7
117.1
113.8
104.6
77.5
77.2
77.0
37.8
36.1
34.1
31.0
28.9
22.4
21.8
14.1
14.1
22.6
22.4
14.12
14.08
OMs
Bu
Bu
N
Ts
251
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shifts (ppm)



3-(*N*-Allyl-*N*-(*p*-toluenesulfonyl)amino)-5-butyl-2-iodophenyl trifluoromethanesulfonate (252). A 50-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with phenol **242** (0.392 g, 0.808 mmol, 1.0 equiv), 4-DMAP (0.197 g, 1.62 mmol, 2.0 equiv), and 8 mL of CH_2Cl_2. The yellow solution was cooled at 0 °C and Tf_2O (0.177 mL, 1.05 mmol, 1.3 equiv) was added dropwise via syringe over 2 min. The reaction mixture was allowed to warm to rt and stirred for a total of 3 h. The resulting orange suspension was diluted with 20 mL of CH_2Cl_2 and 20 mL of 1 M aqueous HCl solution and transferred to a 125-mL separatory funnel. The aqueous phase was separated and extracted with two 15-mL portions of CH_2Cl_2, and the combined organic phases were washed with 30 mL satd aq $NaHCO_3$ solution and 30 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.618 g of an orange oil. This material was dissolved in ca. 6 mL of CH_2Cl_2 and concentrated onto 2.5 g of silica gel. The resulting free-flowing powder was added to the top of a column of 50 g of silica gel and eluted with 10% EtOAc–hexane to afford 0.460 g (92%) of aniline **252** as a pale yellow oil: IR (film) 2959, 2931, 2864, 1646, 1598, 1559, 1427, 1358, 1217, 1166, 1139, 1091, 802, 720, and 664 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (app d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.6 Hz, 2H), 7.09 (d, J = 1.9 Hz, 1H), 6.81 (d, J = 1.8 Hz, 1H), 5.87 (ddt, J = 17.0, 10.1, 6.9 Hz, 1H), 5.07 (dq, J = 10.1, 1.0 Hz, 1H), 4.98 (dq, J = 17.0, 1.3 Hz, 1H), 4.15 (d, J = 6.9 Hz, 2H), 2.56 (t, J = 7.7 Hz, 2H), 2.46 (s, 3H), 1.52 (app quint, J = 7.7 Hz, 2H), 1.32 (sext, J = 7.3 Hz, 2H), and 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.2, 145.7, 144.3, 143.7, 136.1, 132.0, 130.9, 129.8, 128.3, 122.1, 120.4, 118.9 (q, J = 320.7 Hz), 96.0, 54.7, 34.9, 32.9, 22.2, 21.7, and 14.0; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{21}H_{23}F_3INO_5S_2$, 639.9907; found 639.9912.

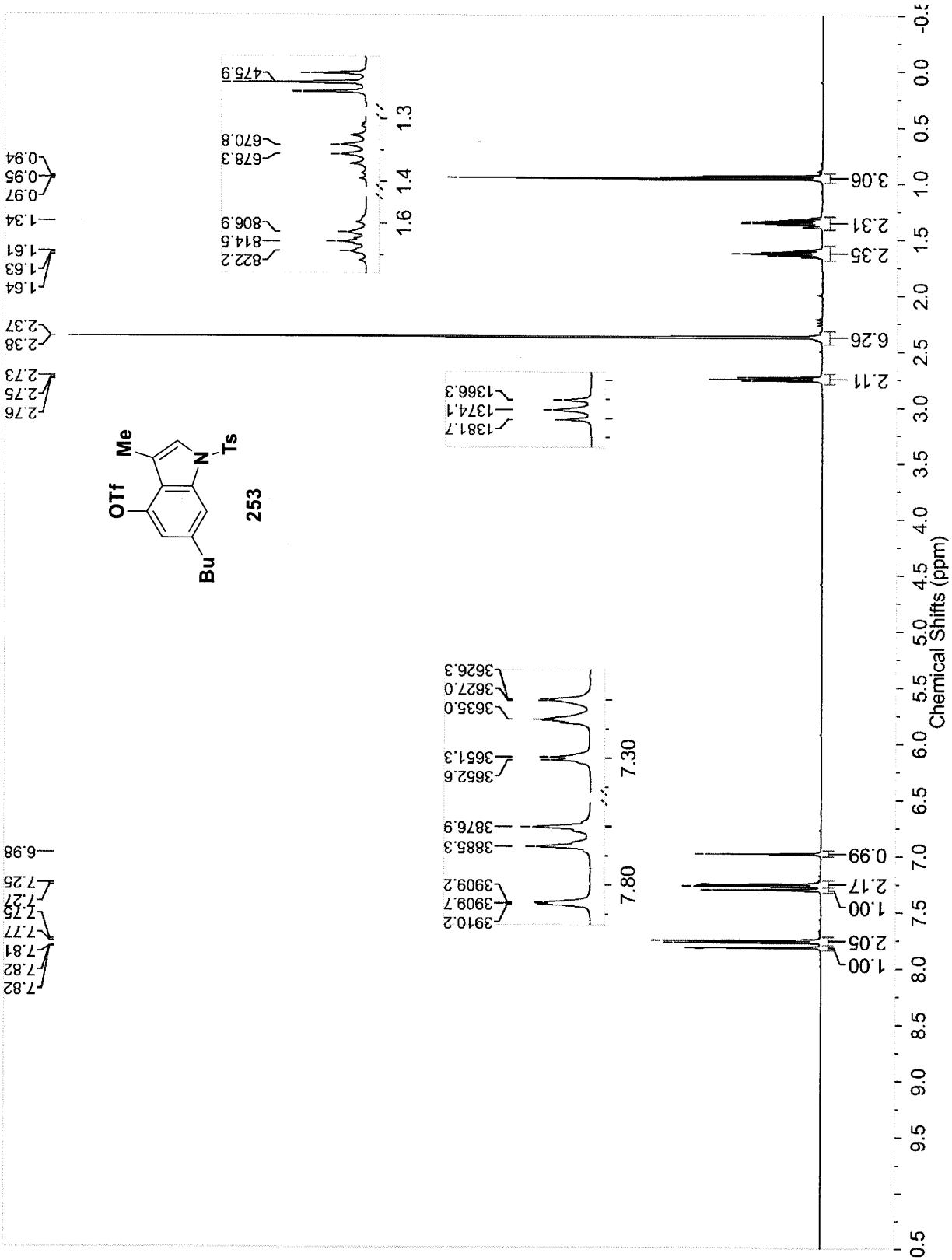
OTf
I
Bu
N
Ts
252
Chemical Shifts (ppm)

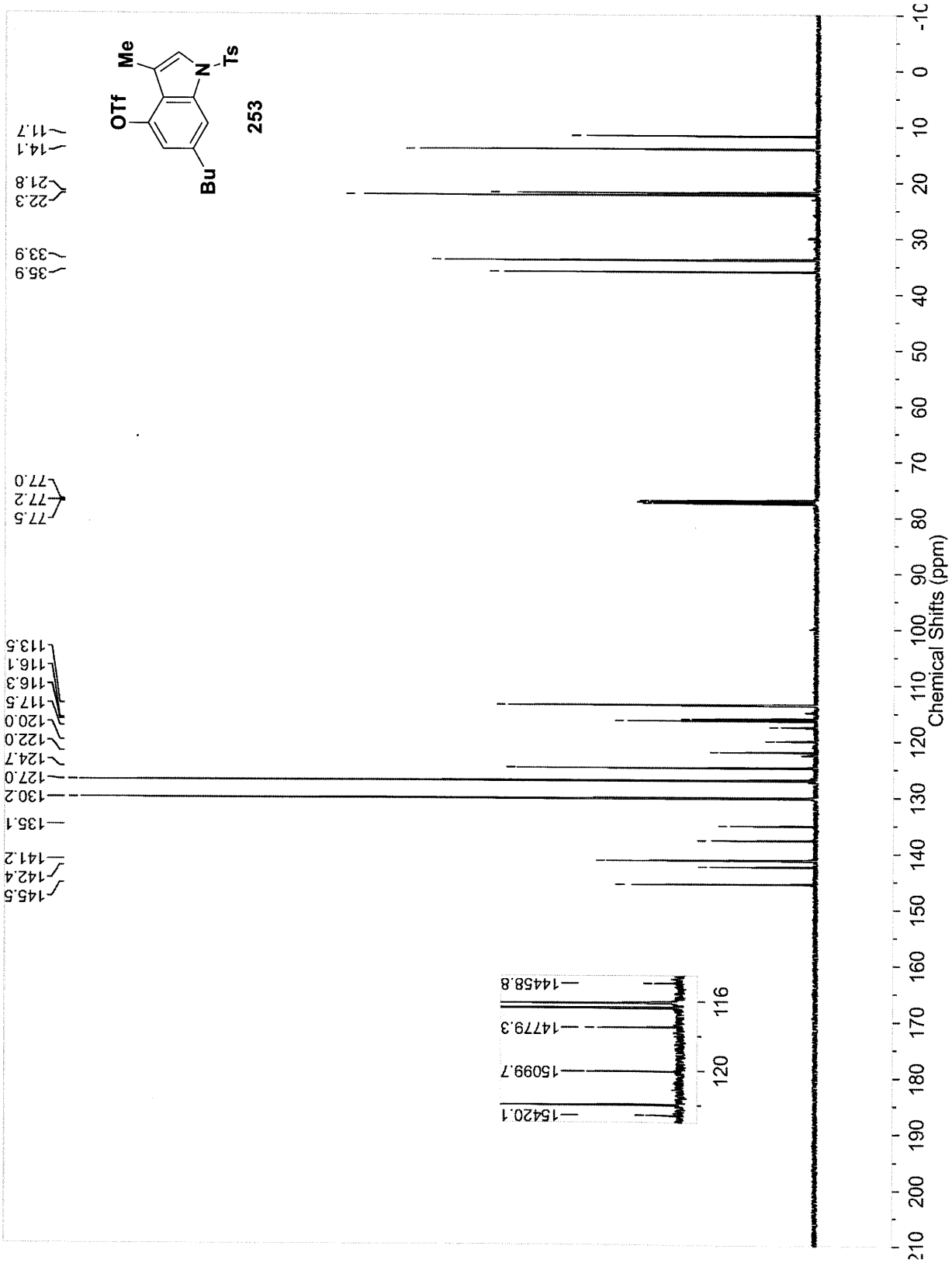

151.2
145.7
144.3
143.7
136.1
132.0
130.9
129.8
128.3
122.1
120.4
120.1
117.6
96.0
77.5
77.2
77.0
54.7
34.9
32.9
22.2
21.7
14.0
OTf
I
Bu
N
Ts
252
15429.4
15108.7
14788.0
14467.3
120
116
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shifts (ppm)

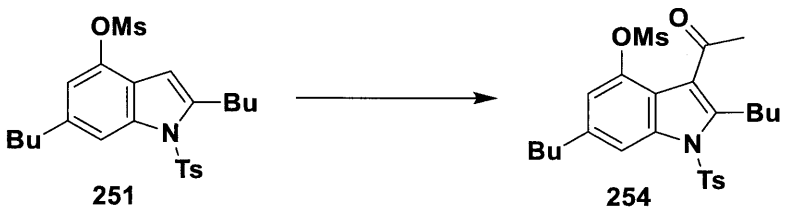


6-Butyl-3-methyl-1-(*p*-toluenesulfonyl)-indol-4-yl trifluoromethanesulfonate (253). A 25-mL pear flask equipped with a rubber septum and argon inlet needle was charged with aryl iodide **252** (0.173 g, 0.280 mmol, 1.0 equiv), $PdCl_2(PPh_3)_2$ (0.020 g, 0.028 mmol, 0.1 equiv), Et_3N (0.078 mL, 0.56 mmol, 2.0 equiv), and 2.8 mL of DMF. The yellow reaction mixture was heated at 55 °C for 24 h and allowed to cool to rt. The resulting orange-brown solution was diluted with 30 mL of Et_2O and 30 mL of satd aq NH_4Cl solution and transferred to a 125-mL separatory funnel. The aqueous phase was separated and extracted with two 15-mL portions of Et_2O, and the combined organic phases were washed with 30 mL of water and 30 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.214 g of an orange oil. This material was dissolved in ca. 5 mL of CH_2Cl_2 and concentrated onto 2 g of silica gel. The resulting free-flowing powder was added to the top of a column of 35 g of silica gel and eluted with 5% EtOAc–hexane. The fractions with R_f = 0.21 in 5% EtOAc–hexane were found to contain indole **253**, while those with R_f = 0.16 in 5% EtOAc–hexane, the exocyclic double bond (3-methylene) isomer. The solution of the latter compound was concentrated and the residue was dissolved in 5 mL of CH_2Cl_2 in a 25-mL pear flask equipped with a reflux condenser, rubber septum, and argon inlet needle. Camphorsulfonic acid (0.050 g, 0.215 mmol) was added and the reaction mixture was heated at 40 °C for 18 h and then allowed to cool to rt. The resulting pale yellow solution was diluted with 10 mL of CH_2Cl_2, transferred to a 60-mL separatory funnel, and washed with 20 mL of satd aq $NaHCO_3$ solution. The aqueous phase was separated and extracted with two 10-mL portions of CH_2Cl_2, and the combined organic phases were washed with 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.042 g of a pale yellow oil. This material was dissolved in ca. 3 mL of CH_2Cl_2 and concentrated onto 1 g of silica gel. The resulting free-flowing powder was added to the top of a column of 15 g of silica gel and eluted with 5% EtOAc–hexane. The pure fractions were combined with the higher-R_f fractions from the first column and concentrated to afford 0.065 g (47%) of indole **253** as a viscous orange oil: IR (film) 2957, 2932, 2872, 1630, 1597, 1423, 1377, 1221, 1178, 1141, 1115, 1034, 824, 671, and 583 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J*

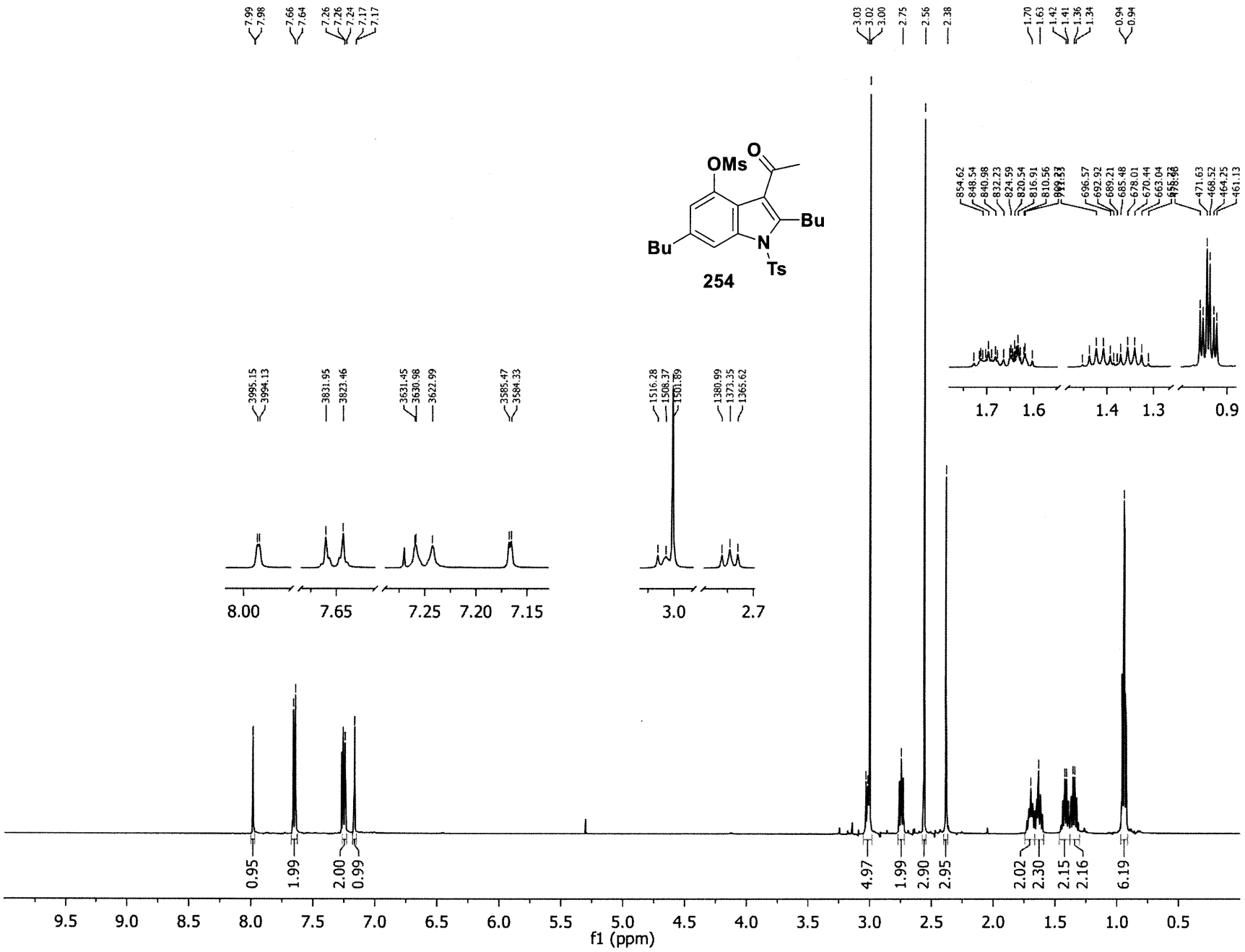
= 1.0 Hz, 1H), 7.76 (app d, J = 8.4 Hz, 2H), 7.30 (d, J = 1.3 Hz, 1H), 7.26 (d, J = 8.7 Hz, 2H), 6.98 (s, 1H), 2.75 (t, J = 7.7 Hz, 2H), 2.38 (s, 3H), 2.37 (s, 3H), 1.63 (app quint, J = 7.6 Hz, 2H), 1.35 (sext, J = 7.5 Hz, 2H), and 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.5, 142.4, 141.2, 137.7, 135.1, 130.2, 127.0, 124.7, 122.0, 118.8 (q, J = 320.4 Hz), 116.3, 116.1, 113.5, 35.9, 33.9, 22.3, 21.8, 14.1, and 11.7; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{21}H_{22}F_3NO_5S_2$, 512.0784; found 512.0775.

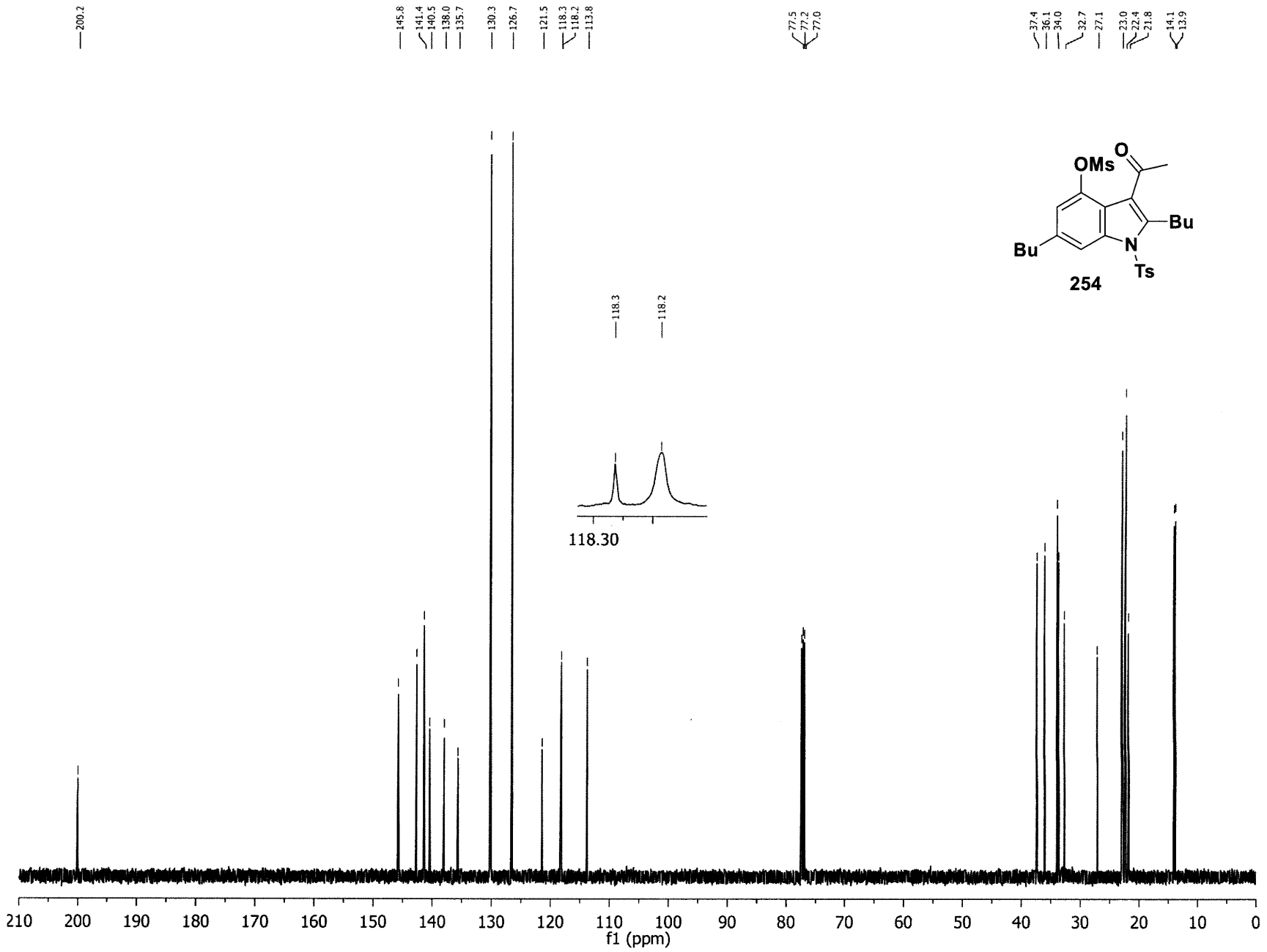

Me
N
Ts
OTf
Bu
253
Chemical Shifts (ppm)

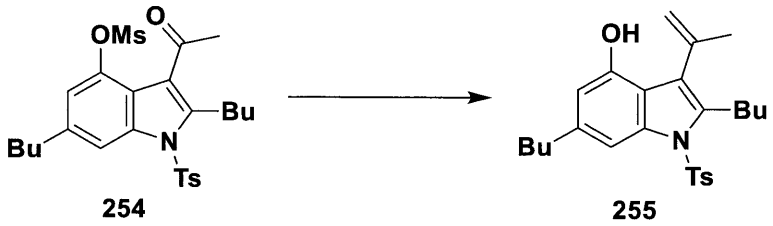

Me
OTf
N
Ts
Bu
253
11.7
14.1
21.8
22.3
33.9
35.9
77.0
77.2
77.5
113.5
116.1
116.3
117.5
120.0
122.0
124.7
127.0
130.2
135.1
141.2
142.4
145.5
144458.8
147793
150997
154201
116
120
Chemical Shifts (ppm)



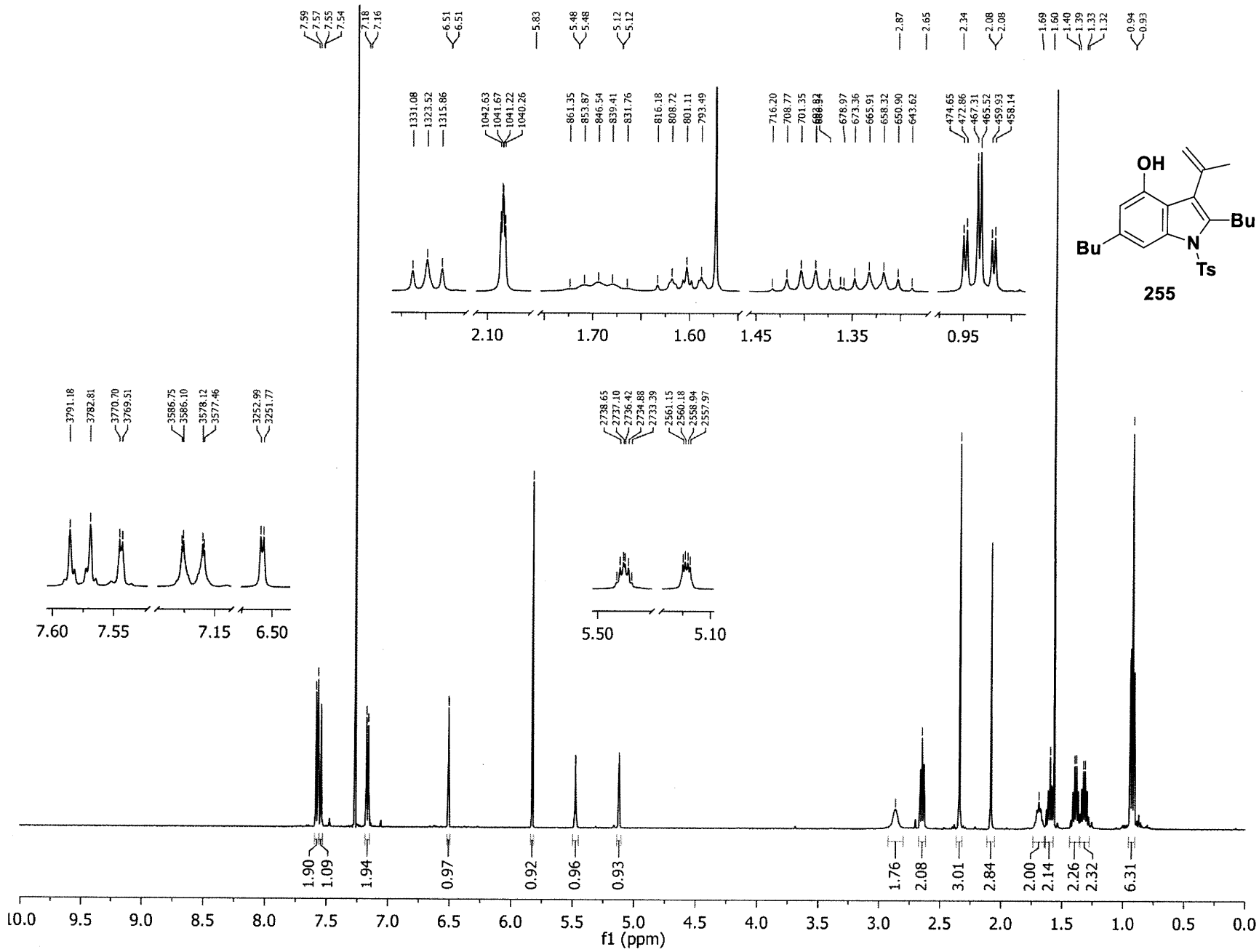
3-Acetyl-2,6-dibutyl-1-(*p*-toluenesulfonyl)-1*H*-indol-4-yl methanesulfonate (254). A 15-mL threaded Pyrex tube (20 mm o.d.; 16 mm I.D.) equipped with a rubber septum and argon inlet needle was charged with $AlCl_3$ (0.209 g, 1.57 mmol, 5.0 equiv), indole **251** (0.150 g, 0.314 mmol, 1.0 equiv) and 2.0 mL of CH_2Cl_2. Ac_2O (0.074 mL, 0.080 g, 0.79 mmol, 2.5 equiv) was added dropwise over 1 min with stirring and the reaction mixture was stirred at rt for 2 h. To the resulting red solution 10 g of crushed ice was carefully added and the mixture was stirred for 5 min. The aqueous phase was separated and extracted with three 4-mL portions of CH_2Cl_2. The combined organic phases were washed with 20 mL satd aq $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.199 g of a viscous orange oil. This material was dissolved in ca. 3 mL of CH_2Cl_2 and concentrated onto 1 g of silica gel. The resulting free-flowing powder was added to the top of a column of 16 g of silica gel and eluted with 18% EtOAc-hexanes to afford 0.124 g (76%) of indole **254** as a viscous orange oil: IR (film) 2958, 2932, 2872, 1688, 1551, 1422, 1377, 1180, 1169, 1103, 1089, 1077, 969, 813, 729, and 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J = 1.2 Hz, 1H), 7.65 (app d, J = 8.4 Hz, 2H), 7.25 (app d, J = 8.6 Hz, 2H), 7.17 (d, J = 1.2 Hz, 1H), 2.99–3.04 (m, 2H), 3.00 (s, 3H), 2.75 (t, J = 7.7 Hz, 2H), 2.56 (s, 3H), 2.38 (s, 3H), 1.70 (app quint, J = 7.8 Hz, 2H), 1.64 (app quint, J = 7.7 Hz, 2H), 1.42 (sext, J = 7.5 Hz, 2H), 1.35 (sext, J = 7.5 Hz, 2H), 0.95 (t, J = 7.4 Hz, 3H), and 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.2, 145.8, 142.7, 141.4, 140.5, 138.0, 135.7, 130.3, 126.7, 121.5, 118.3, 118.2, 113.8, 37.4, 36.1, 34.0, 33.7, 32.7, 27.1, 23.0, 22.4, 21.8, 14.1, and 13.9; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{33}NO_6S_2$, 520.1826; found 520.1802.

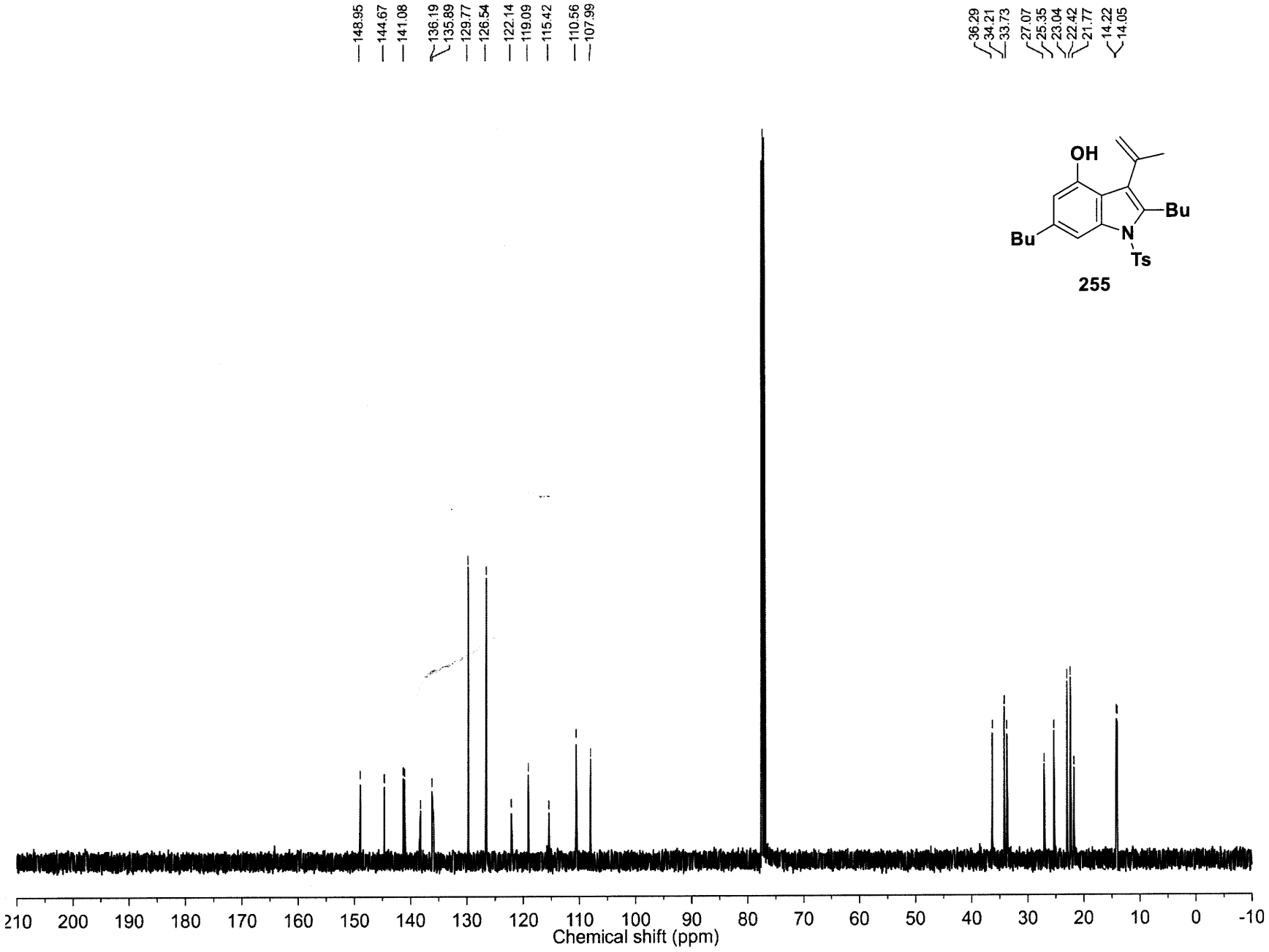

OMs
O
Bu
Bu
N
Ts
254
f1 (ppm)

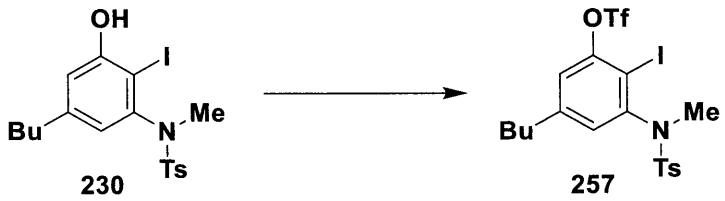

200.2
145.8
141.4
140.5
138.0
135.7
130.3
126.7
121.5
118.3
118.2
113.8
77.5
77.2
77.0
37.4
36.1
34.0
32.7
27.1
23.0
22.4
21.8
14.1
13.9
OMs
O
Bu
Bu
N
Ts
254
118.3
118.2
118.30
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



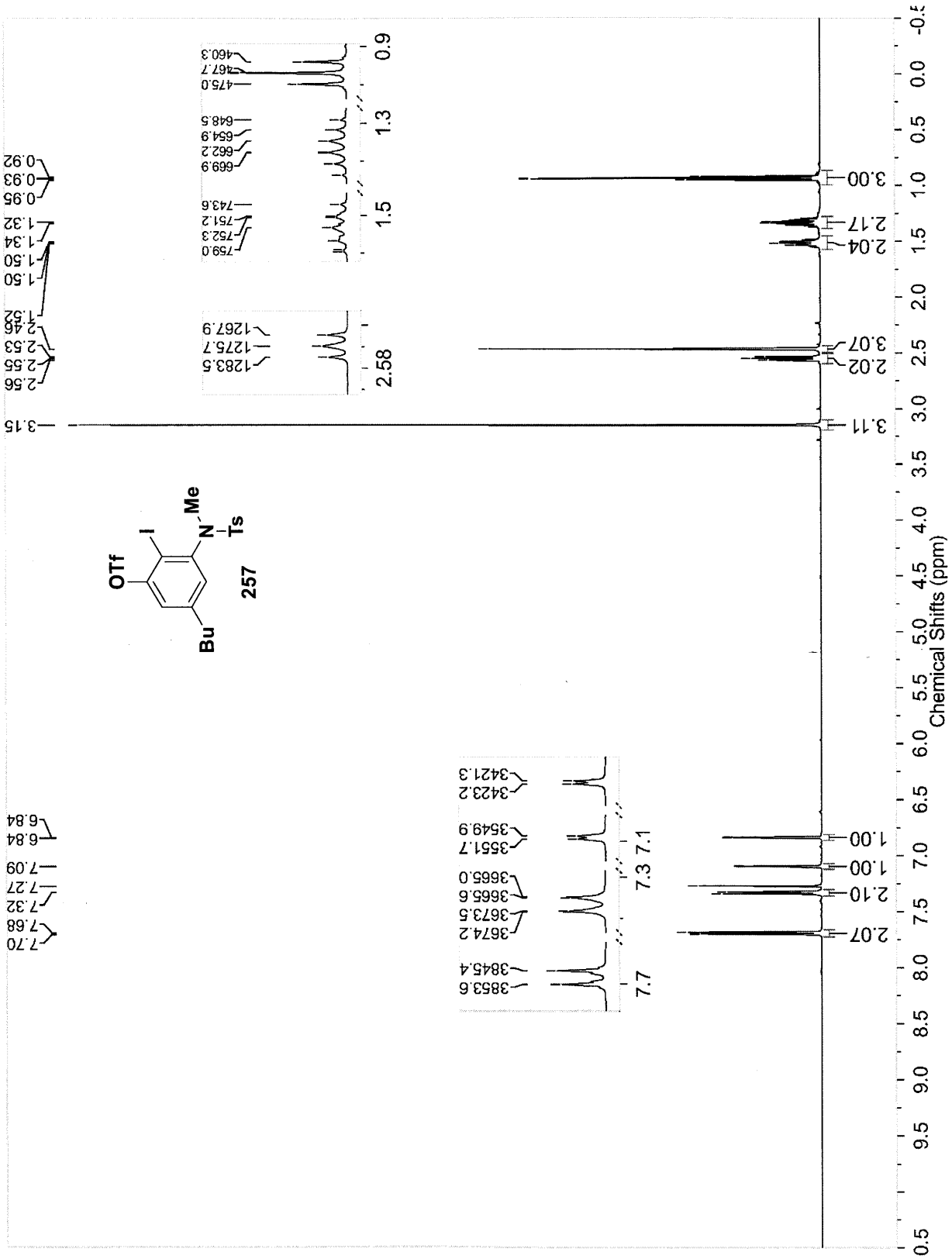
2,6-Dibutyl-3-isopropenyl-1-(*p*-toluenesulfonyl)-1*H*-indol-4-ol (255). A 15-mL threaded Pyrex tube (20 mm o.d.; 16 mm i.d.) equipped with a rubber septum and argon inlet needle was charged with Cs_2CO_3 (0.163 g, 0.500 mmol, 3.0 equiv), PdOAc-SPhos mix (1:1.5, 0.007 g, 0.008 mmol PdOAc, 0.05 equiv), and zinc dust (0.022 g, 0.333 mmol, 2.0 equiv). Indole **254** (0.087 g, 0.167 mmol, 1.0 equiv), 0.83 mL of THF, and a solution of Et_3B (0.83 mL, 1.0 M in THF, 0.83 mmol, 5.0 equiv) were added. The rubber septum was replaced with a threaded Teflon cap and the reaction mixture was stirred at 60 °C for 22 h. The resulting dark brown suspension was allowed to cool to rt, filtered through Celite with the aid of 5 mL of CH_2Cl_2, and the filtrate was concentrated to give 0.182 g of a viscous brown oil. This material was dissolved in ca. 3 mL of CH_2Cl_2 and concentrated onto 0.8 g of silica gel. The resulting free-flowing powder was added to the top of a column of 10 g of silica gel and eluted with a gradient of 3% to 10% EtOAc-hexanes to afford 0.016 g (22%) of indole **255** (R_f = 0.39 in 20% EtOAc-hexanes) as a viscous yellow oil: IR (film) 3491, 2957, 2929, 2871, 2860, 1619, 1597, 1573, 1429, 1368, 1290, 1188, 1169, 1122, 1090, 811, and 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.58 (app d, J = 8.4 Hz, 2H), 7.54 (d, J = 1.2 Hz, 1H), 7.17 (app d, J = 8.6 Hz, 2H), 6.51 (d, J = 1.2 Hz, 1H), 5.83 (s, 1H), 5.48 (dq, J = 2.2, 1.5 Hz, 1H), 5.12 (dq, J = 2.2, 1.0 Hz, 1H), 2.87 (br s, 2H), 2.65 (t, J = 7.6 Hz, 2H), 2.34 (s, 3H), 2.08 (dd, J = 1.4, 1.0 Hz, 3H), 1.69 (br quint, J = 7.4 Hz, 2H), 1.60 (app quint, J = 7.6 Hz, 2H), 1.40 (sext, J = 7.5 Hz, 2H), 1.33 (sext, J = 7.4 Hz, 2H), 0.94 (t, J = 7.4 Hz, 3H), and 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.0, 144.7, 141.3, 141.1, 138.2, 136.2, 135.9, 129.8, 126.5, 122.1, 119.1, 115.4, 110.6, 108.0, 36.3, 34.2, 33.7, 27.1, 25.3, 23.0, 22.4, 21.8, 14.2, and 14.0; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{33}NO_3S$, 440.2254; found 440.2238. Impure indole **256** (R_f = 0.54 in 20% EtOAc-hexanes) was also isolated as 0.013 g of a pale yellow viscous oil.

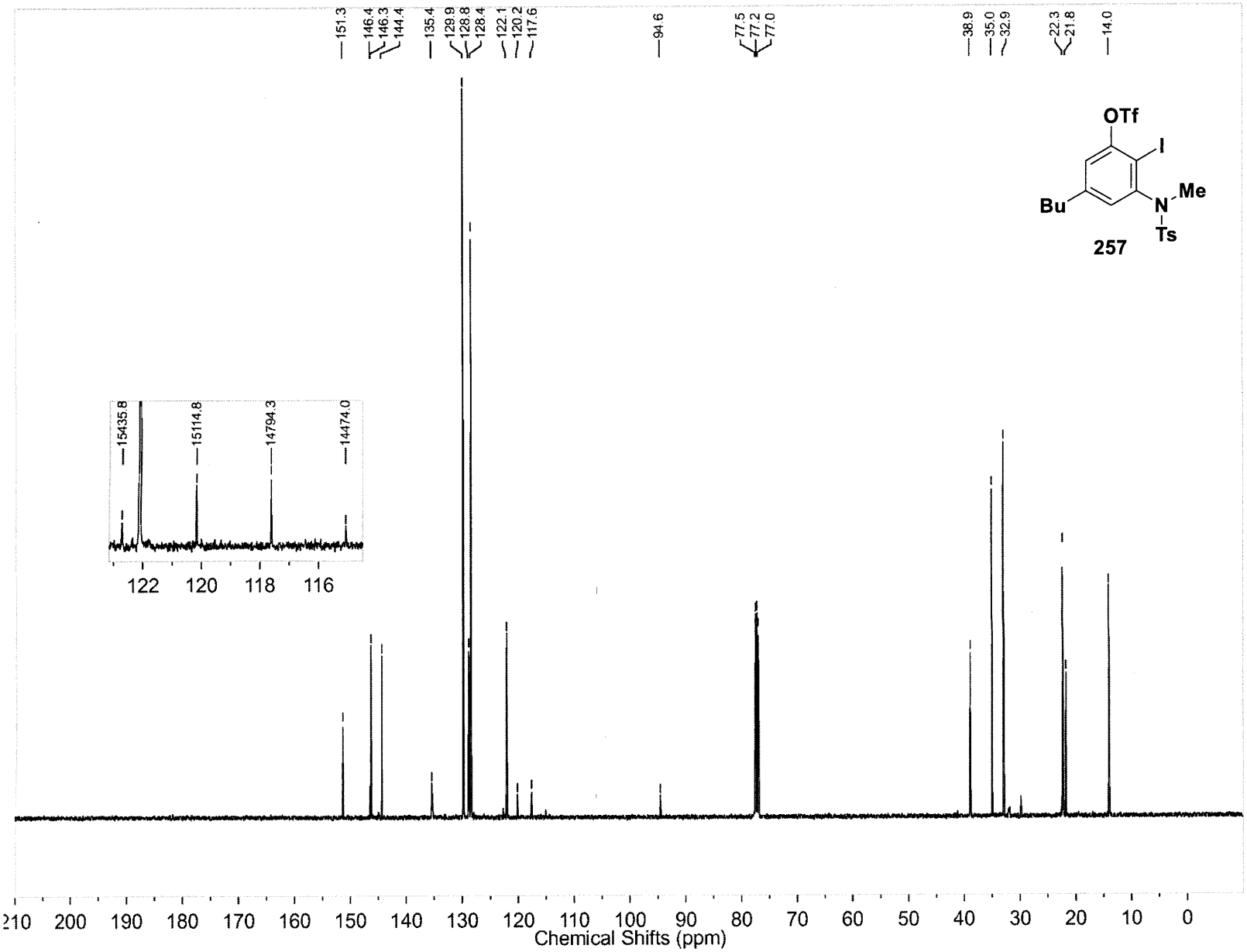

OH
Bu
Bu
N
Ts
255
f1 (ppm)

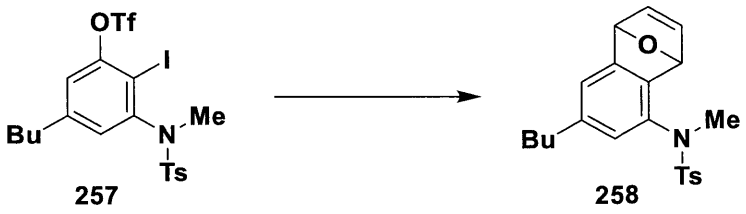

148.95
144.67
141.08
136.19
135.89
129.77
126.54
122.14
119.09
115.42
110.56
107.99
36.29
34.21
33.73
27.07
25.35
23.04
22.42
21.77
14.22
14.05
OH
Bu
Bu
N
Ts
255
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical shift (ppm)



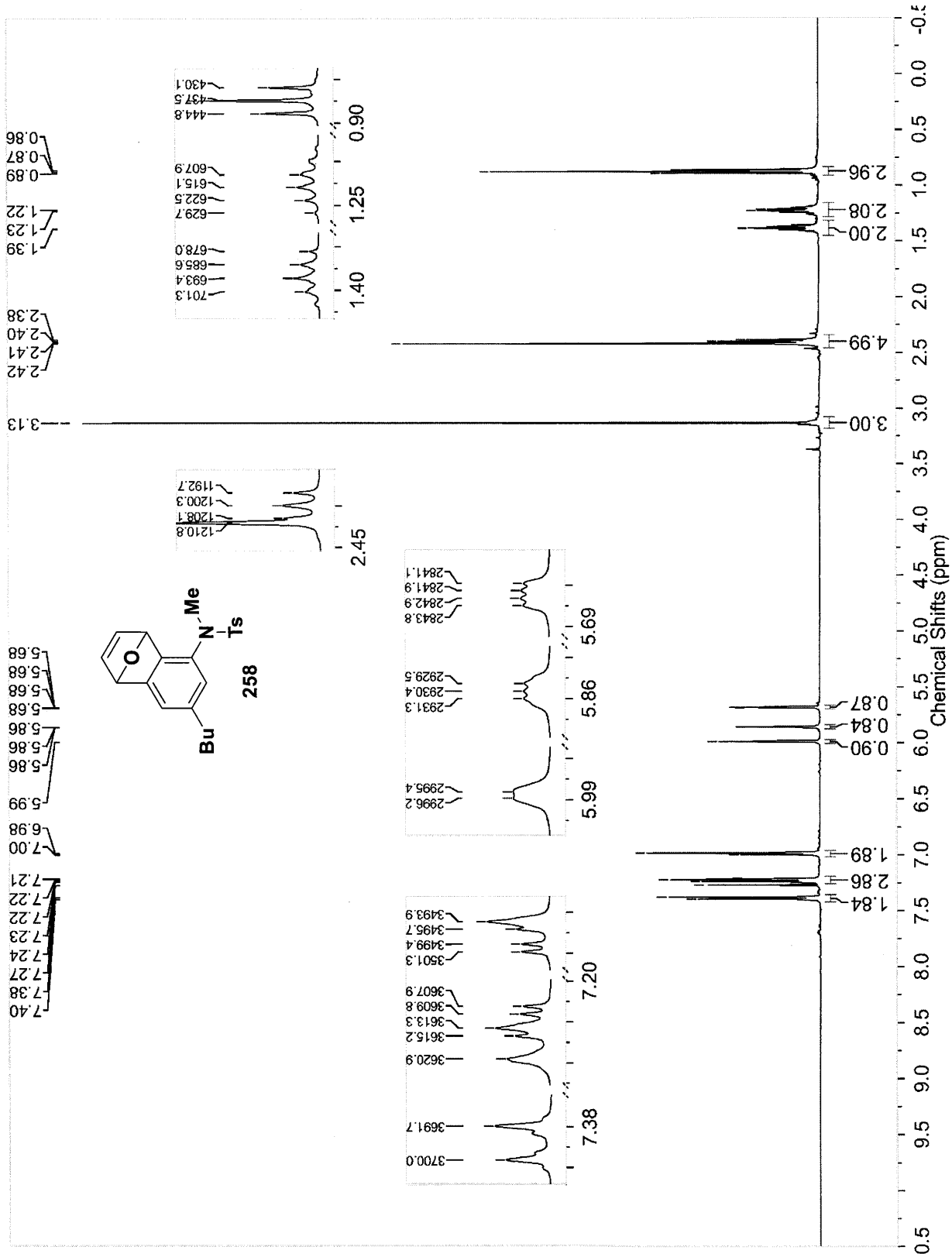
5-Butyl-2-iodo-3-(*N*-methyl-*N*-(*p*-toluenesulfonyl)amino)phenyl trifluoromethanesulfonate (257). A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with phenol **230** (0.231 g, 0.503 mmol, 1.0 equiv), DMAP (0.123 g, 1.01 mmol, 2.0 equiv), and 5 mL of CH_2Cl_2. The yellow solution was cooled at 0 °C and Tf_2O (0.11 mL, 0.65 mmol, 1.3 equiv) was added dropwise via syringe over 1 min. The reaction mixture was allowed to warm to rt and stirred for a total of 1.5 h. The resulting orange suspension was diluted with 10 mL of CH_2Cl_2 and 15 mL of 1 M aqueous HCl solution and transferred to a 60-mL separatory funnel. The aqueous phase was separated and extracted with two 7.5-mL portions of CH_2Cl_2, and the combined organic phases were washed with 20 mL satd aq $NaHCO_3$ and 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.335 g of an orange oil. This material was purified by two columns each containing 100 g of silica gel eluting with 20% EtOAc–hexane to afford 0.206 g (69%) of aniline **257** as pale yellow crystals: mp 107–109 °C; IR (film) 2963, 2930, 2863, 1598, 1562, 1428, 1411, 1351, 1207, 1157, 1144, 970, 757, and 665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 (app d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.6 Hz, 2H), 7.10 (d, J = 1.8 Hz, 1H), 6.84 (d, J = 1.9 Hz, 1H), 3.15 (s, 3H), 2.55 (t, J = 7.8 Hz, 2H), 2.46 (s, 3H), 1.52 (app quint, J = 7.7 Hz, 2H), 1.33 (sext, J = 7.4 Hz, 2H), and 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.3, 146.4, 146.3, 144.4, 135.4, 129.9, 128.8, 128.4, 122.1, 118.9 (q, J = 320.6 Hz), 94.6, 38.9, 35.0, 32.9, 22.3, 21.8, and 14.0; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{21}F_3INO_5S_2$, 591.9931; found 591.9930.

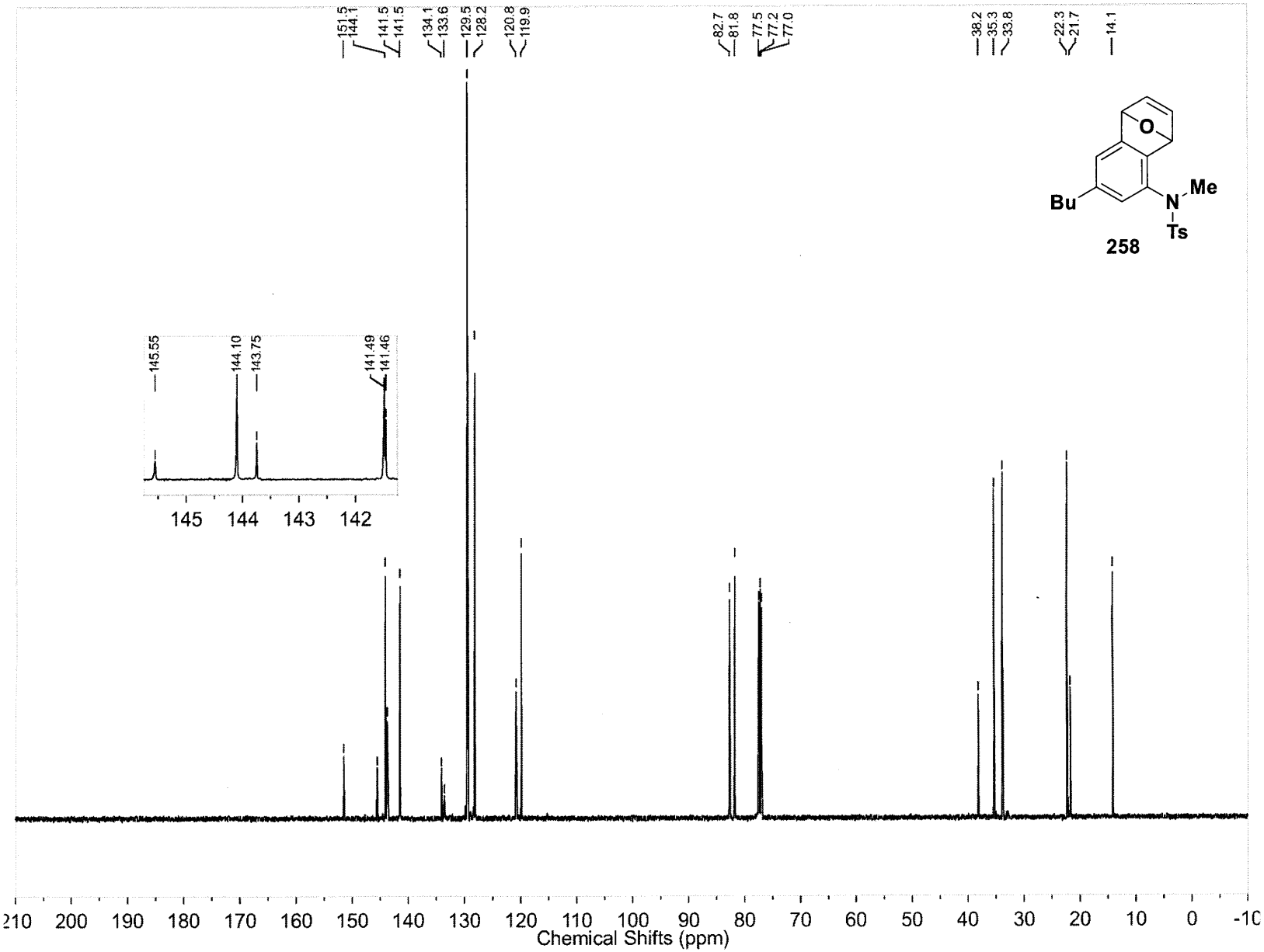

OTf
I
Me
N
Ts
Bu
257
Chemical Shifts (ppm)

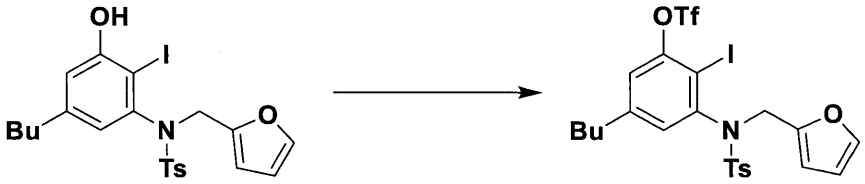

151.3
146.4
146.3
144.4
135.4
129.9
128.8
128.4
122.1
120.2
117.6
94.6
77.5
77.2
77.0
38.9
35.0
32.9
22.3
21.8
14.0
OTf
I
Bu
N
Me
Ts
257
15435.8
15114.8
14794.3
14474.0
122
120
118
116
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shifts (ppm)



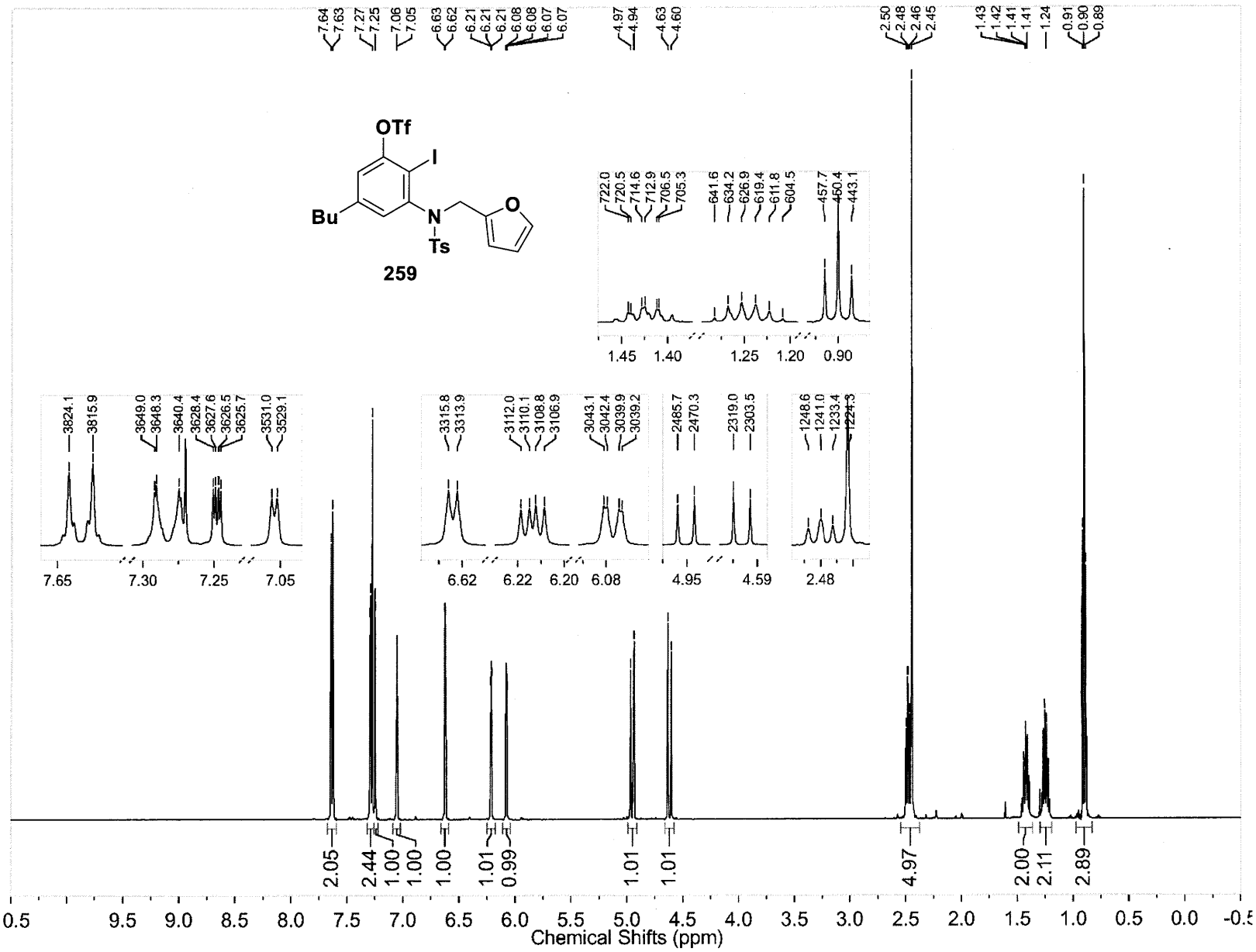
***N*-Methyl-*N*-(*p*-toluenesulfonyl)-(7-butyl-1,4-dihydro-1,4-epoxynaphthalen-5-yl)amine (258).** A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with triflate **257** (0.100 g, 0.169 mmol, 1.0 equiv), furan (0.123 mL, 1.69 mmol, 10 equiv), and 3.4 mL of THF. The pale yellow solution was cooled at -78 °C and a solution of *n*-BuLi (2.52 M in hexane, 0.074 mL, 0.19 mmol, 1.1 equiv) was added dropwise via syringe over 1 min. The reaction mixture was stirred at -78 °C for 3 h, allowed to warm to rt, and diluted with 10 mL of Et_2O and 10 mL of satd aq NH_4Cl solution. The mixture was transferred to a 60-mL separatory funnel and the aqueous phase was separated and extracted with two 5-mL portions of Et_2O. The combined organic phases were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.084 g of a yellow oil. This material was dissolved in ca. 3 mL of CH_2Cl_2 and concentrated onto 1 g of silica gel. The resulting free-flowing powder was added to the top of a column of 10 g of silica gel and eluted with 15% EtOAc-hexane to afford 0.055 g (85%) of cycloadduct **258** as a colorless oil: IR (film) 3024, 2956, 2929, 2859, 1653, 1598, 1457, 1350, 1281, 1187, 1167, 1159, 1089, 965, 850, and 666 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (app d, J = 8.3 Hz, 2H), 7.23 (d, J = 8.6 Hz, 2H), 7.22 (dd, J = 5.4, 1.9 Hz, 1H), 6.99 (dd, J = 5.6, 1.9 Hz, 1H), 6.98 (s, 1H), 5.99 (d, J = 0.8 Hz, 1H), 5.85–5.86 (m, 1H), 5.68–5.69 (m, 1H), 3.13 (s, 3H), 2.42 (s, 3H), 2.40 (t, J = 7.7 Hz, 2H), 1.39 (app quint, J = 7.3 Hz, 2H), 1.22 (sext, J = 7.3 Hz, 2H), and 0.87 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5, 145.6, 144.1, 143.7, 141.49, 141.46, 134.1, 133.6, 129.5, 128.2, 120.8, 119.9, 82.7, 81.8, 38.2, 35.3, 33.8, 22.3, 21.7, and 14.1; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{25}NO_3S$, 384.1628; found 384.1634.

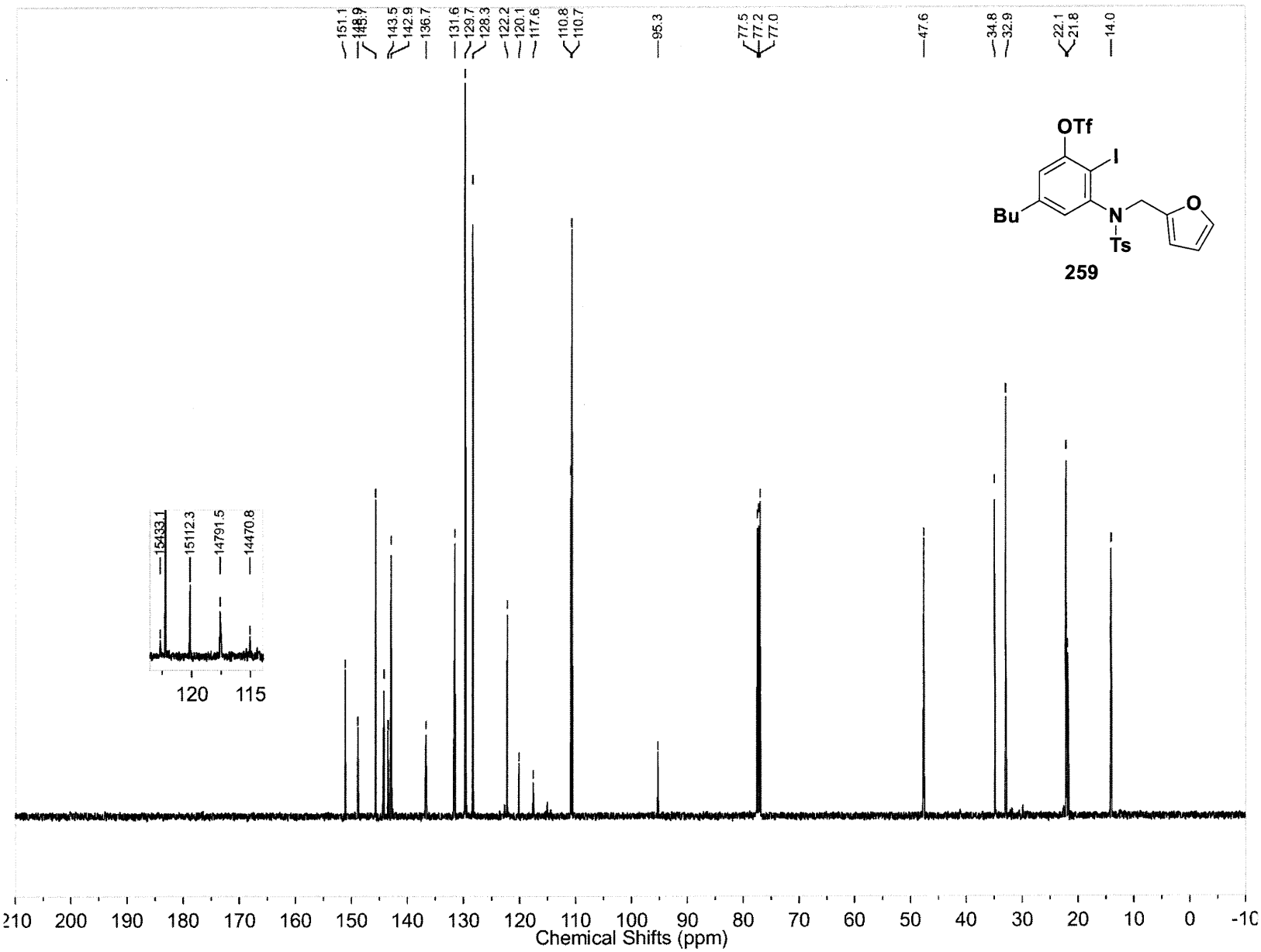

Me
N
Ts
O
Bu
258
Chemical Shifts (ppm)

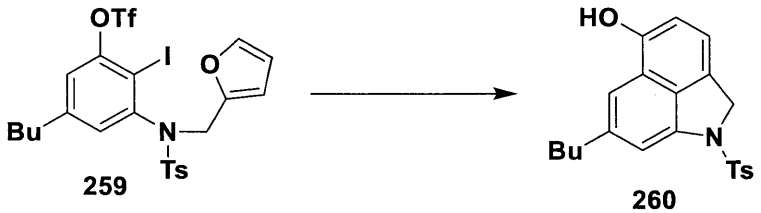

151.5
144.1
141.5
141.5
134.1
133.6
129.5
128.2
120.8
119.9
82.7
81.8
77.5
77.2
77.0
38.2
35.3
33.8
22.3
21.7
14.1
145.55
144.10
143.75
141.49
141.46
145
144
143
142
O
Bu
N
Me
Ts
258
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shifts (ppm)



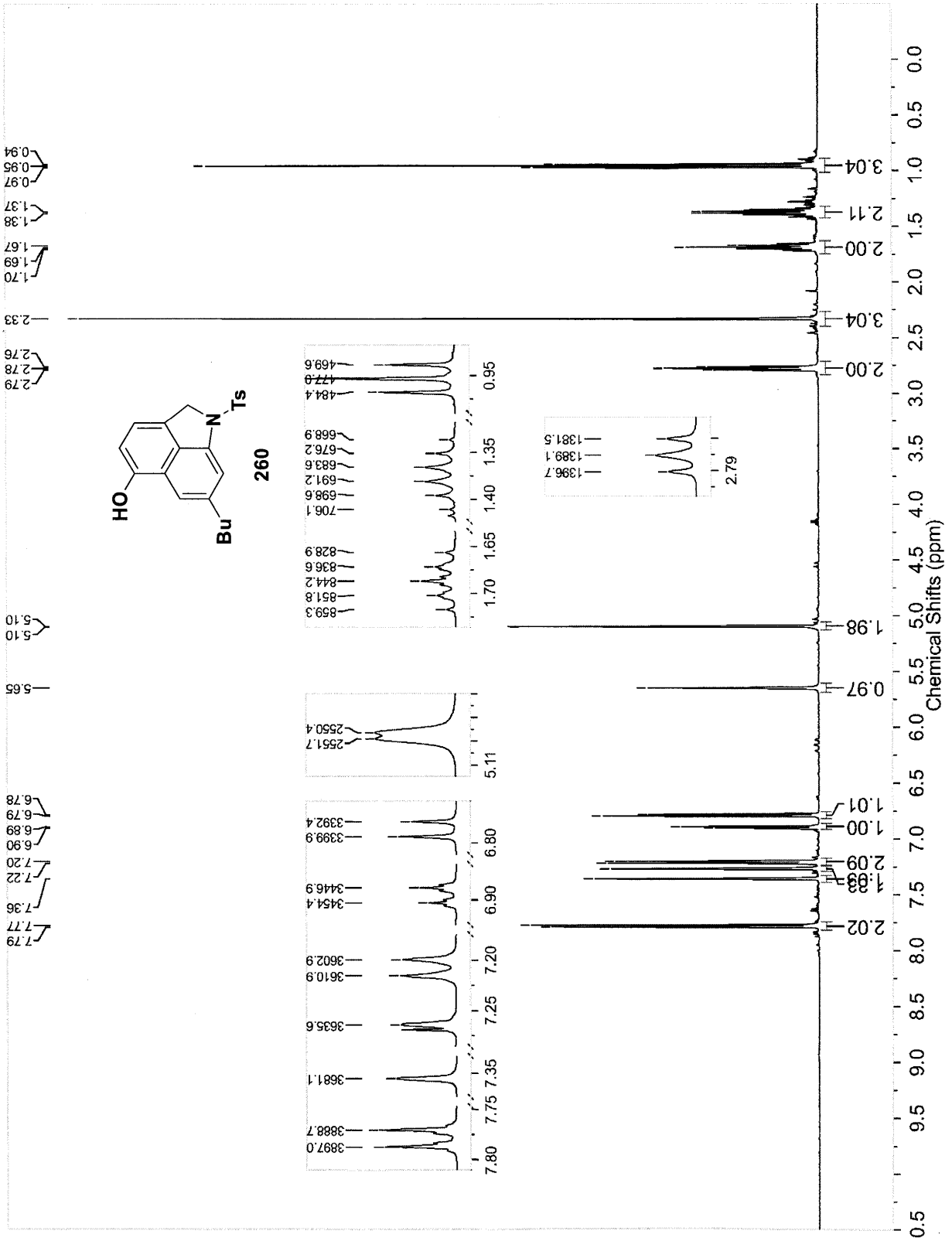
5-Butyl-3-(*N*-(furan-2-ylmethyl)-*p*-toluenesulfonamido)-2-iodophenyl trifluoromethanesulfonate (259). A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with phenol **243** (0.234 g, 0.445 mmol, 1.0 equiv), DMAP (0.109 g, 0.890 mmol, 2.0 equiv), and 4.5 mL of CH_2Cl_2. The pale yellow reaction mixture was cooled to 0 °C and Tf_2O (0.097 mL, 0.58 mmol, 1.3 equiv) was added dropwise over 1 min. The resulting pale yellow suspension was stirred at rt for 1.5 h, diluted with 10 mL 1 M aqueous HCl solution and 10 mL of CH_2Cl_2, and transferred to a 60-mL separatory funnel. The aqueous phase was separated and extracted with two 5-mL portions of CH_2Cl_2, and the combined organic phases were washed with 20 mL of satd aq $NaHCO_3$ solution and 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.293 g of a dark yellow oil. This material was dissolved in ca. 3 mL of CH_2Cl_2 and concentrated onto 1.5 g of silica gel. The resulting free-flowing powder was added to the top of a column of 30 g of silica gel and eluted with 9% EtOAc-hexane to afford 0.205 g (70%) of triflate **259** as a viscous pale yellow oil: IR (film) 2958, 2931, 2872, 1598, 1558, 1427, 1357, 1220, 1164, 1139, 1092, 1010, 815, and 719 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63 (app d, J = 8.2 Hz, 2H), 7.28 (app d, J = 8.6 Hz, 2H), 7.25 (dd, J = 1.9, 0.8 Hz, 1H), 7.05 (d, J = 1.9 Hz, 1H), 6.62 (d, J = 1.9 Hz, 1H), 6.21 (dd, J = 3.2, 1.9 Hz, 1H), 6.08 (dd, J = 3.2, 0.7 Hz, 1H), 4.95 (d, J = 15.4 Hz, 1H), 4.62 (d, J = 15.5 Hz, 1H), 2.48 (t, J = 7.6 Hz, 2H), 2.45 (s, 3H), 1.43 (app quint, J = 7.6 Hz, 2H), 1.25 (sext, J = 7.4 Hz, 2H), and 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.1, 148.9, 145.7, 144.2, 143.5, 142.9, 136.7, 131.6, 129.7, 128.3, 122.2, 118.9 (q, J = 320.8 Hz), 110.8, 110.7, 95.3, 47.6, 34.8, 32.9, 22.1, 21.8, and 14.0; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{23}H_{23}F_3INO_6S_2$, 679.9856; found 679.9865.

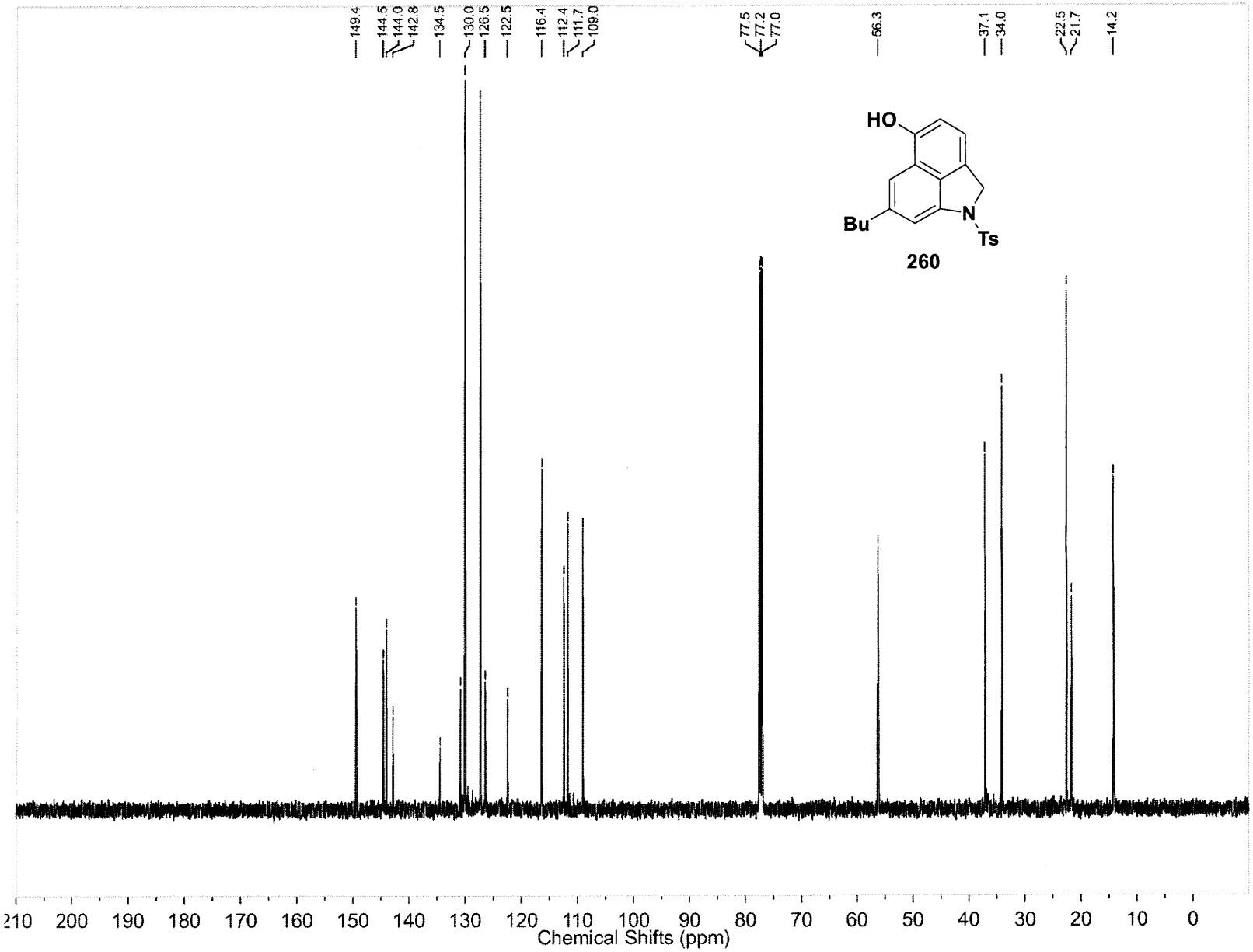

OTf
I
Bu
N
Ts
O
259
Chemical Shifts (ppm)

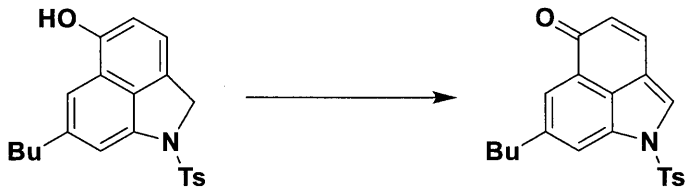

151.1
143.5
142.9
136.7
131.6
129.7
128.3
122.2
120.1
117.6
110.8
110.7
95.3
77.5
77.2
77.0
47.6
34.8
32.9
22.1
21.8
14.0
OTf
I
Bu
N
Ts
O
259
15433.1
15112.3
14791.5
14470.8
120
115
Chemical Shifts (ppm)



7-Butyl-1-(*p*-toluenesulfonyl)-1,2-dihydrobenz[*cd*]indol-5-ol (260). A 500-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with triflate **259** (0.500 g, 0.761 mmol, 1.0 equiv) and 150 mL of THF. The colorless reaction mixture was cooled to -95 °C and a solution of *n*-BuLi (2.48 M in hexane, 0.34 mL, 0.84 mmol, 1.1 equiv) was added dropwise via syringe over 4 min. The resulting pale yellow solution was allowed to slowly warm to rt and stirred for a total of 19 h. The reaction mixture was concentrated to ca. 20 mL, diluted with 50 mL of Et_2O and 50 mL of satd aq NH_4Cl solution, and transferred to a 250-mL separatory funnel. The aqueous phase was separated and extracted with two 20-mL portions of Et_2O, and the combined organic phases were washed with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.520 g of a viscous bright yellow oil. This material was dissolved in ca. 10 mL of CH_2Cl_2 and concentrated onto 3 g of silica gel. The resulting free-flowing powder was added to the top of a column of 100 g of silica gel and eluted with 25% EtOAc-hexane to afford 0.225 g (77%) of naphthol **260** as a sticky pale yellow solid: mp 44–46 °C; IR (film) 3444, 2956, 2929, 1601, 1507, 1384, 1349, 1164, 1123, 1090, 1040, 668, and 601 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (app d, J = 8.3 Hz, 2H), 7.35 (s, 1H), 7.26 (s, 1H), 7.21 (d, J = 8.0 Hz, 2H), 6.89 (dt, J = 7.5, 1.5 Hz, 1H), 6.78 (d, J = 7.5 Hz, 1H), 5.65 (br s, 1H), 5.09 (d, J = 1.3 Hz, 2H), 2.78 (t, J = 7.6 Hz, 2H), 2.33 (s, 3H), 1.69 (app quint, J = 7.6 Hz, 2H), 1.37 (sext, J = 7.4 Hz, 2H), and 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.4, 144.5, 144.0, 142.8, 134.5, 130.8, 130.0, 127.3, 126.5, 122.5, 116.4, 112.4, 111.7, 109.0, 56.3, 37.1, 34.0, 22.5, 21.7, and 14.2; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{22}H_{23}NO_3S$, 404.1291; found 404.1304.

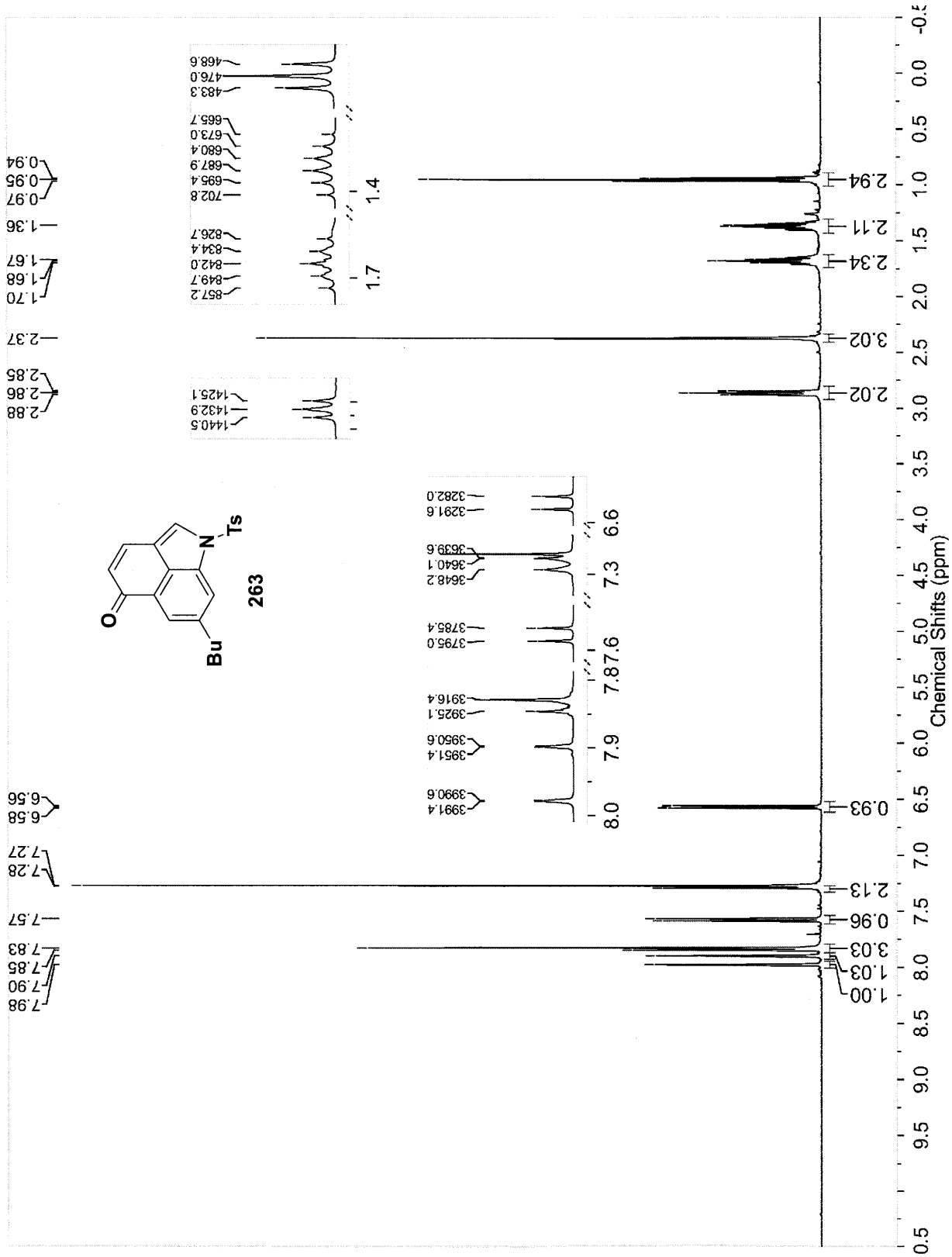

HO
Bu
N
Ts
260
Chemical Shifts (ppm)

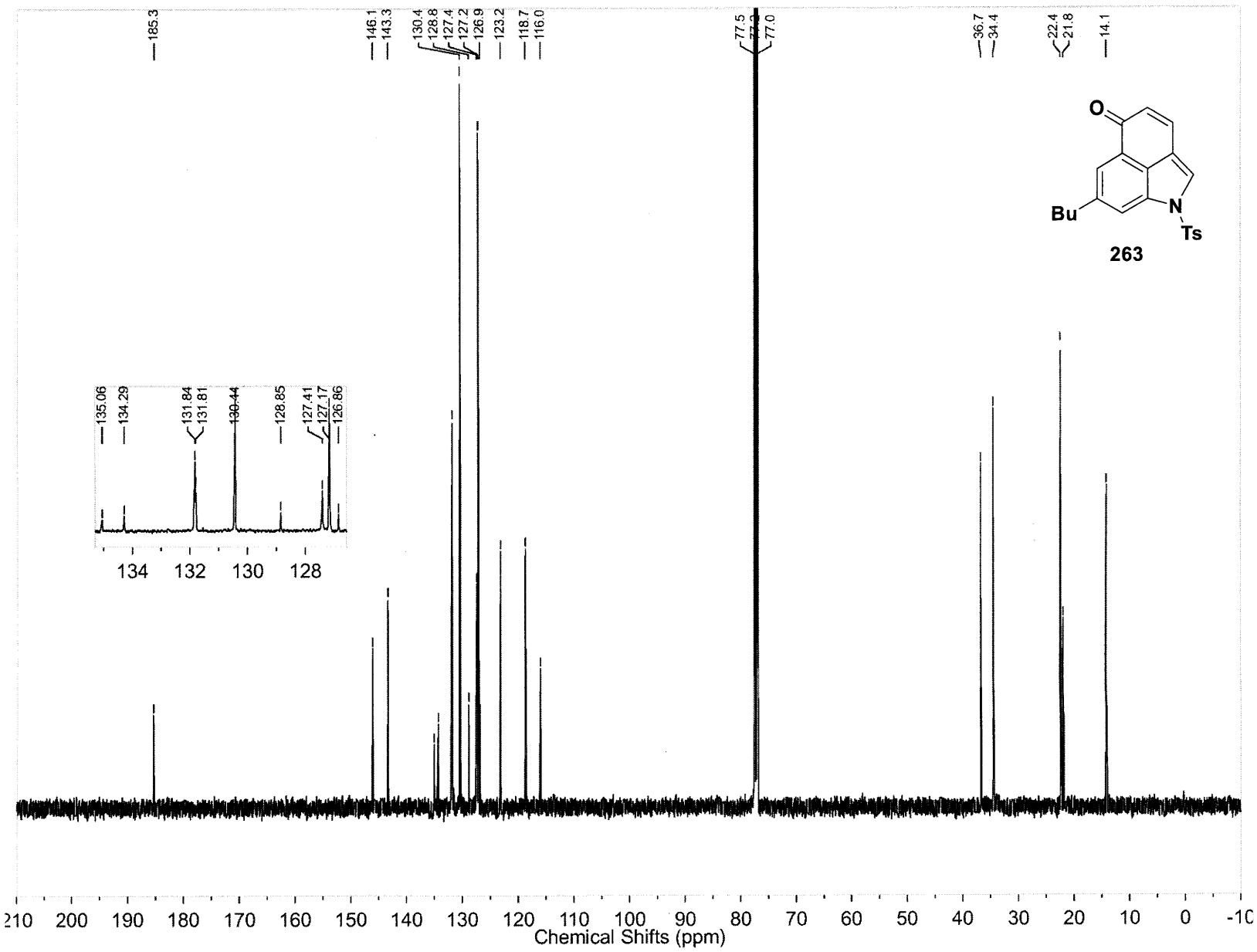

149.4
144.5
144.0
142.8
134.5
130.0
126.5
122.5
116.4
112.4
111.7
109.0
77.5
77.2
77.0
56.3
37.1
34.0
22.5
21.7
14.2
HO
Bu
N
Ts
260
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shifts (ppm)

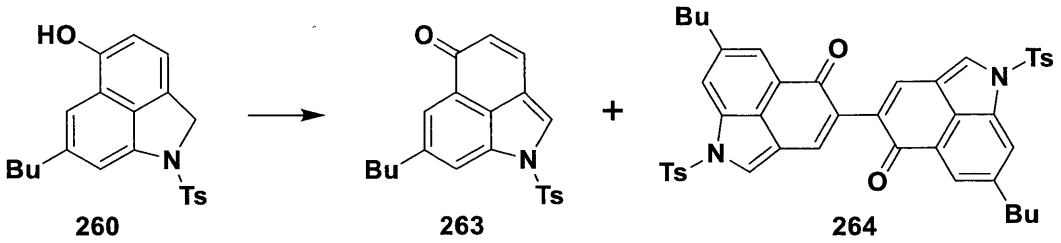


260 263

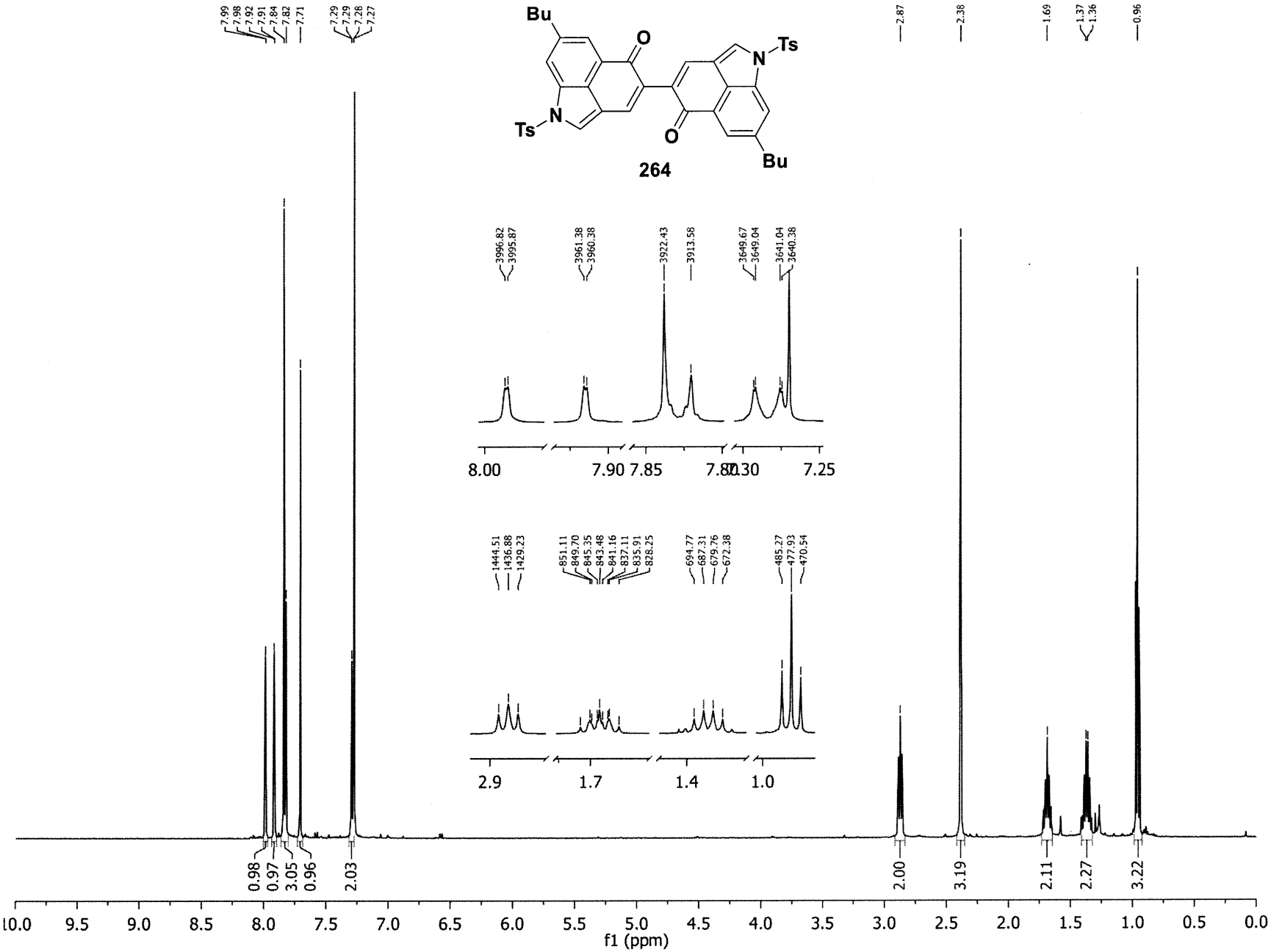
7-Butyl-1-(*p*-toluenesulfonyl)-1*H*-benz[*cd*]indol-5-one (263). A 50-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with naphthol **260** (0.106 g, 0.279 mmol, 1.0 equiv) and 5.6 mL of toluene. DDQ (0.063 g, 0.28 mmol, 1.0 equiv) was added in one portion and the resulting orange suspension was stirred at rt for 20 h. The reaction mixture was filtered with the aid of ca. 20 mL of CH_2Cl_2 and the filtrate was concentrated to afford 0.117 g of a brown slurry. This material was dissolved in ca. 3 mL of CH_2Cl_2 and concentrated onto 1 g of silica gel. The resulting free-flowing powder was added to the top of a column of 20 g of silica gel and eluted with 25% EtOAc-hexane to afford 0.075 g (71%) of ketone **263** as a viscous bright yellow oil: IR (film) 3122, 2956, 2929, 2860, 1738, 1643, 1608, 1568, 1370, 1189, 1177, 1149, 1107, 1089, 1033, 837, 669, and 591 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, J = 0.8 Hz, 1H), 7.90 (d, J = 0.8 Hz, 1H), 7.84 (app d, J = 8.7 Hz, 2H), 7.83 (s, 1H), 7.58 (d, J = 9.6 Hz, 1H), 7.29 (d, J = 8.6 Hz, 2H), 6.57 (d, J = 9.6 Hz, 1H), 2.86 (t, J = 7.7 Hz, 2H), 2.37 (s, 3H), 1.68 (app quint, J = 7.6 Hz, 2H), 1.37 (sext, J = 7.4 Hz, 2H), and 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.3, 146.1, 143.3, 135.1, 134.3, 131.84, 131.81, 130.4, 128.8, 127.4, 127.2, 126.9, 123.2, 118.7, 116.0, 36.7, 34.4, 22.4, 21.8, and 14.1; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{21}NO_3S$, 380.1315; found 380.1303.

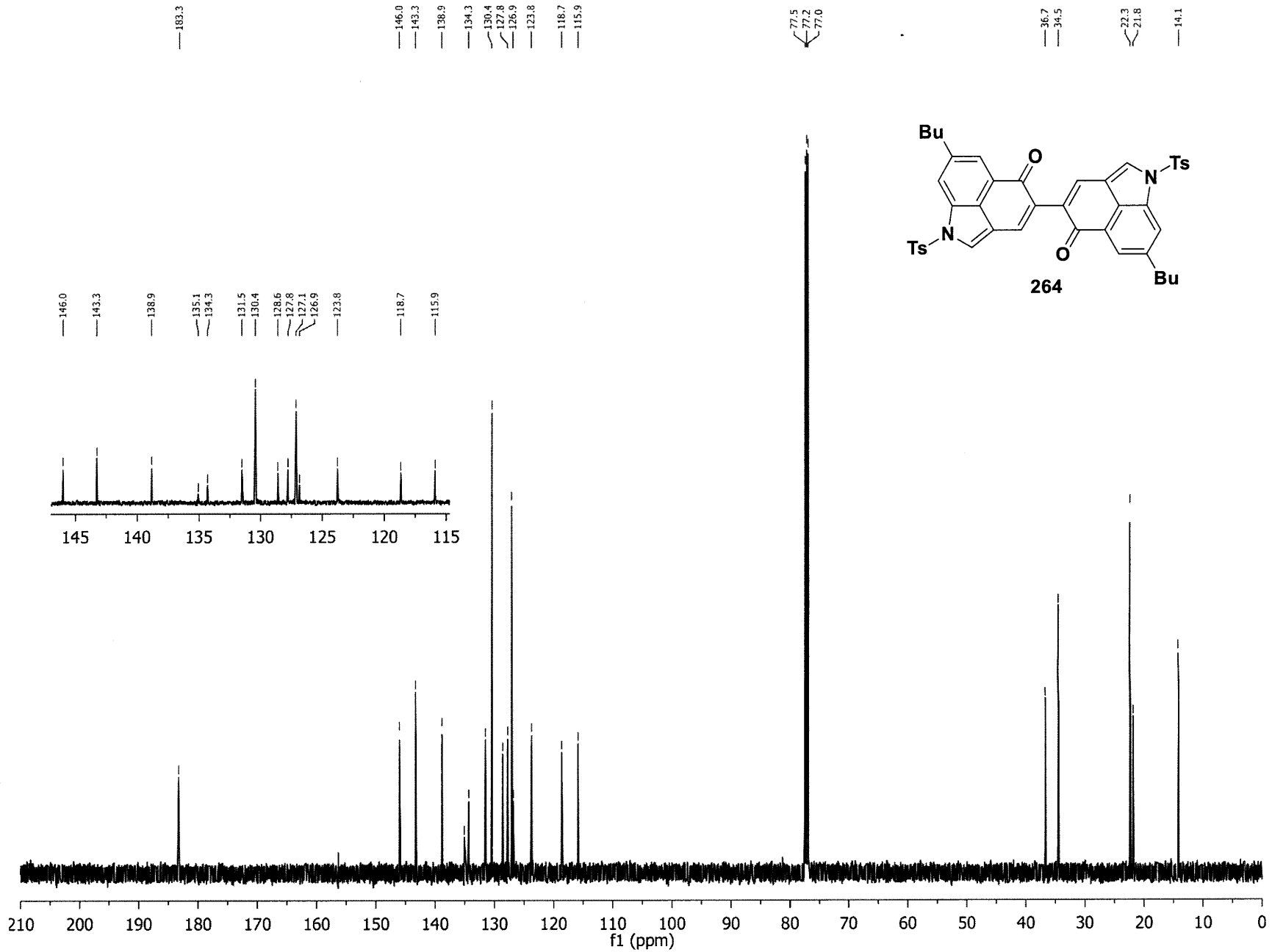

Chemical Shifts (ppm)
Ts
N
O
Bu
263

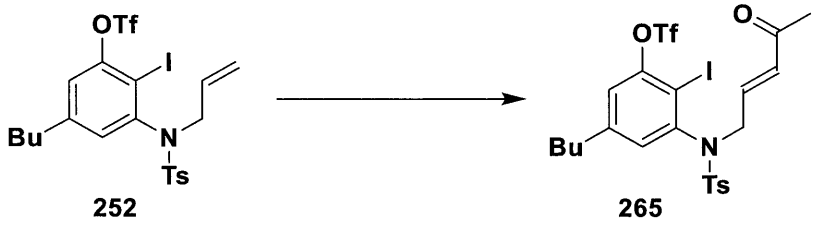

185.3
146.1
143.3
130.4
128.8
127.4
127.2
126.9
123.2
118.7
116.0
77.5
77.0
36.7
34.4
22.4
21.8
14.1
135.06
134.29
131.84
131.81
130.44
128.85
127.41
127.17
126.86
134
132
130
128
O
Bu
N
Ts
263
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shifts (ppm)



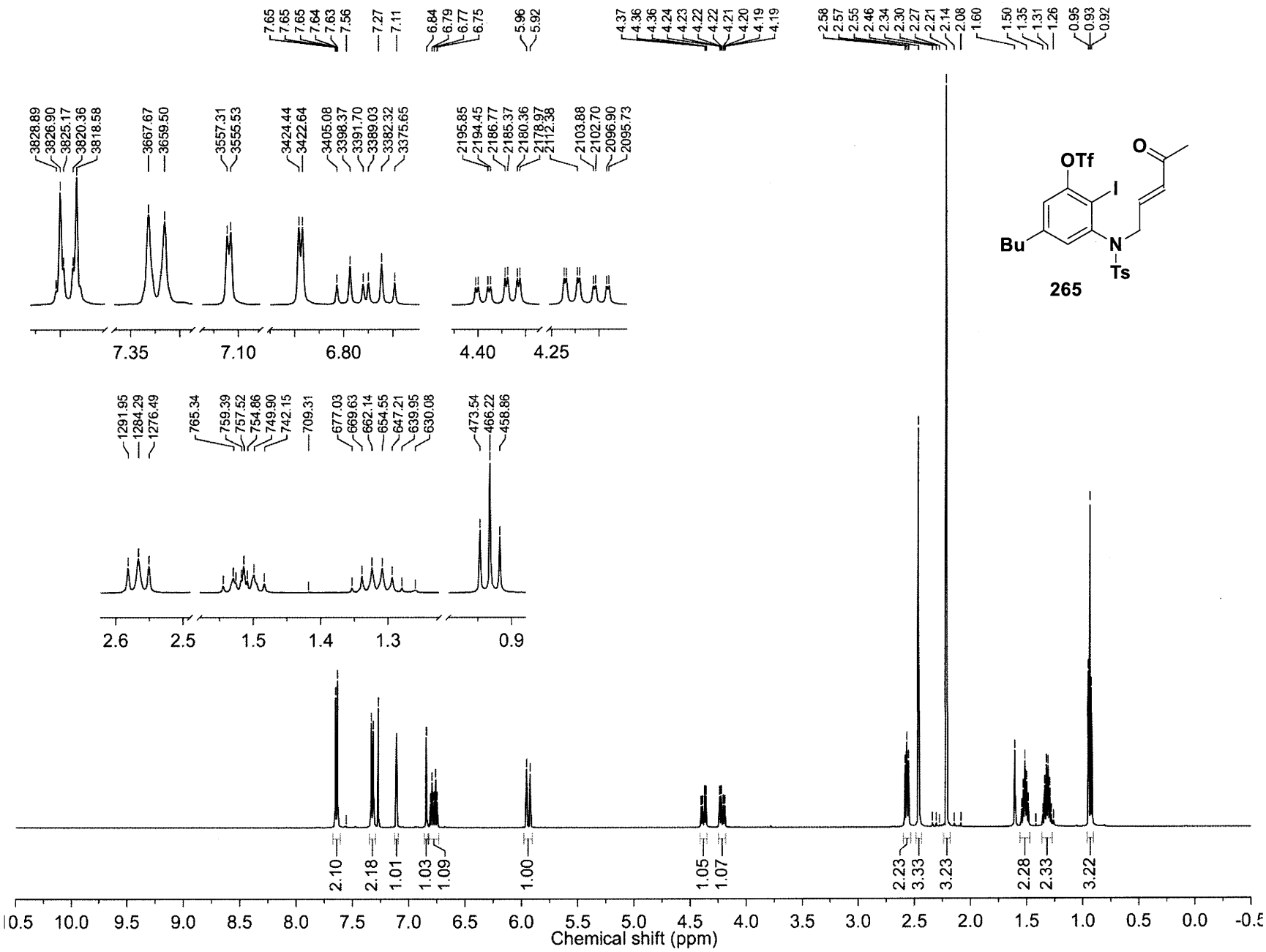
7-Butyl-1-(*p*-toluenesulfonyl)-1*H*-benz[*cd*]indol-5-one (263) and 7,7'-dibutyl-1,1'-bis(*p*-toluenesulfonyl)-[4,4'-(1*H*,1'*H*-bibenz[*cd*]indol)]-5,5'-dione (264). A 50-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with naphthol **260** (0.140 g, 0.367 mmol, 1.0 equiv) and 7.3 mL of CH_2Cl_2. The pale yellow solution was cooled at 0 °C and $PhI(OAc)_2$ (0.118 g, 0.367 mmol, 1.0 equiv) was added in one portion. The reaction mixture immediately turned bright yellow and then gradually turned orange. The resulting mixture was stirred at 0 °C for 1 h, diluted with 15 mL of CH_2Cl_2, washed with two 15-mL portions of satd aq $NaHCO_3$ solution, and then dried over $MgSO_4$, filtered, and concentrated to afford 0.369 g of an orange oil. This material was dissolved in ca. 3 mL of CH_2Cl_2 and concentrated onto 1 g of silica gel. The resulting free-flowing powder was added to the top of a column of 20 g of silica gel and eluted with 25% EtOAc-hexanes. The mixed fractions were concentrated onto 1 g of silica gel, and the resulting free-flowing powder was added to the top of a column of 15 g of silica gel and eluted with 10:40:50 EtOAc-hexanes-benzene. The fractions with $R_f = 0.17$ in the former eluent and 0.18 in the latter eluent were combined and concentrated to afford 0.091 g (65%) of ketone **263** as a viscous bright yellow oil with spectroscopic properties reported previously. The fractions with $R_f = 0.21$ in the former eluent and 0.39 in the latter eluent were combined and concentrated to afford 0.020 g (14%) of dimer **264** as a bright yellow solid: mp 133–135 °C; IR (film) 2955, 2928, 2858, 1640, 1607, 1572, 1371, 1189, 1176, 1149, 1103, 1088, 1038, 667, and 592 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J = 1.0 Hz, 1H), 7.92 (d, J = 1.0 Hz, 1H), 7.84 (s, 1H), 7.83 (app d, J = 8.9 Hz, 2H), 7.71 (s, 1H), 7.28 (d, J = 8.6 Hz, 2H), 2.87 (t, J = 7.7 Hz, 2H), 2.38 (s, 3H), 1.69 (app quint, J = 7.6 Hz, 2H), 1.37 (sext, J = 7.4 Hz, 2H), and 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.3, 146.0, 143.3, 138.9, 135.1, 134.3, 131.5, 130.5, 128.6, 127.8, 127.1, 126.9, 123.8, 118.7, 115.9, 36.7, 34.5, 22.3, 21.8, and 14.1; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{44}H_{40}N_2O_6S_2$, 779.2220; found 779.2212.

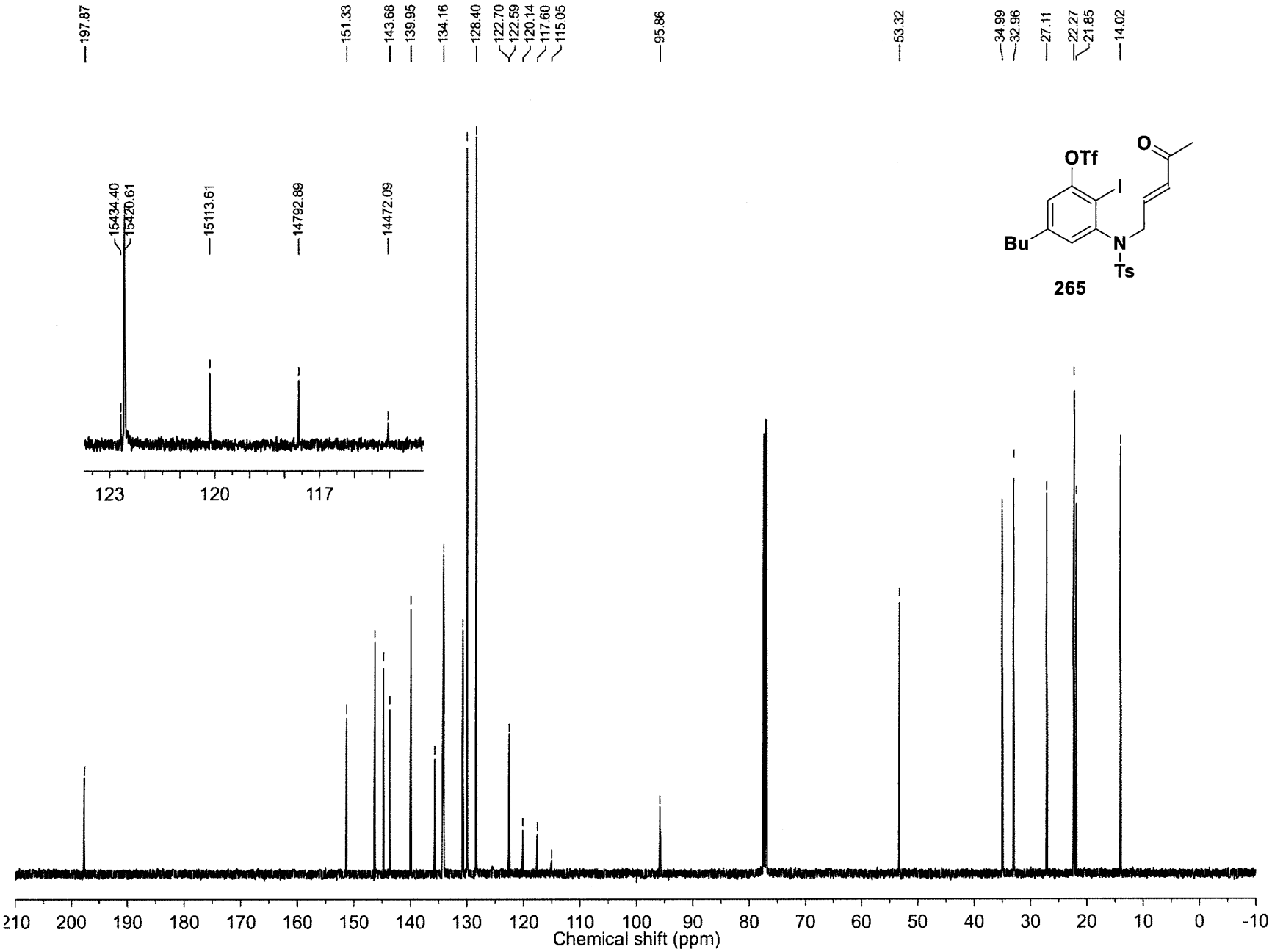

Bu
O
N
Ts
Ts
N
O
Bu
264
7.99
7.98
7.92
7.91
7.84
7.82
7.71
7.29
7.29
7.28
7.27
2.87
2.38
1.69
1.37
1.36
0.96
3996.82
3995.87
3961.38
3960.38
3922.43
3913.58
3649.67
3649.04
3641.04
3640.38
8.00
7.90
7.85
7.80
7.30
7.25
1444.51
1436.88
1429.23
851.11
849.70
845.35
843.48
841.16
837.11
835.91
828.25
694.77
687.31
679.76
672.38
485.27
477.93
470.54
2.9
1.7
1.4
1.0
0.98
0.97
3.05
0.96
2.03
2.00
3.19
2.11
2.27
3.22
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

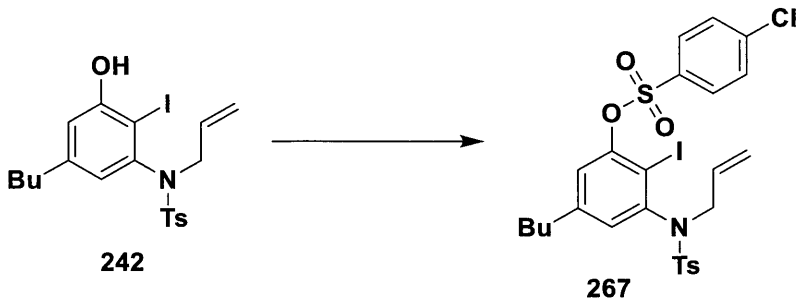

183.3
146.0
143.3
138.9
134.3
130.4
127.8
126.9
123.8
118.7
115.9
77.5
77.2
77.0
36.7
34.5
22.3
21.8
14.1
Bu
O
N
Ts
Ts
N
O
Bu
264
135.1
131.5
128.6
127.1
145
140
135
130
125
120
115
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



(*E*)-5-butyl-2-iodo-3-((*N*-(4-oxopent-2-en-1-yl)-*N*-tosylamido)phenyl trifluoromethanesulfonate (265). A 25-mL, round-bottomed flask equipped with a reflux condenser, rubber septum, and an argon inlet needle was charged with aniline **252** (0.344 g, 0.557 mmol, 1.0 equiv), 5.6 mL of CH_2Cl_2, methyl vinyl ketone (0.23 mL, 2.8 mmol, 5.0 equiv), and Hoveyda-Grubbs' II catalyst (0.017 g, 0.028 mmol, 0.05 equiv). The green reaction mixture was heated at reflux (40 °C) for 16 h and allowed to cool to rt. The resulting green solution was concentrated onto 1.5 g of silica gel. The resulting free-flowing powder was placed on top of a column of 45 g of silica gel and eluted with 20% EtOAc-hexanes to afford 0.298 g (81%) of ketone **265** as a pale brown-orange solid: mp 69–70 °C; IR (film) 2959, 2931, 2872, 1682, 1598, 1558, 1426, 1359, 1218, 1165, 1139, 1091, 975, 819, and 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.64 (app d, J = 8.3 Hz, 2H), 7.32 (app d, J = 8.6 Hz, 2H), 7.11 (d, J = 1.8 Hz, 1H), 6.85 (d, J = 1.9 Hz, 1H), 6.78 (dt, J = 16.0, 6.7 Hz, 1H), 5.94 (dt, J = 16.0, 1.3 Hz, 1H), 4.38 (ddd, J = 15.5, 6.4, 1.5 Hz, 1H), 4.22 (ddd, J = 15.5, 7.0, 1.3 Hz, 1H), 2.57 (t, J = 7.7 Hz, 2H), 2.46 (s, 3H), 2.21 (s, 3H), 1.52 (app quint, J = 7.6 Hz, 2H), 1.32 (sext, J = 7.4 Hz, 2H), and 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.9, 151.3, 146.3, 144.8, 143.7, 140.0, 135.7, 134.2, 130.8, 130.0, 128.4, 122.6, 118.9 (q, J = 320.7 Hz), 95.9, 53.3, 35.0, 33.0, 27.1, 22.3, 21.8, and 14.0; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{25}F_3INO_6S_2$, 660.0193; found 660.0196.

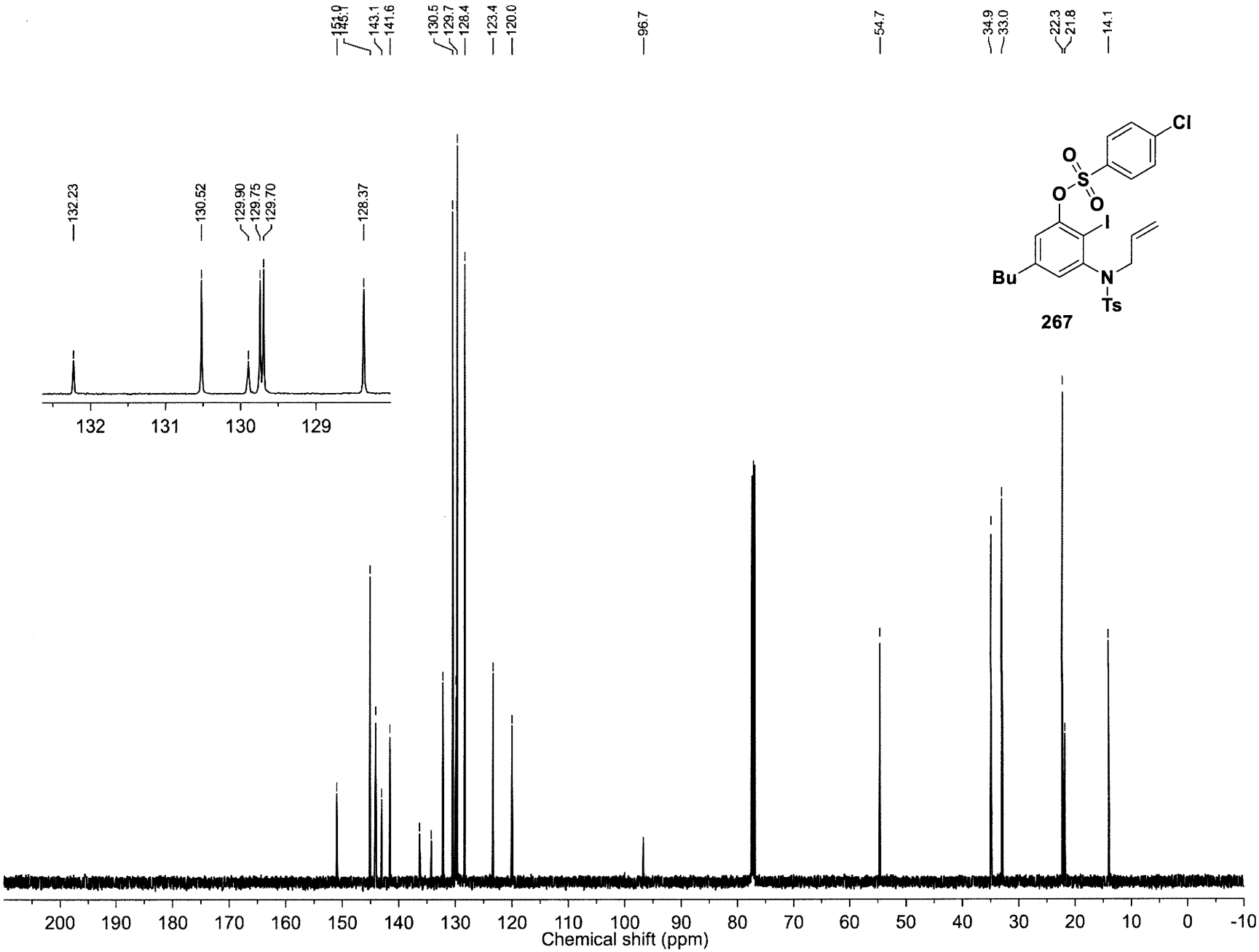

OTf
I
Bu
N
Ts
O
265
Chemical shift (ppm)

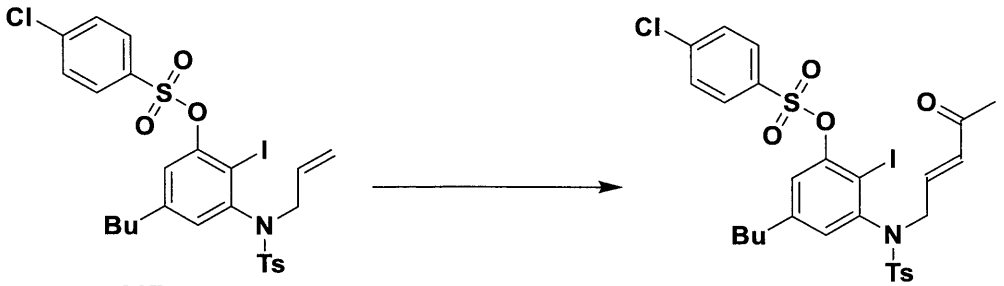

197.87
151.33
143.68
139.95
134.16
128.40
122.70
122.59
120.14
117.60
115.05
95.86
53.32
34.99
32.96
27.11
22.27
21.85
14.02
15434.40
15420.61
15113.61
14792.89
14472.09
123
120
117
OTf
I
O
Bu
N
Ts
265
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical shift (ppm)



3-(*N*-Allyl-*N*-(*p*-toluenesulfonyl)amino)-5-butyl-2-iodophenyl 4-chlorophenylsulfonate (267). A 50-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with phenol **242** (0.319 g, 0.657 mmol, 1.0 equiv), 6.6 mL of CH_2Cl_2, and Et_3N (0.14 mL, 0.99 mmol, 1.5 equiv). 4-Chlorophenylsulfonyl chloride (0.166 g, 0.788 mmol, 1.2 equiv) was added in one portion and the reaction mixture was stirred at rt for 2.5 h. The resulting yellow solution was diluted with 20 mL of CH_2Cl_2 and 30 mL of 1 M aq HCl solution. The aqueous phase was separated and extracted with two 10-mL portions of CH_2Cl_2, and the combined organic phases were washed with 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.614 g of a yellow oil. Column chromatography on 50 g of silica gel (elution with 10% EtOAc-hexanes) afforded 0.380 g (87%) of sulfonate **267** as a pale yellow crystalline solid: mp 126-128 °C; IR (film) 3091, 2957, 2930, 2861, 1643, 1588, 1562, 1476, 1444, 1412, 1383, 1356, 1190, 1163, 1090, 1024, 1015, 989, 931, 815, 796, 773, 746, 720, and 665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 (app d, J = 8.6 Hz, 2H), 7.62 (d, J = 8.2 Hz, 2H), 7.51 (app d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 7.23 (d, J = 1.8 Hz, 1H), 6.64 (d, J = 2.0 Hz, 1H), 5.76 (ddt, J = 17.1, 10.1, 6.9 Hz, 1H), 5.00 (dd, J = 10.1, 1.0 Hz, 1H), 4.91 (dd, J = 17.1, 1.2 Hz, 1H), 4.09 (dd, J = 14.5, 6.7 Hz, 1H), 4.01 (dd, J = 14.5, 7.0 Hz, 1H), 2.53 (t, J = 7.7 Hz, 2H), 2.45 (s, 3H), 1.50 (quint, J = 7.6 Hz, 2H), 1.30 (sext, J = 7.4 Hz, 2H), and 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.0, 145.1, 144.1, 143.1, 141.6, 136.4, 134.3, 132.2, 130.5, 129.9, 129.75, 129.70, 128.4, 123.4, 120.0, 96.7, 54.7, 34.9, 33.0, 22.3, 21.8, and 14.1; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{27}ClINO_5S_2$, 660.0137; found 660.0140.

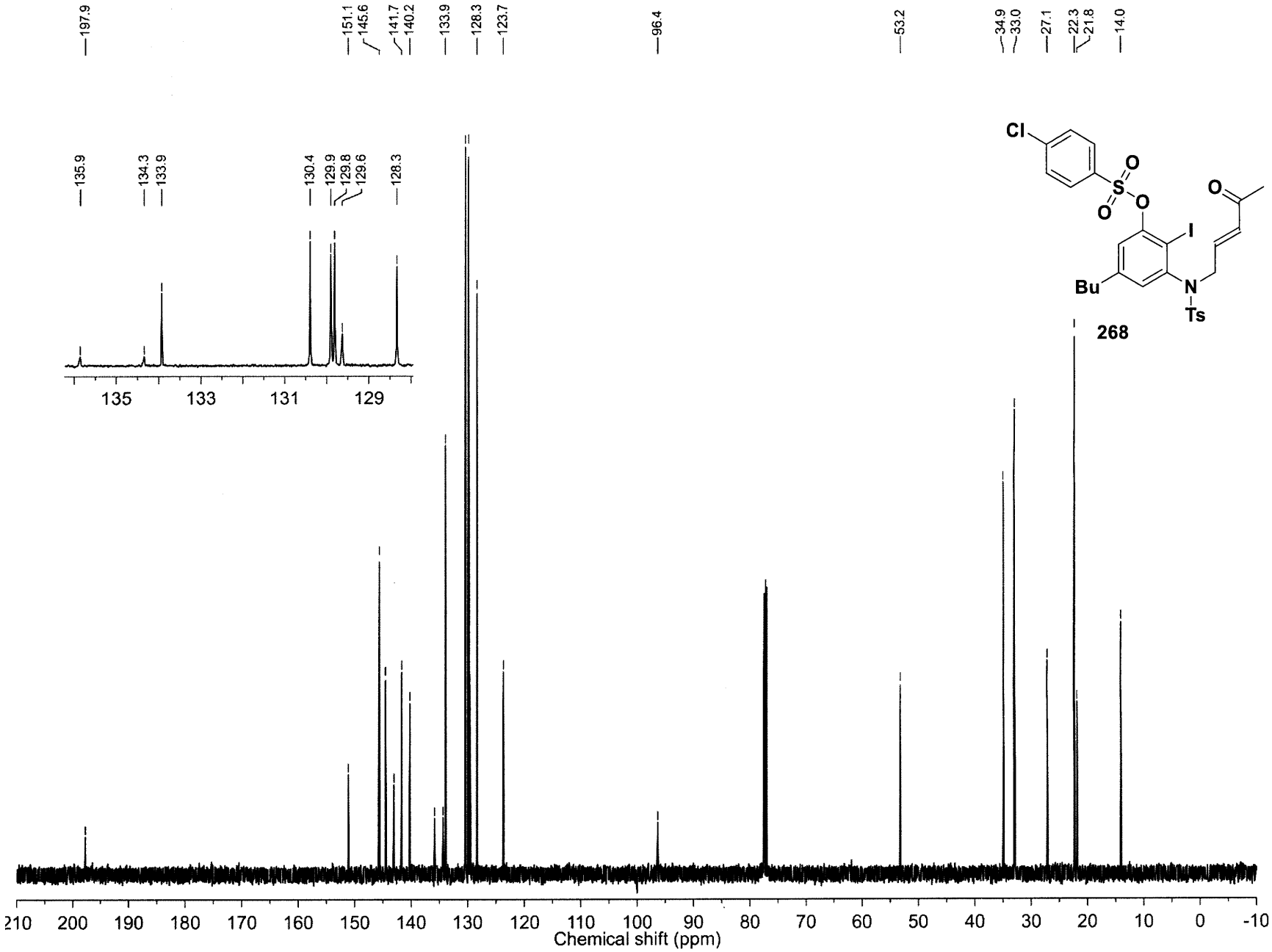
7.83
7.81
7.50
7.30
7.23
7.22
6.64
6.64
5.77
5.76
5.02
4.99
4.93
4.92
4.89
4.89
4.11
4.10
4.08
4.07
4.04
4.02
4.01
3.99
2.53
2.45
1.50
1.31
1.30
0.93
3916.39
3907.76
3813.86
3805.57
3761.39
3752.73
3652.84
3644.84
3615.99
3614.11
3322.44
3320.55
2896.75
2886.66
2879.75
2876.54
2872.85
2869.66
2498.81
2497.82
2464.03
2462.77
2446.99
2445.74
2049.55
2041.80
2035.08
2019.07
2012.05
2004.60
1997.57
1272.72
1265.09
1257.34
766.02
758.71
750.91
743.33
735.60
670.21
662.81
655.44
648.04
640.41
632.99
474.14
466.79
459.45
7.8
7.6
7.5
7.3
7.2
5.8
5.7
5.0
4.9
4.1
4.0
2.5
1.5
1.4
1.3
0.9
1.87
1.93
1.90
2.00
0.97
0.97
0.93
1.00
0.99
1.00
1.02
2.00
3.06
1.98
2.16
2.93
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
Chemical shift (ppm)
Cl
O
S
O
O
O
I
Bu
N
Ts
267

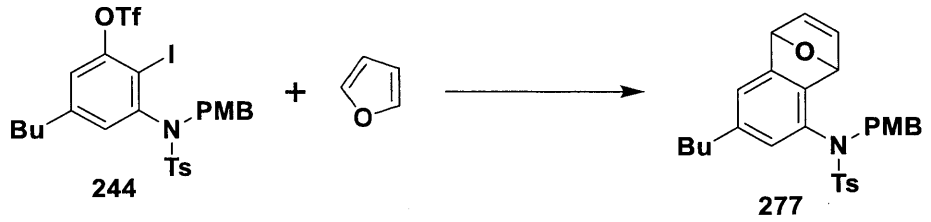

151.0
145.1
143.1
141.6
130.5
129.7
128.4
123.4
120.0
96.7
54.7
34.9
33.0
22.3
21.8
14.1
132.23
130.52
129.90
129.75
129.70
128.37
132
131
130
129
Cl
O
S
O
O
I
Bu
N
Ts
267
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical shift (ppm)



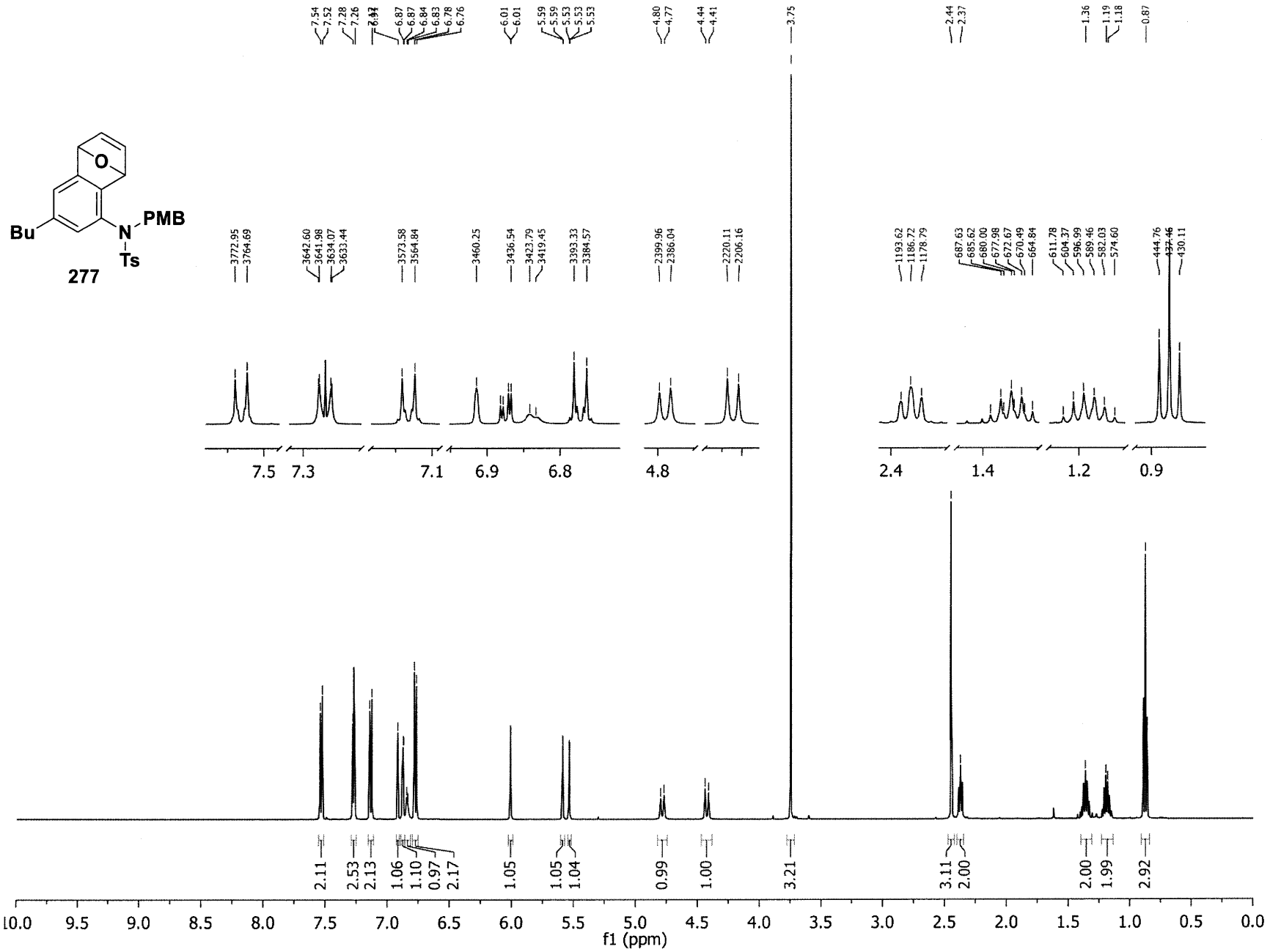
(*E*)-5-butyl-2-iodo-3-((*N*-(4-oxopent-2-en-1-yl)-*N*-tosylamido)phenyl 4-chlorophenylsulfonate (268). A 50-mL, round-bottomed flask equipped with a reflux condenser, rubber septum, and an argon inlet needle was charged with aniline **267** (0.379 g, 0.574 mmol, 1.0 equiv), 5.7 mL of CH_2Cl_2, methyl vinyl ketone (0.24 mL, 2.9 mmol, 5.0 equiv), and Hoveyda-Grubbs' II catalyst (0.018 g, 0.029 mmol, 0.05 equiv). The green reaction mixture was heated at reflux (40 °C) for 22 h and allowed to cool to rt. The resulting green solution was concentrated onto 2 g of silica gel. The resulting free-flowing powder was placed on top of a column of 50 g of silica gel and eluted with 22% EtOAc-hexanes. The mixed fractions were combined and subjected to another column of 120 g of silica gel and eluted with a gradient of 18-22% EtOAc-hexanes. The fractions containing pure ketone **268** (R_f = 0.09 for **268**; 0.16 for the unidentified byproduct in 20% EtOAc-hexanes) from the two columns were combined to afford 0.336 g (83%) of ketone **268** as a viscous pale brown oil: IR (film) 3093, 2957, 2930, 2862, 1701, 1680, 1634, 1588, 1562, 1476, 1441, 1413, 1398, 1383, 1359, 1253, 1190, 1164, 1090, 1015, 978, 929, 815, 768, 742, and 719 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (app d, J = 8.7 Hz, 2H), 7.60 (app d, J = 8.2 Hz, 2H), 7.54 (app d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.6 Hz, 2H), 7.16 (d, J = 1.8 Hz, 1H), 6.72 (dt, J = 16.0, 6.7 Hz, 1H), 6.69 (d, J = 2.0 Hz, 1H), 5.88 (dt, J = 16.0, 1.2 Hz, 1H), 4.29 (ddd, J = 15.5, 6.4, 1.5 Hz, 1H), 4.12 (ddd, J = 15.4, 7.0, 1.2 Hz, 1H), 2.52 (t, J = 7.7 Hz, 2H), 2.45 (s, 3H), 2.19 (s, 3H), 1.48 (app quint, J = 7.6 Hz, 2H), 1.29 (sext, J = 7.4 Hz, 2H), and 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.9, 151.1, 145.6, 144.6, 143.0, 141.7, 140.2, 135.9, 134.3, 133.9, 130.4, 129.9, 129.8, 129.6, 128.3, 123.7, 96.4, 53.2, 34.8, 33.0, 27.1, 22.3, 21.8, and 14.0; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{28}H_{29}ClINO_6S_2$, 724.0062; found 724.0084.

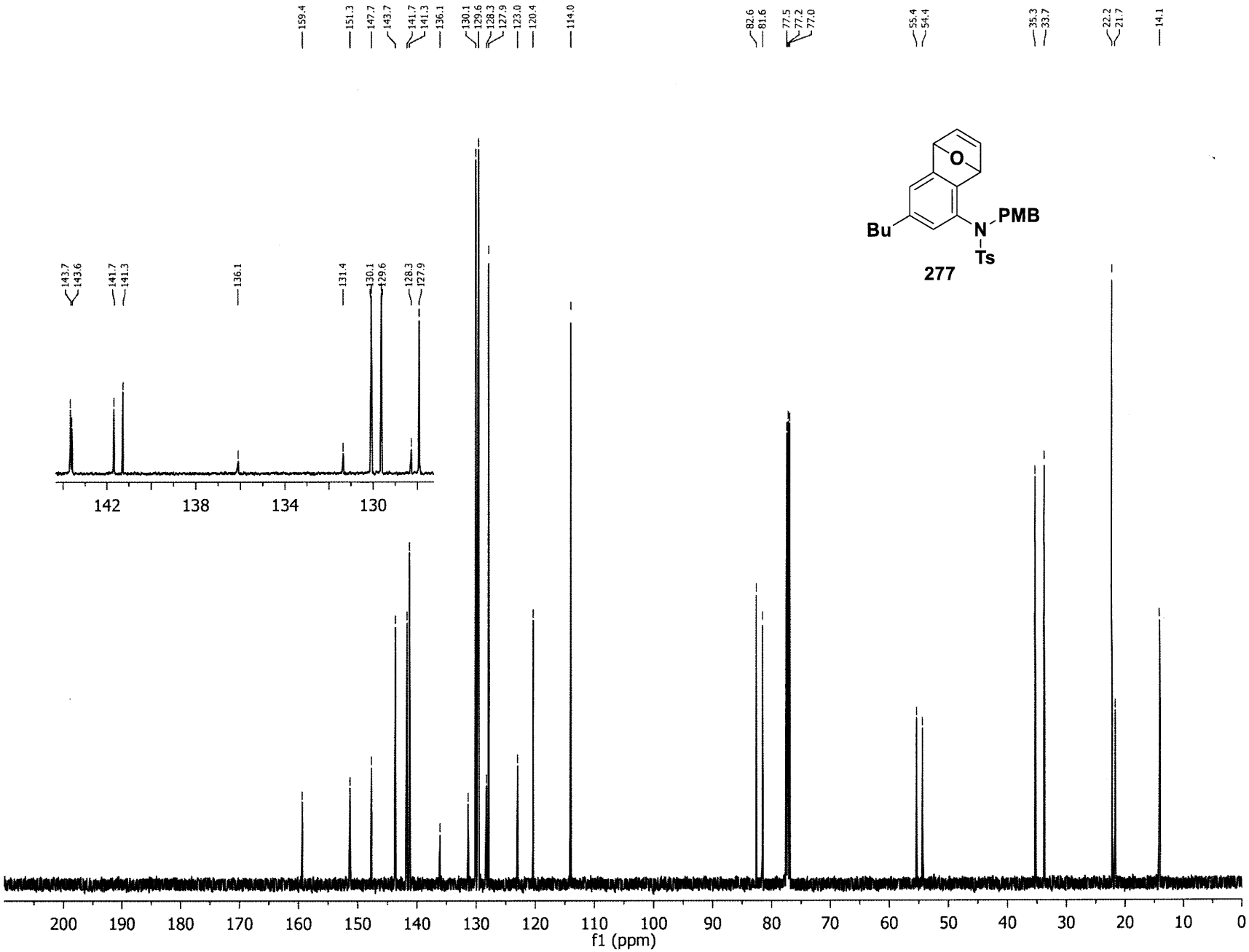
7.84
7.82
7.53
7.31
7.16
7.15
6.69
5.90
5.87
4.28
4.28
4.27
4.27
4.15
4.15
4.13
4.13
2.52
2.45
2.19
1.48
1.30
1.28
0.92
3920.87
3912.05
3804.72
3796.43
3773.65
3764.83
3656.64
3648.71
3648.14
3580.09
3578.18
3370.97
3364.33
3361.68
3354.93
3348.14
3346.19
2950.45
2934.39
2141.78
2140.35
2135.37
2133.95
2075.09
2073.90
2068.10
2066.90
1259.22
738.92
648.22
640.63
460.76
Cl
O
S
O
O
O
I
Bu
N
Ts
268
1.85
1.91
1.91
2.00
0.95
1.99
0.93
0.99
1.01
2.01
3.06
3.00
2.03
2.25
2.97
Chemical shift (ppm)

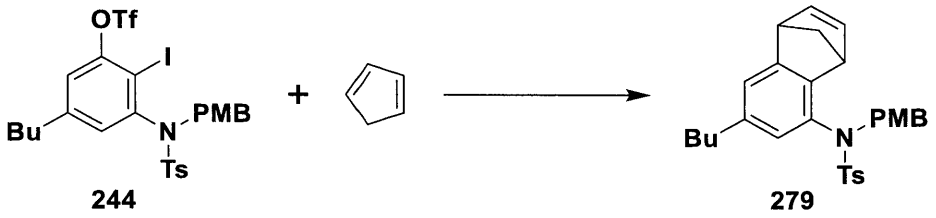

197.9
151.1
145.6
141.7
140.2
133.9
128.3
123.7
96.4
53.2
34.9
33.0
27.1
22.3
21.8
14.0
135.9
134.3
133.9
130.4
129.9
129.8
129.6
128.3
135
133
131
129
Cl
O
S
O
O
O
I
Bu
N
Ts
268
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical shift (ppm)



7-Butyl-*N*-(4-methoxybenzyl)-*N*-(*p*-toluenesulfonyl)-1,4-dihydro-1,4-epoxynaphthalen-5-amine (277). A 10-mL pear flask equipped with a rubber septum and argon inlet needle was charged with triflate **244** (0.086 g, 0.123 mmol, 1.0 equiv) and 2.5 mL of Et_2O. The slightly yellow solution was cooled at -95 °C in an acetone-liquid nitrogen bath and furan (0.018 mL, 0.25 mmol, 2.0 equiv) was added. A solution of *n*-BuLi (2.64 M in hexane, 0.051 mL, 0.13 mmol, 1.1 equiv) was added dropwise via syringe over 1 min and the reaction mixture was allowed to warm to rt over 4 h. The resulting yellow suspension was diluted with 10 mL of Et_2O and 10 mL of satd aq NH_4Cl solution. The aqueous phase was separated and extracted with two 5-mL portions of Et_2O, and the combined organic phases were washed with 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.090 g of a yellow oil. This material was dissolved in ca. 3 mL of CH_2Cl_2 and concentrated onto 1 g of silica gel. The resulting free-flowing powder was added to the top of a column of 10 g of silica gel and eluted with 20% EtOAc-hexanes to afford 0.059 g (99%) of cycloadduct **277** as a colorless oil: IR (film) 3011, 2956, 2930, 2859, 1612, 1514, 1460, 1347, 1248, 1162, 1091, 1034, 850, and 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 (app d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H), 7.13 (app d, J = 8.8 Hz, 2H), 6.92 (br s, 1H), 6.87 (dd, J =5.5, 1.8 Hz, 1H), 6.84 (app d, J = 4.3 Hz, 1H), 6.77 (app d, J = 8.8 Hz, 2H), 6.01 (d, J = 0.9 Hz, 1H), 5.59 (dd, J = 1.8, 0.9 Hz, 1H), 5.53–5.54 (m, 1H), 4.78 (d, J = 13.9 Hz, 1H), 4.42 (d, J = 13.9 Hz, 1H), 3.75 (s, 3H), 2.45 (s, 3H), 2.37 (t, J = 7.4 Hz, 2H), 1.36 (app quint, J = 7.6 Hz, 2H), 1.19 (sext, J = 7.4 Hz, 2H), and 0.87 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 151.3, 147.7, 143.7, 143.6, 141.7, 141.3, 136.1, 131.4, 130.1, 129.6, 128.3, 127.9, 123.0, 120.4, 114.0, 82.6, 81.6, 55.4, 54.4, 35.3, 33.7, 22.2, 21.7, and 14.1; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{29}H_{31}NO_4S$, 512.1866; found 512.1880.

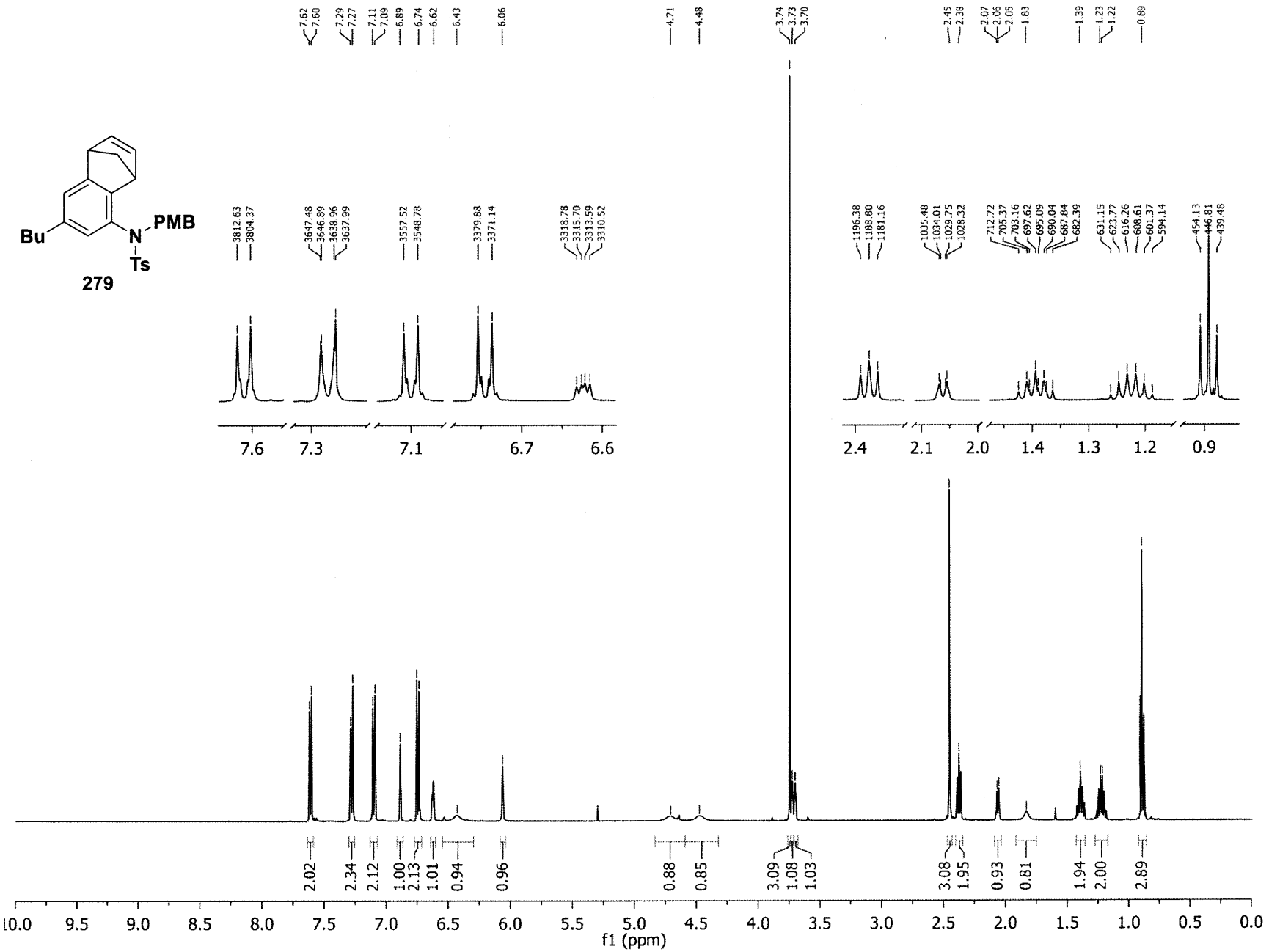

Bu
PMB
N
Ts
277
f1 (ppm)

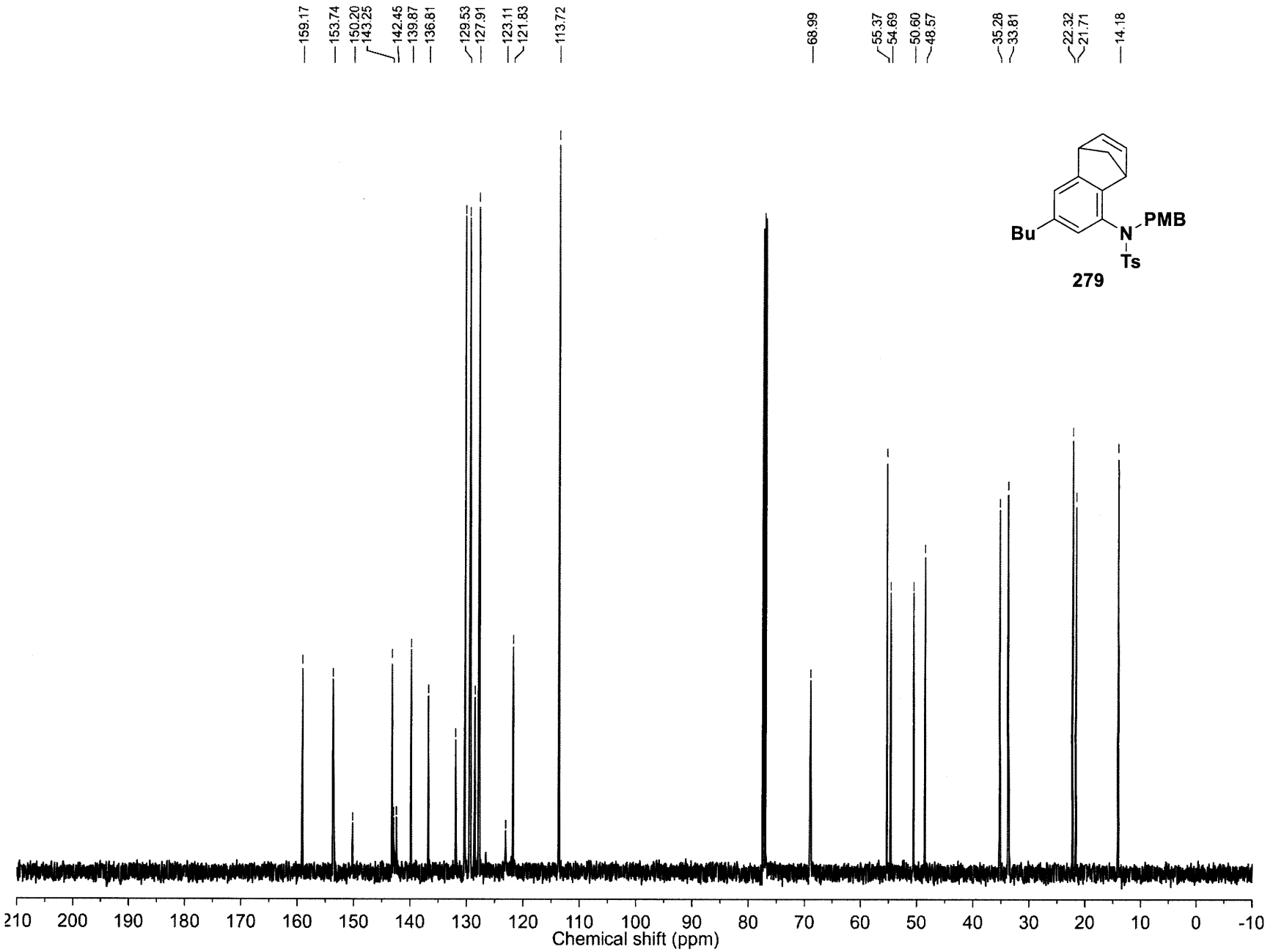

159.4
151.3
147.7
143.7
141.7
141.3
136.1
130.1
129.6
128.3
127.9
123.0
120.4
114.0
82.6
81.6
77.5
77.2
77.0
55.4
54.4
35.3
33.7
22.2
21.7
14.1
143.7
143.6
141.7
141.3
136.1
131.4
130.1
129.6
128.3
127.9
142
138
134
130
Bu
N
PMB
Ts
277
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



7-Butyl-*N*-(4-methoxybenzyl)-*N*-(*p*-toluenesulfonyl)-1,4-dihydro-1,4-methanonaphthalen-5-amine (279). A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with triflate **244** (0.293 g, 0.419 mmol, 1.0 equiv), 8.4 mL of toluene, and freshly prepared cyclopentadiene[157] (0.34 mL, 0.28 g, 4.2 mmol, 10 equiv). The colorless solution was cooled at -78 °C and a solution of *n*-BuLi (2.64 M in hexane, 0.19 mL, 0.50 mmol, 1.2 equiv) was added dropwise via syringe over 3 min. The resulting pale yellow solution was allowed to warm to rt over 15 h. The reaction mixture was diluted with 15 mL of Et_2O and 20 mL of satd aq NH_4Cl solution. The aqueous phase was separated and extracted with two 10-mL portions of Et_2O, and the combined organic phases were washed with 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.318 g of a viscous yellow oil. This material was dissolved in ca. 5 mL of CH_2Cl_2 and concentrated onto 2 g of silica gel. The resulting free-flowing powder was added to the top of a column of 75 g of silica gel and eluted with 8% EtOAc-hexanes to afford 0.186 g (91%) of cycloadduct **279** as a viscous colorless oil: IR (film) 2957, 2932, 2859, 1613, 1597, 1514, 1461, 1348, 1303, 1248, 1162, 1092, 1035, 815, and 664 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.10 (app d, J = 8.6 Hz, 2H), 6.89 (s, 1H), 6.75 (app d, J =8.7 Hz, 2H), 6.63 (dd, J = 5.1, 3.2 Hz, 1H), 6.43 (br s, 1H), 6.07 (s, 1H), 4.71 (br s, 1H), 4.48 (br s, 1H), 3.74 (s, 3H), 3.73 (br s, 1H), 3.71 (br s, 1H), 2.45 (s, 3H), 2.38 (t, J = 7.7 Hz, 2H), 2.07 (d, J = 7.2 Hz, 1H), 1.83 (br s, 1H), 1.40 (app quint, J = 7.6 Hz, 2H), 1.23 (sext, J = 7.4 Hz, 2H), and 0.90 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 153.7, 150.2, 143.3, 143.0, 142.5, 139.9, 136.8, 132.0, 130.3, 129.5, 128.6, 127.9, 123.1, 121.8, 113.7, 69.0, 55.4, 54.7, 50.6, 48.6, 35.3, 33.8, 22.3, 21.7, and 14.2; HRMS (ESI) (*m/z*) $[M+Na]^+$ calcd for $C_{30}H_{33}NO_3S$, 510.2073; found 510.2085.

[157] Prepared by thermal cracking of dicyclopentadiene at 180 °C and distillation through a 10-cm Vigreux column.


Bu
N
PMB
Ts
279
f1 (ppm)

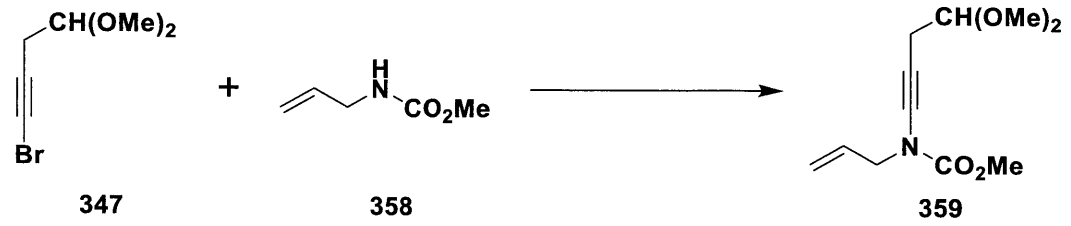

159.17
153.74
150.20
143.25
142.45
139.87
136.81
129.53
127.91
123.11
121.83
113.72
68.99
55.37
54.69
50.60
48.57
35.28
33.81
22.32
21.71
14.18
Bu
N
PMB
Ts
279
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical shift (ppm)

343 324

2-Diazoacetylthiophene (324). A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, a 50-mL pressure-equalizing addition funnel fitted with a rubber septum, and a rubber septum fitted with a thermocouple temperature probe was charged with 1,1,1,3,3,3-hexamethyldisilazane (5.9 mL, 4.54 g, 28.1 mmol, 1.2 equiv) and 35 mL of THF. The colorless solution was cooled at 0 °C while *n*-BuLi (2.60 M in hexane, 9.9 mL, 25.7 mmol, 1.1 equiv) was added dropwise via the addition funnel over 10 min (2 x 2-mL THF wash). After 10 min, the resulting solution was cooled at -78 °C while a solution of 2-acetylthiophene **343** (2.53 mL, 2.96 g, 23.4 mmol, 1.0 equiv) in 35 mL of THF was added dropwise via the addition funnel over 35 min (2 x 2 mL THF wash). After stirring for 45 min at -78 °C, 2,2,2-trifluoroethyl trifluoroacetate (3.77 mL, 5.52 g, 28.2 mmol, 1.2 equiv) was added rapidly in one portion by syringe over ca. 5 sec. After 10 min, the reaction mixture was diluted with 100 mL of 1 M aq HCl solution and 60 mL of Et_2O. The aqueous phase was extracted with two 35-mL portions of Et_2O, and the combined organic phases were washed with 100 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give an orange oil which was immediately dissolved in 35 mL of CH_3CN and transferred via cannula to a 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, a 20-mL pressure-equalizing addition funnel, and a rubber septum (3 x 2 mL CH_3CN wash). Water (0.42 mL, 0.42 g, 23.3 mmol, 1.0 equiv) and Et_3N (4.9 mL, 3.56 g, 35.2 mmol, 1.5 equiv) were added, and a solution of methanesulfonyl azide (4.26 g, 35.2 mmol, 1.5 equiv) in 10 mL of CH_3CN was added dropwise via the addition funnel over 30 min (1 mL CH_3CN wash). The resulting solution was stirred at room temperature for 3 h and then diluted with 100 mL of Et_2O and washed with three 50-mL portions of 10% aq NaOH solution and 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 3.0 g of a dark yellow oil. Column chromatography on 150 g of silica gel (elution with 25% EtOAc-hexanes) furnished 2.75 g (75%) of diazo ketone **324** as a yellow solid with spectral data consistent with that previously reported:[158] mp 67–68 °C (lit. mp 67 °C)[159]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, J = 6.0, 1.2 Hz, 1H), 7.53 (dd, J = 6.0, 1.2 Hz,

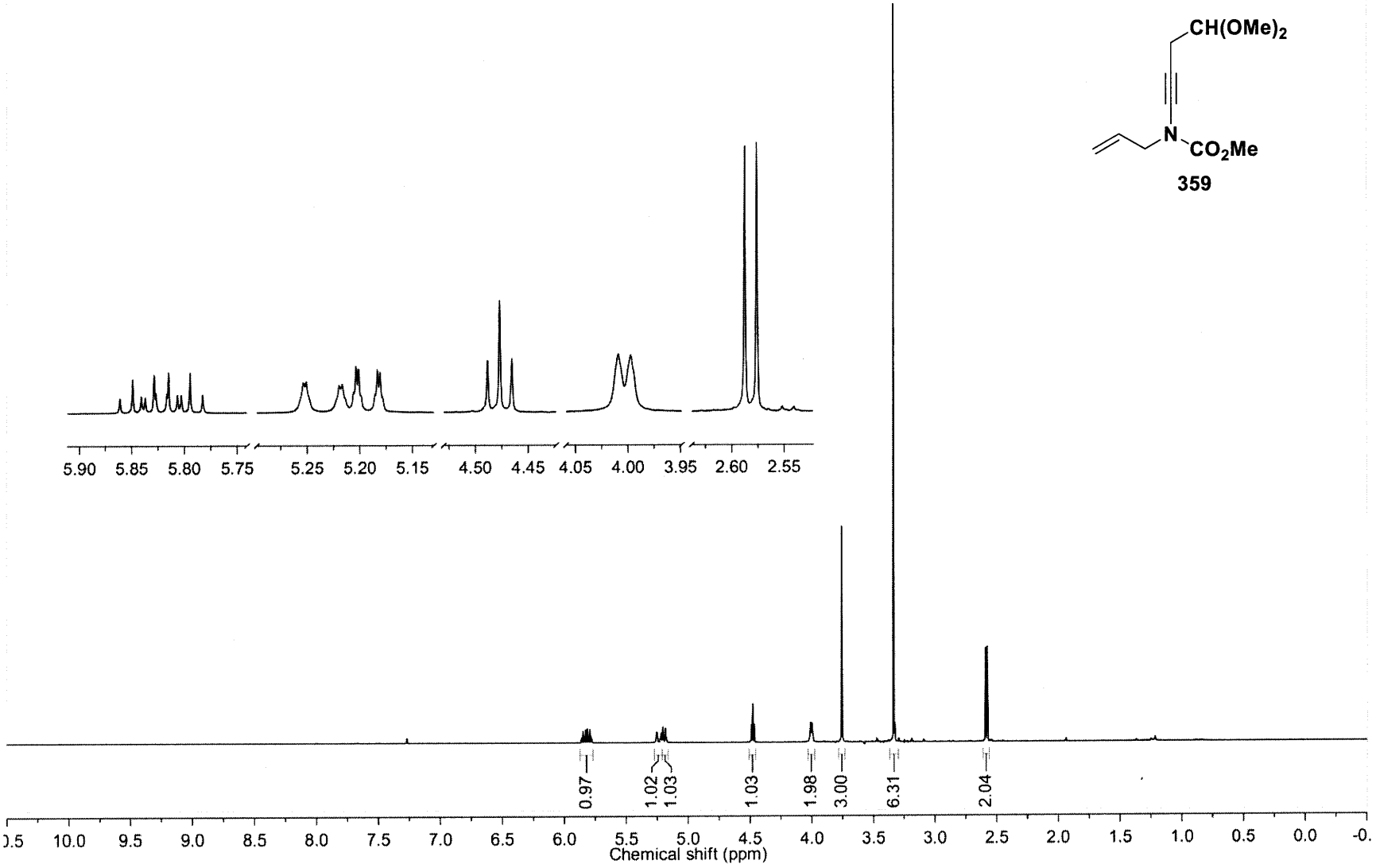
[158] Fu, N.; Allen, A. D.; Chan, W.; Kobayashi, S.; Tidwell, T. T.; Tahmassebi, D.; Aguilar, A.; Cabrera, E. P.; Godoy, J. *Can. J. Chem.* **2008**, *86*, 333–341.
[159] Ihmels, H.; Maggini, M.; Prato, M.; Scorrano, G. *Tetrahedron Lett.* **1991**, *32*, 6215–6218.

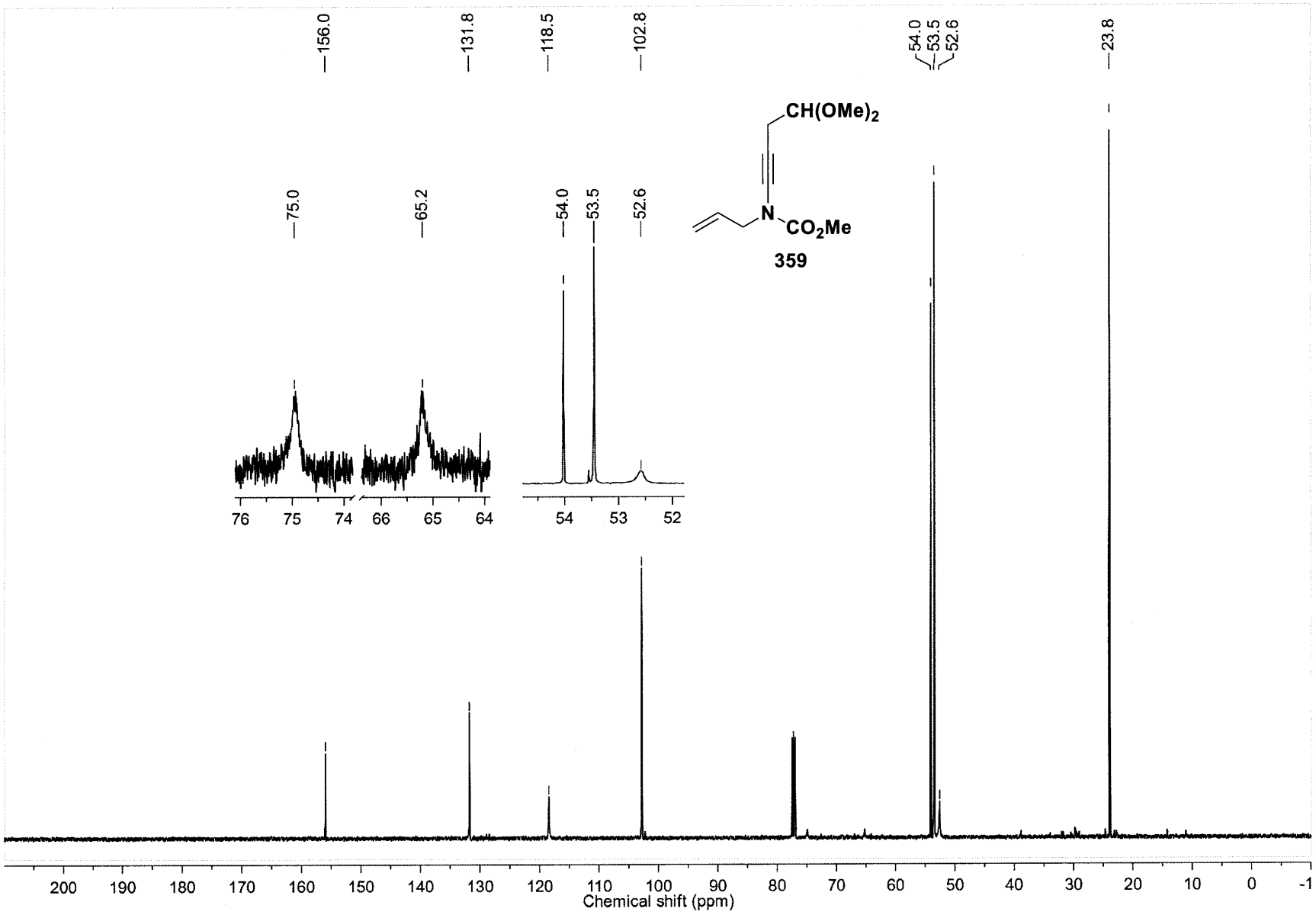
1H), 7.12–7.15 (m, 1H), and 5.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0, 142.7, 132.4, 129.2, 128.2, and 54.5.

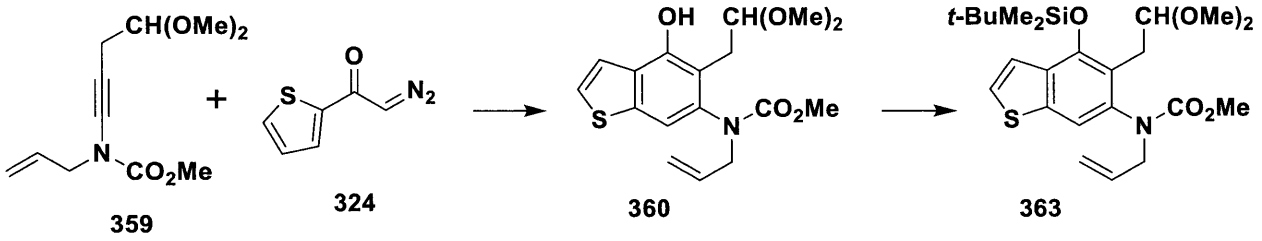


***N*-Allyl-*N*-(methoxycarbonyl)-4,4-dimethoxybut-1-yn-1-ylamine (359).** A 50-mL, round-bottomed flask equipped with a reflux condenser fitted with a rubber septum and argon inlet needle was charged with carbamate **358**[160] (1.15 g, 10.0 mmol, 1.0 equiv), bromoalkyne **347**[125] (2.13 g, 11.0 mmol, 1.1 equiv), $CuSO_4 \cdot 5H_2O$ (0.500 g, 2.00 mmol, 0.2 equiv), 1,10-phenanthroline (0.722 g, 4.01 mmol, 0.4 equiv), K_3PO_4 (4.25 g, 20.0 mmol, 2.0 equiv), and 20 mL of toluene. The green-brown reaction mixture was degassed by evacuation under vacuum briefly and backfilled with argon three times and heated at 75-80 °C with vigorous stirring for 65 h. The resulting brown suspension was allowed to cool to rt, filtered through Celite with the aid of 50 mL of EtOAc, and concentrated to afford 1.95 g of an orange oil. Column chromatography on 250 g of silica gel (elution with 45:40:1 hexanes-benzene-EtOAc) afforded pure ynamide **359** (R_f = 0.30 in 45:40:1 hexanes-benzene-EtOAc) and mixed fractions containing ynamide **359** and the alkyne dimer (R_f = 0.35 in 45:40:1 hexanes-benzene-EtOAc). The mixed fractions were combined and chromatographed on 250 g of silica gel (elution with 45:40:1 hexanes-benzene-EtOAc). The fractions containing pure ynamide **359** from the two columns were combined and concentrated to afford 1.26 g (55%) of ynamide **359** as a yellow oil: IR (film) 3084, 2955, 2833, 2267, 1732, 1646, 1527, 1447, 1194, and 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.82 (ddt, J = 17.1, 10.2, 6.0 Hz, 1H), 5.23 (dd, J = 17.2, 1.4 Hz, 1H), 5.19 (dd, J = 10.3, 1.2 Hz, 1H), 4.48 (t, J = 5.7 Hz, 1H), 4.00 (d, J = 6.0 Hz, 2H), 3.76 (s, 3H), 3.33 (s, 6H), and 2.58 (d, J = 5.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 131.8, 118.5, 102.8, 75.0, 65.2, 54.0, 53.5, 52.6, and 23.8; HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{11}H_{17}NO_4$, 228.1230; found 228.1230.

[160] Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628–4641.


CH(OMe)2
N
CO2Me
359
5.90 5.85 5.80 5.75 5.25 5.20 5.15 4.50 4.45 4.05 4.00 3.95 2.60 2.55
0.97 1.02 1.03 1.03 1.98 3.00 6.31 2.04
Chemical shift (ppm)

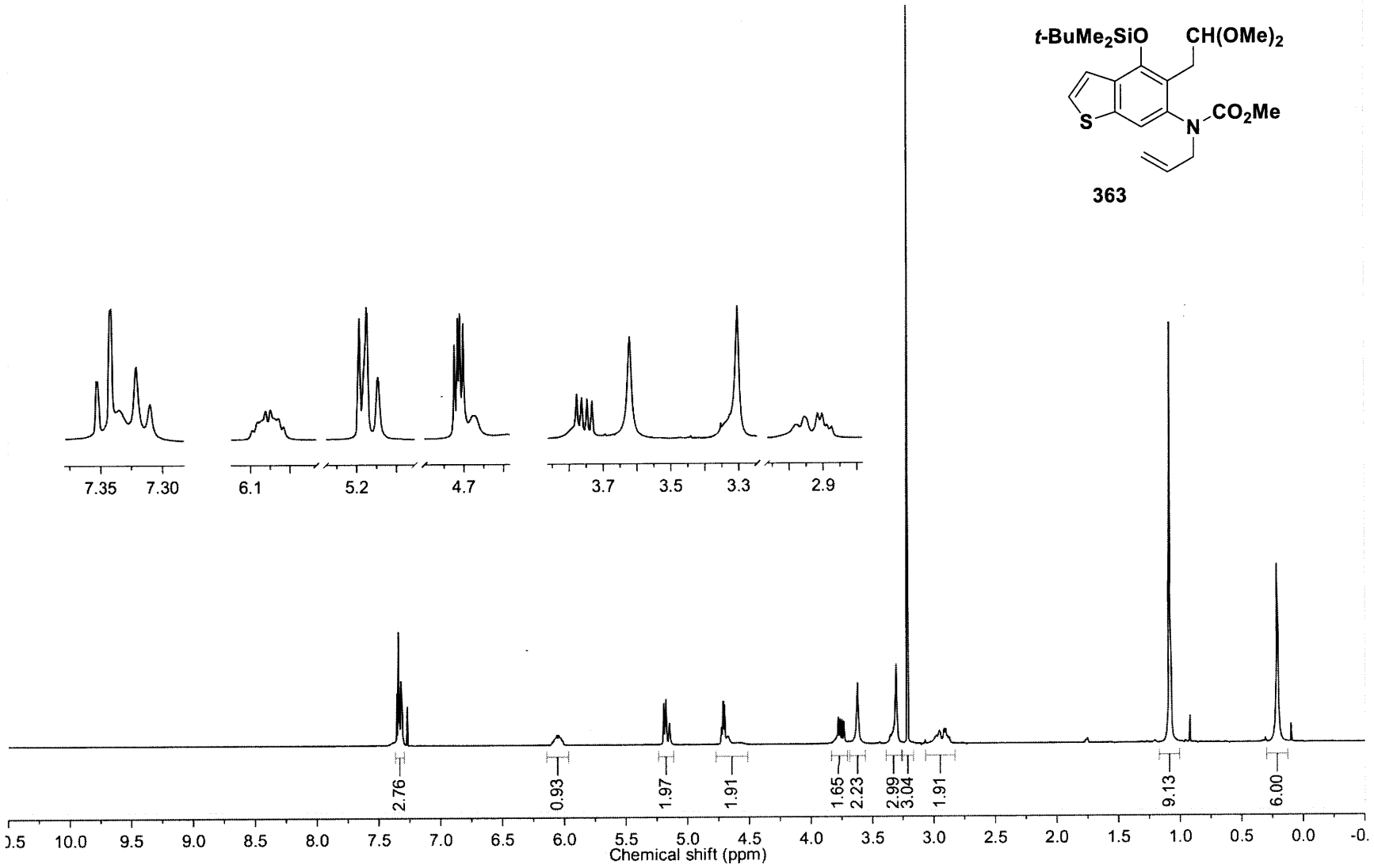

156.0
131.8
118.5
102.8
54.0
53.5
52.6
23.8
75.0
65.2
54.0
53.5
52.6
CH(OMe)2
N
CO2Me
359
76
75
74
66
65
64
54
53
52
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
Chemical shift (ppm)

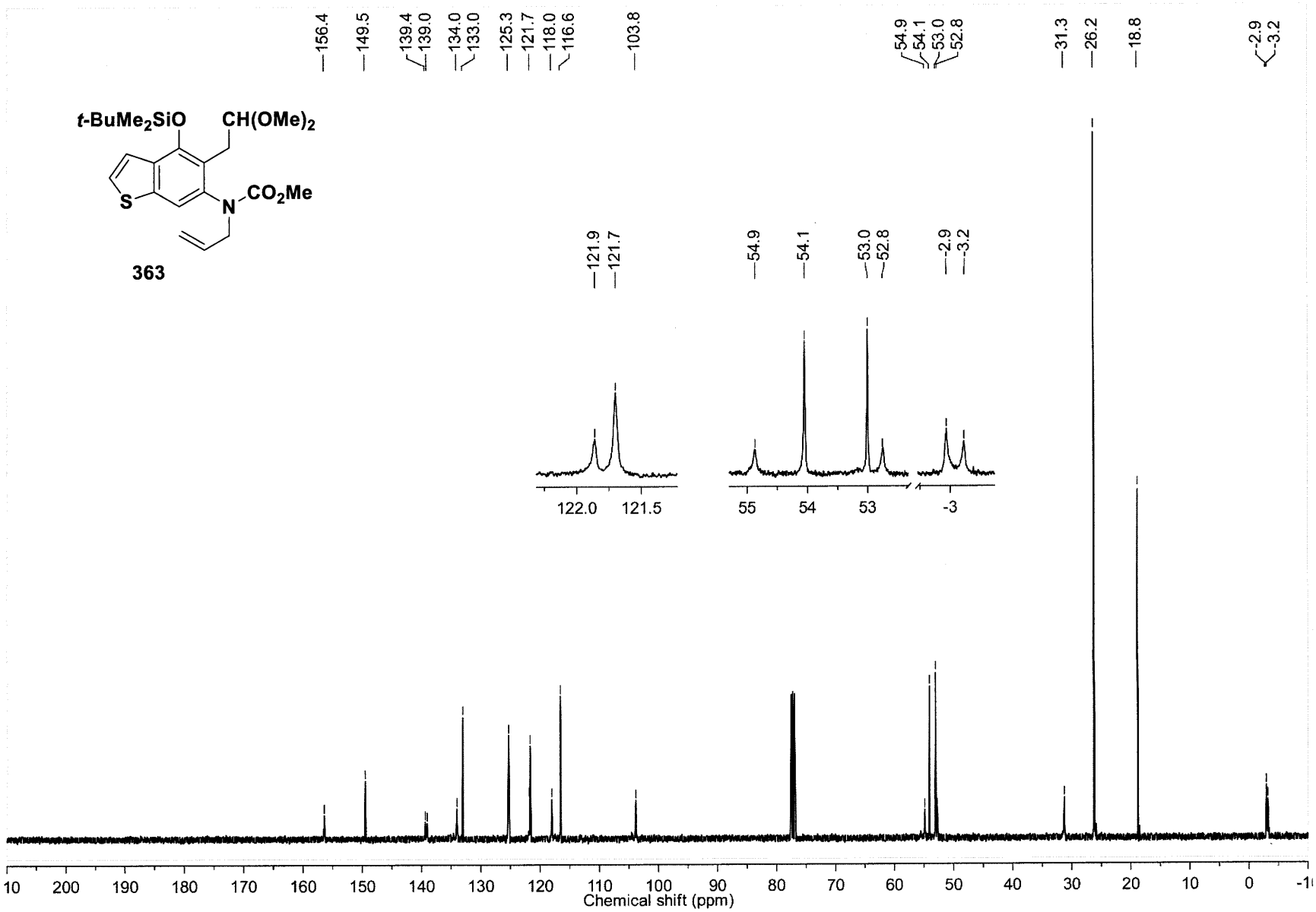


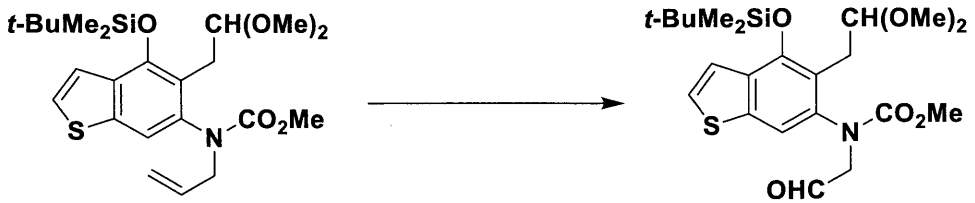
***N*-Allyl-*N*-(methoxycarbonyl)-4-((*tert*-butyldimethylsilyl)oxy)-5-(2,2-dimethoxyethyl)benzo[*b*]thiophen-6-amine (363).** A base-washed 20-cm quartz tube (12 mm i.d., 15 mm o.d.) equipped with a stir bar, rubber septum, and argon inlet needle was charged with diazo ketone **324** (0.460 g, 3.02 mmol, 1.2 equiv), ynamide **359** (0.572 g, 2.52 mmol, 1.0 equiv), and 8.4 mL of CH_2Cl_2. The yellow reaction mixture was degassed by bubbling argon for 10 min. The tube was positioned ca. 20 cm from a Hanovia 450W lamp (quartz immersion well, cooled by recirculating tap water) and irradiated with stirring under argon at 25 °C for 17 h. Buildup of colored polymers was observed so the tube was rotated 180° to allow efficient irradiation. After an additional 24 h of irradiation the resulting orange solution was transferred to a 100-mL, round-bottomed flask via cannula (3 x 1 mL CH_2Cl_2 wash) and concentrated to afford a dark orange oil. This material was dissolved in 25 mL of toluene, the flask was equipped with a stir bar and reflux condenser fitted with an argon inlet adapter, and the reaction mixture was heated at reflux for 23 h. The resulting mixture was concentrated to afford 0.89 g of a dark red oil. Column chromatography on 60 g of silica gel (elution with 69:30:1 hexanes-EtOAc-Et_3N) furnished 0.564 g of crude benzannulation product **360** (ca. 90-95% pure) as a viscous red oil.

A 50-mL pear flask equipped with a rubber septum and argon inlet needle was charged with the crude benzannulation product **360** (0.564 g, 1.0 equiv), 6 mL of CH_2Cl_2, Et_3N (0.58 mL, 0.42 g, 4.17 mmol, 2.6 equiv), 4-DMAP (0.039 g, 0.32 mmol, 0.2 equiv), and *t*-$BuMe_2SiCl$ (0.338 g, 2.25 mmol, 1.4 equiv). The red reaction mixture was stirred at rt for 16.5 h, 1 mL of MeOH was added, and the mixture was stirred for an additional 10 min. The resulting solution was diluted with 20 mL of CH_2Cl_2 and washed with three 10-mL portions of water. The combined aqueous phases (pH = 8–9) were extracted with three 5-mL portions of CH_2Cl_2 and the combined organic phases were washed with 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.892 g of a dark red oil. Column chromatography on 60 g of silica gel (elution with 15% EtOAc-hexanes) afforded 0.665 g (57% over two steps from the ynamide) of benzothiophene **363** as a viscous dark yellow oil: IR (film) 3085, 2933, 2858, 1707, 1596, 1544, 1444, 1414, 1374, 1336, 1299, 1256,

1189, 1118, 1066, and 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, ca. 74:26 mixture of rotamers) (major rotamer) δ 7.31–7.36 (m, 3H), 6.00–6.09 (m, 1H), 5.18 (dd, J = 10.1, 1.2Hz, 1H), 5.16 (d, J = 16.5 Hz, 1H), 4.71 (dd, J = 6.9, 4.3 Hz, 1H), 4.68 (br s, 1H), 3.76 (dd, J = 15.3, 7.3 Hz, 1H), 3.62 (br s, 3H), 3.30 (br s, 3H), 3.21 (s, 3H), 2.97 (dd, J = 13.9, 3.1 Hz, 1H), 2.90 (dd, J = 13.7, 6.7 Hz, 1H), 1.08 (s, 9H), and 0.21 (s, 6H); additional resonances appeared for the minor rotamer at δ 4.59 (br s, 1H) and 3.78 (br s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.4, 149.5, 139.4, 139.0, 134.0, 133.0, 125.3, 121.9, 121.7, 118.0, 116.6, 103.8, 54.9, 54.1, 53.0, 52.8, 31.3, 26.2, 18.8, –2.9, and –3.2; HRMS (DART) *m/z* $[M + NH_4]^+$ calcd for $C_{23}H_{35}NO_5SSi$, 483.2343; found 483.2352.

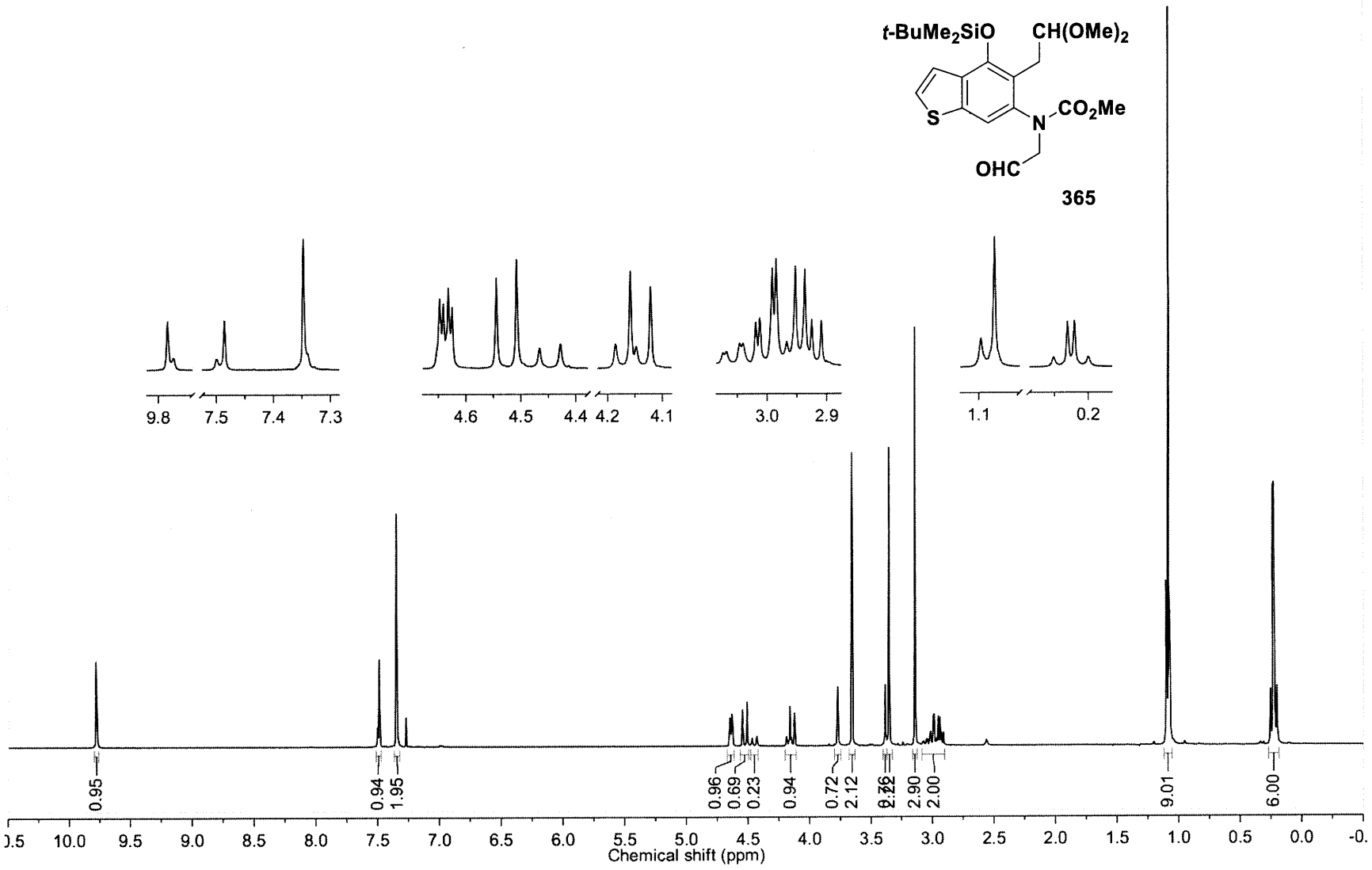

t-BuMe2SiO
CH(OMe)2
S
N
CO2Me
363
7.35
7.30
6.1
5.2
4.7
3.7
3.5
3.3
2.9
2.76
0.93
1.97
1.91
1.65
2.23
2.99
3.04
1.91
9.13
6.00
Chemical shift (ppm)

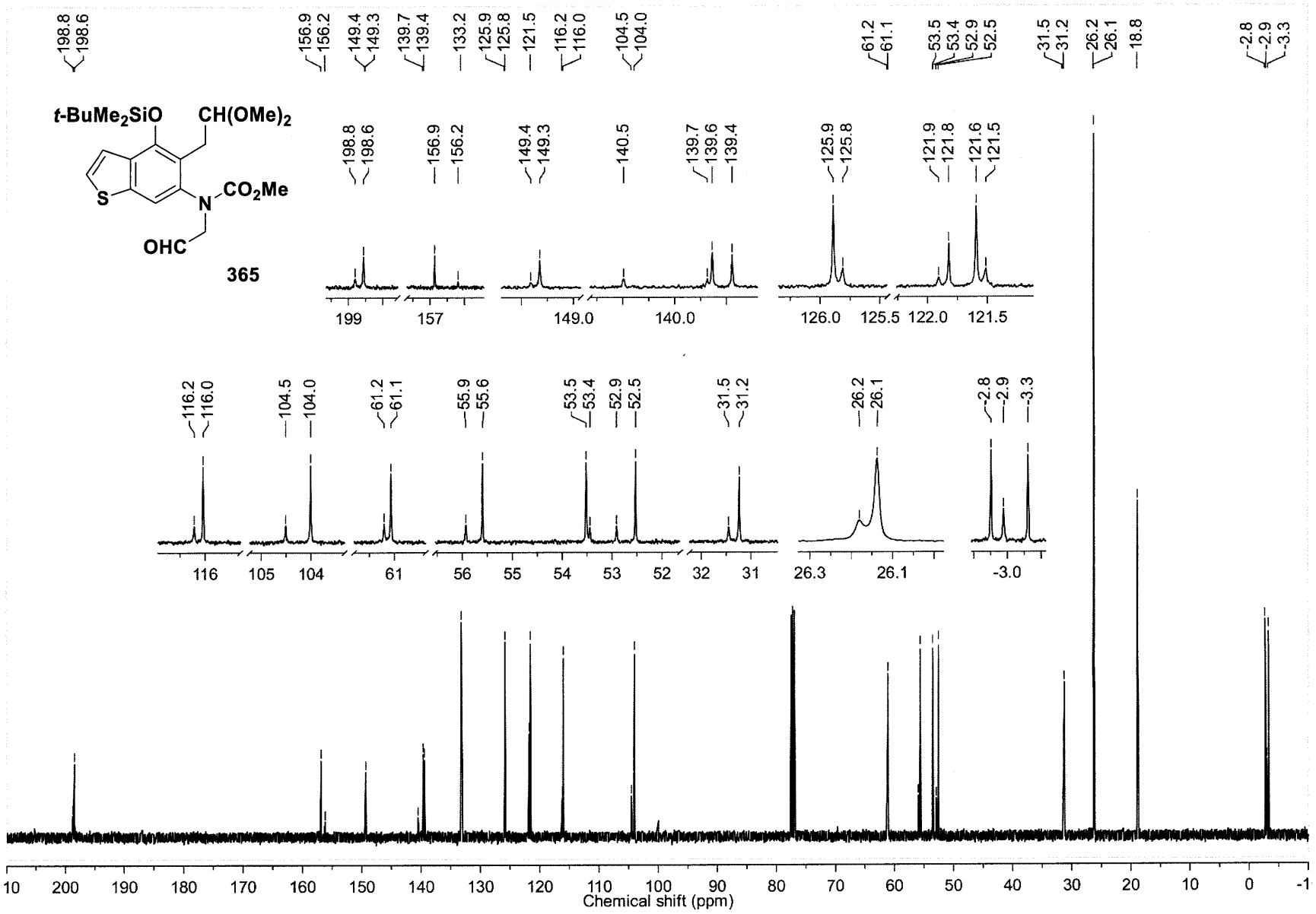

156.4
149.5
139.4
139.0
134.0
133.0
125.3
121.7
118.0
116.6
103.8
54.9
54.1
53.0
52.8
31.3
26.2
18.8
-2.9
-3.2
t-BuMe2SiO
CH(OMe)2
S
N
CO2Me
363
121.9
121.7
122.0
121.5
54.9
54.1
53.0
52.8
55
54
53
-2.9
-3.2
-3
Chemical shift (ppm)

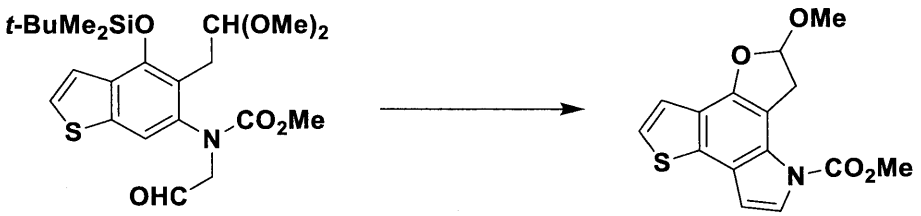


363 365

4-((*tert*-Butyldimethylsilyl)oxy)-5-(2,2-dimethoxyethyl)-*N*-(methoxycarbonyl)-*N*-(2-oxoethyl)benzo[*b*]thiophen-6-amine (365). A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, mechanical stirrer, and rubber septum was charged with **363** (1.86 g, 3.99 mmol, 1.0 equiv), 30 mL of 1,4-dioxane, and 10 mL of water. 2,6-Lutidine (0.925 mL, 0.856 g, 7.99 mmol, 2.0 equiv), OsO_4 (2.54 mL, 4 wt % in water, 0.399 mmol, 0.1 equiv) and $NaIO_4$ (3.42 g, 16.0 mmol, 4.0 equiv) were added, the rubber septum was replaced with a glass stopper, and the resulting thick yellow suspension was stirred at rt for 2.5 h. The reaction mixture was then diluted with 200 mL of water and 300 mL of CH_2Cl_2. The aqueous phase was separated and extracted with three 60 mL portions of CH_2Cl_2. The combined organic phases were washed with 300 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 3.75 g of a dark brown oil. Column chromatography on 120 g of silica gel (elution with 2:1 hexanes-EtOAc) afforded 1.65 g (88%) of aldehyde **365** as a very viscous orange oil: IR (film) 3091, 2955, 2932, 2859, 2832, 2713, 1734, 1706, 1596, 1546, 1448, 1415, 1369, 1338, 1256, 1191, 1118, 1069, 1054, 838, and 781 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, ca. 74:26 mixture of rotamers) (major rotamer) δ 9.78 (s, 1H), 7.49 (s, 1H), 7.35 (s, 2H), 4.64 (dd, J = 7.9, 3.4 Hz, 1H), 4.53 (d, J = 18.5 Hz, 1H), 4.14 (d, J = 18.5 Hz, 1H), 3.65 (s, 3H), 3.35 (s, 3H), 3.14 (s, 3H), 2.91–3.07 (m, 2H), 1.08 (s, 9H), 0.23 (s, 3H), and 0.22 (s, 3H); additional resonances appeared for the minor rotamer at δ 9.77 (s, 1H), 7.50 (s, 1H), 7.34 (s, 2H), 4.45 (d, J = 18.9 Hz, 1H), 4.17 (d, J = 18.9 Hz, 1H), 3.77 (s, 3H), 3.38 (s, 3H), 1.10 (s, 9H), 0.25 (s, 3H), and 0.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) (major rotamer) δ 198.6, 156.9, 149.3, 139.6, 139.4, 133.2, 125.9, 121.8, 121.6, 116.0, 104.0, 61.1, 55.6, 53.5, 52.5, 31.2, 26.1, 18.8, –2.8, and –3.3; additional resonances appeared for the minor rotamer at δ 198.8, 156.2, 149.4, 140.5, 139.7, 125.8, 121.9, 121.5, 116.2, 104.5, 61.2, 55.9, 53.4, 52.9, 31.5, 26.2, and –2.9; HRMS (ESI) *m/z* $[M + NH_4]^+$ calcd for $C_{22}H_{33}NO_6SSi$, 485.2136; found 485.2134.


t-BuMe2SiO
CH(OMe)2
S
N
CO2Me
OHC
365
Chemical shift (ppm)

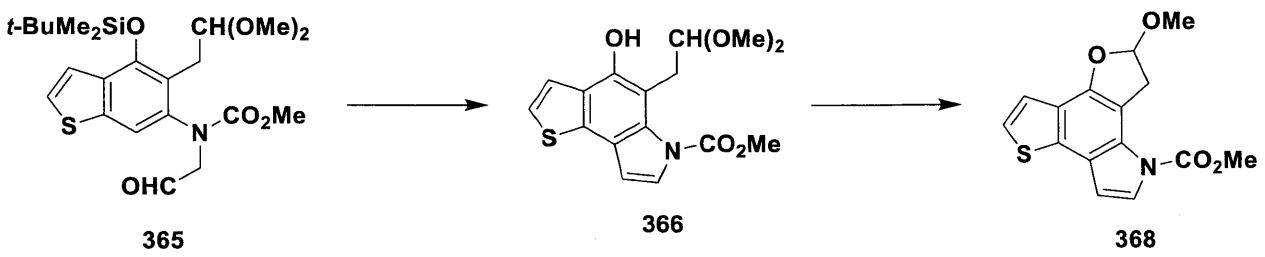

198.8
198.6
156.9
156.2
149.4
149.3
139.7
139.4
133.2
125.9
125.8
121.5
116.2
116.0
104.5
104.0
61.2
61.1
53.5
53.4
52.9
52.5
31.5
31.2
26.2
26.1
18.8
-2.8
-2.9
-3.3
t-BuMe2SiO
CH(OMe)2
CO2Me
N
S
OHC
365
Chemical shift (ppm)



365 368

Methyl 2-Methoxy-2,3-dihydrofuro[2,3-*g*]thieno[2,3-*e*]indole-4-carboxylate (368) – One-Pot Double Cyclization. A 300-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with aldehyde **365** (0.823 g, 1.76 mmol, 1.0 equiv) and 9 mL of *i*-PrOH. TBAF solution (1.94 mL, 1.0 M in THF, 1.94 mmol, 1.1 equiv) was added dropwise over 3 min and the resulting orange solution was stirred at rt for 1 h. K_2CO_3 (1.22 g, 8.80 mmol, 5.0 equiv) was added in one portion and the reaction mixture was heated at 40 °C for 2 h. The resulting orange-brown suspension was cooled to 0 °C and diluted with 90 mL of MeOH. In a separate 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle, a solution of HCl was prepared by adding acetyl chloride (1.38 mL, 1.52 g, 19.4 mmol, 11 equiv) dropwise over 3 min to 10 mL of MeOH cooled at 0 °C. This solution was then rapidly transferred into the reaction mixture via cannula (3 x 1 mL MeOH wash). The cooling bath was removed and the reaction mixture was stirred at rt for 1 h. Additional acetyl chloride (0.13 mL, 0.14 g, 1.8 mmol, 1.0 equiv) was added directly into the reaction mixture dropwise over 30 sec and the mixture was stirred at rt for an additional 30 min. The resulting teal suspension was then diluted with 350 mL of CH_2Cl_2, 200 mL of satd aq $NaHCO_3$ solution, and 100 mL of water. The aqueous phase was extracted with three 75-mL portions of CH_2Cl_2 and the combined organic phases were washed with 200 mL of water and 200 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.621 g of a dark green oil. Column chromatography on 100 g of silica gel (elution with 91:8:1 hexanes-EtOAc-Et_3N) afforded 0.455 g (85%) of tetracycle **368** as a colorless solid: mp 125–127 °C; IR (film) 3107, 2954, 1754, 1583, 1537, 1443, 1421, 1351, 1316, 1271, 1233, 1202, 1145, 1096, and 939 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 3.8 Hz, 1H), 7.46 (d, J = 5.4 Hz, 1H), 7.34 (d, J = 5.4 Hz, 1H), 6.73 (d, J = 3.8 Hz, 1H), 5.80 (dd, J = 6.6, 2.1 Hz, 1H), 4.02 (s, 3H), 3.92 (dd, J = 17.2, 6.6 Hz, 1H), 3.74 (dd, J = 17.2, 2.1 Hz, 1H), and 3.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5, 151.3, 132.8, 129.6, 124.3, 123.8, 122.9, 120.4, 119.8, 107.6, 106.9, 106.7,

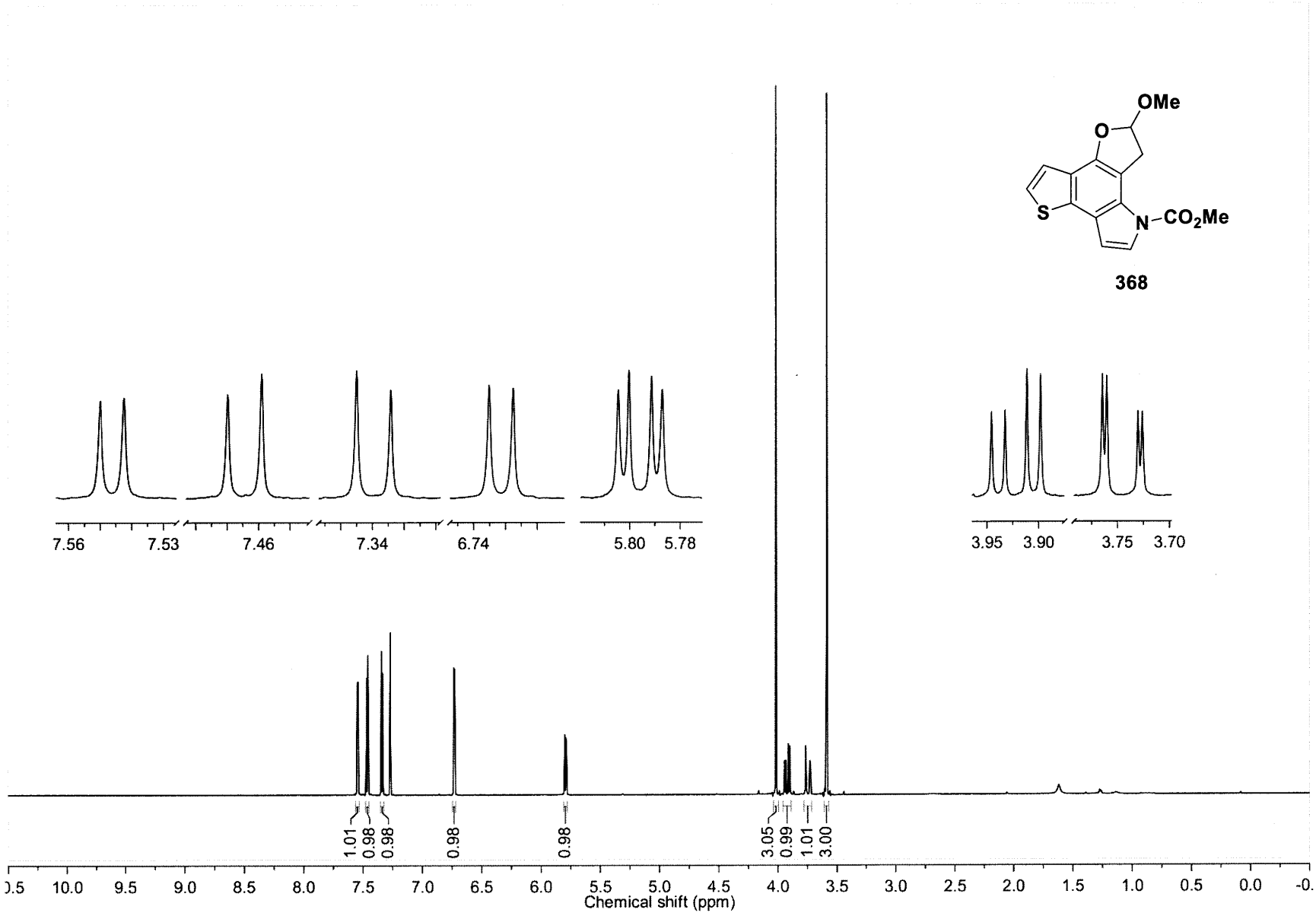
55.7, 54.0, and 39.5; HRMS (DART) *m/z* $[M + H]^+$ calcd for $C_{15}H_{13}NO_4S$, 304.0638; found 304.0649.

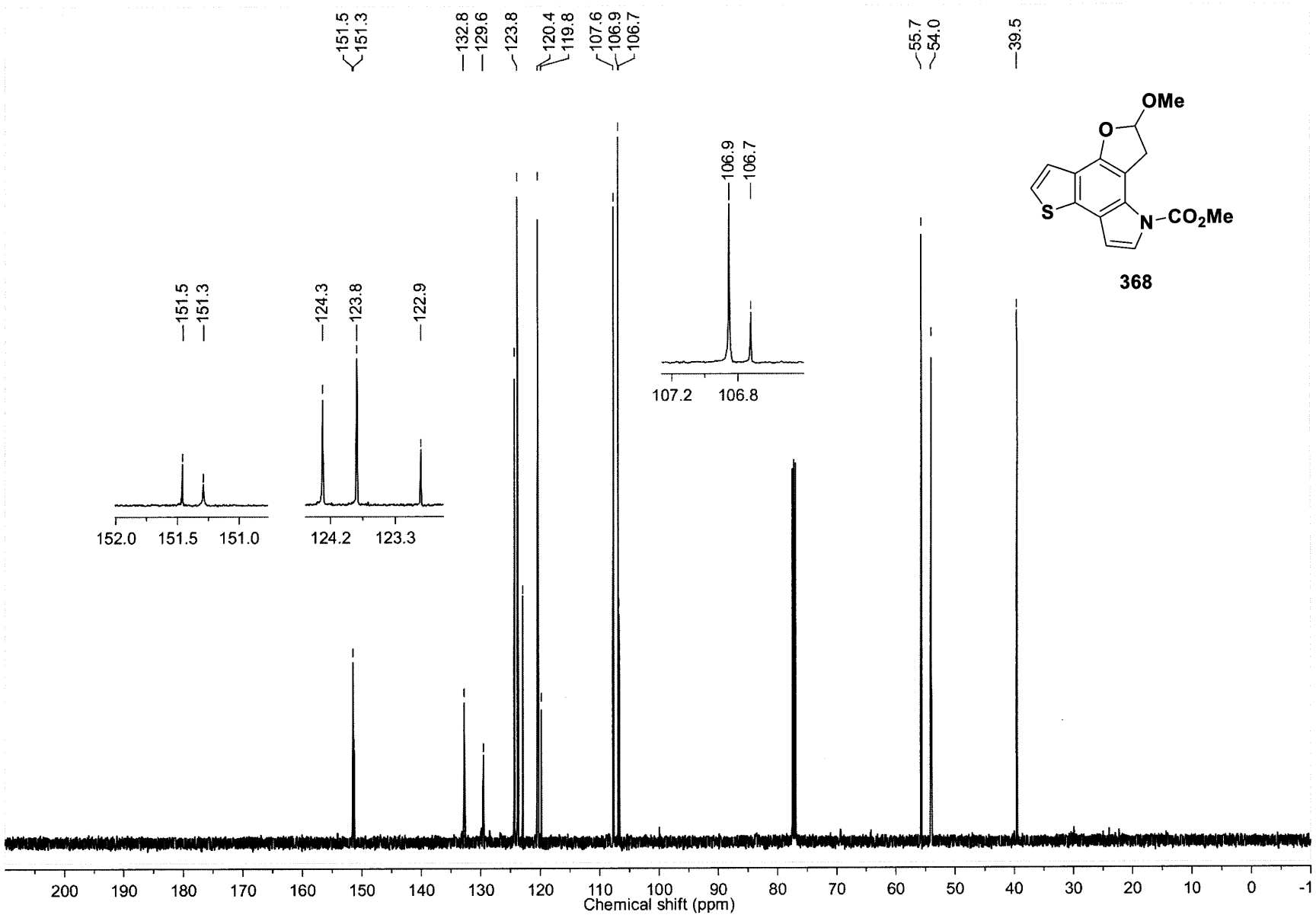


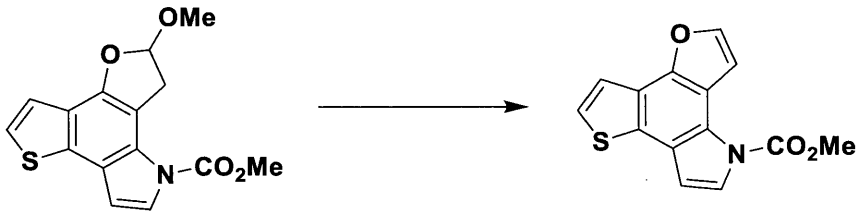
Methyl 2-Methoxy-2,3-dihydrofuro[2,3-*g*]thieno[2,3-*e*]indole-4-carboxylate (368) – Two-Step Cyclization. Isolation of Methyl 5-(2,2-Dimethoxyethyl)-4-hydroxythieno[2,3-*e*]indole-6-carboxylate (366). A 500-mL round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with aldehyde **365** (0.823 g, 1.76 mmol, 1.0 equiv) and 15 mL of *i*-PrOH. TBAF solution (1.94 mL, 1.0 M in THF, 1.94 mmol, 1.1 equiv) was added dropwise over 3 min and the resulting orange solution was stirred at rt for 1.5 h. K_2CO_3 (1.22 g, 8.80 mmol, 5.0 equiv) was added in one portion and the reaction mixture was heated at 40 °C for 2 h. The resulting orange-brown suspension was cooled to 0 °C and diluted with 180 mL of MeOH. In a separate 50-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle, a solution of HCl was prepared by adding acetyl chloride (1.38 mL, 1.52 g, 19.4 mmol, 11 equiv) dropwise over 3 min to 20 mL of MeOH cooled at 0 °C. This solution was then transferred into the reaction mixture via cannula dropwise over 5 min (2 x 1 mL MeOH wash). The cooling bath was removed and the reaction mixture was stirred at rt for 20 min. The resulting green-brown suspension was then diluted with 700 mL of CH_2Cl_2, 600 mL of satd aq $NaHCO_3$ solution, and 100 mL of water. The aqueous phase was extracted with three 150-mL portions of CH_2Cl_2 and the combined organic phases were washed with 400 mL of water and 400 mL of brine, dried over $MgSO_4$, filtered, and concentrated to a dark brown oil. Column chromatography on 100 g of silica gel (elution with 91:8:1 hexanes-EtOAc-Et_3N) afforded 0.480 g (81%) of ca. 90% pure tricycle **366** as a viscous orange oil: R_f = 0.49 in 25% EtOAc–hexanes; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.11 (s, 1H), 7.60 (d, J = 5.4 Hz, 1H), 7.56 (d, J = 3.8 Hz, 1H), 7.30 (d, J = 5.4 Hz, 1H), 6.71 (d, J = 3.8 Hz, 1H), 5.18 (t, J = 5.3 Hz, 1H), 4.02 (s, 3H), 3.59 (s, 6H), and 3.23 (d, J = 5.3 Hz, 2H).

A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with **366** from the previous step (0.480 g, 1.0 equiv) and 14 mL of MeOH. Acetyl chloride (0.102 mL, 0.113 g, 1.43 mmol, 1.0 equiv) was added dropwise over 1 min. The reaction mixture was stirred at rt for 20 min (white precipitates were observed after ca. 5 min) and diluted with 70 mL

each of CH_2Cl_2, water, and satd aq $NaHCO_3$ solution. The aqueous phase was extracted with three 20-mL portions of CH_2Cl_2 and the combined organic phases were washed with 70 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford a yellow solid. Column chromatography on 30 g of silica gel (elution with 90:10:1 hexanes-EtOAc-Et_3N) afforded 0.400 g (75% over two steps from the aldehyde) of tetracycle **368** as a colorless solid: R_f = 0.54 in 10% EtOAc–hexanes; mp 125–127 °C; IR (film) 3107, 2954, 1754, 1583, 1537, 1443, 1421, 1351, 1316, 1271, 1233, 1202, 1145, 1096, and 939 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 3.8 Hz, 1H), 7.46 (d, J = 5.4 Hz, 1H), 7.34 (d, J = 5.4 Hz, 1H), 6.73 (d, J = 3.8 Hz, 1H), 5.80 (dd, J = 6.6, 2.1 Hz, 1H), 4.02 (s, 3H), 3.92 (dd, J = 17.2, 6.6 Hz, 1H), 3.74 (dd, J = 17.2, 2.1 Hz, 1H), and 3.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5, 151.3, 132.8, 129.6, 124.3, 123.8, 122.9, 120.4, 119.8, 107.6, 106.9, 106.7, 55.7, 54.0, and 39.5; HRMS (DART) *m/z* $[M + H]^+$ calcd for $C_{15}H_{13}NO_4S$, 304.0638; found 304.0649.

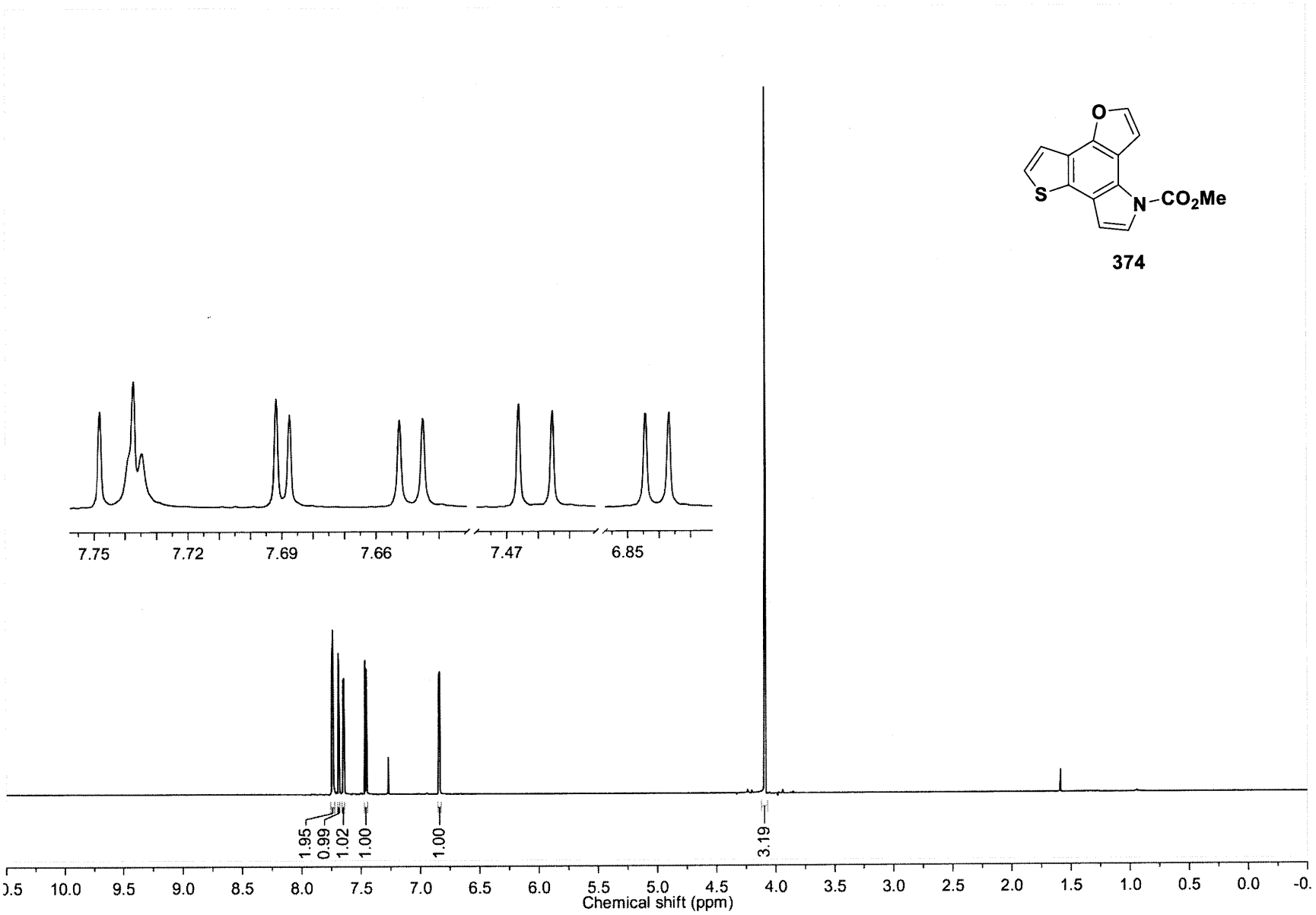

OMe
O
S
N–CO2Me
368
7.56
7.53
7.46
7.34
6.74
5.80
5.78
3.95
3.90
3.75
3.70
1.01
0.98
0.98
0.98
0.98
3.05
0.99
1.01
3.00
Chemical shift (ppm)

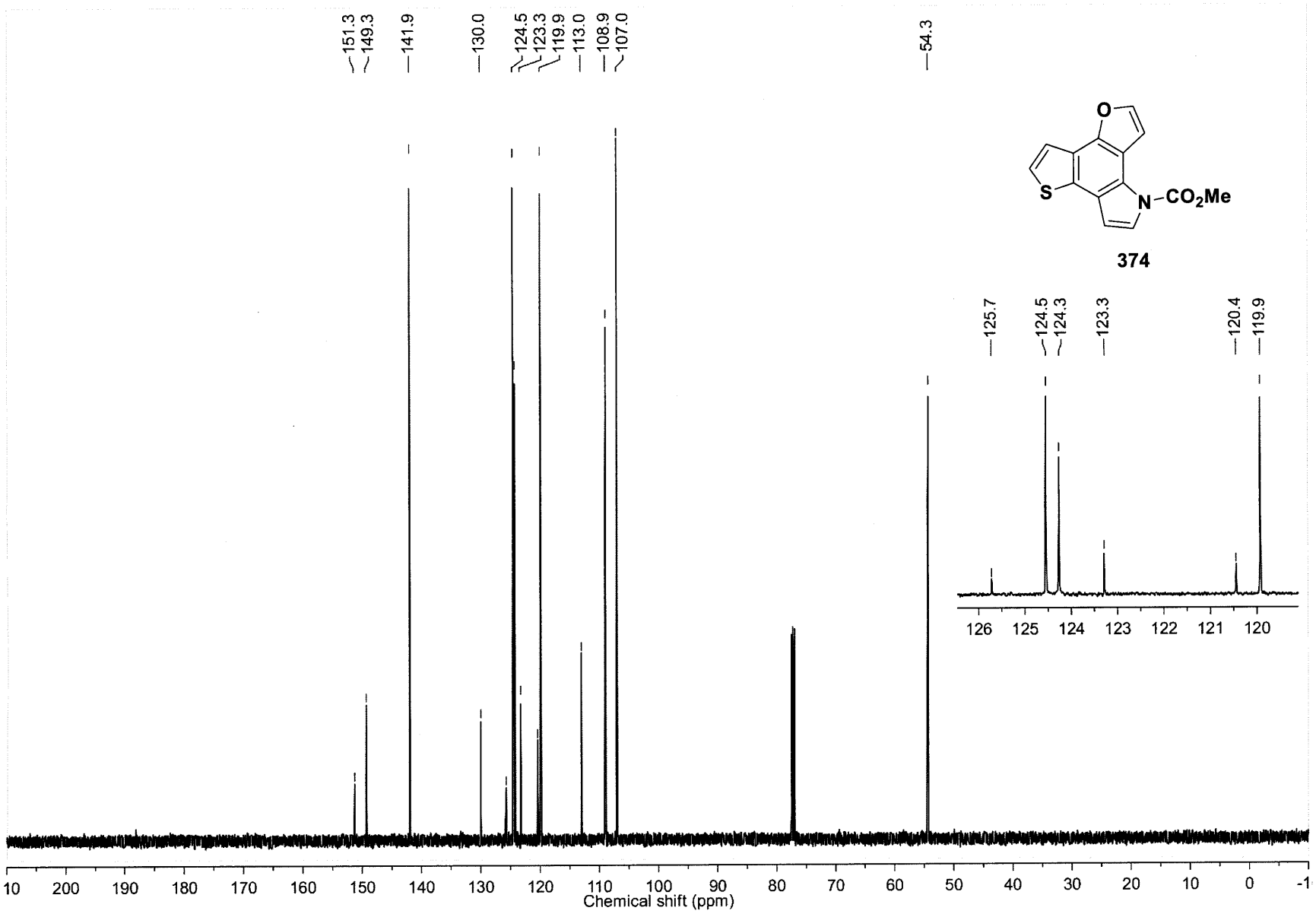

151.5
151.3
132.8
129.6
123.8
120.4
119.8
107.6
106.9
106.7
55.7
54.0
39.5
OMe
O
S
N–CO2Me
368
106.9
106.7
107.2
106.8
151.5
151.3
152.0
151.5
151.0
124.3
123.8
122.9
124.2
123.3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
Chemical shift (ppm)



368 374

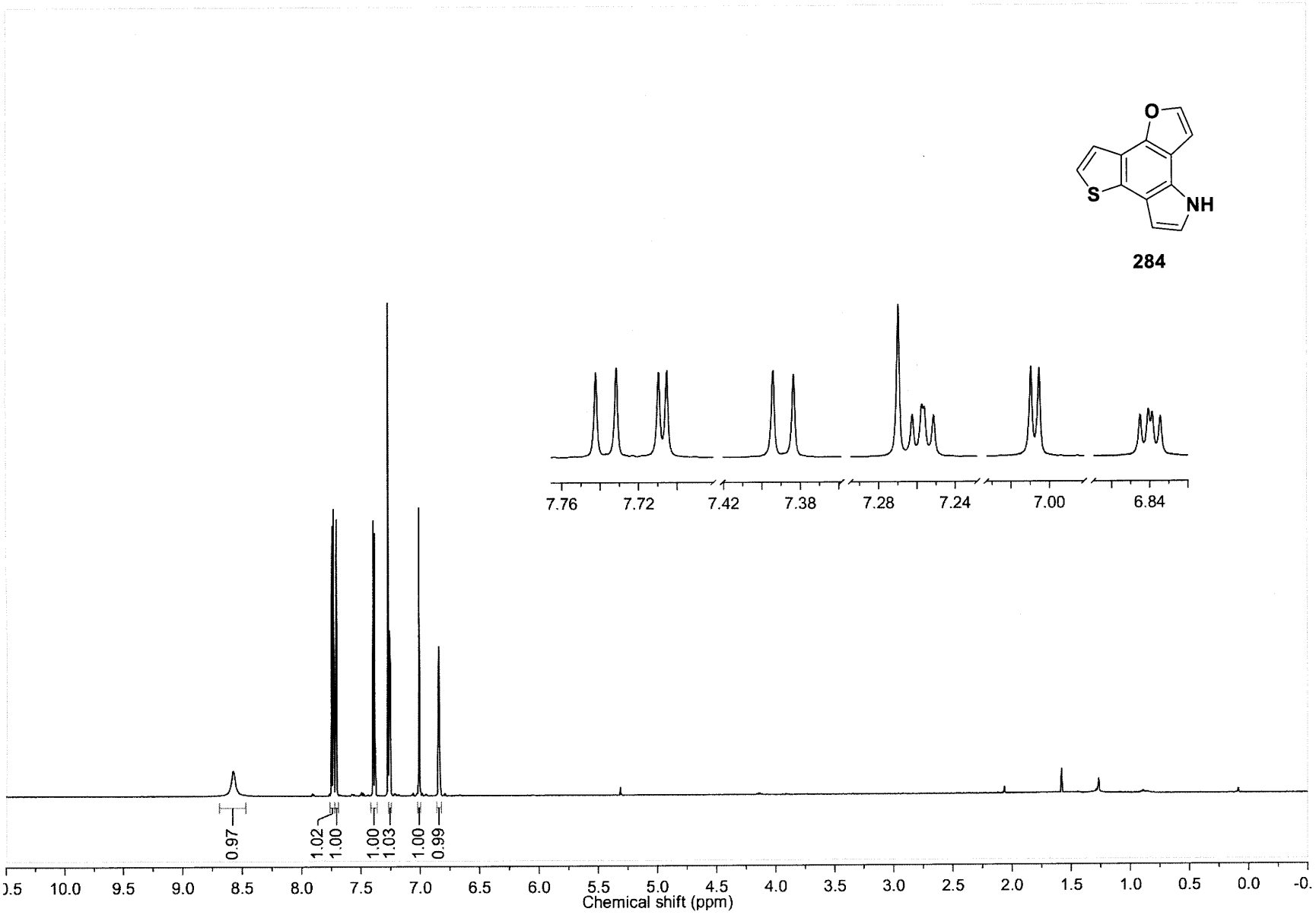
Methyl Furo[2,3-*g*]thieno[2,3-*e*]indole-4-carboxylate (374). A 350 mL threaded Pyrex flask equipped with a rubber septum and argon inlet needle was charged with tetracycle **368** (0.400 g, 1.32 mmol, 1.0 equiv), bis(trimethylsilyl)amine (1.70 mL, 1.30 g, 8.04 mmol, 6.1 equiv), and 130 mL of CH_2Cl_2. Me_3SiOTf (1.44 mL, 1.76 g, 7.91 mmol, 6.0 equiv) was added dropwise over 2 min, the rubber septum was replaced with a threaded Teflon cap, and the colorless reaction mixture was stirred at rt for 44 h. The resulting pale yellow solution was then diluted with 80 mL of satd aq $NaHCO_3$ solution. The aqueous phase was separated and extracted with three 25 mL portions of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated to afford 0.398 g of a pale yellow solid. Column chromatography on 25 g of silica gel (gradient elution with 5% to 10% EtOAc-hexanes) afforded 0.329 g (92%) of tetracycle **374** as colorless crystals: mp 154.5–155 °C; IR (film) 3158, 3107, 2954, 1749, 1587, 1533, 1444, 1402, 1349, 1295, 1272, 1239, 1203, 1159, 1087, 1038, 763, and 703 cm^{-1}; UV (CH_2Cl_2) λ_{max}, nm (ε) 327 (1934), 313 (2308), 301 (1811), 277 (15999), 258 (40090), and 231 (15732); ^1H NMR (500 MHz, $CDCl_3$) δ 7.743 (d, J = 5.3 Hz, 1H), 7.736 (d, J = 2.0 Hz, 1H), 7.69 (d, J = 2.1 Hz, 1H), 7.65 (d, J = 3.7 Hz, 1H), 7.46 (d, J = 5.3 Hz, 1H), 6.84 (d, J = 3.8 Hz, 1H), and 4.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.3, 149.3, 141.9, 130.0, 125.7, 124.5, 124.3, 123.3, 120.4, 119.9, 113.0, 108.9, 107.0, and 54.3; HRMS (DART) *m/z* $[M + H]^+$ calcd for $C_{14}H_9NO_3S$, 272.0376; found 272.0344.

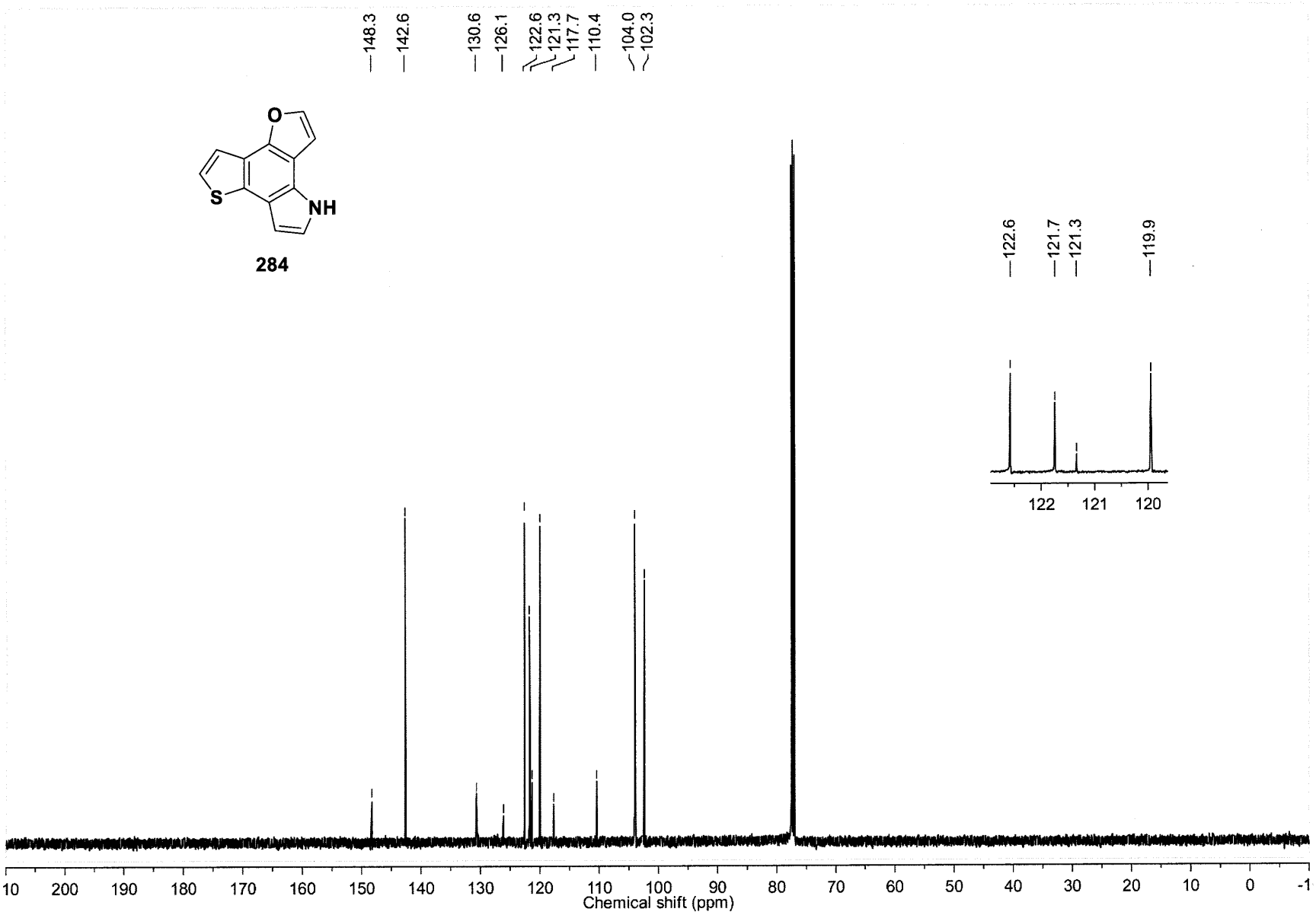

O
S
N–CO2Me
374
7.75
7.72
7.69
7.66
7.47
6.85
1.95
0.99
1.02
1.00
1.00
3.19
Chemical shift (ppm)

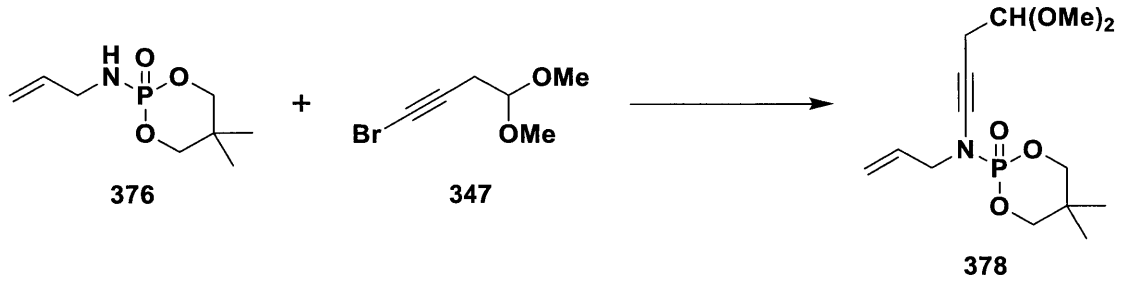

151.3
149.3
141.9
130.0
124.5
123.3
119.9
113.0
108.9
107.0
54.3
O
S
N–CO2Me
374
125.7
124.5
124.3
123.3
120.4
119.9
126 125 124 123 122 121 120
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
Chemical shift (ppm)

374 284

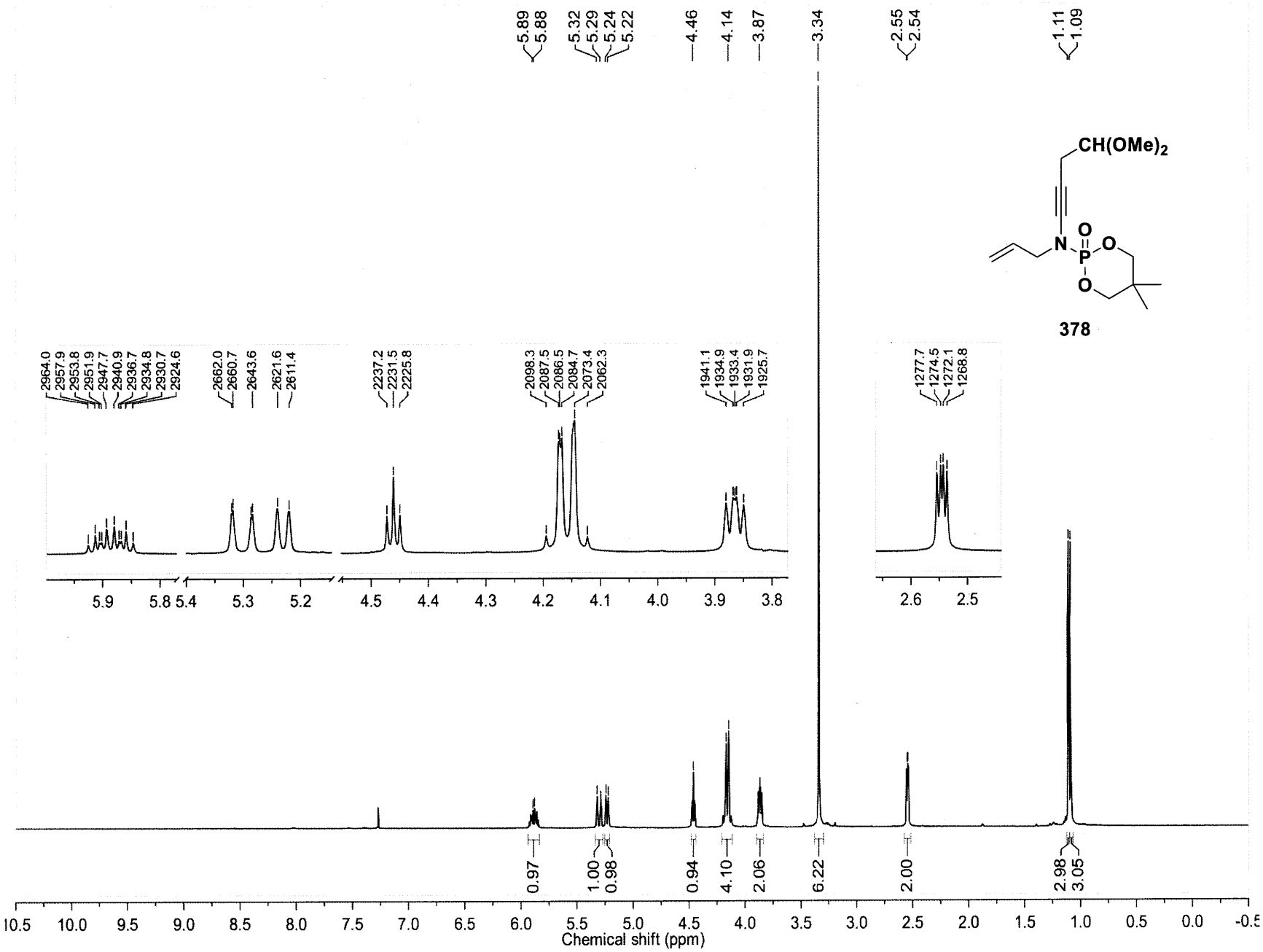
Furo[2,3-*g*]thieno[2,3-*e*]indole (284). A 50 mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with tetracycle **374** (0.131 g, 0.480 mmol, 1.0 equiv), 20 mL of MeOH, and 5 mL of THF. NaOMe (0.032 g, 0.60 mmol, 1.3 equiv) was added and the resulting colorless solution was stirred at rt for 1 h. The reaction mixture was concentrated to a volume of ca. 5 mL and diluted with 50 mL of water and 40 mL of CH_2Cl_2. The aqueous phase was separated and extracted with three 15 mL portions of CH_2Cl_2, and the combined organic phases were washed with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.091 g of an off-white solid. Column chromatography on 12 g of silica gel (elution with 80:20:0.5 hexanes–EtOAc–Et_3N) afforded 0.088 g (86%) of tetracycle **284** as colorless crystals: mp 134–135 °C (sublimed at ca. 126 °C); IR (film) 3412, 3099, 1604, 1523, 1370, 1323, 1308, 1110, 1040, 878, 772, and 702 cm^{-1}; UV (CH_2Cl_2) λ_{max}, nm (ε) 320 (2945), 307 (3191), 277 (8201), and 248 (33998); ^1H NMR (500 MHz, $CDCl_3$) δ 8.58 (br s, 1H), 7.74 (d, J = 5.4 Hz, 1H), 7.71 (d, J = 2.1 Hz, 1H), 7.39 (d, J = 5.4 Hz, 1H), 7.26 (dd, J = 3.1, 2.5 Hz, 1H), 7.01 (d, J = 2.1 Hz, 1H), and 6.84 (dd, J = 3.1, 2.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 142.6, 130.6, 126.1, 122.6, 121.7, 121.3, 119.9, 117.7, 110.4, 104.0, and 102.3; HRMS (DART) *m/z* $[M + H]^+$ calcd for $C_{12}H_7NOS$, 214.0312; found 214.0317; $[M - H]^-$ calcd for $C_{12}H_7NOS$, 212.0176; found 212.0181.

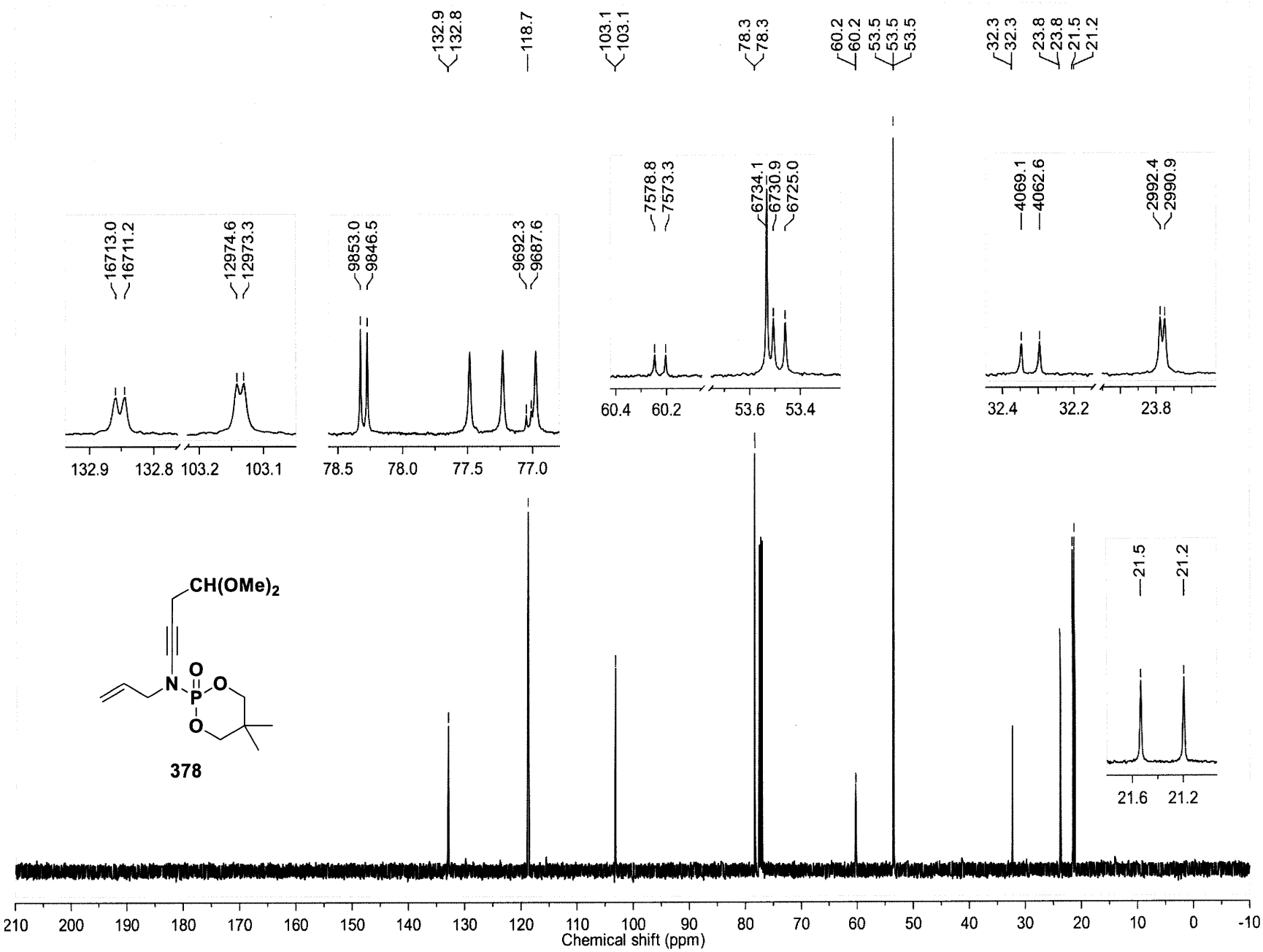

O
S
NH
284
7.76
7.72
7.42
7.38
7.28
7.24
7.00
6.84
0.97
1.02
1.00
1.00
1.03
1.00
0.99
Chemical shift (ppm)

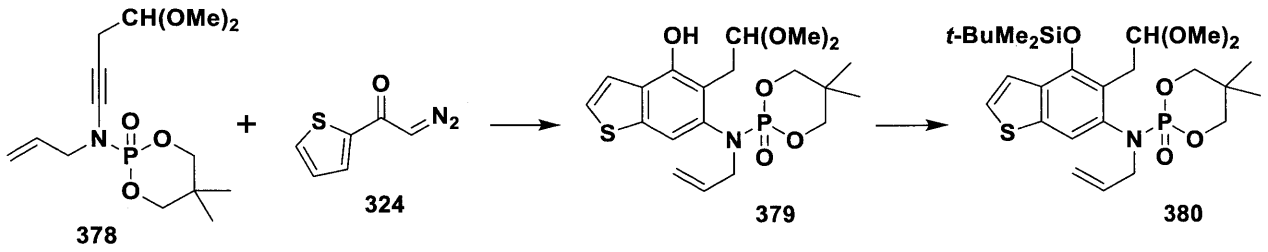

148.3
142.6
130.6
126.1
122.6
121.3
117.7
110.4
104.0
102.3
O
S
NH
284
122.6
121.7
121.3
119.9
122
121
120
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
Chemical shift (ppm)



***N*-Allyl-4,4-dimethoxy-*N*-(5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxide-2-yl)but-1-yn-1-ylamine (378).** A threaded Pyrex tube (26 x 100 mm) equipped with a rubber septum and an argon inlet needle was charged with phosphoramidate **376**[133a,c] (0.125 g, 0.609 mmol, 1.0 equiv), 1-bromo-4,4-dimethoxybut-1-yne **347** (0.153 g, 0.793 mmol, 1.3 equiv), and 1.5 mL of dioxane. CuTC (0.025 g, 0.13 mmol, 0.2 equiv), DMEDA (0.028 mL, 0.023 g, 0.26 mmol, 0.4 equiv), and K_3PO_4 (0.259 g, 1.22 mmol, 2.0 equiv) were added, the rubber septum was replaced with a Teflon screw cap, and the blue reaction mixture was stirred at 50 °C for 48 h. The resulting suspension of orange supernatant and blue-white precipitate was cooled to rt, filtered through Celite with the aid of 15 mL of EtOAc, and concentrated to afford an orange oil. Column chromatography on 15 g of silica gel (elution with 1:1 hexanes- EtOAc) afforded 0.109 g (56%) of ynamide **378** as a pale yellow solid: mp 45–46 °C; IR (film) 2940, 2909, 2833, 2260, 1646, 1473, 1371, 1328, 1273, 1191, 1120, 1047, 1004, 918, 874, 827, and 791 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.89 (ddt, J = 17.1, 10.2, 6.1 Hz, 1H), 5.30 (dd, J = 17.1, 1.4 Hz, 1H), 5.23 (d, J = 10.2 Hz, 1H), 4.46 (t, J = 5.6 Hz, 1H), 4.12–4.20 (m, 4H), 3.84–3.89 (m, 2H), 3.34 (s, 6H), 2.55 (dd, J = 5.7, 3.4 Hz, 2H), 1.11 (s, 3H), and 1.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.9 (d, J = 1.8 Hz), 118.7, 103.1 (d, J = 1.3 Hz), 78.3 (d, J = 6.6 Hz), 77.0 (d, J = 4.7 Hz), 60.2 (d, J = 5.5 Hz), 53.53, 53.48 (d, J = 5.9 Hz), 32.3 (d, J = 6.5 Hz), 23.8 (d, J = 1.6 Hz), 21.5, and 21.2; ^{31}P NMR (121 MHz, $CDCl_3$) δ -1.2; HRMS (DART) *m/z* $[M + H]^+$ calcd for $C_{14}H_{24}NO_5P$, 318.1465; found 318.1459.


5.89
5.88
5.32
5.29
5.24
5.22
4.46
4.14
3.87
3.34
2.55
2.54
1.11
1.09
CH(OMe)2
N
O
P
O
O
O
378
2964.0
2957.9
2953.8
2951.9
2947.7
2940.9
2936.7
2934.8
2930.7
2924.6
2662.0
2660.7
2643.6
2621.6
2611.4
2237.2
2231.5
2225.8
2098.3
2087.5
2086.5
2084.7
2073.4
2062.3
1941.1
1934.9
1933.4
1931.9
1925.7
1277.7
1274.5
1272.1
1268.8
0.97
1.00
0.98
0.94
4.10
2.06
6.22
2.00
2.98
3.05
Chemical shift (ppm)


132.9
132.8
118.7
103.1
103.1
78.3
78.3
60.2
60.2
53.5
53.5
53.5
32.3
32.3
23.8
23.8
21.5
21.2
16713.0
16711.2
12974.6
12973.3
9853.0
9846.5
9692.3
9687.6
7578.8
7573.3
6734.1
6730.9
6725.0
4069.1
4062.6
2992.4
2990.9
132.9
132.8
103.2
103.1
78.5
78.0
77.5
77.0
60.4
60.2
53.6
53.4
32.4
32.2
23.8
21.5
21.2
21.6
21.2
CH(OMe)2
N
O
P
O
O
O
378
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical shift (ppm)

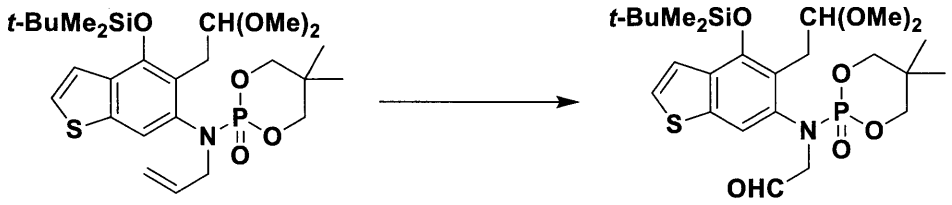


***N*-Allyl- 4-((*tert*-butyldimethylsilyl)oxy)-5-(2,2-dimethoxyethyl)-*N*-(5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxide-2-yl)benzo[*b*]thiophen-6-amine (380).** A 10-mL pear flask equipped with a rubber septum and argon inlet needle was charged with diazo ketone **324** (0.067 g, 0.44 mmol, 1.1 equiv), ynamide **378** (0.127 g, 0.4 mmol, 1.0 equiv), and 1.7 mL of DCE, and the yellow solution was degassed via three freeze-pump-thaw (−196 °C, 0.05 mmHg) cycles. The FEP tubing of the continuous flow reactor was flushed with 3 mL of degassed DCE, the mercury lamp was turned on, and degassed DCE was pumped through the tubing for 5 min at a rate of 0.057 mL/min by syringe pump. The solution of **324** and **378** was transferred to a 5-mL plastic syringe and pumped through the tubing at a rate of 0.057 mL/min into a threaded Pyrex tube (26 x 100 mm) equipped with a stir bar and rubber septum. Once the addition was complete, the tubing was flushed with three portions of degassed DCE (0.4, 0.4, and then 4.0 mL). The collection tube was sealed with a Teflon screw cap and the reaction mixture was heated at 85 °C for 52 h. The resulting dark red solution was allowed to cool to rt and concentrated to afford a dark red oil. Column chromatography on 25 g of silica gel (elution with 50:50:1 EtOAc-CH_2Cl_2-Et_3N) afforded phenol **379** (ca. 95% purity by ^{1}H NMR analysis; R_f = 0.17 in 1:1 hexanes-EtOAc) and mixed fractions containing phenol **379** and cyclized byproduct **381** (R_f = 0.22 in 1:1 hexanes-EtOAc). The mixed fractions were combined and chromatographed on 100 g of silica gel (elution with 1:1 EtOAc-CH_2Cl_2). The fractions containing mostly phenol **379** from the two columns were combined and concentrated to afford 0.108 g (61% crude yield; ca. 95% purity by ^{1}H NMR analysis) of phenol **379** as an orange foam which was used in the next step without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (s, 1H), 7.47 (dd, J = 5.5, 0.8 Hz, 1H), 7.39 (dd, J = 1.4, 0.7 Hz, 1H), 7.31 (dd, J = 5.5, 0.3 Hz, 1H), 5.91 (ddt, J = 17.1, 10.1, 6.7 Hz, 1H), 5.06 (dd, J = 10.1, 0.8 Hz, 1H), 5.00 (ddd, J = 17.1, 2.3, 1.0 Hz, 1H), 4.65 (dd, J = 5.8, 4.7 Hz, 1H), 4.27–4.35 (m, 3H), 3.79 (ddd, J = 21.5, 11.0, 3.0 Hz, 1H), 3.73 (td, J = 15.0, 7.2 Hz, 1H), 3.64 (ddd, J = 21.5, 11.0, 3.0 Hz, 1H), 3.49 (s, 3H), 3.47 (s, 3H), 3.10–3.18 (m, 2H), 0.85 (s, 3H), and 0.79 (s, 3H).

A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with phenol **379** from the previous step (0.108 g, 0.245 mmol, 1.0 equiv), 2.5 mL of CH_2Cl_2, Et_3N (0.085 mL, 0.062 g, 0.61 mmol, 2.5 equiv), 4-DMAP (0.006 g, 0.049 mmol, 0.2 equiv), and *t*-$BuMe_2SiCl$ (0.048 g, 0.32 mmol, 1.3 equiv). The orange reaction mixture was stirred at rt for 24 h. Additional Et_3N (0.085 mL, 0.062 g, 0.61 mmol, 2.5 equiv) and *t*-$BuMe_2SiCl$ (0.081 g, 0.54 mmol, 2.2 equiv) were added, and the reaction mixture was stirred at rt for additional 27 h and then diluted with 0.3 mL of MeOH and 5 mL of CH_2Cl_2. The resulting solution was washed with three 5-mL portions of water and the combined aqueous phases were extracted with three 5-mL portions of CH_2Cl_2. The combined organic phases were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford a viscous dark orange oil. Column chromatography on 15 g of silica gel (elution with 60% EtOAc-hexanes) afforded 0.110 g (49% over two steps from the ynamide) of benzothiophene **380** as a viscous pale yellow oil: IR (film) 3079, 2957, 2932, 2886, 2859, 1542, 1473, 1435, 1413, 1338, 1261, 1214, 1120, 1058, 1010, 921, 834, 780, and 666 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (dd, J = 1.4, 0.7 Hz, 1H), 7.33 (dd, J = 5.6, 0.8 Hz, 1H), 7.31 (d, J = 5.5 Hz, 1H), 6.04 (dddd, J = 18.3, 10.1, 8.2, 5.2 Hz, 1H), 5.09 (d, J = 9.8 Hz, 1H), 5.02 (ddd, J = 17.1, 2.6, 1.5 Hz, 1H), 4.88 (dd, J = 8.5, 3.1 Hz, 1H), 4.48 (dddt, J = 15.1, 6.8, 5.3, 1.5 Hz, 1H), 4.26 (td, J = 11.0, 2.6 Hz, 2H), 3.91 (ddd, J = 18.2, 15.2, 8.2 Hz, 1H), 3.71 (ddd, J = 21.1, 11.0, 3.0 Hz, 1H), 3.58 (ddd, J = 21.1, 11.0, 3.0 Hz, 1H), 3.37 (s, 3H), 3.30 (dd, J = 14.2, 8.5 Hz, 1H), 3.16 (s, 3H), 2.97 (dd, J = 14.3, 3.0 Hz, 1H), 1.06 (s, 9H), 0.76 (s, 3H), 0.64 (s, 3H), 0.20 (s, 3H), and 0.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.6, 138.5 (d, J = 1.6 Hz), 137.7 (d, J = 2.7 Hz), 135.5, 133.0 (d, J = 1.3 Hz), 125.3, 123.7 (d, J = 3.8 Hz), 121.6, 120.1 (d, J = 2.4 Hz), 118.3, 103.8, 76.5 (d, J = 5.4 Hz), 76.4 (d, J = 5.9 Hz), 55.9, 53.9 (d, J = 6.4 Hz), 52.2, 31.9 (d, J = 5.2 Hz), 31.6, 26.3, 21.6, 20.8, 18.8, -3.0, and -3.1; HRMS (DART) *m/z* $[M + H]^+$ calcd for $C_{26}H_{42}NO_6PSSi$, 556.2312; found 556.2311.

7.46
7.46
7.33
7.32
7.31
7.30
6.04
6.04
5.10
5.08
5.04
5.01
4.88
4.87
4.48
4.25
3.92
3.91
3.57
3.30
3.16
2.98
2.96
1.06
0.76
0.64
0.20
0.14
3729.2
3728.6
3727.8
3727.2
3666.1
3665.3
3660.6
3659.8
3654.4
3648.9
3038.4
3033.2
3030.2
3028.3
3025.0
3023.1
3021.3
3020.1
3016.1
3014.9
3013.1
3011.3
3007.9
3006.1
3003.0
2997.8
2550.5
2540.7
2520.8
2519.3
2518.2
2516.7
2503.7
2502.2
2501.1
2499.6
7.46
7.34
7.32
7.30
6.08
6.06
6.04
6.02
6.00
5.10
5.05
5.00
2444.1
2441.0
2435.6
2432.5
2255.5
2254.0
2252.6
2248.7
2247.2
2243.2
2241.8
2240.3
2238.9
2237.4
2235.0
2233.4
2232.0
2230.4
2228.0
2226.7
2225.3
2139.2
2136.6
2128.2
2125.5
2117.1
2114.4
1976.8
1968.6
1961.6
1958.6
1953.4
1950.4
1943.5
1935.2
4.88
4.86
4.52
4.51
4.50
4.49
4.48
4.47
4.46
4.45
4.28
4.24
3.94
3.90
1872.9
1869.9
1861.9
1858.9
1851.8
1848.8
1840.8
1837.8
1805.8
1802.8
1794.8
1791.8
1784.7
1781.7
1773.6
1770.6
1658.2
1649.6
1644.0
1635.5
1491.5
1488.5
1477.2
1474.3
3.76
3.72
3.68
3.64
3.60
3.56
3.30
2.97
t-BuMe2SiO
CH(OMe)2
S
N
O
P
O
O
O
380
0.94
1.02
0.94
0.97
1.01
1.01
0.97
1.01
2.01
1.00
1.02
1.01
0.99
0.97
2.95
0.93
9.22
3.05
2.95
3.04
3.01
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
Chemical shift (ppm)

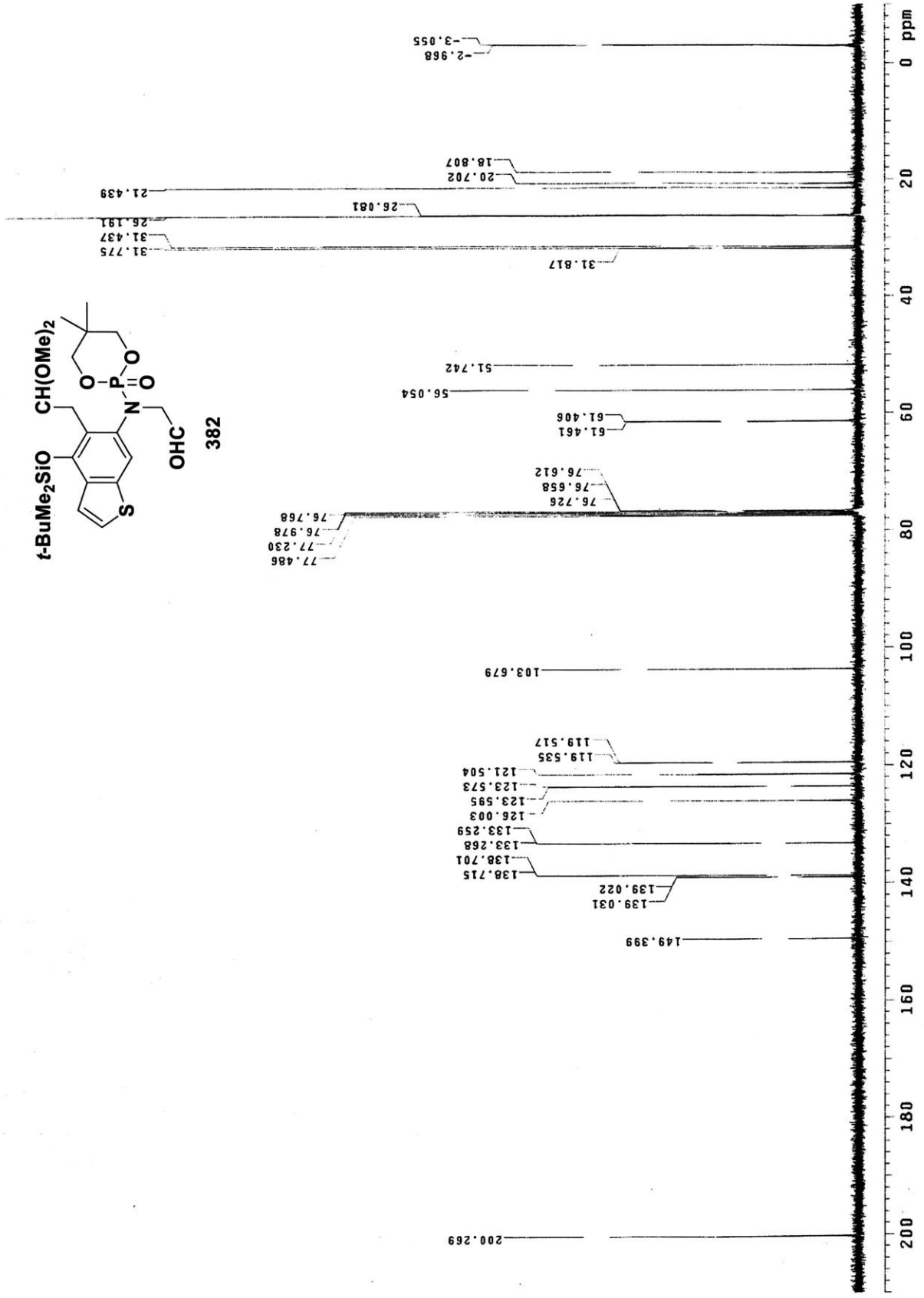
149.6
138.5
135.5
133.0
133.0
125.3
123.7
121.6
120.1
120.1
118.3
103.8
76.5
76.4
76.4
76.4
55.9
53.9
53.9
52.2
31.9
31.9
31.6
26.3
21.6
20.8
18.8
-3.0
-3.1
t-BuMe2SiO
CH(OMe)2
O
P
O
O
S
N
380
17418.1
17416.5
17318.9
17316.2
16730.2
16728.9
15568.2
15564.4
15111.8
15109.4
9619.9
9614.5
9610.6
9604.7
6781.5
6775.1
4013.8
4008.6
3977.4
-3.0
-3.1
138.5
138.4
137.7
137.6
133.0
123.8
120.2
76.6
76.4
54.0
53.8
32.0
31.8
31.6
-2.8
-3.0
-3.2
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical shift (ppm)

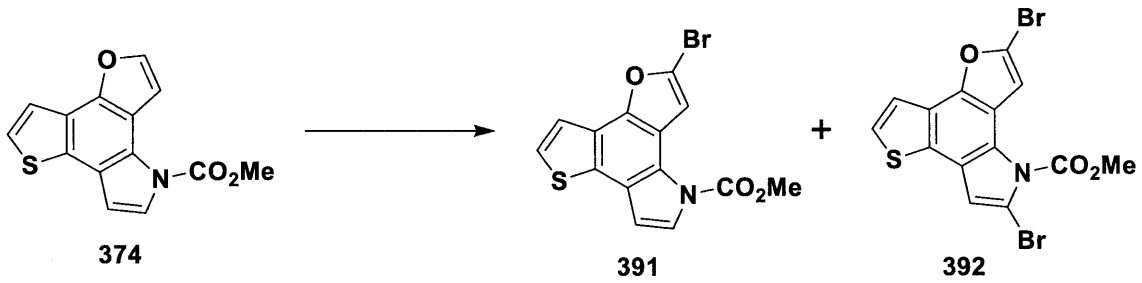


380 382

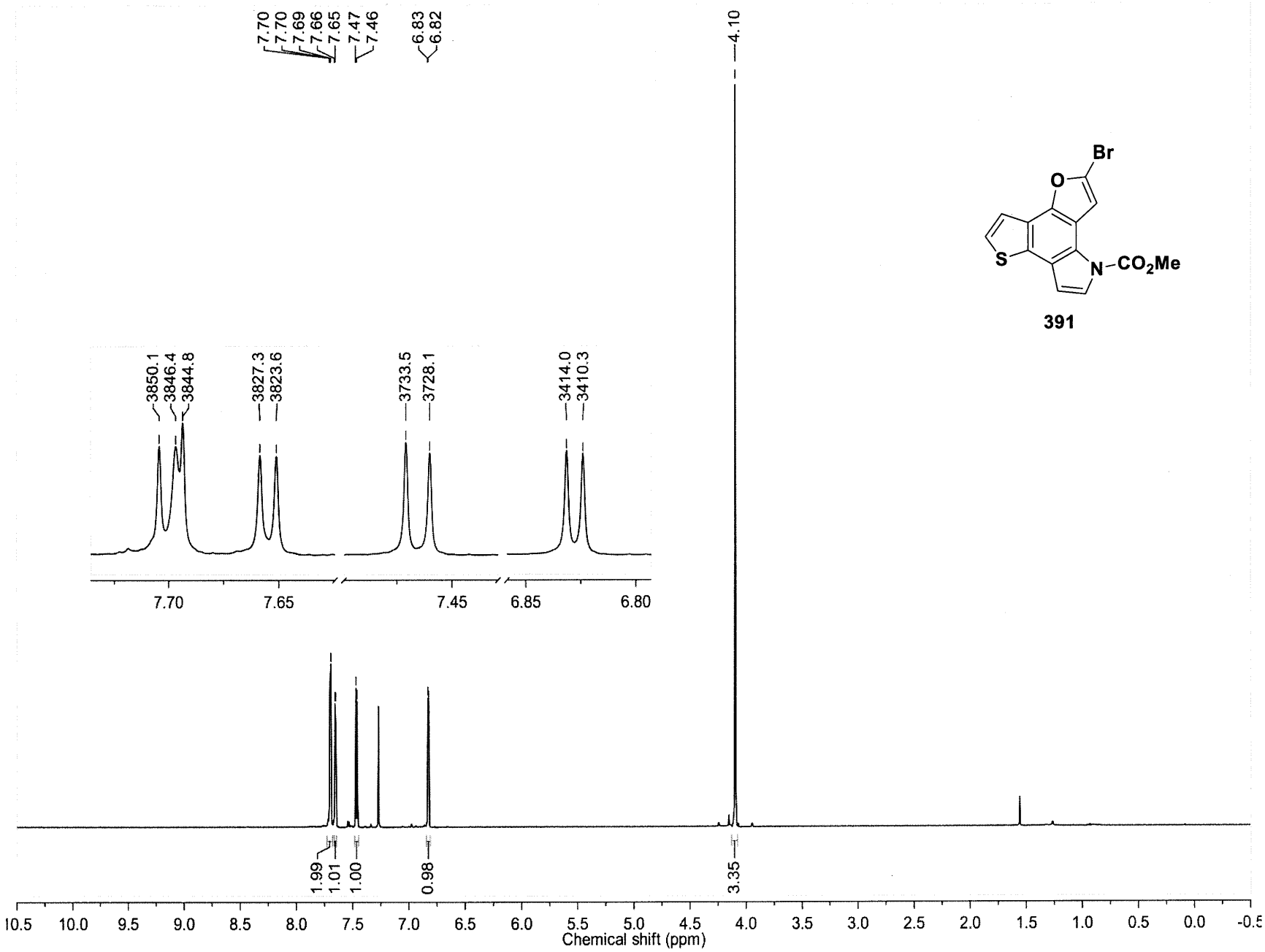
4-((*tert*-Butyldimethylsilyl)oxy)-5-(2,2-dimethoxyethyl)-*N*-(5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxide-2-yl)-*N*-(2-oxoethyl)benzo[*b*]thiophen-6-amine (382). A 25-mL, round-bottomed flask equipped with a rubber septum and an argon inlet needle was charged with **380** (0.109 g, 0.196 mmol, 1.0 equiv), 1.5 mL of 1,4-dioxane, 0.5 mL of water, and 2,6-lutidine (0.045 mL, 0.042 g, 0.39 mmol, 2.0 equiv). OsO_4 (0.125 mL, 4 wt % in water, 0.02 mmol, 0.1 equiv) was added. The resulting brown suspension was then treated with $NaIO_4$ (0.168 g, 0.785 mmol, 4.0 equiv) and the reaction mixture turned white in a few minutes. The reaction mixture was stirred at rt for 3 h and the resulting thick white suspension was then diluted with 10 mL of water and 15 mL of CH_2Cl_2. The aqueous phase was separated and extracted with three 5-mL portions of CH_2Cl_2. The combined organic phases were washed with 15 mL of 5% aqueous $NaHSO_3$ solution and 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford an orange oil. Column chromatography on 9 g of silica gel (elution with 1:1 EtOAc-CH_2Cl_2) afforded 0.061 g (56%) of aldehyde **382** as a very viscous pale yellow oil: IR (film) 3089, 2958, 2932, 2887, 2859, 2832, 2711, 1733, 1544, 1473, 1434, 1413, 1339, 1256, 1181, 1120, 1063, 1035, 1009, 946, 833, and 782 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.72 (s, 1H), 7.34 (d, J = 5.5 Hz, 1H), 7.32 (dd, J = 5.5, 0.6 Hz, 1H), 4.74 (dd, J = 9.2, 2.4 Hz, 1H), 4.32–4.45 (m, 2H), 4.27 (ddd, J = 20.0, 11.0, 1.8 Hz, 2H), 3.75 (ddd, J = 21.6, 11.1, 3.0 Hz, 1H), 3.57 (ddd, J = 21.6, 11.1, 3.0 Hz, 1H), 3.38 (s, 3H), 3.35 (dd, J = 14.0, 9.2 Hz, 1H), 3.10 (s, 3H), 2.98 (dd, J = 14.0, 2.3 Hz, 1H), 1.06 (s, 9H), 0.75 (s, 3H), 0.54 (s, 3H), 0.20 (s, 3H), and 0.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.3, 149.4, 139.0 (d, J = 1.1 Hz), 138.7 (d, J = 1.8 Hz), 133.3 (d, J = 1.1 Hz), 126.0, 123.6 (d, J = 2.8 Hz), 121.5, 119.5 (d, J = 2.3 Hz), 103.7, 76.7 (d, J = 5.3 Hz), 76.6 (d, J = 5.8 Hz), 61.4 (d, J = 6.9 Hz), 56.1, 51.7, 31.8 (d, J = 5.3 Hz), 31.4, 26.2, 21.4, 20.7, 18.8, -3.0, and -3.1; HRMS (DART) *m/z* $[M + Na]^+$ calcd for $C_{25}H_{40}NO_7PSSi$, 580.1925; found 580.1917.

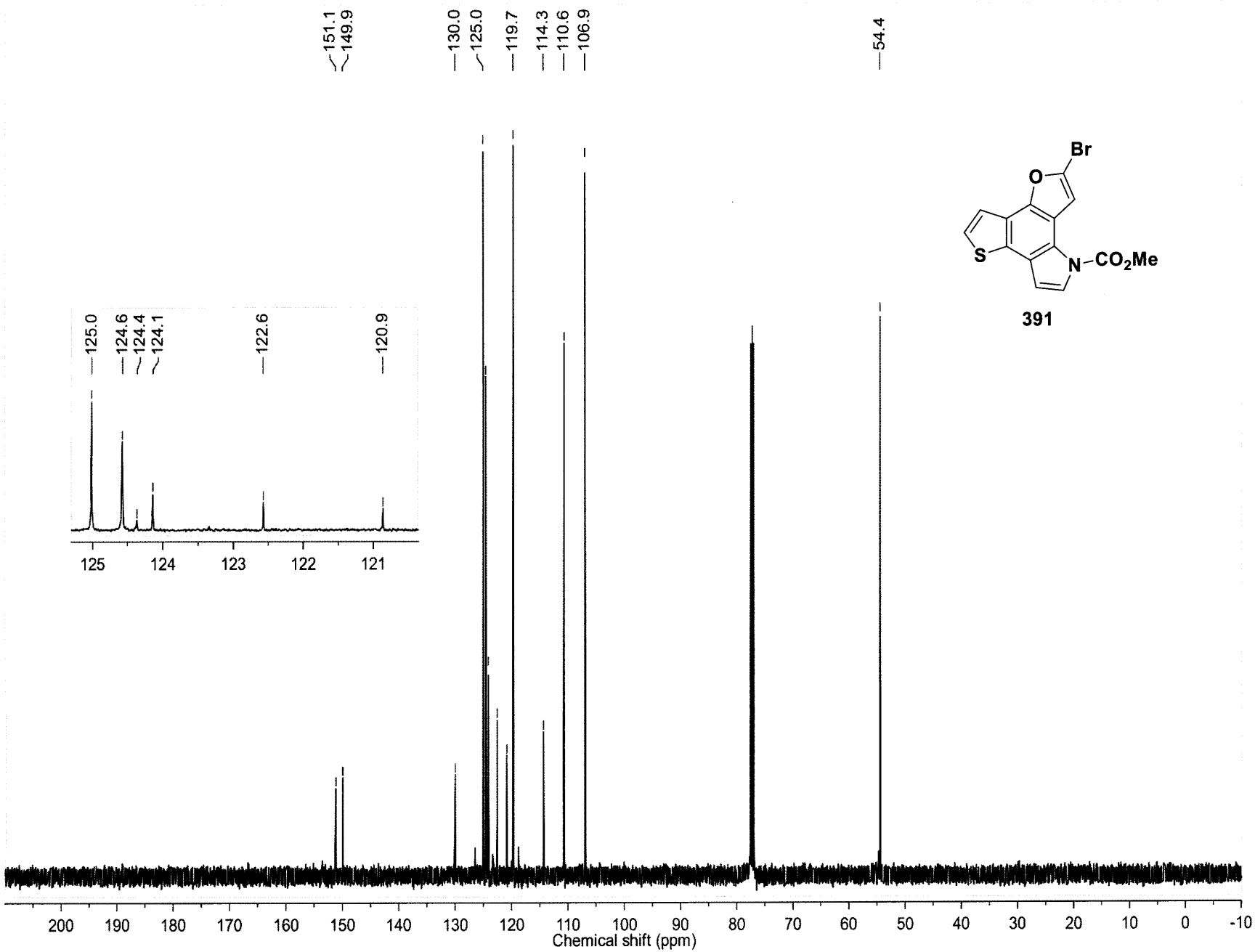
9.81
7.72
7.35
7.34
7.33
7.32
4.75
4.73
4.41
4.39
4.27
4.26
3.76
3.74
3.56
3.35
3.10
2.99
2.96
1.06
0.75
0.54
0.20
0.15
3676.8
3671.3
3666.3
3665.7
3660.8
3660.2
2376.4
2374.0
2367.3
2364.8
2224.6
2213.9
2205.6
2195.0
2179.4
2160.2
2150.7
2148.8
2139.6
2137.7
2130.6
2128.8
2119.5
2117.8
1893.4
1890.5
1882.3
1879.4
1871.9
1869.0
1860.8
1857.8
1803.4
1800.4
1792.3
1789.3
1781.8
1778.8
1770.7
1767.8
1680.0
1675.1
1665.9
1496.8
1494.5
1482.7
1480.5
t-BuMe2SiO
CH(OMe)2
S
N
P
O
O
O
OHC
382
0.86
0.89
0.94
0.93
0.92
1.99
2.03
1.02
1.01
2.82
0.92
9.44
2.94
2.85
3.00
3.11
Chemical shift (ppm)

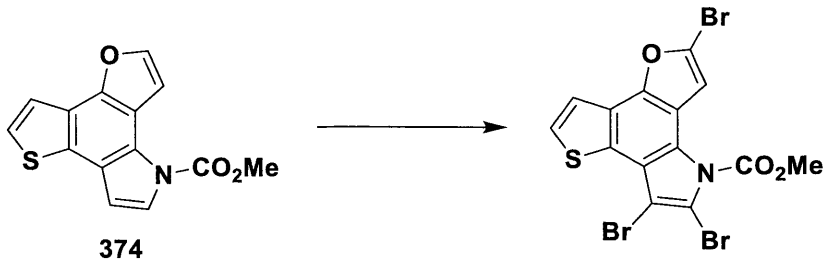

-3.055
-2.968
18.807
20.702
21.439
26.081
26.191
31.437
31.775
31.817
51.742
56.054
61.461
61.406
76.612
76.658
76.726
76.768
76.978
77.230
77.486
103.679
119.517
119.535
121.504
123.573
123.595
126.003
133.259
133.268
138.701
138.715
139.022
139.031
149.399
200.269
0 ppm
20
40
60
80
100
120
140
160
180
200
CH(OMe)2
t-BuMe2SiO
OHC
382



Methyl 2-Bromofuro[2,3-*g*]thieno[2,3-*e*]indole-4-carboxylate (391) and Methyl 2,5-Dibromofuro[2,3-*g*]thieno[2,3-*e*]indole-4-carboxylate (392). A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with tetracycle **374** (0.059 g, 0.217 mmol, 1.0 equiv) and 4 mL of CH_2Cl_2. NBS (0.041 g, 0.228 mmol, 1.05 equiv) was added in one portion and 2 mL of DMF was added dropwise over 2 min. The resulting colorless solution was stirred at rt for 48 h after which TLC showed complete conversion (R_f = 0.48 for the starting material; 0.54 for monobromide **391**; 0.61 for dibromide **392** in 10% EtOAc-hexanes). The resulting orange solution was diluted with 10 mL of water, 10 mL of satd aq $Na_2S_2O_3$ solution, and 20 mL of CH_2Cl_2. The aqueous phase was extracted with three 5-mL portions of CH_2Cl_2 and the combined organic phases were washed with 20 mL of water and 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give a pale orange solid. Column chromatography on 30 g of silica gel (elution with 4% EtOAc-pentane) afforded 0.051 g (67%) of monobromide **391** as a colorless solid: mp 164–165 °C; IR (film) 2956, 1755, 1533, 1446, 1403, 1355, 1333, 1281, 1268, 1183, 1151, 1110, 1052, 920, 760, and 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.699 (d, J = 5.3 Hz, 1H), 7.697 (s, 1H), 7.66 (d, J = 3.7 Hz, 1H), 7.47 (d, J = 5.4 Hz, 1H), 6.83 (d, J = 3.7 Hz, 1H), and 4.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.1, 149.9, 130.0, 125.0, 124.6, 124.4, 124.1, 122.6, 120.9, 119.7, 114.3, 110.6, 106.9, and 54.4; HRMS (DART) *m/z* $[M + H]^+$ calcd for $C_{14}H_8BrNO_3S$, 349.9481; found 349.9474; and 0.007 g (7%) of ca. 90% pure dibromide **392** as a colorless solid: ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J = 5.4 Hz, 1H), 7.48 (d, J = 5.4 Hz, 1H), 7.37 (s, 1H), 7.02 (s, 1H), and 4.16 (s, 3H); HRMS (DART) *m/z* $[M + H]^+$ calcd for $C_{14}H_7Br_2NO_3S$, 427.8586; found 427.8578.

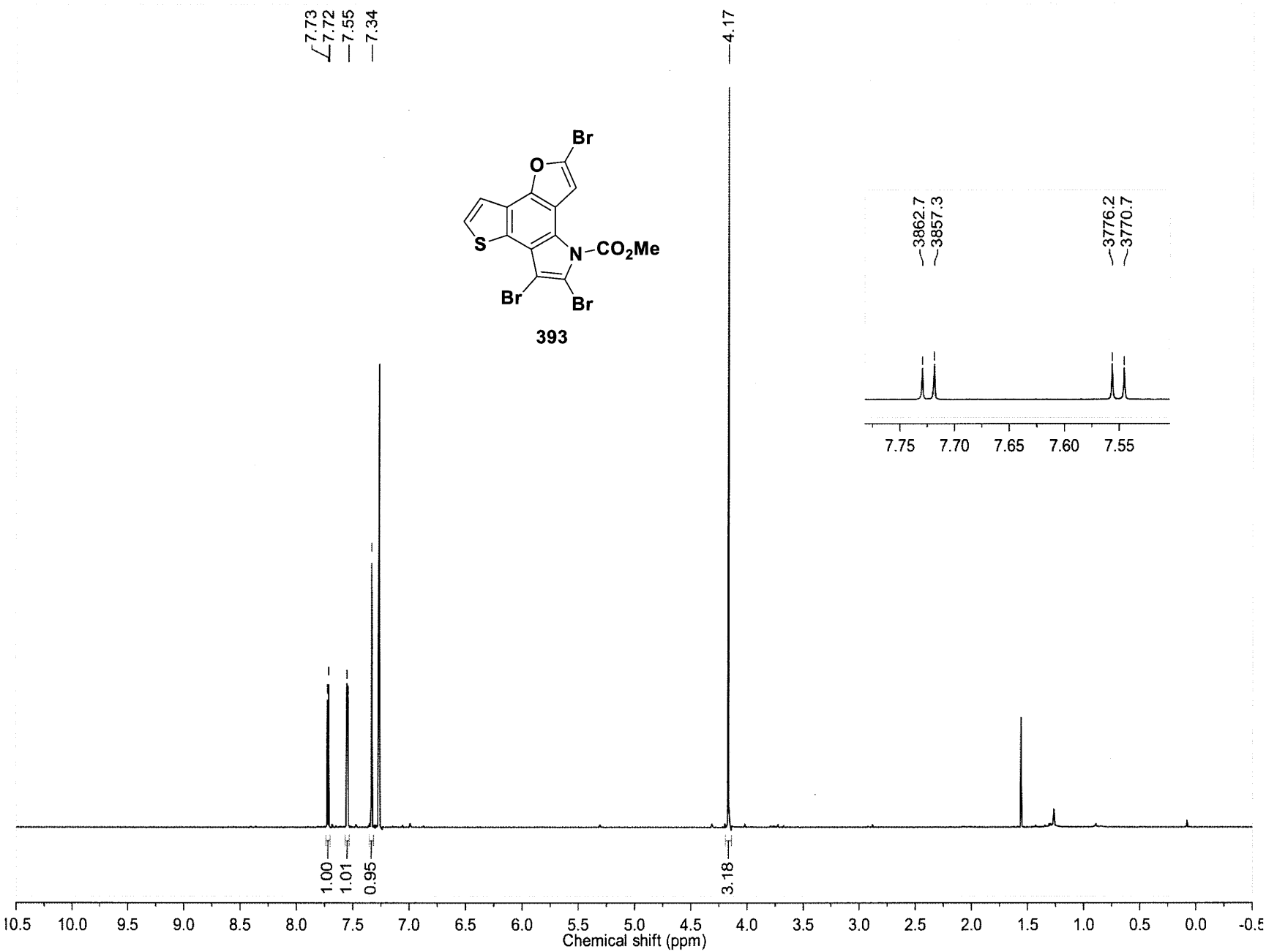

7.70
7.70
7.69
7.66
7.65
7.47
7.46
6.83
6.82
4.10
3850.1
3846.4
3844.8
3827.3
3823.6
3733.5
3728.1
3414.0
3410.3
7.70
7.65
7.45
6.85
6.80
1.99
1.01
1.00
0.98
3.35
Chemical shift (ppm)
Br
O
S
N
CO2Me
391

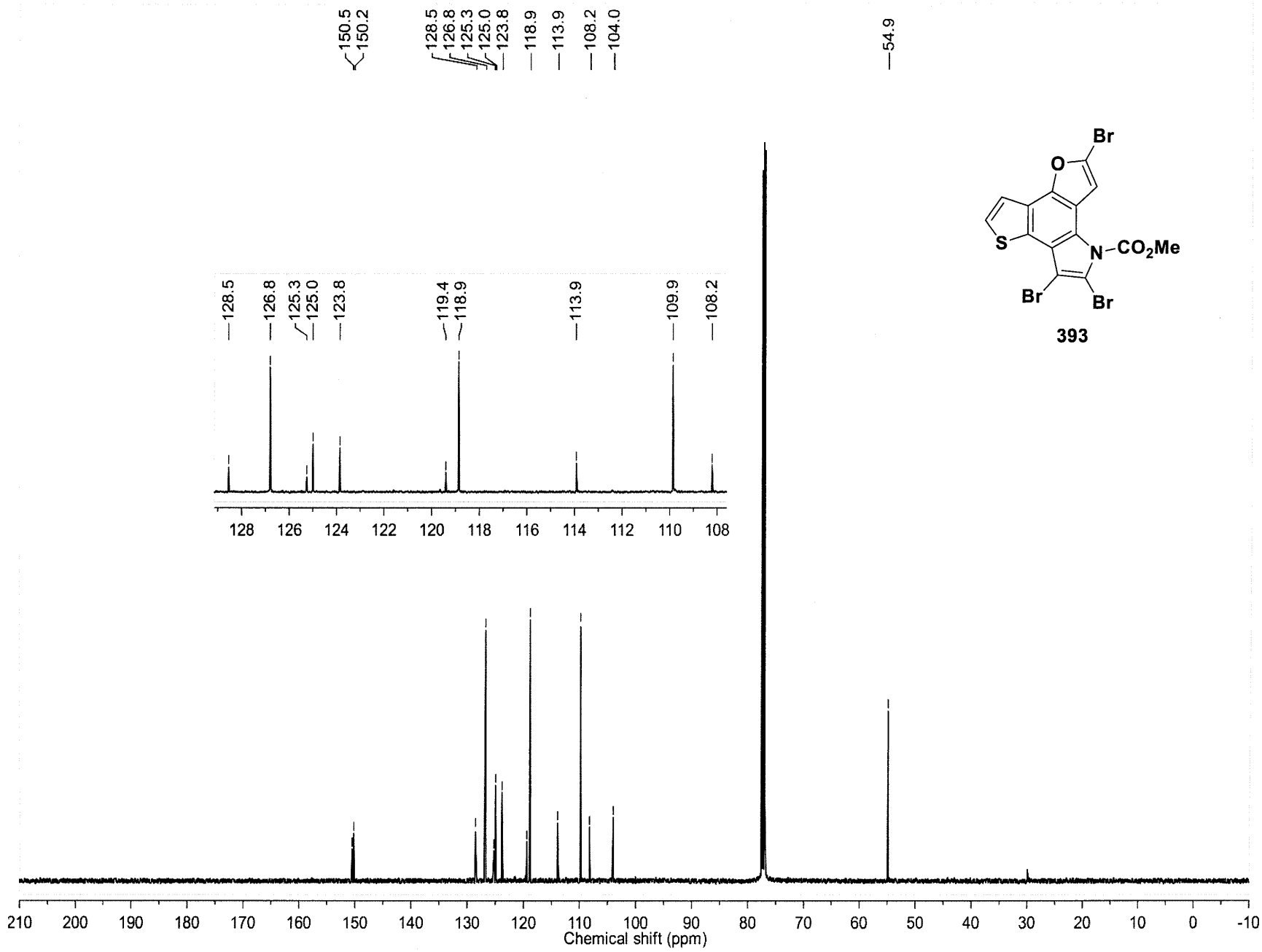

151.1
149.9
130.0
125.0
119.7
114.3
110.6
106.9
54.4
125.0
124.6
124.4
124.1
122.6
120.9
125
124
123
122
121
Br
O
S
N–CO2Me
391
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical shift (ppm)



374 393

Methyl 2,5,6-tribromofuro[2,3-g]thieno[2,3-e]indole-4-carboxylate (393). A 10-mL pear flask equipped with a rubber septum and an argon inlet needle was charged with **374** (0.020 g, 0.074 mmol, 1.0 equiv) and 1.5 mL of $CDCl_3$. NBS (0.028 g, 0.155 mmol, 2.1 equiv) was added, the flask was wrapped with aluminum foil, and the reaction mixture was stirred at rt for 24 h. Additional NBS (0.028 g, 0.155 mmol, 2.1 equiv) was added and the mixture was stirred for another 24 h. The resulting pale orange suspension was diluted with 5 mL of brine, 2 mL of satd aq $NaHCO_3$ solution, and 5 mL of CH_2Cl_2. The aqueous layer was separated and extracted with two 4-mL portions of CH_2Cl_2. The combined organic phases were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford a white solid. Column chromatography on 8 g of silica gel (elution with 3.5% EtOAc in hexanes) afforded 0.020 g (54%) of tribromide **393** as a colorless solid: mp 201 °C (dec.); IR (film) 1748, 1559, 1517, 1438, 1377, 1338, 1276, 1258, 1165, 1084, and 712 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 5.4 Hz, 1H), 7.55 (d, J = 5.4 Hz, 1H), 7.34 (s, 1H), and 4.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.5, 150.2, 128.5, 126.8, 125.3, 125.0, 123.9, 119.4, 118.9, 113.9, 109.9, 108.2, 104.0, and 54.8; HRMS (DART) *m/z* $[M + H]^+$ calcd for $C_{14}H_6Br_3NO_3S$, 509.7658; found 509.7666.


7.73
7.72
7.55
7.34
4.17
Br
O
S
N–CO2Me
Br
Br
393
3862.7
3857.3
3776.2
3770.7
7.75
7.70
7.65
7.60
7.55
1.00
1.01
0.95
3.18
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
Chemical shift (ppm)


150.5
150.2
128.5
126.8
125.3
125.0
123.8
118.9
113.9
108.2
104.0
54.9
Br
O
S
N
CO2Me
Br
Br
393
128.5
126.8
125.3
125.0
123.8
119.4
118.9
113.9
109.9
108.2
128
126
124
122
120
118
116
114
112
110
108
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical shift (ppm)