SYNTHESIS OF HIGHLY SUBSTITUTED BENZO-FUSED NITROGEN HETEROCYCLES VIA TANDEM BENZANNULATION/CYCLIZATION STRATEGIES

By

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For my wife Britt

and

my parents

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ABSTRACT

Benzannulations employing ynamides and vinylketenes (generated in situ from α-diazo ketones) were investigated. Irradiation of the diazo ketones using a batch or continuous-flow reactor leads to the formation of vinylketenes via a photo-Wolff rearrangement. The vinylketenes then react with ynamides via a pericyclic cascade process to produce highly substituted aniline derivatives. Using this vinylketene-based benzannulation, tandem strategies for the synthesis of highly substituted benzo-fused nitrogen heterocycles were investigated. A tandem benzannulation-iodocyclization method for the synthesis of polysubstituted quinolines was established. In addition, a tandem strategy for the synthesis of carbazoles was developed and applied in the total synthesis of the carbazole alkaloid carazostatin as well as formal syntheses of the alkaloids carbazoquinocin C and antiostatin A_4.

Thesis Supervisor: Rick L. Danheiser

Title: Arthur C. Cope Professor of Chemistry

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Part III. Tandem Benzannulation-Cyclization Strategies for the Synthesis of Highly Substituted Carbazoles

Part I

A Benzannulation Strategy for the Regioselective Synthesis of Polysubstituted Aromatic and Heteroaromatic Compounds

Chapter 1
Introduction and Background

Several approaches exist for the regioselective synthesis of highly substituted and functionalized benzene derivatives. Classical approaches rely on multistep strategies that utilize transformations like nucleophilic and electrophilic aromatic substitution, cross-coupling reactions, and metallation-functionalization reactions to install substituents in an iterative fashion. This iterative multistep strategy is effective for the synthesis of benzene derivatives bearing only a few substituents; however, regioselectivity and chemoselectivity often become a problem as the number of substituents increases. As a result, the efficient synthesis of highly substituted and densely functionalized benzenoid aromatic compounds remains a challenge.

One way to overcome this problem is to employ a benzannulation strategy.[1] Relative to stepwise classical approaches, benzannulation-based approaches are convergent, can be efficient, and can provide direct access to a variety of substitution patterns. Benzannulation processes typically involve the combination of non-aromatic reactants and the formation of at least two new carbon-carbon bonds. The newly formed aromatic structure is decorated with functionality dictated by the starting materials.

The development of methodology for the synthesis of polysubstituted aromatic compounds is a long-standing goal in our laboratory. While numerous approaches have been explored, the focus of the research described in this thesis is the continued development of a vinylketene-based benzannulation for the synthesis of amino-substituted aromatic compounds.[2,3] The next section of this chapter presents an overview of general annulation methods for the synthesis of highly substituted benzene derivatives with an emphasis on recent developments.

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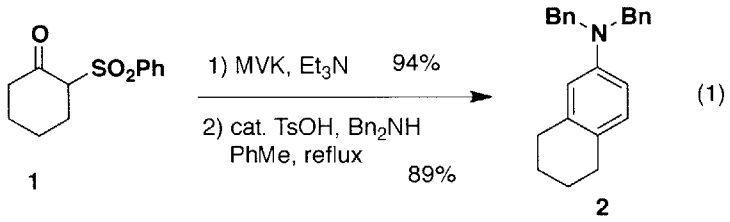
[1] For reviews of benzannulation strategies, see: (a) Kotha, S.; Misra, S.; Halder, S. *Tetrahedron* **2008**, *64*, 10775-10790. (b) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901-2915. (c) Bamfield, P.; Gordon, P. F. *Chem. Soc. Rev.* **1984**, *13*, 441-488.

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

[3] For additional studies. see: (a) 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. (b) Lam, T. L. Synthesis of Indoles via a Tandem Benzannulation-Cyclization Strategy. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, September, 2008.

Annulation Methods for the Synthesis of Highly Substituted Benzene Derivatives

Some of the earliest annulation methods for the synthesis of polysubstituted benzene derivatives were based on condensation reactions. One common approach involves the use of a modified Robinson annulation. A recent example of this strategy begins with the reaction of a 2-sulfonyl substituted ketone **1** and methyl vinyl ketone (MVK) in the presence of triethylamine (eq 1). Heating the resulting Michael addition product in toluene with dibenzylamine furnishes the aniline derivative **2**.[4,5] Other examples of condensation-based benzannulations include miscellaneous strategies relying on Michael-type additions[6,7] and [3 + 3] approaches utilizing the reaction of a dicarbanion equivalent with a dielectrophilic partner.[8]



(1)

Other prior benzannulations for the synthesis of highly substituted benzene derivatives employ cycloadditions as a key step. Our laboratory has developed a formal [2 + 2 + 2] approach to the synthesis of highly substituted arenes.[9] In the example shown in Scheme 1, the intermediate vinylallene **4** is generated from the tethered diyne **3** via a propargylic ene reaction, and subsequently trapped in a Diels-Alder reaction with the alkyne **5**. Isomerization with DBU affords the pentasubstituted aromatic product **7**. Several transition-metal catalyzed [2 + 2 + 2] approaches have also been developed for the synthesis of polysubstituted aromatics (vide infra).

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[4] Kiren, S.; Padwa, A. *J. Org. Chem.* **2009**, *74*, 7781-7789.

[5] For an earlier example of this reaction leading to substituted phenols, see: Boger, D. L.; Mullican, M. D. *J. Org. Chem.* **1980**, *45*, 5002-5004.

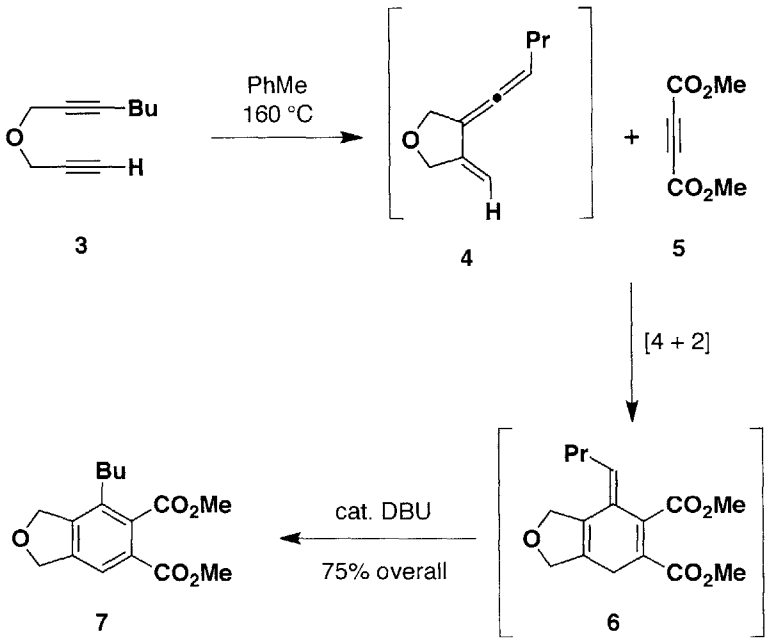
[6] For examples, see: (a) Li, L.; Zhao, M.-N.; Ren, Z.-H.; Li, J.-L.; Guan, Z.-H. *Org. Lett.* **2012**, *14*, 3506-3509. (b) Han, X.-D.; Zhao, Y.-L.; Meng, J.; Ren, C.-Q.; Liu, Q. *J. Org. Chem.* **2012**, *77*, 5173-5178. (c) Xue, D.; Li, J.; Zhang, Z.-T.; Deng, J.-G. *J. Org. Chem.* **2007**, *72*, 5443-5445. (d) Nakaike, Y.; Kamijo, Y.; Mori, S.; Tamura, M.; Nishiwaki, N.; Ariga, M. *J. Org. Chem.* **2005**, *70*, 10169-10171.

[7] For a reviews of the "Hauser Annulation", see: (a) Mal, D.; Pahari, P. *Chem. Rev.* **2007**, *107*, 1892-1918. (b) Rathwell, K.; Brimble, M. A. *Synthesis* **2007**, 643-662. For a review of the "Staunton-Weinreb Annulation", see: (c) Donner, C. D. *Tetrahedron* **2013**, *69*, 3747-3773.

[8] For a review of [3 + 3] approaches, see: Feist, H.; Langer, P. *Synthesis* **2007**, 327-347.

[9] Robinson, J. M.; Sakai, T.; Okano, K.; Kitawaki, T.; Danheiser, R. L. *J. Am. Chem. Soc.* **2010**, *132*, 11039-11041.

Scheme 1



While the above example represents a formal [2 + 2 + 2] annulation, it can also be viewed as a Diels-Alder reaction between a vinylallene and an alkyne. The use of the Diels-Alder cycloaddition as a means of generating highly substituted arenes has been extensively studied. In most cases, the desired aromatic compound is not obtained directly from the [4 + 2] cycloaddition. Typically, the intermediate six-membered ring cycloadduct aromatizes under the reaction conditions. However, some reactions, like the example above, employ the addition of a base, acid, or oxidant in order to generate the desired aromatic product.

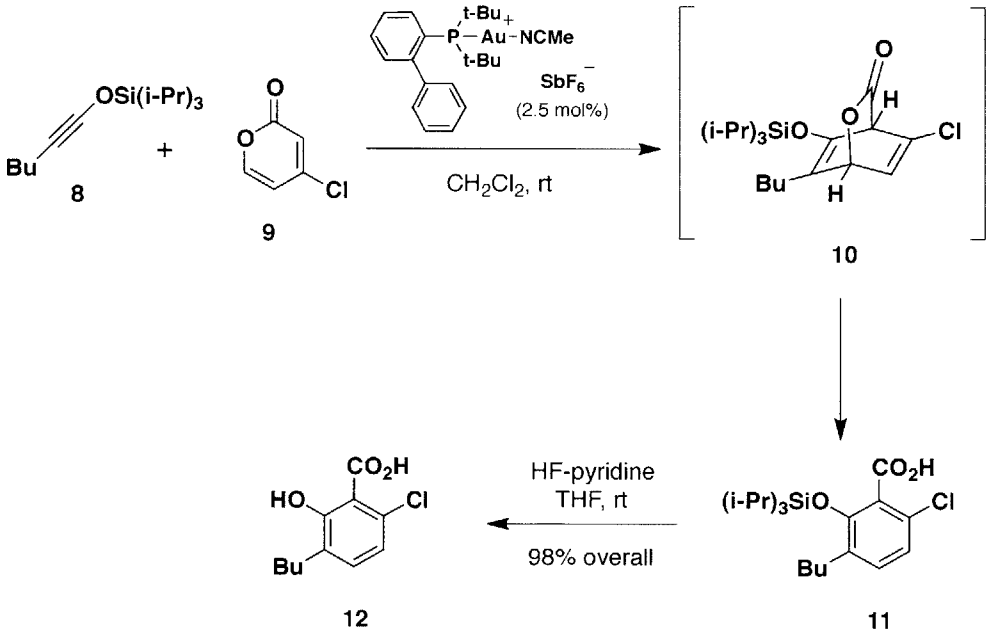
Several strategies have been developed that utilize cycloreversion as the final aromatization step. Examples of this strategy include the Alder-Rickert reaction of alkynes with 1,3-cyclohexadienes[10] and the [4 + 2] cycloaddition of α-pyrones and alkynes.[11,12]

Other approaches use an elimination to aromatize the final product. Arenes have been synthesized using a [4 + 2] cycloaddition approach based on the reaction of various dienophiles

[10] (a) Alder, K.; Rickert, H., F. *Chem. Ber.* **1937**, *70*, 1364. (b) Rickborn, B. *Org. React.* **1998**, *52*, 1-393.
[11] For a review, see: Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111-9171.
[12] For selected recent examples, see: (a) Kirkham, J. D.; Butlin, R. J.; Harrity, J. P. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 6402-6405. (b) Delaney, P. M.; Browne, D. L.; Adams, H.; Plant, A.; Harrity, J. P. A. *Tetrahedron* **2008**, *64*, 866-873. (c) Kranjc, K.; Štefane, B.; Polanc, S.; Kočevar, M. *J. Org. Chem.* **2004**, *69*, 3190-3193.

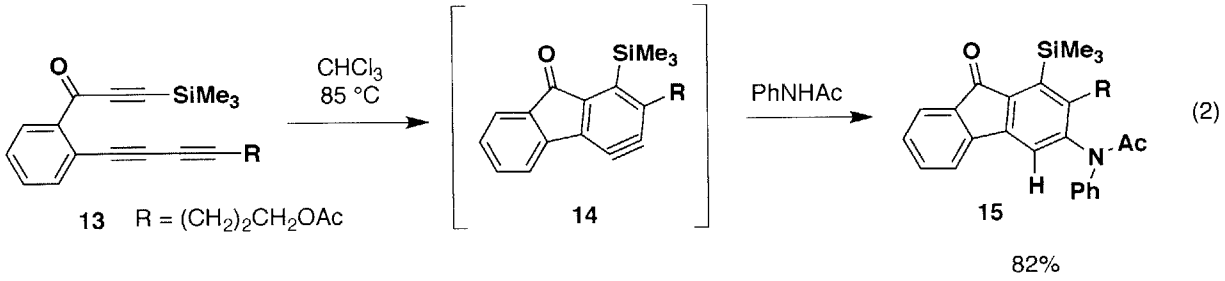
with furan derivatives.[13,14] In these Diels-Alder strategies, the aromatized product is formed via ring-opening of the intermediate oxabicyclic cycloaddition product to form a cyclohexadiene that can then be aromatized via dehydration. Kozmin and co-workers discovered a gold-catalyzed Diels-Alder reaction of substituted α-pyrones, e.g. **9**, and siloxyalkyne dienophiles, e.g. **8**.[15] Unlike many benzannulations that utilize α-pyrones, this process does not employ a cycloreversion with the loss of CO_2 to aromatize the product. In this case, the intermediate **10** aromatizes via ring opening followed by proton transfer. Subsequent desilylation with HF affords the phenolic product **12**. While this method generates the desired phenol in high yield, the limited availability of highly substituted α-pyrones limits the utility of this method in the synthesis of more highly substituted benzenes.

Scheme 2



[13] (a) Vogel, P. *Tetrahedron* **1999**, *55*, 13521-13642 (b) Chiu, P.; Lautens, M. C. *Top. Curr. Chem.* **1997**, *190*, 1-85.
[14] (a) Padwa, A.; Dimitroff, M.; Waterson, A. G.; Wu, T. *J. Org. Chem.* **1997**, *62*, 4088-4096. (b) Padwa, A.; Snyder, J. P.; Curtix, E. A.; Sheehan, S. M.; Worsencroft, K. J.; Kappe, C. O. *J. Am. Chem. Soc.* **2000**, *122*, 8155-8167. (c) Janvier, P.; Bienaymé, H.; Zhu, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 4291-4294.
[15] Cabrera-Pardo, J. R.; Chai, D. I.; Liu, S.; Mrksich, M.; Kozmin, S. A. *Nature Chem.* **2013**, *5*, 423-427.

Several other [4 + 2] cycloaddition-based methods exist. Our laboratory developed a [4 + 2] strategy based on cycloadditions of conjugated enynes with alkynes.[16] The initial product is a strained cyclic allene, which isomerizes to form the final aromatic product. Our laboratory also studied a [4 + 2] strategy employing (silyl)vinylketenes and lithium ynolate dienophiles that utilize tautomerization as the final aromatization step.[17] One final example of a [4 + 2] benzannulation method is the "hexahydro-Diels-Alder reaction" recently reported by Hoye and coworkers.[18] As illustrated in eq 2, heating compound **13** leads to a [4 + 2] cycloaddition, generating the intermediate benzyne **14**, which can subsequently be trapped in situ by an amine nucleophile to provide **15**. Other benzyne trapping agents also work well.



Numerous transition-metal catalyzed (or mediated) benzannulation processes have been explored for the efficient and regioselective synthesis of highly substituted aromatic systems.[19] As mentioned previously, the transition-metal catalyzed [2 + 2 + 2] cyclotrimerization of alkynes has been used for the synthesis of polysubstituted arenes.[20] The intermolecular version of this reaction often suffers from poor regioselectivity and the formation of self-condensation products. However, as demonstrated by Vollhardt and others, the use of partially or fully intramolecular approaches often allows for improved yields and regiochemical reactions.[21] Modified versions of this approach have also been developed. For example, the Rh(I)-catalyzed annulation of

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[16] (a) Danheiser, R. L.; Gould, A. E.; Fernandez de la Pradilla, R.; Helgason, A. L. *J. Org. Chem.* **1994**, *59*, 5514-5515. (b) Hayes, M. E.; Shinokubo, H.; Danheiser, R. L. *Org. Lett.* **2005**, *7*, 3917-3920.

[17] Austin, W. F.; Zhang, Y.; Danheiser, R. L. *Org. Lett.* **2005**, *7*, 3905-3908.

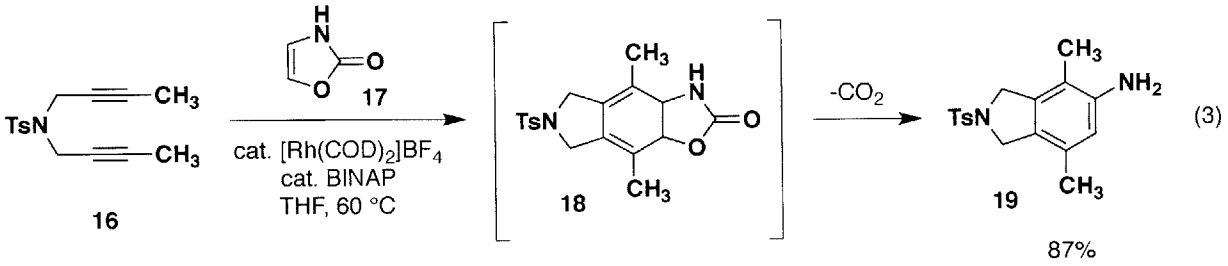
[18] Hoye, T. R.; Baire, B.; Niu, D.; Willoughby, P. H.; Woods, B. P. *Nature* **2012**, *490*, 208-212.

[19] For a recent review see: Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901-2916.

[20] For recent reviews see: (a) Broere, D. L. J.; Ruijter, E. *Synthesis* **2012**, *44*, 2639-2672. (b) Hua, R.; Abrenica, M. V. A.; Wang, P. *Curr. Org. Chem.* **2011**, *15*, 712-729. (c) Agenet, N.; Buisine, O.; Slowinski, F.; Gandon, V.; Aubert, C.; Malacria, M. *Org. React.* **2007**, *68*, 1-302. (d) Chopade, P. R.; Louie, J. *Adv. Synth. Catal.* **2006**, *348*, 2307-2327.

[21] Funk, R. L.; Volhardt, K. P. C. *J. Am. Chem. Soc.* **1980**, *102*, 5253-5261.

diyne **16** and 2-oxazolone **17** results in intermediate **18** which loses CO_2 under the reaction conditions to afford the aniline product **19**.[22]



Several transition-metal catalyzed [4 + 2] annulations have been investigated for the regioselective synthesis of polysubstituted arenes.[23,24] Of particular note is the approach developed by Asao and Yamamoto using π-Lewis acid metal-catalyzed [4 + 2] benzannulation reactions.[25,26]

Despite these recent advances, the Dötz benzannulation[27] remains the most general and regioselective transition-metal catalyzed method for the synthesis of benzene derivatives.[28] The prototypical Dötz benzannulation involves the reaction of a chromium alkoxycarbene **20** with an alkyne **23** to form a chromium-complexed dienylketene that undergoes electrocyclic ring closure and decomplexation to afford the annulation product **24**. Amino substituted products like **25** can also be synthesized from the corresponding chromium aminocarbene **21**. However, aminocarbenes such as **21**, are generally less reactive and frequently undergo a competitive

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[22] Zhang, K.; Louie, J. *J. Org. Chem.* **2011**, *76*, 4686-4691.

[23] For a review, see: Rubin, M.; Sromek, A. W.; Gevorgyan, V. *Synlett* **2003**, 2265-2291.

[24] (a) Hojo, D.; Tanaka, K.; *Org. Lett.* **2012**, *14*, 1492-1495. (b) Han, X.-D.; Zhao, Y.-L.; Meng, J.; Ren, C.-Q.; Liu, Q. *J. Org. Chem.* **2012**, *77*, 5173-5178. (c) Auvinet, A.-L. Harrity, J. P. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 2769-2772. (d) Saito, S.; Uchiyama, N.; Gevorgyan, V.; Yamamoto, Y. *J. Org. Chem.* **2000**, *65*, 4388.

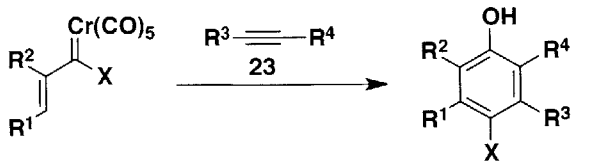
[25] (a) Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12650-12651. (b) Asao, N.; Nogami, T.; Lee, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 10921-10925. (c) For a recent review, see: Asao, N. *Synlett* **2006**, 1645-1656.

[26] For more recent examples, see: (b) Jones, D. M.; Dudley, G. B. *Tetrahedron* **2010**, *66*, 4860-4866. (b) Isogai, Y.; Menggenbateer; Khan, F. N.; Asao, N. *Tetrahedron* **2009**, *65* 9575-9582. (c) For another example that utilizes iodine, see: Kloeckner, U.; Finkbeiner, P.; Nachtsheim, B. J. *J. Org. Chem.* **2013**, *78*, 2751-2756.

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

[28] 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**, *73*, 121-623. (c) Dötz, K. H.; Stendel, J., Jr. In *Modern Arene Chemistry*; Astru, 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.

cyclopentannulation reaction due to the strong donor effect of the nitrogen. Using an acylaminocarbene, such as **22**, attenuates this effect.[29]

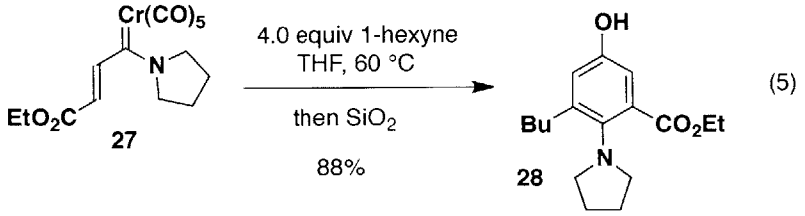


(4)

20 X = OR
21 X = NR_2
22 X = NR(EWG)

24 X = OR
25 X = NR_2
26 X = NR(EWG)

The alkenyl(amino)carbene **27** with an electron-withdrawing group on the alkene, first described by Barluenga, has also proved to be a reliable partner in the Dötz benzannulation. Reaction of **27** with excess 1-hexyne provided the aniline derivative **28** in excellent yield.[30]



(5)

Merlic and co-workers developed an approach to the synthesis of highly substituted anilines that is similar to the Dötz benzannulation.[31] The reaction of Fischer carbene complex **29** with *tert*-butyl isonitrile affords the dienylketenimine complex **30** that undergoes electrocyclization to the naphthalene adduct **31** (eq 6).

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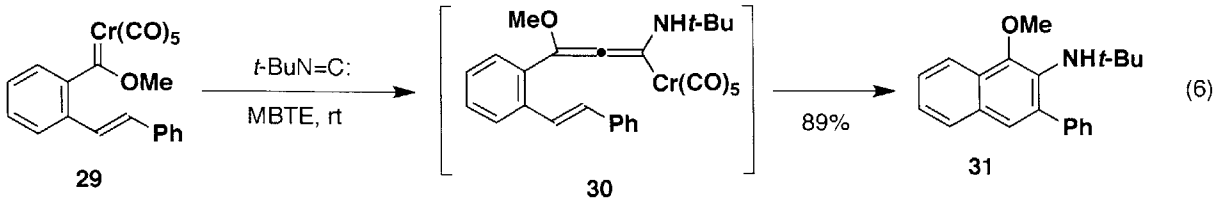
[29] Grotjahn, D. B.; Dötz, K. H. *Synlett*, **1991**, 381-390.

[30] (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.

[31] (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. (d) Merlic, C. A.; Aldrich, C. C.; Albaneze-Walker, J.; Saghtelian, A.; Mammen, J. *J. Org. Chem.* **2001**, *66*, 1297-1309.

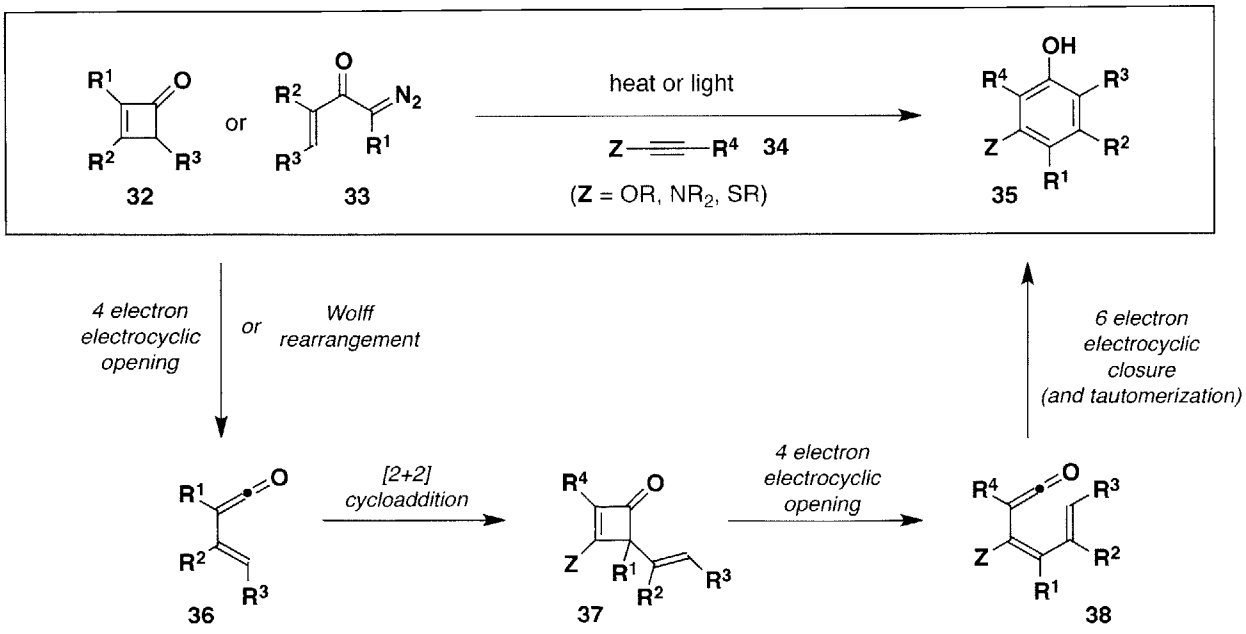


In summary, the development of new benzannulation reactions remains an intense area of research. The next section discusses in detail the vinylketene-based benzannulation method developed in our laboratory.

The Danheiser Benzannulation and Closely Related Benzannulations

Around the same time as the development of the Dötz annulation, our laboratory reported an aromatic annulation strategy based on the reaction of cyclobutenones or α-diazo ketones with activated alkynes.[32,33] As depicted in Scheme 3, the annulation can be triggered by either heat or light and proceeds through a cascade process involving a sequence of 3 to 4 pericyclic reactions to furnish the phenolic product **35**.

Scheme 3



[32] Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1672-1674.
[33] Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc.* **1990**, *112*, 3093-3100.

Vinylketene[34] **36**, generated either via the four-electron electrocyclic cleavage of a cyclobutenone[32] **32** or from the photo-Wolff rearrangement of a diazo ketone[33] **33**, participates in a [2 + 2] cycloaddition[35] with an activated alkyne 2-π component **34** to form vinylcyclobutenone **37**. Subsequent electrocyclic cleavage of **37** is followed by rapid six-electron electrocyclic ring closure and tautomerization to provide the polysubstituted aromatic compound **35**.

"First Generation" Benzannulation Strategy

In the "first generation" benzannulation reaction, exposure of a cyclobutenone[36] is exposed to either thermal[32] or photochemical[37] conditions in order to generate the intermediate vinylketene. The reactivity of the vinylketene in the initial [2 + 2] cycloaddition with an activated alkyne varies depending on the substitution pattern of the cyclobutenone. "Aldoketenes", such as **41,** typically undergo [2 + 2] cycloadditions with alkynes below the temperature required for the electrocyclic ring opening. In contrast, "ketoketenes", such as **44**, which are generated from 2-substituted cyclobutenones (e.g. **43**), require elevated temperatures for the [2 + 2] cycloaddition to proceed.

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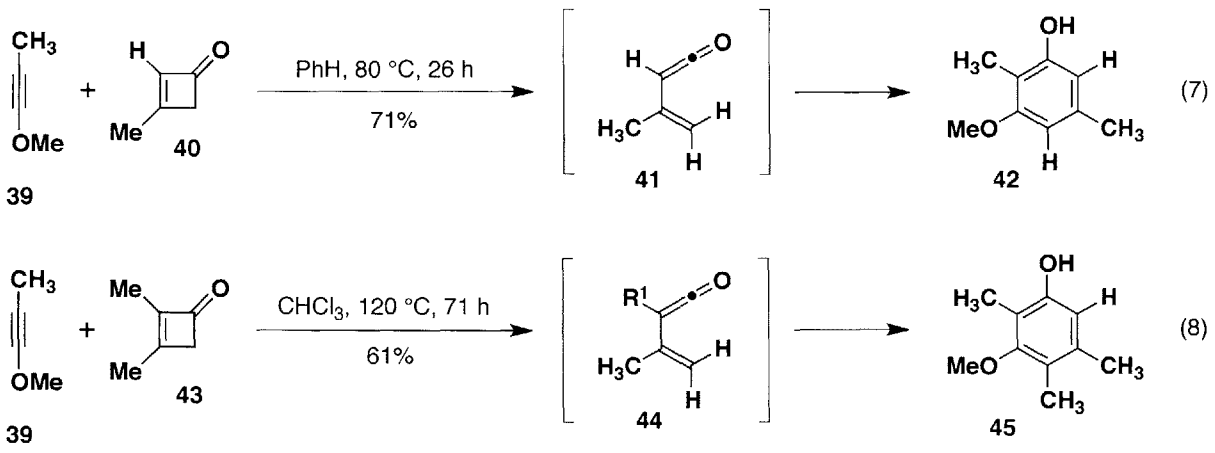
[34] For reviews on the chemistry of vinylketenes, see: (a) Tidwell, T. T. *Ketenes*, 2nd Ed.; Wiley: Hoboken, NJ, 2006, pp 206-214. (b) Danheiser, R. L.; Dudley, G. B.; Austin, W. F. In *Science of Synthesis;* Danheiser, R. L., Ed.; Thieme: Stuttgart, 2006; Vol. 23; pp 493-568.

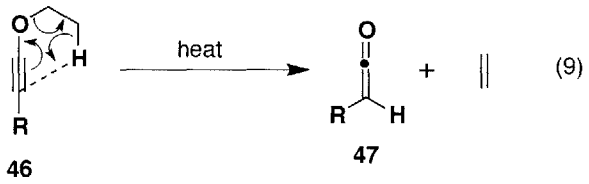
[35] For a review of the [2 + 2] cycloaddition of ketenes, including vinylketenes with alkenes, see: (a) Hyatt, J. A.; Reynolds, P. W. *Org. React.* **1994**, *45*, 159-646. (b) Snider, B. B. *Chem. Rev.* **1988**, *88*, 793-811. (c) ref 33

[36] For reviews on the chemistry of cyclobutenones, see: (a) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485-1537. (b) For references regarding carbocyclic four-membered ring compounds, see: *Methods of Organic Chemistry (Houben-Weyl)*; de Meijere, A., Ed.; Theme: Stuttgart, 1997; Vol. E17e and E17f. (c) Belluš, D.; Ernst, B. *Angew. Chem. Int. Ed.* **1988**, *27*, 797-827.

[37] Pal, K. A Photochemical Annulation Approach to Highly Substituted Aromatic Compounds. Massachusetts Institute of Technology, Cambridge, MA February, 1987.



Benzannulations with alkynyl ethers performed under thermal conditions are typically limited to reactions involving alkynyl ethers that lack β-hydrogens; otherwise, the alkynyl ethers undergo retro-ene reactions to form ketenes at the elevated temperatures (eq 9).[38]



The use of siloxyalkynes as ketenophiles avoids this problem. In addition, trialkylsiloxyalkynes allow for the facile synthesis of resorcinol derivatives by avoiding the harsh conditions often required for methyl ether cleavage.[39,40] Other activated alkynes, like alkynyl thioethers, participate readily in the benzannulation reaction. Because the resulting thioether can be reductively cleaved with Raney-Ni, alkynyl thioethers can serve as surrogates for terminal alkynes.[41]

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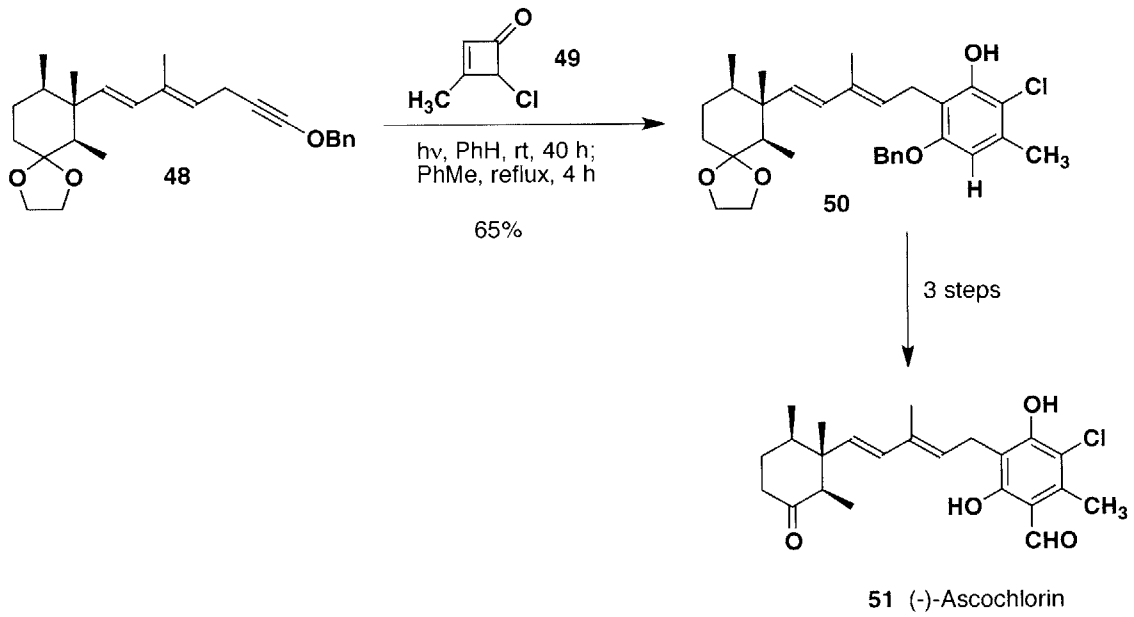
[38] Brandsma, L.; Bos, H. J. T.; Arens, J. F. In *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, 1969; pp 808-810.
[39] Danheiser, R. L.; Nishida,A.; Savariar, S.; Trova, M. P. *Tetrahedron* **1988**, *29*, 4917-4920.
[40] Kowalski, C. J.; Lal, G. S. *J. Am. Chem. Soc.* **1988**, *110*, 3693-3695.
[41] Unactivated alkynes can react with 4,4-dichlorocyclobutenones to give mixtures of monochloro- and dichlorophenols, see: Kowalcyzk, J. J. Annulation Approaches to Highly Substituted Aromatic Compounds. Massachusetts Institute of Technology, Cambridge, MA, June 1988.

The "first generation" benzannulation strategy has been employed in a number of total syntheses by our lab and others.[42] Scheme 4 illustrates the total synthesis of ascochlorin completed in our laboratory in 2000.[42e] The key benzannulation reaction of the advanced intermediate benzyloxy alkynyl ether **48** and cyclobutenone **49** proceeded smoothly to afford the desired pentasubstituted aromatic product in 71% yield. The benzannulation was initiated by irradiation of the reaction solution with a Hanovia lamp. The resulting reaction mixture was then heated in toluene at reflux in order to complete conversion of the remaining vinylcyclobutenone. Only three subsequent steps were required to complete the synthesis.

Scheme 4



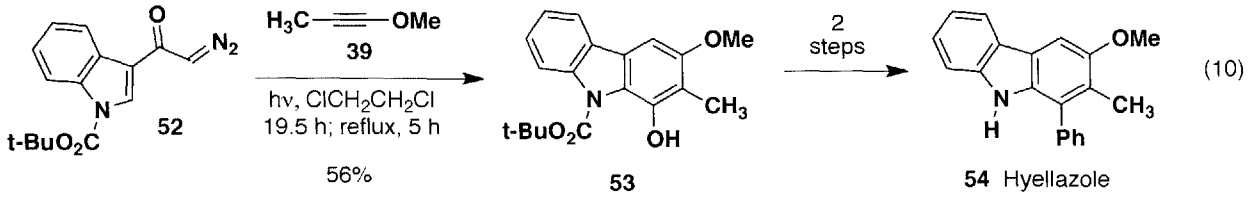
51 (-)-Ascochlorin

"Second Generation" Benzannulation

Our laboratory reported a new variant of the vinylketene-based benzannulation in 1990.[33] This "second generation" version of the benzannulation extended the scope of the method to include the synthesis of polycyclic aromatic compounds as well as heterocyclic derivatives by utilizing α-diazo ketones as the vinylketene precursor. The requisite vinyl-, aryl-, or

[42] (a) ref 32. (b) ref 40. (c) Danheiser, R. L.; Gee, S. K.; Perez, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 806-810. (d) Smith, A. B.; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **1999**, *121*, 7423-7424. (e) Dudley, G. B.; Takaki, K. S.; Cha, D. D.; Danheiser, R. L. *Org. Lett.* **2000**, *2*, 3407-3410.

hetarylketenes were generated in situ via a photo-Wolff rearrangement.[43] The power of this "second generation" benzannulation was demonstrated in the total synthesis of the marine natural product hyellazole. As illustrated in eq 10, irradiation of a solution of the indolyl diazo ketone **52** and methoxypropyne **39** followed by heating at reflux afforded the carbazole **53** in 56% yield. Just two steps were required to complete the total synthesis of hyellazole **54**.



(10)

Other natural product syntheses have since been completed using this variation of the benzannulation strategy. This method has been particularly effective in the construction of diterpene natural products.[44]

The Related Benzannulation Strategies of Liebeskind and Moore

Liebeskind[45] and Moore[46] have independently reported a general method for the synthesis of substituted quinone derivatives. Electrocyclic ring-opening of an aryl or vinylcyclobutenone followed by electrocyclization also comprise the final steps of the mechanism for the Liebeskind and Moore benzannulation. The first step of their general strategy is the nucleophilic addition of an aryl or vinylithium reagent **56** to a squaric acid derivative **55** to

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[43] 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.

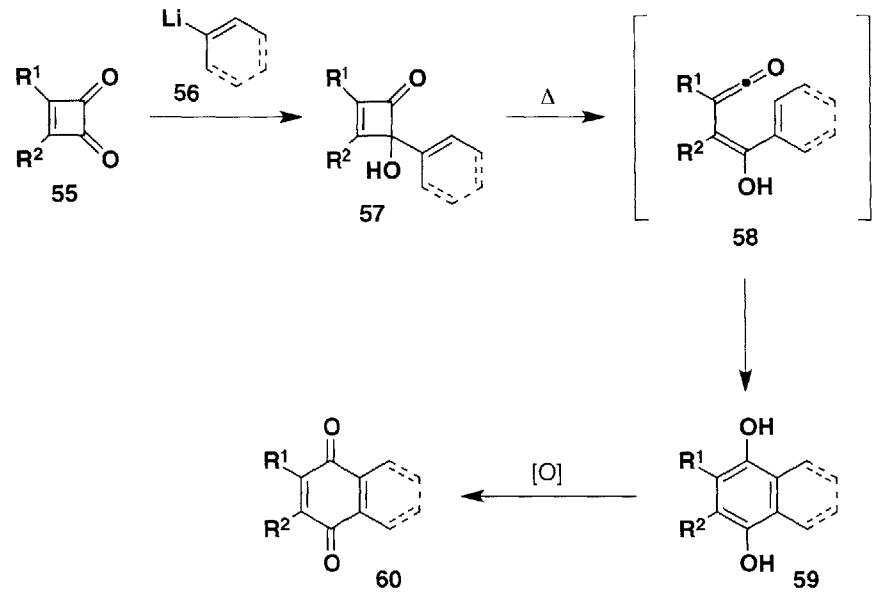
[44] (a) Danheiser, R. L.; Cha, D. C. *Tetrahedron Lett.* **1990**, *31*, 1527-1530. (b) Danheiser, R. L.; Casebier, D. S.; Loebach, J. L. *Tetrahedron Lett.* **1992**, *33*, 1149-1152. (c) Danheiser, R. L.; Casebier, D. S.; Huboux, A. H. *J. Org. Chem.* **1994**, *116*, 4844-4848. (d) Danheiser, R. 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.

[45] (a) Liebeskind, L. S.; Iyer, S.; Jewell, C. F. Jr. *J. Org. Chem.* **1986**, *51*, 3065-3067. (b) Zhang, D.; Llorente, I.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 4330-4338 and references therein. (c) Pena-Cabrara, E.; Liebeskind, L. S. *J. Org. Chem.* **2002**, 67, 1689-1691 and references therein.

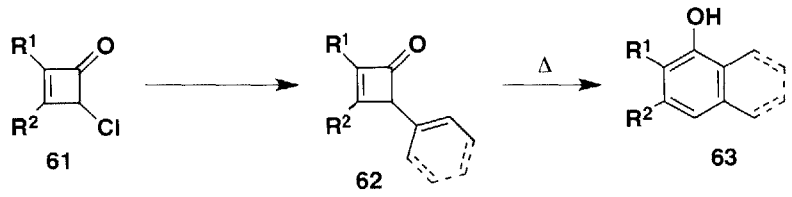
[46] (a) Perri, S. T.; Foland, L. D.; Decker, O. H. W.; Moor, H. W. *J. Org. Chem.* **1986**, *51*, 3067-3068. (b) For a review, see: Moore, H. W.; Yerxa, B. R. In *Advances in Strain in Organic Chemistry*; Halton, B. Ed.; Jai Press: London, 1995; Vol 4, pp 81-162. (c) Tiedemann, R.; Turnbull, P.; Moore, H. W. *J. Org. Chem.* **1999**, *64*, 4030-4041.

form a 4-aryl or 4-vinyl substituted cyclobutenone **57**. Thermolysis of compound **56** leads to hydroquinone adduct **59** that typically undergoes oxidation to form the quinone product **60**.

Scheme 5



Several variants of this strategy for the synthesis of highly substituted arene derivatives have been explored.[47] One variant developed by Liebeskind[48] utilizes transition-metal catalyzed processes to transform 4-chlorocyclobutenones **61** into 4-aryl or 4-vinylcyclobutenones **62**. Thermolysis of the product leads to the formation of polysubstituted phenol derivatives.



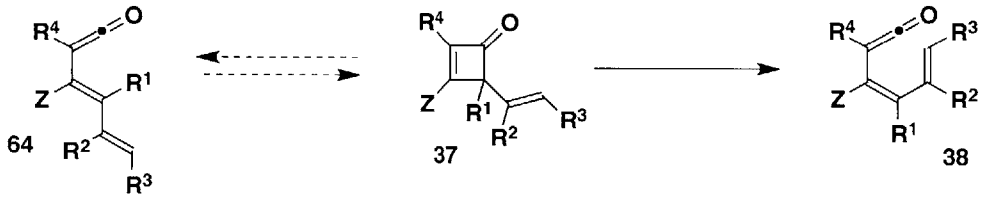
(11)

[47] (a) Liebeskind, L. S.; Granber, K. L.; Zhang, J. *J. Org. Chem.* **1992**, *57*, 4345-4352. (b) Turnbull, P.; Moore, H. W. *J. Org. Chem.* **1995**, *60*, 644-649. (c) Liu, F.; Liebeskind, L. S. *J. Org. Chem.* **1998**, *63*, 2835-2844. (d) Hamura, T.; Miyamoto, M.; Matsumoto, T.; Suzuki, K. *Org. Lett.* **2002**, *4*, 229-232. (e) Hamura, T.; Miyamoto, M.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **2003**, *44*, 167-170.

[48] (a) Krysan, D. J.; Gurski, A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1992**, *114*, 1412-1418. (b) Liebeskind, L. S.; Wang, J. *J. Org. Chem.* **1993**, *58*, 3550-35556. (c) Edwards, J. P.; Krysan, D. J.; Liebeskind, L. S. *J. Org. Chem.* **1993**, *58*, 3942-3952.

Important Mechanistic Considerations

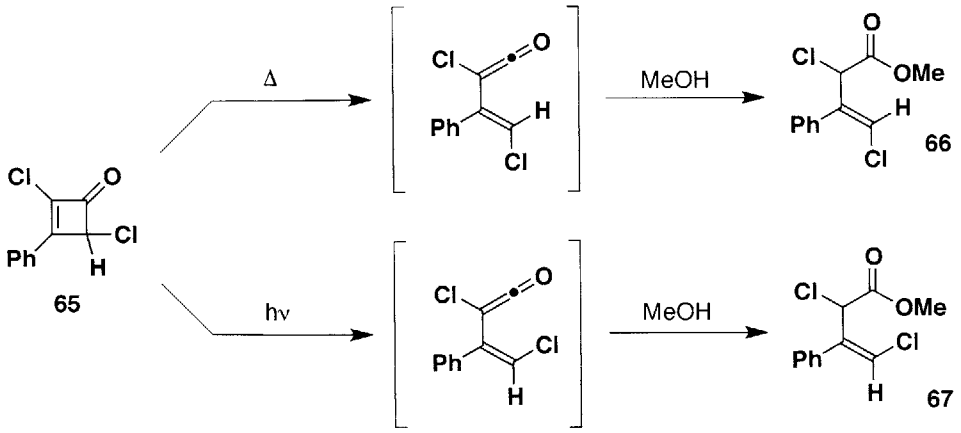
As outlined previously, the benzannulation reaction proceeds through a vinylcyclobutenone intermediate that can be isolated in some cases depending on the substrates and the reaction conditions.[37,49] Based on the mechanism discussed previously, there is a potential stereochemical issue with the electrocyclic cleavage of intermediate **37**. The pathway leading to an aromatic product requires the formation of a dienylketene with the stereochemistry shown in **38**. However, electrocyclic ring-opening of **37** can also lead to the stereoisomeric dienylketene **64**, which cannot undergo 6-π electrocyclic ring closure.



(12)

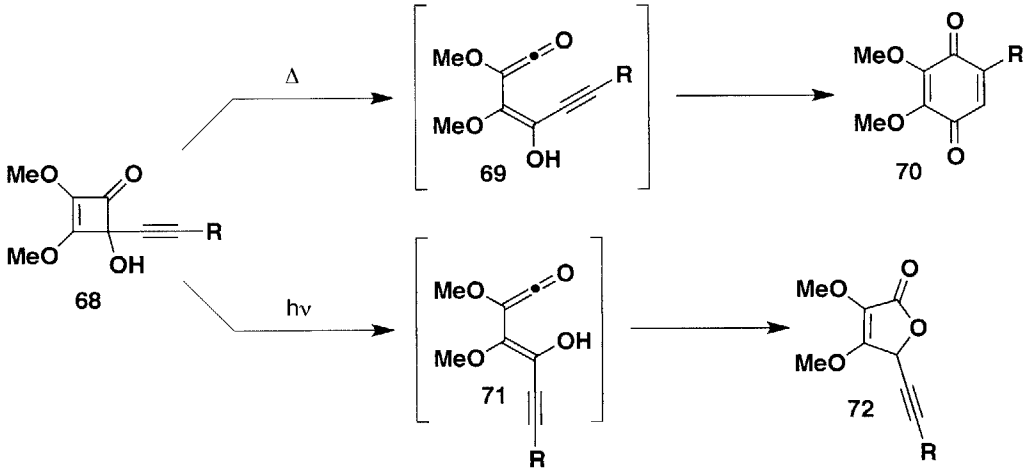
Studies by Houk and colleagues have shown that the torquoselectivity of the four-electron electrocyclic ring-opening of cyclobutenones is influenced by the nature of the substituents at the C-4 position.[50] Calculations show that under thermal conditions, electron-donating substituents at the C-4 position prefer to rotate outwards. Under photochemical conditions, this tendency is reversed and electron-donating substituents at C-4 prefer to rotate inwards. Experimental observations correlate well with these predictions.[51] For example, thermolysis of compound **65** in MeOH leads to the ester **66**, while irradiation of compound **65** leads to the stereoisomeric ester **67**. As predicted by the calculations performed by Houk, the electron-donating Cl atom rotates out upon thermolysis and rotates in upon irradiation.

[49] Gee, S. K. Annulation Approaches to Cyclooctanes and Aromatic Compounds. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, February, 1984.
[50] (a) Niwayama, S.; Kallel, E. A.; Sheu, C.; Houk, K. N. *J. Org. Chem.* **1996**, *61*, 2517-2522. (b) Niwayama, S.; Kallel, E. A.; Spellmeyer, D. C.; Sheu, C.; Houk, K. N. *J. Org. Chem.* **1996**, *61*, 2813-2825.
[51] Baldwin, J. E.; McDaniel, M. C. *J. Am. Chem. Soc.* **1968**, *90*, 6118-6124.



Another example of the torquoselective ring opening of cyclobutenones comes from Moore and coworkers.[52] Moore found that thermolysis of the cyclobutenone derivative **68** leads to the formation of the quinone **70** via the intermediate ketene **69**. In contrast, irradiation of **68** produces the stereoisomeric ketene **71** that closes to form the lactone **72**.

Scheme 7



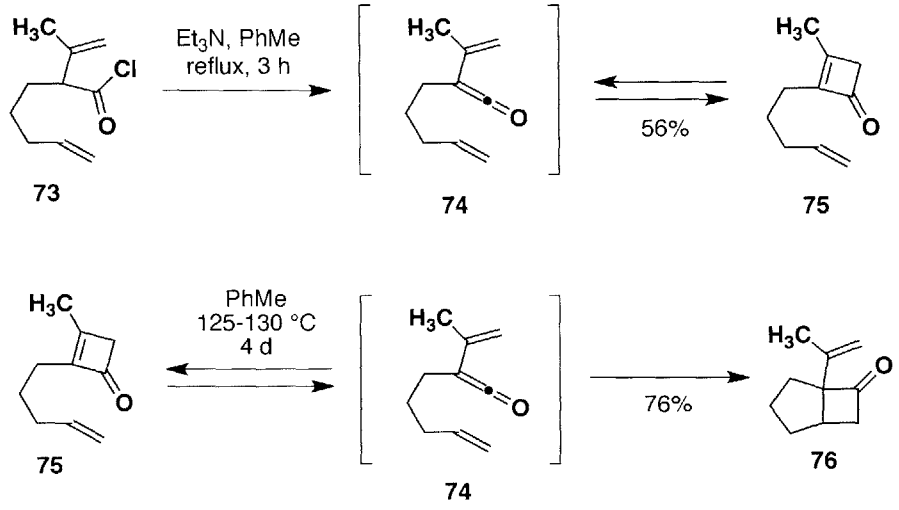
An analysis of our benzannulation reveals that, of the two C-4 substituents, the vinyl or aryl substituent is predicted to be a slightly more electron donating than the R^1 group, which is usually H or alkyl (eq 12). Thus, the theory developed by Houk predicts that the undesired stereoisomer **64** should be slightly favored in the thermal cyclobutenone ring opening. The fact

[52] Foland, L. D.; Karlsson, J. O.; Perri, S. T.; Schwabe, R.; Xu, S. L.; Patil, S.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 975-989.

that most of our benzannulation reactions proceed in high yield can be attributed to the reversibility of the ring opening. The undesired stereoisomer can revert to cyclobutenone **37**, and eventually undergo the desired reaction via electrocyclic ring-opening to the minor dienylketene **38**.

One example of the reversibility of cyclobutenone opening was reported by Snider, who found that the vinylketene **74**, generated via dehydrohalogenation of the acid chloride **73**, undergoes electrocyclic ring closure to form cyclobutenone **75**.[53,54] Heating a solution of cyclobutenone **75** in a sealed tube results in electrocyclic opening followed by an intramolecular [2 + 2] cycloaddition to form compound **76**.

Scheme 8



It is also worth noting that other alternative pathways for the conversion of **37** to **38** under photochemical conditions cannot be dismissed. For example, this transformation may proceed through a biradical generated via type I α-cleavage of the cyclobutenone ring **37**.

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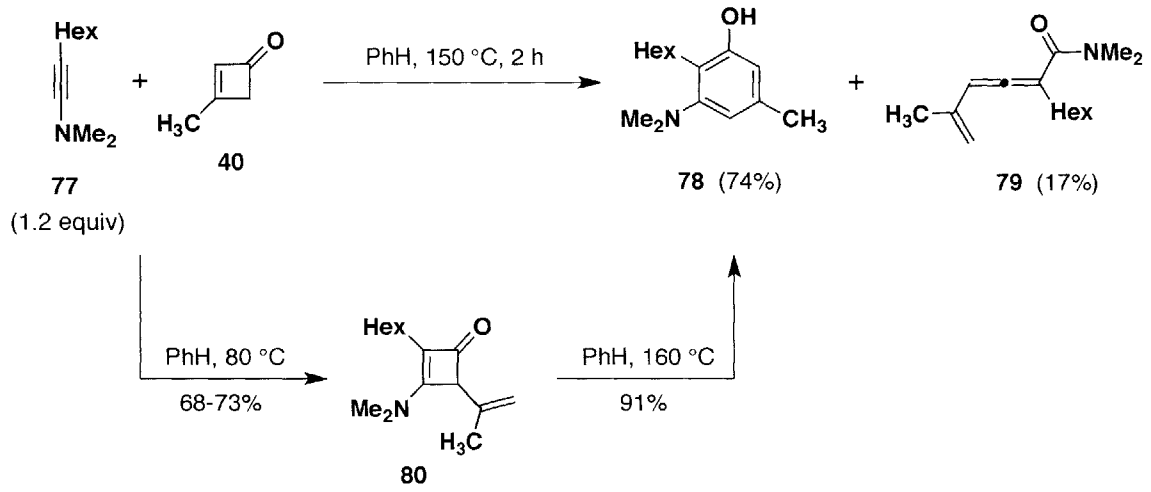
[53] Lee, S. Y.; Yashwant, S. K.; Burbaum, B. W.; Johnston, M. I.; Snider, B. B. *J. Org. Chem.* **1988**, *53*, 1848-1855.
[54] (a) For a discussion on the reversibility of cyclobutenone ring opening see ref 34b. (b) For an additional example of cyclobutenone reversibility see: Moore, H. W.; Perri, S. T. *J. Org. Chem.* **1988**, *53*, 996-1003.

Benzannulations with Ynamines

In addition to exploring benzannulations with oxygen- and sulfur-activated alkynes, early work in our laboratory also examined reactions utilizing nitrogen-substituted alkynes (ynamines) as the activated 2-π components.[32] Ynamines are highly reactive, electron-rich compounds that react readily with a number of electrophilic partners.[55] One early example of the use of ynamines in our benzannulation is shown in Scheme 9. Dialkylynamine **77** reacts with cyclobutenone **40** to give the desired aniline product **78** and the undesired allenamide side-product **79**. It was found that the formation of the allenamide could be avoided by performing the reaction in two stages.

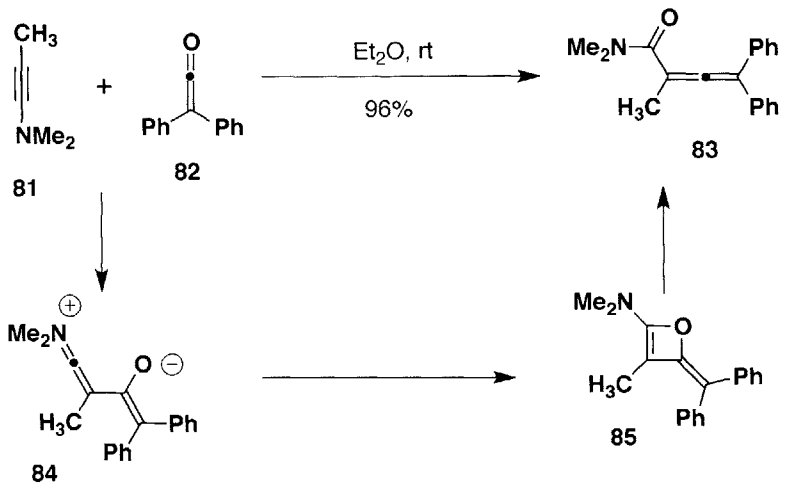
Scheme 9



[55] For reviews on the chemistry of ynamines, see: (a) Witulski, B.; Alayrac, C. In *Science of Synthesis;* de Meijere, A., Ed.; Theime: Stuttgart, 2005; Vol 24, pp 1007-1030. (b) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L. L. *Tetrahedron* **2001**, *57*, 7575-7606. (c) Ficini, J. *Tetrahedron*, **1976**, *32*, 1449-1486.

The formation of allenamides via the reaction of ynamines and ketenes is a known process that has been previously reported.[56] Ghosez and Delaunois reported that the reaction of diphenylketene and the ynamide **81** produces allenamide **83** in 96% yield.[56b] The formation of allenamide **83** likely occurs through the polar mechanism shown in Scheme 10.

Scheme 10



If a zwitterionic intermediate, such as **84** in Scheme 10, were operational in our benzannulation, then it is possible that different regioisomeric products might result. As shown in Scheme 11, the intermediate **87** could close to form cyclobutenone **88,** which would continue along the pericyclic cascade pathway to form the "pericyclic" product **89**. However, the same intermediate **87** could also close to form the six-membered ring adduct **90**, which would rapidly tautomerize to the regioisomeric "zwitterionic" product **91**. In some cases, it might be rather difficult to distinguish between these two isomers, which differ only by the interchange of the positions of R^1 and R^3 in the products.

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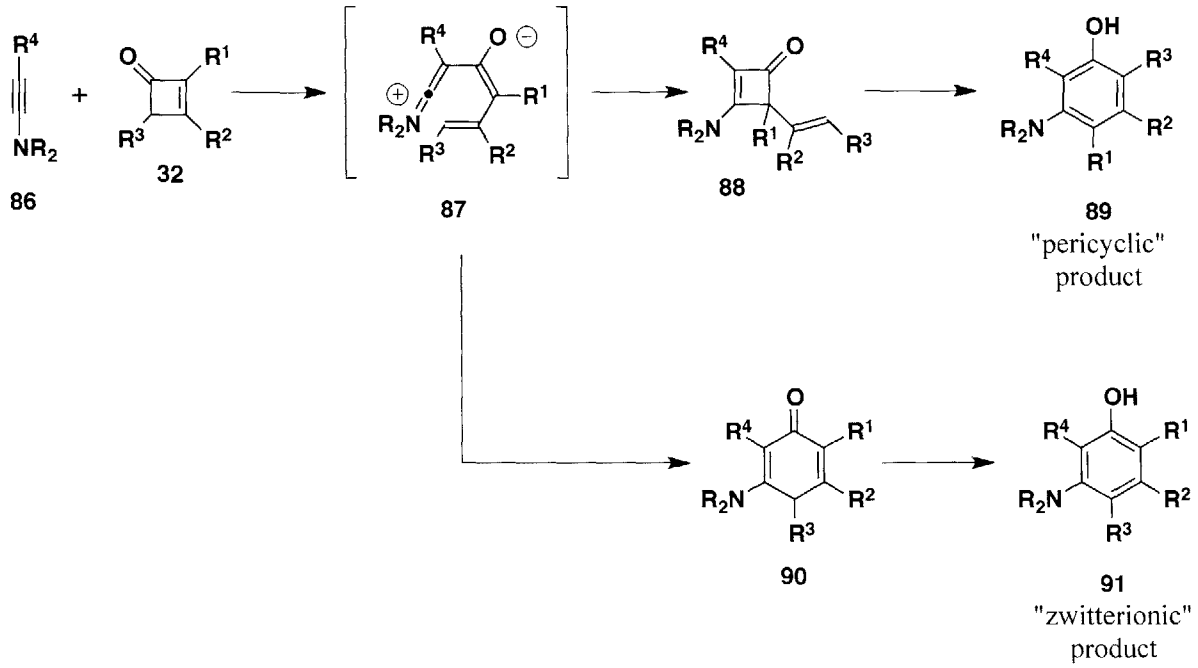
[56] For prior examples of reactions of ynamines with ketene derivatives, see: (a) Kuehne, M. E.; Sheeran, P. J. *J. Org. Chem.* **1968**, *33*, 4406-4413. (b) Delaunois, M.; Ghosez, L. *Angew. Chem. Int. Ed.* **1969**, *8*, 72-73. (c) Ficini, J.; Pouliquen, J. *Tetrahedron Lett.* **1972**, *12* 1135-1138. (d) Ficini, J.; Pouliquen, J. *Tetrahedron Lett.* **1972**, *12*, 1139-1141. (e) Himbert, G. *Angew. Chem. Int. Ed.* **1976**, *15*, 51-52. (f) ref 51a and references therein. (g) Himbert, G. *Liebigs Ann. Chem.* **1979**, 829-841. (h) Henn, L.; Himbert, G. *Chem. Ber.* **1981**, *114*, 1015-1026. (i) Himbert, G.; Henn, L. *Liebigs Ann. Chem.* **1984**, 1358-1366. (j) Henn, L.; Himbert, G.; Diehl, K.; Kaftory, M. *Chem. Ber.* **1986**, *119*, 1953-1963. (k) Barbaro, G.; Battaglia, A.; Giorgianni, P. *J. Org. Chem.* **1987**, *52*, 3289-3296. (l) Schulte, N.; Möller, M. H.; Rodewald, U.; Würthwein, E.-U. *Chem. Ber.* **1994**, *127*, 1287-1293.

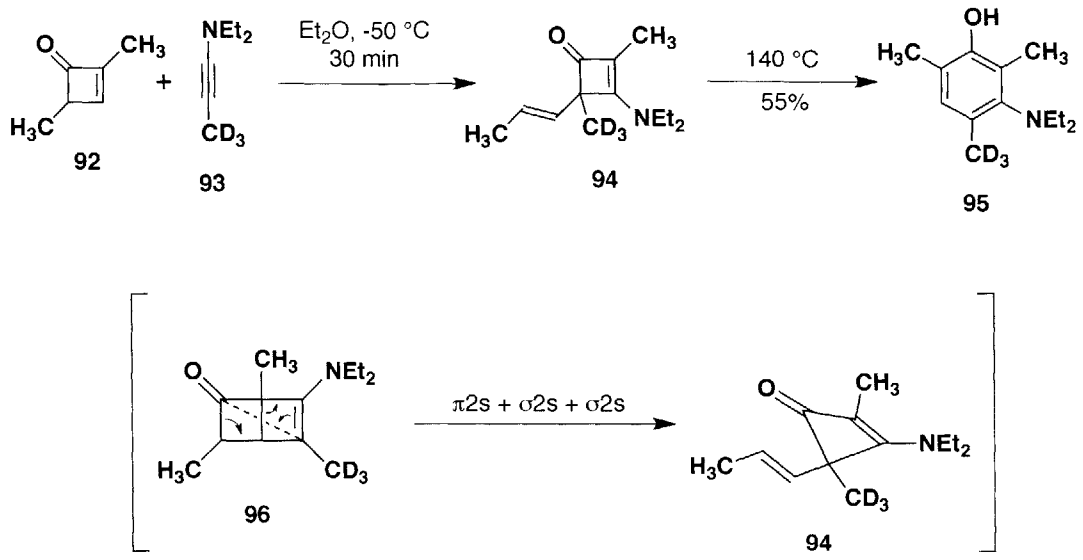
Scheme 11



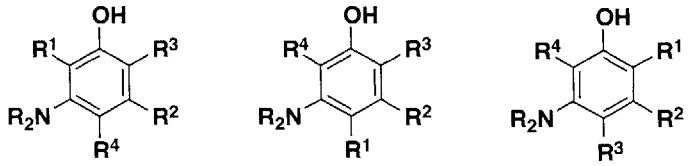
Based on the interesting work of Ficini, a third regiochemical isomer might also form in the benzannulation.[57] Ficini found that at low temperatures ynamine **93** reacts with cyclobutenone **92** to give the vinylcyclobutenone **94**. Deuterium labeling of the C-methyl group of the ynamine provided the basis for the structure assignment shown.

[57] Ficini, J.; Falou, S.; d'Angelo, J. *Tetrahedron Lett.* **1977**, *18*, 1931-1934.

Scheme 12



Ficini proposed that the cyclobutenone **92** and ynamine **93** initially react in a stepwise polar fashion to afford the strained adduct **96,** which subsequently undergoes a concerted rearrangement to generate the vinylcyclobutenone **94**. Heating compound **94** affords aniline **95**. What may not be immediately obvious is that aniline **95** posseses a different regiochemistry than either the "pericyclic" mechanism or the "zwitterionic" mechanism would predict. This suggests that ynamines and cyclobutenones can potentially react under our standard benzannulation conditions to form any of the three different regioisomeric products shown below.



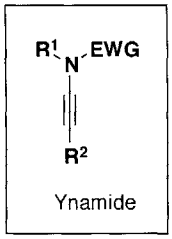
97
"Ficini"
product

89
"pericyclic"
product

91
"zwitterionic"
product

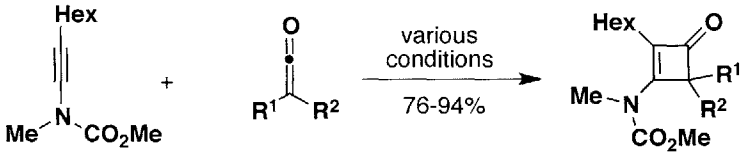
Benzannulations with Ynamides

In addition to the regiochemical concerns associated with benzannulations with ynamines (vide supra), the general limitations in the synthesis and storage of ynamines led our laboratory to explore a more stable class of ynamines – *ynamides*. Ynamides, which possess an electron-withdrawing group on the nitrogen atom, demonstrate an increased stability relative to ynamines, while maintaining a fair degree of reactivity.[58]



Ynamide

In order to get a better understanding of the potential reactivity of ynamides in the benzannulation, our laboratory initially studied the reactions of ynamides with relatively simple ketenes.[59] Ynamides proved to be competent reaction partners in [2 + 2] cycloadditions with a variety of ketenes (e.g., eq 13).



(13)

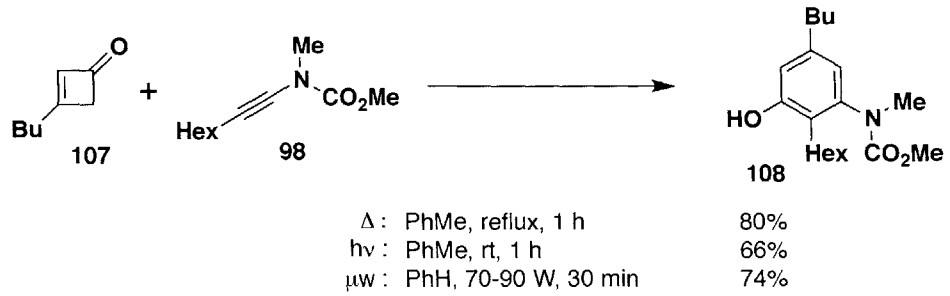
99	$R^1 = R^2 = H$	**103**
100	$R^1 = R^2 = Me$	**104**
101	$R^1 = R^2 = Cl$	**105**
102	$R^1 = H$, $R^2 = SPh$	**106**

Competition experiments revealed that ynamides and alkynyl ethers undergo [2 + 2] cycloadditions with ketene itself at similar rates.[59] Buoyed by these promising results, the feasibility of an ynamide-based benzannulation was explored. Early results demonstrated that ynamide **98** reacts with cyclobutenone **107** under thermal (including microwave) and photochemical conditions to furnish the desired aniline product in good yields.[2]

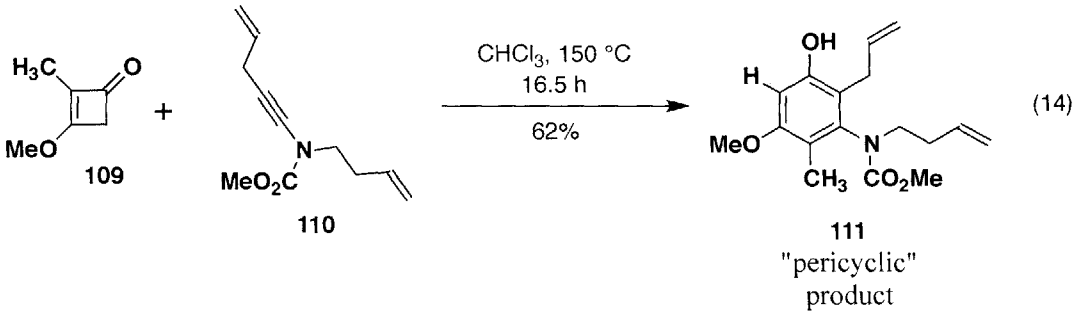
[58] For recent reviews on the synthesis and reactivity of ynamides, see: (a) Evano, G.; Jouvin, K.; Coste, A. *Synthesis* **2013**, *45*, 17-26. (b) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064-5106. (c) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 2840-2859.

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

Scheme 13



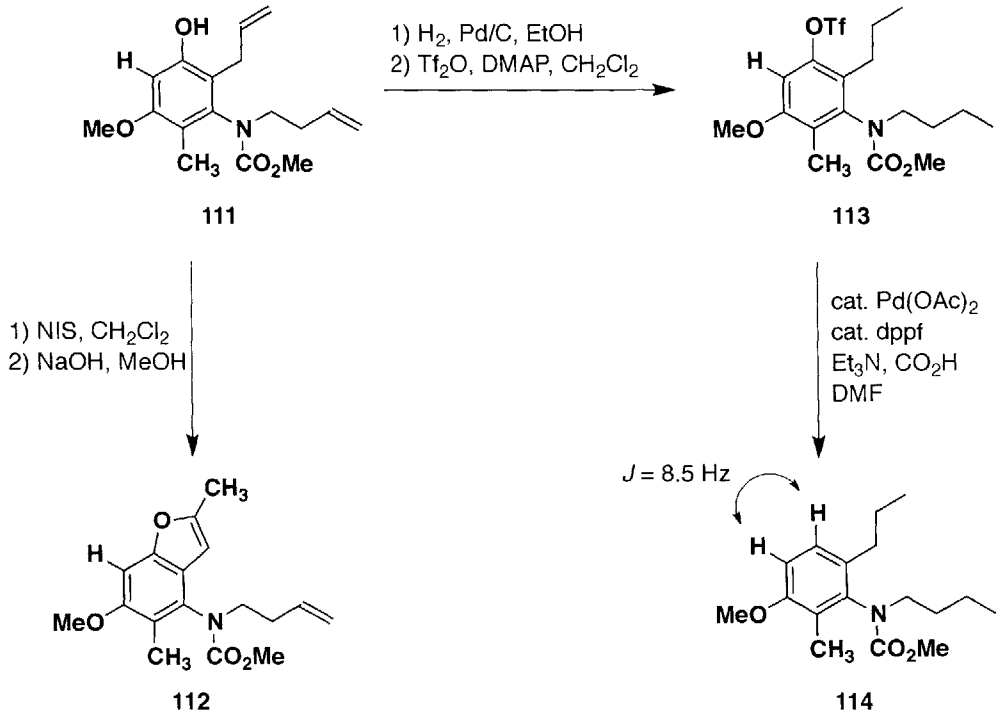
The next question of immediate importance was the regiochemistry of the benzannulation. Benzannulation of cyclobutenone **109** and ynamide **110** afforded a single regioisomeric product tentatively assigned as phenol **111** (eq 14).[2]



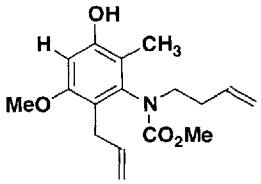
(14)

Confirmation that the benzannulation was proceeding via the desired pericyclic cascade pathway to produce isomer **111** was obtained by the following experiments performed on the benzannulation product (Scheme 14).[2]

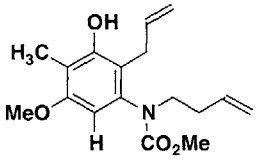
Scheme 14



Iodoetherification followed by treatment with base led to the furan **112**. This experiment indicated that the allyl and hydroxyl groups were adjacent on the aromatic ring, ruling out the "Ficini" product. Hydrogenation of **111** followed by triflation and subsequent reduction of the resulting aromatic triflate furnished the amine **114**. NMR analysis of **114** confirmed the ortho relationship between the two aryl hydrogens. This indicated that the phenol and hydrogen were adjacent on **111** thus ruling out the "zwitterionic" product. Together these experiments confirmed that **111** was the indeed the product of the benzannulation and supported the pericyclic cascade mechanism.

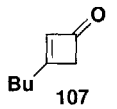
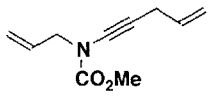
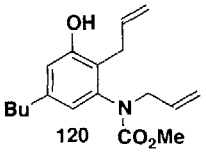
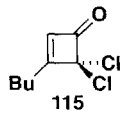
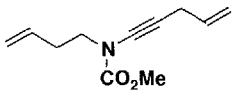
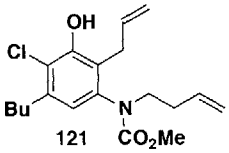
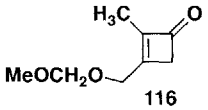
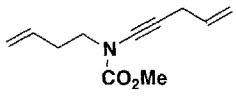
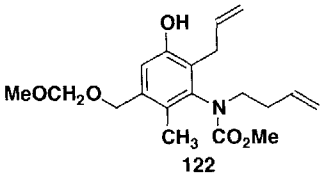
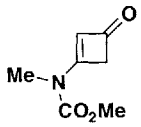
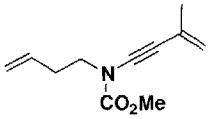
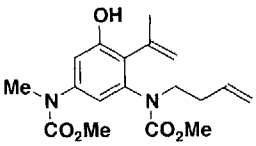


hypothetical "Ficini" product



hypothetical "zwitterionic" product

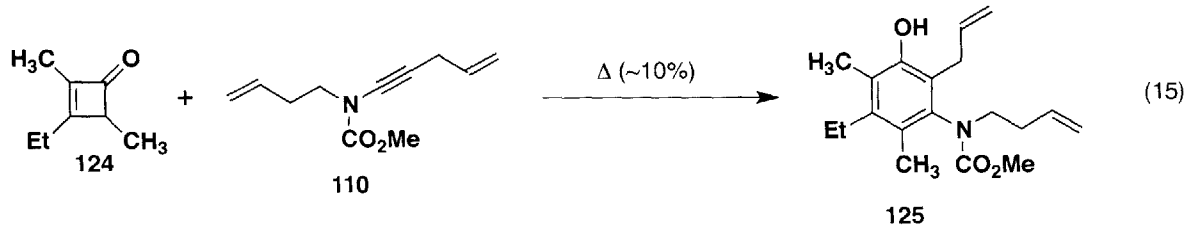
Table 1. Scope of the 'First Generation' Benzannulation

entry	cyclobutenone	ynamide	conditions	product	yield (%)[a]
1	 107	 118	PhMe, 80 °C, 1.5 h; then reflux, 1.5 h	 120	84
2	 115	 110	PhMe, 135 °C, 4 h[b]	 121	45
3	 116	 110	$CHCl_3$, 150 °C 16.5 h; then KOH, MeOH 65 °C, 2-3 h	 122	60
4	 117	 119	PhMe, reflux, 10 h; then KOH, MeOH 65 °C, 2-3 h	 123	53

[a] Isolated yield of products purified by column chromatography on silica gel. Yileds based on ynamide (using 1.2-2.0 equiv of cyclobutenone) [b] Reaction performed in the presence of 2.0 equiv of BHT using 1.0 equiv cyclobutenone and 1.5 equiv of ynamide

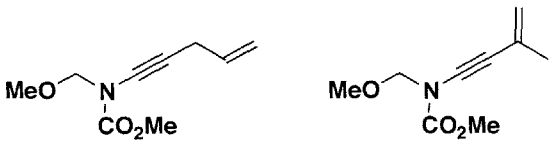
The scope of the benzannulation reaction with ynamides was found to be quite good as illustrated by the examples in Table 1.[2] The reaction tolerates a variety of functional groups on both the ynamide and the cyclobutenone. During the benzannulation, nucleophilic addition of the phenolic product to vinylketene intermediates is sometimes observed. This results in the formation of esters. The extent of this side reaction is dependent on the specific reactants, the solvent, and the exact reaction conditions. When esters are produced treatment of the crude product with KOH in methanol coverts them to the desired phenolic product.

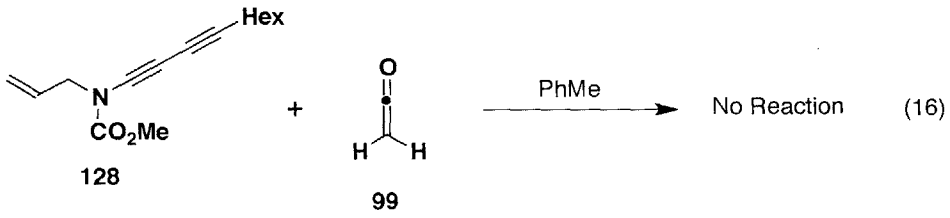
The benzannulation of ynamides and cyclobutenones is not without its limitations. Mak found that ynamides are slow to react with trisubstituted cyclobutenones even under forcing conditions (eq 15).[3a] The reaction of the trisubstituted cyclobutenone **124** and ynamide **110** resulted in decomposition of both products under a variety of reaction conditions.



(15)

Prior work by Lam has also shown that the reactivity of the ynamide is attenuated by the presence of electron-withdrawing groups.[3b] Ynamides **126** and **127** showed reduced reactivity in the benzannulation, presumably because of the electron-withdrawing methoxy group. Similarly, Mak found that diynamide **128** was unreactive in [2 + 2] cycloadditions with ketene (eq 16).[3a] The electron-withdrawing nature of the second alkyne is likely responsible for the reduced ketenophilicity of dinynamide **128**.





(16)

As discussed previously, the "first generation" version of the benzannulation (based on cyclobutenones) is not easily applied to the synthesis of polycyclic compounds. In the past, this limitation was overcome by using diazo ketones in our "second generation" benzannulation approach. One of the goals of my research was to explore the application of the diazo ketone-based version of the benzannulation to reactions involving ynamides. The next section discusses the synthesis of the ynamides and diazo ketones that were used to explore the feasibility of the "second generation" ynamide benzannulation.

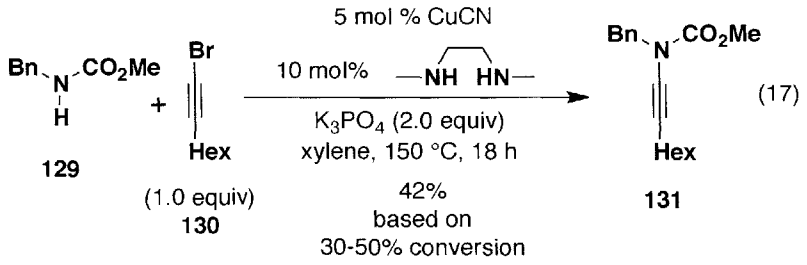
Chapter 2

The Synthesis of Ynamides and Diazo Ketones

Nearly all of the substrates used in our "second generation" studies were known and synthesized according to literature methods. This chapter provides a brief overview of the methods used for the synthesis of the requisite ynamides and α-diazo ketones.

The Synthesis of Ynamides

Pioneering studies by Stang showed that certain ynamides can be synthesized from alkyliodonium salts.[60,61] However, a lack of generality and the overall expense and effort associated with the preparation of alkynyliodonium salts limits the utility of this method. In 2003, Hsung and Danheiser independently reported protocols for the copper-mediated *N*-alkynylation of amides with alkynyl bromides.[62] In their preliminary report, Hsung and co-workers disclosed conditions employing the use of catalytic CuCN in the presence of a diamine ligand and K_3PO_4 at elevated temperatures (eq 17). This procedure is an adaptation of the method developed by Buchwald for the *N*-arylation of amides.[63] While the Hsung method furnished the desired ynamides in good yield in the case of oxazolidinones, it worked poorly for the synthesis of other ynamides including those with acyclic carbamates as protecting groups.



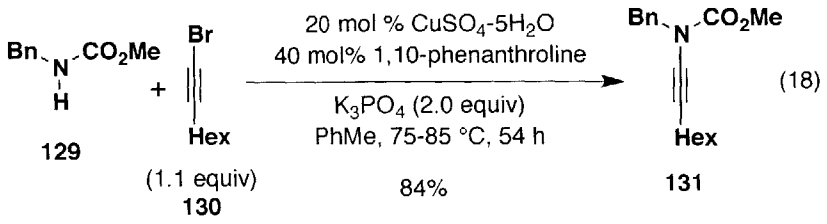
[60] (a) Murch, P.; Williamson, B. L.; Stang, P. J. *Synthesis* **1994**, 1255-1256. (b) Feldman, K. S.; Bruendl, M. M.; Schildknegt, K.; Bohnstedt, A. C. *J. Org. Chem.* **1996**, *61*, 5440-5452. (c) Witulski, B.; Stengel, T. *Angew. Chem. Int. Ed.* **1998**, *37*, 489-492.

[61] 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.

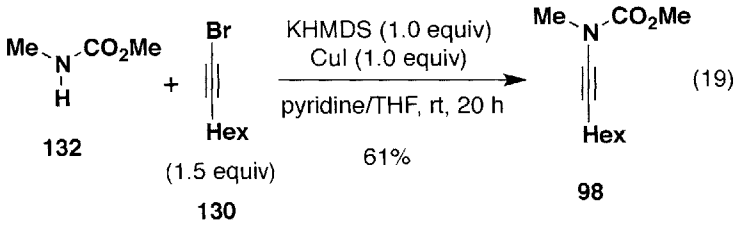
[62] (a) Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368-2369. (b) Dunetz, J. R.; Danheiser, R. L. *Org. Lett.* **2003**, *5*, 4011-4014.

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

Hsung reported an improved "second generation" protocol utilizing catalytic $CuSO_4.5H_2O$ and catalytic 1,10-phenanthroline with either K_2CO_3 or K_3PO_4 in 2004 (eq 18).[64] This procedure also requires the use of elevated temperatures.



The procedure developed by Danheiser employs a strong base (e.g., KHMDS) and a stoichiometric amount of CuI, but has the advantage of operating at room temperature (eq 19).[65] An excess of the alkynyl bromide is used in some cases; however, most cases use only 1.1-1.2 equivalents.



The Danheiser method is complementary to the approach developed by Hsung in that it allows for the synthesis of thermally sensitive substrates. This is exemplified in the synthesis of diynamide **128**.[65b] The use of the protocol developed by provided the desired diynamide **128** in 80% yield. The method of Hsung gave this ynamide in only 34-38% yield.

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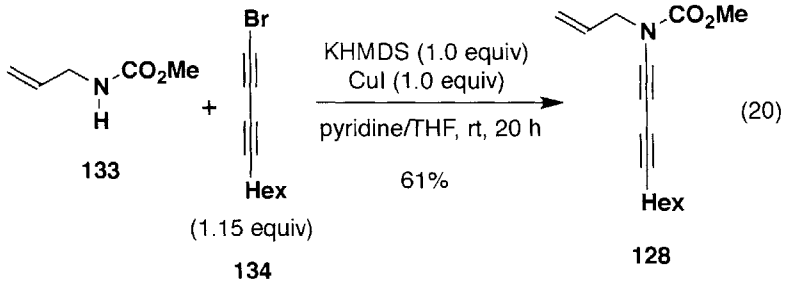
[64] (a) Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151-1154. (b) Zhang, X.; Zhang, Y.; Huang, J.; Hsung, R. P.; Kurtz, K. C. M.; Oppenheimer, J.; Petersen, M. E.; Sagamanova, I. K.; Shen, L.; Tracey, M. R. *J. Org. Chem.* **2006**, *71*, 4170-4177.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

[65] For a slightly modified version of the Danheiser procedure, see: (a) ref 58. (b) Kohnen, A. L.; Dunetz, J. R.; Danheiser, R. L. *Org. Synth.* **2007**, *84*, 88-95.

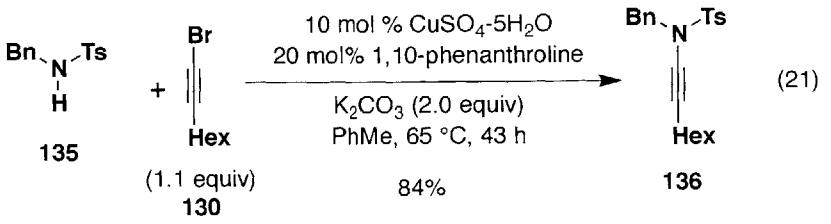


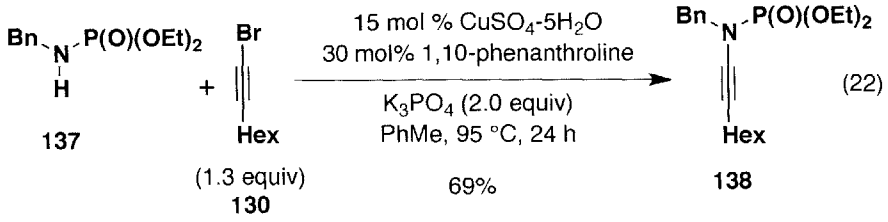
Both the Hsung and Danheiser methods have been used extensively in our laboratory for the preparation of ynamides with the choice of method determined on a case-by-case basis. With the advent of these general methods for the synthesis of ynamides, the past decade has seen an explosion of research exploring the reactivity and synthesis of alkynes.[58,66]

Nearly all of the work in our laboratory on the "first generation" benzannulation focused on reactions utilizing *N*-carbamate substituted ynamides. In order to further explore the scope the benzannulation, we decided to study other electron-withdrawing groups. We were interested in nitrogen protective groups that could be cleaved under other conditions, and also hoped to identify ynamide derivatives that might exhibit improved reactivity in the benzannulation. The *N*-sulfonyl substituted ynamide **136** and the *N*-phosphoryl[67] substituted ynamide **138** were therefore prepared as shown below to serve as additional substrates for our "second generation" benzannulation studies.

[66] For other useful coupling routes to ynamides, see: (a) Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833-835. (b) Jouvin, K.; Coste, A.; Bayle, A.; Legrand, F.; Karthikeyan, G.; Tadiparthi, K.; Evano, G. *Organometallics* **2012**, *31*, 7933-7947. (c) Jouvin, K.; Couty, F.; Evano, G. *Org. Lett.* **2010**, *12*, 3272-3275.

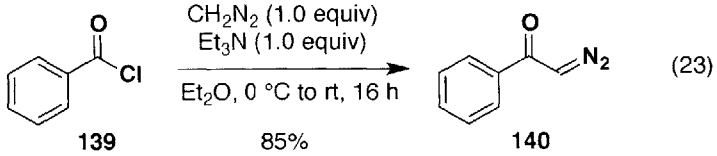
[67] For the synthesis of phosphoryl protected ynamides, see: DeKorver, K. A.; Walton, M. C.; North, T. D.; Hsung, R. P. *Org. Lett.* **2011**, *13*, 4862-4865





The Synthesis of α-Diazo Ketones

There are numerous methods available for the synthesis of α-diazo ketones.[68] The synthesis of aryl substituted diazo ketones is easily achieved via the addition of diazoalkanes to an acyl chloride or a mixed anhydride in the presence of a mild base (eq 23).[69]



Unfortunately, this method is does not work well for the synthesis of α,β-unsaturated diazo ketones due to competitive 1,3-dipolar cycloaddition of diazomethane to the carbon-carbon double bond (eq 24).[70,71]

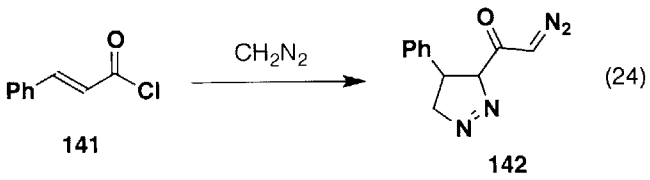
---

[68] For reviews on the synthesis and reactivity of diazo ketones, see: (a) Maas, G. *Angew. Chem. Int. Ed.* **2009**, *48*, 8186-8195. (b) Zhang, Y.; Wang, J. *Chem. Commun.* **2009**, 5350-5361. (c) Zhang, Y.; Wang, J. *Tetrahedron* **2008**, *64*, 6577-6605. (d) Doyle, M. P.; McKervey, M. A.; Ye, T. Synthesis of α-Diazocarbonyl Compounds. *Modern Catalytic Methods for Organic Synthesis of Diazo Compounds: from Cyclopropanes to Ylides*; Wiley & Sons: New York, 1998; pp 1-60. (e) Regitz, M.; Maas, G. *Diazo Compounds: Properties and Synthesis;* Academic Press: Orlando, Fl, 1986.

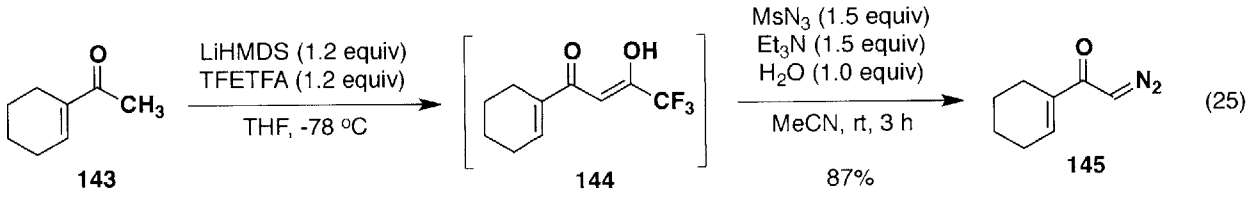
[69] Bridson, J. N.; Hooz, J. *Org. Synth.* **1973**, *53*, 35-38.

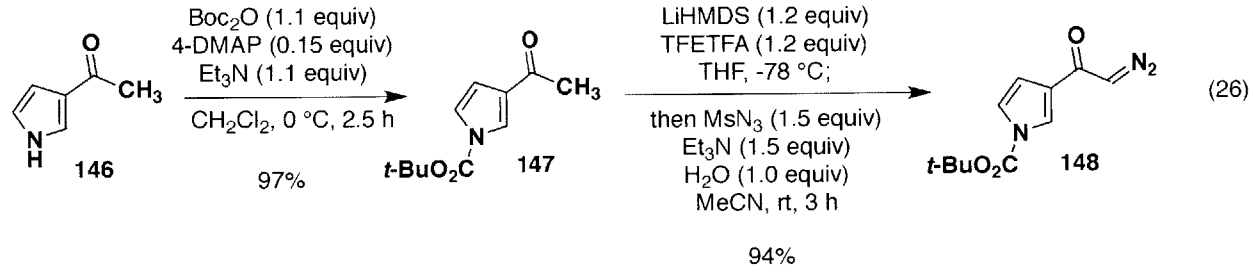
[70] For example, see: Harmon, R. E.; Sood, V. K.; Gupia, S. K. *Synthesis* **1974**, 577-578.

[71] For further discussion, see: Rosenquist, N. R.; Chapman, O. L. *J. Org. Chem.* **1976**, *41*, 3326-3327.



While several alternative strategies exist, one of the most effective is the detrifluoroacetylative diazo transfer protocol developed in our laboratory.[72,73] This method involves initial reaction of the lithium enolate of a ketone with 2,2,2-trifluoroethyl trifluoroacetate (TFETFA) to give a 1,3-dicarbonyl compound. The crude product is then treated with methanesulfonyl azide (MsN_3) in the presence of Et_3N and water to yield the desired diazo ketone. As illustrated in eq 25 and 26 below, this method works well for the synthesis of both α,β-unsaturated and aryl diazo ketones.





With the exception of diazo ketone **148**, all of the diazo ketones used in the current study were known compounds that were previously synthesized using this method.

---

[72] (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.

[73] For other key diazo transfer references, see: ref 68d.

Chapter 3

Photochemical Benzannulations of Ynamides and Diazo Ketones Performed in Batch and Flow

Previous Studies

Xiao Yin Mak performed initial studies on benzannulations employing ynamides and diazo ketones in our laboratory.[3a] Continuing her work, I examined photochemical aromatic annulation reactions in quartz reaction tubes either placed in a Rayonet photochemical reactor fitted with a circular array of 16 low-pressure mercury lamps (254 or 300 nm) or next to a water-cooled quartz immersion well containing a Hanovia 450W medium pressure mercury lamp (wavelength range 250-600 nm). The Hanovia based set-up is illustrated in Figure 1.

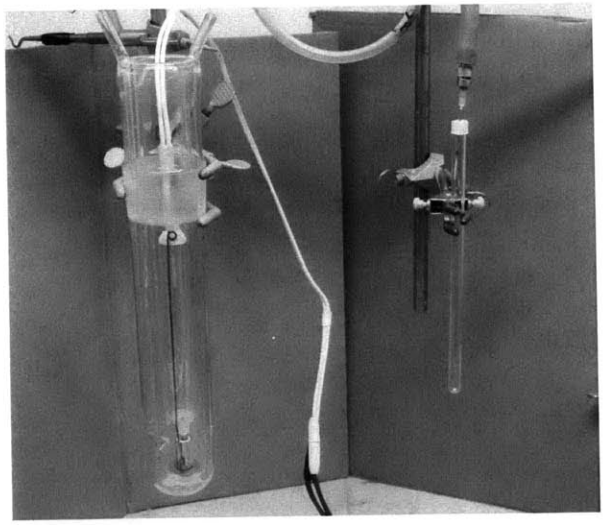


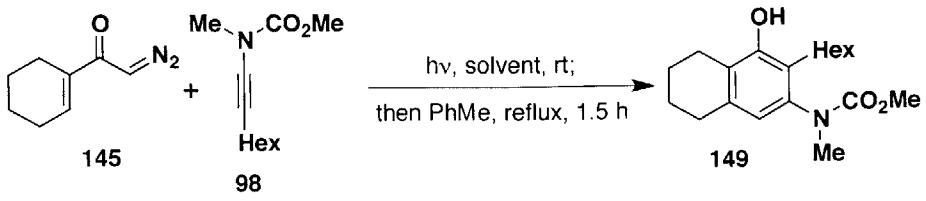
Figure 1. Hanovia photochemical reaction: Water-cooled quartz immersion equipped with 450W lamp (left). Quartz reaction tube (right).

Each reaction mixture was degassed with a stream of argon for 15 min or via three cycles of freeze-pump-thaw (0.05 mmHg) prior to irradiation. Irradiation of the reaction mixture was continued until complete consumption of the diazo ketone was observed as indicated by TLC analysis. As seen in some previous photochemical benzannulations, a mixture of the intermediate vinylcyclobutenone and the desired phenolic annulation product was observed after irradiation. The incomplete conversion of the vinylcyclobutenone to product, even upon continued irradiation in some cases, is attributed to the build up of colored polymeric residues on the walls of the reaction tubes. Consequently, the crude reaction products were generally heated to complete the conversion of vinylcyclobutenone to phenol.

Initial studies by X. Y. Mak focused on the reaction of α,β-unsaturated diazo ketone **145** and ynamide **98**.[3a] Mak obtained the phenol **149** in 48% yield when 1.1 equiv of diazo ketone was used (Table 2, entry 3). Side reactions involving the intermediate vinylketene were thought to limit the yield in this reaction, so Mak explored using an excess of diazo ketone. When 2.5 equiv of diazo ketone was used, the yield improved to 67% (Table 2, entry 4). One of the most likely side reactions of the vinylketene intermediate is dimerization. In order to limit the concentration of vinylketene and thus suppress dimerization, Mak employed slow addition of the diazo ketone. The slow addition of 1.5 equiv of diazo ketone resulted in a 65% yield of phenol (Table 2, entry 5). The best result, an 85% yield, was obtained with the slow addition of 2.5 equiv of diazo ketone (Table 2, entry 6).

In most of the experiments carried out by Mak, irradiation was performed in dichloromethane. After irradiation, the solution was concentrated and the solvent switched to toluene since temperatures around 110 °C are needed to complete the benzannulation by converting the intermediate vinylcyclobutenone to the desired phenol. This solvent swap can be avoided by performing both steps in 1,2-dichloroethane (bp 83 °C). However, significantly longer reaction times are required for the thermolysis step in 1,2-dichloroethane relative to toluene due to the lower reaction temperature (Table 2, entry 7).

Table 2. Mak's Initial 'Second Generation' Benzannulation Studies

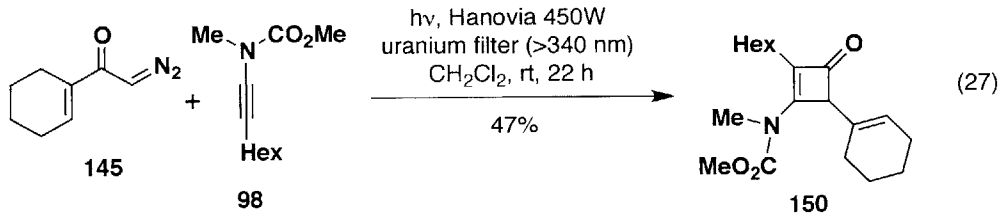


145 98 149

entry	diazo ketone	solvent	irradiation method	irradiation time (h)	yield (%)[a]
1	1.0 equiv	PhMe	Rayonet (254 nm)	1.5	25[b]
2	1.0 equiv	CH_2Cl_2	Rayonet (254 nm)	1.5	40[b]
3	1.1 equiv	CH_2Cl_2	Hanovia	8	48
4	2.5 equiv	CH_2Cl_2	Hanovia	5.5	67
5	1.5 equiv	CH_2Cl_2	Hanovia	4.5	65[c]
6	2.5 equiv	CH_2Cl_2	Hanovia	10	85[c]
7	2.5 equiv	$ClCH_2CH_2Cl$	Hanovia	9	73[c,d]

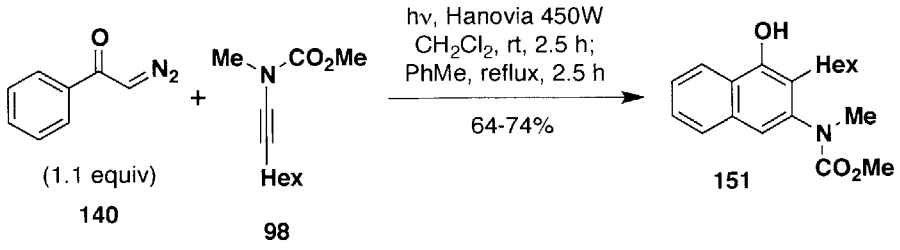
[a] Isolated yields of products purified by column chromatography. [b] Reaction was performed in the presence of 1,4-dimethoxybenzene as internal standard. [c] Diazo ketone **145** was added as a 0.4 M solution to a solution of ynamide **98** via syringe pump at a rate of ca. 0.009 mL/min. [d] Heated at reflux in 1,2-dichloroethane for 24 h after irradiation.

During the course of these optimization studies, Mak also found that the use of a uranium filter, which blocks wavelengths of light below 340 nm, results in the production of only the vinylcyclobutenone **150** and none of the final phenolic product (eq 27).



145 98 150 (27)

Mak obtained excellent results when she explored the benzannulation of ynamide **98** and diazoacetophenone (**140**). In this case, a high yield was obtained without the need for slow addition or a large excess of diazo ketone.



(28)

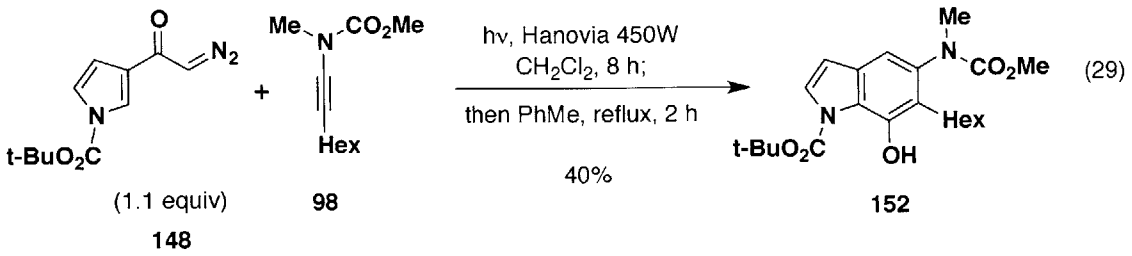
The higher yields observed for aryl as compared to vinyl diazo ketones is probably related to the stability of the initially formed aryl- and vinylketenes. The arylketene derived from **140** is slower to dimerize as compared to the vinylketene derived from **145**, thus permitting the [2 + 2] cycloaddition with the ynamide partner to compete more efficiently wit undesired side reactions.

Exploring the Synthesis of Benzo-Fused Heteroaromatic Compounds

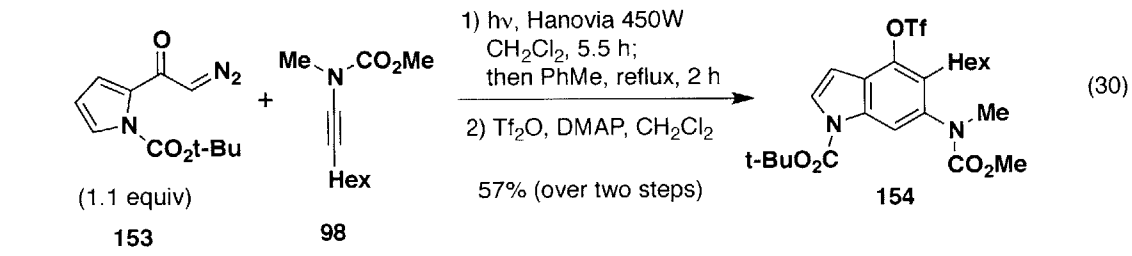
Building on the early results achieved by Mak, we turned our attention to benzannulations utilizing heteroaryl diazo ketones.[74] Indoles **152** and **154**[75] were both synthesized in good yield using the vinylketene-based benzannulation. The assembly of indoles bearing a high level of substitution on the benzenoid ring is a challenging synthetic problem. These results demonstrate the ability of the benzannulation to provide regioselective access to indoles bearing multiple substituents on the six-membered ring.

[74] (a) Diazo ketone **153** was prepared according to ref 72. (b) Diazo ketone **155** was prepared by Clarissa Forneris using the detrifluoroacetylative diazo transfer protocol (ref 72). For characterization of **155**, see: 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.

[75] Mak originally examined the benzannulation of **98** and **153**, but the product was assigned incorrectly.



(29)



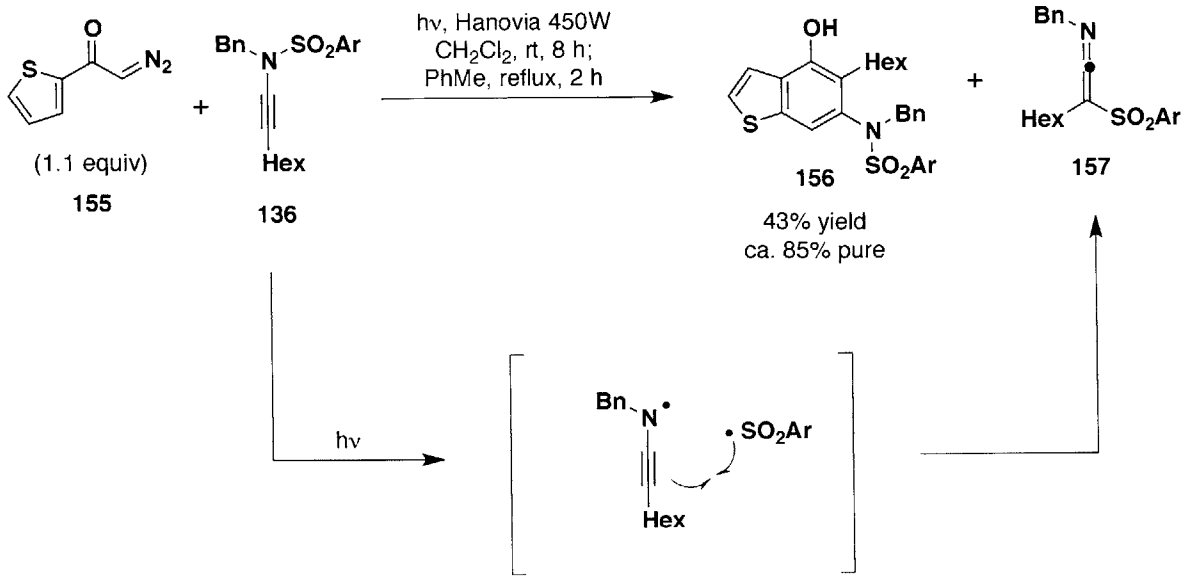
(30)

The isolated yield for indole **154** was obtained over two steps after triflation of the phenol. Protecting the phenol prevents oxidation of the product and aids in the purification. In principle, any protecting group can be used. In these cases, triflation was performed because the resulting aryl triflates can serve as a functional handle for further elaboration of the products via coupling reactions.

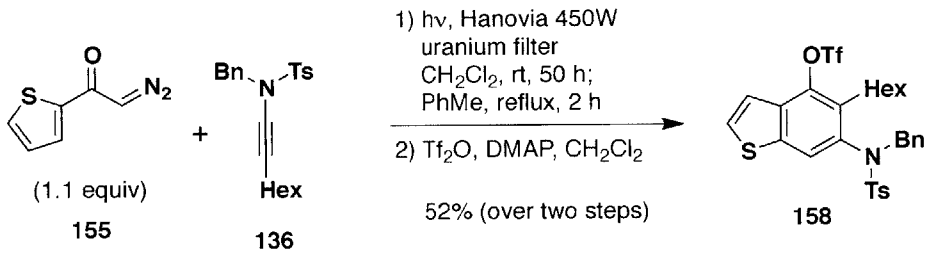
Benzannulation of thienyl diazo ketone **155** and *N*-sulfonyl ynamide **136** under our standard "second generation" benzannulation conditions resulted in the formation of impure phenol **156** and the ketenimine **157**. The ketenimine results from photochemical decomposition of the ynamide, likely through a photo-Fries type process (scheme 15).[76]

[76] For a review of the photo-Fries rearrangement, see: (a) Miranda, M. A.; Galindo, F. The Photo-Fries Rearrangement. In *Molecular and Supramolecular Photochemistry;* Ramamurthy, V.; Shanze, K. S. Eds.; Marcel, Dekker: New York, 2003; pp 43-131. (b) For leading references on the photo-Fries rearrangement of sulfonamides, see: Park, K. K.; Lee, J. L.; Ryu, J. *Tetrahedron*, **2003**, *59*, 7651-7659 and references cited therein.

Scheme 15



When the benzannulation of thienyl diazo ketone **155** and *N*-sulfonyl ynamide **136** is conducted with a uranium filter, only trace amounts ketenimine are observed. The reaction affords benzothiophene **158** in 52% overall yield over two steps after triflation.



(31)

Exploring Photochemical Benzannulations Run with a Continuous-Flow Photochemical Reactor

The development of continuous-flow photochemical reactors is a burgeoning area of research with applications in both pharmaceutical development and academic research.[77,78] Interest in this area of research is based on a desire to avoid many of the limitations associated with batch photochemistry as well as the numerous potential benefits of running reactions in flow (vide infra).

Among the many limitations associated with batch photochemical processes, inefficient light absorption and complications due to secondary photoreactions of the product are the most significant. Inefficient light absorption is caused by the fact that the reaction solution nearest to the lamp absorbs light before it can reach the rest of the solution. This effect can be quantified by applying Beer's Law ($A = \varepsilon cl$). For a typical photochemical reaction (ε = 20,000 M^{-1} cm^{-1} and c = 0.05 M), ca. 90% of the incident light is absorbed at a distance of 0.001 cm into the solution. This "shielding" effect can make it difficult to drive reactions to completion and frequently results in prolonged reaction times.

An additional problem is some batch processes is that the desired products may be subject to further reaction on irradiation. This becomes an especially serious concern when extended reaction times are required for full conversion of reactants.

Continuous-flow photochemical reactors use a pump to force a reaction solution at a controlled rate through narrow channels in close proximity to a light source. This reactor design affords several benefits. The close proximity to the light source and narrow channels lead to efficient and uniform irradiation of the reaction solution. Efficient irradiation allows shorter reaction times that lead to savings in time and energy and minimize detrimental side-reactions

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[77] For recent reviews, see: (a) Knowles, J. P.; Elliott, L. D.; Booker-Milburn, K. I. *Beilstein J. Org. Chem.* **2012**, *8*, 2025-2052. (b) Wegner, J.; Ceylan, S.; Kirschning, A. *Chem. Commun.* **2011**, *47*, 4583-4592. (c) Oelgemöller, M.; Shvydkiv, O. *Molecules* **2011**, *16*, 7522-7550.

[78] For selected recent examples, 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.

and decomposition pathways. Scaling up continuous-flow reactions is simple and merely requires carrying out the reaction over longer time.

In order to expand the utility of the "second generation" benzannulation, we explored the use of a continuous-flow photochemical reactor. We hypothesized that the reactor might increase the efficiency of the benzannulation reactions, aid in reaction scale up, and potentially increase the yield of those products that undergo further reaction on irradiation.

Both micro and macro continuous-flow photochemical reactors have been developed. While micro reactors are important for both reaction design and optimization,[77a,c] our focus was on larger macro reactors.[77a,b] Several macro reactor designs exist.[77a] We chose to utilize a design first described by Berry and Booker-Milburn.[79] This reactor is constructed by wrapping fluorinated ethylenepropylene (FEP) tubing[80] (0.030 in. I.D., 0.0625 in. O. D.) around a water-jacketed quartz immersion well. The tubing was secured with Teflon tape. The well is equipped with a 450W Hanovia lamp and cooled by recirculating tap water. The top end of the tubing is fitted with a nut, a ferrule, and a thread to female Luer adapter.[81]

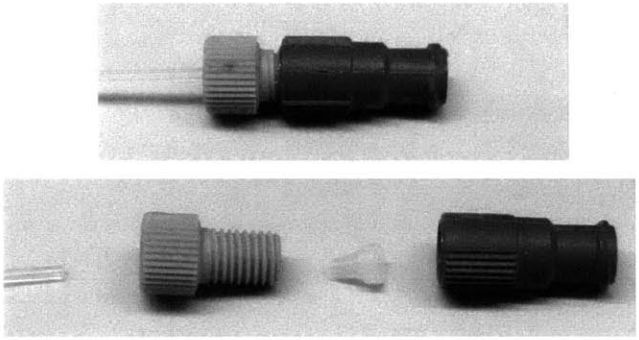

Figure 2. Telescoped view of nut (left), ferrule (middle), and thread to female Luer adapter (right).

The bottom end of the tubing is connected through a rubber septum to a receiving flask equipped with an argon inlet needle and a needle vent. Figure 3 shows the flow reactor set-up.

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[79] 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.

[80] FEP tubing was purchased from IDEX Health sciences (1520XL).

[81] The nut (P-235), ferrule (P-200Nx), and thread to female Leur adaptor (P-678) were purchased from IDEX Health sciences.

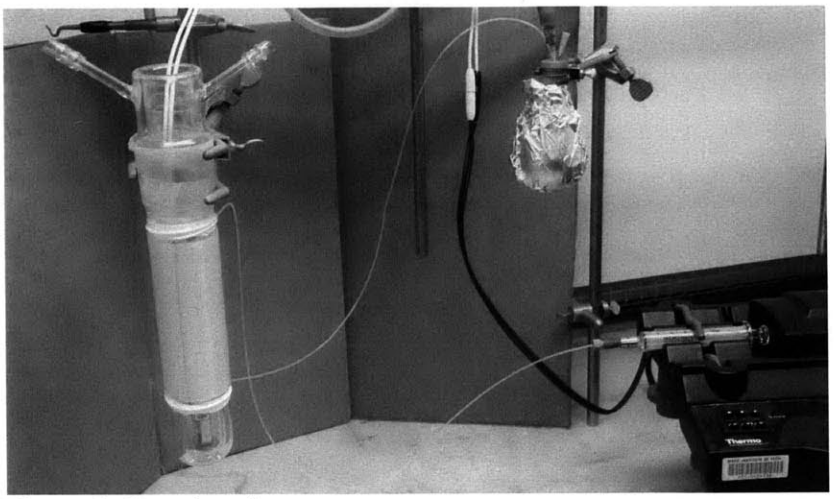


Figure 3. Complete flow reactor set-up.

We constructed two different reactors utilizing this design. The first was made by wrapping ca. 9 ft of tubing around the immersion well leaving 2.5 ft of tubing on either end to create a reactor with a total internal volume of about 2 mL. A larger reactor was constructed by wrapping 45 ft of tubing around the well leaving 2.5 ft of tubing on either end to create a reactor with a total internal volume of about 6.3 mL.

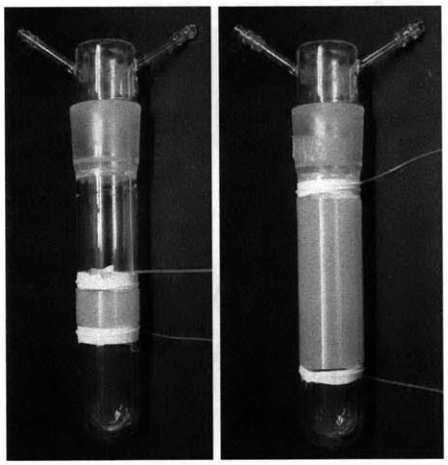
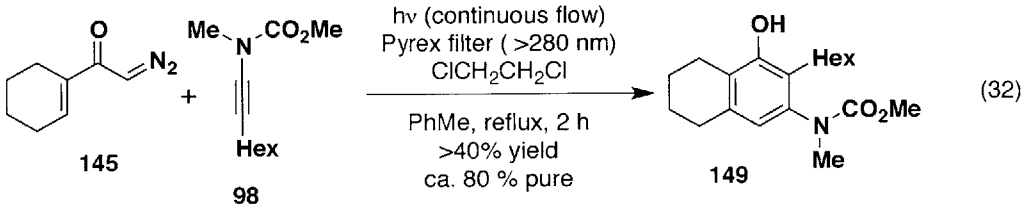


Figure 4. Flow reactors: 2-mL reactor (left) 6.3-mL reactor (right)

Most benzannulation reactions were performed in the 2-mL reactor. For all benzannulation reactions, the immersion well was equipped with a Pyrex (>280 nm) or uranium (>340 nm) filter in order to prevent polymer buildup on the interior of the tubing. A syringe

pump was used to pump the reaction solution through the tubing into the receiving flask.[82] All benzannulations were performed with premixed degassed solutions of ynamide and a slight excess of diazo ketone in 1,2-dichloroethane. As seen in many previous photochemical benzannulations, a mixture of the intermediate vinylcyclobutenone and the desired phenolic annulation product were observed after irradiation. Consequently, the crude reaction products were heated to complete the conversion of vinylcyclobutenone intermediate to phenol.

Our studies began with the reaction of α,β-unsaturated diazo ketone **145** and ynamide **98**. When performed using a continuous-flow photochemical reactor, this reaction did afford some product, but the yield was typically poor. As observed in some batch reactions, side reactions of the intermediate vinylketene, such as dimerization, appear to limit the yield of phenol in this case. Although this problem could be circumvented in the case of the corresponding batch reaction by using slow addition and a larger excess of diazo ketone, these modifications of procedure were not attractive or easily applied to the photochemical flow process. In addition, as discussed later in this chapter, we subsequently found that reactions of α,β-unsaturated diazo ketones could be achieved in good yield simply by employing ynamides with a different electron-withdrawing group. As a result, we turned our attention to the use of aryl diazo ketones that have less tendency to undergo dimerization.



(32)

As expected, benzannulations of ynamides and aryl diazo ketones proceed well using the continuous-flow affording similar yields to those obtained in the corresponding batch reactions (Table 3). Residence times for the benzannulation in flow were ca. 21-33 min depending on the filter. It is difficult to compare batch and flow reaction times directly. As a result, batch and flow processes are often compared with respect to their efficiency. We define efficiency here as the

[82] For more details regarding the operation of the reactor see the experimental section.

number of mmol of reactant divided by the hours of irradiation.[83] For entries 1-3, the batch efficiencies are ca. 0.1-0.2 mmol/h, while the flow efficiencies are ca. 0.8-0.9 mmol/h. It should be noted that we conducted the continuous-flow reactions in entries 1-3 with a Pyrex filter.[84] The corresponding batch reactions did not employ a filter, yet they were still ca. five to ten times less efficient.

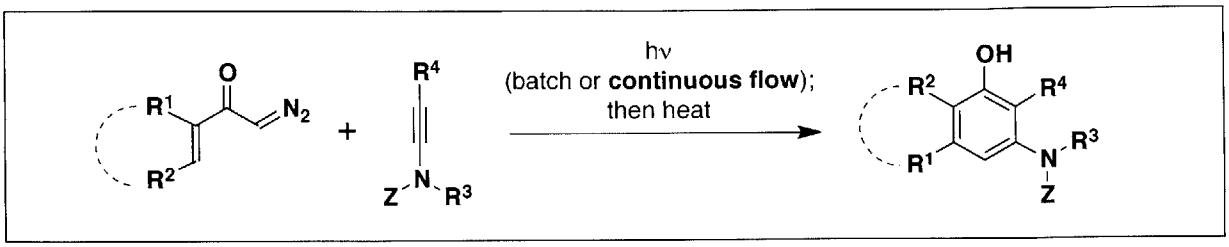
In entry 4, both the batch and flow reactions required a uranium filter to prevent decomposition of the *N*-sulfonyl ynamide **136**. Because both the batch and flow benzannulations were conducted with filters, we observed a far more dramatic difference in efficiency. The efficiency of the batch benzannulation leading to **158** is only 0.01 mmol/h, while the efficiency of the flow benzannulation is 50-fold greater, 0.5 mmol/h.

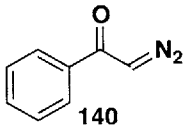
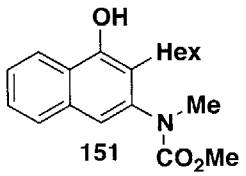
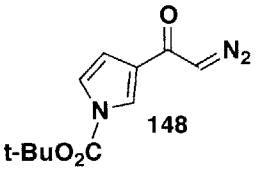
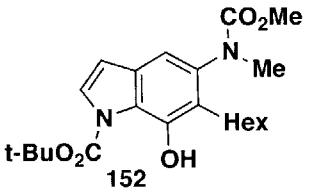
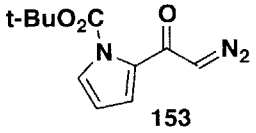
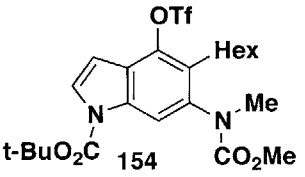
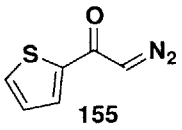
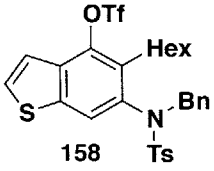
The general increase in efficiency for reactions performed with a continuous-flow reactor demonstrates that processes are more efficient and scalable. Given the advantages of running reactions in flow, we wanted to find conditions that would allow for benzannulations using α,β-unsaturated diazo ketones. We hypothesized that the decreased yields observed with α,β-unsaturated diazo ketones was do to side reactions of the intermediate vinylketene. We therefore decided to explore the use of more ketenophilic ynamides, with the expectation that their [2 + 2] cycloadditions would be able to compete more effectively with the unproductive side reactions of ketene.

[83] In these reactions efficiency was calculated based on the amount of ynamide used since the diazo ketone was employed in slight excess. The flow rate and hence the reaction time was optimized to allow for full conversion of the diazo ketone.

[84] The use of a Pyrex filter (>280 nm) is needed in order to prevent polymer buildup on the interior of the tubing.

Table 3. Benzannulations with Aryl Diazo Ketones Performed in Batch and Continuous Flow

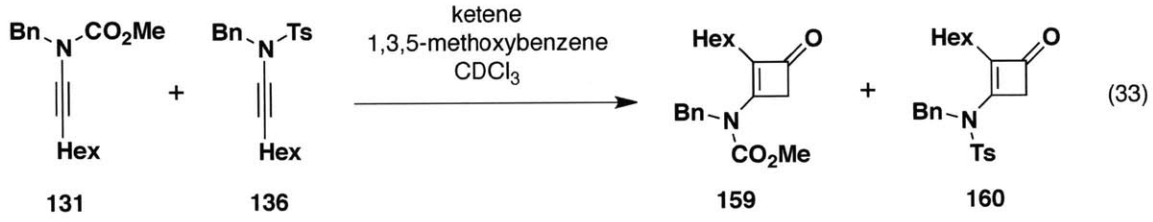


entry	diazo ketone	ynamide	product	% yield[a] (method)[b,c]
1	 140	98	 151	74 (batch) **66 (continuous flow)**
2	 148	98	 152	40 (batch) **37 (continuous flow)**
3	 153	98	 154	57[d] (batch) **50[d] (continuous flow)**
4	 155	136	 158	52[d] (batch) **47[d] (continuous flow)**

[a] Isolated yield of products purified by column chromatography. [b] Batch reactions: 1.1 equiv of diazo ketone, irradiation at 254 nm in CH_2Cl_2; then reflux, toluene, 1.5-2.5 h. For entry 4, irradiation at >340 nm (uranium filter). [c] Continuous-flow reactions: 1.1 equiv of diazo ketone, irradiation at >280 nm (Pyrex filter) in $ClCH_2CH_2Cl$, residence time = 21 min; then reflux, $ClCH_2CH_2Cl$, 40-48 h (entries 1 and 4) or reflux, toluene, 2 h (entries 2 and 3). For entry 4, irradiation was at >340 nm (uranium filter), residence time = 33 min. [d] Overall yield for 2 steps. Benzannulation product was treated with 1.2 equiv Tf_2O, 2.0 equiv 4-DMAP, CH_2Cl_2 (0 °C to rt, 2-4 h).

Comparing Ynamides with Different Electron-Withdrawing Groups

In order to increase the reactivity of the ynamide in [2 + 2] cycloadditions, we explored the use of different electron-withdrawing groups. We hypothesized that *N*-sulfonyl ynamides might be more electron rich[85] and thus more reactive than *N*-carbomethoxy ynamides in the initial [2 + 2] reaction with the vinylketene. In order to test this hypothesis, we performed a competition experiment. A solution of equal amounts of the ynamides **131** and **136** was treated with ketene in the presence of 1,3,5-trimethoxybenzene as an internal standard. As shown in Figure 5, analysis of aliquots by ^{1}H NMR indicated that *N*-sulfonyl ynamide **136** reacts with ketene roughly twice as fast as *N*-carbomethoxy ynamide **131**.



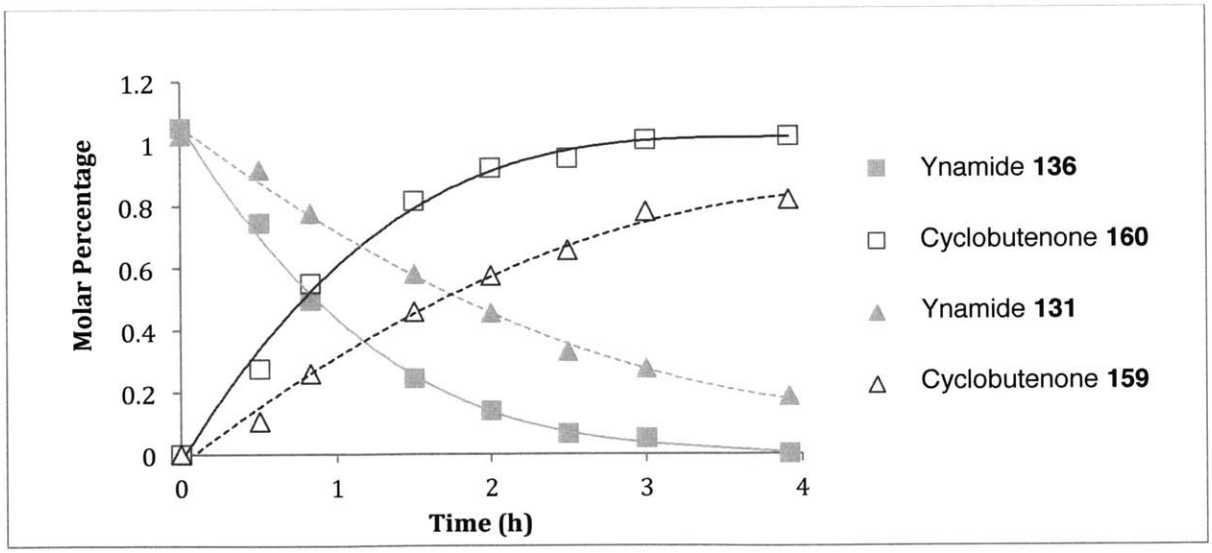


Figure 5. Comparison of the rates of [2 + 2] cycloaddition of ketene with *N*-carbomethoxy ynamide **131** and *N*-sulfonyl ynamide **136** in $CDCl_3$ at rt.

[85] For examples, see: (a) Chataigner, I.; Panel, C.; Gérard, H.; Piettre, S. R. *Chem. Commun.* **2007**, 3288-3290 and references cited therein. (b) Witulski, B.; Schweikert, T.; Schollmeyer, D.; Nemkovich, N. A. *Chem. Commun.* **2010**, *46*, 2953-2955. (c) Li, H.; Hsung, R. P.; DeKorver, K. A.; Wei, Y. *Org. Lett.* **2010**, *12*, 3780-3783.

The change from an *N*-carbomethoxy ynamide to an *N*-sulfonyl ynamide lead to an improvement in reactivity, but we wanted to try and increase the reactivity further, so we explored the reaction of an *N*-phosphoryl ynamide. Because a phosphoryl group is less electron withdrawing than a sulfonyl group, we speculated that *N*-phosphoryl ynamide **138** should be more electron rich and thus more ketenophilic than *N*-sulfonyl ynamide **136.** A competition experiment, similar to that described above, was performed. A solution of equal amounts of the ynamides **138** and **136** was treated with ketene in the presence of 1,3,5-trimethoxybenzene as an internal standard. As shown in Figure 6, analysis of aliquots by ^{1}H NMR indicated that *N*-phosphoryl ynamide **138** reacts roughly five times faster than *N*-sulfonyl ynamide **136**. Combining the results of these competition experiments leads to the conclusion that *N*-phosphoryl ynamide **138** ynamide should react ten times faster than *N*-carbomethoxy ynamide **131** in the initial [2 + 2] step involved in the benzannulation.

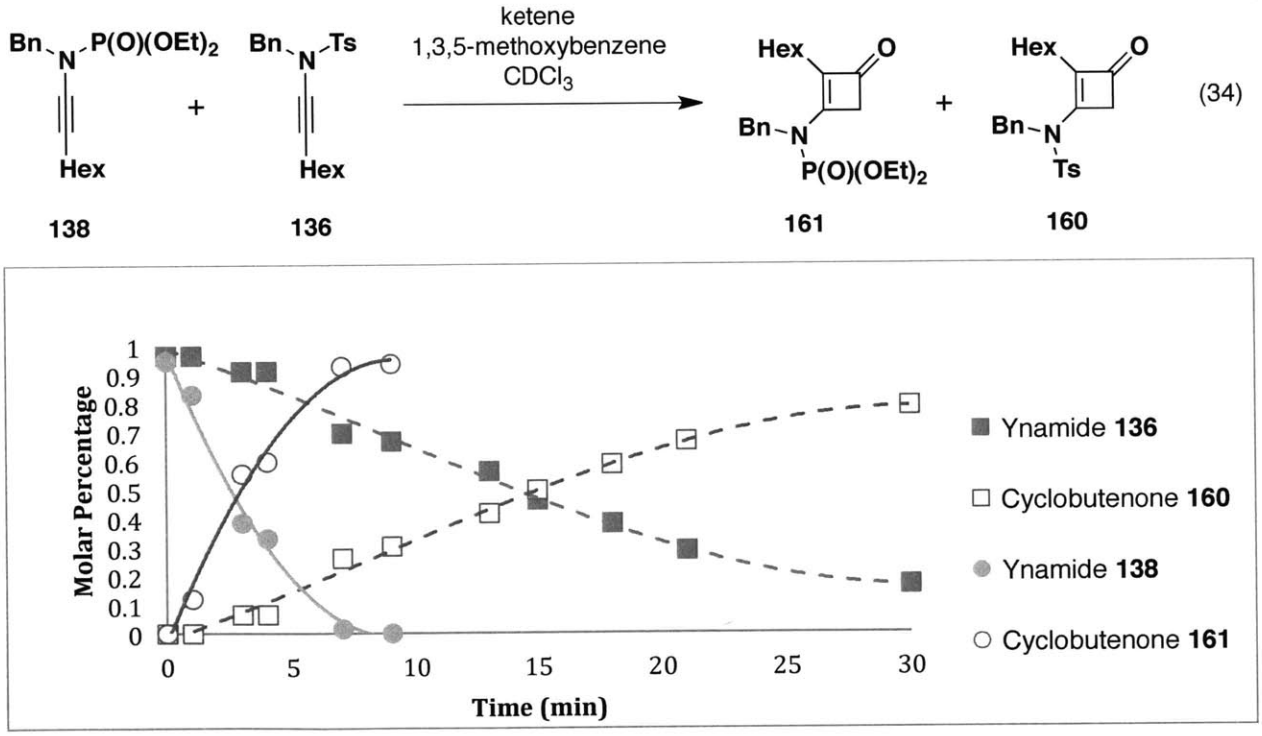
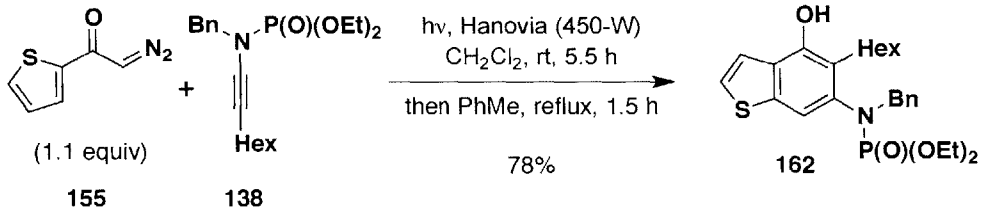


Figure 6. Comparison of the rates of [2 + 2] cycloaddition of ketene with *N*-phosphoryl ynamide **138** and *N*-sulfonyl ynamide **136** in $CDCl_3$ at rt.

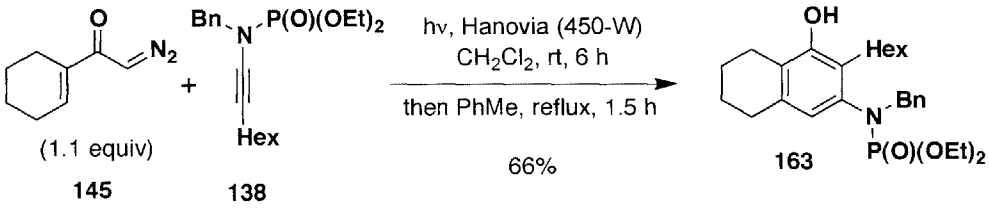
With this promising result in hand, we turned our attention to benzannulation reactions with *N*-phosphoryl ynamides.

Benzannulations with *N*-Phosphoryl Ynamides

Benzannulation reactions of *N*-phosphoryl ynamide **138** were first studied as batch processes. Ynamide **138** reacted with thienyl diazo ketone **155** to afford benzothiophene **162** in excellent yield. Even more impressive was the reaction of ynamide **138** with α,β-unsaturated diazo ketone **145** that resulted in the formation of **163** in 66% yield without the need for slow addition or a large excess of the diazo ketone. Under similar conditions, the diazo ketone **145** and the *N*-carbomethoxy ynamide **98** reacted to form the desired phenol in only 48% yield.[86] These results demonstrate that *N*-phosphoryl ynamides are excellent substrates for the benzannulation.



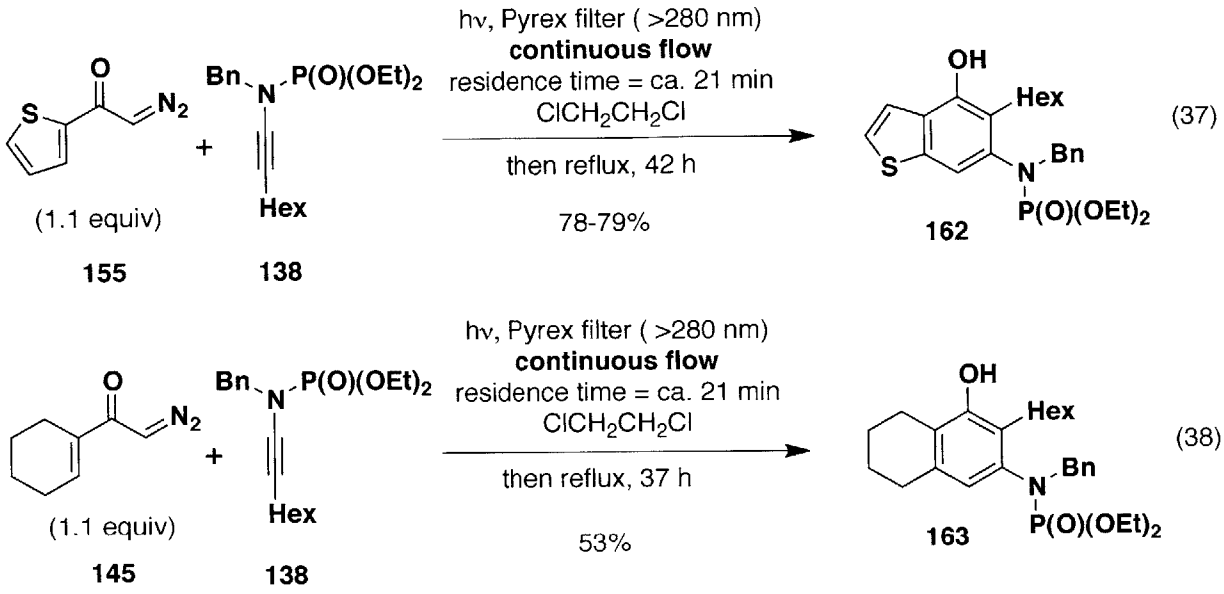
(1.1 equiv) **155** **138** **162** (35)



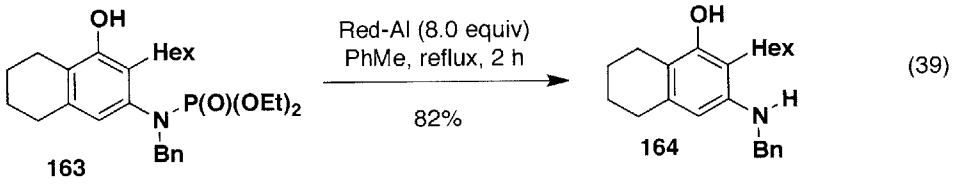
(1.1 equiv) **145** **138** **163** (36)

Performing the same benzannulation reactions using a continuous-flow reactor led to equally notable results. Benzothiophene **162** formed in good yield when the reaction was conducted under flow conditions. It was especially gratifying to find that the reaction of α,β-unsaturated diazo ketone **145** and *N*-phosphoryl ynamide **138** proceeded in 53% yield using the continuous-flow reactor. This is a significant improvement over the >40% yield of impure phenol obtained for a similar benzannulation with *N*-carbomethoxy ynamide **98** (eq 32). This result demonstrates that the scope of ynamide-based benzannulations run in flow can be extended to include α,β-unsaturated diazo ketones when an *N*-phosphoryl ynamides are used as the reaction partner.

[86] See Table 2, entry 3



It should be noted that while phosphoryl groups are not widely used as protecting groups, they can serve that purpose.[87] The removal of a phosphoryl group can be achieved with strong acid[88] or by reaction with hydride reagents,[88] as illustrated in in eq 39.



Based on the results discussed in this chapter, it is clear that a wide variety of highly substituted aniline derivatives can be synthesized via the benzannulation reaction of ynamides and diazo ketones. Aryl diazo ketones perform well in both batch and flow benzannulation reactions. α,β-Unsaturated diazo ketones perform well in batch reactions and can be used in flow reactions if an *N*-phosphoryl ynamide is used.

[87] Wuts, P. G. M. *Greene's Protective Groups in Organic Synthesis*, 4th ed.; Wuts, P. G. M.; Greene, T. W., Eds.; Wiley & Sons: Hoboken, 2007, pp 845-846.
[88] For example, see: Shintani, R.; Murakami, M.; Hayashi, T. *Org. Lett.* **2009**, *11*, 457-459.

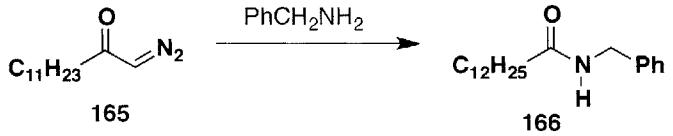
Chapter 4

Ynamide Benzannulations Triggered by the Thermal Wolff Rearrangement

The Thermal Wolff Rearrangement

All of our prior work with the diazo ketone based "second generation" benzannulation utilized the photochemical version of the Wolff rearrangement. However, the use of thermal conditions to trigger the Wolff rearrangement of diazo ketones is also possible and has been known since the discovery of the reaction in 1902.[89] Thermal conditions are infrequently used to trigger the Wolff rearrangement because the reactions typically require high temperature and can lead to complex mixtures of products.[43] For example, heating diazo ketone **165** in benzylamine at 100 °C for 20 min resulted in little to no reaction with near quantitative recovery of starting material.[90] Increasing the reaction temperature to reflux (ca. 185 °C) for 5 min resulted in a 45% yield of the amide **166**. Improved results were seen with the use of microwave conditions (Table 4).

Table 4. Amide Synthesis via Thermal Wolff Rearrangement



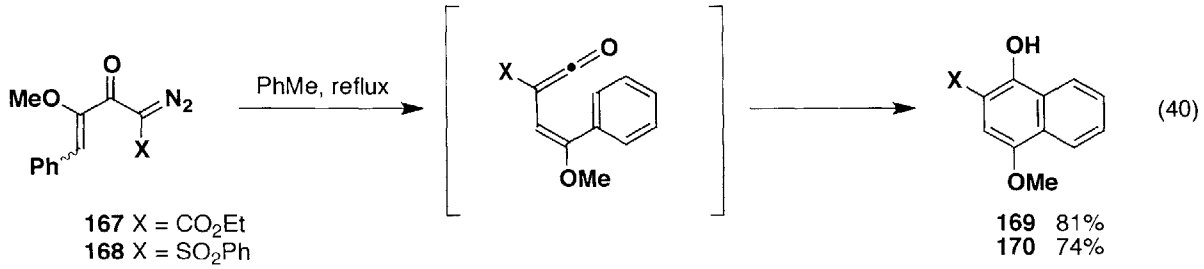
165 166

Entry	Conditions	Yield(%)
1	100 °C, 20 min	0[a]
2	reflux (ca. 185 °C), 5 min	45
3	μw (300 or 600 W), 15-30 min	75

[a] Near quanititavie recovery of starting material

[89] Wolff, L. *Justus Liebigs Ann. Chem.* **1902**, *325*, 129-195.
[90] Sudrik, S. G.; Chavan, S. P.; Chandrakumar, K. R. S.; Pal, S.; Date, S. K.; Chavan, S. P.; Sonawane, H. R. *J. Org. Chem.* **2002**, *67*, 1574-1579.

The temperature required for the thermal Wolff rearrangement varies with the substrate. Doutheau utilized the thermal Wolff rearrangement of diazo ketones to generate dienylketenes that subsequently undergo electrocyclic ring closure to form phenols in a method related to the last step in our benzannulation.[91] Heating compound **167** or **168** at reflux in toluene resulted in good yields of the corresponding phenolic products.

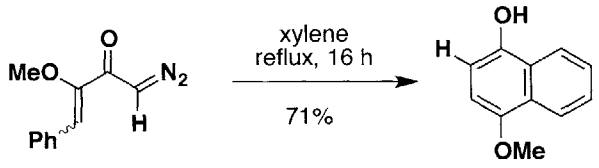


(40)

167 X = CO_2Et
168 X = SO_2Ph

169 81%
170 74%

In contrast, diazo ketone **171**, which does not bear an additional electron-withdrawing group at C-1, reacted sluggishly in refluxing toluene.[91] Heating **171** at reflux in the higher boiling solvent xylenes afforded the desired phenol in 71% yield.



(41)

171 **172**

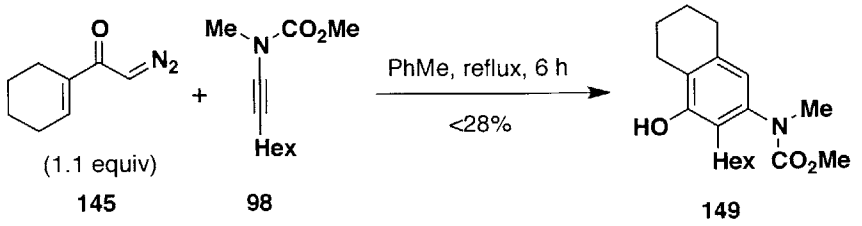
Based on these results, the use of a thermal Wolff rearrangement as a trigger for the benzannulation seemed to be a viable option. If successful, the method might allow for the use of photochemically unstable ynamides in our "second generation" benzannulation.

Benzannulations Triggered by the Thermal Wolff Rearrangement

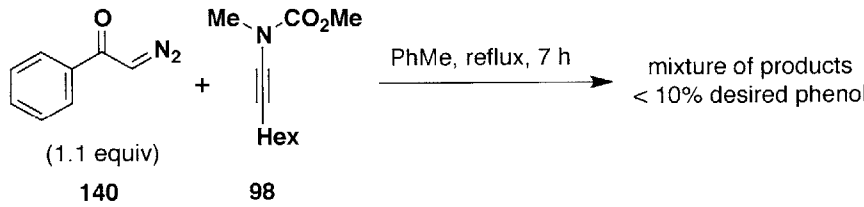
In order to increase the scope of the "second generation" benzannulation, we explored reactions initiated by a thermal Wolff rearrangement. Initial experiments gave mixed results. Heating a mixture of ynamide **98** and diazo ketone **145** afforded the desired product **149**, but in

[91] Collomb, D.; Deshayes, C.; Doutheau, A. *Tetrahedron* **1996**, *52*, 6665-6684.

low yield. The reaction of the aryl diazo ketone **140** and ynamide **98** led to a mixture of products. Optimization of thermal benzannulations utilizing aryl diazo ketones was not pursued further, but it is possible that acceptable yields might still be achieved with further study.

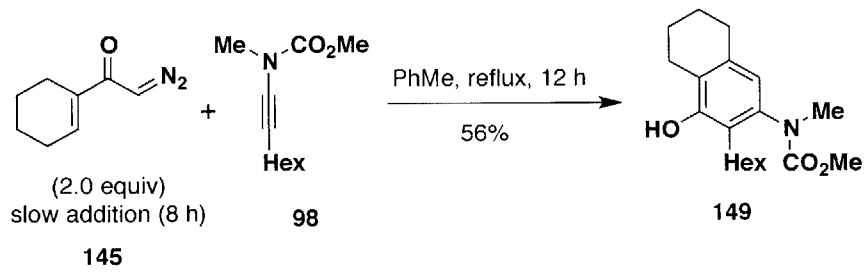


(42)



(43)

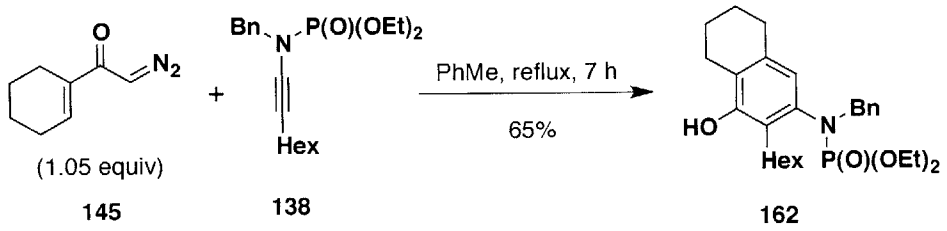
Further attempts were made to optimize benzannulations utilizing α,β-unsaturated diazo ketones. Based on the hypothesis that side reactions of the intermediate vinylketene were once again a problem, the reaction was performed with the slow addition of a 2-fold excess of diazo ketone. Under these conditions the reaction worked well, furnishing the desired phenol in 56% yield.



(44)

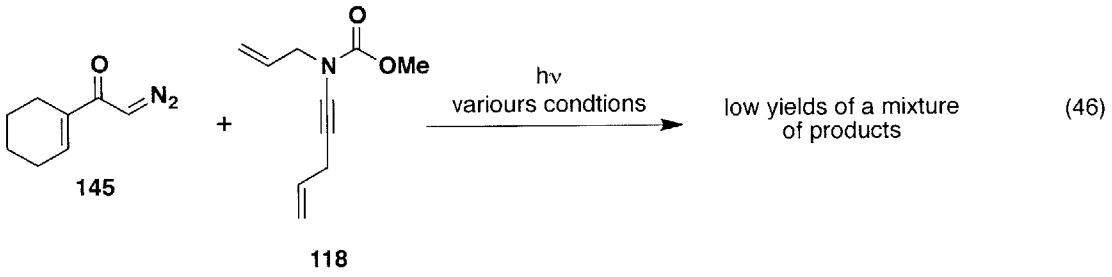
This result supported the idea that side reactions of the intermediate α,β-unsaturated ketene were an issue with this thermal benzannulation approach. Based on our prior work with photochemical benzannulations, we speculated that the *N*-phosphoryl ynamide **138** might be a superior partner in the benzannulation. A more ketenophilic ynamide might allow us to avoid the use of an excess of diazo ketone as well as the need for slow addition. This hypothesis

proved to be correct. Heating a mixture of diazo ketone **145** and the *N*-phosphoryl ynamide **138** afforded the desired phenol **162** in 65% yield. This yield compares well to the 66% yield obtained for the batch photochemical benzannulation using the same substrates (eq 35).



(45)

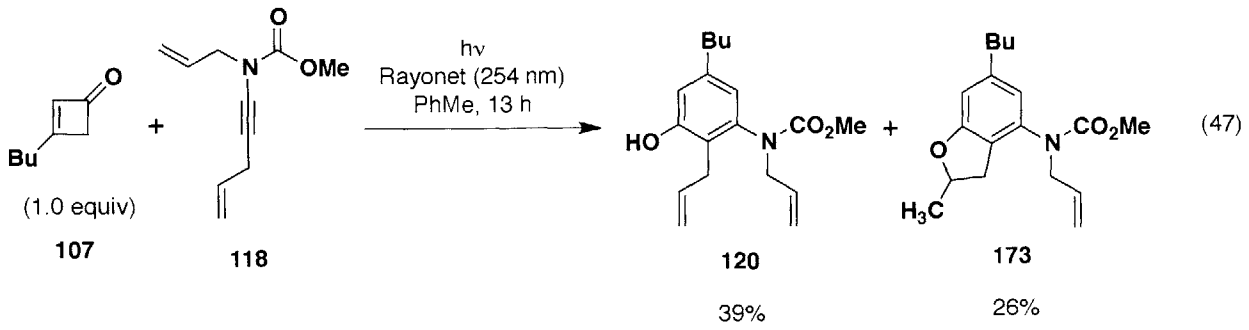
Clearly, vinylketene benzannulations initiated by a thermal Wolff rearrangement are an effective method for the synthesis of highly substituted phenols. Beyond simply providing another set of conditions with which the benzannulation can be performed, this method expands the scope of the "second generation" benzannulation to include photochemically unstable substrates. For example, photochemical benzannulation of ynamide **118** and diazo ketone **145** leads to low yields of the desired product under a variety of conditions.[92]



(46)

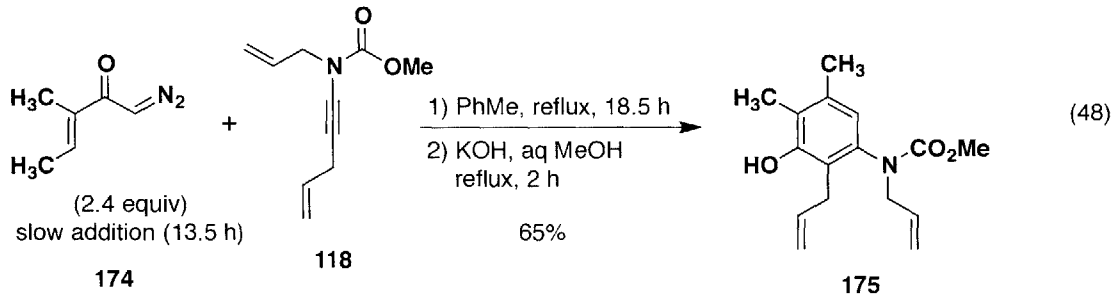
Previous observations in our laboratory suggest that the desired benzannulation product is undergoing further reaction upon irradiation. For example, X. Y. Mak observed that *photochemical* benzannulation of **107** and **118** resulted in a mixture of products including **120** and **173**, with **173** resulting from the undesired photochemical cyclization of **120** (eq 47).[3a]

[92] These reactions were performed by X. Y. Mak.



In contrast to this photochemical reaction, Mak found that the *thermal* benzannulation using cyclobutenone **107** and ynamide **118** worked well.[93] Inview of the photochemical instability of products resulting from ynamide **118**, and this successful thermal benzannulation, we decided to explore the thermal Wolff initiated benzannulation of this ynamide.

As shown in eq 48, the slow addition of an excess of diazo ketone **174**[94] to a solution of ynamide **118**[95] in toluene at reflux led the desired aniline product **175** in 65% yield after hydrolysis. The yield is significantly higher than any yield obtained with this ynamide using photochemical conditions.



This result demonstrates how thermal Wolff triggered benzannulations expand the scope of our "second generation" benzannulation strategy for the synthesis of highly substituted aniline derivatives.

[93] See Table 1, Entry 1
[94] Prepared according to ref 72.
[95] Prepared according to ref 2.

Summary

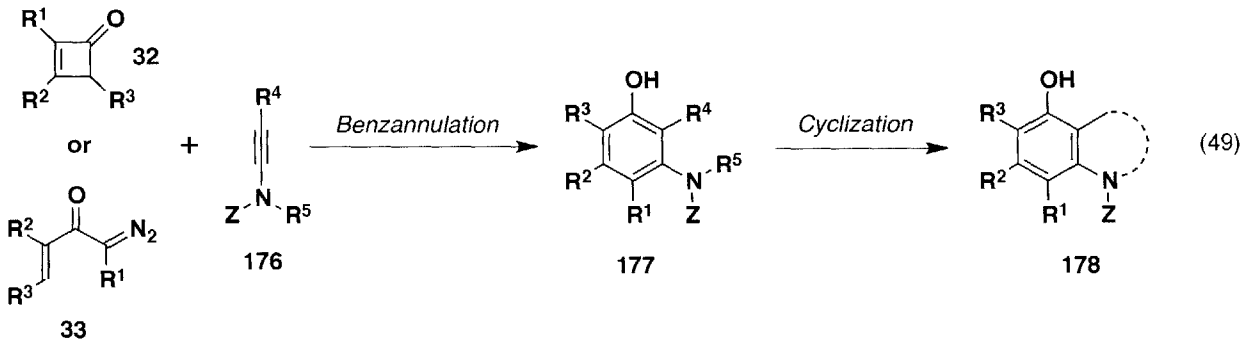
We have found that ynamides work well in our "second generation" benzannulation. The reaction can be initiated photochemically, using either a batch or continuous-flow reactor, and also thermally. Our benzannulation strategy allows for polysubstituted bicyclic and heteroaromatic anilines to be synthesized in good yield from readily available starting materials. The next two parts of this thesis will discuss the use of both "first" and "second generation" benzannulations in tandem strategies for the synthesis of highly substituted benzofused nitrogen heterocycles.

Part II

Tandem Benzannulation-Cyclization Strategies for the Synthesis of Highly Substituted Quinolines

Chapter 1
Introduction and Background

The efficient synthesis of highly substituted benzofused nitrogen heterocycles presents a challenging synthetic problem. The synthesis of this class of compounds is important because they are incorporated in numerous natural products and pharmaceutical targets. In conjunction with the ynamide-based vinylketene benzannulation methodology discussed in Part I, our laboratory has been interested in the development of tandem ynamide benzannulation-cyclization strategies for the synthesis of highly substituted nitrogen heterocycles. Eq 49 illustrates our general approach. In the first stpe, Our vinylketene-based benzannulation produces a functionalized aniline derivative of general type **177**. Depending the desired heterocyclic target, a number of different cyclizations can then be employed to achieve the synthesis of a polysubstituted benzofused nitrogen heterocycle (**178**).

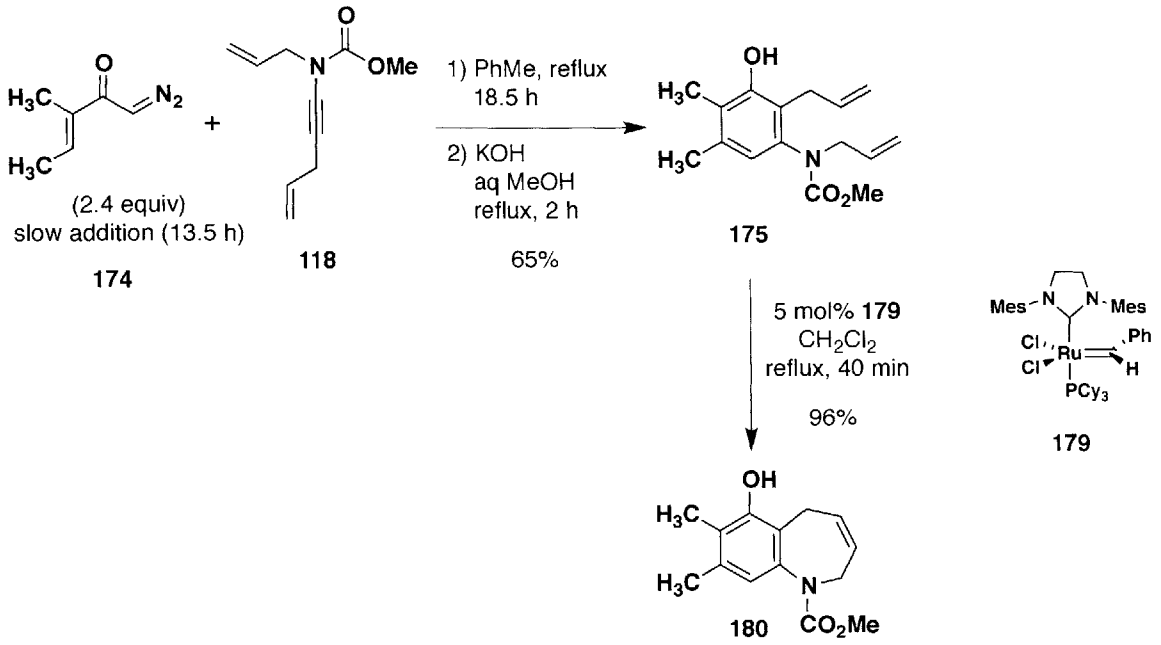


(49)

Previous group members X. Y. Mak and A. Crombie developed a tandem benzannulation-ring closing metathesis strategy[2] for the synthesis of polysubstituted dihydroquinoline, benzazepine, and benzazocine derivatives. Scheme 16 shows an example of this strategy based on benzannulations triggered by the thermal Wolff rearrangement; a variant of this strategy developed more recently (see Part I, Chapter 4). In this example, the vinylketene-based benzannulation allows for the facile synthesis of the highly substituted aniline **175**. Esters that result from the nucleophilic addition of the phenol to vinylketene intermediates are observed as side products in this reaction. Consequently, improved yields of phenol are obtained by hydrolyzing these esters via treatment of the crude product with KOH in methanol

immediately after the benzannulation. Exposing aniline **175** to the "second generation" Grubbs catalyst **179**[96] afforded the desired benzazepine **180** in excellent yield.

Scheme 16

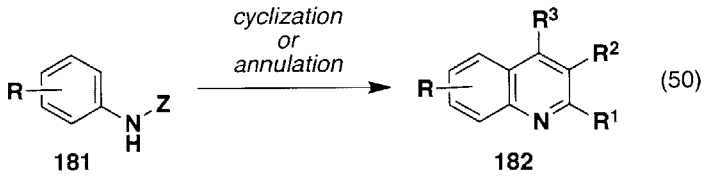


Additional studies in our laboratory by Lam,[3b] Haze, and Wang have led to the development of several different tandem strategies for the synthesis of highly substituted indoles. This chapter describes the extension of our general tandem benzannulation-cyclization strategy to the synthesis of another important class of benzofused nitrogen heterocycles, highly substituted quinolines.[97]

[96] School, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953-956.
[97] Initial studies on this method were carried out by Paul Boudreau.

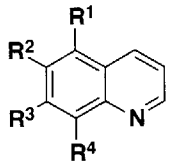
Strategies for the Synthesis of Highly Substituted Quinolines

Quinolines are important synthetic targets due to their wide occurrence in natural products, pharmaceuticals, fungicides, and advanced materials.[98] Numerous methods exist for the synthesis of quinolines.[99] Most of these methods utilize aniline derivatives that undergo cyclization or annulation reactions to form the heterocyclic ring.[100,101] These methods can be very effective for the synthesis of quinolines of general type **182** that bear a high level of substitution on the pyridyl ring. However, applying these methods to the synthesis of quinolines bearing a high level of substitution on the benzenoid ring can be challenging because of difficulties in accessing the necessary polysubstituted aniline starting materials.



181 **182** (50)

In order to address this problem, a number of strategies for the synthesis of quinolines of type **183** bearing multiple substituents on the benzenoid ring have been developed. Nearly all of these strategies employ a benzannulation or cyclization to generate the desired quinoline from a suitably substituted pyridine starting material. Because an overview of benzannulation methods was provided in Part I of this



183

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[98] (a) McAteer, C. H.; Balasubramanian, M.; Murugan, R. "Pyridines and their Benzo Derivatives: Applications" In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K. Eds.; Pergamon Press: Oxford, 2008; Vol. 7, pp 309-336. (b) Balasubramanian, M.; Keay, J. G. "Pyridines and their Benzo Derivatives: Applications" In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 5, pp 245-300. (c) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166-187. (d) Michale, J. P. *Nat. Prod. Rep.* **2007**, *24*, 223-246.

[99] For reviews on the synthesis of quinolines, see: (a) Alford, P. E. In *Progress in Heterocyclic Chemistry*; Gribble, G. W.; Joule, J. A., Ed.; Elsevier Science: New York, 2011; Vol. 22, pp. 349-391. (b) Alford, P. E. In *Progress in Heterocyclic Chemistry*; Gribble, G. W.; Joule, J. A., Ed.; Elsevier Science: New York, 2011; Vol. 23, pp. 329-369. (c) Madapa, S.; Zehra, T.; Batra, S. *Current Organic Chemistry* **2008**, *12*, 1116-1183. (d) Larsen, R. D.; Cai, D. In *Science of Synthesis*; Thomas, E. J., Ed.; Thieme: Stuttgart, 2004; Vol. 15, pp 389-550.

[100] For selected recent methods, see the following and references cited there in: (a) Wang, Y.; Chen, C.; Peng, J.; Li, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 5323-5327. (b) Reddy, M. S.; Thirupathi, N.; Kumar, Y. K. *RCS Adv.* **2012**, *2*, 3986-3992. (c) Huang, H.; Jiang, H.; Chen, K. Liu, H. *J. Org. Chem.* **2009**, *74*, 5476-5480. (d) Horn, J.; Marsden, S. P.; Nelson, A.; House, D.; Weingarten, G. G. *Org. Lett.* **2008**, *10*, 4117-4120. (e) Movassaghi, M.; Hill, M. D.; Ahmad, O. K. *J. Am. Chem. Soc.* **2007**, *129*, 10096-10097.

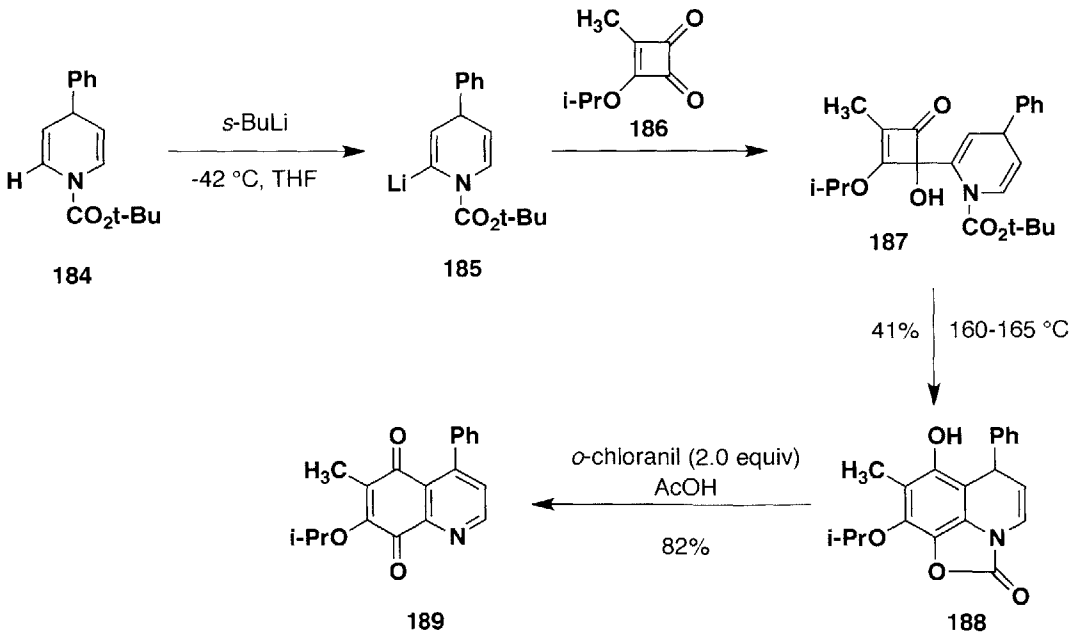
[101] For a discussion of the limitations and problems associated with many methods for quinoline synthesis, see: Tanaka, S.-y.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2006**, *71*, 800-803.

thesis, the following section highlights specific benzannulation approaches that have been employed in the synthesis of quinolines.

Benzannulation Strategies for the Synthesis of Quinolines

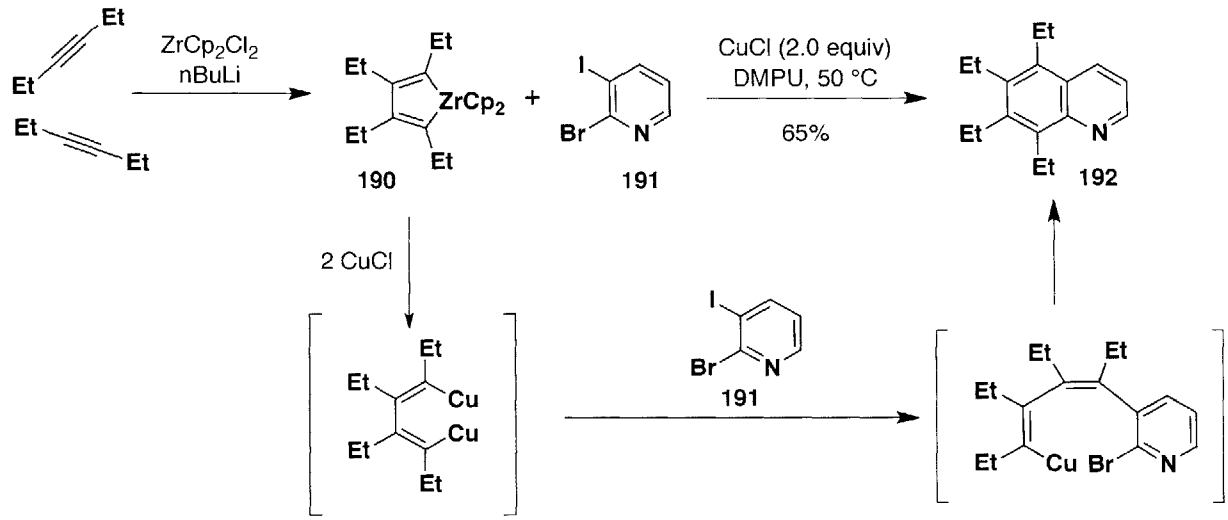
The Liebeskind and Moore benzannulation provides the foundation for one of the more efficient strategies for the synthesis of polysubstituted quinolines.[45b] The addition of lithiated 1,4-dihydropyridine **185** to the squaric acid derivative **186** affords intermediate **187**. Thermolysis of **187** followed by treatment with acetic acid furnishes the quinoline quinone **189**. While this approach does allow for the synthesis highly substiuted quinolines, it has limitations. The synthesis of squaric acid derivatives such as **186** can be challenging and can require lengthy routes. The synthesis of 1,4-dihydropyridines of type **184** can also be challenging depending on the desired level of substitution. In addition, this method only provides access to quinoline quinones.

Scheme 17



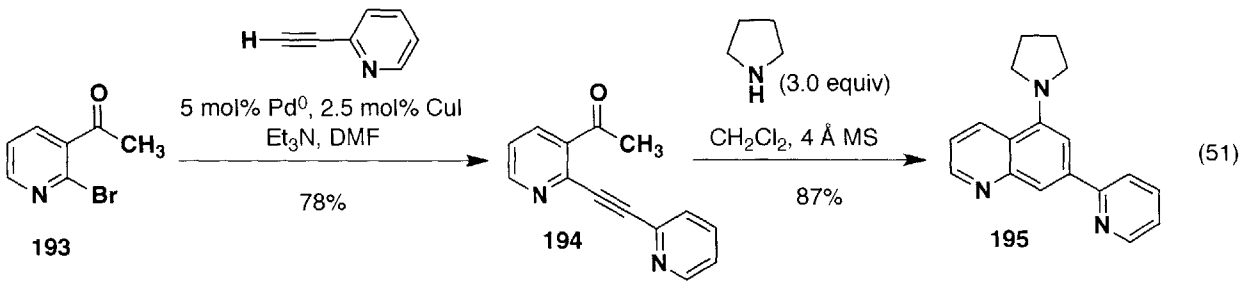
Takahashi developed the copper-mediated benzannulation approach to the synthesis of quinolines illustrated in Scheme 18.[102] Heating zirconacyclopentadienes (e.g., **190**) with 2,3-dihalopyridines (e.g., **191**) in the presence of CuCl affords moderate to good yields of highly substituted quinoline products. The availability of the starting materials, most notably compounds of type **190**, severely limits the scope of this reaction. Takahashi forms the requisite zicronacyclopentadienes in situ from two alkynes, which can be tethered. Without the use of a tether, the reaction can only efficiently access quinolines of type **192** that bear four identical substituents.

Scheme 18



Belmont recently reported a 2-step amino-benzannulation reaction that utilizes 1-(2-bromopyridin-3-yl)ethanone (**193**) as starting material.[103] As shown in eq 51, the reaction produces 5-aminoquinolines, such as **195**. This reaction is limited to the use of dialkylamines and cannot produce quinolines substituted at the C-6 and C-8 positions.

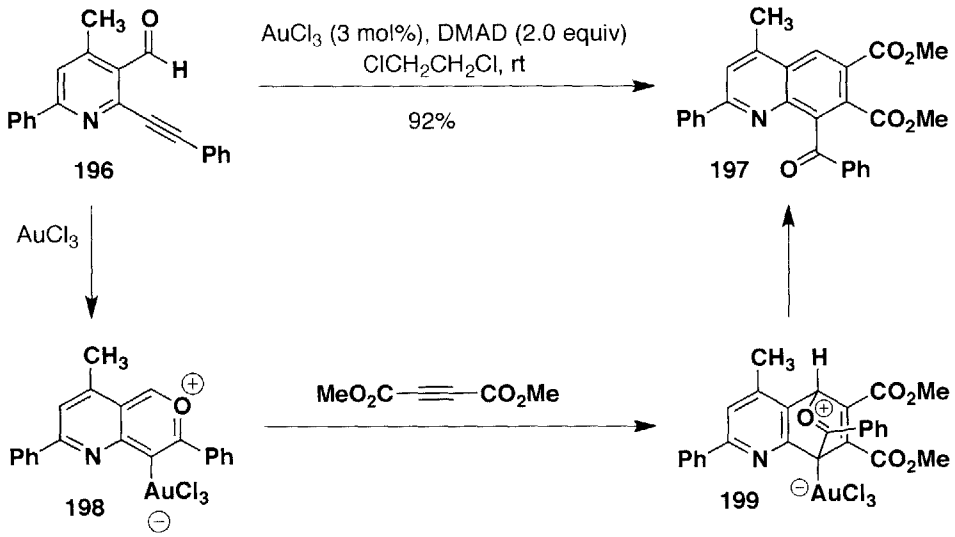
[102] Takahashi, T.; Li, Y.; Stepnicka, P.; Kitamura, M.; Liu, Y.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **2002**, *124*, 576-582.
[103] Tiano, M.; Belmont, P. *J. Org. Chem.* **2008**, *73*, 4101-4109.



(51)

One final example of a benzannulation approach to the synthesis of highly substituted quinolines comes from Sarkar[104] and coworkers, who applied a modified version of the Asao-Yamamoto benzannulation[25] to the synthesis of highly substituted quinolines such as **197**. This reaction requires the use of electron deficient alkynes and is limited by the availability of polysubstituted pyridines of type **196**.

Scheme 19



[104] Panda, B.; Bhadra, J.; Sarkar, T. *Synlett* **2011**, 689-693.

Other methods for the synthesis of highly substituted quinolines have been reported.[105] Nearly all of the known methods suffer from several limitations, most notably a requirement for non-trivial starting materials, an inability to access varied substitution patterns, and difficulty achieving high levels of substitution on *both* the pyridyl and the benzenoid ring. The goal of our research has been the development of a new tandem benzannulation-cyclization strategy for the synthesis of highly substituted quinolines not subject to these limitations.

[105] For selected additional examples, see: (a) Wang, Y.; Tan, C.; Zhang, X.; He, Q.; Xie, Y.; Yang, C. *Eur. J. Org. Chem.* **2012**, 6622-6629. (b) Shukla, S. P.; Tiwari, R.; Verma, A. K. *Tetrahedron* **2012**, *68*, 9035-9044. (c) Song, G.; Gong, X.; Li, X. *J. Org. Chem.* **2011**, *76*, 7583-7589. (d) Huang, C.-C.; Chang, N.-C. *Org. Lett.* **2008**, *10*, 673-676. (e) Narender, P.; Srinivas, U.; Ravinder, M.; Ananda Rao, B.; Ramesh, Ch.; Harakishore, K.; Gangadasu, B.; Murthy, U. S. N.; Jayathirtha Rao, V. *Bioorg. Med. Chem.* **2006**, *14*, 4600-4609. (f) Savarin, C. G.; Murry, J. A.; Dormer, P. G. *Org. Lett.* **2002**, *4*, 2071-2074. (g) Ghera, E.; Ben-David, Y.; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 774-779. (h) Ghera, E.; David, Y. B.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 2059-2065. (i) van Leusen, A. M.; Terpstra, J. W. *Tetrahedron Lett.* **1981**, *22*, 5097-5100. (j) Jones, G.; Jones, R. K. *J. Chem. Soc., Perkin Trans. 1* **1972**, 26-32.

Chapter 2

Tandem Benzannulation-Iodocyclization Strategy for the Synthesis of Quinolines

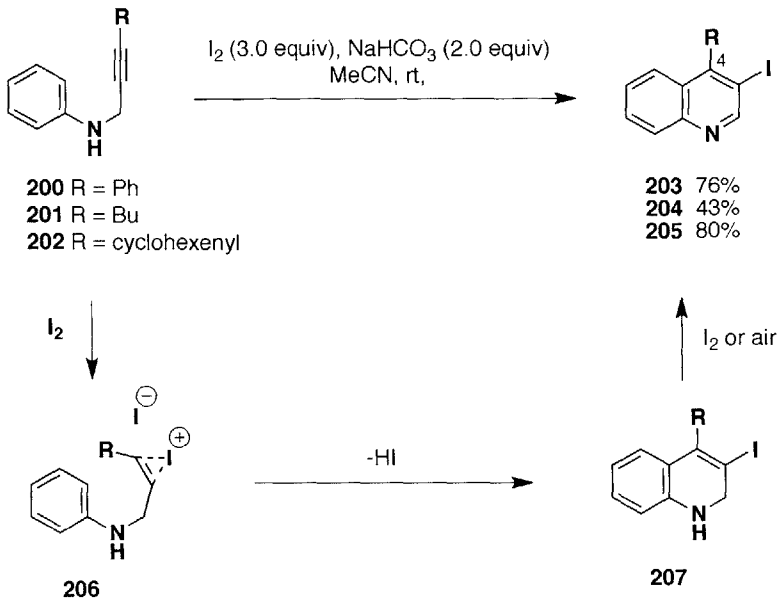
Our aim was to develop a strategy for the synthesis of quinolines that allowed for the installation of a variety of groups at *all* seven positions of the quinoline ring system with regiochemical control. Since our previous work had established the ability of the ynamide-based benzannulation to access highly substituted anilines, what remained was to identify a suitable cyclization method. Of the numerous cyclization strategies available, we chose to examine the iodocyclization protocol developed by Larock[106] because of its mild conditions and its ability to produce a variety of substitution patterns on the pyridyl ring.[107] The Larock method involves the cyclization of propargylic aniline derivatives upon exposure to iodine and base. The reaction results in the formation of 3-iodoquinolines bearing aryl, alkyl, or vinyl groups at the 4-position of the quinoline product. Scheme 20 shows a general mechanism for the iodocyclization. This method has broad substrate scope with two key limitations. Larock found that unsubstituted propargyl groups (e.g., R = H) do not cyclize, so the 4-position in the quinoline product must always bear a substituent. Larock also found that alkynes bearing large groups (e.g., *tert*-butyl, trimethylsilyl) do not undergo cyclization.

---

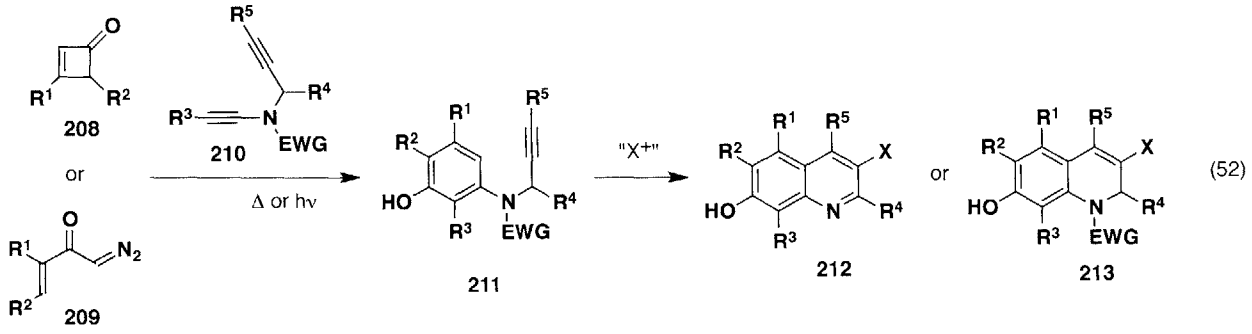
[106] (a) Zhang, X.; Campo, M. A.; Yao, T.; Larock, R. C. *Org. Lett.* **2005**, *7*, 763-766. (b) Zhang, X.; Yao, T.; Campo, M. A.; Larock, R. C. *Tetrahedron* **2010**, *66*, 1177-1187.

[107] For similar strategies for the synthesis of 3-halo quinolines, see: (a) Fei, N.; Yin, H.; Wang, S.; Wang, H.; Yao, Z.-J. *Org. Lett.* **2011**, *13*, 4208-4211. (b) Gurunathan, S.; Perumal, P. T. *Tetrahedron* **2011**, *52*, 1783-1787.

Scheme 20



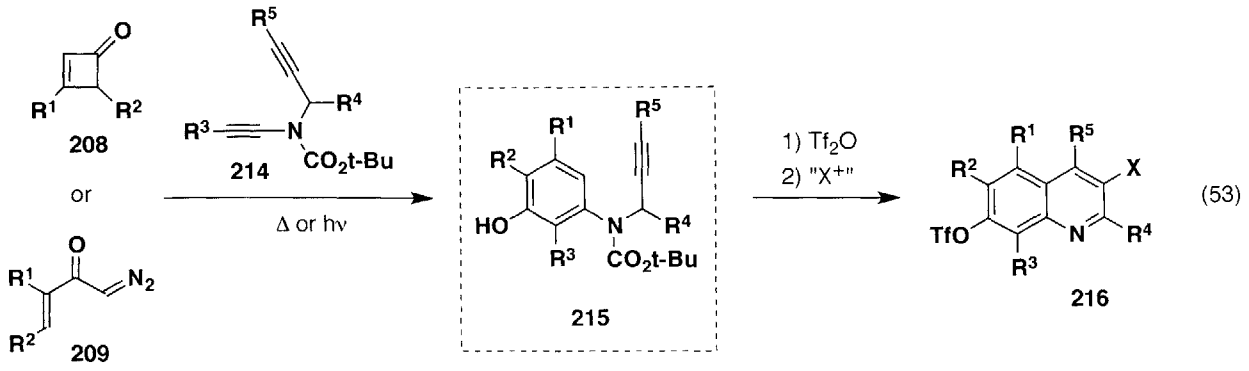
The implementation of this cyclization in a tandem strategy would require benzannulations with *N*-propargyl ynamides. Eq 52 presents our proposed tandem strategy. Benzannulation with an *N*-propargyl ynamide would lead to the aniline derivative **211** and iodocyclization of **211** would then furnish the desired quinoline (or dihydroquinoline) product.



(52)

In preliminary studies, we found that deprotection and triflation were required prior to cyclization in order to obtain the quinoline product in good yields (vide infra). Because it was necessary to deprotect **211** prior to cyclization, we chose to employ *N*-(*tert*-butoxycarbonyl) ynamides in the benzannulation. The resulting *tert*-butoxycarbonyl (Boc) protected aniline

derivatives can then be deprotected under mild conditions.[108] Eq 53 outlines our final tandem strategy.



(53)

This strategy not only provides an efficient route to highly substituted quinolines, but also affords products that possess iodine and triflate substituents at the 3- and 7-positions respectively. Subsequent chemoselective transformation of the aryl iodide and triflate could allow for the synthesis of a myriad of highly decorated quinolines.

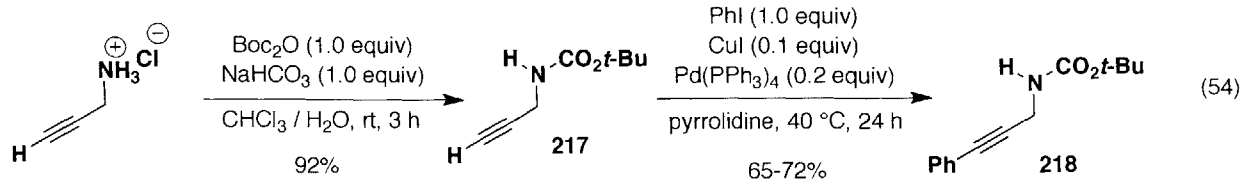
Synthesis of Benzannulation Substrates

We began our investigation with the synthesis of Boc protected *N*-propargyl amines and alkynyl bromides. Copper-mediated coupling of these substrates would furnish the *N*-proparyl ynamides required for our tandem benzannulation-iodocyclization strategy.

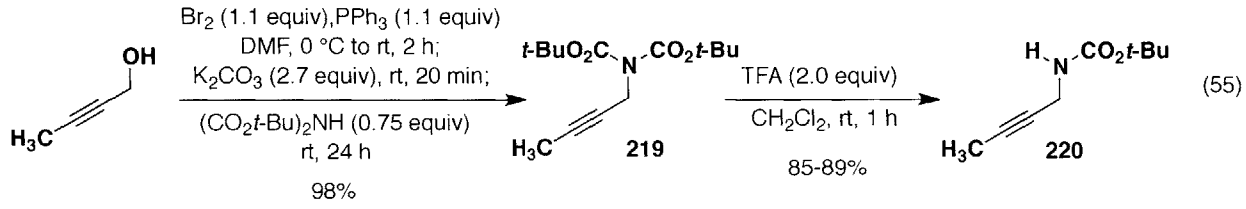
As shown in eq 54-56, the synthesis of a variety of differentially substituted propargylamine derivatives proceeded smoothly. The propargyl amine derivatives **218**[109] and **220**[110] are known compounds that were synthesized according literature procedures. For the synthesis of the propargyl amine derivative **222**, we employed a general method developed by Mecozzi and Petrini.[111] Exposure of the known sulfone **221**[112] to ca. 2 equiv of lithiated *iso*-propenynylacetylide resulted in the elimination of sulfinate followed by nucleophilic addition to

[108] Kocienski, P. J. *Protecting Groups*, 3rd ed.; Georg Thieme, Verlag: New York, 2005, pp. 487-644.
[109] Paul Boudreau prepared compound **218** according to: Miller, K. M., Molinaro, C. Jamison, T. F. *Tetrahedron: Asymmetry*. **2003**, *14*, 3619-3625.
[110] For the preparation of **220**, see: Walters, M. A., Hoem, A. B. *J. Org. Chem.* **1994**, *59*, 2645-2647.
[111] Mecozzi, T.; Petrini, M. *J. Org. Chem.* **1999**, *64*, 8970-8972.
[112] Klepacz, A.; Zwierzak, A. *Tetrahedron Lett.* **2002**, *43*, 1079-1080.

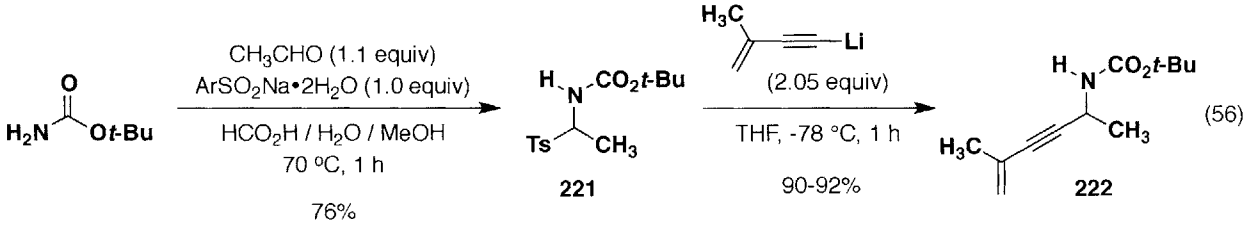
the resulting imine to afford the propargyl amine derivative **222** in high yield. This method is not limited to the use of sulfone **221** and could easily be applied to the synthesis of other propargyl amine carbamates.



(54)

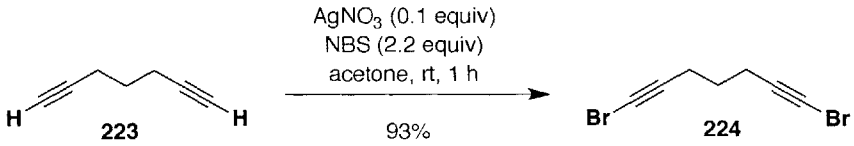


(55)



(56)

The previously known alkynyl bromides **130** and **228** were synthesized from the corresponding terminal alkynes in near quantitative yield by the method developed by Hofmeister utilizing silver(I) nitrate and NBS.[113,114] Eq 57 illustrates the synthesis of dibromide **224** using the same method.



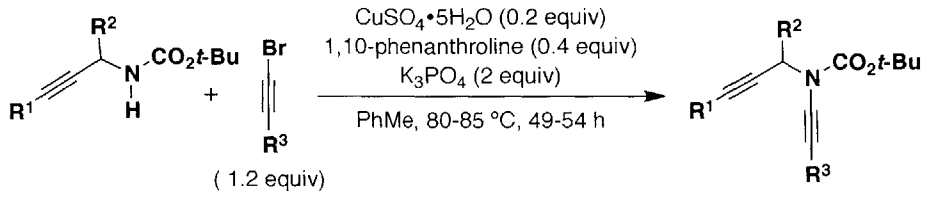
(57)

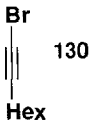
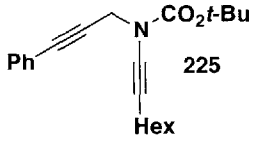
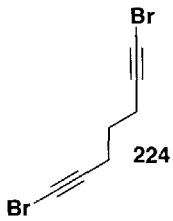
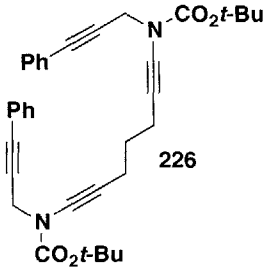
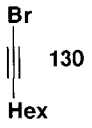
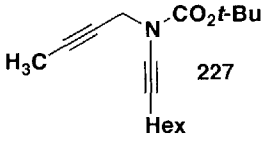
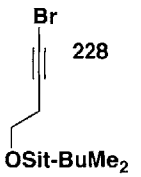
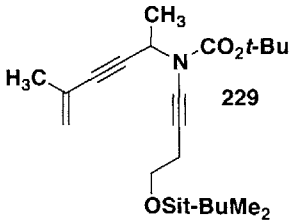
Both the Danheiser[65] and Hsung[64] methods were investigated for the synthesis of the desired ynamides. We found that the Hsung method provided better yields for the synthesis of

[113] Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R. *Angew. Chem. Int. Ed.* **1984**, *23*, 727-729.
[114](a) For the preparation of alkynyl bromide **130**, see ref 62b. (b) For the preparation of alkynyl bromide **228**, see: Li, L.-S.; Wu, Y.-L. *Tetrahedron Lett.* **2002**, *43*, 2427-2430.

the *N*-proparyl ynamides used in our investigation. Table 5 summarizes our results.[115] We obtained all four ynamides, including the diynamide **226**, in good yield using this method. It should be noted that we obtained the best yields using K_3PO_4 purchased from Acros.[116]

Table 5. Synthesis of *N*-Propargyl Ynamides



entry	carbamate	alkynyl bromide	ynamide	yield (%)[a]
1	**218**	 **130**	 **225**	80
2	**218**	 **224**	 **226**	58-60[b]
3	**220**	 **130**	 **227**	83
4	**222**	 **228**	 **229**	59-68

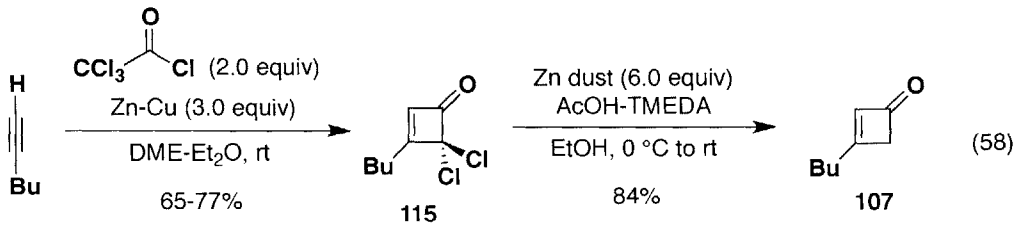
[a] Isolated yield of product purified by column chromatography. [b] Reaction was performed using 2.5 equiv **216**, 0.4 equiv $CuSO_4•5H_2O$, and 0.8 equiv 1,10-phenanthroline

[115] Paul Boudreau synthesized ynamide **225.**

[116] The effect of K_3PO_4 from different suppliers on the Hsung method has been studied in detail, see: Dooleweerdt, K.; Birkedal, H.; Ruhland, T.; Skrydstrup, T. *J. Org. Chem.* **2008**, *73*, 9447-9450.

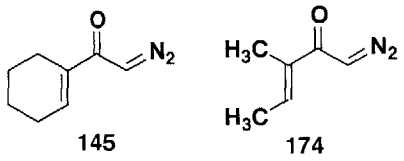
In addition to *N*-propargyl ynamides, the benzannulation reaction employed in our tandem strategy requires a vinylketene precursor. All of the precursors used in this investigation were well known and synthesized according to literature procedures.

We used 3-butylcyclobutenone (**107**) as the vinylketene precursor in our "first-generation" benzannulation studies. Eq 58 shows the synthesis of **107** using a procedure previously developed in our group.[117]



(58)

For our "second-generation" benzannulation studies, we employed diazo ketones **145** and **174** as the vinylketene precursors. We synthesized both diazo ketones via a detrifluoroacetylative diazo transfer as previously described by our group.[72]



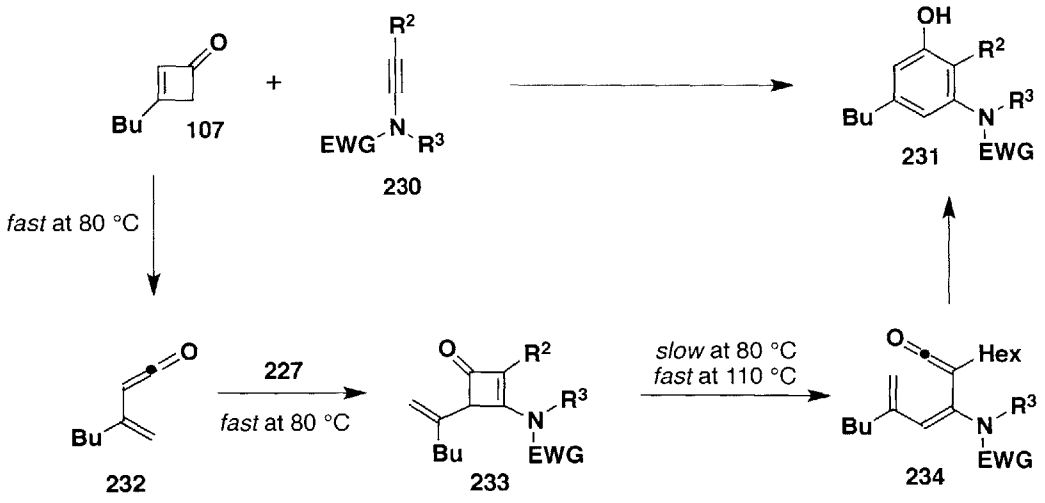
With necessary substrates in hand, we began to explore tandem benzannulation-iodocyclization strategies for the synthesis of highly substituted quinolines.

[117] (a) Danheiser, R. L.; Savariar, S. *Tetrahedron Lett.* **1987**, *28*, 3299-3302. (b) Danheiser, R. L.; Savariar, S.; Cha, D. D. *Org. Synth.* **1990**, *68*, 32-38.

"First Generation" Benzannulations

Our study of the feasibility of the "first generation" version of the benzannulation with *N*-propargyl ynamides utilized cyclobutenone **107** as the vinylketene precursor. We performed these benzannulations by heating the reaction in two stages. Initial heating at 80 °C triggers four-electron electrocyclic ring-opening of cyclobutenone **107**. The resulting "aldoketene" **232** reacts with an activated alkyne (e.g., ynamide **230**) smoothly at this temperature to furnish the intermediate vinylcyclobutenone **233**. Typically, heating the reaction mixture at 80 °C for 1-2 h results in complete consumption of the ynamide. The conversion of intermediate vinylcyclobutenone **233** to the desired phenol occurs slowly at 80 °C and can require more than 18 h.[3b] In order to expedite the reaction, we typically increased the reaction temperature to reflux (ca. 110 °C). We speculated that an *N*-propargyl ynamide of type **230**, might undergo undesired sigmatropic rearrangements [118] at elevated temperatures. [119] Using the two-stage heating conditions described above, the ynamide itself is never heated above 80 °C, which helps avoid any undesired side reactions. In many cases the reaction can simply be heated at reflux from the beginning.[2,3]

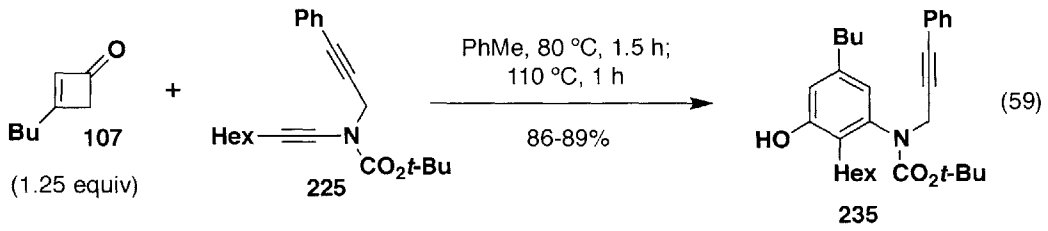
Scheme 21



[118] For a review of intramolecular pericyclic reactions of acetylenic compounds, see: Viola, A.; Collins, J. J.; Filipp, N. *Tetrahedron*, **1981**, *37*, 3765-3811.

[119] For the [3,3] sigmatropic rearrangement of alkynyl propargyl sulfides, see: (a) Aoyagi, S.; Kikuchi, K.; Shimada, K.; Takikawa, Y. *Synlett*, **2007**, 2553-2556. (b) Aoyagi, S.; Hakoishi, M.; Suzuki, M.; Nakanoya, Y. Shimada, K.; Takikawa, Y. *Tetrahedron Lett.* **2006**, *47*, 7763-7766.

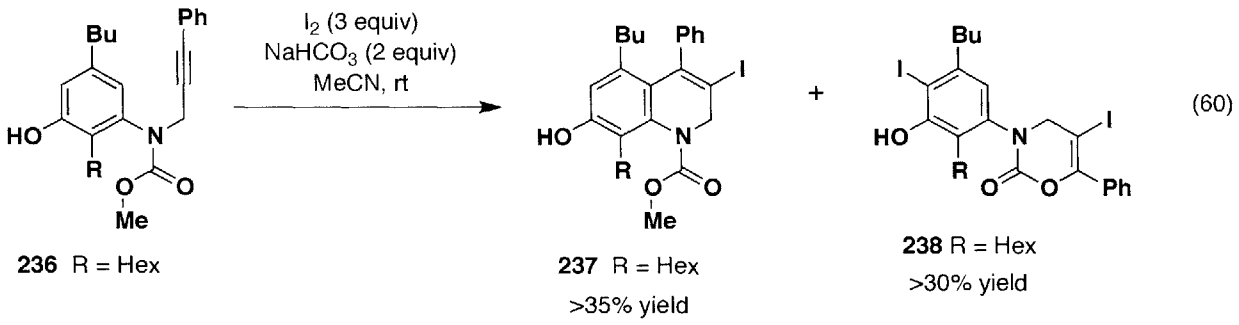
An initial study by Paul Boudreau established that *N*-propargyl ynamide **225** performs well in the benzannulation. Heating a mixture of ynamide **225** with a slight excess of cyclobutenone **107** in toluene at 80 °C for 1.5 h and then at reflux for 1 h affords phenol **235** in 86-89% yield.



(59)

Initial Iodocyclization Studies

Paul Boudreau performed the initial studies on the iodocyclization of *N*-propargyl aniline derivatives in our laboratory. Boudreau first investigated the cyclization of the protected *N*-propargyl aniline **236**.[120] Treatment of **236** with 3 equiv of I_2 and 2 equiv of $NaHCO_3$, according to the procedure reported by Larock,[106] afforded the dihyrdoquinoline **237** in poor yield. Competitive cyclization to form dihydrooxazinone **238** causes of the low yield observed for this reaction.[121]



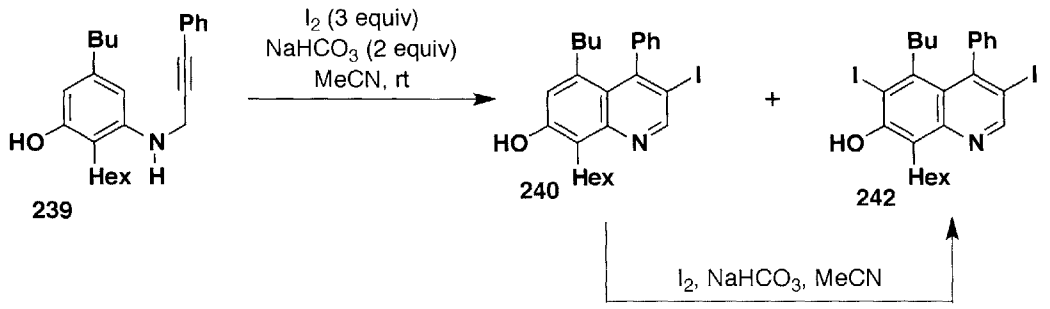
(60)

[120] Boudreau synthesized aniline **236** in a benzannulation reaction similar to the one shown in eq 59, but with the corresponding *N*-carbomethoxy ynamide.

[121] Larock has shown that *N*-sulfonyl *N*-propargyl anilines cyclize upon exposure to iodine and base to form dihydroquinolines similar to **237**. See ref 106b.

In order to avoid the formation of this undesired side product, Boudreau investigated the cyclization of deprotected *N*-propargyl aniline derivative **239**.[122] Unfortunately, Boudreau found that the iodocyclization of **239** afforded quinoline **240** and diiodo product **241**. A subsequent control experiment showed that the 7-hydroxyquinoline **240** undergoes electrophilic aromatic substitution under the reaction conditions to form the undesired side product **241**.

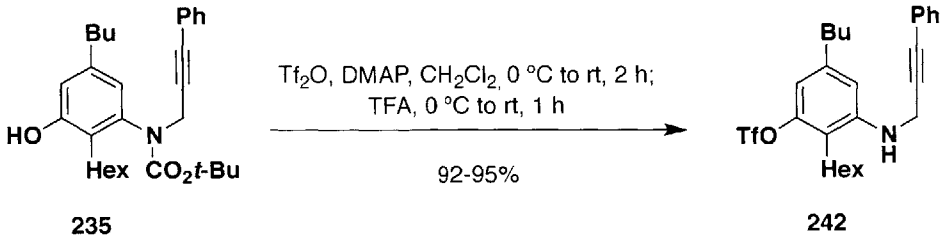
Scheme 22



We speculated that protecting the phenol with an electron-withdrawing group would suppress electrophilic aromatic substitution and lead to clean formation of a single product. To test this hypothesis we protected the phenol with a trifluoromethylsulfonyl group. We chose to employ this protecting group because the resulting aryl triflates could serve as a functional handle for further elaboration after the cyclization.

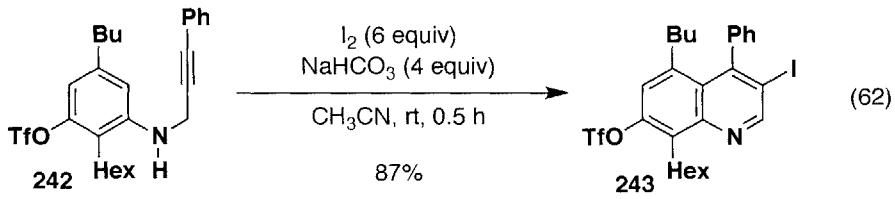
Thus our strategy was adjusted to include triflation of the phenol and cleavage of the *tert*-butoxy carbamate. Boudreau found that after triflation of the phenol with triflic anhydride, the addition of excess trifluoroacetic acid to the reaction mixture allows for the cleavage of the carbamate. This one-pot process furnished the cyclization precursor, *N*-propargyl aniline **242**, in excellent yield. The two-step yield from ynamide **225** is greater than 79%, making material throughput straightforward.

[122] Paul Bodreau synthesized compound **239** via the deprotection of **235** with trifluoroacetic acid in CH_2Cl_2.



235 242 (61)

The iodocyclization of **242** proceeded smoothly. Eq 62 shows the optimized reaction developed by Boudreau. Cyclization of **242** with 6 equiv of iodine and 4 equiv of $NaHCO_3$ in acetonitrile furnishes quinoline **243** in 87% yield. The conditions used by Boudreau utilize twice as much iodine and base as those originally reported by Larock. Boudreau observed only ca. 65% conversion of the starting material when 3 equiv of iodine were used. Extended reaction times (ca. 18 h) did not lead to complete conversion.

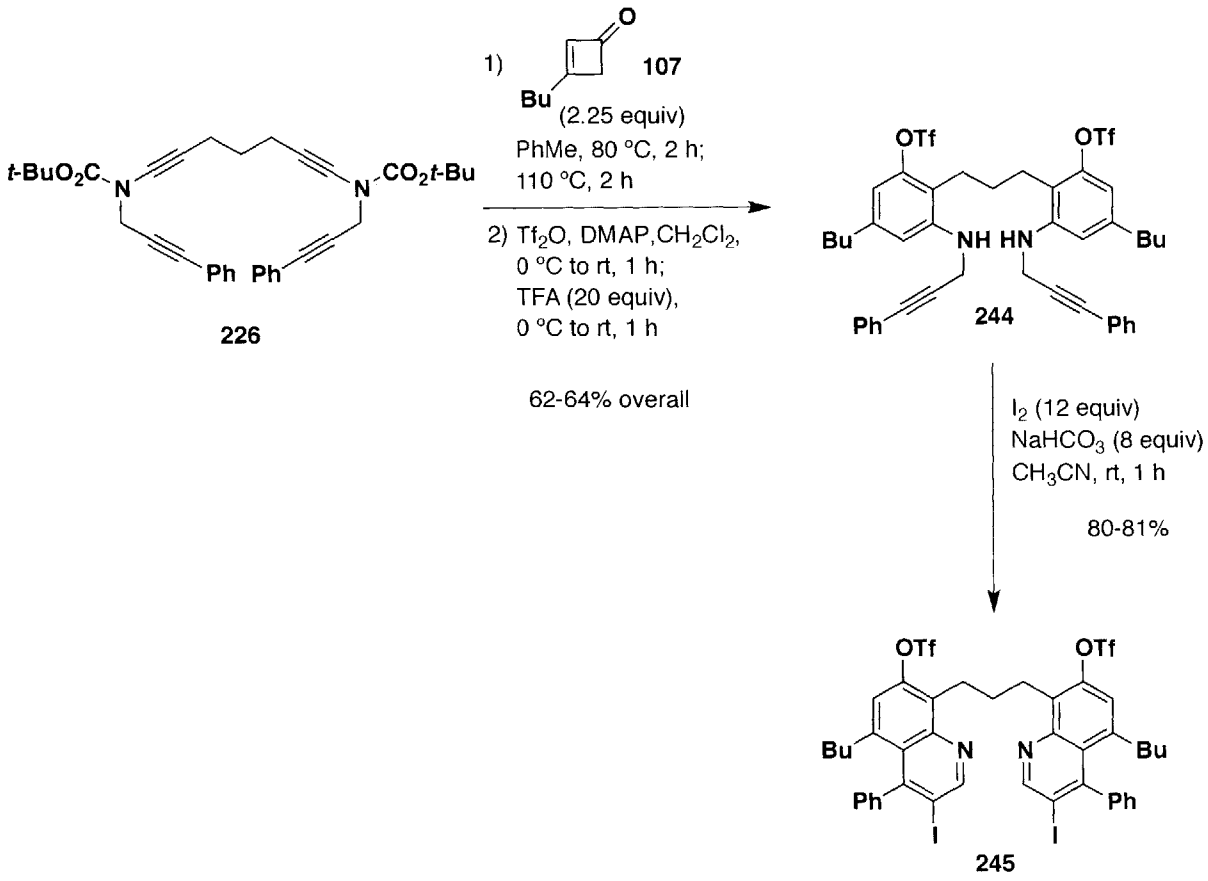


242 243 (62)

Additional "First Generation" Benzannulation-Iodocyclization Studies

I completed the synthesis of bisquinoline **245** as outlined in Scheme 23. Heating diynamide **226** with 2.25 equiv of cyclobutenone **107** leads to the formation of four new C-C bonds and two new aromatic rings. Triflation and deprotection of the crude product furnishes **244** in 62-64% overall yield over two steps from the diynamide. Cyclization of **244** with 12 equiv of iodine and 8 equiv of $NaHCO_3$ affords two quinolines tethered to one another by a three-carbon chain at their respective 8-positions. I found the use of 12 equiv of iodine to be necessary to achieve complete cyclization of both rings.

Scheme 23



In summary, using the "first generation benzannulation" in tandem with an iodocyclization we were able to rapidly access the highly substituted quinolines **243** and **245**. The next section examines the utilization of the "second generation" benzannulation in this tandem strategy.

"Second Generation" Benzannulation-Iodocyclization Studies

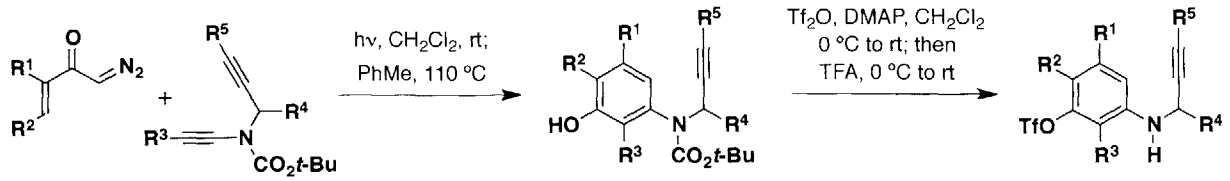
For our "second generation" benzannulation studies we employed α,β-unsaturated diazo ketones **145** and **174**. As discussed in Part I, Chapter 3, studies in our laboratory, demonstrated that benzannulations utilizing α,β-unsaturated diazo ketones require the slow addition of excess diazo ketone to achieve high yields. During our investigation of "second generation" benzannulations utilizing *N*-propargyl ynamides, we found that the rate of addition had minimal effect on the yield of these reactions, and we consequently we performed these benzannulations

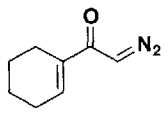
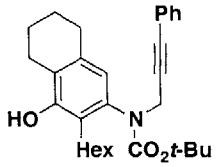
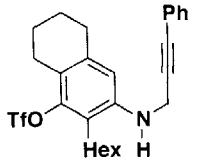
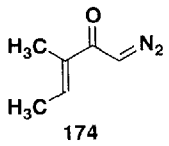
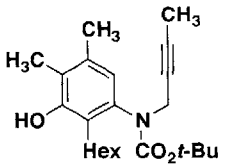
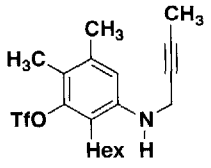
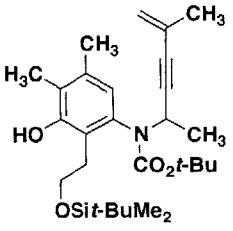
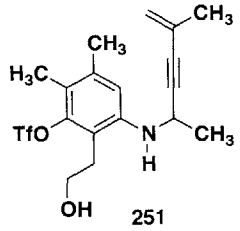
without slow addition. All of the benzannulations in this study utilize an excess of diazo ketone because our previous studies demonstrated that using less diazo ketone leads to a significant drop in yield. In a typical experiment, a quartz tube was charged with *N*-propargyl ynamide, 2.5 equiv of diazo ketone, and dichloromethane (0.25 M in ynamide). The solution was degassed with a stream of argon and then irradiated for ca. 30 h. After irradiation we obtained a mixture of the intermediate vinylcyclobutenone and the desired phenolic annulation product. Consequently, the crude reaction products were heated in toluene at reflux to complete the conversion of vinylcyclobutenone to phenol. The incomplete conversion of the vinylcyclobutenone to product, even upon continued irradiation in some cases, is attributed to the build up of colored polymeric residues on the walls of the reaction tubes.

The benzannulation of ynamide **225** and diazo ketone **145** furnished the desired benzannulation product **246** in 58% yield (Table 6 entry 1). Triflation and deprotection of **246** afforded cyclization precursor **247** in 91% yield. The synthesis of **249** proceeded similarly. The benzannulation of ynamide **229** and diazo ketone **174** provided phenol **250**, which was taken into the next step without purification. Subsequent triflation and cleavage of the carbamate[123] furnished cyclization precursor **251** in 51-54% overall yield over two steps. With an array of *N*-propargyl anilines in hand, we proceeded to investigate the scope of the iodocyclization.

[123] Cleavage of the silyl group occurred during the deprotection step.

Table 6. Scope of the 'Second-Generation' Benzannulation with *N*-Propargyl Ynamides

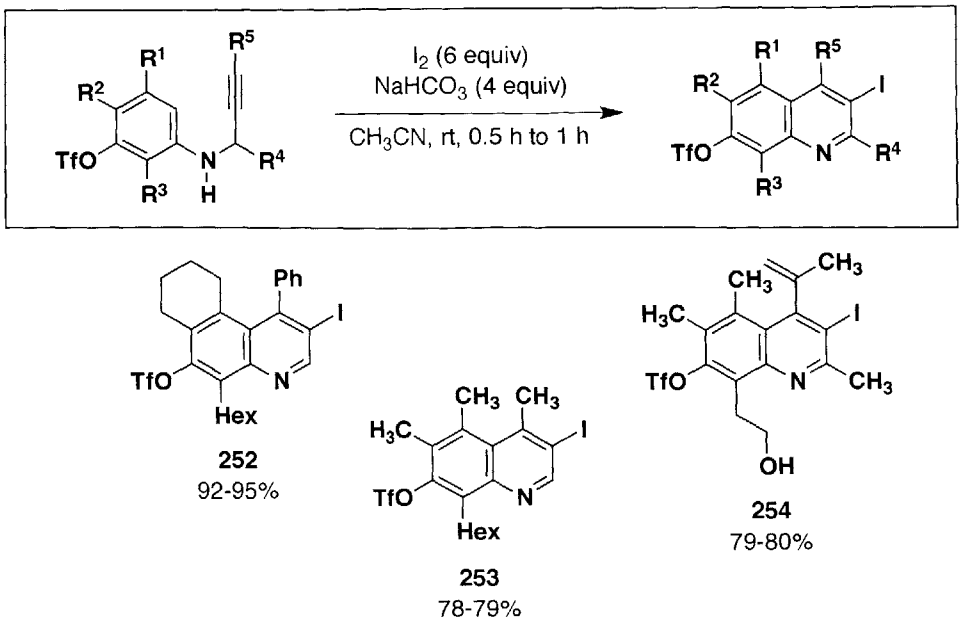


entry	diazo ketone	ynamide	benzannulation product[a]	yield (%)[b]	propargylic amine[c]	yield (%)[b]
1	 **145**	**225**	 **246**	58	 **247**	91
2	 **174**	**227**	 **248**	55-57	 **249**	88-92
3	**174**	**229**	 **250**		 **251**	51-54[d]

[a] Conditions: ynamide (1.0 equiv), diazo ketone (2.5 equiv), CH_2Cl_2, hν, rt, 30-33 h; then toluene, reflux, 2-2.5 h. [b] Isolated yield of product purified by column chromatography. [c] Conditions: DMAP (2.5-3 equiv), Tf_2O (1.1-1.3 equiv), CH_2Cl_2, 0 °C to rt, 1-2 h; then TFA (20 equiv), 0 °C to rt, 0.7-1.5 h. [d] Overall yield for two steps.

Scheme 24 shows the iodocyclization of *N*-proparyl aniline derivatives **247**, **249**, and **251**. The reaction tolerates a variety of substituents R^5 on the alkyne and affords the desired quinoline products in 79-95% yield. One of the more impressive quinolines synthesized using our tandem strategy is quinoline **251** that bears a substituent on all seven positions of the quinoline ring system. This a significant achievement because quinolines bearing this high level of substitution are not efficiently synthesized using current methodology (vide supra).

Scheme 24



Starting from commercially available materials, we achieved the synthesis of penta-, hexa-, and heptasubstituted quinolines in only six linear steps. Our strategy allows us to install a variety of groups at different positions on the quinoline core by simply utilizing different N-propargyl ynamides and vinylketene precursors (cyclobutenones or diazo ketones). All of the quinolines synthesized using our tandem strategy bear an iodine substituent at the C-3 position and a trifloxy group at the C-7 position. The next chapter examines chemoselective transformations of these functional handles as well as an alternative cyclization method for the synthesis of quinolines that are not iodinated.

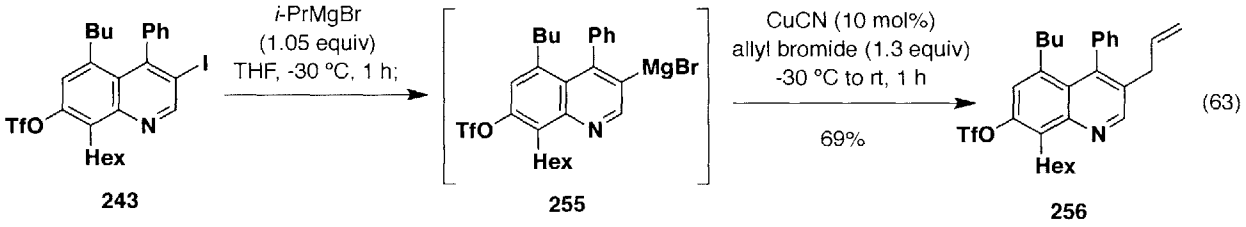
Chapter 3

Transformations of Quinoline Products and Alternative Cyclization Methods

Chemoselective Transformations of Quinolines Synthesized via the Tandem Strategy

The quinolines produced by our tandem strategy possess an iodine substituent at the C-3 position and a triflloxy group at the C-7 position. Chemoselective transformations at these positions would allow for the rapid synthesis of an assortment of quinolines bearing an array of groups at these positions.

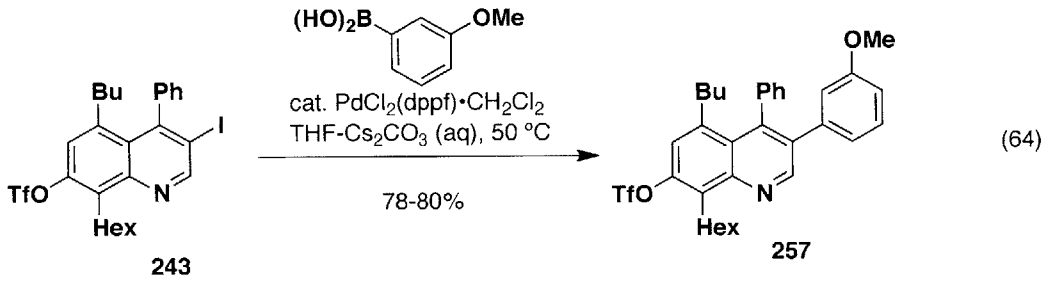
The first transformation we investigated was magnesium-iodine exchange, followed by trapping with an electrophile. This type of reaction, pioneered by Knochel,[124] would allow for the installation of a variety of electrophiles at C-3 without any reaction occurring at the C-7. As shown in eq 63, treatment of **243** with *i*-PrMgBr at low temperature leads to magnesium-iodine exchange and the formation of intermediate **255**. The addition of catalytic CuCN and allyl bromide furnishes the desired product in 69% yield.



(63)

[124] (a) Abarbri, M.; Thibonnet, J.; Bérillon, L.; Dehmel, F.; Rottländer, M.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 4618-4634. (b) Ila, H.; Baron, O.; Wagner, A. J.; Knochel, P. *Chem. Commun.* **2006**, 583-593.

Subsequent experiments focused on chemoselective transition-metal catalyzed cross-coupling reactions.[125] The order of reactivity for aryl electrophiles in cross-coupling reactions is generally accepted to be Ar-I > Ar-Br ~ Ar-OTf >> Ar-Cl.[125a,126] As a result, achieving the chemoselective reaction of an iodide in the presence of a triflate should be possible. Chemoselective cross-coupling reactions of polyhalogenated quinolines have been studied.[125b, 127] Selective cross-coupling reactions of quinolines bearing a halogen and a trifloxy group has also been studied, though less extensively.[128] Of the many possible cross-coupling reactions, we chose to explore chemoselective Suzuki and Sonogashira reactions due to their mild conditions and broad scope. The Suzuki reaction of quinoline **243** proceeded with complete regioselectivity affording **257** in 78-80% yield (eq 64). For this reaction we utilized conditions reported by Wokenberg and co-workers for the chemoselective Suzuki reaction of polyhalogentated quinolines.[129]



(64)

The Sonogashira reaction of iodide **253** also proceeded smoothly furnishing the quinoline **258** in 90-91% yield (eq 65). For this Sonogashira reaction, we employed a standard set of reaction conditions that operate at room temperature because we knew that competitive reaction of the triflate would likely require higher temperatures (vide infra).

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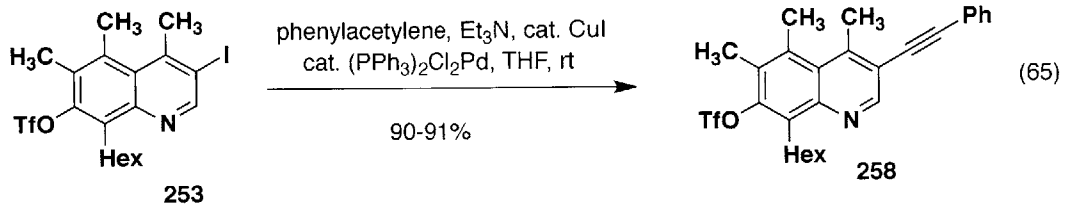
[125] (a) For leading references regarding cross-coupling reactions, see: *Metal-Catalyzed Cross Coupling Reactions*, 2nd ed.; de Meijere, A.; Diederich, F., Eds.; Wiley-VHC: Weinheim, Germany, 2004; Vol. 1 and 2. (b) For a recent review regarding cross-coupling reactions of halogenated quinolines, see: Mphahlele, M. J.; Lesenyeho, L. G. *J. Heterocycl. Chem.* **2013**, *50*, 1-16.

[126] This general order of reactivity does not apply to all catalytic systems. For an exception, see: Fu, G. C. *Acc. Chem. Res.* **2008**, *41*, 1555-1564.

[127] For a review of chemoselective Suzuki reactions of a variety of heterocycles including quinolines, see: Rossi, R.; Bellina, F.; Lessi, M. *Adv. Synth. Catal.* **2012**, *354*, 1181-1255.

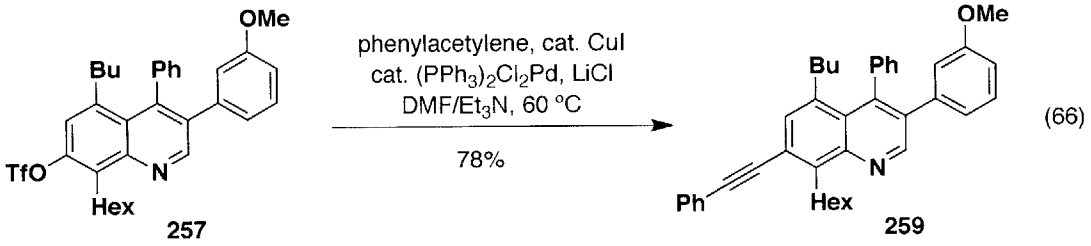
[128] For a recent example of the chemoselective cross-coupling of a quinoline derivative employing the Suzuki reaction of bromine substituents in the presence of a trifloxy group, see: Eleya, N.; Mahal, A.; Hein, M.; Villinger, A.; Langer, P. *Adv. Syn. Catal.* **2011**, *353*, 2761-2774.

[129] Nolt, M. B.; Zhao, Z.; Wolkenberg, S. E. *Tetrahedron Lett.* **2008**, *49*, 3137-3141.

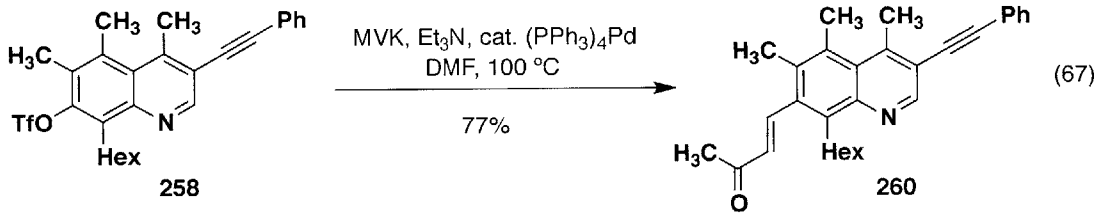


(65)

We subsequently investigated transformations of the triflates **257** and **258**.[130] The Sonogashira reaction of the triflate **257** occurred at 60 °C in in DMF/Et_3N furnishing the highly decorated quinoline **259** in 78% yield. The Heck reaction of triflate **258** afforded quinoline **260** in 77% yield.



(66)



(67)

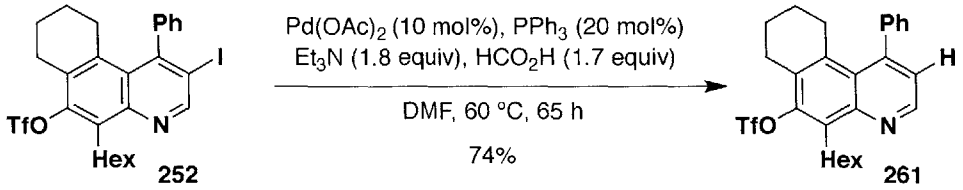
Reduction of the Iodide and Alternative Cyclization Methods

In addition to exploring the functionalization of the iodide at the 3-position, we also wanted to explore its removal.[131] Early attempts to reduce the iodide with tributyltin hydride worked well, but we found it difficult to obtain pure product using this method. As a result, we

[130] Conditions for both transformations were based on those reported by Kerr for similar reactions of indolyl triflates, see: England, D. B.; Kerr, M. A. *J. Org. Chem.* **2005**, *70*, 6519-6522.

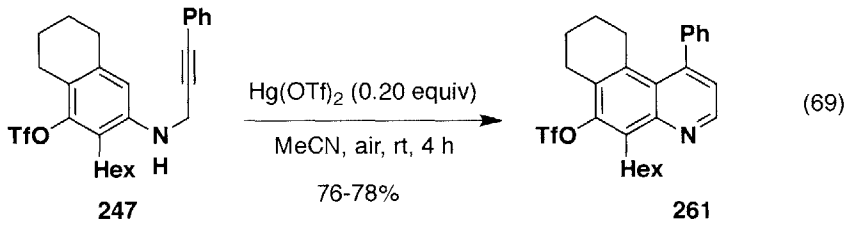
[131] For a review of metal-mediated halide reductions, see: Alonso, F.; Beletskaya, I.; Yus, M. *Chem. Rev.* **2002**, *102*, 4009-40091.

turned our attention to Pd-catalyzed reduction.[132] Exposure of quinoline **252** to catalytic palladium acetate and triphenylphosphine in the presence of triethylamine and formic acid resulted in the formation of the reduced product **261** in 74% yield.[133]



(68)

A more attractive means of synthesizing quinoline **261** is the use of alternative cyclization conditions that do not result in the formation of an aryl iodide. Larock[106b] and others[134] have employed π-Lewis acid metal-catalyzed cyclizations to achieve this goal. Eq 69 shows a cyclization using the conditions developed by Larock. Exposure of compound **247** to catalytic mercury (II) triflate in acetonitrile under an atmosphere of air affords the desired quinoline **261** in 76-78% yield.



(69)

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[132] For an example of the chemoselective reduction of an iodide in the presence of a triflate using cat. $Pd(OAc)_2$, see: Chu, Q.; Brahmi, M. M.; Solovyev, A.; Ueng, S.-H.; Curran, D. P.; Malacria, M.; Fensterbank, L.; Lacôte, E. *Chem. Eur. J.* **2009**, *15*, 12397-12940.

[133] (a) For the reduction of halides using Pd and triethylammonium formate, see: Cortese, N. A.; Heck, R. F. *J. Org. Chem.* **1977**, *42*, 3491-3494. (b) For the application of these conditions to the reduction of a similar 3-iodoquinoline, see: Ozeki, M.; Muroyama, A.; Kajimoto, T.; Watanabe, T.; Wakabayashi, K.; Node, M. *Synlett*, **2009**, 1781-1784.

[134] (a) Martín-Matute, B.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2003**, *125*, 5757-5766. (b) Pastine, S. J.; Youn, S. W.; Sames, D. *Org. Lett.* **2003**, *5*, 1055-1058. (c) Kuninobu, Y.; Inoue, Y.; Takai, K. *Chem. Lett.* **2007**, *36*, 1422; (d) Xiao, F.; Chen, Y.; Liu, Y.; Wang, J. *Tetrahedron*, **2008**, *64*, 2755-2761; (e) Cao, K.; Zhang, F.-M.; Tu, Y.-Q.; Zhuo, X.-T.; Fan, C.-A. *Chem. Eur. J.* **2009**, *15*, 6332-6334. (f) Majumdar, K. C., Nandi, R. K.; Ganai, S.; Taher, A. *Synlett*, **2011**, 116-120.

Summary

In conclusion, we have developed an efficient tandem benzannulation-iodocyclization strategy for the synthesis of highly substituted quinolines. Benzannulation products were obtained using both "first" and "second" generation vinylketene benzannulations. Iodocyclizations proceeded in good yield to afford polysubstituted quinoline products that can be chemoselectively transformed to generate a diverse array of quinoline structures.

Part III

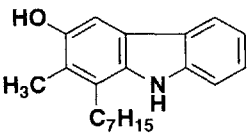
Tandem Benzannulation-Cyclization Strategies for the Synthesis of Highly Substituted Carbazoles

Chapter 1

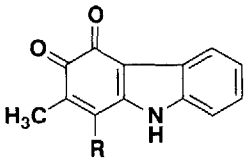
Introduction and Background

The carbazole ring system is the key structural feature in a number of interesting natural products. Scheme 25 depicts several biologically active carbazole alkaloids that all possess a highly substituted benzenoid ring.[135]

Scheme 25

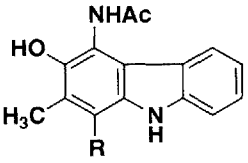


Carazostatin



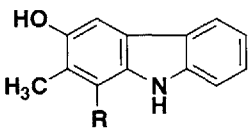
Carbazoquinocin A - F

A R = $(CH_2)_2CH(CH_3)CH_2CH_3$
B R = $(CH_2)_4CH(CH_3)_2$
C R = $(CH_2)_6CH_3$
D R = $(CH_2)_4CH(CH_3)CH_2CH_3$
E R = $(CH_2)_5CH(CH_3)_2$
F R = $(CH_2)_6CH(CH_3)_2$



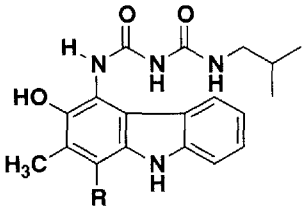
Antiostatin A_1 - A_4

A_1 R = $(CH_2)_4CH_3$
A_2 R = $(CH_2)_2CH(CH_3)CH_2CH_3$
A_3 R = $(CH_2)_4CH(CH_3)_2$
A_4 R = $(CH_2)_6CH_3$



Lipocarbazoles A1 - A4

A1 R = $(CH_2)_7CH{=}CHCH_2CH{=}CHCH_2CH{=}CHCH_2CH_3$
A2 R = $(CH_2)_7CH{=}CHCH_2CH{=}CH(CH_2)_4CH_3$
A3 R = $(CH_2)_7CH{=}CH(CH_2)_7CH_3$
A4 R = $(CH_2)_{16}CH_3$



Antiostatin B_2 - B_5

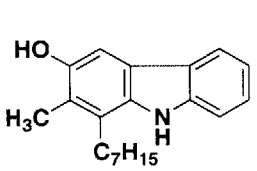
B_2 R = $(CH_2)_5CH_3$
B_3 R = $(CH_2)_4CH(CH_3)_2$
B_4 R = $(CH_2)_6CH_3$
B_5 R = $(CH_2)_5CH(CH_3)_2$

---

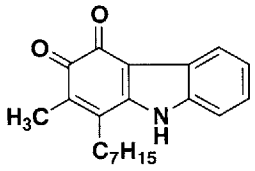
[135] For reviews of carbazole alkaloids and their synthesis, see: (a) Schmidt, A. W.; Reddy, K. R.; Knölker, H.-J. *Chem Rev.* **2012**, *112*, 3193-3328. (b) Roy, J.; Jana, A. K.; Mal, D. *Tetrahedron* **2012**, *68*, 6099-6121. (c) Ghazala, Y.; Hussain, E. A.; Rehman, M. A.; Mateen, B. *Asian J. Chem.* **2009**, *21*, 2485-2520. (d) Knölker, H.-J. *Top. Curr. Chem.* **2005**, *244*, 115-148. (e) Charkraborty, D. P.; Roy, S. " Carbazole Alkaloids IV" In *Progress in the Chemistry of Organic Natural Products*; Herz, W.; Falk, H.; Kirby, G. W., Eds.; Springer: Wien, 2003; Vol. 85, pp 125-230. (f) Gallagher, P. T. In *Science of Synthesis*; Thomas, E. J., Ed.; Thieme: Stuttgart, 2000; Vol. 10, pp 693-744. (g) Chakraborty, D. P. "Chemistry and Biology of Carbazole Alkaloids" In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1993; Vol. 44, pp 257-364.

As discussed in detail below, in general the strategies currently used to synthesize these natural products are not convergent and often employ linear routes involving multiple functional group transformations. We anticipated that the application of our tandem benzannulation-cyclization strategy would facilitate the synthesis of highly substituted carbazole alkaloids, thereby providing rapid and efficient access to these biologically interesting heterocycles.

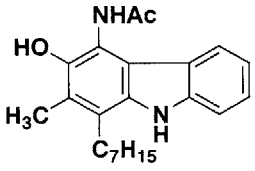
To demonstrate the utility of our tandem benzannulation-cyclization strategy, we decided to focus on the synthesis of three natural products bearing similar substitution patterns, namely carazostatin (**262**), carbazoquinocin C (**263**), and antiostatin A_4 (**264**). All three natural products are isolated from various *Streptomyces* microorganisms[136] and exhibit antioxidant activity suggesting their potential as lead compounds for the treatment of ischemia, atherosclerosis, and inflammation.[136a,137] The next section provides an overview of the previous total and formal syntheses of carazostatin, carbazoquinocin C, and antiostatin A_4.



Carazostatin (**262**)



Carbazoquinocin C (**263**)



Antiostatin A_4 (**264**)

[136] For the isolation and biological activity of carazostatin, see: (a) Kato, S.; Kawai, H.; Kawasaki, T.; Toda, Y.; Urata, T.; Hayakawa, Y. *J. Antibiot.* **1989**, *42*, 1879-1881. (b) Kato, S.; Kawasaki, T.; Urata, T.; Mochizuki, J. *J. Antibiot.* **1993**, *46*, 1859-1865. For carbazoquinocin C, see: (c) Tanaka, M.; Shin-Ya, K.; Furihata, K.; Seto, H. *J. Antibiot.* **1995**, 326-328. For antiostatin A_4, see: (d) Mo, C.-J.; Shin-Ya, K.; Furihata, K.; Furihata, K.; Shimazu, A.; Hayakawa, Y.; Seto, H. *J. Antibiot.* **1990**, *43*, 1337-1340.

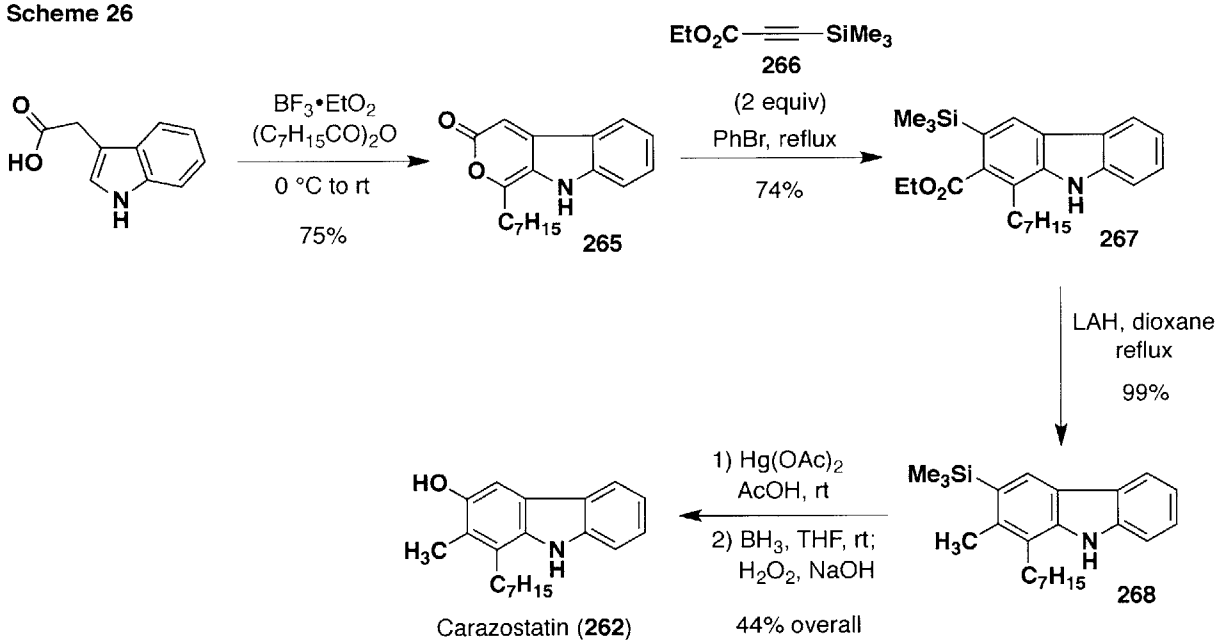
[137] For recent studies on the pharmacological potential of carbazoquinocin C and related carbazoles, see: (a) Choi, T. A.; Czerwonka, R.; Forke, R.; Jäger, A.; Knöll, J.; Krahl, M. P.; Krause, T. K.; Reddy, K. R.; Franzblau, S. G.; Knölker, H.-J. *Med. Chem. Res.* **2008**, *17*, 374-385. (b) Aygün, A.; Pindur, U. *J. Heterocyclic Chem.*, **2003**, *40*, 411-417.

Previous Total Syntheses of Carazostatin

Moody Total Synthesis of Carazostatin

Moody and co-workers completed the first total synthesis of carazostatin in 1990, a year after its isolation. The benzannulation-based strategy employed by Moody utilized the [4 + 2] cycloaddition of an α-pyrone as the key step (Scheme 26).[138] The reaction of indolylacetic acid with heptanoic anhydride in the presence of $BF_3.OEt_2$ afforded the requisite α-pyrone **265**. Heating **265** in PhBr with two equivalents of alkynyl ester **266** furnished carbazole **267** in 74% yield with complete regioselectivity. Only select alkynes afford good regiochemical control in this key Diels-Alder reaction.[138c] As a result, only a few substituents can be easily installed at the C-2 and C-3 positions of the product. Reduction of the ester to a methyl group and conversion the arylsilane to a hydroxyl group completed the synthesis, which required only five steps and proceeded in 24% overall yield.

Scheme 26

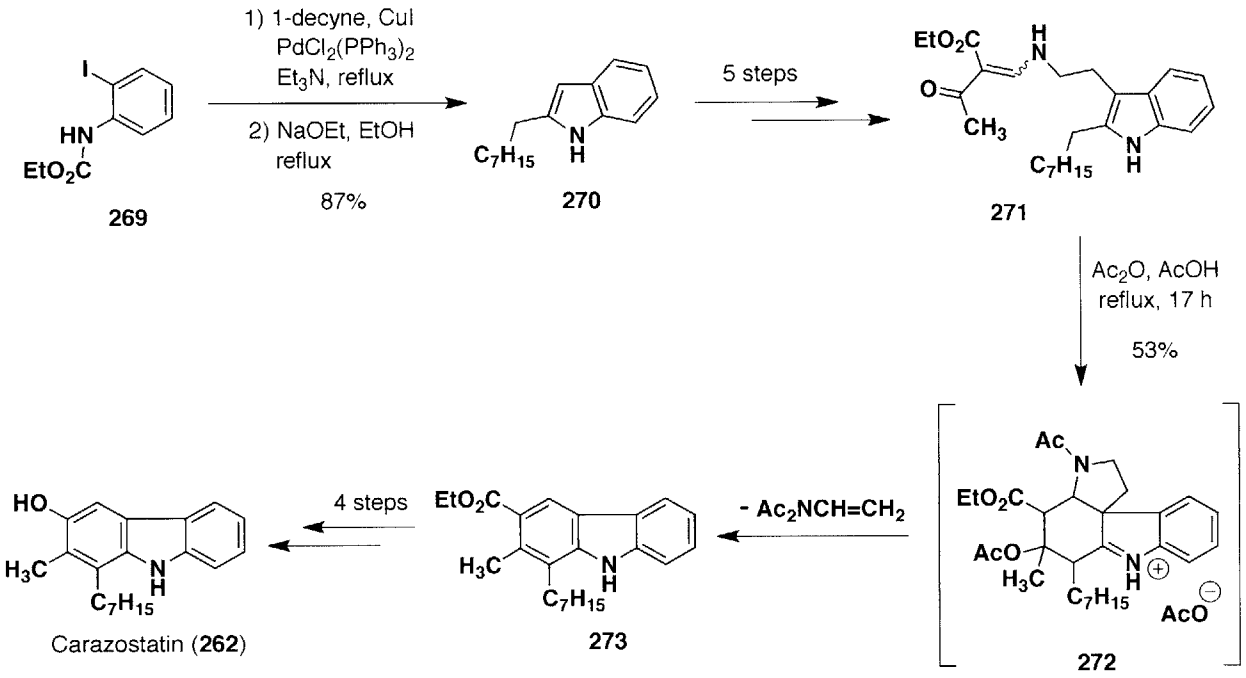


[138] (a) Jackson, M. P.; Moody, C. J. *Synlett*, **1990**, 521-522. (b) Jackson, M. P.; Moody, C. J.; Mortimer, R. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2941-2944. (c) For additional background on the key cycloaddition, see: Moody, C. J.; Shah, P. *J. Chem. Soc., Perkin Trans. 1*, **1988**, 1407-1415.

Ogasawara Total Synthesis of Carazostatin

Five years later, Ogasawara and Shin disclosed a second synthetic route to carazostatin.[139] Their synthesis, outlined in Scheme 27, began with iodoaniline derivative **269**. Sonogashira reaction of **269** with 1-decyne followed by base-mediated cyclization and deprotection afforded indole **270**. Ogasawara then used five steps to construct enamine **271**. Heating **271** in a mixture of acetic anhydride and acetic acid triggered a cascade of reactions forming the intermediate **272** that undergoes a series of eliminations to furnish carbazole **273**. Ogasawara completed his synthesis of carazostatin with 4 additional steps.

Scheme 27



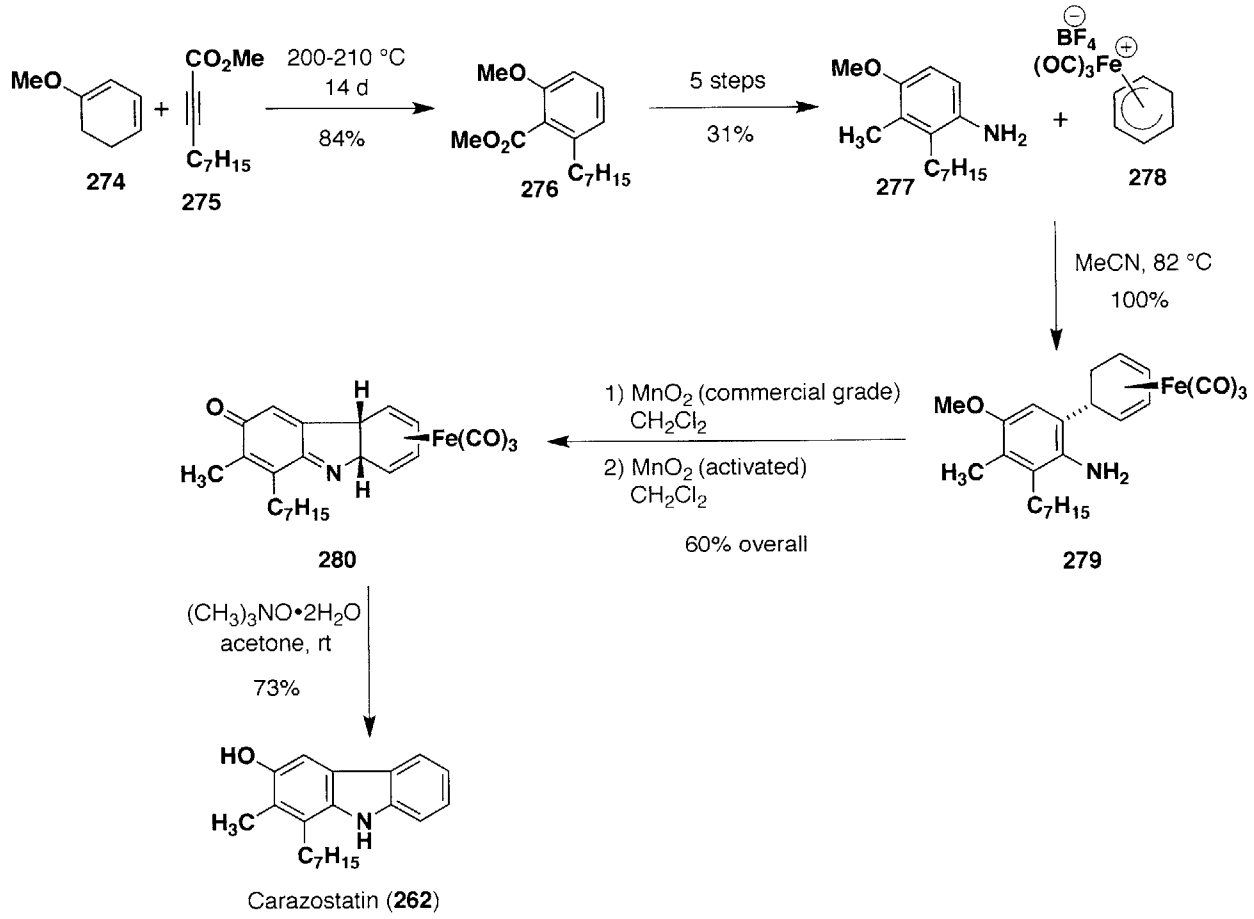
[139] Shin, K.; Ogasawara, K. *Chem. Lett.* **1995**, 289-290.

Knölker Total Synthesis of Carazostatin

Knölker also reported a synthesis of carazostatin in 1995. His strategy employs an iron-mediated construction of the carbazole nucleus as the key step.[140] After forming ester **276** via an Alder-Rickert reaction,[10] Knölker utilized a five-step route to achieve the synthesis of substituted aniline derivative **277**. Electrophilic aromatic substitution of aniline **277** with iron complex **278** afforded **279**. Oxidation with commercial grade MnO_2 led to the corresponding quinone imine. A second oxidation with very active[141] MnO_2 furnished the desired product **280**. Previous studies by Knölker demonstrated that performing the oxidation in two stages affords the desired product in better yield than a single oxidation with MnO_2.[142] Demetallation of **280** with trimethylamine *N*–oxide followed by rapid tautomerization completed the total synthesis. Nearly all of the steps in this synthesis furnished the product in good to excellent yield; however the linear strategy employed by Knölker leads to a synthesis that requires 10 steps.

[140] (a) Knölker, H.-J.; Hopfmann, T. *Synlett* **1995**, 981-983. (b) Knölker, H.-J.; Hopfmann, T. *Tetrahedron* **2002**, *58*, 8937-8945.
[141] For the synthesis of very active MnO_2 and the general reactivity of MnO_2, see: Fatiadi, A. J. *Synthesis* **1976**, 65-104.
[142] Knölker, H.-J.; *Synlett*, **1992**, 371-387.

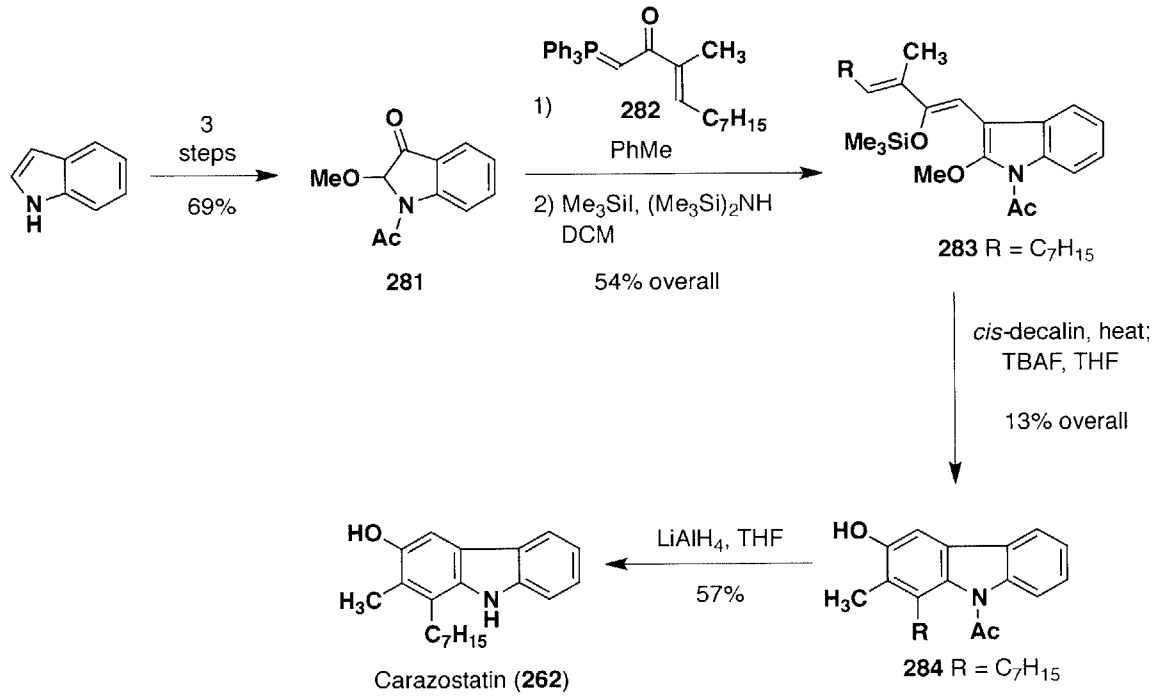
Scheme 28


MeO
CO2Me
C7H15
274
275
200-210 °C
14 d
84%
MeO
MeO2C
C7H15
276
5 steps
31%
MeO
H3C
NH2
C7H15
277
BF4
(OC)3Fe
278
MeCN, 82 °C
100%
MeO
Fe(CO)3
H3C
NH2
C7H15
279
1) MnO2 (commercial grade)
CH2Cl2
2) MnO2 (activated)
CH2Cl2
60% overall
O
H
Fe(CO)3
H3C
N
H
C7H15
280
(CH3)3NO•2H2O
acetone, rt
73%
HO
H3C
N
H
C7H15
Carazostatin (262)

Sakamoto Total Synthesis of Carazostatin

Sakamoto et al. employed a 6-π electrocyclic ring closure as the key step in their total synthesis of carazostatin.[143] Starting from indole itself, Sakamoto utilized a 3-step sequence for the synthesis of indolone **281**. Wittig reaction of **281** with ylide **282** followed by silyl enol ether formation furnished indolyl diene **283** in 54% overall yield. Heating **283** in *cis*-decalin led to E/Z isomerization of the enol ether, six-electron electrocyclic ring closure, and elimination of methanol to form the carbazole core. Subsequent desilylation with TBAF afforded *N*-acylated carbazole **284** in 13% overall yield. Deprotection with $LiAlH_4$ completed the synthesis of carazostatin.

Scheme 29

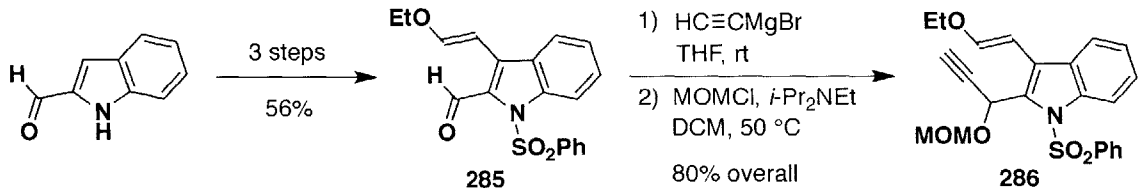


[143] Nonaka, Y.; Kawasaki, T.; Sakamoto, M. *Heterocycles* **2000**, 53, 1681-1684

Hibino Total Synthesis of Carazostatin and Carbazoquinocin C

Hibino has also disclosed a total synthesis of carazostatin.[144] One year after his initial report, Hibino demonstrated that carazostatin could be oxidized to form carbazoquinocin C.[145] The strategy employed by Hibino for the synthesis of carazostatin utilized an allene-mediated electrocyclization as the key step. Scheme 30 shows the synthesis of the key cyclization precursor **286**.

Scheme 30



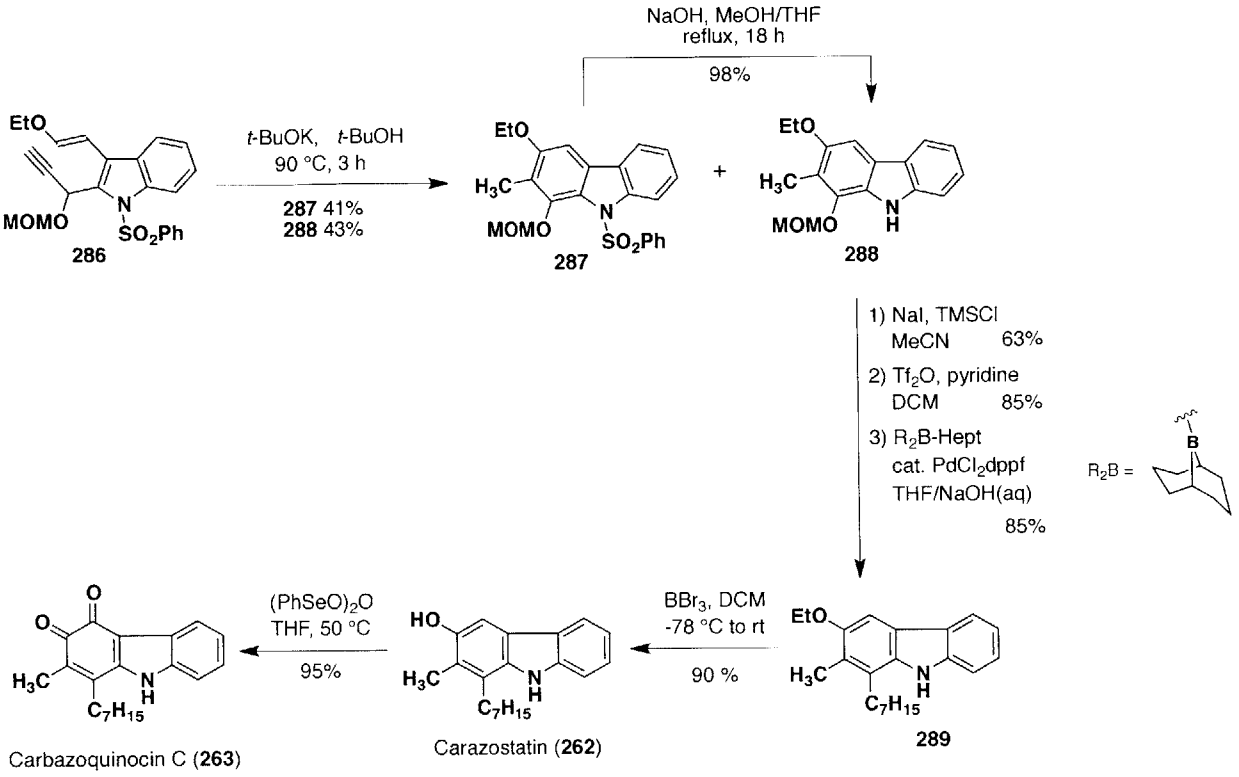
Heating **286** in *t*-BuOK/*t*-BuOH isomerized the alkyne to an allene that subsequently underwent six-electron electrocyclic ring closure and isomerization to form the carbazole ring system. Under the reaction conditions, some cleavage of the sulfonyl-protecting group occurred and Hibino obtained ca. 1:1 mixture of sulfonyl-protected carbazole **287** and deprotected carbazole **288**. Deprotection of **287** with sodium hydroxide furnished additional **288**. After cleavage of the MOM ether and triflation of the resulting hydroxyl group, a Suzuki reaction installed the heptyl chain at the C-1 position of carbazole **289**. Cleavage of the ethyl ether with boron tribromide completed the synthesis of carazostatin in 11 steps.

Scheme 31 also shows the synthesis of carbazoquinocin C reported by Hibino. Oxidation of carazostatin (**262**) with phenyl selenic anhydride afforded carbazoquinocin C in nearly quantitative yield. The next section provides an overview of the strategies directed toward the synthesis of carbazoquinocin C that do not utilize carazostatin as an intermediate.

---

[144] Choshi, T.; Sada, T.; Fujimoto, H.; Nagayama, C.; Sugino, E.; Hibino, S. *Tetrahedron Lett.* **1996**, *37*, 2593-2596.
[145] Choshi, T.; Sada, T.; Fujimoto, H.; Nagayama, C.; Sugino, E.; Hibino, S. *J. Org. Chem.* **1997**, *62*, 2535-2543.

Scheme 31



Previous Total Syntheses of Carbazoquinocin C

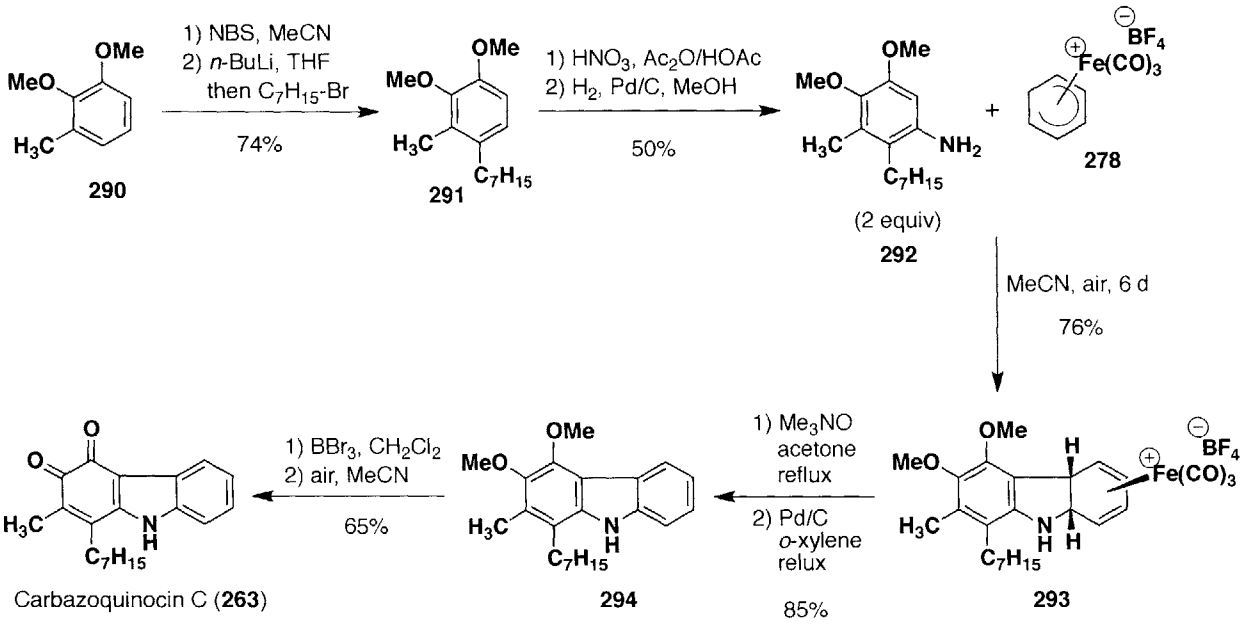
Knölker Total Syntheses of Carbazoquinocin C

Knölker and co-workers have extensively investigated the synthesis of carbazoquinocin C.[146] Scheme 32 outlines their first route to the natural product that utilizes an iron-mediated annulation as the key step.[146a] Bromination of catechol derivative **290** followed by lithium-halogen exchange and alkylation afforded arene **291**. Nitration of **291** followed by reduction to form the amine provided aniline **292**. Electrophilic aromatic substitution of aniline **292** with the iron complex **278** followed by oxidative cyclization under air furnished the iron-complexed dihydrocarbazole **293** in 76% yield based on **278**. Knölker et al. do not discuss the need for

[146] (a) Knölker, H.-J., Fröhner, W. *Tetrahedron Lett.* **1997**, *38*, 1535-1538. (b) Knölker, H.-J.; Reddy, K.R.; Wanger, A. *Tetrahedron Lett.* **1998**, *39*, 8267-8270. (c) Knölker, H.-J., Reddy, K. R. *Synlett* **1999**, 596-598. (d) Knölker, H.-J.; Fröhner, W.; Reddy, K. R. *Synthesis* **2002**, 557-564.

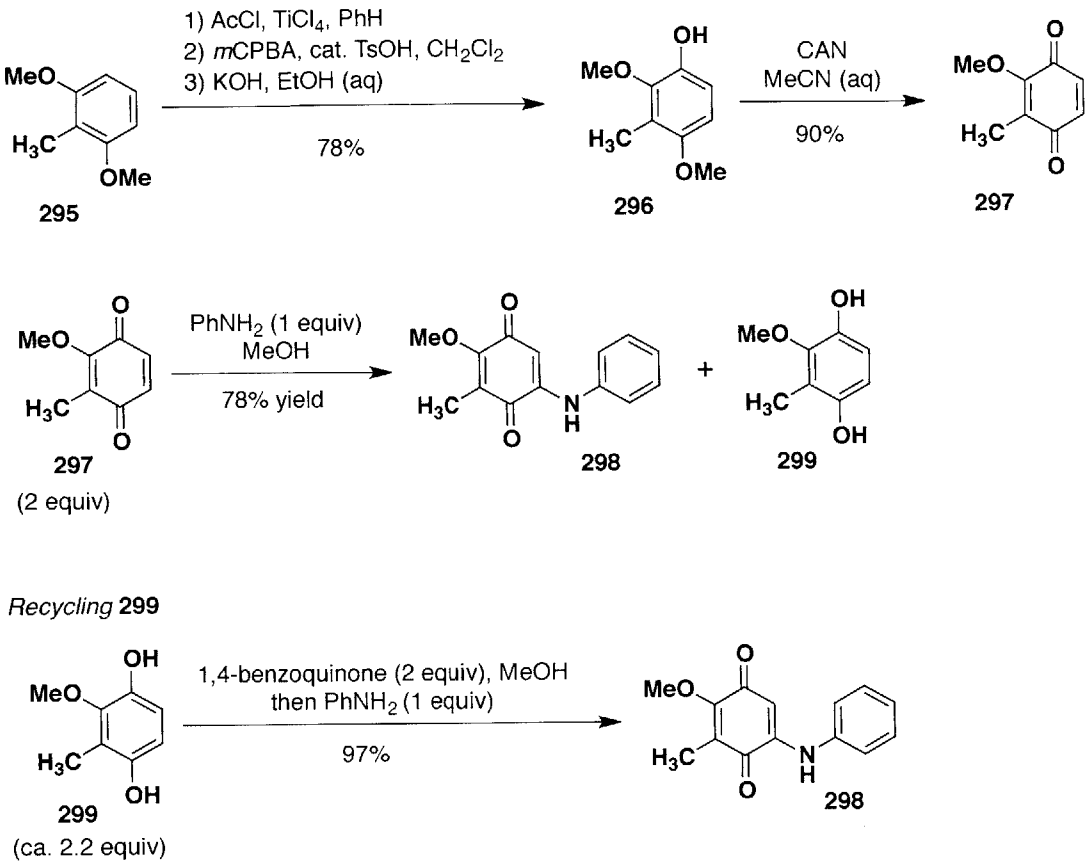
excess aniline **292** in this reaction nor do they disclose whether or not **292** can be recovered after the reaction. Knölker et al. completed the synthesis with a four-step sequence culminating in autoxidation to form carbazoquinocin C.

Scheme 32



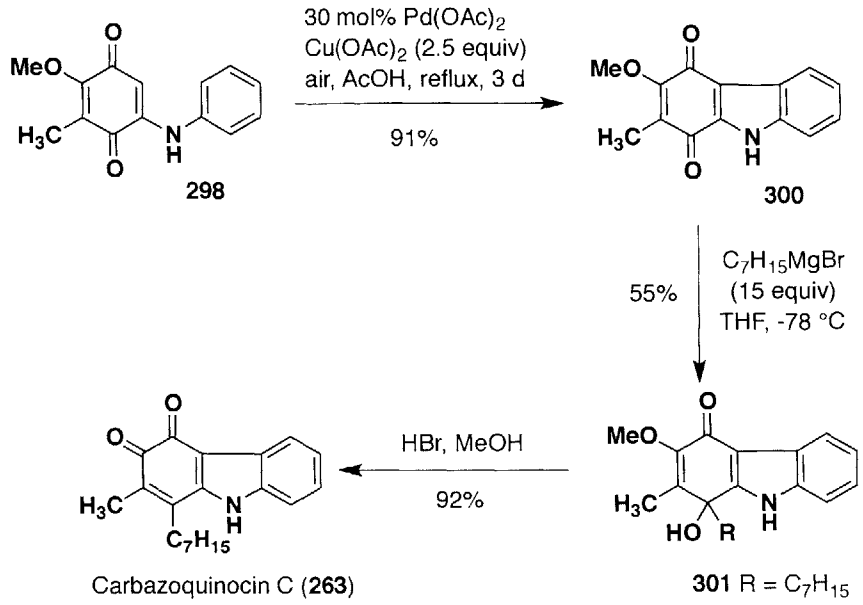
Knölker employed a Pd-mediated cyclization as the key step in his second synthesis of carbazoquinocin C, which began with resorcinol derivative **295**.[146b,c] Conversion to phenol **296** was achieved in three steps, after which oxidation with cerium(IV) ammonium nitrate furnished 1,4-quinone **297**. Treatmetn aniline with 2 equiv of quinone **297** afforded cyclization precursor **298** in 78% yield. The excess quinone employed by Knölker acts as an oxidant during the reaction. This leads to the formation of diol **299**, which can be recycled to furnish additional **298**.

Scheme 33



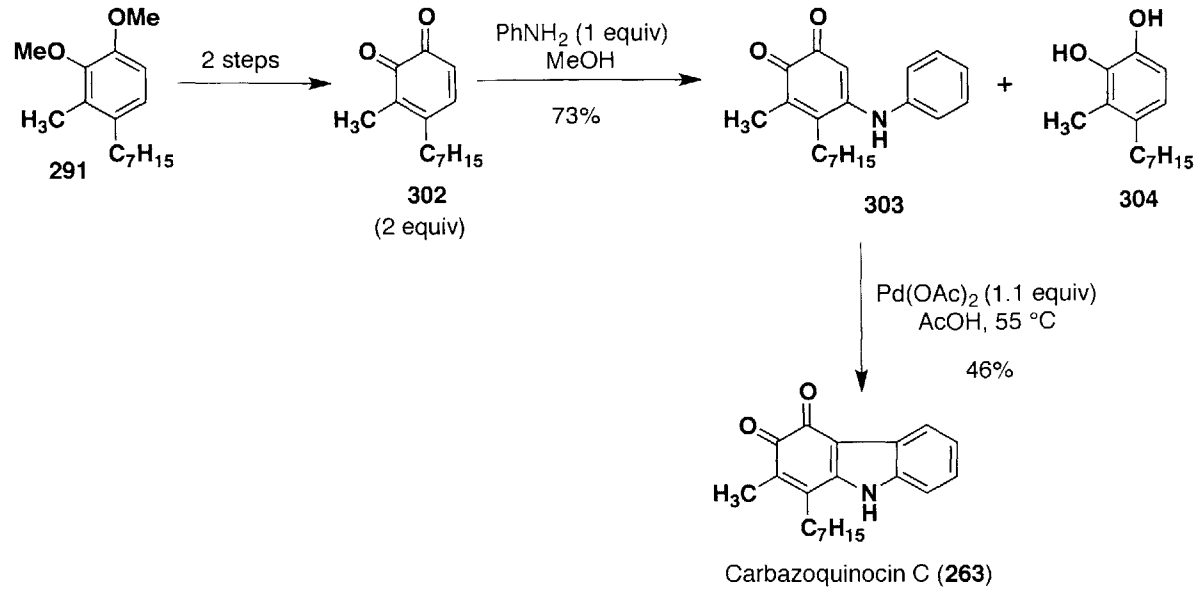
Heating **298** with 30 mol% $Pd(OAc)_2$ in acetic acid leads to two consecutive C-H activation steps followed by reductive elimination to furnish carbazole-1,4-quinone **300** in 91% yield (Scheme 34). This cyclization results in the formation of Pd(0) which is reoxidized in situ with $Cu(OAc)_2$ and air to regenerate the active Pd(II) species. In the next step, Knölker et al. found that the use of a large excess of a Grignard reagent afforded the desired addition product **301** in moderate yield. Treating **301** with HBr in methanol completed the synthesis.

Scheme 34



Scheme 35 outlines the third synthesis of carbazoquinocin C reported by Knölker.[146d] This synthesis begins with the previously synthesized catechol derivative **291**. Deprotection of **291** followed by oxidation with *o*-chloranil generated orthoquinone **302**. Treatment of aniline with 2 equiv of **302** furnished amine **303** and the diol **304**. The excess orthoquinone in this reaction acts as an oxidant forming diol **304** as a byproduct. Knölker does not discuss if diol **304** was recovered or recycled after this reaction. Heating **303** with 1.1 equiv of $Pd(OAc)_2$ in acetic acid leads to two consecutive C-H activation steps followed by reductive elimination to afford carbazoquinocin C in 46% yield. Knölker found that this reaction was very sensitive to temperature since higher temperatures led to decomposition and lower temperatures led to incomplete conversion of starting material. Knölker did not discuss if any attempt was made to render this reaction catalytic via the addition of an oxidant.

Scheme 35



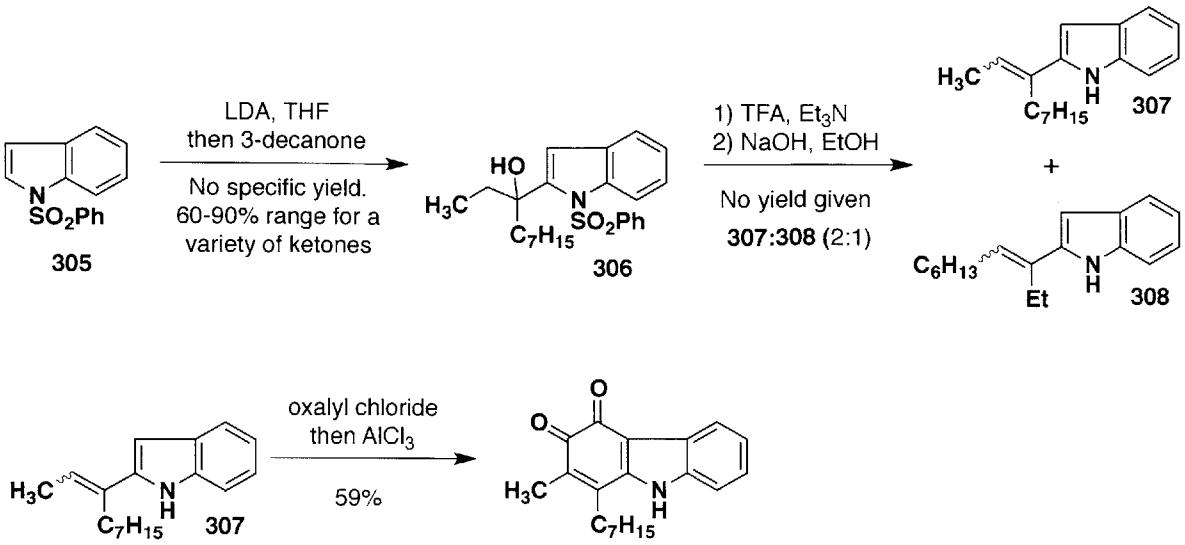
All three syntheses of carbazoquinocin C reported by Knölker are inefficient and discard a significant amount of a key intermediate. The third synthesis, shown in Scheme 35, requires the fewest steps, but it utilizes a stoichiometric amount of palladium to achieve the key bond construction.

Pindur Total Synthesis of Carbazoquinocin C

By focusing on the construction of the 1,2-quinone, Pindur and Aygün developed the rapid synthesis of carbazoquinocin C shown in Scheme 36.[147] After metallation of protected indole **305** with LDA, the addition of 3-decanone afforded alcohol **306**. Pindur does not report a specific yield, other than to say that the general reaction proceeded in 60-90% yield for a variety of ketones. Elimination of the alcohol with TFA, followed by deprotection of the indole furnished a 2:1 ratio of the isomeric 2-vinylindoles **307** and **308**. Pindur does not report the yield for either step. The desired isomer, indole **307** is the major product, and the two isomers can be separated by column chromatography. Treatment of **307** with oxalyl chloride and $AlCl_3$ afforded carbazoquinocin C in 59% yield.

[147] Aygün, A.; Pindur, U. *Synlett*, **2000**, 1757-1760.

Scheme 36



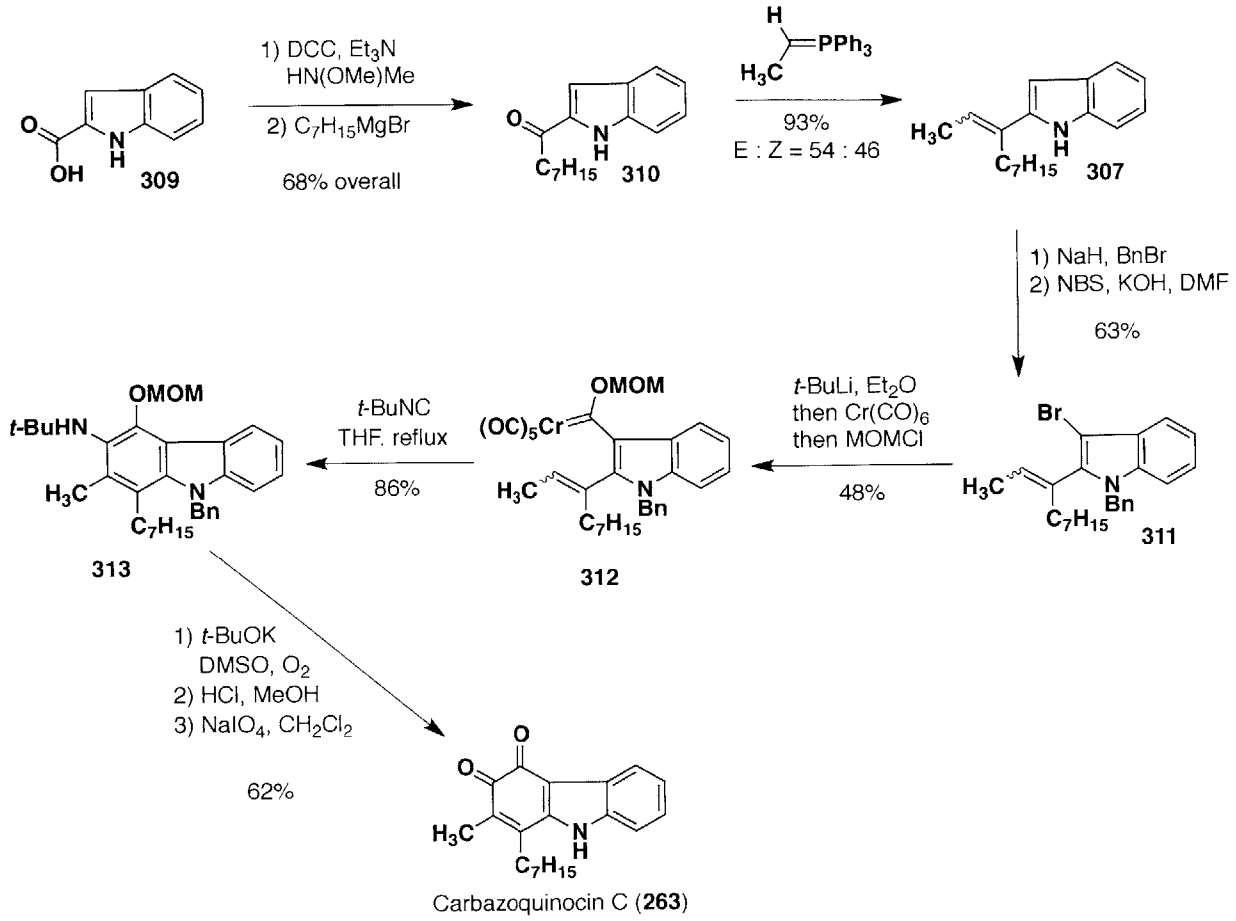
The synthesis reported by Pindur completes carbazoquinocin C in only four steps, but it is difficult to draw any real conclusions about the efficiency of this synthesis with so little experimental detail.

Wulff Total Synthesis of Carbazoquinocin C

Inspired by the modified Dötz annulation developed by Merlic,[31] Wulff and Rawat synthesized carbazoquinocin C using the route shown in Scheme 37.[148] Starting from carboxylic acid **309**, they achieved the synthesis of the key chromium carbene **312** in six steps. Heating **312** at reflux in THF with *tert*-butyl isonitrile furnished highly substituted carbazole **313** in 86% yield. Two deprotection steps followed by oxidation with $NaIO_4$ provided carbazoquinocin C. In the same report,[148] Wulff and Rawat disclosed a second, slightly longer route to carbazoquinocin C. Because of its similarity to the synthesis shown in Scheme 37, it is not illustrated here. Both syntheses reported by Wulff and Rawat contain interesting chemistry, but they employ linear strategies that require 10 or more steps.

[148] Rawat, M.; Wulff, W. D. *Org. Lett.* **2004**, *6*, 329-332.

Scheme 37



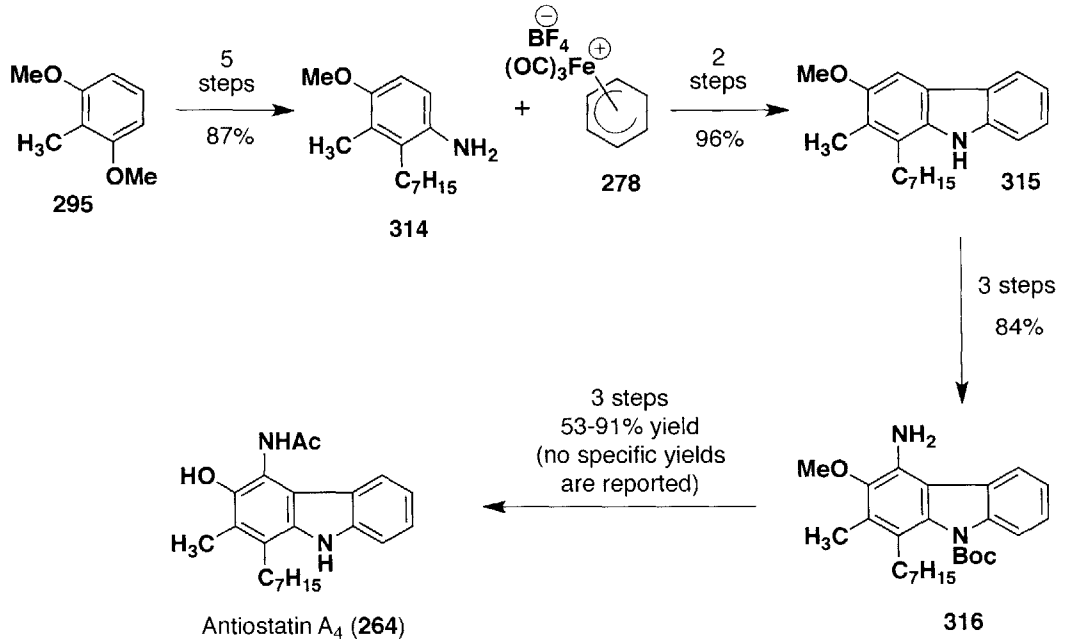
Previous Total Syntheses of Antiostatin A_4

Knölker Total Syntheses of Antiostatin A_4

Knölker reported the first total synthesis of the whole series of antiostatins A_1-A_4 and B_1-B_4 in 2009.[149,150] Scheme 38 outlines the synthesis of antiostatin A_4. Knölker employed an 5-step approach to achieve the synthesis of aniline **314**. Iron-mediated annulation of **314** afforded carbazole **315**. Knölker completed the synthesis with six additional steps to install the acetamide and to remove the protecting groups. Knölker achieved good overall yields in the syntheses of the antiostatins A_1-A_4 (37-64% overall yield) but his linear approach is inefficient and requires 13 steps.

[149] Knott, K. E.; Auschill, S.; Jäger, A.; Knölker, H.-J. *Chem. Commun.* **2009**, 1467-1469.
[150] At the same time Witulski published the first total synthesis of antiostatin A_1 (vide infra).

Scheme 38



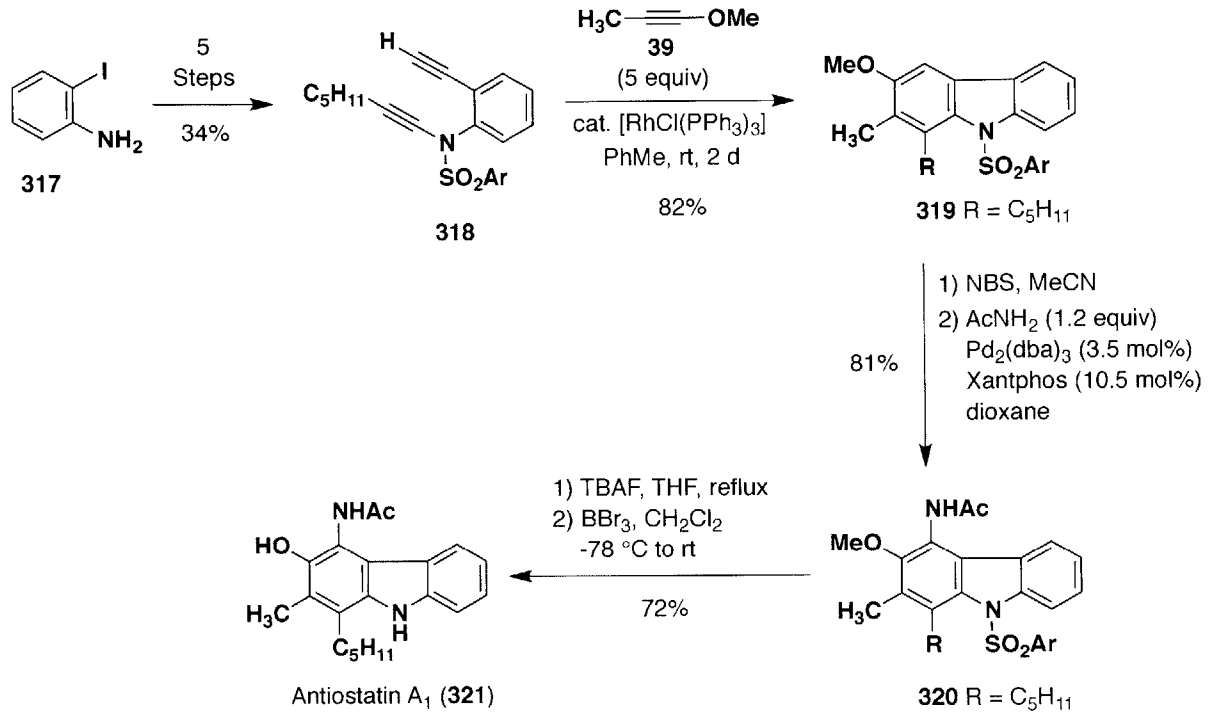
Previous Total Syntheses of Antiostatin A_1 and Lipocarbazole A4

Witulski Total Synthesis of Antiostatin A_1

While Knölker developed his strategy for the synthesis of the antiostatin A family shown in Scheme 38, Witulski was studying a benzannulation-based approach to the same natural products. Witulski chose to focus on the synthesis of antiostatin A_1. The Rh-catalyzed [2 + 2 + 2] annulation of diyne **318** and methoxy propyne (**39**) served as the key benzannulation step in his synthesis. As shown in Scheme 39, this reaction furnished carbazole **319** in 82% yield as a 22:1 ratio of regioisomers in favor of the desired compound.[151] Due to competitive trimerization, this reaction requires a large excess (5 equiv) of alkyne **39**. Bromination of **319** followed by Pd-catalyzed amination afforded protected carbazole **320**. Two subsequent deprotection steps provided antiostatin A_1 in 10 steps overall.

[151]Wiltuski also studied the reaction of other diynes bearing alkyl chains that correspond to other members of the antiostatin A family. These reactions proceeded in similar yield with similar regiochemical ratios.

Scheme 39

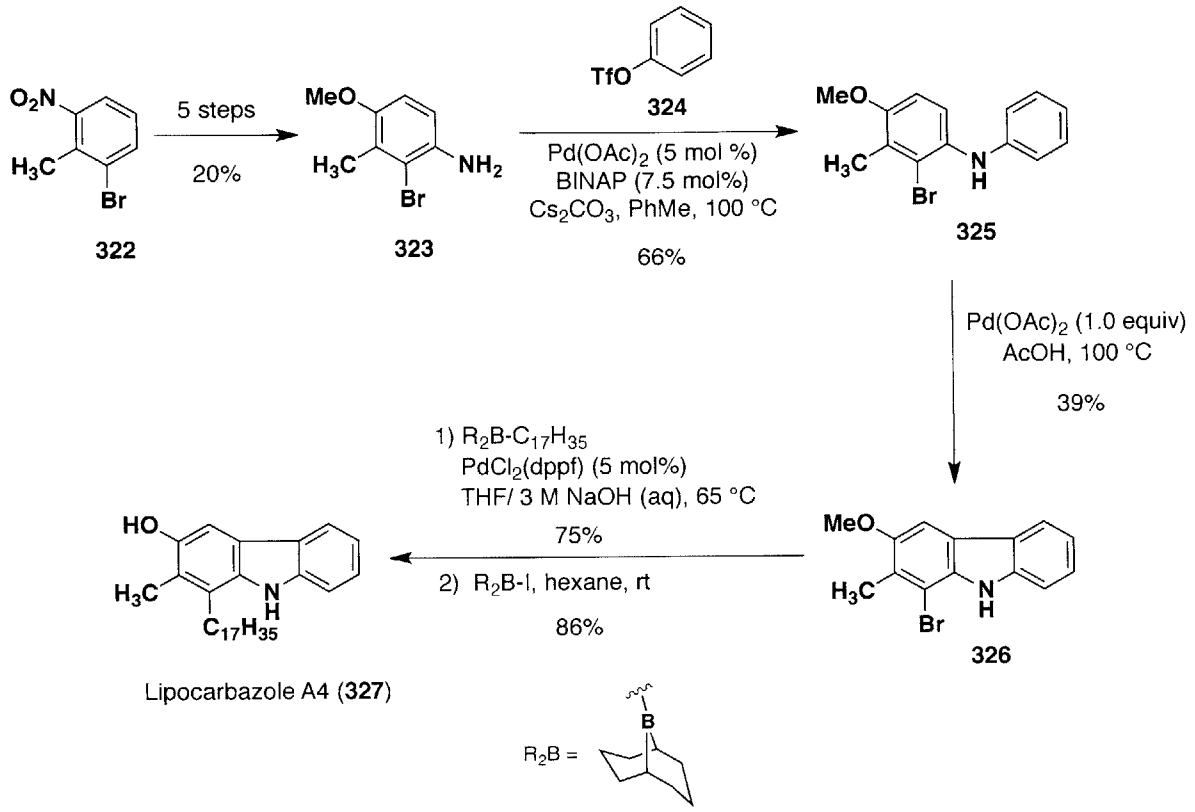


Süssmuth Total Syntheses of Lipocarbazole A4

We complete the overview of prior total syntheses with the synthesis of lipocarbazole A4 reported by Süssmuth.[152] Lipocarbazole A4 and carazostatin possess very similar structures; only the length of the alkyl chain at the C-1 position of the carbazole distinguishes these natural products (heptyl for carazostatin, heptadecyl for lipocarbazole A4). Starting from commercially available 2-bromo-6-nitrotoluene (**322**), Süssmuth employed a five-step sequence for the synthesis of the complex aniline derivative **323**. Arylation of the nitrogen via the Buchwald-Hartwig amination followed by oxidative cyclization with stoichiometric palladium furnished the carbazole **326** but only in 39% yield. Installation of the alkyl chain via Suzuki reaction followed by cleavage of the methyl ether afforded lipocarbazole A4 (**327**).

[152] For the isolation and biological activity of lipocarbazoles A1-A4, see: (a) Schneider, K.; Nachtigall, J.; Hänchen, A.; Nicholson, G.; Goodfellow, M.; Süssmuth, R. D.; Fiedler, H.-P. *J. Nat. Prod.* **2009**, *72*, 1768-1772. For their total synthesis, see: (b) Hänchen, A.; Süssmuth, R. D. *Synlett*, **2009**, 2483-2486.

Scheme 40



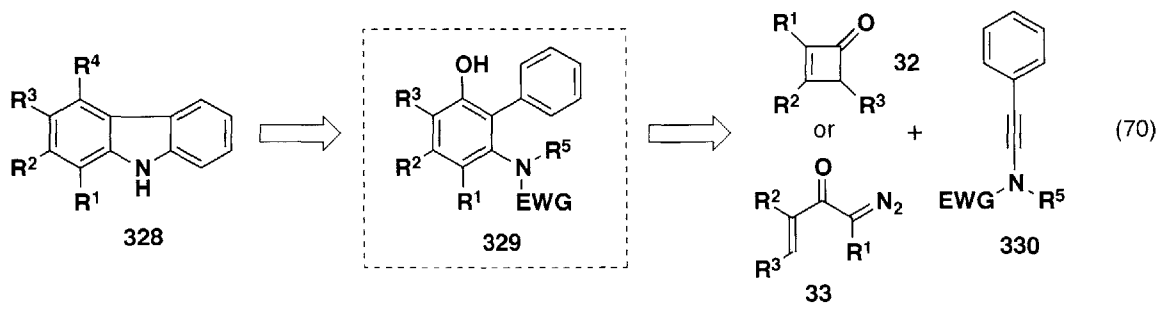
Our Tandem Benzannulation Strategy

Most of the previously described syntheses require 8-10 steps and proceed in low overall yield. The goal of our research in this area has been the development of a new tandem strategy for the efficient synthesis of highly substituted carbazole alkaloids that possess interesting biological activity. We envisioned two potential tandem benzannulation-cyclization strategies for the synthesis of carbazoles.[153] Starting from carbazole **328,** one option would utilize a Pd-catalyzed oxidative cyclization to furnish the desired carbazole via the formation of a C-N bond.[154] A benzannulation employing a C-aryl ynamide (**330**) would be used to synthesize the requisite biaryl intermediate (**329**).

---

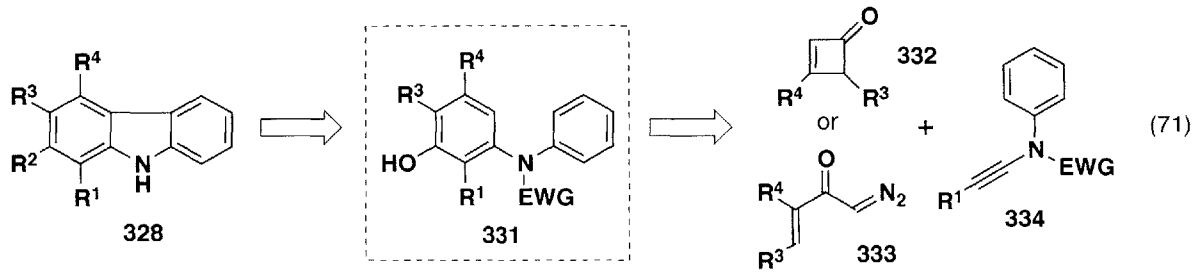
[153] For general strategies directed toward the synthesis of carbazoles, see: ref 106a and b.

[154] For selected examples of this type of cyclization, see: (a) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560-14561. (b) Tsange, W. C. P.; Munday, R. H.; Brasche, G.; Zheng, N.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7603-7610. (c) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184-16186. (d) Antonchick, A. P.; Samanta, R.; Kulikov, K.; Lategahn, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 8605-8608. (e) Cho, S. H.; Yoon, J.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 5996-6005.



(70)

An alternative strategy would utilize a Pd-catalyzed oxidative cyclization[155] or a photochemical cyclization[156] to furnish the desired carbazole via the formation of a C-C bond in a diarylamine of type **331**. In particular, we were interested in a report by Fagnou[155a] that disclosed the use of catalytic $Pd(OAc)_2$ in pivalic acid for the oxidative cyclization of electron rich diarylamines. We hoped that these conditions would provide superior results to those obtained by other groups for similar cyclizations. A benzannulation employing an N-aryl ynamide (**334**) would be used to synthesize the requisite diarylamine system (**331**).



(71)

A critical analysis of both strategies led us to focus our efforts on the second strategy using *N*-aryl ynamides because it allows for more convergent approaches to the natural products carazostatin, carbazoquinocin C, and antiostatin A_4.

---

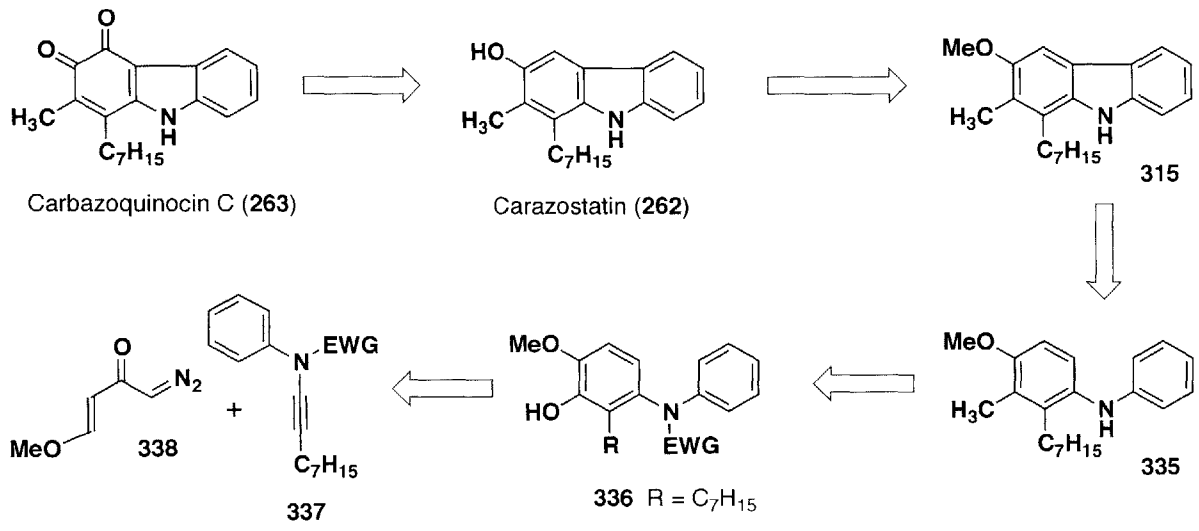
[155] For leading references on the Pd-catalyzed oxidative cyclization of diarylamines, see: (a) Liegault, B.; Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008**, *73*, 5022-5028 and references cited therein. (b) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2009**, *74*, 4720-4726 and references cited therein. (c) Wang, S.; Mao, H.; Ni, Z.; Pan, Y. *Tetrahedron Lett.* **2012**, *53*, 505-508.

[156] For reviews on the photochemical cyclization of diarylamines, see: (a) Schultz, A. G.; Motyka, L. *Org. Photochem.* **1983**, *6*, 1–119. (b) Mallory, F. B.; Mallory, C. W. *Org. React.* **1984**, *30*, 1-456. (c) Gilbert A.; Synthesis of Heterocycles by Photocyclization of Arenes. *In CRC Handbook of Organic Photochemistry and Photobiology,* 2nd ed.; Horspool, W., Lenci, F., Eds.; *CRC Press,* Boca Raton, 2004; 34/1–34/20.

Retrosynthetic Analysis of Carazostatin, Carbazoquinocin C, and Antiostatin A_4

Scheme 41 outlines our plan for the synthesis of carazostatin and carbazoquinocin C. Based on the work of Hibino, we knew that oxidation of carazostatin would furnish carbazoquinocin C. We envisioned that carazostatin could arise from carbazole **315** via late stage deprotection of a methyl ether. Carbazole **315** would be derived from the cyclization of diarylamine **335**. Functional group manipulations and deprotection would furnish diarylamine **335** from phenol **336**. Finally, the benzannulation reaction of *N*-phenyl ynamide **337** and diazo ketone **338** would be used to synthesize phenol **336**.

Scheme 41

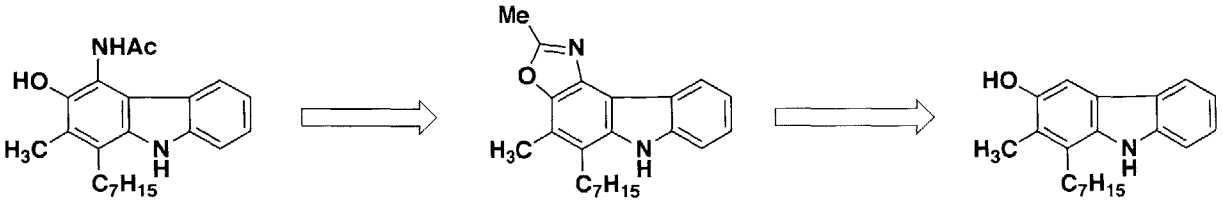


We expected that this strategy would provide efficient access to both carazostatin and carbazoquinocin C. This route also leads to a formal synthesis of antiostatin A_4, because compound **315** is an intermediate in the total synthesis of antiostatin A_4 reported by Knölker (vide supra). The synthesis reported by Knölker requires six steps to transform compound **315** into antiostatin A_4. With the formal synthesis as a fallback plan, we wanted to explore a new route to antiostatin A_4 starting from carazostatin. Scheme 42 outlines our strategy. We envisioned the acetamide and phenol forming via hydrolysis of benzoxazole **339**.[157] Based on the prior work

[157] For examples of this transformation, see: (a) Ainge, D.; Booker, J. E. M.; Pedge, N.; Sinclair, R.; Sleigh, C.; Štefinović, M.; Vaz, L.-M.; Way, E. *Org. Process Res. Dev.* **2010**, *14*, 72-84. (b) Brunner, H.; Olschewski, G.; Nuber, B. *Synthesis* **1999**, 429-434. (c) Hoffman, J. M.; Smith, A. M.; Rooney, C. S.; Fisher, T. E.; Wai, J. S.;

of Moody[138b] (see Part III, Chapter 3) and others,[158] we speculated that oxazole **339** might be synthesized from carazostatin (**262**) by reaction with ethylamine and MnO_2.

Scheme 42



Antiostatin A_4 (**264**) **339** Carazostatin (**262**)

It should be noted that the synthetic plan outlined in Schemes 41 and 42 allows us to easily change the alkyl chain at the C-1 position of the carbazole by simply utilizing a different ynamide in the benzannulation. As a result, this general strategy would potentially provide a route to all of the alkaloids shown in Scheme 25.

The next chapter describes our investigation of tandem strategies for the synthesis of carbazoles. Our goal was to establish general conditions for the vinylketene-based benzannulation of *N*-aryl ynamides and the cyclization of the resulting diarylamines.

Thomas, C. M.; Bamberger, D. L.; Barnes, J. L.; Williams, T. M.; Jones, J. H.; Olson, B. D.; O'Brien, J. A.; Goldman, M. E.; Nunberg, J. H.; Quintero, J. C.; Schleif, W. A.; Emini, E. A.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 953-966. (d) Werstiuk, N. H.; Ju, C. *Can. J. Chem.* **1989**, *67*, 812-815. (e) Adams, R.; Stewart, J. M. *J. Am. Chem. Soc.* **1952**, *74*, 3660-3664.

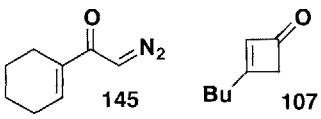
[158] For the formation of benzoxazoles via the oxidation of phenolic carbazoles, see: (a) Sundaramoorthi, R.; Kansal, V. K.; Das, B. C.; Potier, P. *J. Chem. Soc., Chem. Commun.* **1986**, 371-372. For the formation of benzoxazoles via the oxidation of phenolic indoles, see: (b) Boger, D. L.; Cerbone, L. R.; Yohannes, D. *J. Org. Chem.* **1988**, *53*, 5163-5166.

Chapter 2

Tandem Benzannulation-Cyclization Strategy for the Synthesis of Highly Substituted Carbazoles

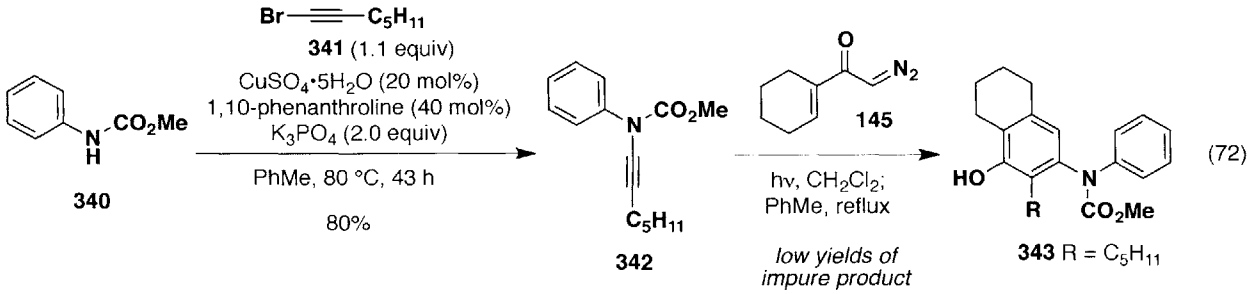
Benzannulations with *N*-Aryl Ynamides

Our tandem strategy for the synthesis of carbazole alkaloids employs a benzannulation utilizing *N*-aryl ynamides and a suitable vinylketene precursor. This chapter describes our studies of the feasibility of the proposed strategy, the optimization of conditions for the reactions, and the investigation of the scope of the method. For these studies, we used diazo ketone **145**[72] and cyclobutenone **107**[117] as the vinylketene precursors. Both of these compounds were synthesized according to well known procedures developed previously in our laboratory.



The synthesis of *N*-aryl ynamides has been reported using the protocol developed by Hsung.[159] We synthesized the previously unknown ynamide **342** in good yield via the coupling of the known alkynyl bromide **341**[160] and *N*-phenyl carbamate **340** using the Hsung method.

Eq 72 describes the synthesis of ynamide **342** and the "second generation" benzannulation of this ynamide with α,β-unsaturated diazo ketone **145**. Unfortunately, under a variety of conditions, we only obtained impure product in low yield in this benzannulation.



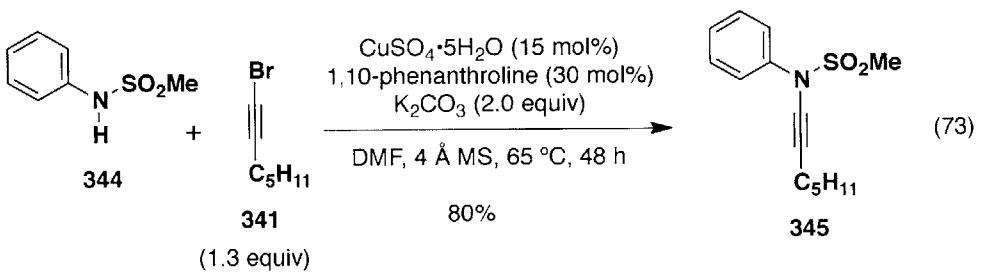
[159] For an examples, see: (a) ref 64a. (b) Istrate, F. M.; Buzas, A. K.; Jurberg, I. D.; Odabachian, Y.; Gagosz, F. *Org. Lett.* **2008**, *10*, 925-928.

[160] Alkynyl bromide **341** was prepared from the corresponding terminal alkyne using silver nitrate and NBS, see: Maleczka, R. E., Jr.; Terrell, L. R.; Clark, D. H.; Whitehead, S. L.; Gallagher, W. P.; Terstiege, I. *J. Org. Chem.* **1999**, *64*, 5958-5965.

We speculated that the phenyl group on the nitrogen of the ynamide was responsible for the low yield obtained in this benzannulation. The phenyl group draws electron density away from the nitrogen resulting in a less electron-rich and therefore less ketenophilic π bond. Less ketenophilic ynamides do not perform well in benzannulations with α,β-unsaturated diazo ketones because side reactions of the intermediate vinylketene such as dimerization compete with the desired [2 + 2] cycloaddition. In the past, we overcame this problem by minimizing the concentration of vinylketene via the slow addition of the diazo ketone, which was also used in excess. However, these conditions did not substantially improve reactions with ynamide **342**. As a result, we investigated an alternative ynamide derivative in which the electron-withdrawing group on the nitrogen was changed from carbamate to sulfonamide. In previous studies[161] we demonstrated that *N*-sulfonyl ynamides are more ketenophilic than *N*-carbomethoxy ynamides. We hypothesized that an *N*-sulfonyl ynamide would compete more effectively with the unproductive side reactions of the vinylketene and would thus increase the yield of the benzannulation.

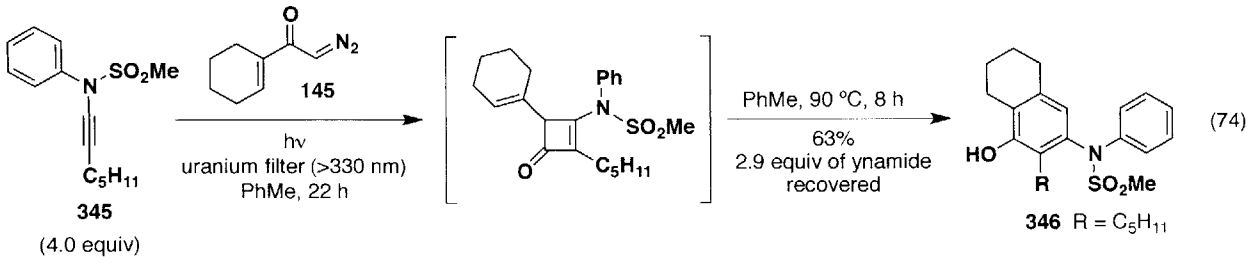
The synthesis of *N*-sulfonyl ynamide **345** did not proceed well under the standard conditions reported by Hsung. We attributed the low yields obtained in this coupling to poor solubility of *N*-phenylmethanesulfonamide (**344**) in toluene. Changing the solvent from toluene to DMF[162] resulted in a cleaner reaction furnishing the desired ynamide in 80% yield (eq 73). This reaction sometimes resulted in the formation of small amounts of difficult to separate side products. While these side products were never isolated and fully characterized, we speculated that they were the result of ynamide hydrolysis. In order to suppress potential hydrolysis reactions, we added molecular sieves. We found that the addition of molecular sieves to the reaction mixture leads to cleaner and higher yielding reactions. In principle, it should be possible to run the reaction without sieves after rigorous drying of the solvent and copper salt. We found the addition of sieves to be operationally simpler, so alternative reaction conditions were not explored.

[161] See Part I, Chapter 3 of this thesis.
[162] For specific substrates Hsung has also performed the reaction in DMF, see: ref 64a.



(73)

"Second generation" benzannulation reactions with *N*-sulfonyl ynamide **345** were performed with a uranium filter to prevent decomposition of the ynamide. As was the case with our previous work[163] utilizing *N*-sulfonyl ynamide **136**, ynamide **345** decomposes to form a ketenimine when irradiated without a uranium filter. Because the use of a uranium filter leads to nearly exclusive formation of the intermediate vinylcyclobutenone, the reaction mixture was heated after irradiation to convert the vinylcyclobutenone to the desired phenol. Irradiation in dichloromethane and toluene produced similar results. We chose toluene as the solvent because its higher boiling point facilitates the thermolysis step. Initial experiments using only one equivalent of ynamide led to the formation of the desired product in low yields (ca. 30%). We obtained superior results using 4 equivalents of the ynamide under dilute conditions (0.04 M in diazo ketone). These conditions suppress side reactions such as dimerization of the vinylketene intermediate by minimizing its concentration. The optimized reaction conditions, shown in eq 74, lead to the formation of phenol **346** in 63% yield. We found using an excess of the ynamide to be more attractive than employing slow addition of an excess of diazo ketone because nearly all of the unreacted ynamide (2.9 equiv) can be recovered after the benzannulation.

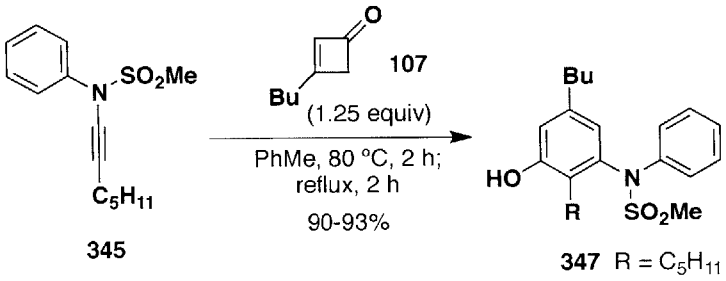


(74)

Reactions employing our "first generation" benzannulation protocol also proceeded smoothly. Heating ynamide **345** with a slight excess of cyclobutenone **107** in toluene at 80 °C for

[163] See page 45 of this thesis.

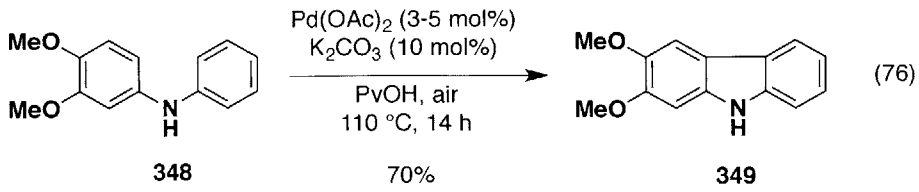
2 h and then reflux for 2 h afforded the phenol **347** in 90-93% yield. Performing the "first generation" benzannulation with two-stage heating was done as a precaution to avoid any decomposition of the ynamide, since it is known that some *N*-sulfonyl ynamides decompose in the temperature range 120-200 °C.[164] However, it should be noted that a number of tosyl ynamides have been shown to participate in the benzannulation without complication in previous studies in our laboratory.[2,3a]



(75)

Exploring Pd-Mediated Cyclizations of Diarylamines

Having successfully established conditions for vinylketene-based benzannulations with *N*-phenyl ynamides, we began to explore cyclization methods for the conversion of the products to carbazoles. Our original plan called for the application of the Pd-catalyzed oxidative cyclization conditions reported by Fagnou.[155a] As illustrated in eq 76, the protocol developed by Fagnou involves treatment with catalytic $Pd(OAc)_2$ in the presence of both K_2CO_3 and pivalic acid. Fagnou found that performing the reaction in pivalic acid suppresses the formation of oxidative side products and speculated that the pivalate ligand on palladium plays a key role in a C-H bond cleavage.

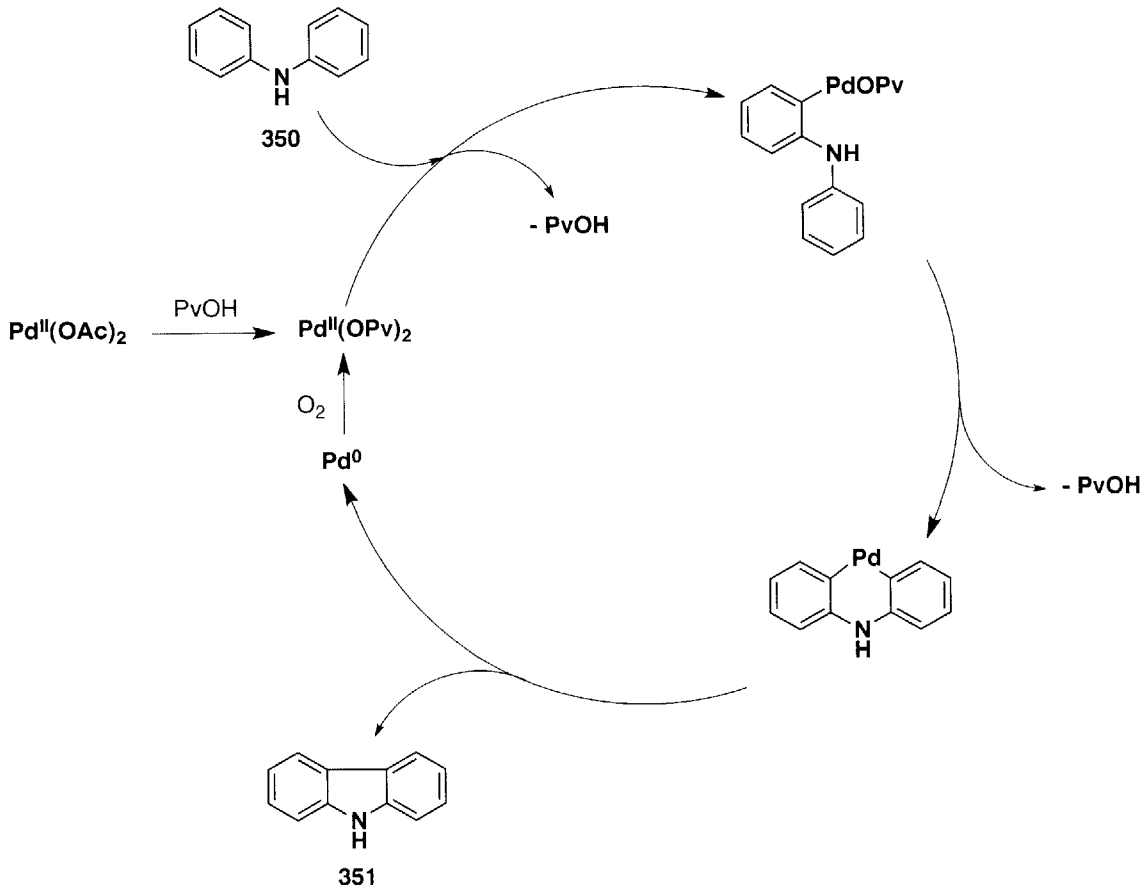


(76)

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

Scheme 43 shows the mechanism of the cyclization of *N*,*N*-diphenylamine (**350**) by this method. The reaction proceeds via two consecutive C-H activation steps followed by reductive elimination to furnish carbazole (**351**) and Pd(0). Aerobic oxidation of Pd(0) regenerates the active Pd(II) species.

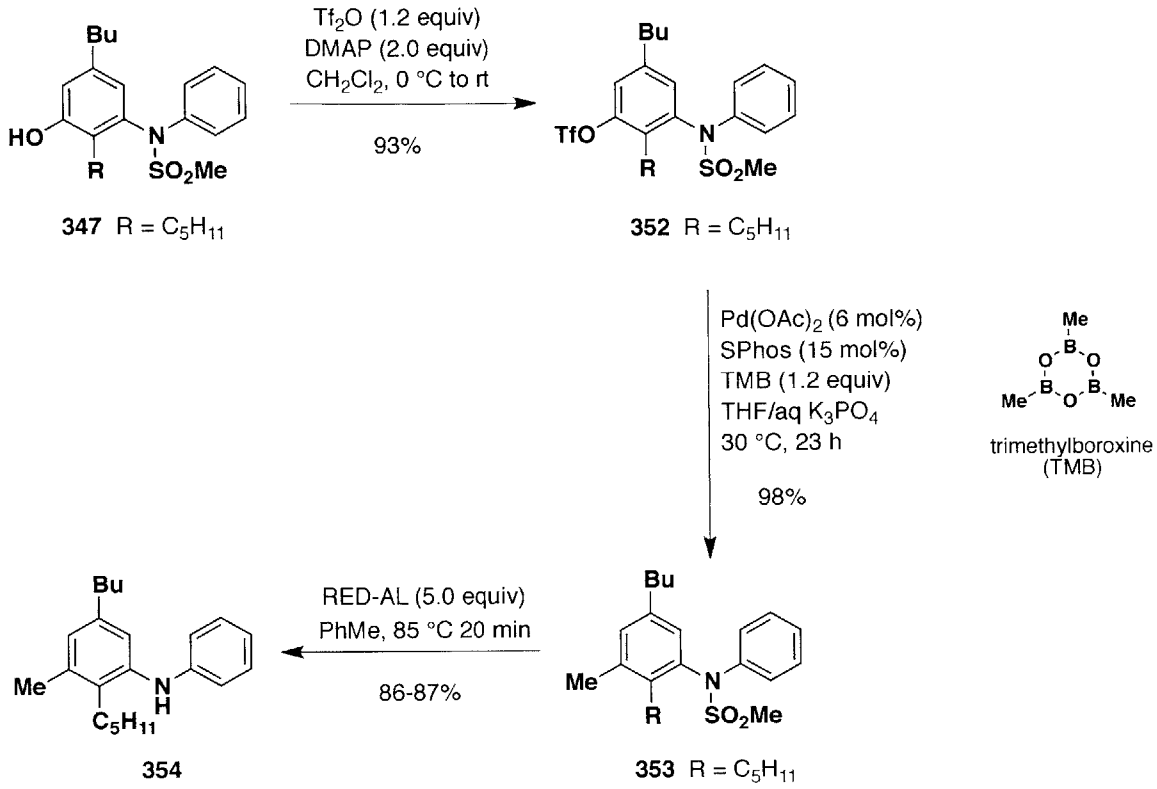
Scheme 43



It was unclear if a phenol would survive the conditions reported by Fagnou, so we converted phenol **347** into a more suitable cyclization precursor **354**, via the three-step sequence shown in Scheme 44. Note that our projected application of this chemistry required eventual replacement of the hydroxyl group with an alkyl substituent in any case. Several methods for the

cross-coupling reaction leading to **353** were examined and the best yields were obtained with a Suzuki reaction utilizing conditions developed by Buchwald.[165,166]

Scheme 44

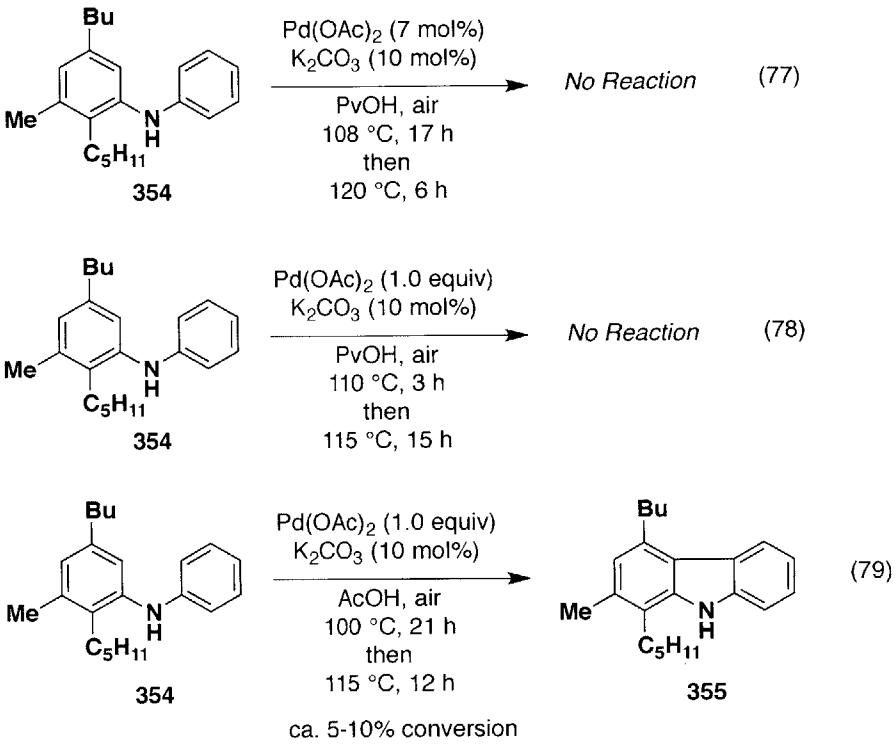


Attempts to cyclize diarylamine **354** with catalytic $Pd(OAc)_2$ in pivalic acid under an atmosphere of air, as reported by Fagnou, failed to provide any product even upon prolonged heating (eq 77). Most of the starting material remained after the reaction, though some decomposition was observed. We subsequently tried to cyclize **354** with stoichiometric $Pd(OAc)_2$, but this reaction also failed to produce the desired product (eq 78). After switching the solvent to acetic acid, we observed ca. 5-10% conversion of the starting material to the desired product (eq 79). The improved results in acetic acid suggested that the cyclization of **354** requires $Pd(OAc)_2$ as the active catalyst as opposed to the much larger $Pd(OPv)_2$. We speculated that the butyl group might be hindering Pd insertion into the neighboring C-H bond. Given the

[165] (a) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461-1473. (b) Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14073-14075.

[166] I would like to thank the Buchwald laboratory for a donation of S-Phos.

inconsistent results obtained by others using this type of cyclization in the past, we did not explore the reaction further. Instead we turned our attention to photochemical cyclization methods.

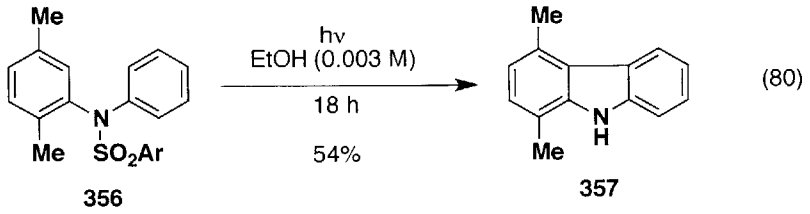


Investigating the Photochemical Cyclizations of *N,N*-Diarylsulfonamides

Initial Feasibility Study

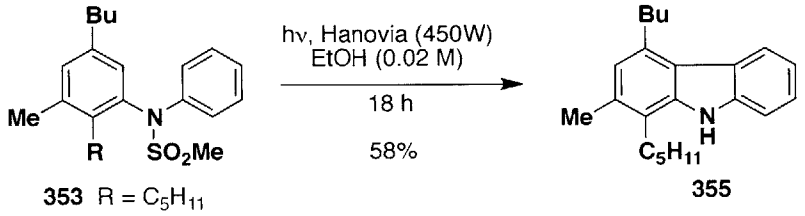
Among numerous photochemical cyclization methods, we were drawn to the cyclization of 4-methyl-*N,N*-diarylbenzenesulfonamides reported by Shannon.[167] Eq 80 shows a typical example of this transformation.

[167] Hall, R. J.; Marchant, J.; Oliveira-Campos, A. M. F.; Queiroz, M.-J. R. P.; Shannon, P. V. R. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3439-3450.



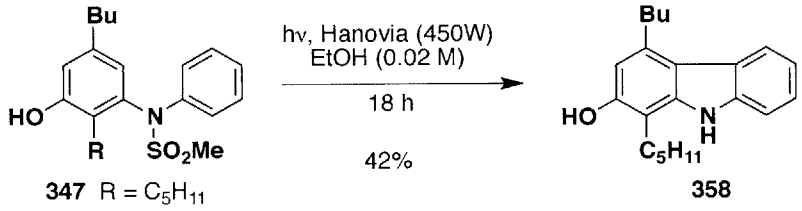
(80)

An attractive feature of this approach is that it would not require a deprotection step and would allow us to rapidly access carbazoles from our *N,N*-diarylsulfonamide benzannulation products. Intrigued by this possibility, we investigated the photochemical cyclization of *N,N*-diarylmethanesulfonamide **353**. We found that irradiation of **353** in degassed ethanol using our Hanovia system furnished the carbazole **355** in 58% yield (eq 81).



(81)

Products obtained directly from our vinylketene-based benzannulation can also be cyclized using this method. As shown in eq 82, irradiation of the phenol **347** afforded the carbazole **358** in 42% yield. While the cyclization proceeds in moderate yield, its use allows us to rapidly generate polysubstituted carbazoles.

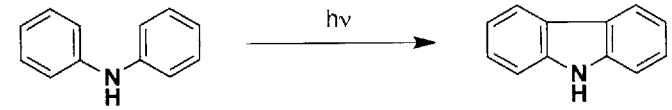


(82)

Prior to our work shown in eq 81 and 82, the reactions reported by Shannon were the only examples of the photochemical cyclization of *N,N*-diarylsulfonamides; however, the cyclization of other diarylamine derivatives is well known in the literature. The following section provides a brief review of the mechanism, reaction conditions, and scope of this reaction.

Review of the Photochemical Cyclization of Diarylamines

While performing experiments with fluorimeters in 1957, Parker and Barnes discovered that irradiation of diphenylamine with ultraviolet light results in the formation of carbazole. [168] Since their discovery, several groups have investigated this transformation from both a mechanistic and a synthetic point of view. The photochemical cyclization of diarylamines has been the subject of several reviews.[156]



diphenylamine (**350**) carbazole (**351**)

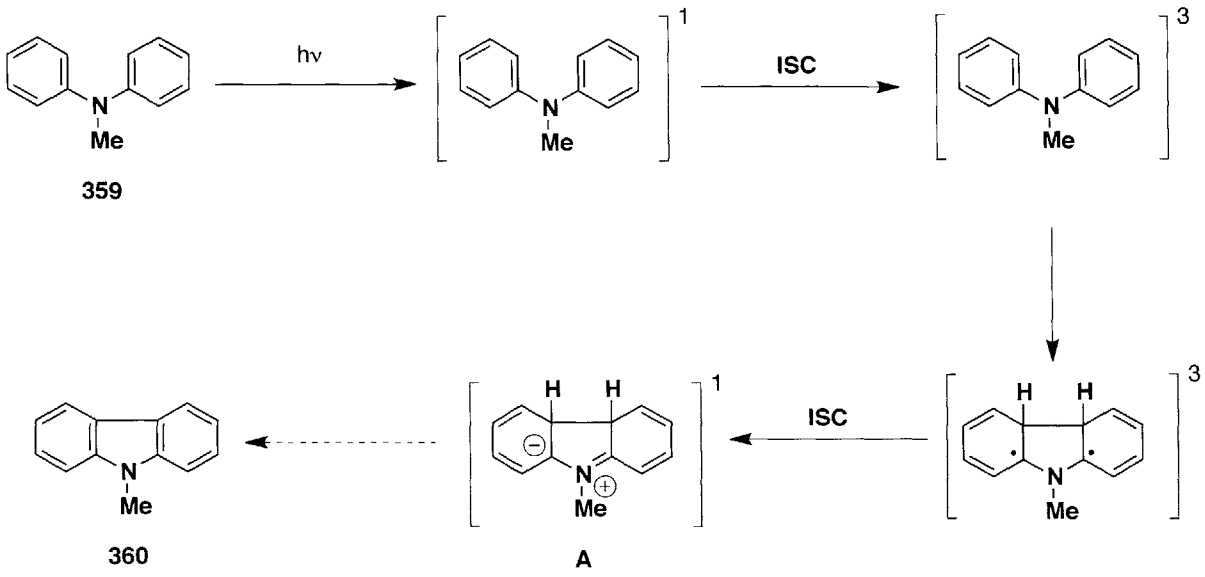
Mechanism of the Cyclization of N-Methyl-N,N-diphenylamine and Related Systems

The mechanism of this photochemical cyclization has been studied in detail.[169] The exact mechanism varies depending on whether or not oxygen is present, but the initial steps remain the same in most cases. Scheme 45 illustrates the mechanism using *N*-methyl-*N,N*-diphenylamine (**359**) as the substrate. Irradiation of **359** produces an excited singlet state species that undergoes intersystem crossing to the excited triplet state. The excited triplet state then cyclizes and relaxes to form a singlet state intermediate (**A**). This singlet state intermediate can ring-open to form the starting material, or it can continue down other reaction pathways, depending on the substrate and conditions, to afford the desired carbazole product **360**.

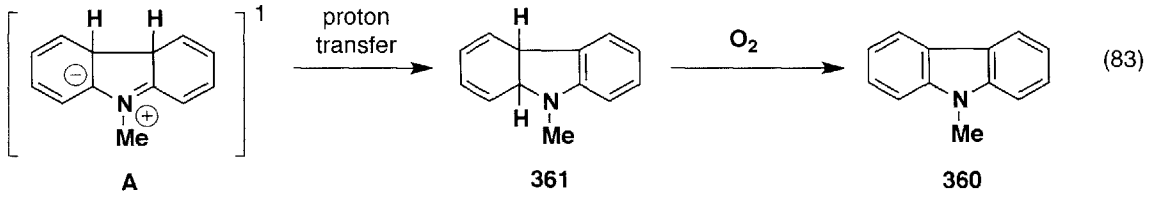
[168] Parker, C. A.; Barnes, W. J. *Analyst*, **1957**, *82*, 606-618.

[169] For references regarding the mechanism, see: (a) Grellmann, K.-H.; Kühnle, W.; Weller, H.; Wolff, T. *J. Am. Chem. Soc.* **1981**, *103*, 6889-6893 and references cited therein. (b) Görner, H. *J. Phys. Chem., A* **2008**, *112*, 1245-1250.

Scheme 45

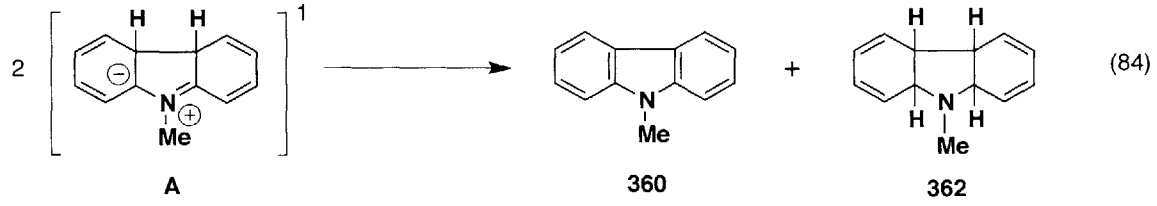


Under *aerobic* conditions, intermediate **A** forms the desired product via proton transfer followed by oxidation, as shown in eq 83.



(83)

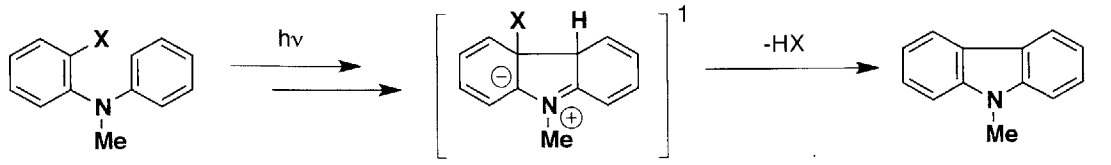
Under *anaerobic* conditions intermediate **A** can disproportionate to furnish the *N*-methylcarbazole (**360**) along with tetrahydrocarbazole **362**, as shown in eq 84.[170]



(84)

[170] In the absence of oxygen, intermediate **A** can also undergo proton transfer to produce a dihydrocarbazole of unknown structure; however, disproportionation is the main reaction pathway. See reference 169a.

A third mechanistic pathway exists for substrates that have a suitable leaving group X. Substrates with this substitution pattern lose HX from the singlet state intermediate **364** to afford the desired carbazole product.



363 **364** **360** (85)

The leaving group X is most often F or Cl, but CN and OMe have been shown to participate in this reaction pathway.[171] For substrates where X = Cl, radical[171c] or carbene[171d] mechanisms cannot be ruled out. It should be noted that other mechanisms operate for halide-substituted substrates under highly basic conditions.[172]

Reaction Conditions for the Photochemical Cyclization of Diarylamines

No single set of reaction conditions has proved optimal for all cases of the photochemical cyclization of diarylamines. Most examples of the cyclization occur at room temperature with irradiation wavelengths ranging from 254 to 310 nm. Solvent choice depends on the substrate; cyclizations have been performed in benzene, acetonitrile, hydrocarbons, ethers, and alcohols. For secondary diarylamines (Ar_2NH), Amano et al. found that the addition of an alcohol or amine to the reaction mixture accelerates the reaction.[173] Their experiments demonstrated that the addition of alcohol to the reaction mixture suppresses non-radiative decay. Additional experiments revealed that amines affect the reaction differently. Instead of suppressing non-radiative decay, amines accelerate the photochemical cyclization by increasing the rate of

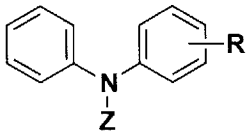
[171] For examples with X = F, see: (a) Fokin, E. P.; Gerasimova, T. N.; Fomenko, T. V.; Semikolenova, N. V. *J. Org. Chem. (USSR) (Engl. Transl.)* **1978**, *14*, 772-778. (b) Groundwater, P. W.; Hughes, D.; Hursthouse, M. B.; Lewis, R. *J. Chem. Soc., Perkin Trans. 1*, **1996**, 669-673. For examples with X = Cl, see: (c) Svanfelt, J.; Kronberg, L. *Environ. Chem. Lett.* **2011**, *9*, 141-144. (d) Görner, H. *J. Photochem. Photobiol., A* **2010**, *211*, 1-6. (e) Encias, S.; Bosca, F.; Miranda, M. A. *Photochem. Photobiol.* **1998**, *68*, 640-645. For an example with X = CN, see: (f) Ferris, J. P.; Antonucci, F. R. *J. Am. Chem. Soc.* **1974**, *96*, 2010-2014. For an example with X = OMe, see: (g) Groundwater, P. W.; Hughes, D.; Hursthouse, M. B.; Lewis, R. *J. Chem. Soc., Perkin Trans. 1*, **1996**, 669-673.

[172] Budén, M. E.; Vaillard, V. A.; Martin, S. E.; Rossi, R. A. *J. Org. Chem.* **2009**, *74*, 4490-4498.

[173] Amano, K.; Hinohara, T.; Hoshino, M. *J. Photochem. Photobiol., A* **1991**, *59*, 43-54.

intersystem crossing. Both of these effects are thought to be the result of hydrogen bonding between the diarylamine and the added alcohol or amine. In cases where X = F, Fokin et al. have shown that the addition of triethylamine or butylamine promotes the reaction, presumably by facilitating the loss of HF.[171a]

Scope of the Photochemical Cyclization



A comprehensive study of the effect of substituents on the photochemical cyclization of diarylamines has not been reported; however, some substituent effects and general trends are known. The group Z on nitrogen can be hydrogen, alkyl, benzyl, or phenyl. The group Z *cannot* be acyl because in that case the photo-Fries product predominates.[174] The aromatic rings can be either electron rich or electron poor, but the reaction does not tolerate strong electron withdrawing groups (e.g., CO_2H) at the position *ortho* to the nitrogen.[171d] In general, the reaction provides the desired carbazole in moderate to good yield (50-70%).

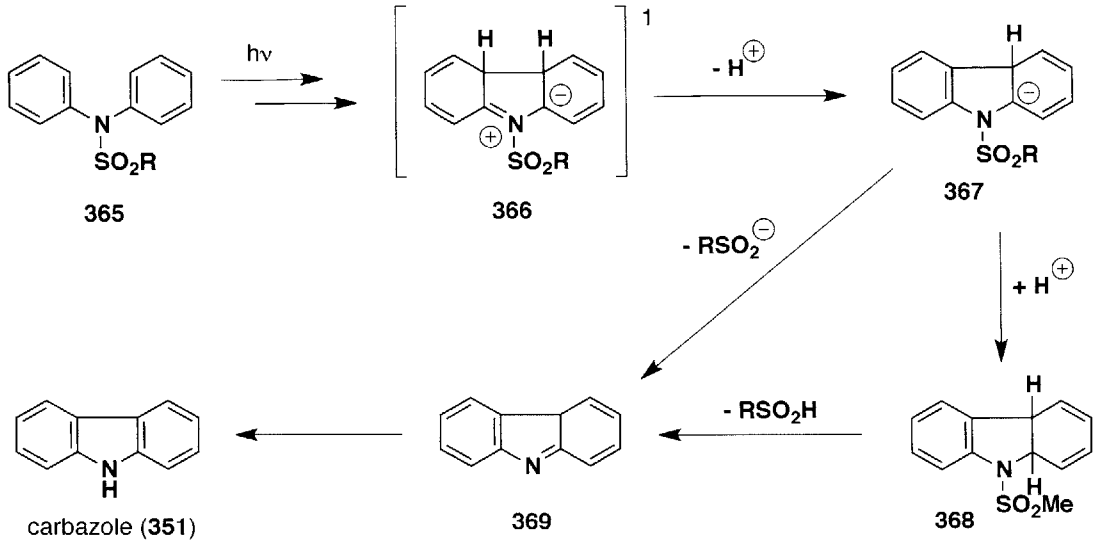
Mechanism of the Cyclization of *N,N*-Diarylsulfonamides

While the mechanism for the cyclization of *N,N*-diphenylamine and *N*-methyl-*N,N*-diphenylamine have been studied in detail (vide supra), much less is known about the cyclization of *N,N*-diarylsulfonamides. Shannon did not discuss the mechanism of the cyclization of *N,N*-diarylsulfonamides in his 1992 report.[167]

We speculate that two mechanistic pathways could be operational. Scheme 46 shows one potential mechanism based on the established pathway for the cyclization of *N*-methyl-*N,N*-diphenylamine. Excitation of *N,N*-diarylsulfonamide **365** followed by cyclization furnishes dihydrocarbazole intermediate **366**. Deprotonation followed by elimination of sulfinic acid and then tautomerization leads to carbazole (**351**).

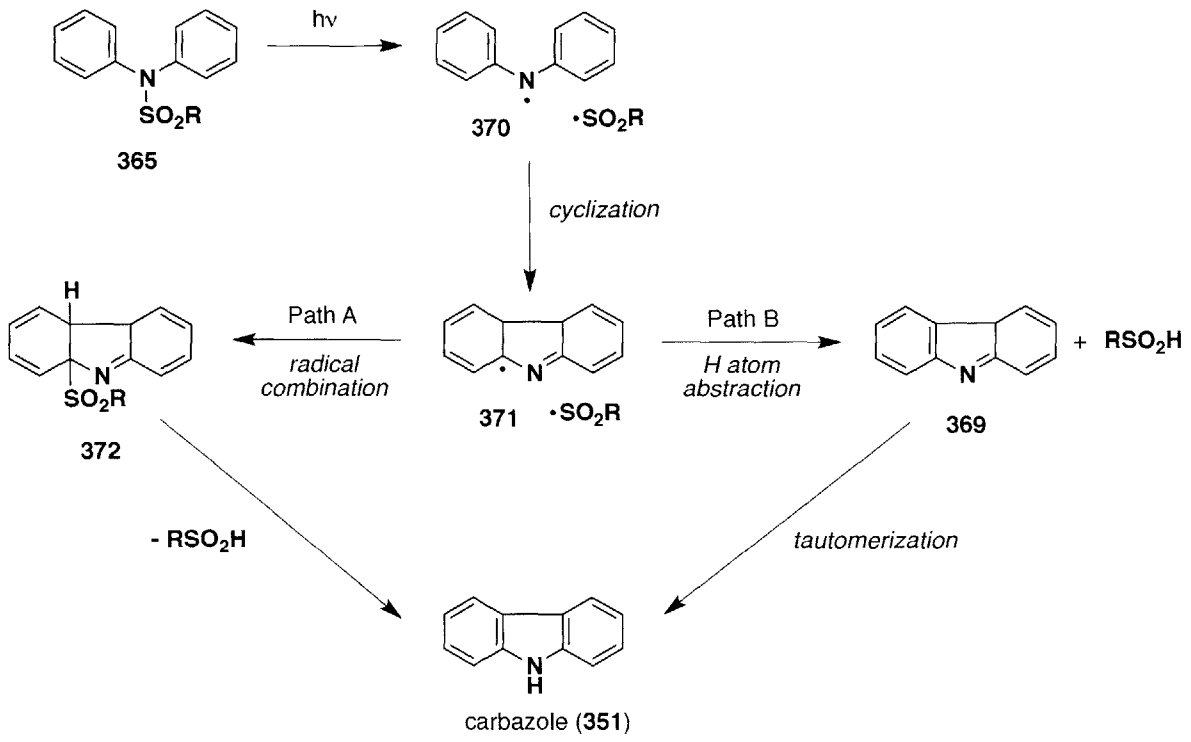
[174] Jackson, A. H.; Jenkins, P. R.; Shannon, P. V. R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1698-1704.

Scheme 46

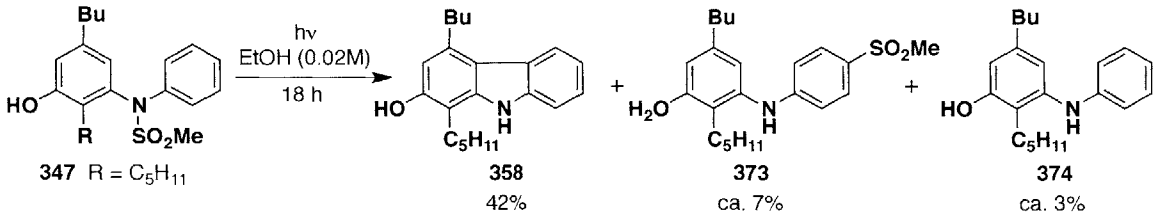


We also envisioned an alternative radical pathway based on the known reactivity of sulfonamides upon irradiation. As illustrated in Scheme 47, irradiation of *N,N*-diarylsulfonamide **365** could lead to homolysis of the N-S bond. Cyclization of the resulting radical intermediate **370** affords **371**, which can then furnish carbazole (**351**) via pathway A or B.

Scheme 47



With the hope of gaining insight into the mechanism of the cyclization we isolated the side products that formed during the cyclization of the benzannulation product **347**. We found that the photo-Fries type side product (**373**) and deprotected starting material (**374**) also form under the reaction conditions (eq 86).[175]

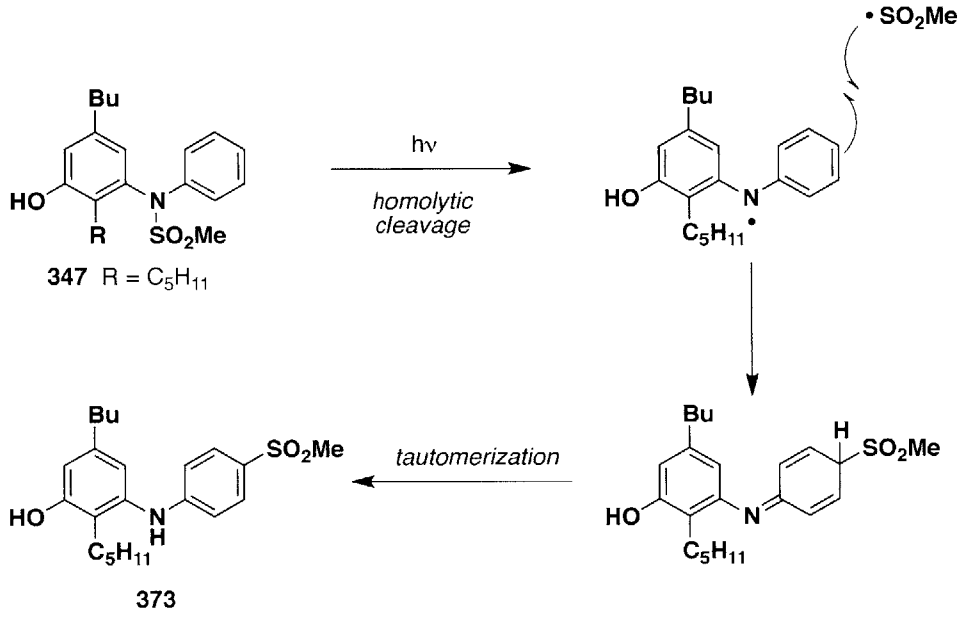


(86)

[175] The ^{1}H NMR spectrum of the crude reaction mixture shows no other significant peaks. The remainder of the material decomposes to a number of uncharacterizable minor products during the reaction.

The side products **373** and **374** are not entirely unexpected.[176] Given the potential homolytic cleavage of the N-S bond, recombination to form a photo-Fries type product is reasonable (Scheme 48).

Scheme 48

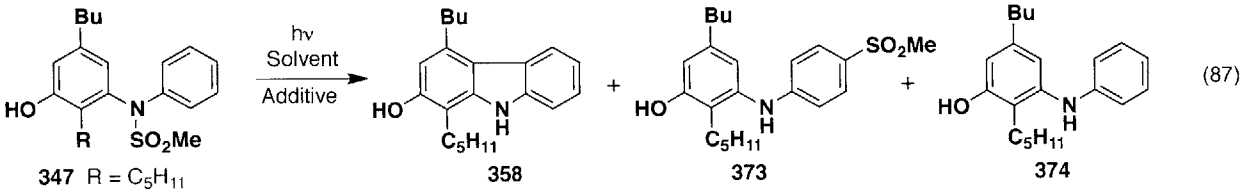


The presence of this photo-Fries type product suggests a radical type mechanism. However, the mechanisms outlined in Scheme 46 and 47 may both be operational under the reaction conditions. During the reaction, homolysis of the N-S bond can lead to the photo-Fries type product while the desired carbazole forms via the pathway depicted in Scheme 46. We have not performed any mechanistic studies and either or both mechanisms may be operational under the reaction conditions.

[176] Weiss, B.; Durr, H.; Haas, H. J. *Angew. Chem. Int. Ed.* **1980**, *19*, 648-650.

Optimization the of Photochemical Cyclization

We investigated the optimization of the photochemical cyclization using the benzannulation product **347** (eq 87). Reactions for our optimization studies were conducted in quartz tubes and irradiated with a using the Hanovia system unless otherwise noted. Similar to the work of Shannon and others, we performed cyclizations with high dilution (0.02-0.01 M) to avoid any undesired intermolecular side reactions.



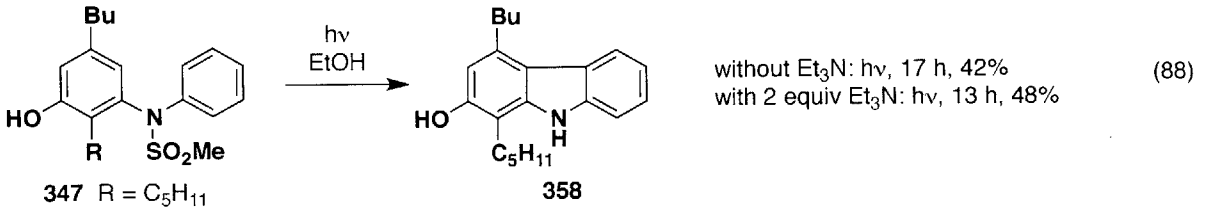
(87)

We examined cyclizations of **347** in MeOH, EtOH, *i*-PrOH, Et_2O, THF, and PhH. We found that the use of nonalcoholic solvents led to lower yields of the desired product. Polymeric buildup on the walls of the reaction tubes suggested that decomposition is a problem for these reactions. Cyclizations performed in *i*-PrOH and EtOH afforded similar results while those performed in MeOH lead to an increase in the formation of deprotected starting material (**374**).

We conducted cyclizations with varied irradiation conditions. Reactions performed with the Hanovia system using a uranium filter (>340 nm) resulted in little to no product formation. When a Pyrex filter (>280 nm) was used, the reaction afforded only trace amounts of product after 20 h of irradiation. Reactions performed with a Rayonet reactor equipped with 253.7 nm bulbs led to poor yields of the desired product. When a Rayonet reactor equipped with 300 nm bulbs was used the reaction proceed smoothly, but the yield was not improved relative to our initial experiments.

Based on the previous cyclizations of diarylamines (vide supra), We next examined the effect of additives, such as a triplet sensitizer or a base, to the reaction. Attempts to sensitize the reaction with acetone, propiophenone, and benzophenone resulted in no reaction. When the reaction was performed in the presence of 6 equiv of NaOEt, there was a significant increase in the formation of the undesired deprotection product **374**. We found that the cyclization of **347** occurs more rapidly and in slightly better yield when 2.0 equiv of triethylamine, diethylamine, or

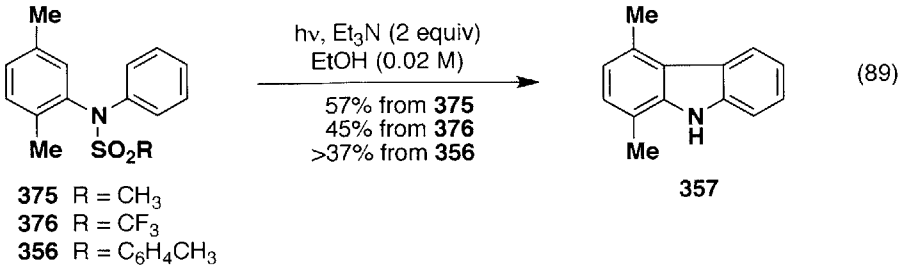
DABCO is added to the reaction mixture. The increase in the yield of the desired product was similar regardless of the amine used. We utilized triethylamine in future reactions.



(88)

The potential benefits of added amine vary depending on the mechanism. Should the mechanism in Scheme 46 be operative, we speculate that the addition of an amine may facilitate proton transfer. If the mechanism in Scheme 47 is operational, then the amine may facilitate the elimination of the sulfinate along pathway A. In general, the amine may prevent some decomposition pathways by quenching the sulfinic acid byproduct.

Our final optimization experiments explored the effect of different sulfonyl groups. For these studies we compared the cyclization of *N,N*-diarylsulfonamides **375**, **376**, and **356** .[177] We found that methanesulfonamide **375** afforded the product **357** in best yield (eq 89). We had hoped that the cyclization of trifluoromethanesulfonamide **376** might furnish the product in greater yield by suppressing the undesired photo-Fries type reaction. However, the cyclization of **376** afforded the product in lower yield and a photo-Fries type product was still observed in the crude reaction mixture. The worst results were obtained with sulfonamide **356**. Shannon obtained a 54% yield using this substrate (eq 80), but his reaction was performed on a larger scale in a reactor under more dilute conditions.



(89)

[177] All three *N,N*-diarylsulfonamides were synthesized from the corresponding *N*-arylsulfonamide and benzyne, which was generated in situ, see: Liu, Z.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3198-3209.

Photochemical Cyclizations Performed in Batch and Flow

After we completing our optimization studies, we explored the photochemical cyclization of our benzannulations substrates using batch and continuous-flow reactors. Table 7 summarizes our results. We performed most batch mode cyclizations with 2.0 equiv of triethylamine in a degassed 0.015 M solution of absolute ethanol. The reactions were conducted in a 20-cm quartz tube (12 mm I.D., 14 mm O.D.) and irradiated using the Hanovia system[178] for 14-17 h. Because of the dilute reaction conditions, ca. 12 mL of solvent was required for a reaction affording 30 mg of product. One large-scale batch reaction was performed in a 350-mL immersion-well reactor using **347** as the substrate (entry 1). Irradiation of a 0.003 M solution of **347** with 50 equiv of triethylamine furnished more than 100 mg of the desired carbazole. A large volume of solvent is required for effective irradiation in the 350-mL reactor. As a result, we decreased the concentration of this large-scale batch reaction. The amount of amine was increased to compensate for the increased dilution. Reactions performed with 20 equiv of amine performed similarly. For this large-scale run, irradiation was conducted for 2 h using a Corex filter (>260 nm). Reactions performed without a filter occurred more rapidly but afforded slightly lower yields. The different reaction conditions employed in the small- and large-scale batch runs are exemplary of the challenges often encountered during the scale up of batch photochemical reactions.

In order to facilitate the scale up of the photochemical cyclizations, we investigated reactions in flow. Continuous-flow reactions were performed with 2.0 equiv of triethylamine in a degassed 0.015 M solution of absolute ethanol using the 6.3-mL reactor.[179] The reactions were performed with a flow rate of ca. 1.0 mL/min providing a residence time of ca. 6 min. Continuous-flow reactions gave consistent results and a reaction lasting less than 90 min easily provided more than 100 mg of the desired carbazole. It is difficult to compare batch and flow reaction times directly. As a result, batch and flow processes are often compared with respect to their efficiency. We define efficiency here as the number of mmol of reactant divided by the hours of irradiation. Table 7 shows that cyclizations performed in flow occur with greater efficiency than those performed in batch.

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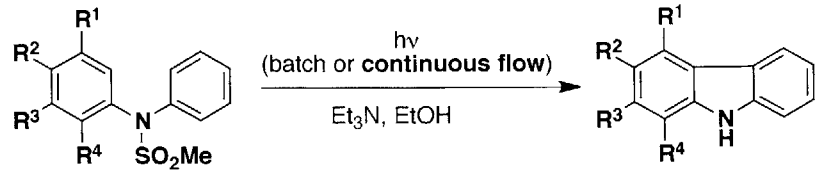
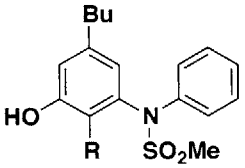
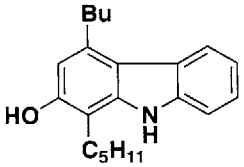
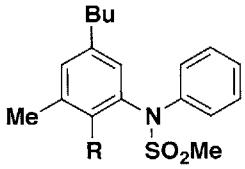
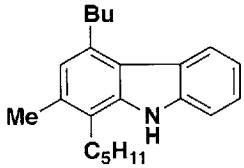
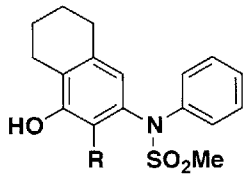
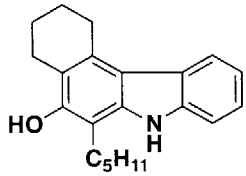
[178] For a more complete description see Part I, Chapter 3 of this thesis.

[179] For a detailed description of the set-up and operation of the continuous-flow reactor see Part I, Chapter 3 of this thesis.

Table 7. Photochemical Cyclization of *N,N*-Diarylsulfonamides in Batch and Flow



entry	diarylamine	carbazole	% yield[a] (method)[b,c]	efficiency (mmol/h)[e]
1	 **347** R = C_5H_{11}	 **358**	48 (batch) 44[d] (batch) **45 (continuous flow)**	0.02 0.42 **0.78**
2	 **353** R = C_5H_{11}	 **355**	56 (batch) **58 (continuous flow)**	0.01 **0.73**
3	 **346** R = C_5H_{11}	 **377**	56 (batch) **56 (continuous flow)**	0.02 **0.84**

[a] Isolated yield of products purified by column chromatography. [b] Batch reactions: Irradiation in a 10-cm quartz tube placed 20 cm from a 450W Hanovia lamp in a water-cooled quartz well. [c] Continuous flow reactions: Irradiation with a 6.3 mL flow reactor at a flow rate of 1.0 mL/min (residence time = ca. 6 min). See experimental section for details regarding construction and operation of the flow reactor. [d] Run using a Corex filter (>260 nm) in a 350 mL Pyrex reactor. [e] Efficiency is defined as mmol of starting material divided by hours of irradiation time.

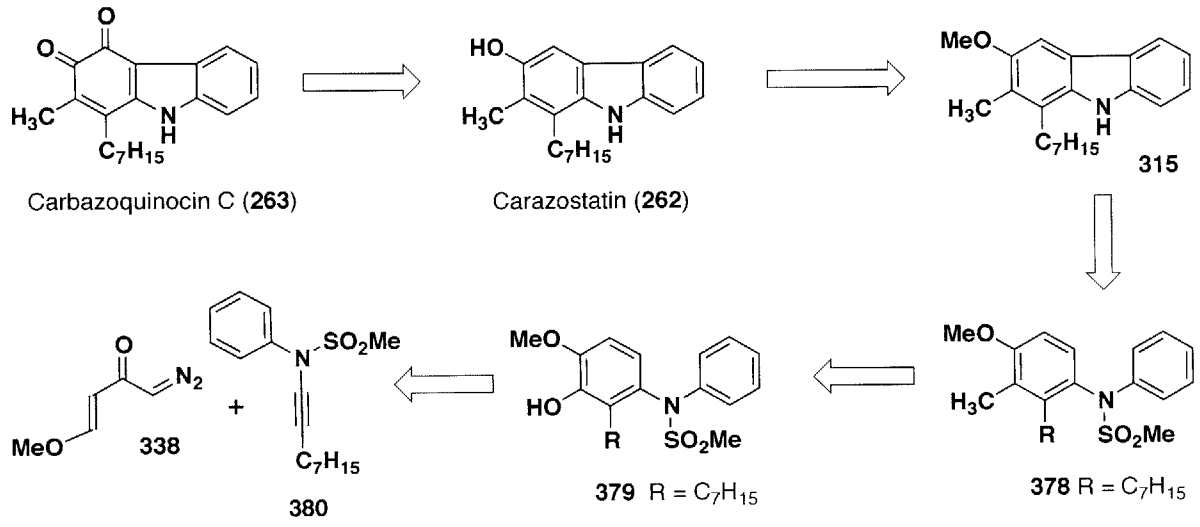
Utilizing a vinylketene-based benzannulation and a photochemical cyclization in tandem, we have developed an effective strategy for the synthesis of highly substituted carbazoles. The next chapter explores the application of this strategy to the total synthesis of carbazole alkaloids.

Chapter 3

Total Synthesis of Carbazole Alkaloids

With our tandem strategy for the synthesis of carbazoles established, we next directed our efforts to the synthesis of carazostatin and related carbazole alkaloids. Scheme 49 shows our route for the synthesis carbazoquinocin C and carazostatin. Carazostatin (**262**) can be oxidized using the protocol reported by Hibino[145] to furnish carbazoquinocin C. We envisioned carazostatin forming from via photochemical cyclization of *N,N*-diarylsulfonamide **378** followed by cleavage of the methyl ether. Sulfonamide **378** could be synthesized from the phenol **379** which is the product of the benzannulation of diazo ketone **338** ynamide **380**.

Scheme 49

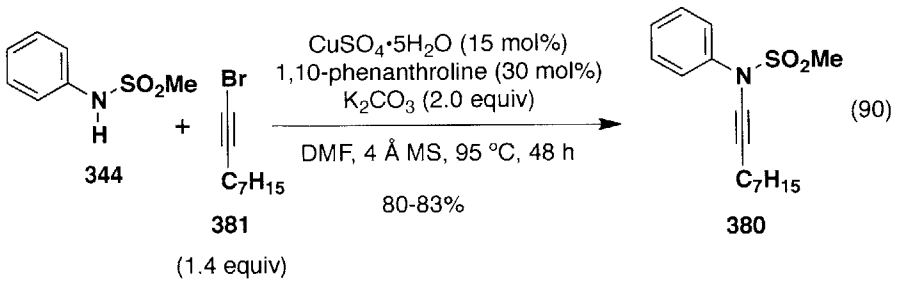


Synthesis of the Ynamide and the Diazo Ketone

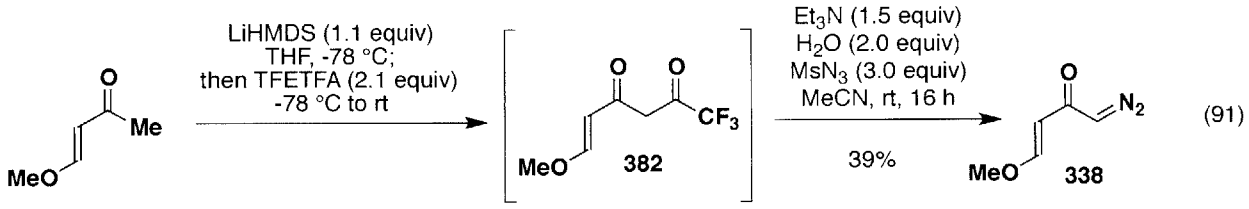
Our total synthesis begins with the coupling of sulfonamide **344** and the known alkynyl bromide **381**. [180] We prepared alkynyl bromide **381** from 1-nonyne in near quantitative yield via the method developed by Hofmeister[113] utilizing silver(I) nitrate and NBS. Coupling sulfonamide

[180] For the synthesis of alkyne bromide **380** from the corresponding alkynyl lithium and bromine, see: Zhang, X.; Burton, D. J. *Tetrahedron Lett.* **2000**, *41*, 7791-7794.

344 and bromide **381** using a modified[181] version of the Hsung method furnished ynamide **380** in 80-83% yield (eq 90).



With the ynamide in hand, we turned our attention to the synthesis of the vinylketene precursor, diazo ketone **338**. This diazo ketone had previously been prepared as a key intermediate in the total synthesis of maesanin developed in our lab. [44a] In that report, diazo ketone **338** was prepared in 39% yield using our detrifluoroacetylative diazo transfer method (eq 91).

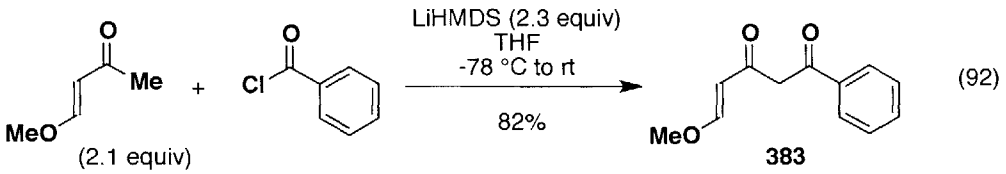


We experienced some difficulty in obtaining pure diazo ketone using this method and found it necessary to chromatograph the material three and sometimes four times in order to obtain pure **338**. This extensive chromatography wasted time and solvent and led to reduced yields of the desired product. We speculated that the impurities we found difficult to separate were generated during the formation of diketone **382**. We hypothesized that if the intermediate diketone could be purified prior to the diazo transfer step, then it would be easier to obtain pure diazo ketone. Unfortunately, diketone **382** is unstable and decomposes readily, so it is unsuitable for column chromatography. In order to improve on this procedure, we consequently explored alternative diazo transfer methods. Based on the work of Taber,[182] we hoped to employ

[181] For a discussion of these modifications, see page 112 of this thesis.

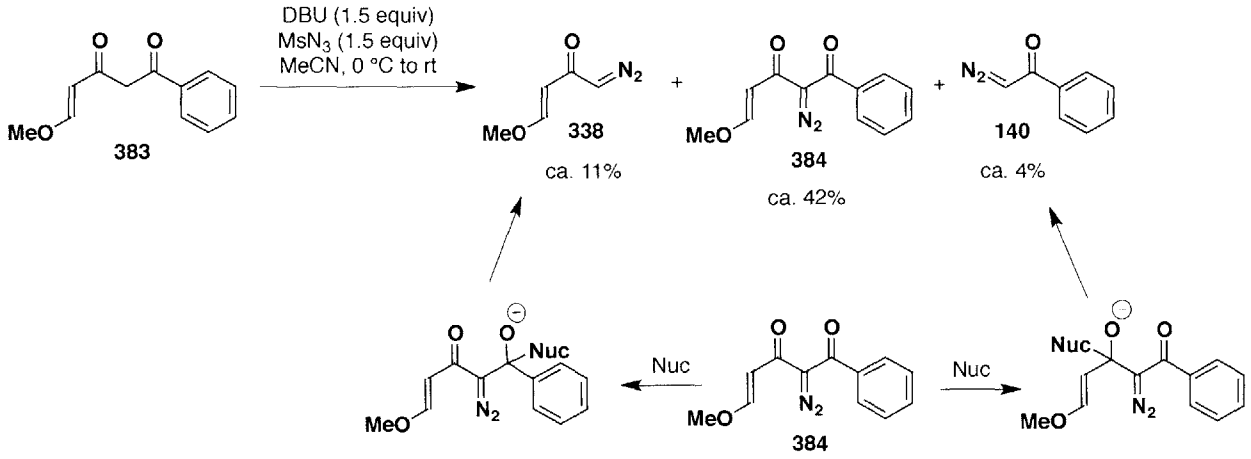
[182] (a) Taber, D. F.; You, K.; Song, Y. *J. Org. Chem.* **1995**, *60*, 1093-1094. (b) Taber, D. F.; Gleave, M. D.; Herr, R. J.; Moody, K.; Hennessy, M. J. *J. Org. Chem.* **1995**, *60*, 2283-2285. (c) Taber, D. F.; Herr, R. J.; Pack, S. K.;

debenzoylative diazo transfer. The requisite diketone (**383**)[183] was synthesized according to a known procedure and was found to be stable to standard chromatography conditions (eq 92).



Subjecting diketone **383** to the diazo transfer protocol reported by Taber resulted in the formation of the desired product **338**, diazo diketone **384**, and diazoacetophenone (**140**). We speculate that the diazo diketone **384** was formed first under the reaction conditions. Subsequent acyl cleavage of **384** would then furnish **338** or **140**, depending on which carbonyl group reacted with the nucleophilic species in the cleavage step.

Scheme 50



Our primary concern at this point was not the incomplete conversion of diazo diketone **384**, but the poor selectivity in the acyl cleavage step. We hoped to improve the selectivity of the cleavage by changing the aryl group. A report by Korneev[184] led us to theorize that use of a 4-nitrophenyl group would allow for more facile and selective cleavage. The synthesis of diketone

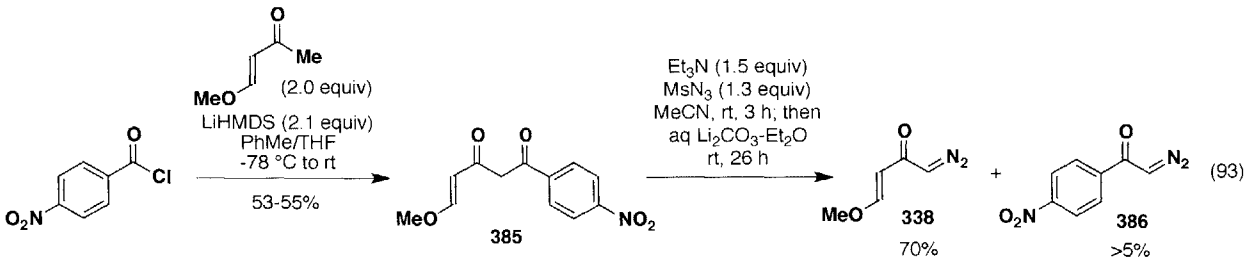
---

Geremia, J. M. *J. Org. Chem.* **1996**, *61*, 2908-2910. (d) Taber, D. F.; Sheth, R. B.; Joshi, P. V. *J. Org. Chem.* **2005**, *70*, 2851-2854.

[183] Koreeda, M.; Akagi, H. *Tetrahedron Lett.* **1998**, *21*, 1197-1200.

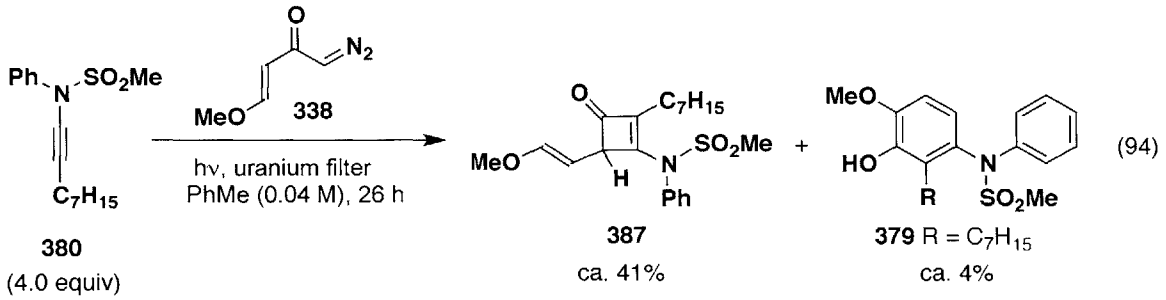
[184] Korneev, S.; Richter, Ch. *Synthesis* **1995**, 1248-1250.

385 proceeded smoothly. Subjecting diketone **385** to diazo transfer conditions with triethylamine as base[185] followed by cleavage of the 4-nitrobenzoyl group with 0.1 M aq Li_2CO_3 furnished the desired diazo ketone in 70% yield. Less than 5% of the undesired 4-nitrodiazoacetophenone (**386**) was observed in the crude NMR spectrum, and purification of **338** required only one chromatography column.



Benzannulation Studies

With the ynamide and diazo ketone in hand, we investigated the key benzannulation using the conditions we established during our previous studies.[186] Irradiation of a mixture of diazo ketone **338** and 4 equiv of ynamide **380** furnished vinylcyclobutenone **387** and the desired phenol **379** in ca. 45% combined yield (eq 94). We observed near exclusive formation of the intermediate vinylcyclobutenone because a uranium filter was used to prevent decomposition of the ynamide.[187]

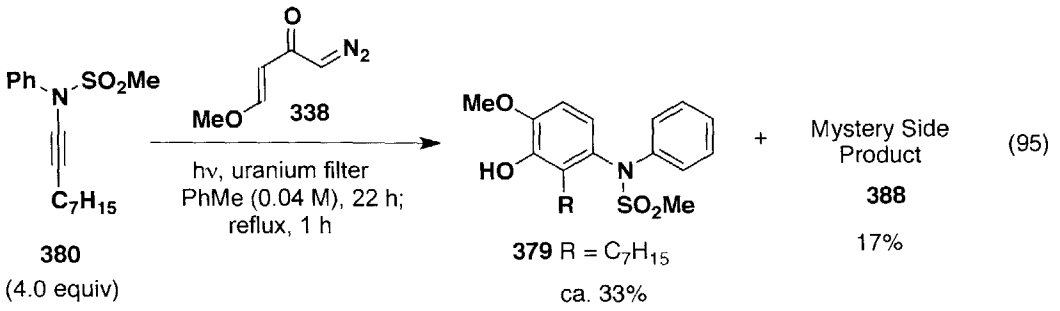


[185] Additional experiments demonstrated that diazo ketone **338** decomposes slowly in the presence of DBU. In order to obtain the best yield for this reaction, triethylamine was used as base.

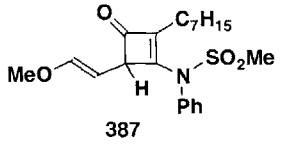
[186] For our prior work with the benzannulation of *N*-aryl ynamides, see Part III, Chapter 2 of this thesis.

[187] Similar to *N*-sulfonyl ynamide **136** (see Part I, Chapter 3), ynamide **360** decomposes to form a ketenimine when irradiated without a uranium filter.

In order to complete the conversion of the intermediate vinylcyclobutenone to the desired phenol, the reaction mixture was heated at reflux in toluene for 1 h after irradiation. Unfortunately, we isolated both the desired phenol (**379**) and a mysterious undesired side product **338** after heating (eq 95).



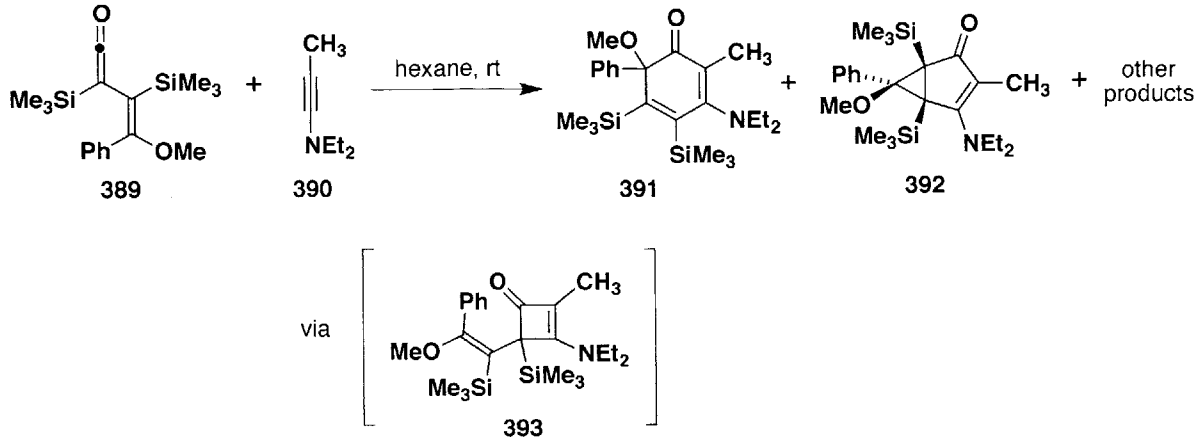
The IR spectrum of the side product showed that both a ketone and a sulfonamide were present in the structure. The ^{1}H NMR spectrum indicated that the heptyl chain, the phenyl ring, the methoxy group, and the sulfonamide were all present in the side product. Comparing the ^{1}H NMR spectrum of the intermediate vinylcyclobutenone **387** and the side product **388** revealed that both of the protons on the enol ether had shifted upfield. This suggested that the alkene was no longer present. The ^{13}C NMR spectrum confirmed this hypothesis. Based on the similarity between the intermediate vinylcyclobutenone **387**, the desired product **379**, and the side product **388**, we speculated that the side product formed via a competitive intramolecular reaction of the intermediate dienylketene. After exploring the literature on dienylketenes, we found that they can sometimes cyclize to form [3.1.0] bicyclic ketones depending on their substitution pattern. Furthermore, Dötz had reported the formation of a [3.1.0] bicyclic ketone (**392**) in the reaction of the stable silylvinylketene **389** with ynamine **390** (Scheme 51).[188]



387

[188] Dötz, K. H.; Mühlemeir, J.; Trenkle, B. *J. Organomet. Chem.* **1985**, *289*, 257-262.

Scheme 51



The ^{1}H and ^{13}C NMR spectra of the side product we obtained in our benzannulation correlate well with the spectra expected for the bicyclic ketone **388**. 2-D ^{1}H NMR analysis subsequently confirmed this structural assignment. The relative stereochemistry around the cyclopropyl ring is based on the coupling constants of the three methine protons. Previous work by Schöllkopf[189] demonstrated that [3.1.0] bicyclic structures such as **394**, with all three protons syn to one another, have ^{3}J coupling constants of ca. 6 Hz. In contrast, [3.1.0] bicyclic structures such as **395** have ^{3}J coupling constants of ca. 1 Hz. We observed coupling constants of ca. 1 Hz in the spectrum of **388**, so we concluded that there is a trans relationship between the protons at the ring junction and the proton alpha to the methoxy group (Figure 7).

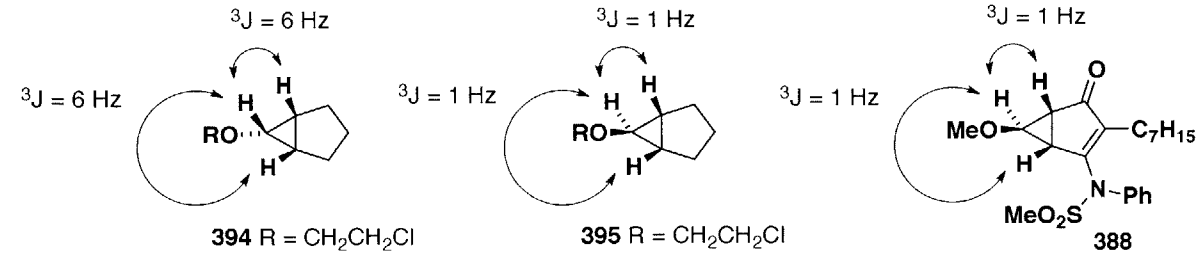
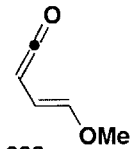


Figure 7.

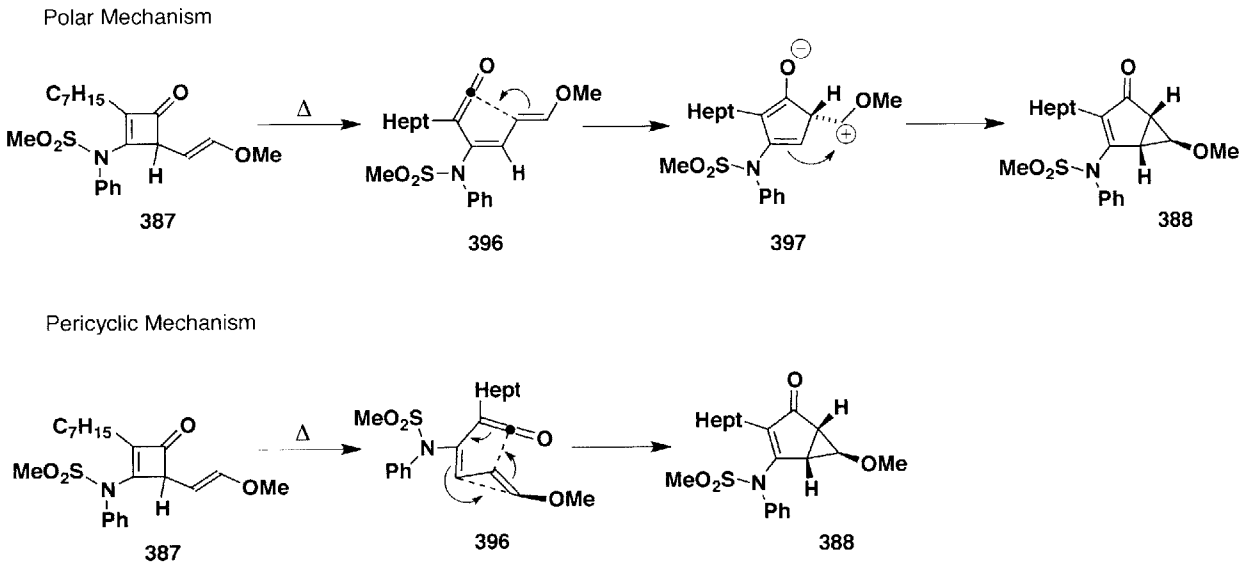
[189] Schöllkopf, U.; Paust, J.; Al-Azrak, A.; Schumacher, H. *Chem. Ber.* **1966**, *99*, 3391-3401.

The conversion of vinylcyclobutenone **387** to bicyclic ketone **388** likely occurs via the intermediacy of dienylketene **396**.[190,191] Scheme 52 outlines two potential mechanisms for this transformation. After electrocyclic ring opening of **387**, the enol ether could add to the carbonyl of the ketene to form zwitterionic intermediate **397**. Cyclization of intermediate **397** would furnish bicyclic ketone **388**. Alternatively, a concerted [4 + 2] cycloaddition could lead to the formation of both rings in one step. Both of these mechanisms are facilitated by the methoxy group, which stabilizes the cation in the polar mechanism and raises the energy of HOMO for the dienophile in the pericyclic mechanism. Without this methoxy group it is unlikely that a bicyclic ketone of type **388** would form during the benzannulation. Given that most of our benzannulations do not utilize vinylketenes that possess a methoxy group this position it is not surprising that we have not observed the formation of bicyclic side products, such as **388**, in previous reactions.



398

Scheme 52

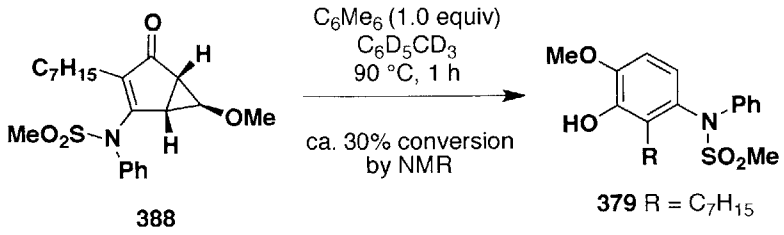


Additional experiments demonstrated that the ratio of phenol **379** and bicyclic ketone **388** vary with reaction time. The longer we heated the crude benzannulation mixture, the greater the

[190] For early examples of the formation of bicyclic ketones from dienylketenes, see: (a) Hart, H.; Collins, P. M.; Waring, A. J.; *J. Org. Chem.* **1966**, *88*, 1005-1013. (b) Griffiths, J.; Hart, H. *J. Am. Chem. Soc.* **1968**, *90*, 3297-3298. (c) Quinkert, G. *Angew. Chem. Int. Ed.* **1972**, *11*, 1072-1087.

[191] Dötz, K. H.; Mühlemeier, J.; Trenkle, B. *J. Organomet. Chem.* **1985**, *289*, 257-262.

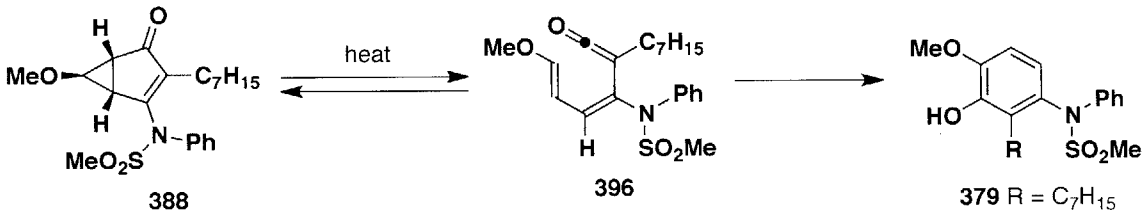
ratio of the desired phenol **379** to the side product **388**. We also found that heating bicyclic side product alone in toluene led to the formation of the desired phenol.



(96)

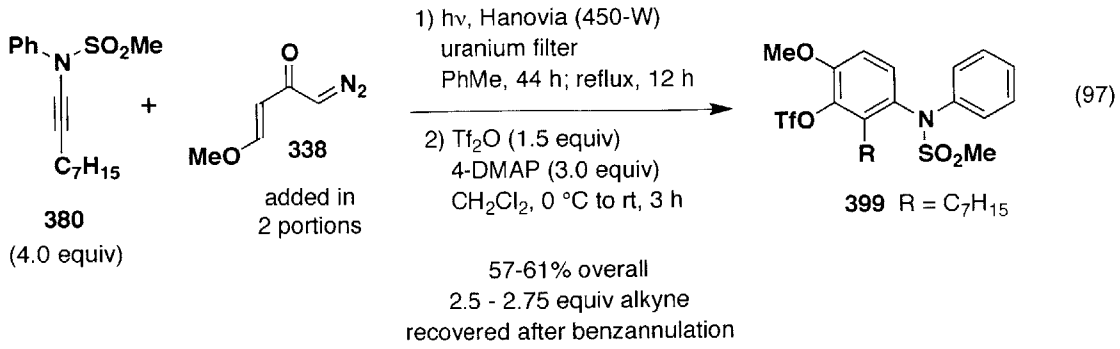
Based on these results, we concluded that the formation of bicyclic ketone **388** is reversible. Heating **388** affords dienylketene **396** that closes to form ketone **388** again or undergoes 6-electron electrocyclic ring closure to form the desired phenol. We therefore speculated that prolonged heating of the reaction mixture after irradiation would lead to exclusive formation of the desired phenol.

Scheme 53



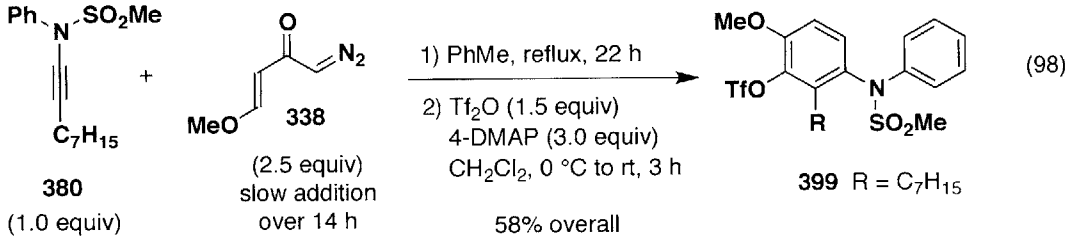
This hypothesis proved to be correct; eq 91 shows our optimized benzannulation conditions. Irradiation with portion-wise addition[192] of diazo ketone **338** furnishes a mixture of the intermediate cyclobutenone and the desired phenol. Heating the reaction mixture for 12 h after irradiation leads to exclusive formation of the desired phenol. Subsequent triflation of the phenol affords triflate **399** in 57-61% overall yield over two steps.[193] It should be noted that we recover most of the unreacted ynamide after the benzannulation.

[192] Adding the diazo ketone in portions results in a modest increase in yield. This procedure is used to limit the concentration of the intermediate vinylketene.
[193] We found that triflation of the product facilitates purification.



(97)

We also demonstrated that this benzannulation could be initiated via a thermal Wolff rearrangement. The slow addition of an excess of diazo ketone **338** to a solution of ynamide **380** in toluene at reflux led to the formation of the desired phenol. Triflation then furnished the product (**399**) in 58% overall yield over two steps (eq 98).



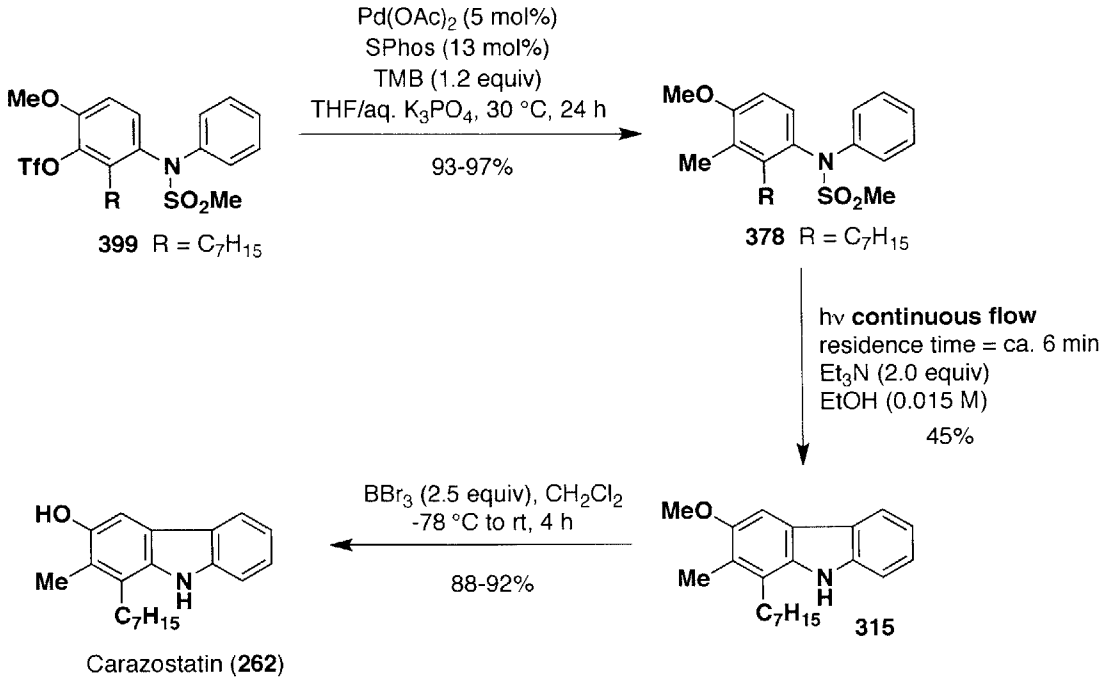
(98)

Completing the Synthesis of Carazostatin and the Formal Synthesis of Carbazoquinocin C

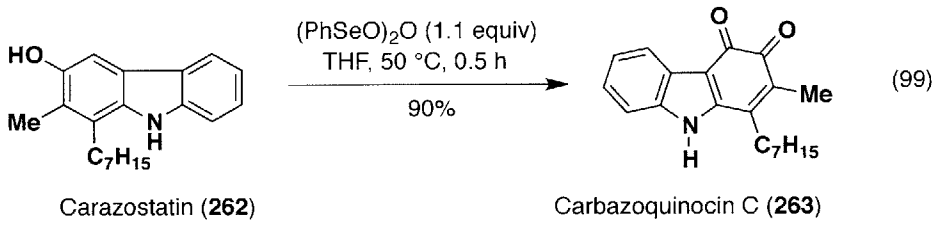
Scheme 46 illustrates the final steps of our synthesis of carazostatin. Suzuki reaction of the triflate **399** installs the methyl group. The photochemical cyclization of **378** furnishes carbazole **315** in 45% yield. Deprotection of the methyl ether with boron tribromide in dichloromethane affords carazostatin (**262**) in 88-92% yield. We synthesized more than 180 mg of the natural product in our largest single run. The spectral data we obtained for our synthetic sample of carazostatin closely matches that reported in original isolation paper.[136a,194]

[194] See experimental section for a side-by-side comparison of the spectral data.

Scheme 54



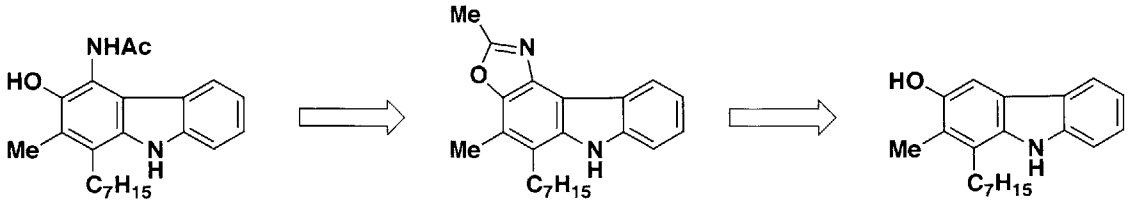
Our synthesis of carazostatin furnishes the natural product in just six steps and ca. 18% overall yield from *N*-phenylmethanesulfonamide. This also completes a formal synthesis carbazoquinocin C, which Hibino[145] synthesized from carazostatin in 95% yield using $(PhSeO)_2$. We repeated the reaction based on the procedure reported by Hibino and obtained carbazoquinocin C in 90% yield from carazostatin.



Efforts Directed Toward the Total Synthesis of Antiostatin A_4

As discussed previously, we hoped to synthesize antiostatin A_4 via the hydrolysis of a benzoxazole. Based on prior work by Moody (vide infra) we anticipated that the necessary oxazole (**339**) could be synthesized from carazostatin (**262**). Scheme 55 outlines our plan.

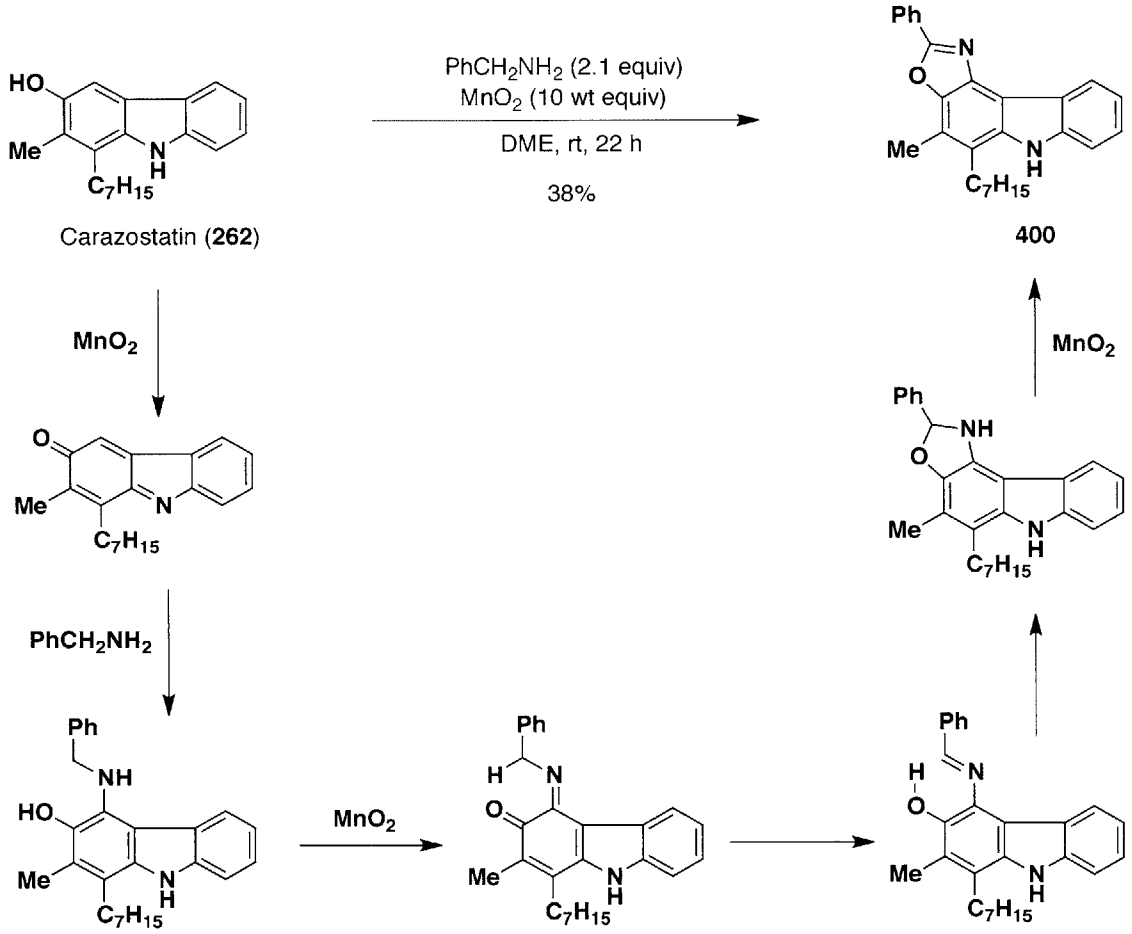
Scheme 55



Antiostatin A_4 (**264**) **339** Carazostatin (**262**)

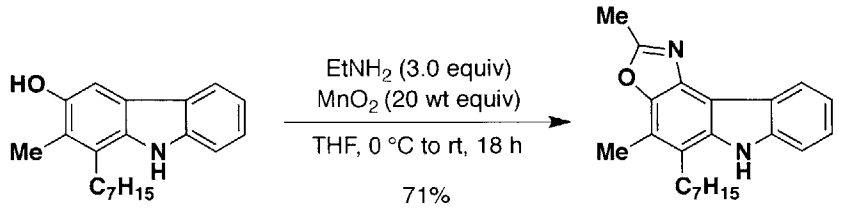
Moody et al. reported[138b] that treating carazostatin with MnO_2 and benzylamine affords benzoxazole **370** in 38% yield. Scheme 56 shows this reaction and the mechanism proposed by Moody.

Scheme 56



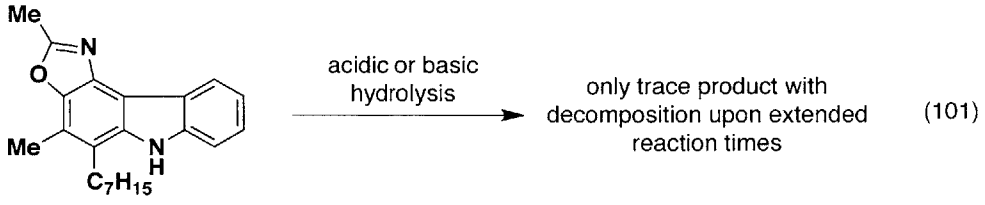
Carazostatin (**262**) **400**

We hoped to utilize a modified version of this protocol to generate the methyl-substituted benzoxazole we required for the synthesis of antiostatin A_4. We found that treatment of carazostatin (**262**) with MnO_2 and ethylamine affords oxazole **339** in 71% yield (eq 100).



Carazostatin (**262**) **339** (100)

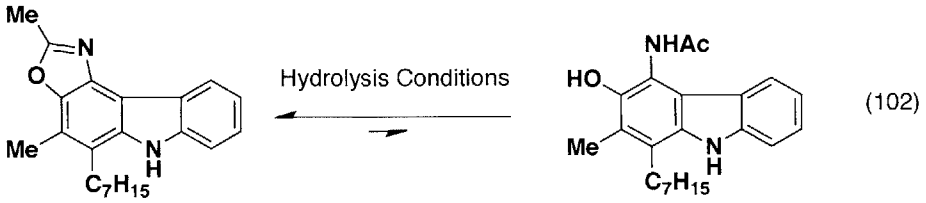
All that remained to complete the total synthesis of antiostatin A_4 was the hydrolysis of oxazole **339**. We attempted to hydrolyze **339** under a variety of acidic[157a,c] conditions with little success. No reaction was observed when the oxazole **339** was mixed with TFA in aq THF at rt. Reactions performed in aq dioxane using TFA or HCl at temperatures >80 °C led to less than 10% conversion of the starting material to the desired product. These reactions also resulted in a significant amount of decomposition. Heating **339** at 40 °C in a 1:9 mixture of 1 M HCl and EtOH for 18 h resulted in only trace formation of the desired product. Mostly starting material remained. Increased reaction time or temperature using these conditions resulted in less than 5% conversion of the starting material to the desired product and decomposition was observed upon prolonged heating. Hydrolysis under basic conditions (e.g., aq KOH-MeOH)[157b,e] afforded some of the desired product, but these reactions mostly led to decomposition.



339 (101)

Our inability to access antiostatin A_4 via the hydrolysis of benzoxazole **339** may be due to the reversibility of the process. The formation of benzoxazoles from *N*-acyl 2-aminophenols

occurs upon heating with acid,[195] but many reactions require the removal of water. Moore et al. observed that simply heating a sterically crowded *N*-acyl 2-aminophenol at reflux in ethanol forms the benzoxazole.[196] We speculate that oxazole **339** experiences fewer non-bonded interactions than the corresponding *N*-acyl 2-aminophenol, so its formation is favored under the reaction conditions.



339 Antiostatin A_4 (**263**) (102)

While we were unable to complete the total synthesis of antiostatin A_4, we still achieved a formal synthesis by intersecting the route reported by Knölker[149] via compound **315**.

Summary

We developed a tandem benzannulation-cyclization strategy for the synthesis of highly substituted carbazoles. This efficient strategy requires only three steps to furnish a polysubstituted carbazole from *N*-phenylmethanesulfonamide. We utilized this strategy to achieve a six-step synthesis of the biologically active carbazole alkaloid, carazostatin. We also completed formal syntheses of the alkaloids carbazoquinocin C and antiostatin A_4.

[195] For example, see: Perry, R. J.; Wilson, B. D.; Miller, R. J. *J. Org. Chem.* **1992**, *57*, 2883-2887.
[196] For an example of this sort of cyclization, see: Pearce, D. S.; Lee, M.-S.; Moore, H. W. *J. Org. Chem.* **1974**, *39*, 1362-1368.

Part IV

Experimental Procedures

General Experimental Procedures

General Procedures. All reactions were performed in flame-dried or oven-dried glassware under a positive pressure of argon. Reactions were magnetically stirred unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred by syringe or cannula and introduced into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated by rotary evaporation at ca. 20 mmHg and then at 0.1 mmHg (vacuum pump) unless otherwise indicated. Thin layer chromatography was performed on EMD precoated glass-backed silica gel 60 F-254 0.25 mm plates. Column chromatography was performed on Sorbet Technologies Standard Grade silica gel 60 (230-400 mesh) or on EMD Chromatographic Grade basic alumina (80-325 mesh). FEP tubing, nuts, ferrules, and adaptors for the continuous-flow reactor were all purchased from IDEX Health & Science. For a detailed description of the reactor construction see Part I, Chapter 3 of this thesis.

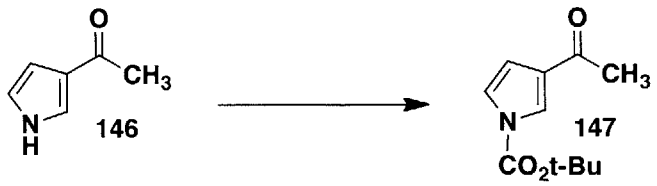
Materials. Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane and tetrahydrofuran were purified by pressure filtration through activated alumina. Toluene was purified by pressure filtration through activated alumina and Cu(II) oxide. Triflic anhydride was distilled under argon from P_2O_5. Acetonitrile, 1,2-dichloroethane, 1,1,1,3,3,3-hexamethyldisilazane, triethylamine, and 2,2,2-trifluoroethyl trifluoroacetate were distilled under argon from CaH_2. DMF was stirred over CaH_2 for 24 h and then filtered and distilled neat under argon at 20 mmHg onto molecular sieves (4 Å). But-2-yn-1-ol was distilled under argon from potassium carbonate at 50 mmHg. Formic acid was distilled under argon at 40 mmHg. *trans*-4-Methoxy-3-butenone was distilled under argon at 12 mmHg. Isopropenylacetylene and allyl bromide were filtered through a plug of activated alumina prior to use. Triphenylphosphine and 4-nitrobenzoyl chloride were recrystallized from boiling hexanes. N-Bromosuccinimide was recrystallized from boiling water. 4-DMAP was recrystallized from boiling toluene. Copper (I) iodide was extracted with THF from 24 h in a Soxhlet extractor and then dried under vacuum (0.1 mmHg). LiCl was dried under vacuum (0.1 mmHg) at 150 °C for 24 h before use. MnO_2 was dried under vacuum (0.3 mmHg) at 125 °C for 20 h before use. *iso*-Propylmagnesium bromide was prepared from magnesium turnings and 2-bromopropane.[197] *n*-Butyllithium and *i*-propylmagnesium bromide were titrated using menthol in

[197] Jensen, A. E.; Dohle, W.; Sapountzis, I.; Lindsay, D. M.; Vu, V. A.; Knochel, P. *Synthesis* **2002**, 565-569.

THF with 1,10-phenanthroline as an indicator.[198] Methanesulfonyl azide was prepared from methanesulfonyl chloride and sodium azide.[72]

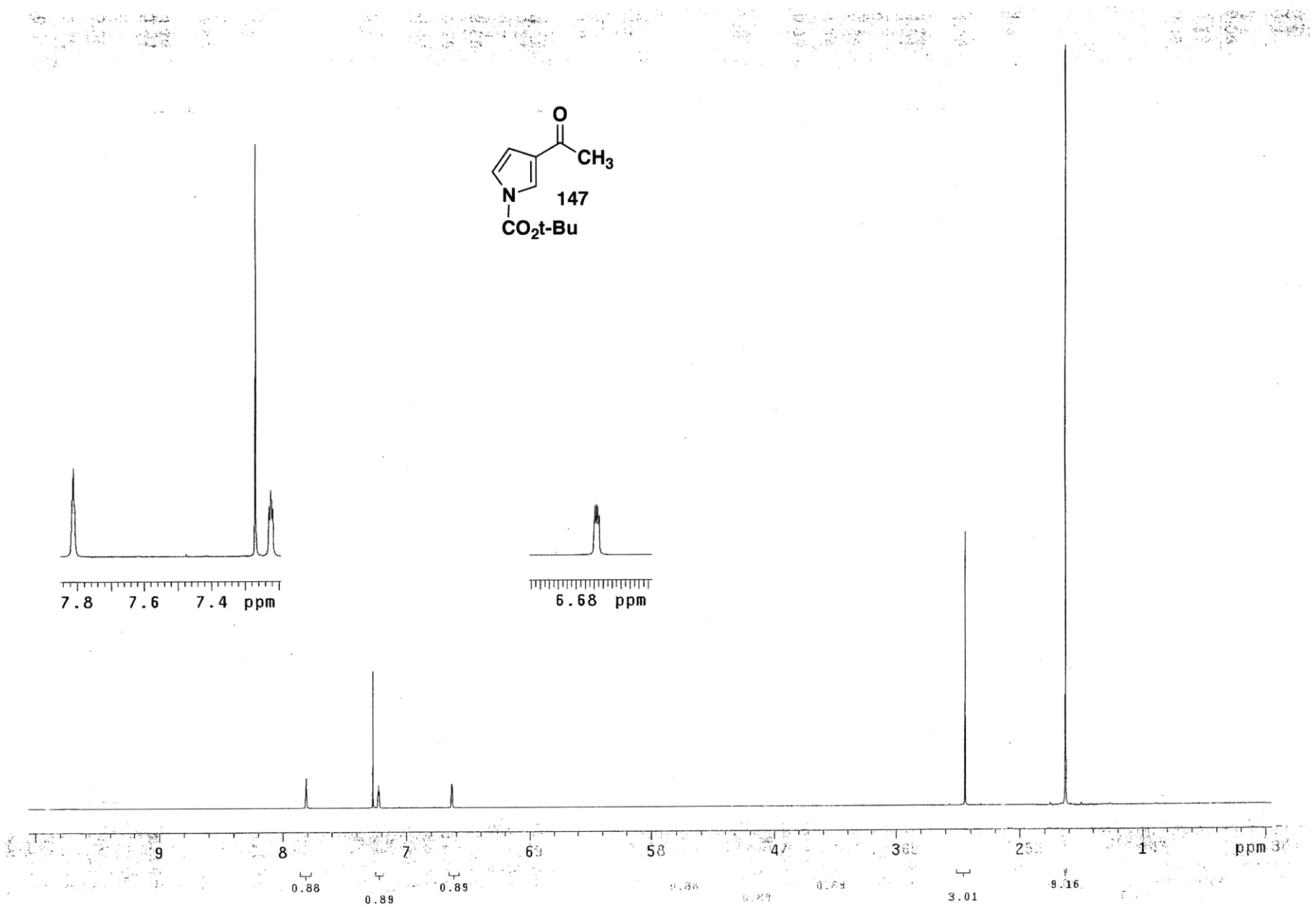
Instrumentation. Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained using a Perkin Elmer 2000 FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on Varian XL-300 (300 MHz), and Varian Inova 500 (500 MHz). ^{1}H NMR chemical 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 recorded on Varian XL-300 (75 MHz), and Varian Inova 500 (125 MHz). ^{13}C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the central peak of $CHCl_3$ at 77.23 ppm used as a standard). ^{31}P NMR were recorded on a Varion XL-300 (120 MHz) spectrometer. ^{31}P NMR chemical shifts are expressed in parts per million (δ) downfield from an external 85% H_3PO_4 standard (0.0 ppm). High resolution mass spectra (HRMS) were measured on a Bruker Daltonics APEXII 3 telsa Fourier transform mass spectrometer. Ultraviolet-visible spectra (UV-VIS) were recorded with an Agilent 8453 spectrophotometer, and absorptions are reported in nanometers (nm). Elemental analyses were performed by Atlantic Microlab, Inc.: Norcross, Georgia.

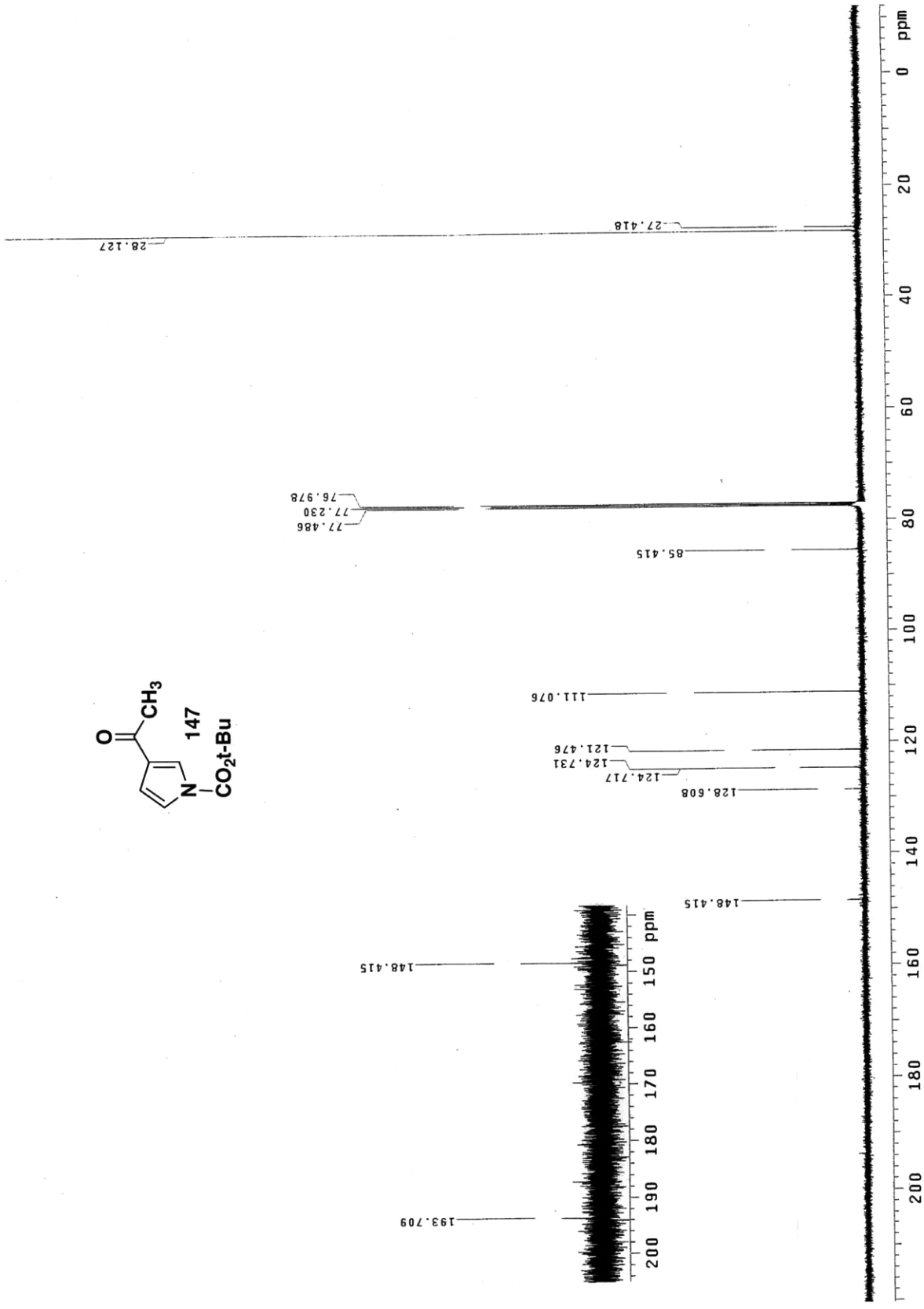
[198] For the titration of *n*-butyllithium see: (a) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165-167. (b) Ellison, R. A.; Griffin, R. ; Kotsonis, F. N. *J. Organomet. Chem.* **1972**, *36*, 209-213. For the titration of *i*-PrMgBr see: (c) Lin, H.-S.; Paquette, L. *Synth. Commun.* **1994**, *24*, 2503-2505.

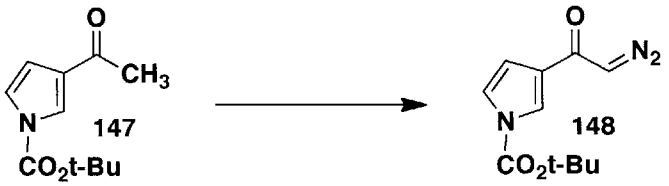


1-(*tert*-Butoxycarbonyl)-3-acetylpyrrole (147). A 50-mL, pear flask equipped with a rubber septum and argon inlet needle was charged with pyrrole **146**[199] (0.510 g, 4.67 mmol, 1.0 equiv) and 9 mL of CH_2Cl_2. The resulting solution was cooled to 0 °C and a solution of Boc_2O (1.05 g, 4.79 mmol, 1.1 equiv) in 7.5 mL of CH_2Cl_2 was added via cannula over 15 min. After 10 min, a solution of 4-DMAP (0.085 g, 0.70 mmol, 0.15 equiv) and Et_3N (0.67 mL, 4.79 equiv, 1.1 equiv) in 6.5 mL of CH_2Cl_2 was added dropwise via cannula over 20 min. The reaction mixture was stirred at 0 °C for 2.5 h and then washed with two 25-mL portions of water, dried over $MgSO_4$, filtered, and concentrated to yield 1.07 g of a yellow oil. Column chromatography on 50 g of silica gel (elution with 7% EtOAc-hexanes) furnished 0.952 g (97%) of pyrrole **147** as a white solid: mp 69-71 °C; IR (neat) 2977, 1752, 1673, 1494, 1396, 1280, 1150 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.80-7.83 (m, 1H), 7.21-7.24 (m, 1H), 6.62-6.65 (m, 1H), 2.45 (s, 3H), 1.63 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.7, 148.4, 128.6, 124.7, 121.5, 111.1, 85.4, 28.1, 27.4; HRMS-ESI (*m/z*) [M + Na] calculated for $C_{11}H_{15}NO_3$: 232.0944, found: 232.0945.

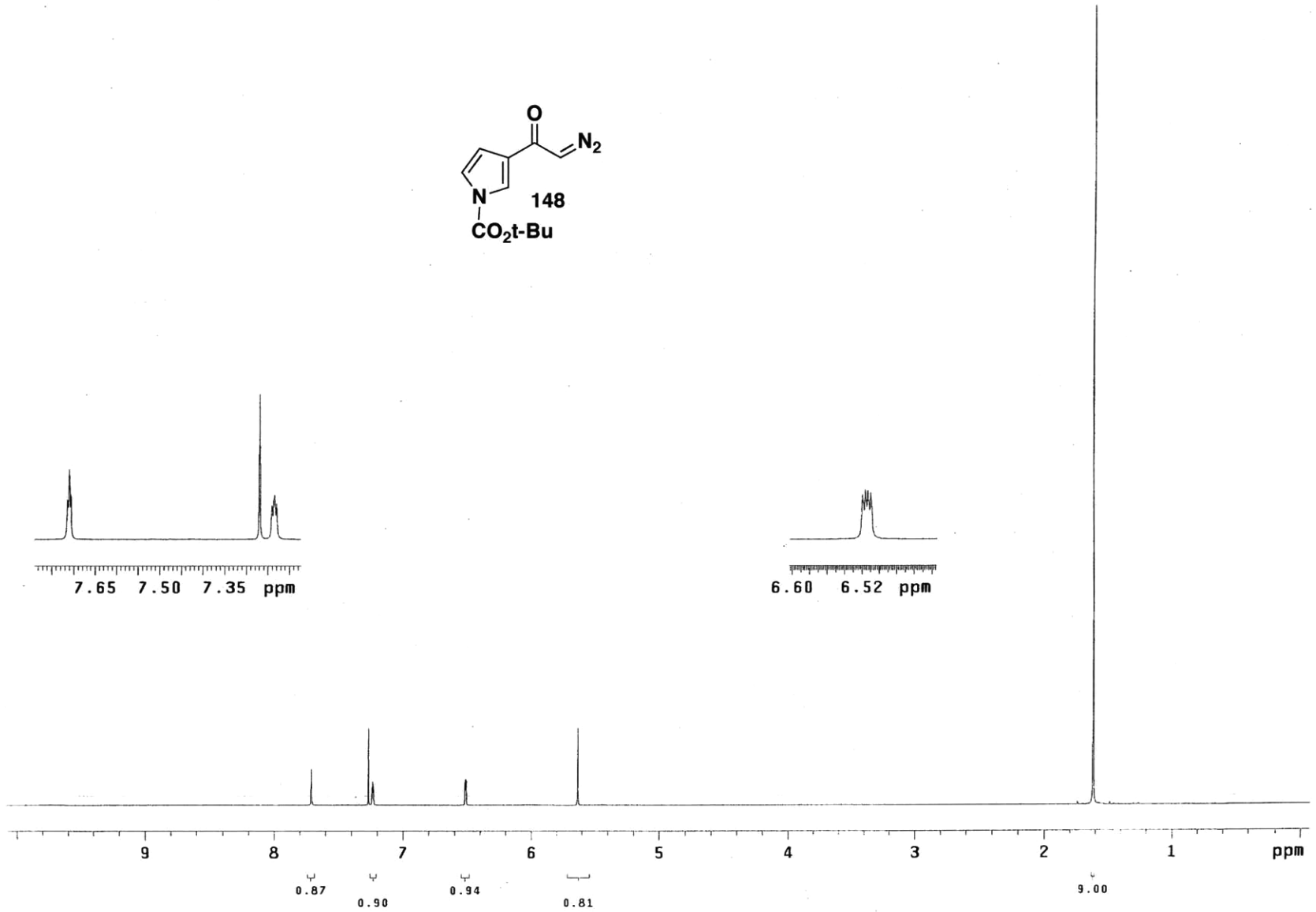
[199] Synthesized according to the route described in: By He, Y.; Lin, M.; Li, Z.; Liang, X.; Li, G.; Antilla, J. C. *Org. Lett.* **2011**, *13*, 4490-4493.

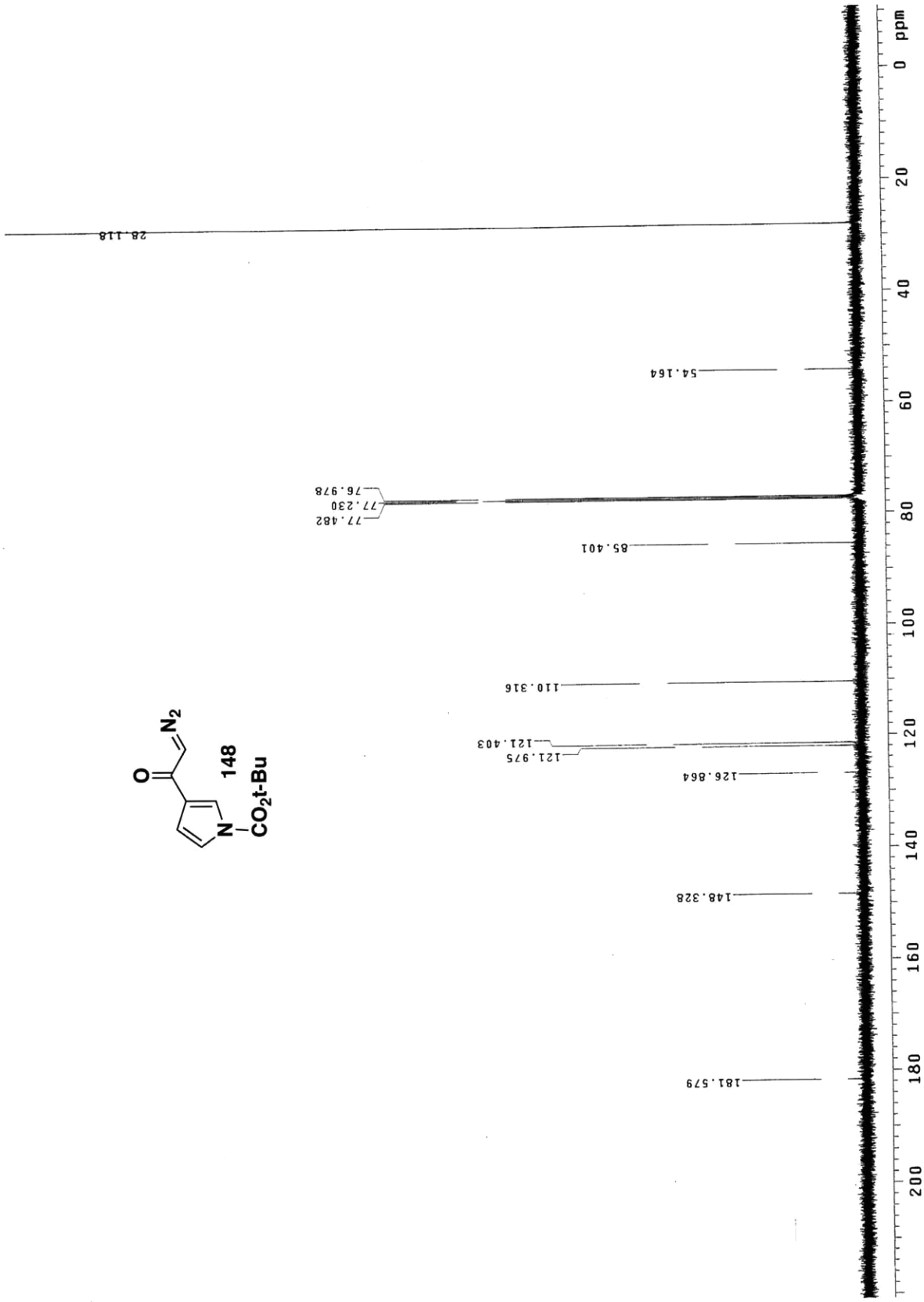

O
CH3
N
147
CO2t-Bu
7.8
7.6
7.4 ppm
6.68 ppm
9
8
7
6
5
4
3
2
1
ppm
0.88
0.89
0.89
3.01
9.16

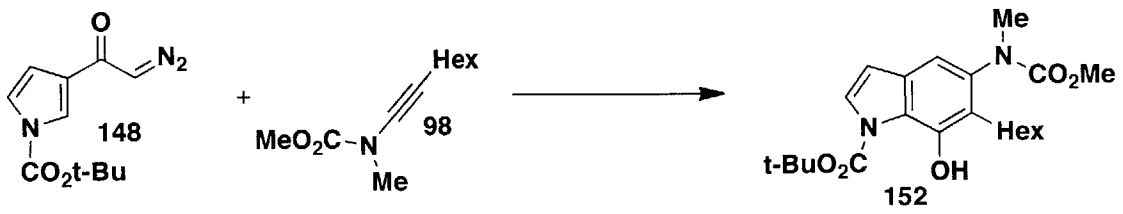

O
CH3
147
N
CO2t-Bu
28.127
27.418
77.486
77.230
76.978
85.415
111.076
121.476
124.731
124.717
128.608
148.415
193.709
148.415
ppm



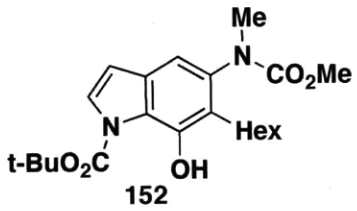
1-(*tert*-Butoxycarbonyl)-3-diazoacetylpyrrole (148). A 100-mL, three-necked, round-bottomed flask equipped with two rubber septa, an argon inlet adapter, and a thermocouple was charged with a solution of 1,1,1,3,3,3-hexamethyldisilazane (1.15 mL, 5.45 mmol, 1.2 equiv) in 12 mL of THF and then cooled at 0 °C while *n*-BuLi (2.64 M in hexane, 1.9 mL, 5.02 mmol, 1.1 equiv) was added dropwise over 5 min. After 10 min, the resulting solution was cooled at -78 °C while a solution of pyrrole **147** (0.951 g, 4.55 mmol, 1.0 equiv) in 12 mL of THF was added dropwise via cannula over 35 min (0.8 mL THF wash). After 45 min, 2,2,2-trifluoroethyl trifluoroacetate (0.73 mL, 5.45 mmol, 1.2 equiv) was added rapidly by syringe. After 10 min, the reaction mixture was diluted with 25 mL of 1 M aq HCl solution and 30 mL of Et_2O. The aqueous phase was extracted with two 15-mL portions of Et_2O, and the combined organic phases were washed with 30 mL of brine, dried over Na_2SO_4, filtered, and concentrated to give 1.62 g of an orange oil which was immediately dissolved in 12 mL of CH_3CN and transferred to a 100-mL pear flask equipped with a rubber septum and argon inlet needle. Water (0.08 mL, 4.43 mmol, 1.0 equiv) and Et_3N (0.95 mL, 6.82 mmol, 1.5 equiv) were added, and a solution of methanesulfonyl azide (0.880 g, 7.27 mmol, 1.6 equiv) in 14 mL of CH_3CN was added dropwise via cannula over 30 min (1 mL CH_3CN wash). The resulting solution was stirred at room temperature for 3 h and then diluted with 50 mL of Et_2O and washed with three 20-mL portions of 10% aq NaOH solution and 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated to afford 1.199 g of a yellow oil. Column chromatography on 53 g of silica gel (gradient elution with 10-20% EtOAc-hexanes) furnished 1.004 g (94%) of diazo ketone **148** as a yellow solid: mp 58-59 °C; IR (neat) 3124, 2982, 2103, 1752, 1617, 1496, 1396, 1336, 1255, 1154 cm^{-1}; UV (CH_3CN) λ_{max}, nm (ε) 294 (20642), 245 (19339), 229 (22817); ^1H NMR (500 MHz, $CDCl_3$) δ 7.70-7.72 (m, 1H), 7.23-7.25 (m, 1H), 6.51-6.52 (m, 1H), 5.63 (s, 1H), 1.62 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.6, 148.3, 126.9, 122.0, 121.4, 110.3, 85.4, 54.2, 28.1; HRMS-ESI (*m/z*) [M + Na] calculated for $C_{11}H_{13}N_3O_3$: 258.0849, found: 258.0848.


O
N2
N
148
CO2t-Bu
7.65 7.50 7.35 ppm
6.60 6.52 ppm
9 8 7 6 5 4 3 2 1 ppm
0.87
0.90
0.94
0.81
9.00


28.118
54.164
76.978
77.230
77.482
85.401
110.316
121.403
121.975
126.864
148.328
181.579
0 ppm
20
40
60
80
100
120
140
160
180
200
148
CO_2t-Bu



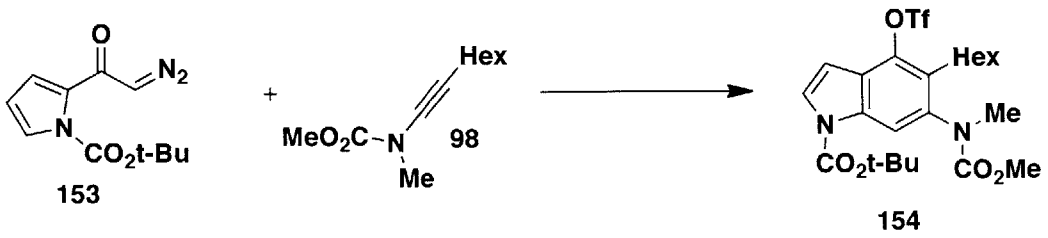
1-(*tert*-Butoxycarbonyl)-6-hexyl-7-hydroxy-5-(N-(methoxycarbonyl)-N-(methyl)amino)indole (152). A 20-cm quartz tube (7 mm I.D., 10 mm O.D.) equipped with a rubber septum and argon inlet needle was charged with diazo ketone **148** (0.135 g, 0.574 mmol, 1.1 equiv), ynamide **98**[62b] (0.103 g, 0.522 mmol, 1.0 equiv), and 2.2 mL of CH_2Cl_2. The yellow solution was degassed for 10 min with a stream of argon. The quartz tube was positioned ca. 20 cm from a Hanovia 450W lamp (quartz immersion well, cooled by recirculating tap water) and irradiated under argon at 25 °C for 8 h. The reaction mixture was transferred to a 25-mL pear flask with the aid of two 4-mL portions of CH_2Cl_2 and concentrated to afford 0.222 g of an orange oil. This material was dissolved in 5.2 mL of toluene, the flask was equipped with a stir bar and cold-finger condenser, and the reaction mixture was heated at reflux for 2 h. The resulting mixture was concentrated to afford 0.234 g of an orange oil. Column chromatography on 25 g of silica gel (gradient elution with 10-20% EtOAc-hexanes) furnished 0.084 g (40%) of phenol **152** as a yellow oil: IR (neat) 3162 (broad), 2930, 2857, 1708, 1688, 1584, 1452, 1380, 1353, 1242, 1156, 1120 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 88:12 mixture of rotamers δ 11.13 and 11.09 (rotamers, s, 1H), 7.36-7.42 (m, 1H), 6.88 and 6.82 (rotamers, s, 1H), 6.43-6.49 (m, 1H), 3.80 and 3.62 (rotamers, s, 3H), 3.24 and 3.22 (rotamers, s, 3H), 2.53-2.68 (m, 2H), 1.65 (s, 9H), 1.50-1.60 (m, 2H), 1.36-1.45 (m, 2H), 1.27-1.36 (m, 4H), 0.90 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 152.7, 143.6, 139.5, 131.1, 126.7, 124.8, 123.3, 110.7, 109.4, 86.3, 53.0, 38.9, 32.0, 30.2, 29.4, 28.2, 26.6, 22.8, 14.3; HRMS-ESI (*m/z*) [M + Na] calculated for $C_{22}H_{32}N_2O_5$, 427.2203; found 427.2208.


Me
N
CO2Me
N
Hex
t-BuO2C
OH

152

11
10
9
8
7
6
5
4
3
2
1
ppm
0.93
0.94
0.90
0.96
2.98
2.97
2.00
2.03
3.90
8.92
2.00
2.78

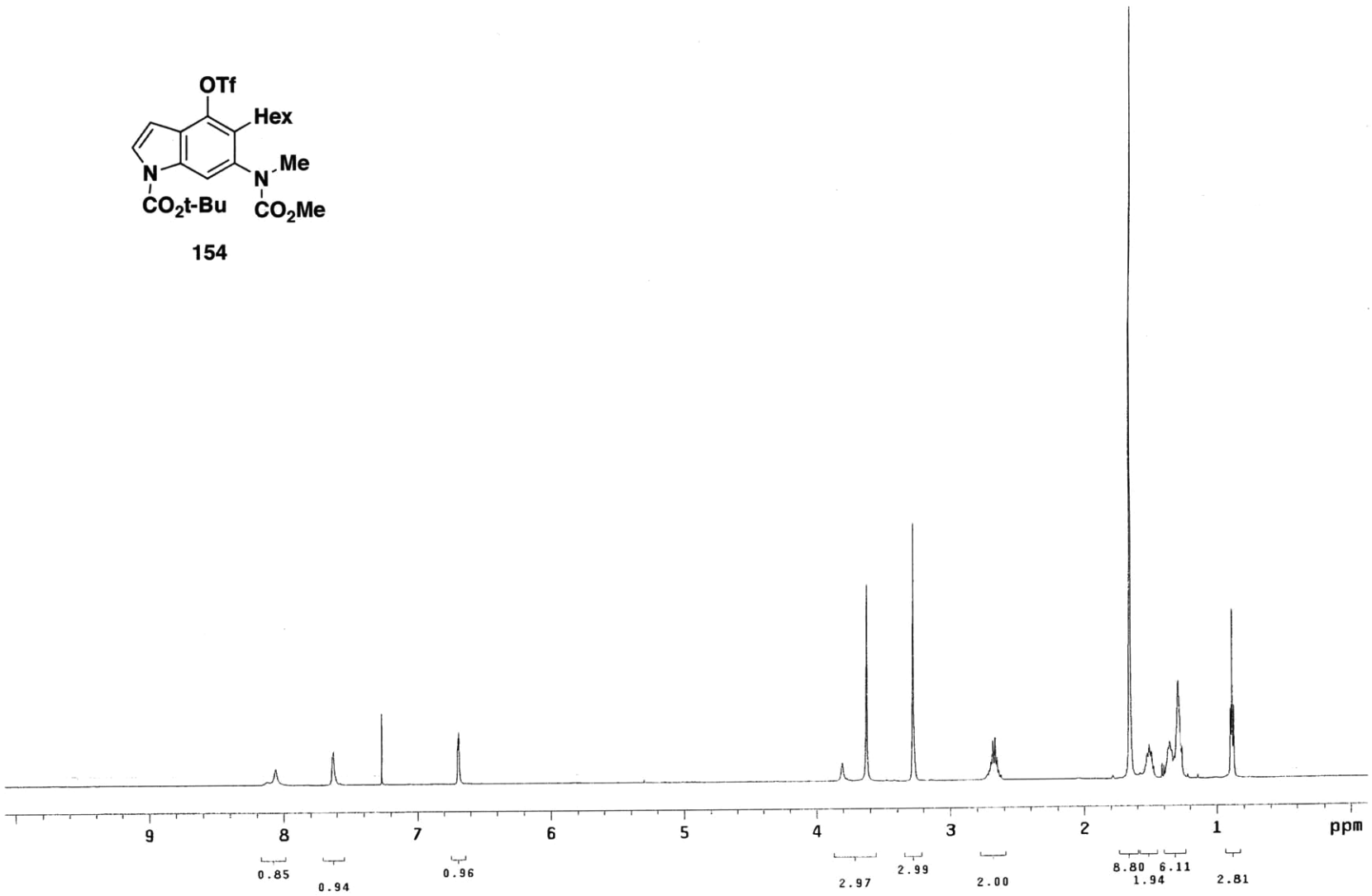
Me
N
CO2Me
Hex
N
t-BuO2C
OH
152
157.030
152.684
143.553
139.470
131.090
126.686
124.768
123.266
110.674
109.358
86.342
77.485
77.230
76.975
52.975
38.941
32.002
30.157
29.425
28.209
26.676
22.844
14.331
200
180
160
140
120
100
80
60
40
20
0
ppm



5-Hexyl-4-(trifluoromethylsulfonyloxy)-6-(N-(diethylphosphoryl)-N-(benzyl)amino)indole (154). A 20-cm quartz tube (7 mm I.D., 10 mm O.D.) equipped with a rubber septum and argon inlet needle was charged with diazo ketone **153**[72a] (0.137 g, 0.582 mmol, 1.1 equiv), ynamide **98**[62b] (0.103 g, 0.522 mmol, 1.0 equiv), and 2.2 mL of CH_2Cl_2. The yellow reaction mixture was degassed via three freeze-pump-thaw (-196 °C, 0.05 mmHg) cycles. The quartz tube was positioned ca. 20 cm from a Hanovia 450W lamp (quartz immersion well, cooled by recirculating tap water) and irradiated under argon at 25 °C for 5.5 h. The reaction mixture was transferred to a 25-mL pear flask with the aid of two 4-mL portions of CH_2Cl_2 and concentrated to afford 0.249 g of a dark orange oil. This material was dissolved in 5.2 mL of toluene, the flask was equipped with a stir bar and cold-finger condenser, and the reaction mixture was heated at reflux for 2 h. The resulting mixture was concentrated to afford 0.262 g of a dark orange oil. Column chromatography on 30 g of silica gel (elution with 15% EtOAc-hexanes) furnished 0.152 g of ca. 85-90% pure phenol as an orange oil.

A 25-mL pear flask equipped with a rubber septum and argon inlet needle was charged with phenol (0.152 g, 1.0 equiv), 4-DMAP (0.092 g, 0.753 mmol, 2.0 equiv), and 2.7 mL of CH_2Cl_2. The orange solution was cooled to 0 °C and triflic anhydride (0.07 mL, 0.416 mmol, 1.1 equiv) was added dropwise by syringe over ca. 2 min. The reaction mixture was allowed to warm to rt, stirred for 2 h, and then diluted with 20 mL of CH_2Cl_2 and washed with two 10-mL portions of 1 M HCl solution. The combined aqueous layers were extracted with 10 mL of CH_2Cl_2, and the combined organic layers 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 0.187 g of orange oil. Column chromatography on 28 g of silica gel (elution with 10% EtOAc-hexanes) afforded 0.160 g (57% over two steps from the ynamide) of triflate **154** as an orange oil: IR (neat) 2958, 2932, 2860, 1744, 1716, 1529, 1449, 1409, 1373, 1347, 1304, 1249, 1215, 1154 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 80:20 mixture of rotamers δ 8.12 and 8.06 (rotamers, s, 1H), 7.57-7.67 (m, 1H), 6.65-6.72 (m, 1H), 3.81 and 3.63 (rotamers, s, 3H), 3.29 (s, 3H), 2.61-2.76 (m, 2H), 1.66 (s, 9H),

1.46-1.57 (m, 2H), 1.32-1.40 (m, 2H), 1.25-1.32 (m, 4H), 0.89 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 149.2, 139.7, 139.5, 135.0, 129.0, 128.1, 124.0, 118.9 (q, J = 318 Hz), 115.6, 103.9, 85.0, 53.2, 39.1, 31.8, 29.8, 29.8, 28.3, 26.6, 22.7, 14.2; HRMS-ESI (*m/z*) [M + Na] calculated for $C_{23}H_{31}F_3N_2O_7S$, 559.1696; found 559.1703.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Hex
N
Me
N
CO2t-Bu
CO2Me
154
9
8
7
6
5
4
3
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ppm
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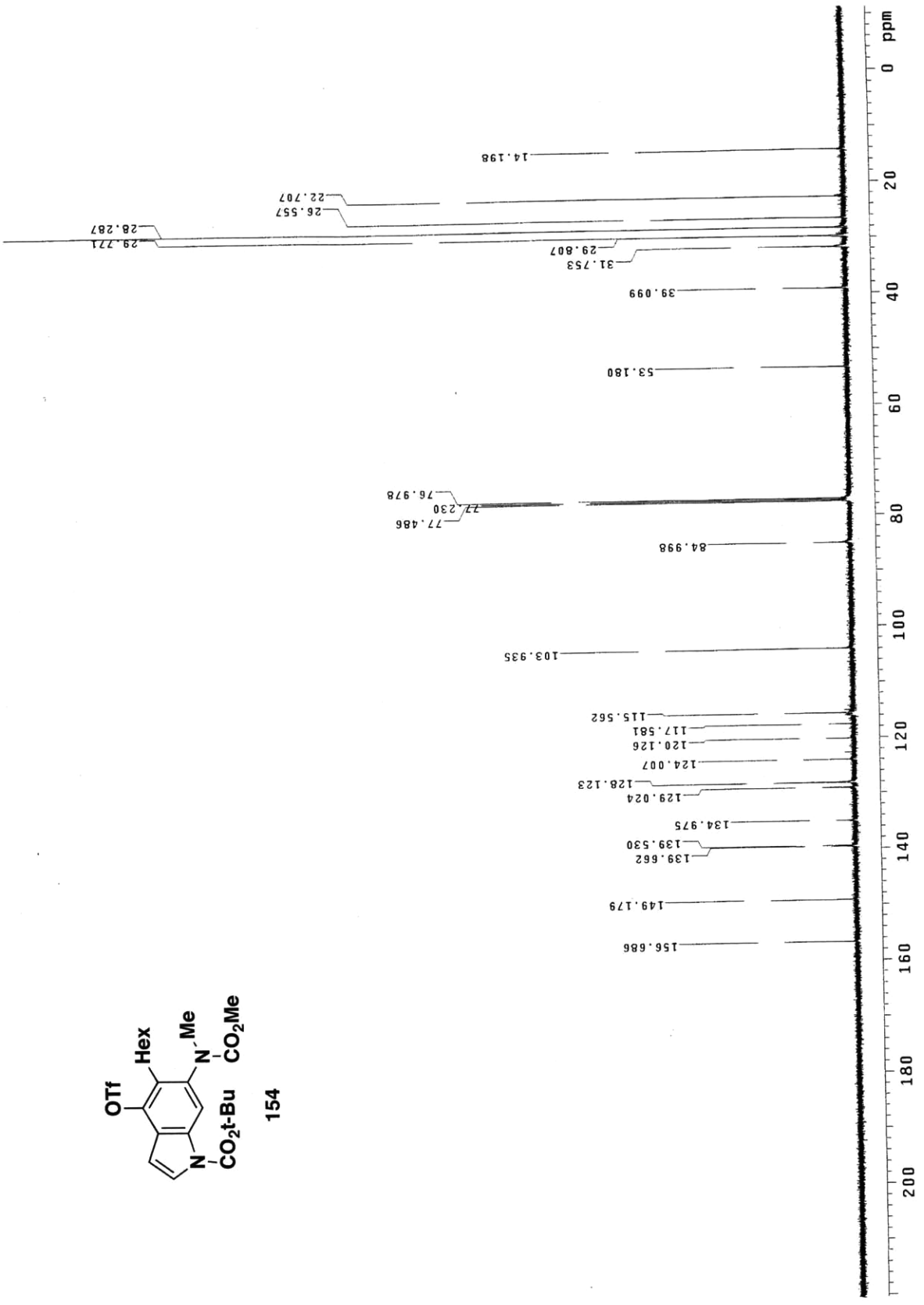
0.94
0.96
2.97
2.99
2.00
8.80
1.94
6.11
2.81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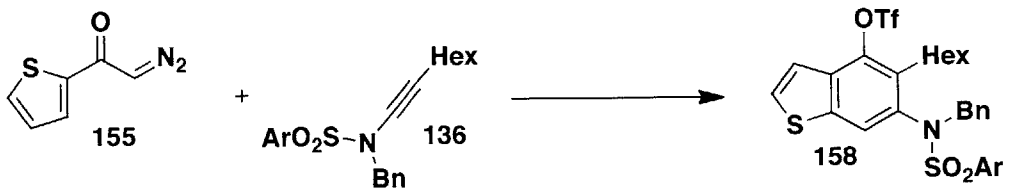
115.562
117.581
120.126
124.007
128.123
129.024
134.975
139.530
139.662
149.179
156.686
0 ppm
20
40
60
80
100
120
140
160
180
200

OTf
Hex
Me
N
CO2Me
CO2t-Bu
N

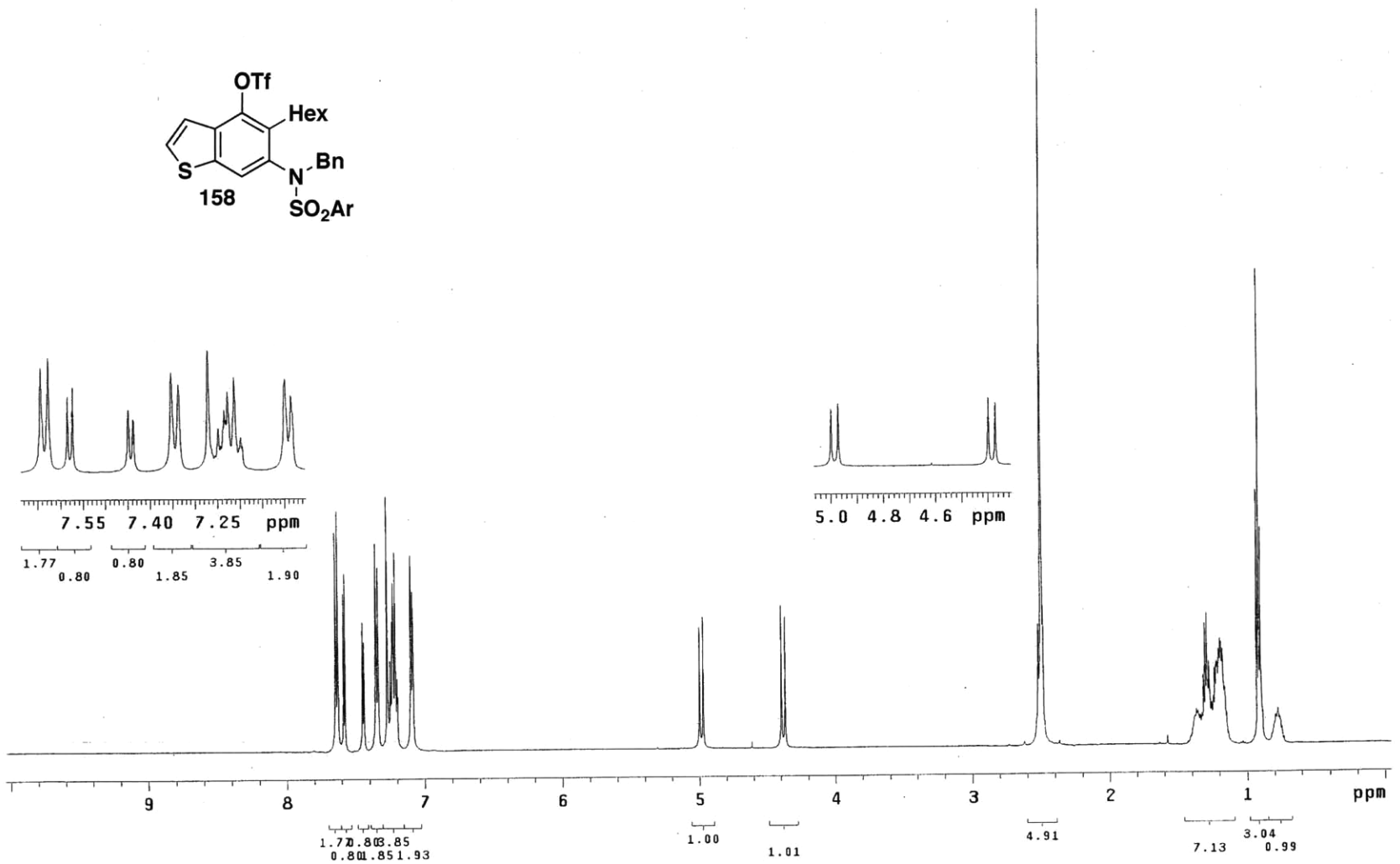
154



5-Hexyl-4-(trifluoromethylsulfonyloxy)-6-(*N*-(*p*-toluenesulfonyl)-*N*-(benzyl)amino)benzo[b]thiophene (158). A 20-cm quartz tube (5 mm I.D., 7 mm O.D.) equipped with a rubber septum and argon inlet needle was charged with diazo ketone **155**[74] (0.063 g, 0.414 mmol, 1.1 equiv), ynamide **136**[64a] (0.134 g, 0.363 mmol, 1.0 equiv), and 1.6 mL of CH_2Cl_2. The yellow reaction mixture was degassed via three freeze-pump-thaw (-196 °C, 0.05 mmHg) cycles. The quartz tube was positioned ca. 20 cm from a Hanovia 450W lamp (quartz immersion well, uranium filter (hν < 330 nm), cooled by recirculating tap water) and irradiated under argon at 25 °C for 50 h. The reaction mixture was transferred to a 25-mL pear flask with the aid of two 4-mL portions of CH_2Cl_2 and concentrated to afford 0.211 g of a red oil. This material was dissolved in 4.0 mL of toluene, the flask was equipped with a stir bar and cold-finger condenser, and the reaction mixture was heated at reflux for 2 h. The resulting mixture was concentrated to afford 0.235 g of a dark red oil. Column chromatography on 20 g of silica gel (elution with 10% EtOAc-hexanes) furnished 0.125 g of ca. 85-90% pure phenol as an orange oil.

A 25-mL pear flask equipped with a rubber septum and argon inlet needle was charged with phenol (0.125 g, 1.0 equiv), 4-DMAP (0.062 g, 0.753 mmol, 2.0 equiv), and 3 mL of CH_2Cl_2. The orange solution was cooled to 0 °C and triflic anhydride (0.05 mL, 0.297 mmol, 1.2 equiv) was added dropwise by syringe over ca. 2 min. The reaction mixture was allowed to warm to rt, stirred for 4 h, and then diluted with 10 mL of CH_2Cl_2 and washed with two 6-mL portions of 1 M HCl solution. The combined aqueous layers were extracted with 10 mL of CH_2Cl_2, and the combined organic layers were washed with 15 mL of satd aq $NaHCO_3$ solution and 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.250 g of orange oil. Column chromatography on 16 g of silica gel (elution with 7% EtOAc-hexanes) afforded 0.117 g (52% over two steps from the ynamide) of triflate **158** as an off-white solid: mp 97-100 °C; IR (neat) 2929, 2858, 1598, 1408, 1350, 1245, 1214, 1163, 1138, 939 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 6.0 Hz, 1H), 7.44 (d, J = 6.0 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.26 (s, 1H), 7.18-7.26 (m, 2H), 7.09 (d, J = 6.5 Hz, 2H), 4.90 (d, J = 13.5 Hz, 1H),

4.38 (d, J = 13.5 Hz, 1H), 2.45-2.56 (m, 2H), 2.50 (s. 3H), 1.12-1.44 (m, 7H), 0.91 (t, 7.3 Hz, 3H), 0.72-0.84 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3, 142.1, 138.8, 136.1, 135.7, 135.0, 134.9, 134.0, 130.2, 129.9, 129.8, 128.8, 128.4, 128.3, 123.8, 120.5, 118.7 (q, J = 318 Hz), 57.1, 31.6, 30.1, 29.0, 27.1, 22.8, 21.8, 14.3; HRMS-ESI (*m/z*) [M + Na] calculated for $C_{29}H_{30}F_3N_2O_5S_3$, 648.1130; found 648.1120.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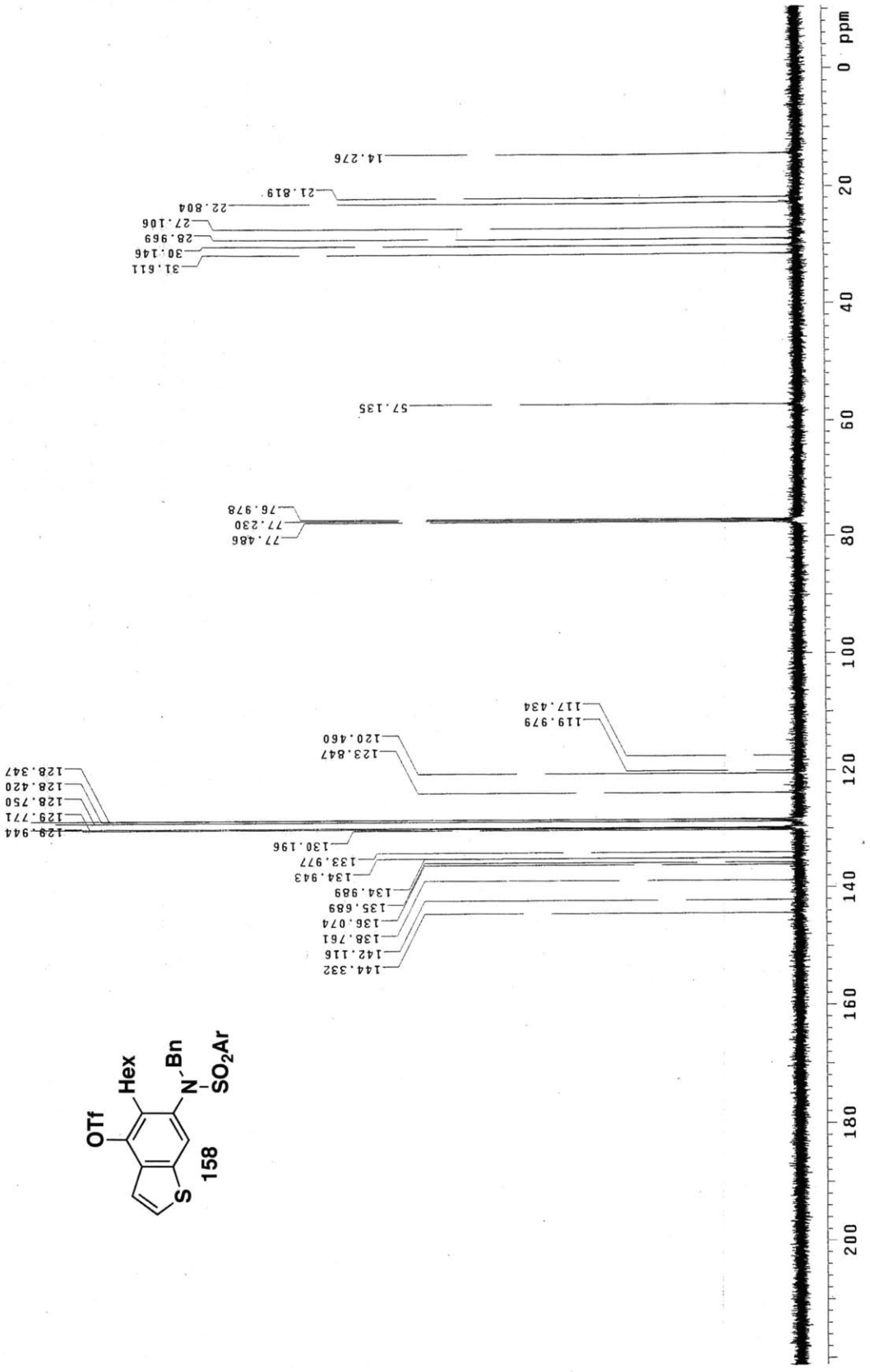
1.01
4.91
7.13
3.04
0.99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134.943
134.989
135.689
136.074
138.761
142.116
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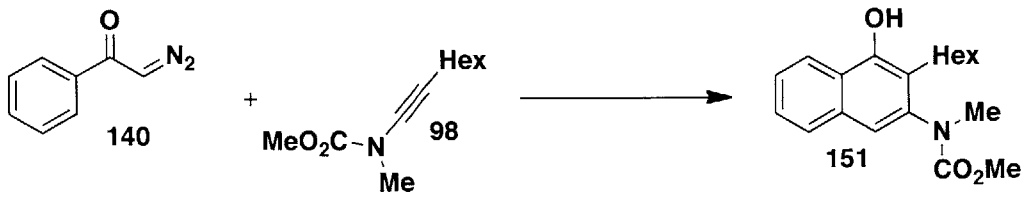
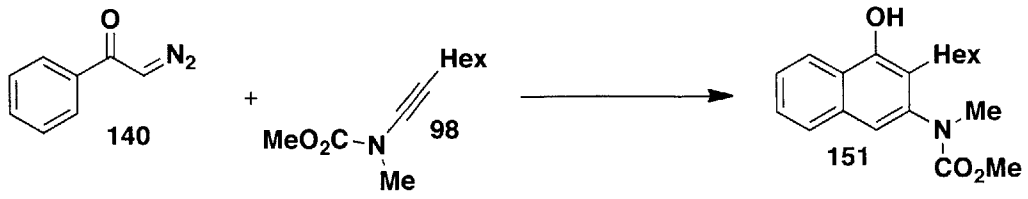


3-[*N*-(Carbomethoxy)-*N*-(methyl)amino]-2-hexyl-naphthalen-1-ol (151). FEP tubing (ca. 440-cm length, 0.030 in. I.D., 0.0625 in. O.D., total internal volume ca. 2.0 mL) was wrapped around a quartz immersion well surrounding a water-jacketed, 450W Hanovia lamp equipped with a Pyrex filter and cooled by recirculating tap water. Approximately 90 cm of tubing was left at either end so that the length wrapped around the well was ca. 260 cm. The top end of the tubing was fitted with a nut, a ferrule, and a thread to female Luer adapter. The bottom end of the tubing was connected through a rubber septum to a 25-mL pear flask equipped with an argon inlet needle and a needle vent.[200] The tubing was flushed with 3 mL of degassed DCE, and then the 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.

A 25-mL pear flask equipped with a rubber septum and argon inlet needle was charged with diazo ketone **140**[72a] (0.088 g, 0.602 mmol, 1.1 equiv), ynamide **98**[62b] (0.108 g, 0.548 mmol, 1.0 equiv), and 2.2 mL of DCE. The yellow reaction mixture was degassed via three freeze-pump-thaw (-196 °C, 0.05 mmHg) cycles. The solution was then transferred to a 5-mL glass syringe, pumped through the tubing at a rate of 0.0057 mL/min, collected in the 25-mL pear flask. Once the addition was complete, 0.4 mL of degassed DCE was drawn into the syringe and pumped through the tubing. This process was repeated with 0.4 and 4.0 mL portions of degassed DCE. The collection flask was equipped with a stir bar and cold-finger condenser, and the reaction mixture was heated at reflux for 48 h and then concentrated to afford 0.188 g of orange oil. This material was dissolved in 3 mL of CH_2Cl_2 and concentrated onto 2 g of silica gel. The free-flowing powder was deposited on a column of 25 g of silica gel and eluted with 10% EtOAc-10% benzene-80% hexanes to furnish 0.114 g (66%) of phenol **151** as a yellow oil with specral data consistent with that previously reported.[3a]

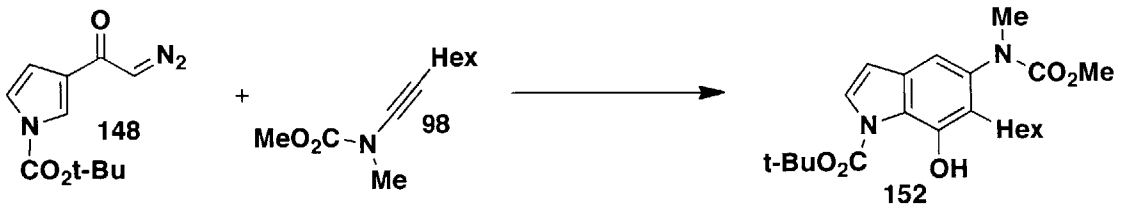
[200] For a more complete description of the construction of the continuous-flow reactor see pages 47-48 of this thesis.



3-[*N*-(Carbomethoxy)-*N*-(methyl)amino]-2-hexyl-naphthalen-1-ol (151). FEP tubing (ca. 50-ft length, 0.030 in. I.D., 0.0625 in. O.D., total internal volume ca. 6.6 mL) was wrapped around a quartz immersion well surrounding a water-jacketed, 450W Hanovia lamp equipped with a Pyrex filter and cooled by recirculating tap water. The top end of the tubing was fitted with a nut, a ferrule, and a thread to female Luer adapter. Approximately 2.5 ft of tubing was left at either end so that the length wrapped around the well was ca. 45 ft. The bottom end of the tubing was connected through a rubber septum to a 50-mL pear flask equipped with an argon inlet needle and a needle vent.[201] The tubing was flushed with 3 mL of degassed DCE, and then the lamp was turned on and degassed DCE was pumped through the tubing for 5 min at a rate of 0.32 mL/min by syringe pump.

A 25-mL pear flask equipped with a rubber septum and argon inlet needle was charged with diazo ketone **140**[72a] (0.184 g, 1.26 mmol, 1.1 equiv), ynamide **98**[62b] (0.223 g, 1.13 mmol, 1.0 equiv), and 4.8 mL of DCE. The yellow reaction mixture was degassed via three freeze-pump-thaw (-196 °C, 0.05 mmHg) cycles. The solution was then transferred to a 10-mL glass syringe, pumped through the tubing at a rate of 0.32 mL/min, collected in the 50-mL pear flask. Once the addition was complete, 0.6 mL of degassed DCE was drawn into the syringe and pumped through the tubing. This process was repeated with 0.6 and 9.0 mL portions of degassed DCE. The collection flask was equipped with a stir bar and cold-finger condenser, and the reaction mixture was heated at reflux for 40 h and then concentrated to afford 0.500 g of orange oil. This material was dissolved in 5 mL of CH_2Cl_2 and concentrated onto 5 g of silica gel. The free-flowing powder was deposited on a column of 50 g of silica gel and eluted with 10% EtOAc-10% benzene-80% hexanes to furnish 0.220 g (63%) of phenol **151** as a yellow oil with specral data consistent with that previously reported.[3a]

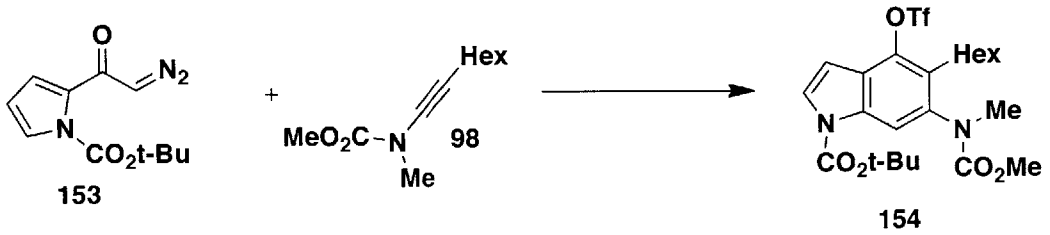
[201] For a more complete description of the construction of the continuous-flow reactor see pages 47-48 of this thesis.



1-(*tert*-Butoxycarbonyl)-6-hexyl-7-hydroxy-5-(N-(methoxycarbonyl)-N-(methyl)amino)indole (152). FEP tubing (ca. 440-cm length, 0.030 in. I.D., 0.0625 in. O.D., total internal volume ca. 2.0 mL) was wrapped around a quartz immersion well surrounding a water-jacketed, 450W Hanovia lamp equipped with a Pyrex filter and cooled by recirculating tap water. Approximately 90 cm of tubing was left at either end so that the length wrapped around the well was ca. 260 cm. The top end of the tubing was fitted with a nut, a ferrule, and a thread to female Luer adapter. The bottom end of the tubing was connected through a rubber septum to a 25-mL pear flask equipped with an argon inlet needle and a needle vent.[202] The tubing was flushed with 3 mL of degassed DCE, and then the 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.

A 25-mL pear flask equipped with a rubber septum and argon inlet needle was charged with diazo ketone **148** (0.134 g, 0.570 mmol, 1.1 equiv), ynamide **98**[62b] (0.100 g, 0.507 mmol, 1.0 equiv), and 2.2 mL of DCE. The yellow reaction mixture was degassed via three freeze-pump-thaw (-196 °C, 0.05 mmHg) cycles. The solution was then transferred to a 5-mL glass syringe, pumped through the tubing at a rate of 0.057 mL/min, and collected in the 25-mL pear flask. Once the addition was complete, 0.4 mL of degassed DCE was drawn into the syringe and pumped through the tubing. This process was repeated with 0.4 and 4.0 mL portions of degassed DCE. The reaction mixture was concentrated to afford 0.209 g of orange oil. This material was dissolved in 5.0 mL of toluene, the flask was equipped with a stir bar and cold-finger condenser, and the reaction mixture was heated at reflux for 2 h. The resulting mixture was concentrated to afford 0.189 g of a dark orange oil. Column chromatography on 25 g of silica gel (elution with 12% EtOAc-hexanes) furnished 0.075 g (37%) of phenol **152** as a yellow oil.

[202] For a more complete description of the construction of the continuous-flow reactor see pages 47-48 of this thesis.



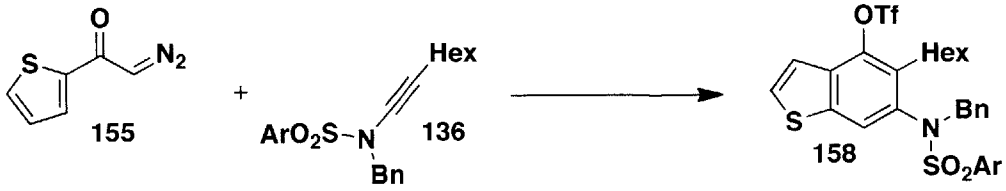
5-Hexyl-4-(trifluoromethylsulfonyloxy)-6-(N-(diethylphosphoryl)-N-(benzyl)amino)indole (154). FEP tubing (ca. 440-cm length, 0.030 in. I.D., 0.0625 in. O.D., total internal volume ca. 2.0 mL) was wrapped around a quartz immersion well surrounding a water-jacketed, 450W Hanovia lamp equipped with a Pyrex filter and cooled by recirculating tap water. Approximately 90 cm of tubing was left at either end so that the length wrapped around the well was ca. 260 cm. The top end of the tubing was fitted with a nut, a ferrule, and a thread to female Luer adapter. The bottom end of the tubing was connected through a rubber septum to a 25-mL pear flask equipped with an argon inlet needle and a needle vent.[203] The tubing was flushed with 3 mL of degassed DCE, and then the 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.

A 25-mL pear flask equipped with a rubber septum and argon inlet needle was charged with diazo ketone **153**[72a] (0.570 g, 013.4 mmol, 1.1 equiv), ynamide **98**[62b] 0.100 g, 0.507 mmol, 1.0 equiv), and 2.2 mL of DCE. The yellow reaction mixture was degassed via three freeze-pump-thaw (-196 °C, 0.05 mmHg) cycles. The solution was then transferred to a 5-mL glass syringe, pumped through the tubing at a rate of 0.057 mL/min, and collected in the 25-mL pear flask. Once the addition was complete, 0.4 mL of degassed DCE was drawn into the syringe and pumped through the tubing. This process was repeated with 0.4 and 4.0 mL portions of degassed DCE. The reaction mixture was concentrated to afford 0.202 g of orange oil. This material was dissolved in 5.0 mL of toluene, the flask was equipped with a stir bar and cold-finger condenser, and the reaction mixture was heated at reflux for 2 h. The resulting mixture was concentrated to afford 0.232 g of a dark orange oil. Column chromatography on 25 g of silica gel (elution with 12% EtOAc-hexanes) furnished 0.113 g of ca. 85-90% pure phenol as an orange oil.

A 25-mL pear flask equipped with a rubber septum and argon inlet needle was charged with phenol (0.113 g, 1.0 equiv), 4-DMAP (0.070 g, 0.573 mmol, 2.0 equiv), and 3.0 mL of CH_2Cl_2. The orange solution was cooled to 0 °C and triflic anhydride (0.06 mL, 0.357 mmol,

[203] For a more complete description of the construction of the continuous-flow reactor see pages 47-48 of this thesis.

1.3 equiv) was added dropwise by syringe over ca. 2 min. The reaction mixture was allowed to warm to rt, stirred for 2 h, and then diluted with 20 mL of CH_2Cl_2 and washed with two 10-mL portions of 1 M HCl solution. The combined aqueous layers were extracted with 10 mL of CH_2Cl_2, and the combined organic layers 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 0.151 g of orange oil. Column chromatography on 18 g of silica gel (elution with 10% EtOAc-hexanes) afforded 0.127 g (47% over two steps from the ynamide) of triflate **154** as an orange oil.



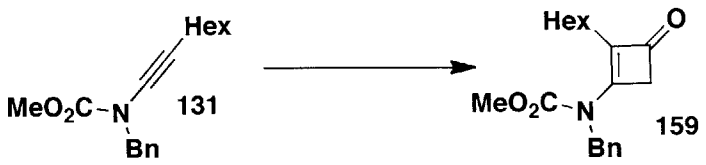
5-Hexyl-4-(trifluoromethylsulfonyloxy)-6-(*N*-(*p*-toluenesulfonyl)-*N*-(benzyl)amino)benzo[b]thiophene (158). FEP tubing (ca. 440-cm length, 0.030 in. I.D., 0.0625 in. O.D., total internal volume ca. 2.0 mL) was wrapped around a quartz immersion well surrounding a water-jacketed, 450W Hanovia lamp equipped with a uranium filter and cooled by recirculating tap water. Approximately 90 cm of tubing was left at either end so that the length wrapped around the well was ca. 260 cm. The top end of the tubing was fitted with a nut, a ferrule, and a thread to female Luer adapter. The bottom end of the tubing was connected through a rubber septum to a 25-mL pear flask equipped with an argon inlet needle and a needle vent.[204] The tubing was flushed with 3 mL of degassed DCE, and then the lamp was turned on and degassed DCE was pumped through the tubing for 5 min at a rate of 0.036 mL/min by syringe pump.

A 25-mL pear flask equipped with a rubber septum and argon inlet needle was charged with diazo ketone **155**[74] (0.062 g, 0.407 mmol, 1.1 equiv), ynamide **136**[64a] (0.134 g, 0.363 mmol, 1.0 equiv), and 1.6 mL of DCE. The yellow reaction mixture was degassed via three freeze-pump-thaw (-196 °C, 0.05 mmHg) cycles. The solution was then transferred to a 5-mL glass syringe, pumped through the tubing at a rate of 0.036 mL/min, and collected in the 25-mL pear flask. Once the addition was complete, 0.4 mL of degassed DCE was drawn into the syringe and pumped through the tubing. This process was repeated with 0.4 and 4.0 mL portions of degassed DCE. The collection flask was equipped with a stir bar and cold-finger condenser, and the reaction mixture was heated at reflux for 42 h and then concentrated to afford 0.195 g of red oil. Column chromatography on 20 g of silica gel (elution with 10% EtOAc-hexanes) furnished 0.102 g of ca. 85-90% pure phenol as an orange oil.

A 25-mL pear flask equipped with a rubber septum and argon inlet needle was charged with phenol (0.102 g, 1.0 equiv), 4-DMAP (0.050 g, 0.409 mmol, 2.0 equiv), and 1.6 mL of CH_2Cl_2. The orange solution was cooled to 0 °C and triflic anhydride (0.04 mL, 0.238 mmol,

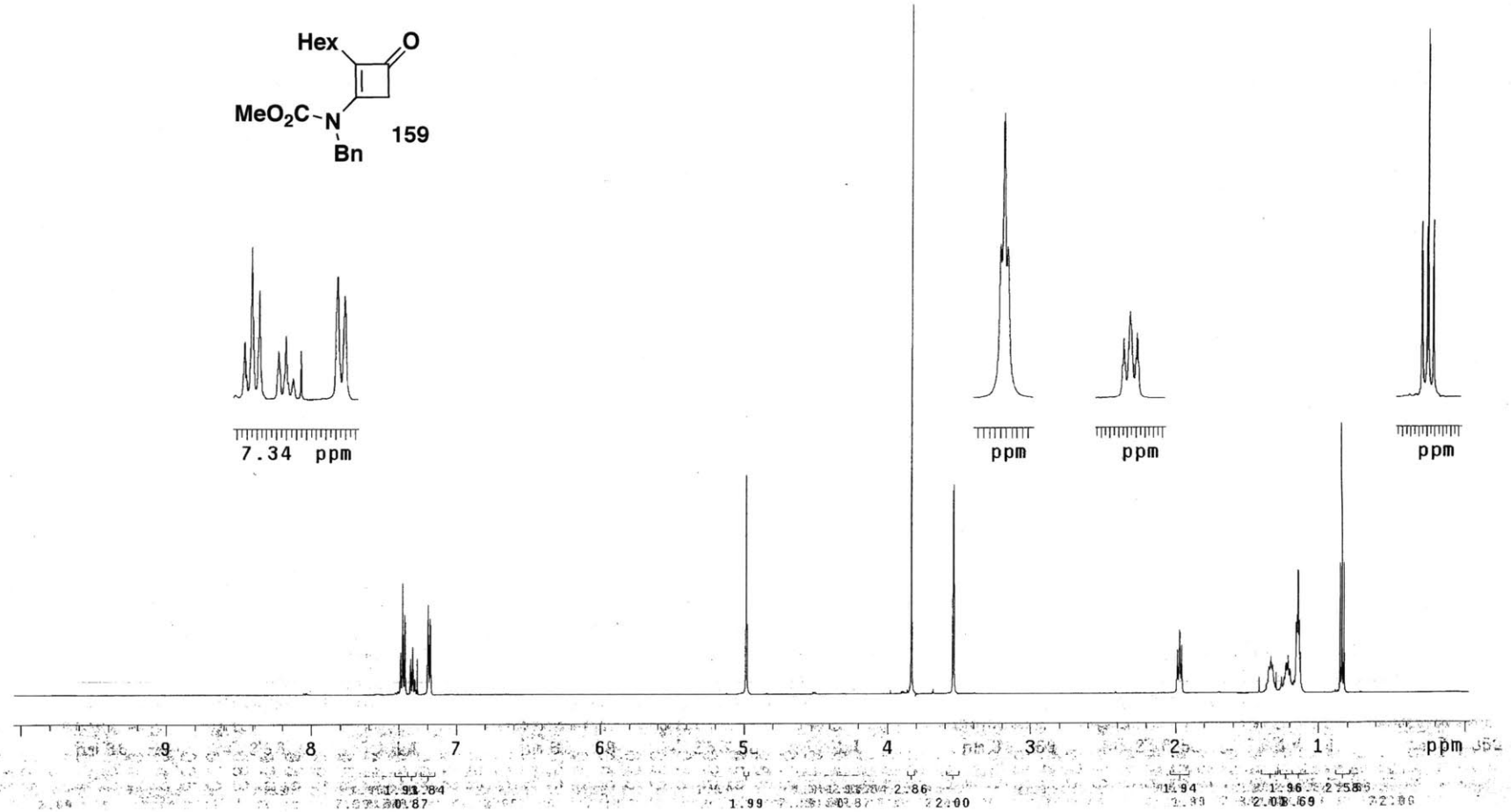
[204] For a more complete description of the construction of the continuous-flow reactor see pages 47-48 of this thesis.

1.2 equiv) was added dropwise by syringe over ca. 2 min. The reaction mixture was allowed to warm to rt, stirred for 4 h, and then diluted with 10 mL of CH_2Cl_2 and washed with two 5-mL portions of 1 M HCl solution. The combined aqueous layers were extracted with 5 mL of CH_2Cl_2, and the combined organic layers were washed with 15 mL of satd aq $NaHCO_3$ solution and 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.125 g of a red oil. Column chromatography on 13 g of silica gel (elution with 7% EtOAc-hexanes) afforded 0.106 g (47% over two steps from the ynamide) of triflate **158** as an off-white solid.



2-Hexyl-3-(*N*-benzyl-*N*-(methoxycarbonyl))-2-cyclobuten-1-one (159). Ketene was generated by pyrolysis of acetone over an electrically heated metal filament using the apparatus described by Williams and Hurd.[205] A 12x75 mm test tube fitted with a rubber septum was charged with ynamide **131**[62b] (0.098 g, 0.358 mmol, 1.0 equiv) and 3.0 mL of toluene. The septum was fitted with an inlet needle connected to the ketene generator and an outlet needle connected via tubing to a column of calcium sulfate leading into a trap of water. Ketene was bubbled into the solution at rt over a period of 6 h. The reaction mixture was then concentrated to afford 0.127 g of an orange oil. Column chromatography on 12 g of silica gel (elution with 15% EtOAc-hexane) yielded 0.051 g of unreacted ynamide **131** as a colorless oil and 0.045 g (40%) of cyclobutenone **159** as a yellow oil: IR (thin film) 2956, 2929, 2857, 1737, 1611, 1453, 1393, 1364, 1233 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (t, J = 7.0 Hz, 2H), 7.30 (t, J = 7.0 Hz, 1H), 7.19 (d, J = 7.5 Hz, 2H), 4.99 (s, 2H), 3.84 (s, 3H), 3.54 (t, J = 1.5 Hz, 2H), 1.97 (t, J = 7.5 Hz, 2H), 1.30-1.38 (m, 2H), 1.20-1.30 (m, 2H), 1.10-1.20 (m, 4H), 0.84 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.1, 159.6, 153.7, 136.5, 129.1, 127.9, 127.7, 125.9, 54.4, 51.2, 50.9, 31.6, 29.4, 28.5, 24.0, 22.7, 14.2; HRMS-ESI (*m/z*) [M+H] calcd for $C_{19}H_{25}NO_3$, 316.1907, found 316.1911.

[205] Williams, J. W.; Hurd, C. D. *J. Org. Chem.* **1940**, *5*, 122. See also Hanford, W.E.; Sauer, J.C. Preparation of Ketenes and Ketene Dimers. *Org. React.* **1958**, *3*, 108-140.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MeO2C
N
Bn
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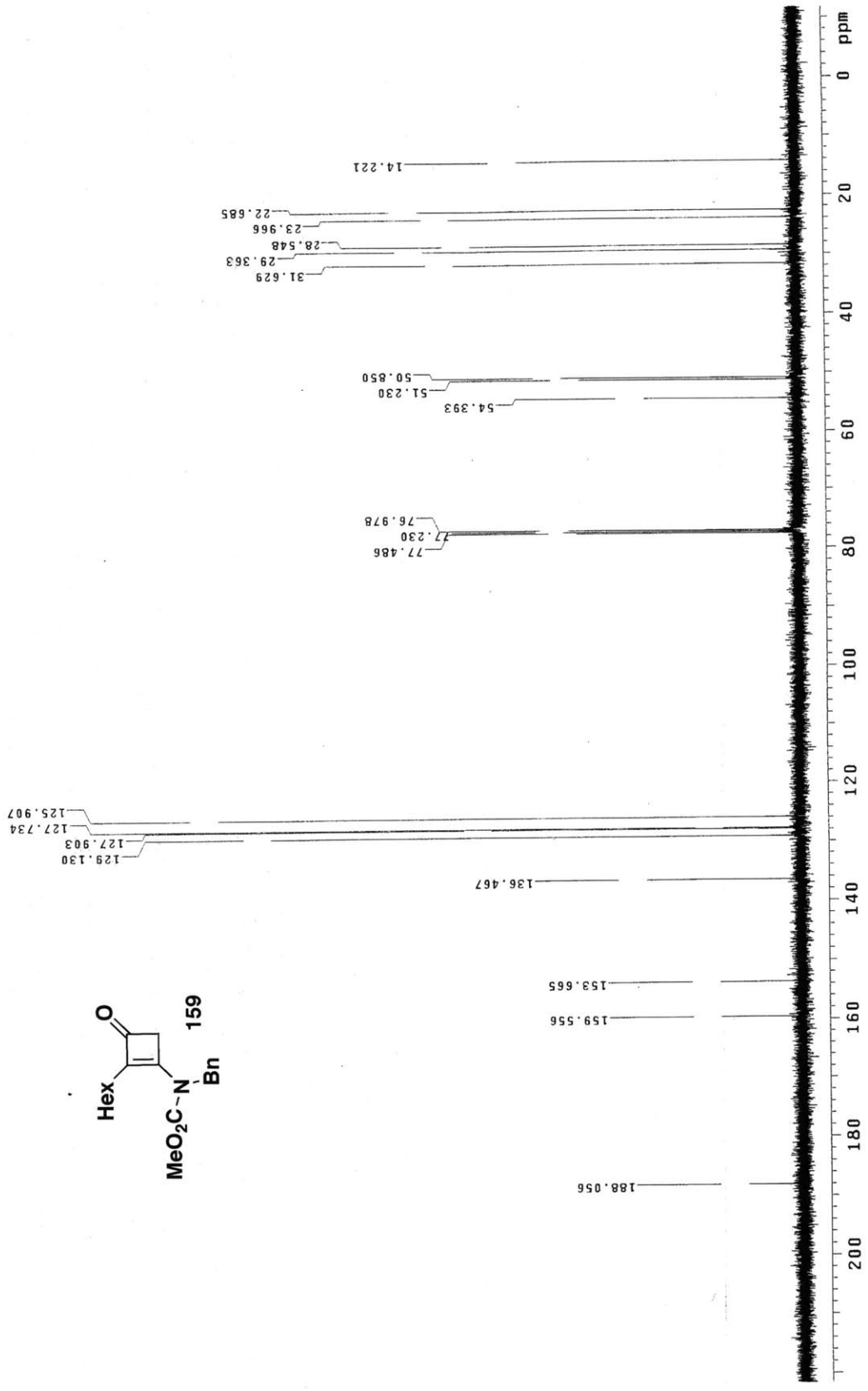
ppm
ppm
ppm
9
8
7
6
5
4
3
2
1
ppm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28.548
29.363
31.629
50.850
51.230
54.393
76.978
77.230
77.486
125.907
127.734
127.903
129.130
136.467
153.665
159.556
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ppm
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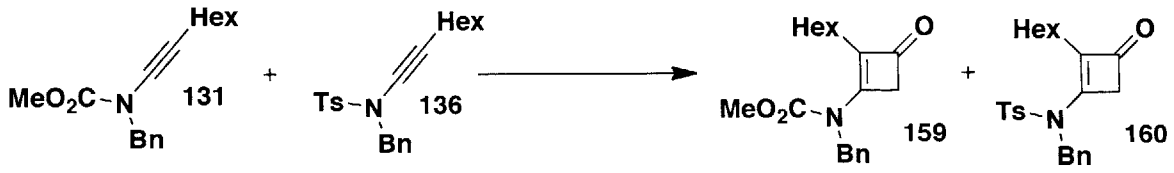
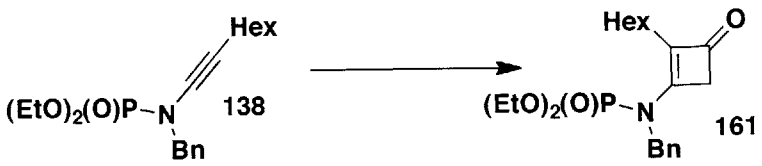
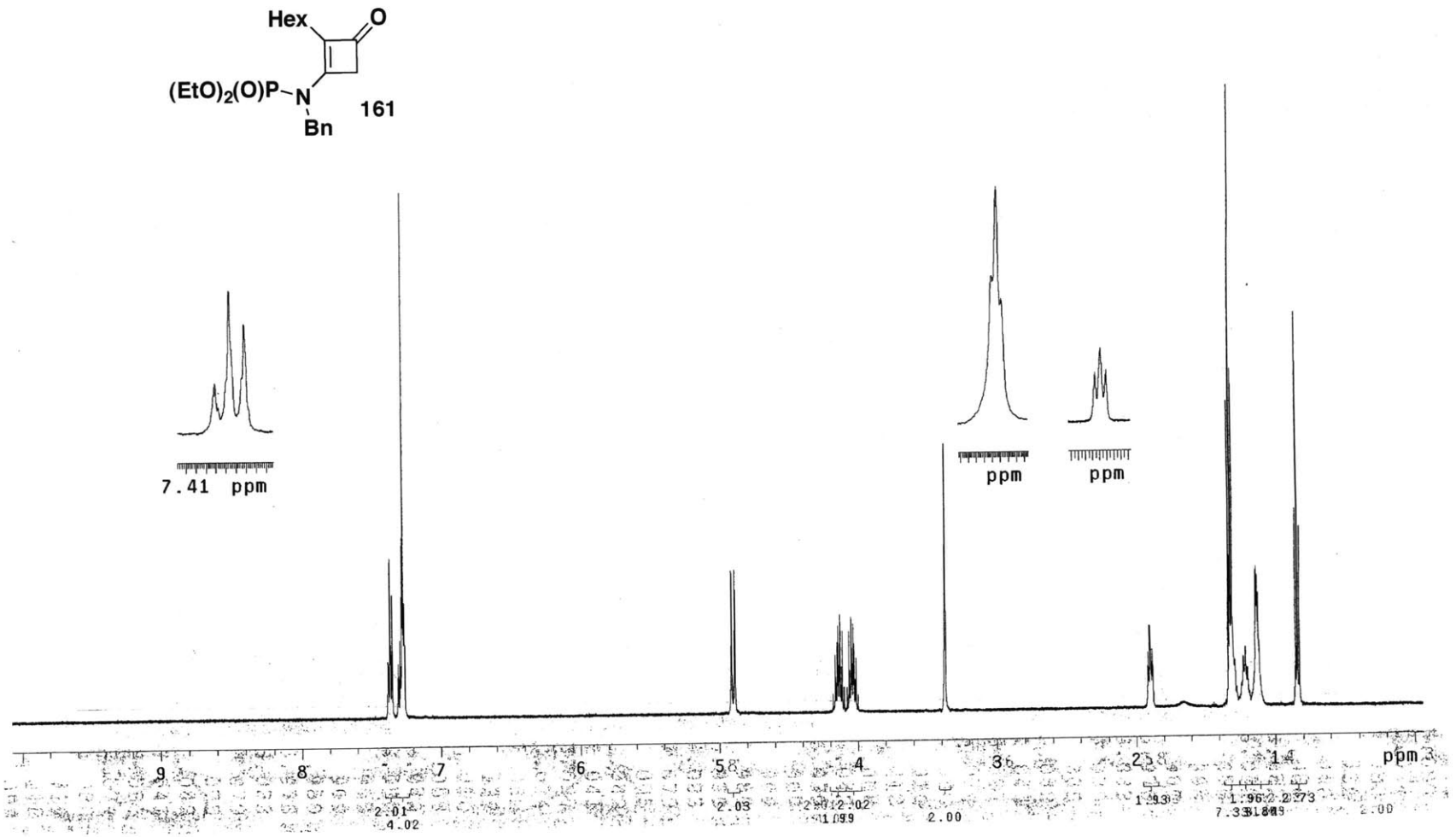
20
40
60
80
100
120
140
160
180
200
O
Hex
MeO2C
N
Bn
159



Ketene was generated by pyrolysis of acetone over an electrically heated metal filament using the apparatus described by Williams and Hurd.[205] A 5-mL conical vial fitted with a rubber septum was charged with ynamide **131** (0.103 g, 0.377 mmol), ynamide **136** (0.140 g, 0.379 mmol) and 1.5 mL of $CDCl_3$ containing 1,3,5-trimethoxybenzene (0.063 g, 0.375 mmol) as an internal standard. The septum was fitted with an inlet needle connected to the ketene generator and an outlet needle connected via tubing to a column of calcium sulfate leading into a trap of water. Ketene was bubbled into the solution at rt over a period of 4 h. Aliquots (ca. 0.1 mL) of the reaction mixture were taken at intervals, diluted with $CDCl_3$, and examined by ^{1}H NMR (500 MHz) with a relaxation time $d1$ = 20 s to ensure accurate integration and auto phasing or manual phasing to ensure a level baseline. For cyclobutenone **159** the resonance at 4.96 ppm was integrated; for cyclobutenone **160** the resonance at 5.04 ppm was integrated. For ynamide **131** the resonance at 4.61 ppm was integrated; for ynamide **136** the resonance at 4.45 ppm was integrated.



2-Hexyl-3-(*N*-benzyl-*N*-(diethyl phosphoryl))-2-cyclobuten-1-one (161). Ketene was generated by pyrolysis of acetone over an electrically heated metal filament using the apparatus described by Williams and Hurd.[205] A 10x75 mm test tube fitted with a rubber septum was charged with ynamide **138**[67] (0.061 g, 0.174 mmol, 1.0 equiv) and 1.5 mL of toluene. The septum was fitted with an inlet needle connected to the ketene generator and an outlet needle connected via tubing to a column of calcium sulfate leading into a trap of water. Ketene was bubbled into the solution at rt over a period of 40 min. The reaction mixture was then concentrated to afford 0.082 g of an orange oil. Column chromatography on 7 g of silica gel (elution with 30% EtOAc-hexane) yielded 0.062 g (90%) of cyclobutenone **161** as a yellow oil: IR (thin film) 2929, 2857, 1751, 1602, 1455, 1384, 1351, 1270, 1020 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (t, J = 7.5 Hz, 2H), 7.25-7.34 (m, 3H), 4.90 (d, J = 11.5 Hz, 2H), 3.90-4.20 (m, 4H), 3.37 (t, J = 1.5 Hz, 2H), 1.90 (t, J = 7.5 Hz, 2H), 1.29-1.39 (m, 8H), 1.18-1.29 (m, 2H), 1.04-1.18 (m, 4H), 0.84 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.1, 161.6 (d, J = 5.1 Hz), 137.4, 129.0, 127.9, 126.3, 125.6 (d, J = 9.8 Hz), 64.2 (J = 5.8 Hz), 52.2 (d, J = 5.0 Hz), 49.7, 31.7, 29.5, 28.6, 23.9, 22.7, 16.2 (d, J = 6.9 Hz) 14.2; ^{31}P NMR (121 MHz, $CDCl_3$) δ 2.17; HRMS-ESI (*m/z*) [M+H] calcd for $C_{21}H_{32}NO_4P$, 394.2142, found 394.2141.


Hex
O
(EtO)2(O)P
N
Bn
161
7.41 ppm
ppm
ppm
9
8
7
6
5
4
3
2
1
ppm

Hex
O
(EtO)2(O)P
N
Bn
161
187.072
161.630
161.589
137.397
129.034
127.853
126.273
125.628
125.550
77.486
77.230
76.978
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64.221
52.127
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29.455
28.649
23.916
22.730
16.267
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180
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100
80
60
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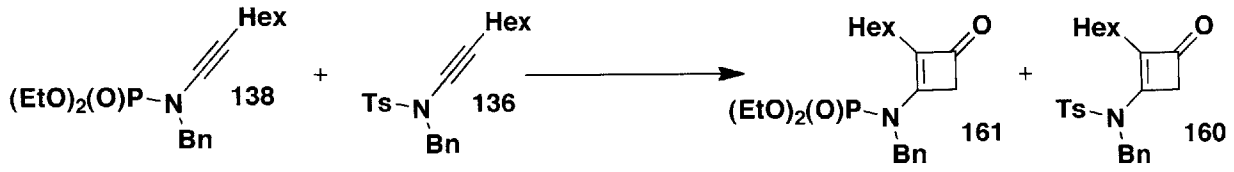
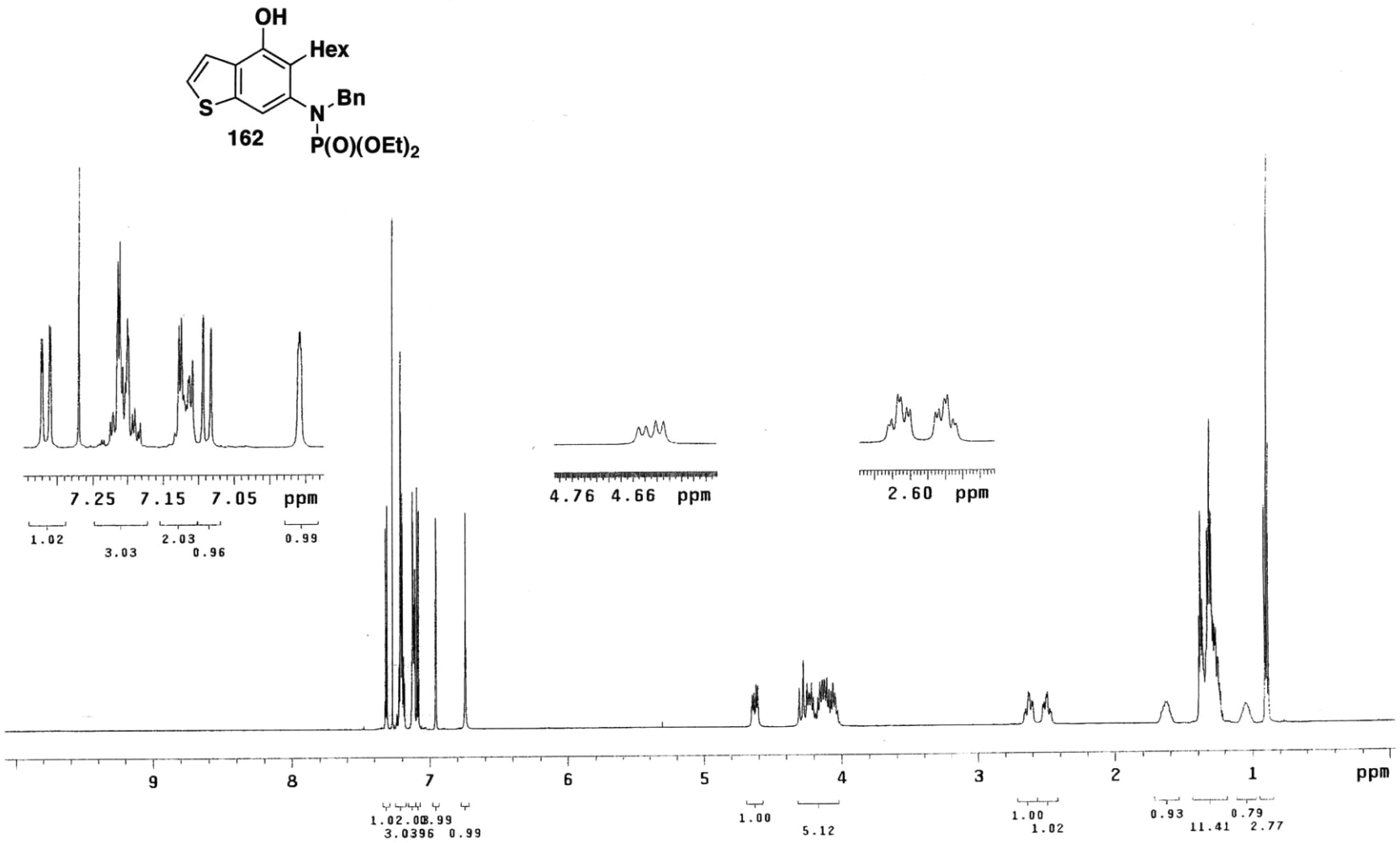
ppm



Ketene was generated by pyrolysis of acetone over an electrically heated metal filament using the apparatus described by Williams and Hurd.[205] A 13x100 mm test tube fitted with a rubber septum was charged with 3.5 mL $CDCl_3$ then fitted with an inlet needle connected to the ketene generator and an outlet needle connected via tubing to a column of calcium sulfate leading into a trap of water. Ketene was bubbled into the solution at rt for 5 min, then a solution of ynamide **138** (0.124 g, 0.353 mmol), ynamide **136** (0.130 g, 0.352 mmol), and 1,3,5-trimethoxybenzene (0.059 g, 0.351 mmol) as an internal standard in 0.5 mL of $CDCl_3$ was added via syringe, and the addition of ketene continued over a period of 2 h. Aliquots (ca. 0.1 mL) of the reaction mixture were taken at intervals, diluted with $CDCl_3$, and examined by ^1H NMR (500 MHz) with a relaxation time $d1$ = 20 s to ensure accurate integration and auto phasing or manual phasing to ensure a level baseline. For cyclobutenone **161** the resonance at 4.90 ppm was integrated; for cyclobutenone **160** the resonance at 5.04 ppm was integrated. For ynamide **138** the resonance at 4.40 ppm was integrated; for ynamide **136** the resonance at 4.45 ppm was integrated.

5-Hexyl-4-hydroxy-6-(*N*-(diethylphosphoryl)-*N*-(benzyl)amino)benzo[b]thiophene (162). A 20-cm quartz tube (5 mm I.D., 7 mm O.D.) equipped with a rubber septum and argon inlet needle was charged with diazo ketone **155**[74] (0.049 g, 0.322 mmol, 1.1 equiv), ynamide **138**[67] (0.099 g, 0.282 mmol, 1.0 equiv), and 1.3 mL of CH_2Cl_2. The yellow reaction mixture was degassed via three freeze-pump-thaw (-196 °C, 0.05 mmHg) cycles. The quartz tube was positioned ca. 20 cm from a Hanovia 450W lamp (quartz immersion well, cooled by recirculating tap water) and irradiated under argon at 25 °C for 5.5 h. The reaction mixture was transferred to a 25-mL pear flask with the aid of two 4-mL portions of CH_2Cl_2 and concentrated to afford 0.143 g of an orange oil. This material was dissolved in 3 mL of toluene, the flask was equipped with a stir bar and cold-finger condenser, and the reaction mixture was heated at reflux for 1.5 h. The resulting mixture was concentrated to afford 0.159 g of a dark orange oil. Column chromatography on 15 g of silica gel (elution with 30% EtOAc-hexanes) furnished 0.115 g of an orange oil which was further purified by column chromatography on 15 g of silica gel (elution with 0.5% MeOH-CH_2Cl_2) to afford 0.105 g (78%) of phenol **162** as an orange oil: IR (neat) 3225 (broad), 2924, 2856, 1605, 1552, 1495, 1424, 1392, 1330, 1215, 1126, 1051, 970 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (dd, J = 0.8 Hz, J = 5.5 Hz, 1H) 7.18-7.24 (m, 3H), 7.10-7.14 (m, 2H), 7.09 (d, J = 5.5 Hz), 6.95-6.97 (m, 1H), 6.74 (s, 1H), 4.59-4.67 (m, 1H), 4.02-4.32 (m, 5H), 2.58-2.68 (m, 2H), 2.45-2.55 (m, 2H), 1.57-1.70 (m, 1H), 1.21-1.42 (m, 12H), 0.99-1.11 (m, 1H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.4, 137.9 (d, J = 1.4 Hz), 137.7 (d, J = 3.4), 137.6 (d, J = 2.9 Hz), 129.9, 129.1 (d, J = 1.1 Hz), 128.3, 127.7, 124.2, 123.4 (d, J = 4.0 Hz), 120.3, 116.3, 63.2 (m), 55.9 (d, J = 4.5 Hz), 31.9, 30.5, 29.2, 26.2, 23.0, 16.4 (m), 14.4; ^{31}P NMR (121 MHz, $CDCl_3$) δ 6.18; HRMS-ESI (*m/z*) [M + H] calculated for $C_{25}H_{34}NO_4PS$, 476.2019; found 648.1120.


OH
Hex
Bn
N
S
P(O)(OEt)2
162
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1.02
3.03
2.03
0.96
0.99
4.76 4.66 ppm
2.60 ppm
9
8
7
6
5
4
3
2
1
ppm
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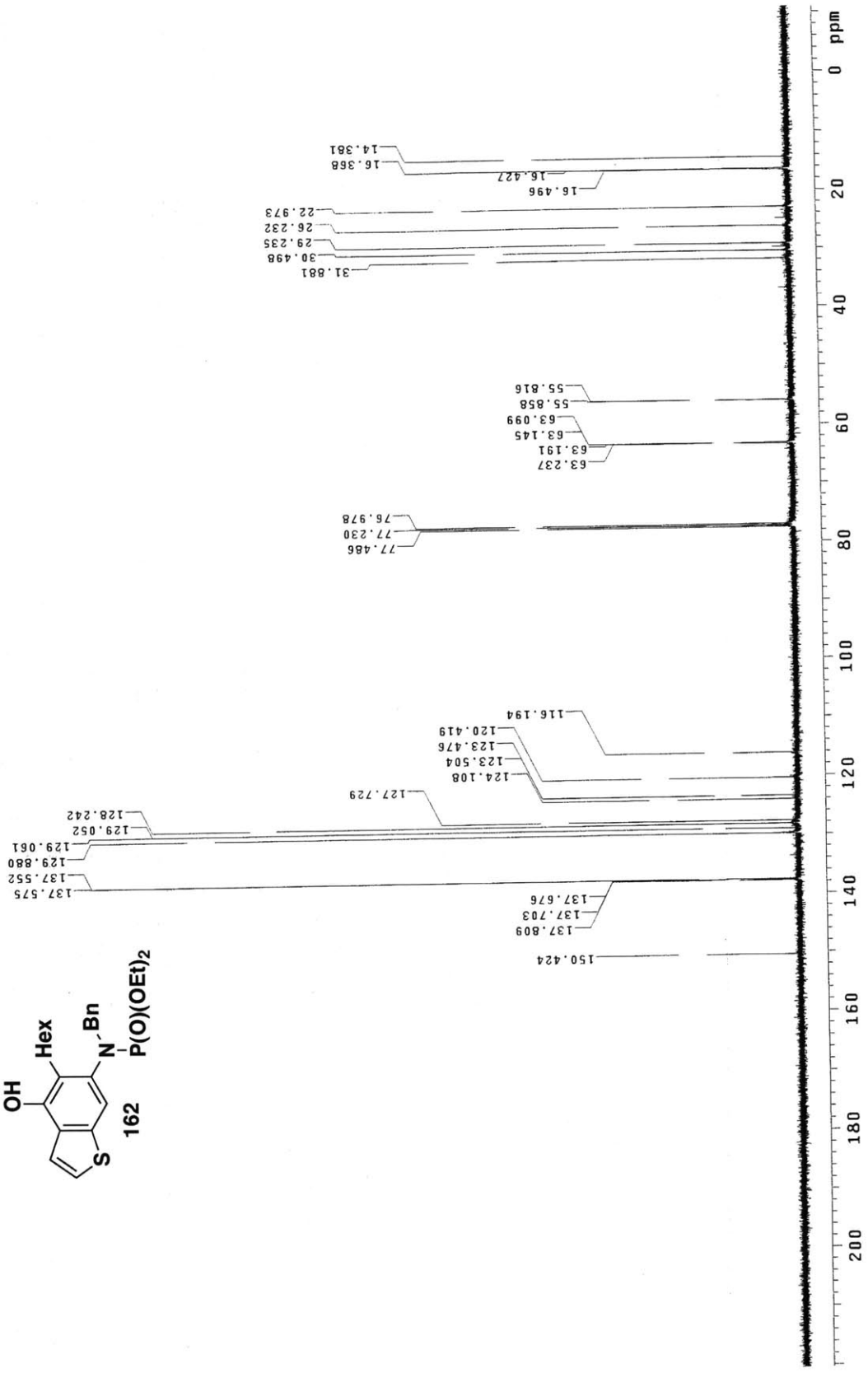
3.0396 0.99
1.00
5.12
1.00
1.02
0.93
11.41
0.79
2.77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16.427
16.496
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30.498
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63.237
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127.729
128.242
129.052
129.061
129.880
137.552
137.575
137.676
137.703
137.809
150.424
ppm
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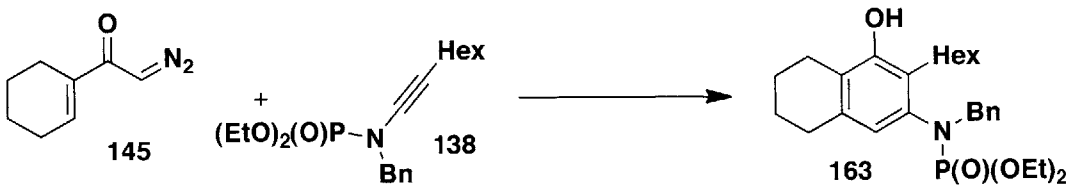
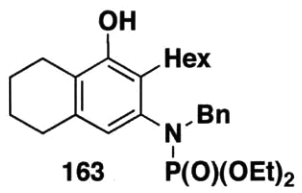
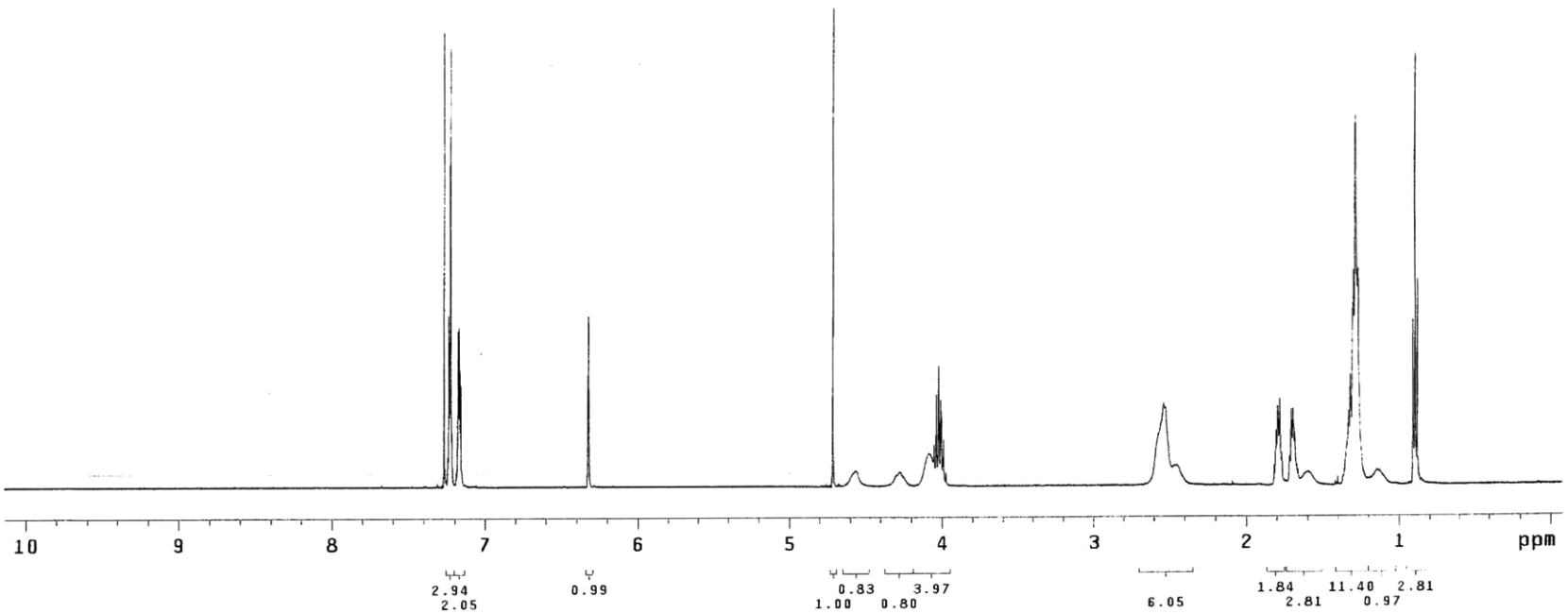
40
60
80
100
120
140
160
180
200
OH
Hex
N
Bn
P(O)(OEt)2
S
162



3-[*N*-(Diethylphosphoryl)-*N*-(benzyl)amino]-2-hexyl-5,6,7,8-tetrahydro-naphthalen-1-ol (163). A 20-cm quartz tube (7 mm I.D., 10 mm O.D.) equipped with a rubber septum and argon inlet needle was charged with diazo ketone **145**[72a] (0.073 g, 0.486 mmol, 1.1 equiv), ynamide **138**[67] (0.151 g, 0.430 mmol, 1.0 equiv), and 2.0 mL of CH_2Cl_2. The yellow solution was degassed for 10 min with a stream of argon. The quartz tube was positioned ca. 20 cm from a Hanovia 450W lamp (quartz immersion well, cooled by recirculating tap water) and irradiated under argon at 25 °C for 6 h. The reaction mixture was transferred to a 25-mL pear flask with the aid of two 4-mL portions of CH_2Cl_2 and concentrated to afford 0.222 g of orange oil. This material was dissolved in 4.4 mL of toluene, the flask was equipped with a stir bar and cold-finger condenser, and the reaction mixture was heated at reflux for 2 h. The resulting mixture was concentrated to afford 0.234 g of orange oil. Column chromatography on 30 g of silica gel (gradient elution with 20-40% EtOAc-hexanes) furnished 0.149 g of an yellow oil which was further purified by column chromatography on 25 g of silica gel (elution with 1% MeOH-CH_2Cl_2) to afford 0.135 g (66%) of phenol **163** as a yellow oil: IR (neat) 3296 (broad), 2929, 2858, 1572, 1439, 1421, 1211, 1125, 1097, 1055, 1029, 966 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.20-7.26 (m, 3H), 7.14-7.20 (m, 2H), 6.32 (s, 1H), 4.80 (s, 1H), 4.50-4.66 (m, 1H), 4.21-4.35 (m, 1H), 3.96-4.16 (m, 4H), 2.37-2.67 (m, 6H), 1.75-1.84 (m, 2H), 1.65-1.75 (m, 2H), 1.54-1.65 (m, 1H), 1.22-1.38 (m, 12H), 1.06-1.21 (m, 1H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7, 138.4 (d, J = 2.5 Hz), 138.1 (d, J = 3.8 Hz), 135.7 (d, J = 1.8 Hz), 129.9, 128.2, 127.6, 125.3 (d, J = 4.0 Hz), 123.5, 122.1 (d, J = 1.8 Hz), 62.9 (d, J = 5.6 Hz), 56.0 (d, J = 5.1 Hz), 32.0, 30.5, 29.5, 29.1, 26.4, 23.2, 23.0, 22.9, 16.4 (d, J = 6.9 Hz), 14.2; ^{31}P NMR (121 MHz, $CDCl_3$) δ 6.65; HRMS-ESI (*m/z*) [M + H] calculated for $C_{27}H_{40}NO_4P$, 474.2768; found 474.2780.


OH
Hex
Bn
N
P(O)(OEt)2

163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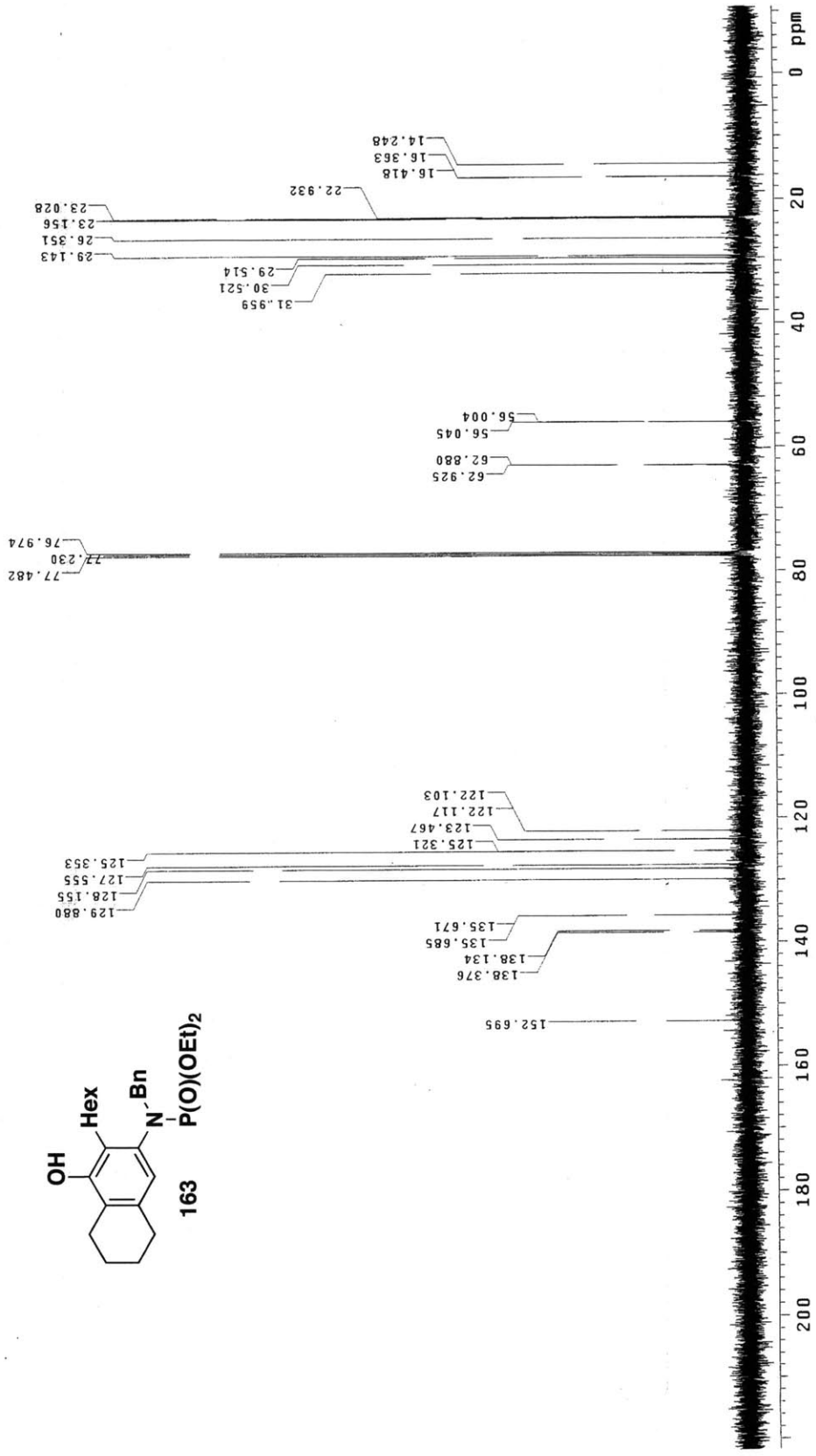
2.81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135.671
135.685
138.134
138.376
152.695
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60
80
100
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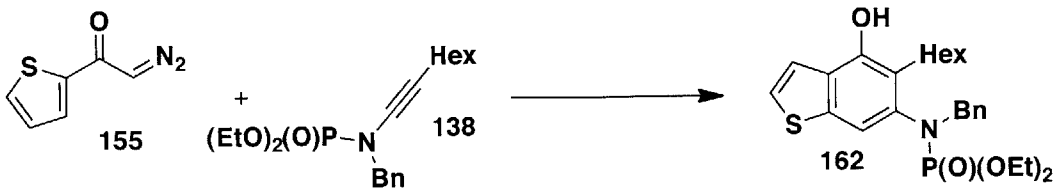
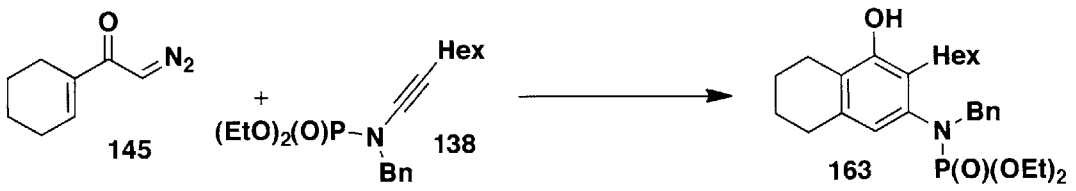
140
160
180
200
OH
Hex
N
Bn
P(O)(OEt)2
163



5-Hexyl-4-hydroxy-6-(*N*-(diethylphosphoryl)-*N*-(benzyl)amino)benzo[b]thiophene (162). FEP tubing (ca. 440-cm length, 0.030 in. I.D., 0.0625 in. O.D., total internal volume ca. 2.0 mL) was wrapped around a quartz immersion well surrounding a water-jacketed, 450W Hanovia lamp equipped with a Pyrex filter and cooled by recirculating tap water. Approximately 90 cm of tubing was left at either end so that the length wrapped around the well was ca. 260 cm. The top end of the tubing was fitted with a nut, a ferrule, and a thread to female Luer adapter. The bottom end of the tubing was connected through a rubber septum to a 25-mL pear flask equipped with an argon inlet needle and a needle vent.[206] The tubing was flushed with 3 mL of degassed DCE, and then the 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.

A 25-mL pear flask equipped with a rubber septum and argon inlet needle was charged with diazo ketone **155**[74] (0.069 g, 0.448 mmol, 1.1 equiv), ynamide **138**[67] (0.143 g, 0.407 mmol, 1.0 equiv), and 1.7 mL of DCE. The yellow reaction mixture was degassed via three freeze-pump-thaw (-196 °C, 0.05 mmHg) cycles. The solution was then transferred to a 5-mL glass syringe, pumped through the tubing at a rate of 0.057 mL/min, and collected in the 25-mL pear flask. Once the addition was complete, 0.4 mL of degassed DCE was drawn into the syringe and pumped through the tubing. This process was repeated with 0.4 and 4.0 mL portions of degassed DCE. The collection flask was equipped with a stir bar and cold-finger condenser, and the reaction mixture was heated at reflux for 42 h and then concentrated to afford 0.199 g of red oil. This material was dissolved in 2 mL of CH_2Cl_2 and concentrated onto 2 g of silica gel. The free-flowing powder was deposited on a column of 20 g of silica gel and eluted with 30% EtOAc-hexanes to furnish 0.159 g of an orange oil which was further purified by column chromatography on 20 g of silica gel (elution with 1% MeOH-CH_2Cl_2) to afford 0.154 g (79%) of phenol **162** as an orange oil.

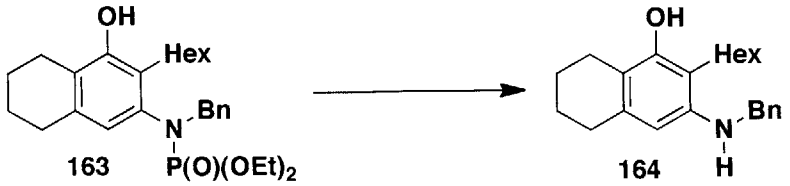
[206] For a more complete description of the construction of the continuous-flow reactor see pages 47-48 of this thesis.



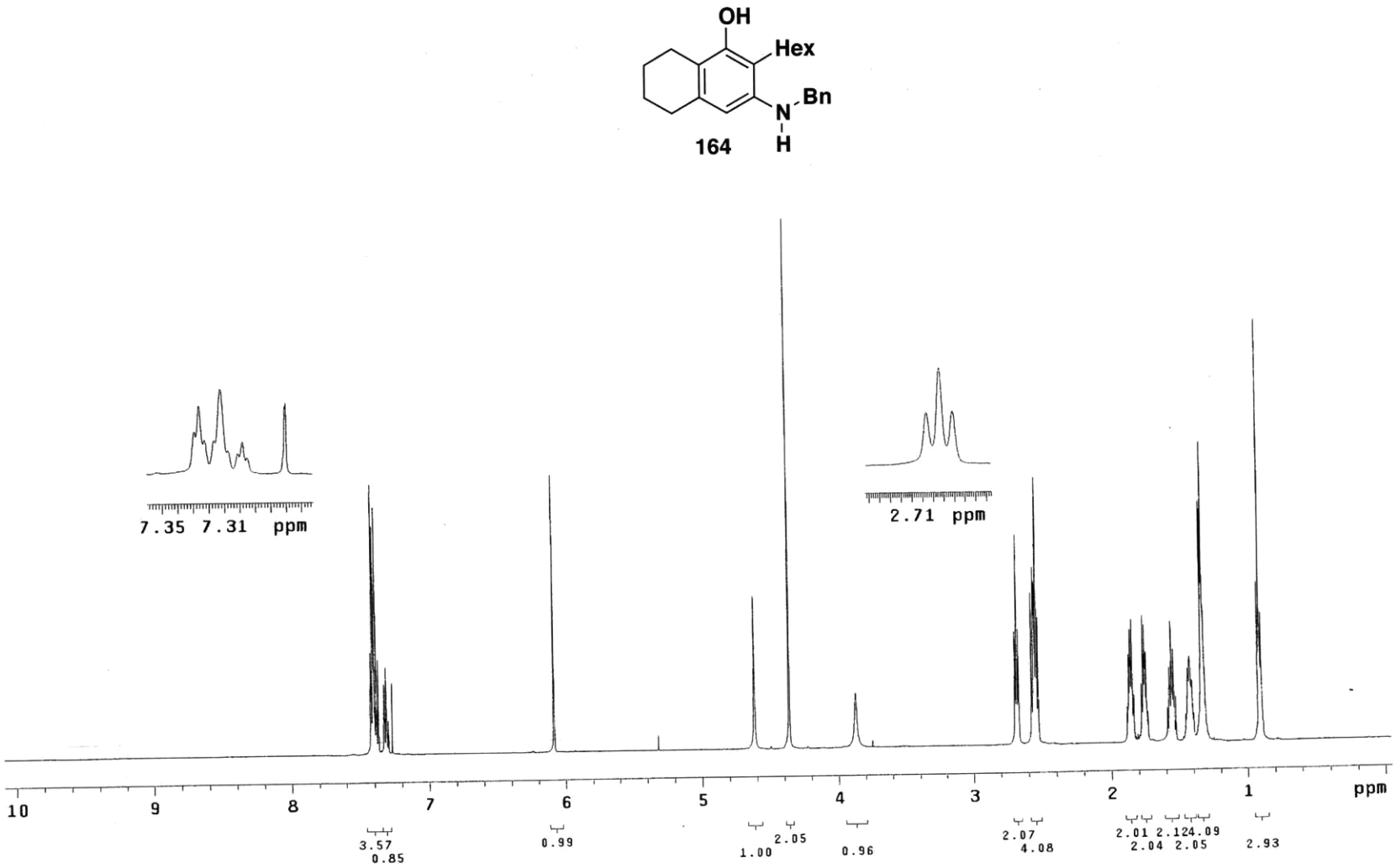
3-[*N*-(Diethylphosphoryl)-*N*-(benzyl)amino]-2-hexyl-5,6,7,8-tetrahydro-naphthalen-1-ol (163). FEP tubing (ca. 440-cm length, 0.030 in. I.D., 0.0625 in. O.D., total internal volume ca. 2.0 mL) was wrapped around a quartz immersion well surrounding a water-jacketed, 450W Hanovia lamp equipped with a Pyrex filter and cooled by recirculating tap water. Approximately 90 cm of tubing was left at either end so that the length wrapped around the well was ca. 260 cm. The top end of the tubing was fitted with a nut, a ferrule, and a thread to female Luer adapter. The bottom end of the tubing was connected through a rubber septum to a 25-mL pear flask equipped with an argon inlet needle and a needle vent.[207] The tubing was flushed with 3 mL of degassed DCE, and then the 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.

A 25-mL pear flask equipped with a rubber septum and argon inlet needle was charged with diazo ketone **145**[72a] (0.115 g, 0.766 mmol, 1.1 equiv), ynamide **138**[67] (0.240 g, 0.683 mmol, 1.0 equiv), and 2.9 mL of DCE. The yellow reaction mixture was degassed via three freeze-pump-thaw (-196 °C, 0.05 mmHg) cycles. The solution was then transferred to a 5-mL glass syringe, pumped through the tubing at a rate of 0.057 mL/min, and collected in the 25-mL pear flask. Once the addition was complete, 0.4 mL of degassed DCE was drawn into the syringe and pumped through the tubing. This process was repeated with 0.4 and 4.0 mL portions of degassed DCE. The collection flask was equipped with a stir bar and cold-finger condenser, and the reaction mixture was heated at reflux for 40 h and then concentrated to afford 0.386 g of orange oil. This material was dissolved in 5 mL of CH_2Cl_2 and concentrated onto 5 g of silica gel. The free-flowing powder was deposited on a column of 55 g of silica gel and eluted with 35% EtOAc-hexanes to furnish 0.204 g of an orange oil which was further purified by column chromatography on 33 g of silica gel (gradient elution with 0-1% MeOH-CH_2Cl_2) to afford 0.176 g (53%) of phenol **163** as an orange oil.

[207] For a more complete description of the construction of the continuous-flow reactor see pages 47-48 of this thesis.



3-[*N*-(Benzyl)amino]-2-hexyl-5,6,7,8-tetrahydro-naphthalen-1-ol (164). A 25-mL, pear flask equipped with a rubber septum and argon inlet needle was charged with phosphoramide **163** (0.132 g, 2.79 mmol, 1.0 equiv) and 4 mL of toluene. Red-Al (≥65 wt% in toluene, 0.65 mL, 2.13 mmol, 8.0 equiv) was added and the resulting solution was heated at 85 °C for 2 h. The reaction mixture was quenched at room temperature by the addition of 10 mL of satd K_2CO_3 solution, diluted with 10 mL of ether, and the organic layer was washed with 10 mL of satd K_2CO_3 solution. The combined aqueous layers were extracted with three 10-mL portions of Et_2O. The combined organic layers were washed with 20 mL of brine, dried over Na_2SO_4, filtered, and concentrated to give 0.122 g of red oil. Column chromatography on 11 g of silica gel (elution with 2% EtOAc-hexanes) provided 0.077 g (84%) of amine **164** as a red solid: mp 58-60 °C; IR (neat) 3556 (broad), 3452 (broad) 2926, 2856, 1621, 1582, 154, 1438, 1352, 1317, 1198, 1143 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.45 (m, 4H), 7.31 (tt, J = 7.0 Hz, J = 1.5 Hz, 1H), 6.09 (s, 1H), 4.62 (s, 1H), 4.36 (s, 2H), 3.87 (s, 1H), 2.68 (t, J = 6.3 Hz, 2H), 2.52-2.60 (m, 4H), 1.83-1.89 (m, 2H), 1.73-1.79 (m, 2H), 1.52-1.60 (m, 2H), 1.38-1.47 (m, 2H), 1.29-1.38 (m, 4H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.8, 144.5, 140.1, 136.2,128.8, 127.7, 127.3, 112.1, 110.7, 104.1, 48.9, 32.0, 30.0, 29.9, 28.8, 24.1, 23.3, 23.2, 22.9, 22.6, 14.3; HRMS-ESI (*m/z*) [M + H] calculated for $C_{23}H_{31}NO$, 338.2478; found 338.2470.


OH
Hex
N
Bn
H
164
7.35 7.31 ppm
2.71 ppm
10
9
8
7
6
5
4
3
2
1
ppm
3.57
0.85
0.99
1.00
2.05
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4.08
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2.04
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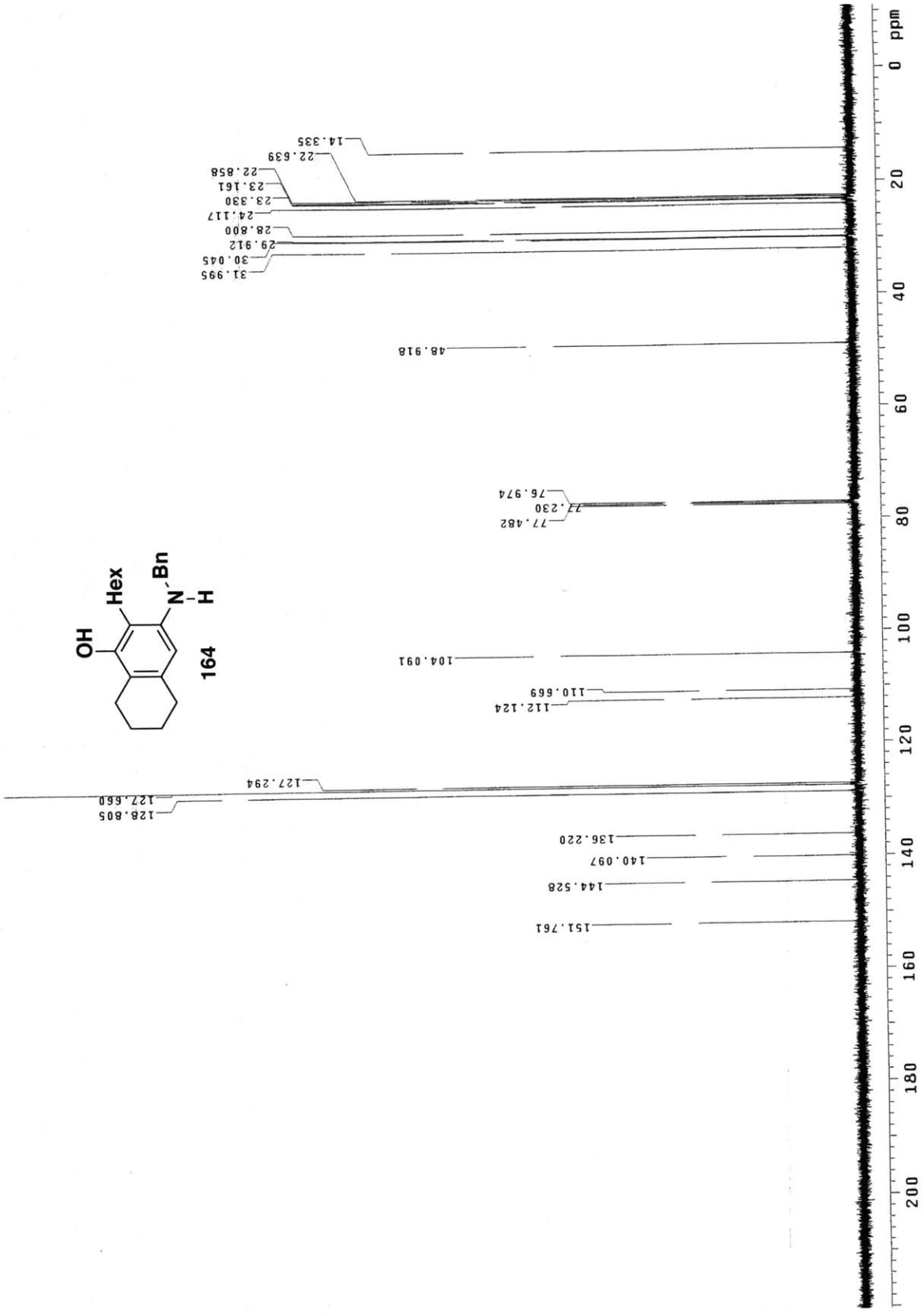
2.05
4.09
2.93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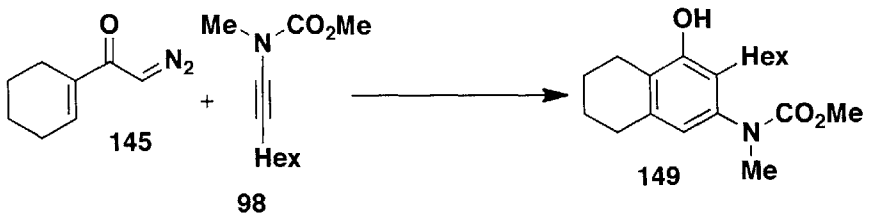
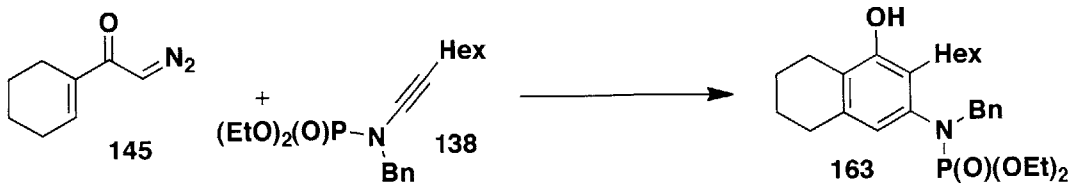
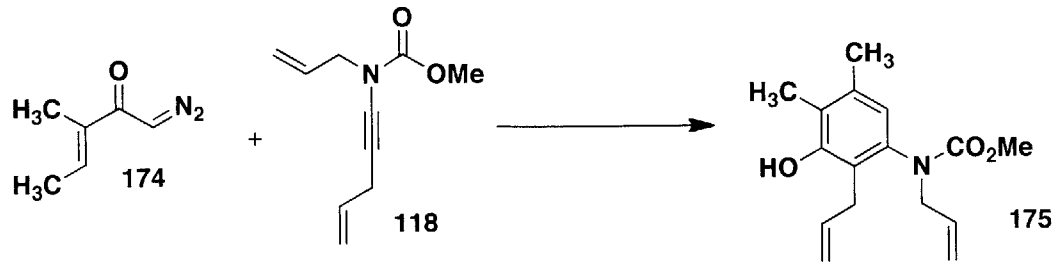


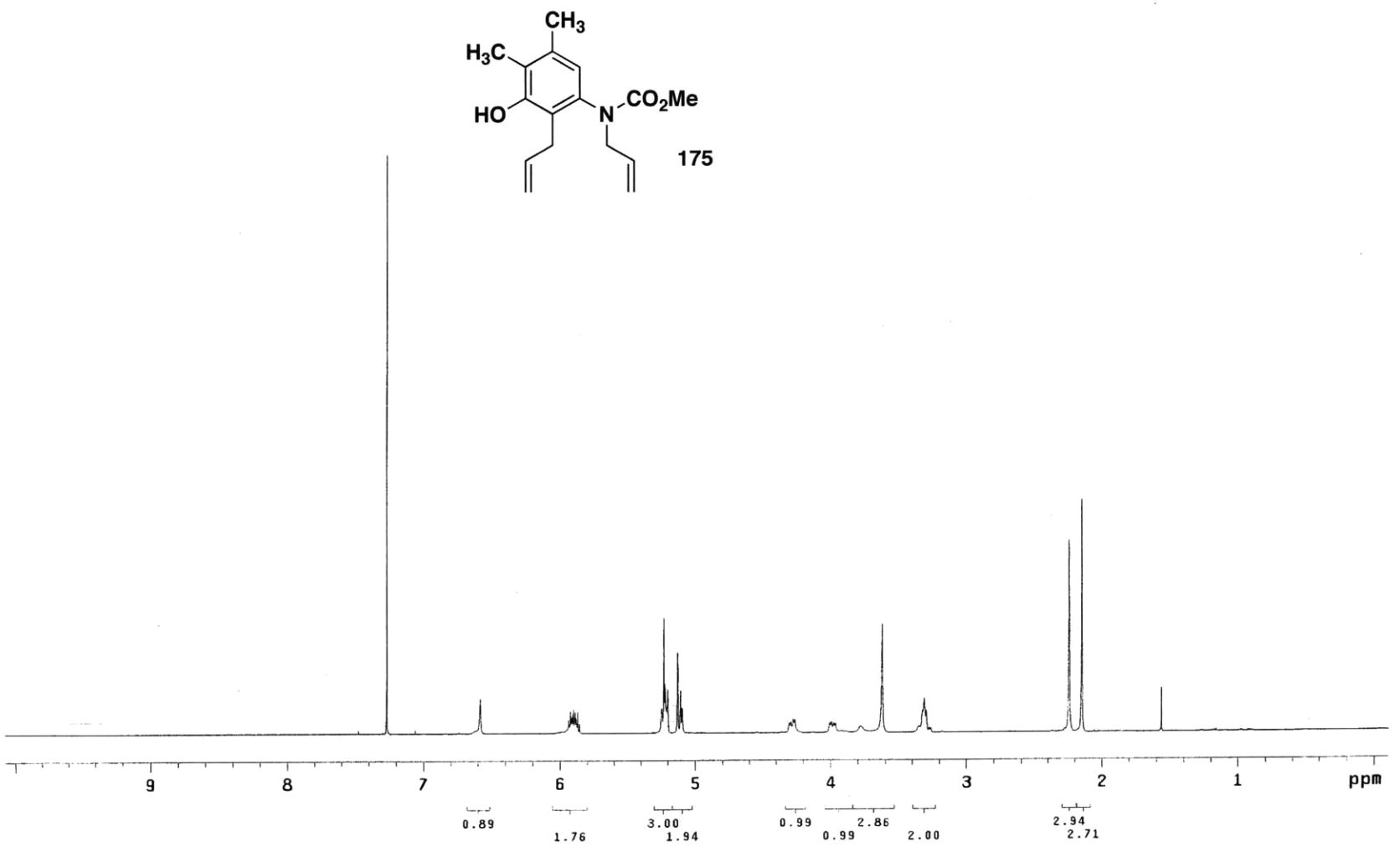
3-[*N*-(carbomethoxy)-*N*-(methyl)amino]-2-hexyl-5,6,7,8-tetrahydro-naphthalen-1-ol (149). A 10-mL round-bottomed flask equipped with a condenser, rubber septum and argon inlet needle was charged with ynamide **98**[62a] (0.060 g, 0.306 mmol, 1.0 equiv) and 1.5 mL of toluene. A 10-mL pear flask fitted with a rubber septum and argon inlet needle was charged with diazo ketone **145**[72a] (0.092 g, 0.612 mmol, 2.0 equiv) and 3 mL of toluene. Both solutions were degassed with a stream of argon for 15 min. The solution of diazo ketone was taken up in a 5-mL glass syringe wrapped in aluminum foil and fitted with a 20-gauge, 20-cm long steel needle. The reaction mixture was heated at reflux and the diazo ketone solution was added through the condenser via syringe pump. After the addition was completed (ca. 8 h), the pear flask was rinsed with 0.5 mL of toluene and added with the same syringe in one portion to the reaction mixture. Heating was continued for 4 h. After cooling to rt, the reaction mixture was concentrated to afford 0.148 g of orange oil. Purification by column chromatography on 20 g of silica gel (elution with 5% EtOAc-10% benzene-85% hexanes) afforded 0.074 g of a yellow oil that was further purified by column chromatography on 16 g of silica gel (elution with 5% EtOAc-10% benzene-85% hexanes) to afford 0.055 g (56%) of phenol **149** as a yellow oil with specral data consistent with that previously reported.[3a]



3-[*N*-(Diethyl phosphoryl)-*N*-(benzyl)amino]-2-hexyl-5,6,7,8-tetrahydro-naphthalen-1-ol (163). A 25-mL round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with ynamide **138**[67] (0.154 g, 0.438 mmol, 1.0 equiv), diazo ketone **145**[72a] (0.070 g, 0.466 mmol, 1.1 equiv), and 5.5 mL of toluene. The septum was replaced with a condenser fitted with an argon inlet adapter and the yellow reaction mixture was stirred at reflux for 7 h. The resulting orange mixture was concentrated to yield 0.220 g of orange oil. Column chromatography on 42 g of silica gel (elution with 20% EtOAc-hexanes + 5% Et_3N) provided 0.154 g of an orange oil that was further purified by column chromatography on 21 g of silica gel (elution with 20% EtOAc-hexanes) to afford 0.137 g (65%) of phenol **163** as a pale yellow oil.



***N*-(Methoxycarbonyl)-*N*-allyl-[2-allyl-4,5-dimethyl-3-hydroxy phenyl]-amine (175).** A 25-mL recovery flask equipped with a condenser, rubber septum and argon inlet needle was charged with ynamide **118**[2] (0.146 g, 0.815 mmol, 1.0 equiv) and 6.0 mL of toluene. A 25-mL pear flask fitted with a rubber septum and argon inlet needle was charged with diazo ketone **174**[72a] (0.244 g, 1.96 mmol, 2.4 equiv) and 8 mL of toluene. Both solutions were degassed with a stream of argon for 15 min. The solution of diazo ketone was taken up in a 10-mL glass syringe wrapped in aluminum foil and fitted with an 20-gauge, 20-cm long steel needle. The reaction mixture was heated at reflux and the diazo ketone solution was added through the condenser via syringe pump. After the addition was completed (ca. 13.5 h), the pear flask was rinsed with 0.5 mL of toluene and added with the same syringe in one portion to the reaction mixture. Heating was continued for 5 h. After cooling to rt, the reaction mixture was concentrated to afford 0.450 g of orange oil that was diluted with 5 mL of MeOH and 3 mL of 5 M KOH solution. After heating at 60-70 °C for 2 h, the resulting mixture was cooled to rt, then quenched with 16 mL of 1 M HCl solution, and diluted with 20 mL of Et_2O. The aqueous layer was extracted with two 20-mL portions of Et_2O and the combined organic layers were washed with 40 mL of satd $NaHCO_3$ solution, 40 mL of brine, dried over $MgSO_4$, filtered, and concentrated to provide 0.308 g of orange oil. Purification by column chromatography on 39 g of silica gel (gradient elution with 15-20% EtOAc-hexanes) afforded 0.146 g of aniline **175** (65%) as a yellow solid: mp 70-72 °C; IR (neat) 3412, 3078, 2925, 2857, 1686, 1575, 1455, 1389, 1320, 1257, 1196 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.58 (s, 1 H), 5.85-6.02 (m, 2 H), 5.18-5.30 (m, 3 H), 5.07-5.15 (m, 2 H), 4.21-4.32 (m, 1 H), 3.85-4.03 (m, 1 H), 3.78 and 3.62 (rotamers, s, 3 H), 3.26-3.39 (m, 2 H), 2.24 (s, 3 H), 2.15 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.4, 153.5, 137.8, 136.8, 135.9, 133.4, 123.4, 122.1, 120.2, 118.4, 117.3, 54.1, 53.1, 30.9, 20.2, 12.0; HRMS-ESI (*m/z*) [M + H] calculated for $C_{16}H_{21}NO_3$, 276.1594; found 276.1598.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HO
N
CO2Me
175
9
8
7
6
5
4
3
2
1
ppm
0.89
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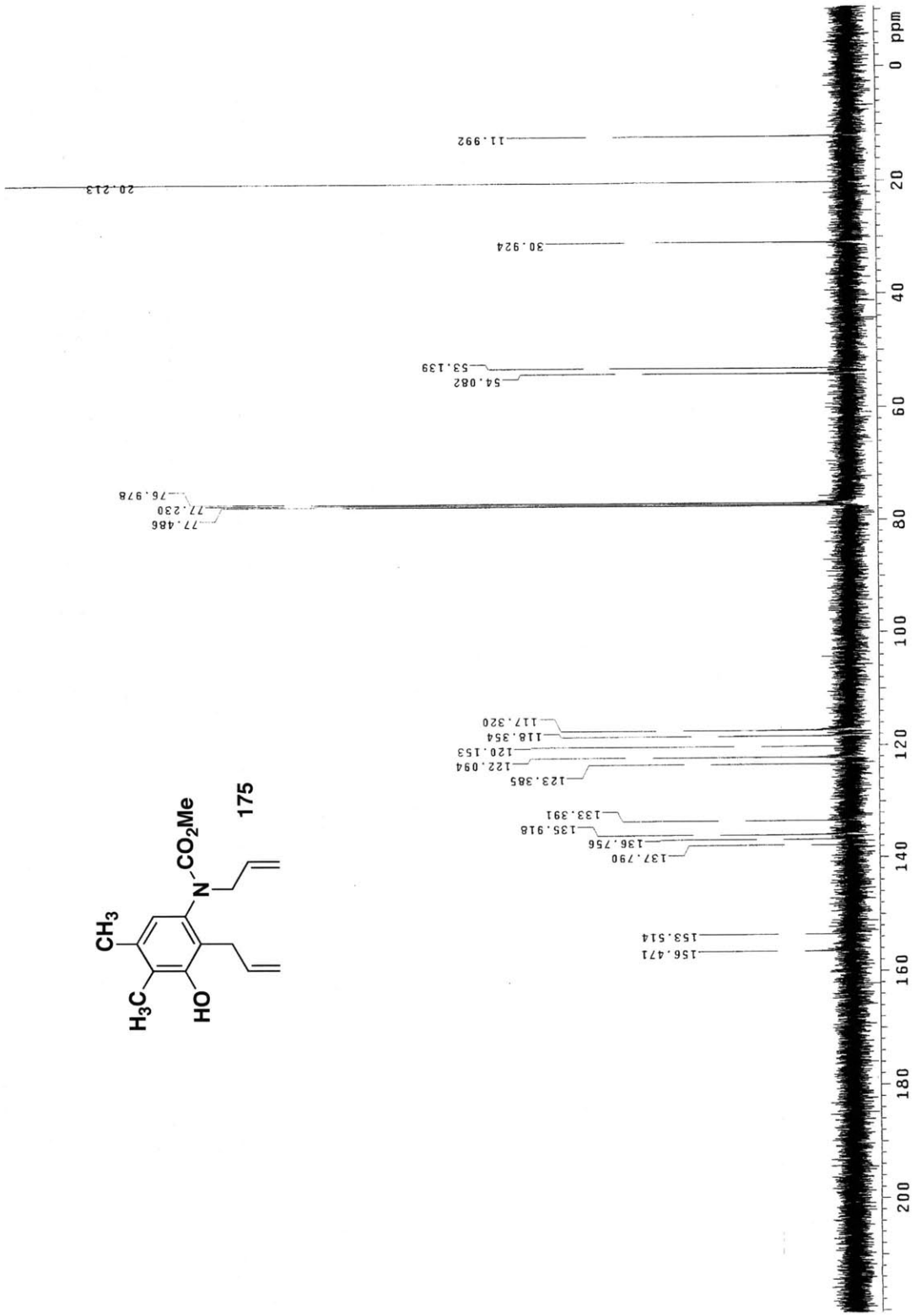
3.00
1.94
0.99
0.99
2.86
2.00
2.94
2.71


175
CO2Me
N
CH3
H3C
HO
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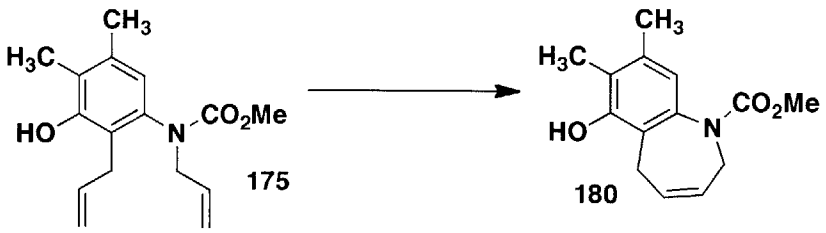
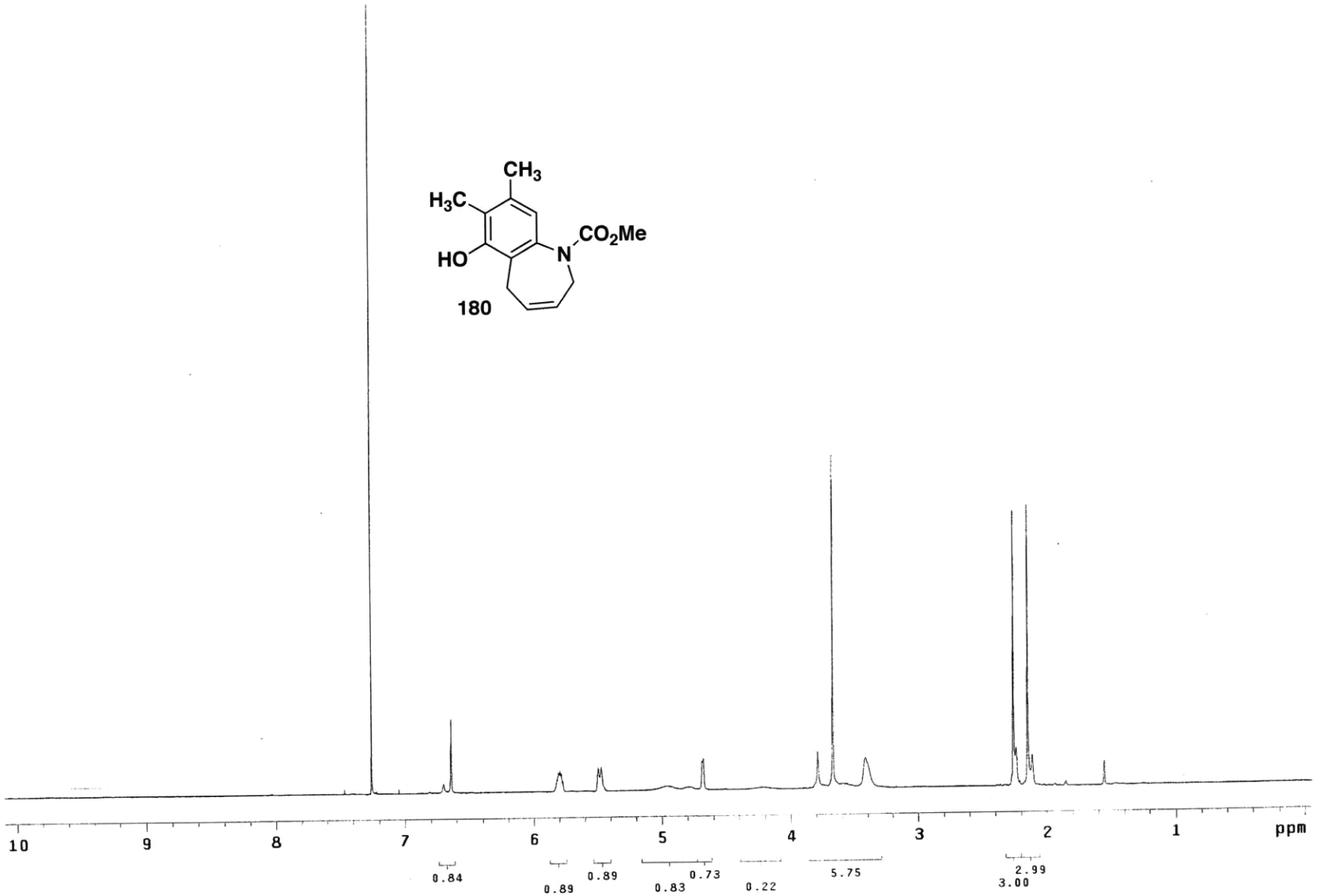
30.924
53.139
54.082
76.978
77.230
77.486
117.320
118.354
120.153
122.094
123.385
133.391
135.918
136.756
137.790
153.514
156.471
0 ppm
20
40
60
80
100
120
140
160
180
200



6-Hydroxy-7,8-dimethyl-2,5-dihydro-benzo[*b*]azepine-1-carboxylic acid methyl ester (180). A 100-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with a solution of the Grubbs catalyst **179** (0.014 g, 0.016 mmol, 0.05 equiv) in 30 mL of CH_2Cl_2. The aniline **175** (0.094 g, 0.341 mmol, 1.0 equiv) in 6 mL of CH_2Cl_2 was added to the reaction flask via cannula in one portion and the rubber septum was replaced with a reflux condenser fitted with an argon inlet adapter. The pale pink-colored reaction mixture was heated at reflux for 40 min, allowed to cool to rt, and then concentrated onto 2 g of silica gel. The free-flowing powder was deposited on a column of 20 g of silica gel and eluted with 25% EtOAc-hexanes to afford 0.081 g (96%) of dihydrobenzoazepine **180** as a tan wax: IR (neat) 3399, 3024, 2955, 1685, 1615, 1579, 1456, 1395, 1333, 1262, 1193, 1088 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 80:20 mixture of rotamers δ 6.70 and 6.64 (rotamers, s, 1 H), 5.75-5.84 (m, 1 H), 5.43-5.52 (m, 1 H), 4.72-5.16 (m, 1 H), 4.69 and 4.22 (rotamers, s, 1 H), 3.79 and 3.67 (rotamers, s, 3 H), 3.34-3.66 (m, 3 H), 2.26 and 2.24 (rotamers, s, 3 H), 2.15 and 2.12 (rotamers, s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.4, 150.4, 139.5, 135.8, 127.3 and 126.9 (rotamers), 126.0, 125.2, 123.8, 121.5 and 121.4 (rotamers), 53.4, 48.3 and 48.1 (rotamers), 23.3 and 23.1 (rotamers), 20.4, 12.3; HRMS-ESI (*m/z*) [M + H] calculated for $C_{14}H_{17}NO_3$, 248.1281; found 248.1272.


CH3
H3C
HO
N
CO2Me
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10
9
8
7
6
5
4
3
2
1
ppm
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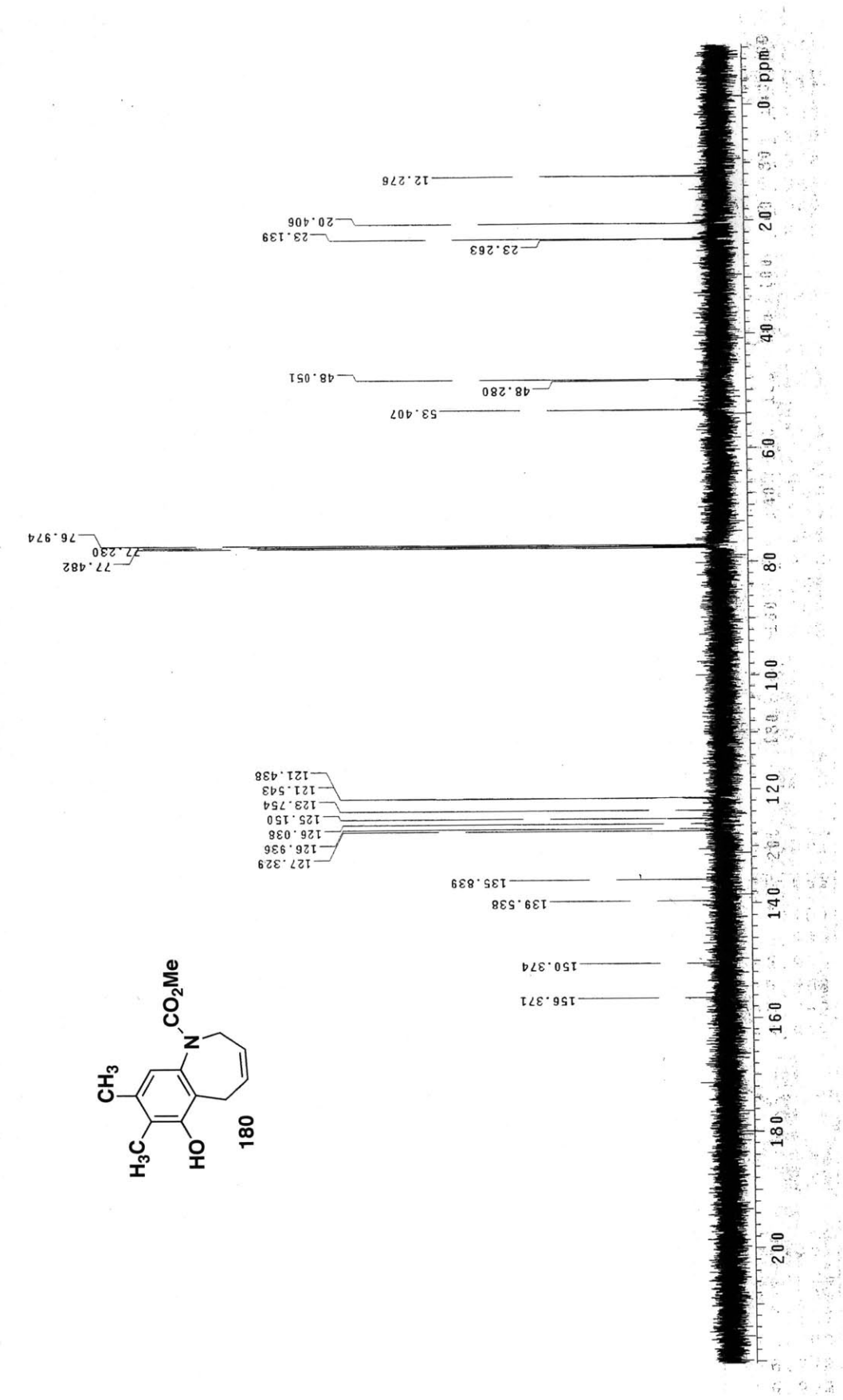
0.89
0.89
0.83
0.73
0.22
5.75
2.99
3.00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123.754
125.150
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127.329
135.839
139.538
150.374
156.371
ppm
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80
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140
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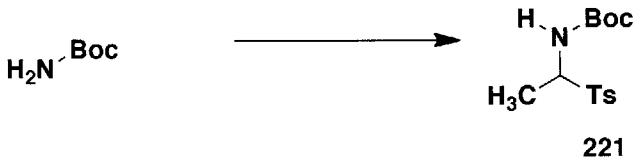
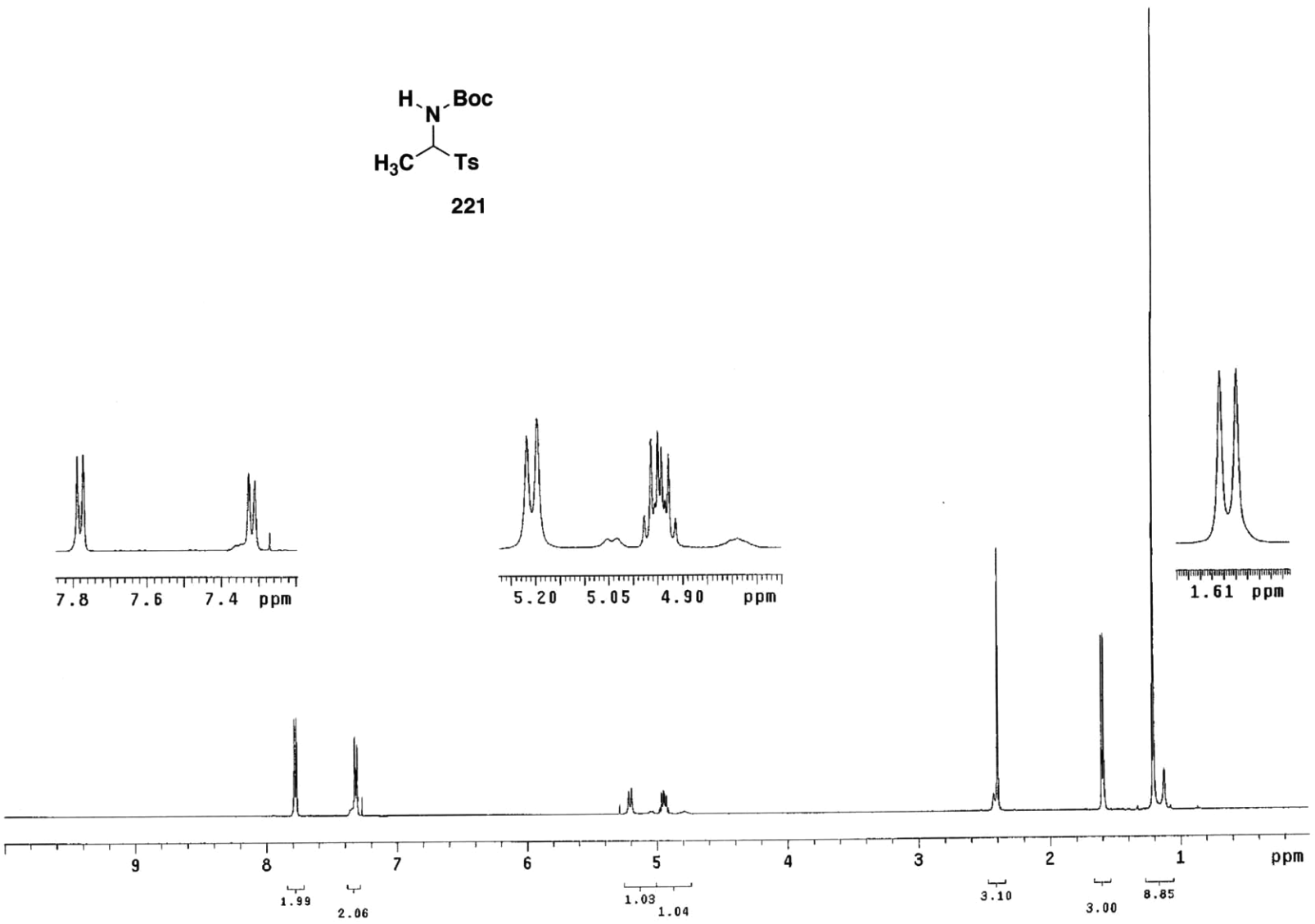
200
CO2Me
N
CH3
H3C
HO
180

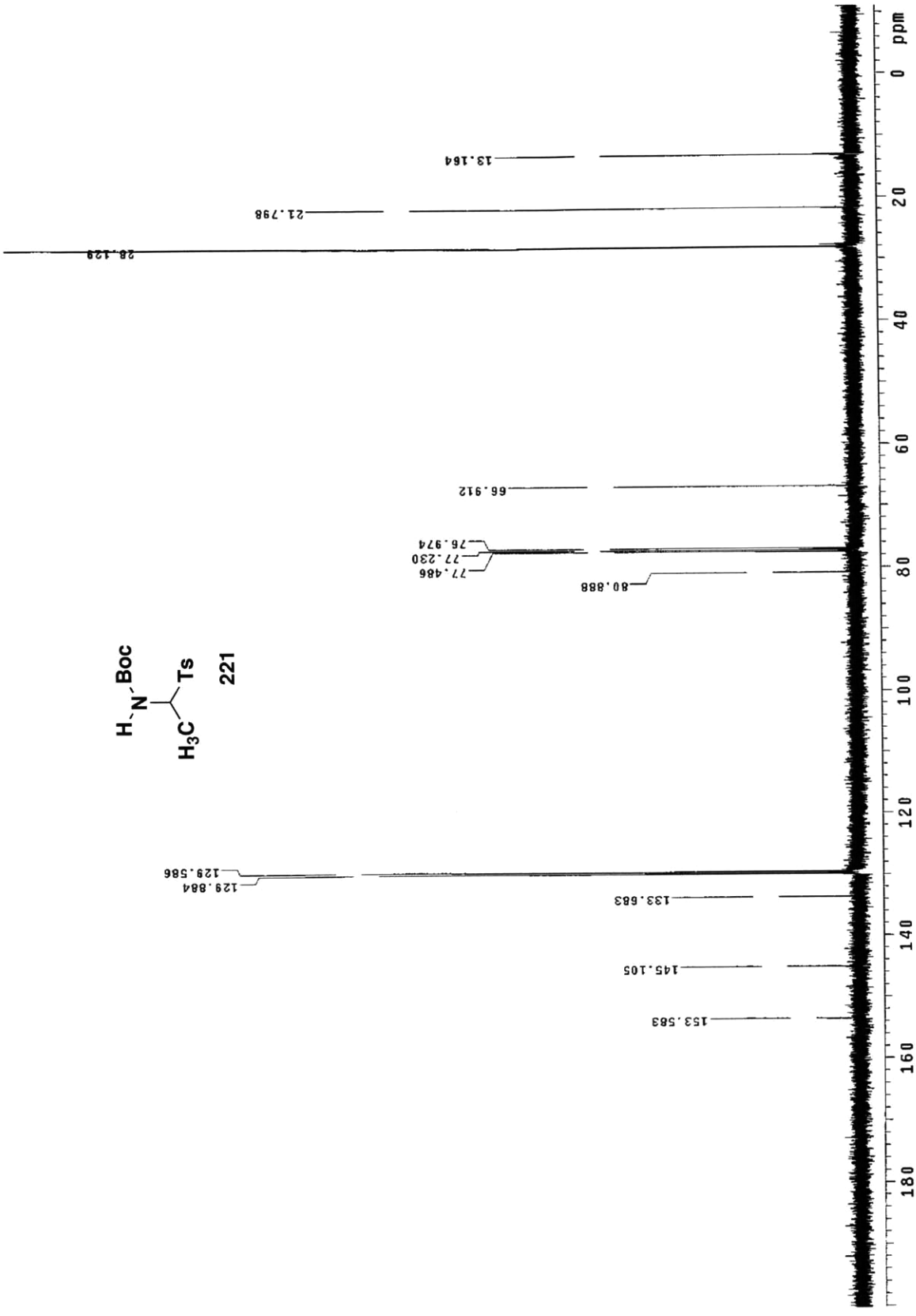


221

tert-Butyl (1-tosylethyl) carbamate (221)[208]. A 50-mL pear flask equipped with a rubber septum and argon inlet needle was charged with *tert*-butyl carbamate (0.703 g, 6.0 mmol, 1.0 equiv), sodium *p*-toluensulfinate dihydrate (1.29 g, 6.0 mmol, 1.0 equiv), acetaldehyde (0.37 mL, 6.6 mmol, 1.1 equiv), formic acid (1.6 mL, 42.4 mmol, 7.0 equiv), 0.7 mL methanol, and 6 mL H_2O. The septum was replaced with a cold-finger condenser fitted with an argon inlet and the heterogeneous reaction mixture was stirred at 70 °C for 1h. The condenser was replaced with a cap and the reaction was cooled at 4 °C for 5 h. The resulting crystals were collected by filtration, washed with 30 mL of cold water, and then transferred to a 25-mL recovery flask and dried overnight at 0.1 mmHg to provide 1.36 g (76%) of carbamate **221** as a white solid: mp 108-109 °C; IR (neat) 3441, 2981, 2933, 1728, 1494, 1322, 1168, 1146 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) some peaks show rotamers δ 7.79 (d, J = 8 Hz, 2H), 7.33 (d, J = 8 Hz, 2H), 5.10 (d, J = 10.5 Hz, 1H), 4.83-4.88 (d, minor rotamer), 4.91-4.99 (qd, J = 7.0, 11.0 Hz, 1H), 4.75-4.84 (m, minor rotamer), 2.44 (s, minor rotamer), 2.41 (s, 3H), 2.61 (d, J = 7.0 Hz, 3H) 1.22 (s, 18H), 1.13 (s, minor rotamer); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 145.1, 133.7, 129.9, 129.6, 80.9, 66.9, 28.1, 21.8, 13.2; HRMS-DART-ESI (*m/z*) [M + NH_4] calculated for $C_{14}H_{21}NO_4S$: 317.1530, found: 317.1522.

[208] This procedure is based on Pearson, W. H., Lindbeck, A. C., Kampf, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 2622-2636.


H
N
Boc
H3C
Ts
221
7.8
7.6
7.4
ppm
5.20
5.05
4.90
ppm
1.61
ppm
9
8
7
6
5
4
3
2
1
ppm
1.99
2.06
1.03
1.04
3.10
3.00
8.85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77.486
80.888
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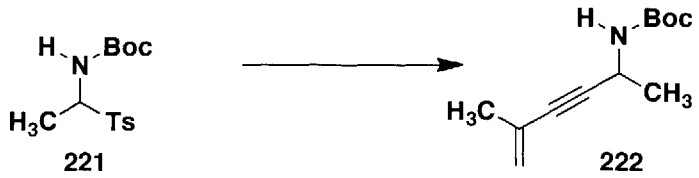
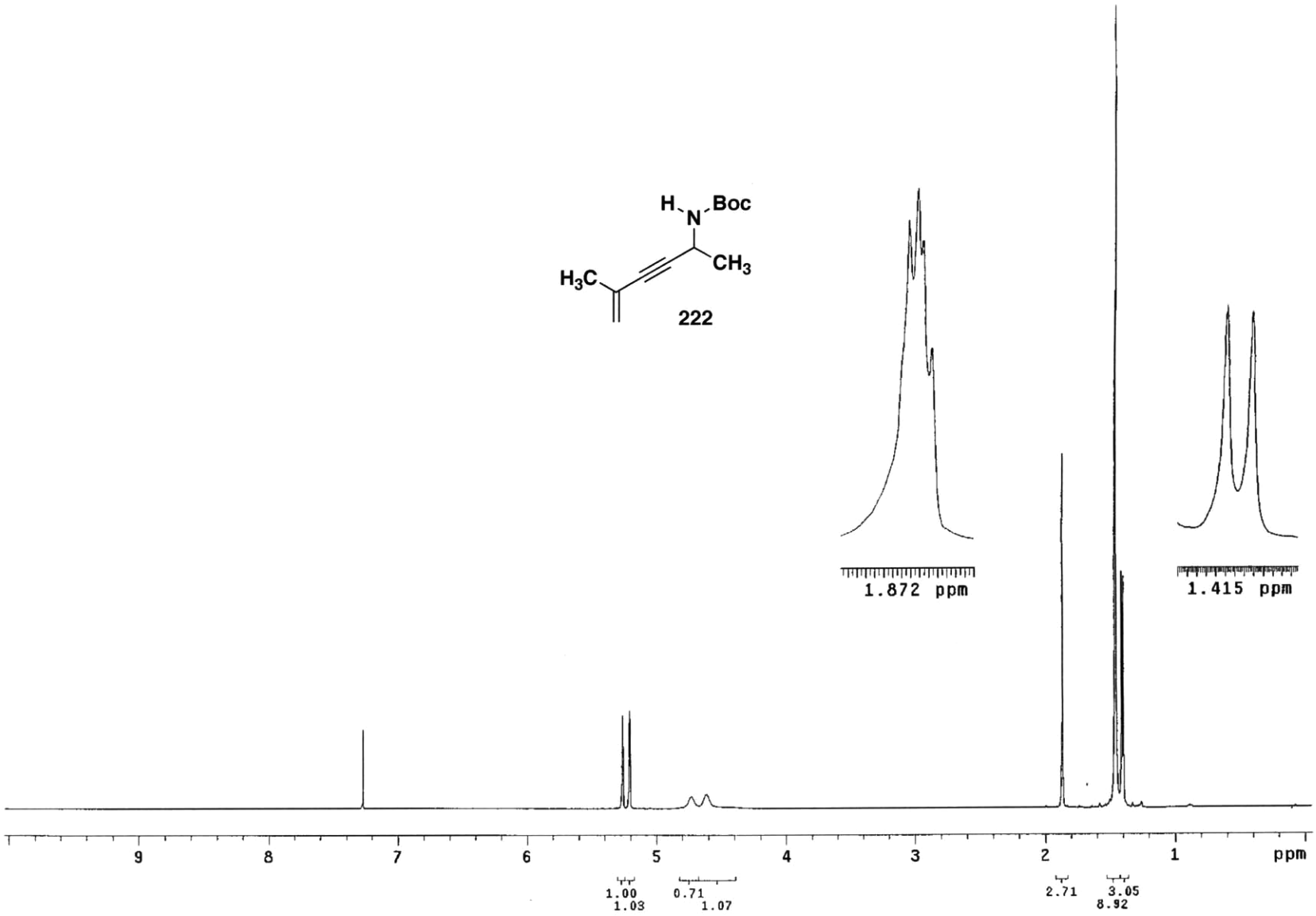
129.586
133.683
145.105
153.583
0 ppm
20
40
60
80
100
120
140
160
180
Boc
N
H
Ts
H3C
221



tert-Butyl (5-methylhex-5-en-3-yn-2-yl)carbamate (222)[209]. A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, two rubber septa, and a thermocouple probe was charged with isopropenylacetylene (0.23 mL, 0.16g, 2.4 mmol, 2.0 equiv) and 10 mL of THF. The reaction mixture was cooled to -20 °C and *n*-BuLi solution (2.6 M in hexanes, 0.95 mL, 2.5mmol, 2.1 equiv) was added dropwise over 5 min. The bright yellow reaction mixture was stirred at -20 °C for 20 min and then cooled to -78 °C. A solution of carbamate **221** (0.361 g, 1.2 mmol, 1.0 equiv) in 2.5 mL of THF was added via cannula over 7 min (0.5 mL THF rinse). The reaction mixture was stirred at -78 °C for 1 h, and then 4 mL of satd aq NH_4Cl was added dropwise over 2 min. The resulting mixture was allowed to warm to rt and then diluted with 7 mL of H_2O and extracted with four 12-mL portions of CH_2Cl_2. The combined organic phases were washed with 40 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.247 g of a pale yellow solid. Column chromatography on 13 g of silica gel (elution with 2% EtOAc-hexanes) afforded 0.228 g (90%) of carbamate **222** as a white solid: mp 71-72 °C; IR (neat) 3456, 2980, 2932, 1719, 1453, 1368, 1244, 1173 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.22-5.26 (m, 1H), 5.17-5.5.21 (m, 1H), 4.72-4.85 (m, 1H), 4.54-4.64 (m, 1H), 1.84-1.88 (m, 3H), 1.46 (s, 9H), 1.40 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 126.6, 122.1, 89.0, 83.6, 79.9, 39.1, 28.6, 23.7, 23.1; HRMS-DART-ESI (*m/z*) [M + H] calculated for $C_{12}H_{19}NO_2$: 210.1489, found: 210.1486.

[209] This procedure is based on ref 111.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H3C
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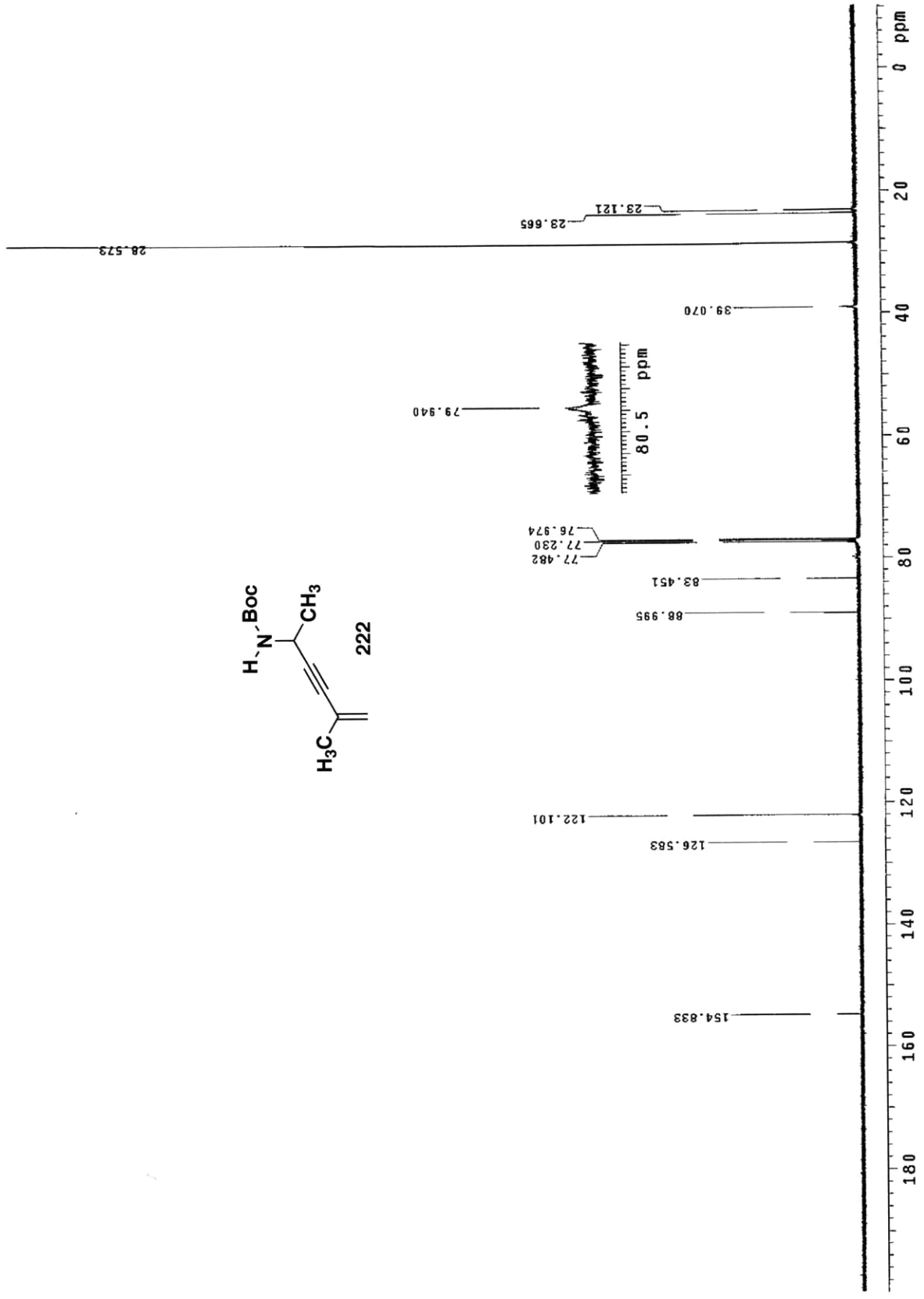
1.415 ppm
9
8
7
6
5
4
3
2
1
ppm
1.00
1.03
0.71
1.07
2.71
3.05
8.92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39.070
79.940
80.5 ppm
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77.230
76.974
83.451
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20
40
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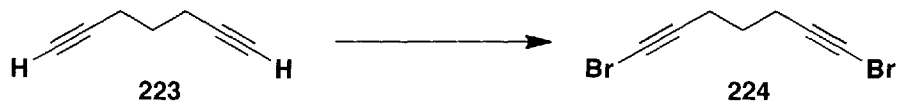
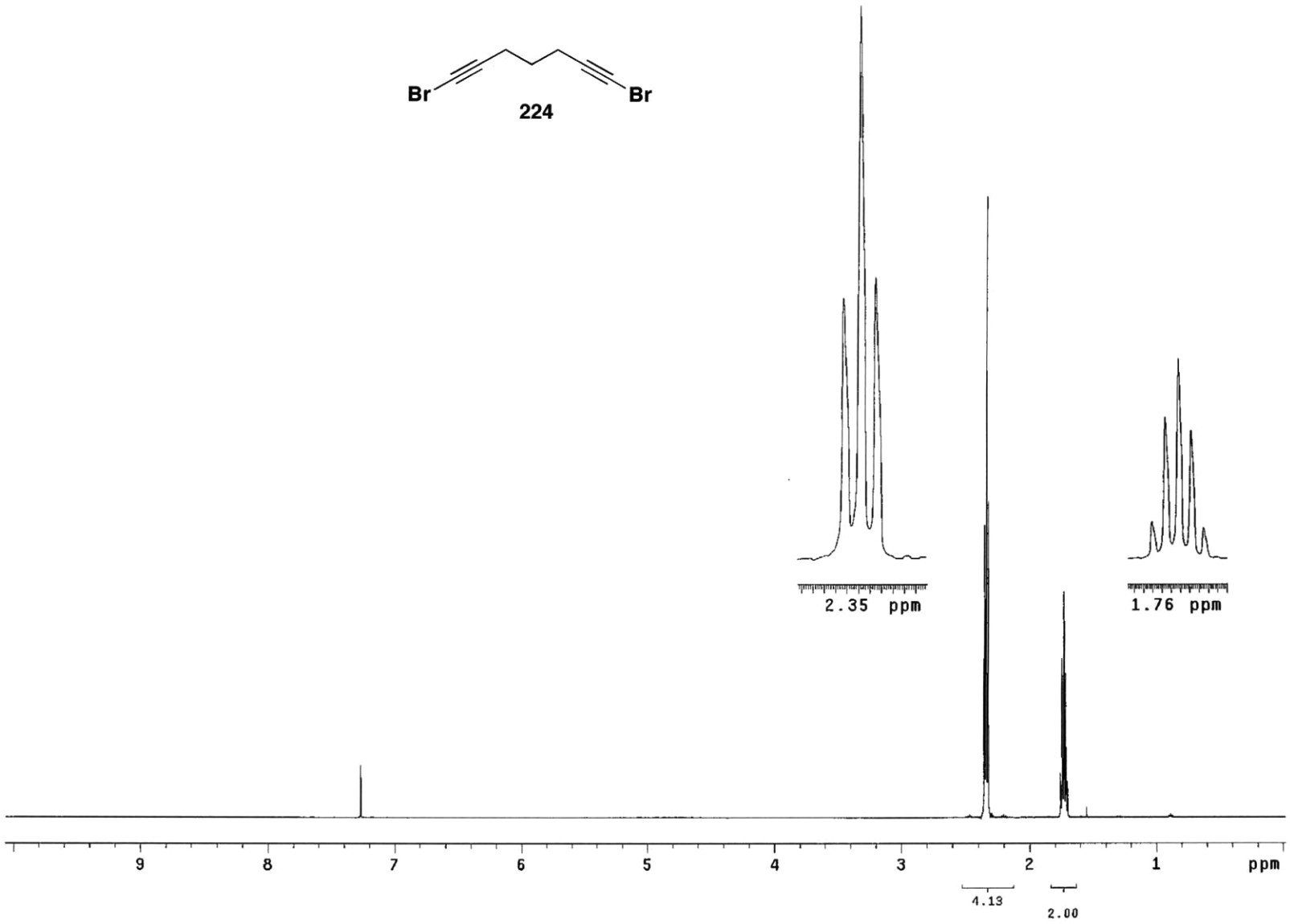
100
120
140
160
180



1,7-Dibromohepta-1,6-diyne (224). A 100-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and glass stopper was charged with 1,6-heptadiyne (**223**) (0.62 mL, 5.4 mmol, 1.0 equiv), NBS (2.13 g, 11.9 mmol, 2.2 equiv), $AgNO_3$ (0.100 g, 0.54 mmol, 0.1 equiv), and 18 mL of acetone. The resulting mixture was stirred in the dark at rt for 1 h and then diluted with 25 mL of pentane and 37 mL of water. The organic layer was washed with three 10-mL portions of satd aq $Na_2S_2O_3$ solution and 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated to yield 1.30 g of a pale yellow oil. Filtration through a 6 g plug of silica gel (elution with pentane) afforded 1.25 g (93%) of alkynyl bromide **224** as a pale yellow oil: IR (thin film) 2956, 2938, 2908, 2218, 1452, 1430, 1345, 1327, 1309, 1291 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.34 (t. J = 7.0 Hz, 4H), 1.73 (quint, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 79.3, 38.9, 27.2,19.0; HRMS-ESI (*m/z*) [M + H] calculated for $C_7H_6Br_2$, 250.8892; found, 250.8901.


Br
Br
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1.76 ppm
9
8
7
6
5
4
3
2
1
ppm
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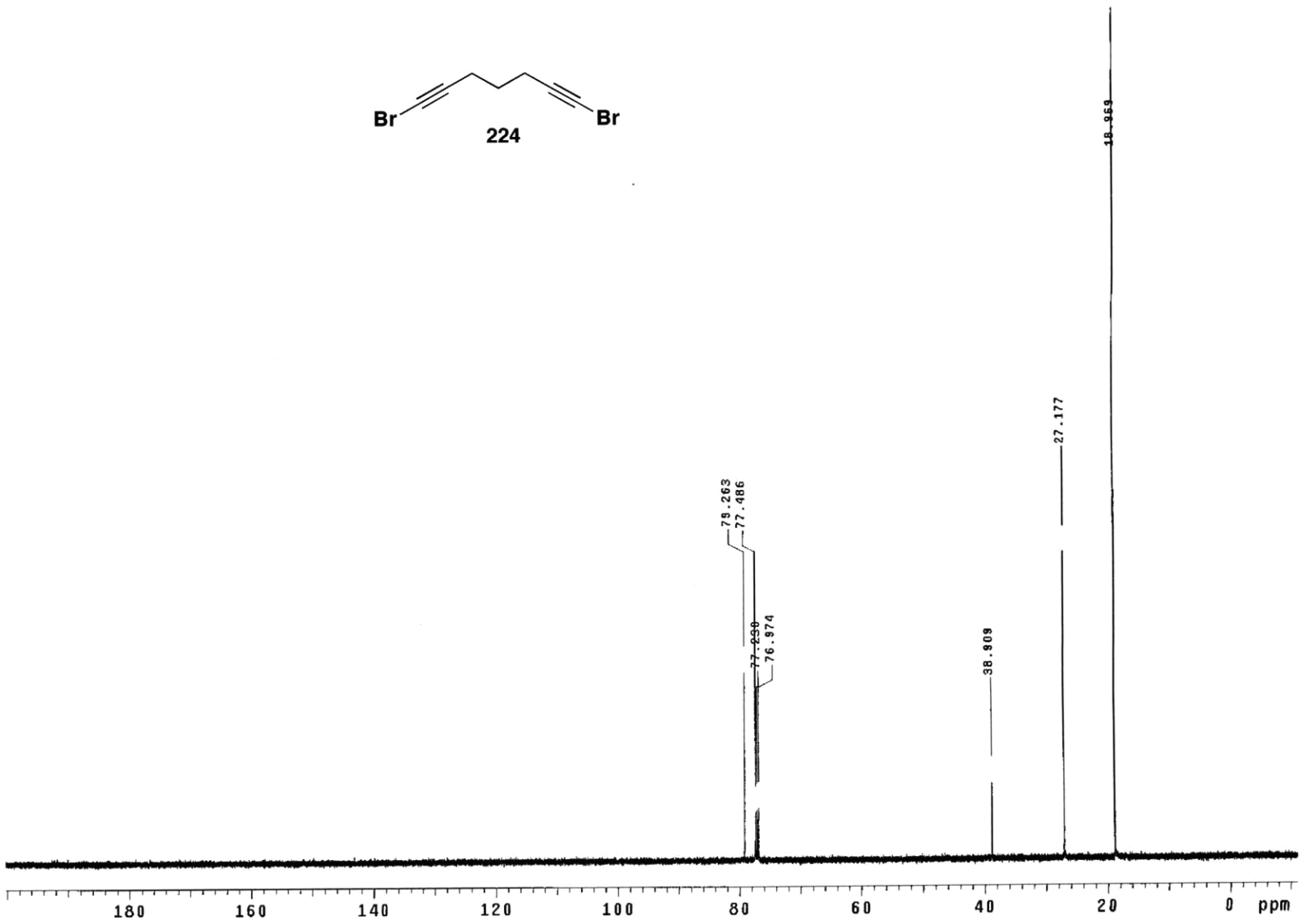
2.00


Br
Br
224
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77.486
77.230
76.974
38.909
27.177
18.969
180
160
140
120
100
80
60
40
20
0
ppm

tert-Butyl oct-1-ynyl(3-phenylprop-2-ynyl) carbamate (225). A 100-mL recovery flask equipped with a rubber septum and argon inlet needle was charged with carbamate **218**[109] (3.29 g, 14 mmol, 1.0 equiv), K_3PO_4 (6.05 g, 28 mmol, 2.0 equiv), $CuSO_4 \cdot 5H_2O$ (0.356 g, 1.4 mmol, 0.10 equiv), 1,10-phenanthroline (0.514 g, 2.9 mmol, 0.20 equiv), and 10 mL of toluene. A solution of 1-bromooctyne **130**[62b] (3.0 g, 16 mmol, 1.1 equiv) in 5 mL of toluene was added via cannula over 2 min (3 mL of toluene rinse). The septum was replaced with a cold-finger condenser fitted with an argon inlet adaptor and the heterogeneous reaction mixture was stirred at 85 °C for 25 h. The resulting mixture was allowed to cool to rt and $CuSO_4 \cdot 5H_2O$ (0.356 g, 1.4 mmol, 0.10 equiv) and 1,10-phenanthroline (0.514 g, 2.8 mmol, 0.20 equiv) were added. The reaction mixture was stirred at 88 °C for 24 h, allowed to cool to rt, and diluted with 10 mL of EtOAc. The mixture was filtered through a ca. 4-g plug of Celite with the aid of five 15-mL portions of EtOAc, and the filtrate was concentrated to yield ca. 6.69 g of red-brown oil. Purification by column chromatography on 150 g of silica gel (elution with 1% EtOAc-hexanes) afforded 3.88 g (80%) of ynamide **225** as a yellow oil: IR (neat) 2931, 2858, 2264, 1721, 1290, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.45 (m, 2H), 7.28-7.31 (m, 3H), 4.41 (s, 2H), 2.33 (t, J = 6.8 Hz, 2H), 1.49-1.55 (m, 2H), 1.52 (s, 9H), 1.36-1.47 (m, 2H), 1.25-1.28 (m, 4H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 131.9, 128.5, 128.3, 122.8, 84.6, 83.6, 82.6, 73.7, 70.4, 40.0, 31.5, 29.1, 28.6, 28.2, 22.7, 18.7, 14.2; HRMS-ESI (*m/z*) [M + Na] calculated for $C_{22}H_{29}NO_2$: 362.2091, found: 362.2098.

Boc
N
Ph
Hex
225
2.4
ppm
0.9
ppm
9
8
7
6
5
4
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2
1
ppm
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2.89
1.94
2.00
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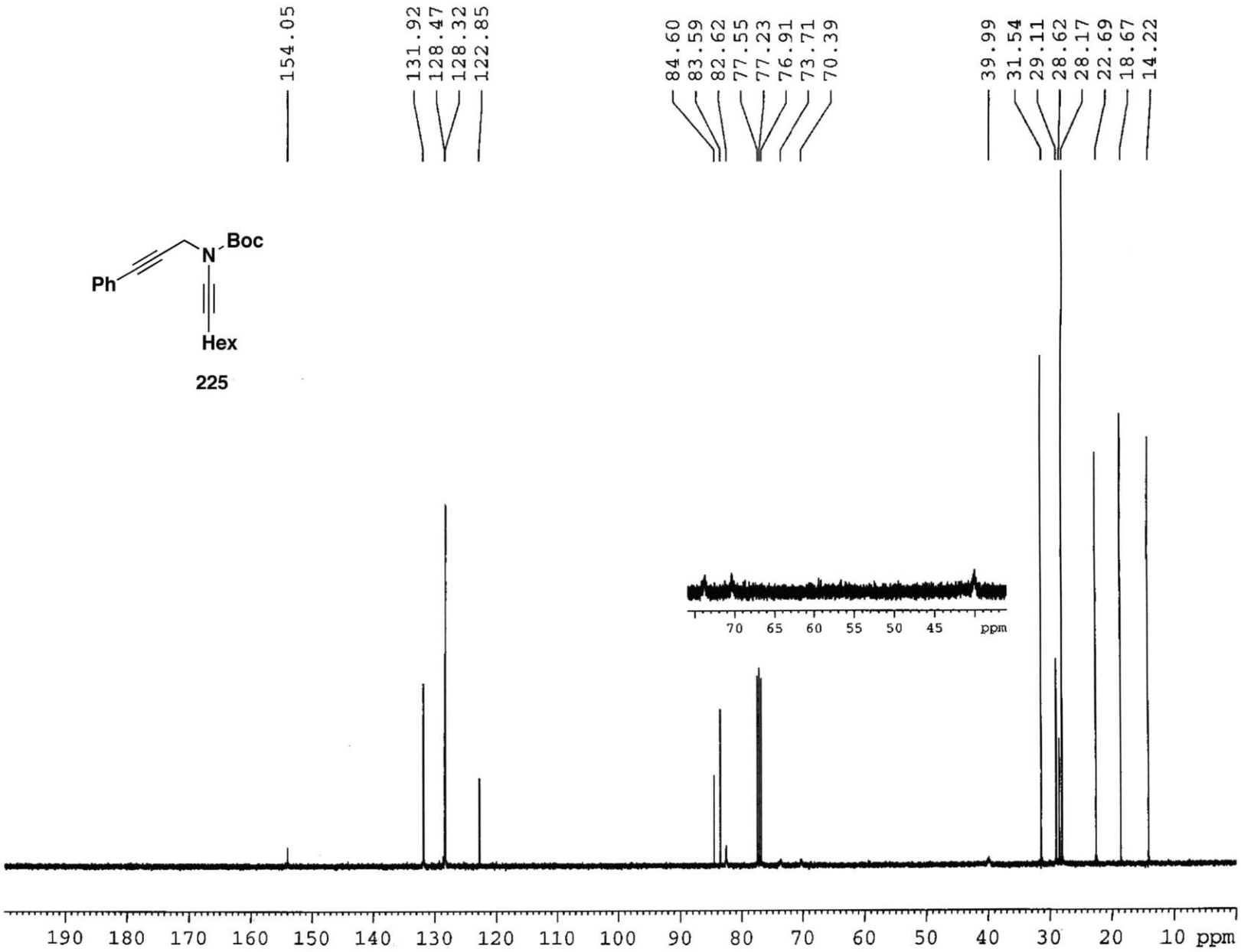
3.07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82.62
77.55
77.23
76.91
73.71
70.39
39.99
31.54
29.11
28.62
28.17
22.69
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Hex
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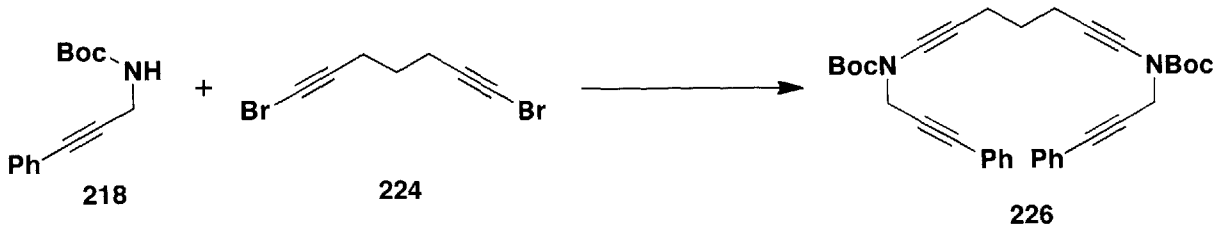
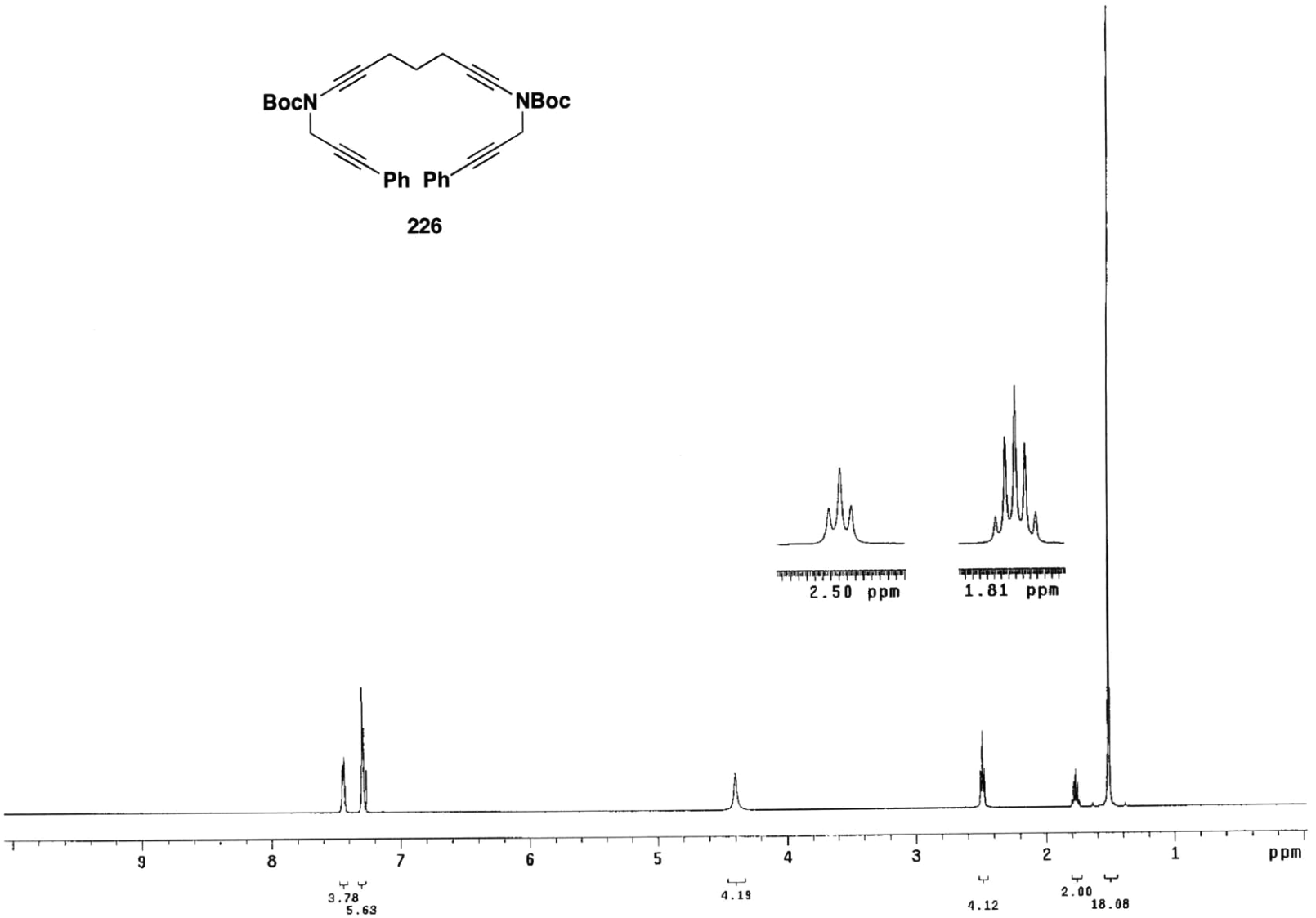
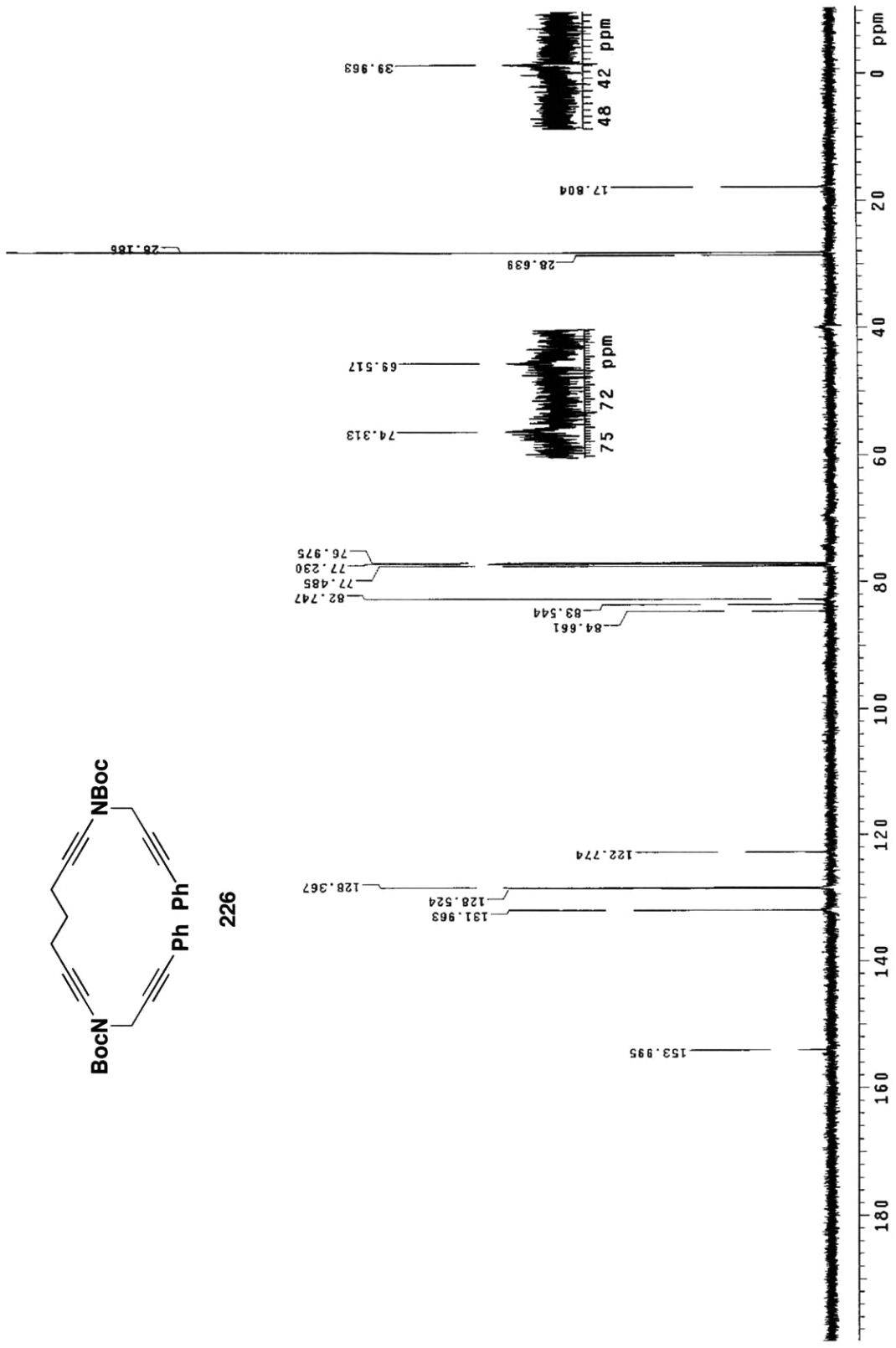
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



di-tert-Butyl hepta-1,6-diyne-1,7-diylbis((3-phenylprop-2-yn-1-yl)carbamate) (226). A 25-mL pear flask equipped with a rubber septum and argon inlet needle was charged with carbamate **218**[109] (0.238 g, 1.0 mmol, 2.5 equiv), K_3PO_4 (0.350 g, 1.6 mmol, 4.0 equiv), $CuSO_4 \cdot 5H_2O$ (0.041 g, 0.16 mmol, 0.40 equiv), 1,10-phenanthroline (0.059 g, 0.33 mmol, 0.80 equiv), 1,7-dibromohepta-1,6-diyne **224** (0.103 g, 0.41 mmol, 1 equiv), and 1.6 mL of toluene. The septum was replaced with a cold-finger condenser fitted with an argon inlet adapter and the reaction mixture was stirred at 80-85 °C for 52 h and then allowed to cool to rt. The resulting mixture was diluted with 5 mL of EtOAc and filtered through a ca. 2-g plug of Celite with the aid of five 5-mL portions of EtOAc. Concentration of the filtrate yielded 0.317 g of a brown oil. Purification by column chromatography on 64 g of Brockman II alumina (elution with benzene) afforded 1.73 g of a yellow oil which was further purified by column chromatography on 18 g of silica gel (elution with 5% EtOAc-hexanes) to afford 0.137 g (60%) of ynamide **226** as a yellow oil: IR (neat) 2979, 2933, 2265, 1720, 1490. 1389, 1291, 1160 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43-7.46 (m, 4H), 7.28-7.31 (m, 6H), 4.40 (s, 4H), 2.49 (t, J = 7.0 Hz, 4H), 1.77 (quint, J = 7 Hz, 2H), 1.51 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.0, 132.0, 128.5, 128.4, 122.8, 84.7, 83.5, 82.7, 74.3, 69.5, 40.0, 28.6, 28.2, 17.8; HRMS-ESI (*m/z*) [M + Na] calculated for $C_{35}H_{38}N_2O_4$, 573.2724; found, 573.2737.


BocN
NBoc
Ph Ph
226
2.50 ppm
1.81 ppm
9
8
7
6
5
4
3
2
1
ppm
3.78
5.63
4.19
4.12
2.00
18.08


NBoc
Ph
Ph
BocN
226
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128.367
128.524
131.963
122.774
84.661
83.544
82.747
77.485
77.230
76.975
74.313
69.517
39.963
28.638
28.186
17.804
ppm
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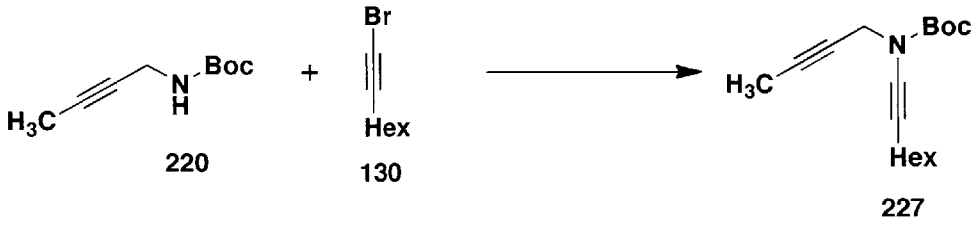
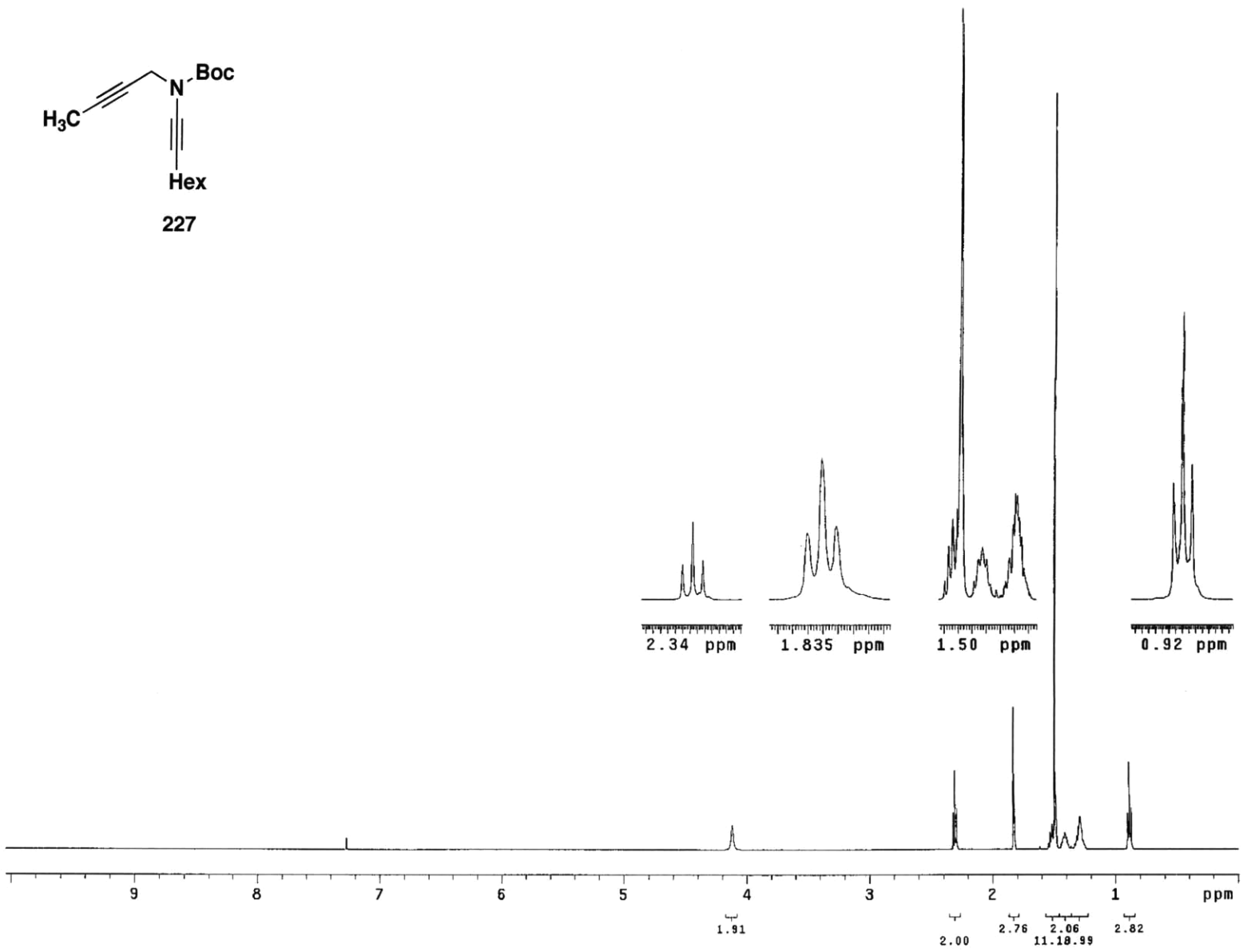
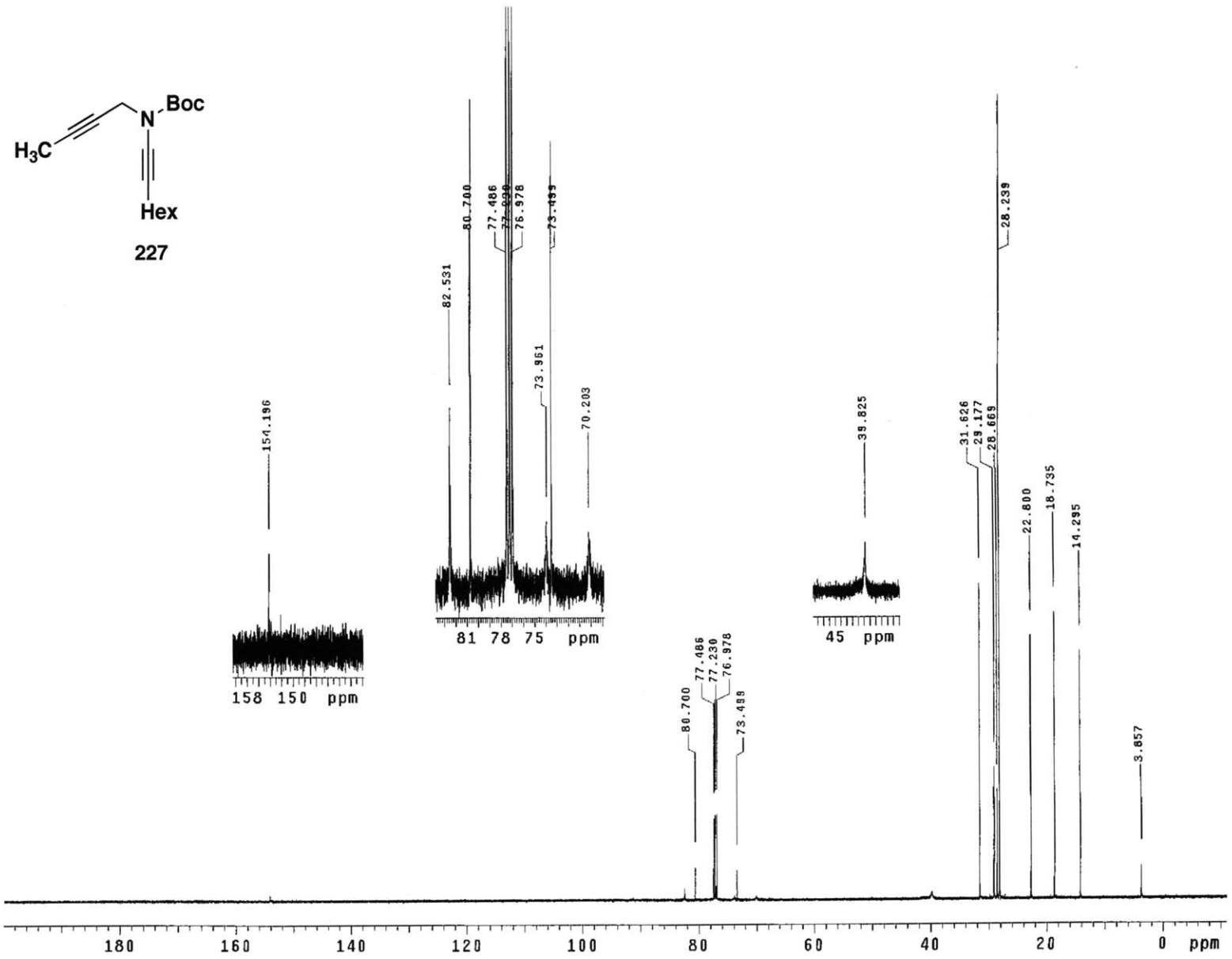
40
60
80
100
120
140
160
180
48
42
75
72



tert-Butyl but-2-yn-1-yl(oct-1-yn-1-yl)carbamate (227). A 25-mL pear flask equipped with a rubber septum and argon inlet needle was charged with carbamate **220**[110] (0.177 g, 1.0 mmol, 1.0 equiv), K_3PO_4 (0.444 g, 0.21 mmol, 2.0 equiv), $CuSO_4 \cdot 5H_2O$ (0.026 g, 0.11 mmol, 0.10 equiv), 1,10-phenanthroline (0.036 g, 0.21 mmol, 0.20 equiv), and 0.5 mL of toluene. A solution of 1-bromooctyne **130**[62b] (0.217 g, 1.2 mmol, 1.1 equiv) in 0.5 mL of toluene was added via cannula over 1 min (0.5 mL of toluene rinse). The septum was replaced with a cold-finger condenser fitted with an argon inlet adapter and the heterogeneous reaction mixture was stirred at 85-90 °C for 24 h. The resulting mixture was allowed to cool to rt and $CuSO_4 \cdot 5H_2O$ (0.0.26 g, 0.11 mmol, 0.10 equiv) and 1,10-phenanthroline (0.036 g, 0.21 mmol, 0.20 equiv) were added. The reaction mixture was stirred at 85-90 °C for 26 h, allowed to cool to rt, and diluted with 3 mL of EtOAc. The mixture was filtered through a ca. 2-g plug of Celite with the aid of five 5-mL portions of EtOAc, and the filtrate was concentrated to yield ca. 0.376 g of red-brown oil. Purification by column chromatography on 19 g of silica gel (elution with 3% EtOAc-hexanes) afforded 0.239 g (83%) of ynamide **227** as a faint yellow oil: IR (neat) 2932, 2859, 2265, 1721, 1292, 1163 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.05-4.19 (m, 2H), 2.31 (t, J = 7.0 Hz, 2H), 1.83 (t, J = 2.2 Hz, 3H) 1.48-1.55 (m, 2H), 1.49 (s, 9H), 1.36-1.45 (m, 2H), 1.24-1.34 (m, 4H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 82.8, 81.0, 74.2, 73.8, 70.5, 40.1, 31.9, 29.4, 28.9, 28.5, 23.1, 19.0, 14.6, 4.1; HRMS-DART-ESI (*m/z*) [M + NH_4] calculated for $C_{17}H_{27}NO_2$: 295.2380, found: 295.2389.


Boc
N
H3C
Hex
227
2.34 ppm
1.835 ppm
1.50 ppm
0.92 ppm
9
8
7
6
5
4
3
2
1
ppm
1.91
2.00
2.76
2.06
11.18.99
2.82


Boc
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H3C
Hex
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77.230
76.978
73.961
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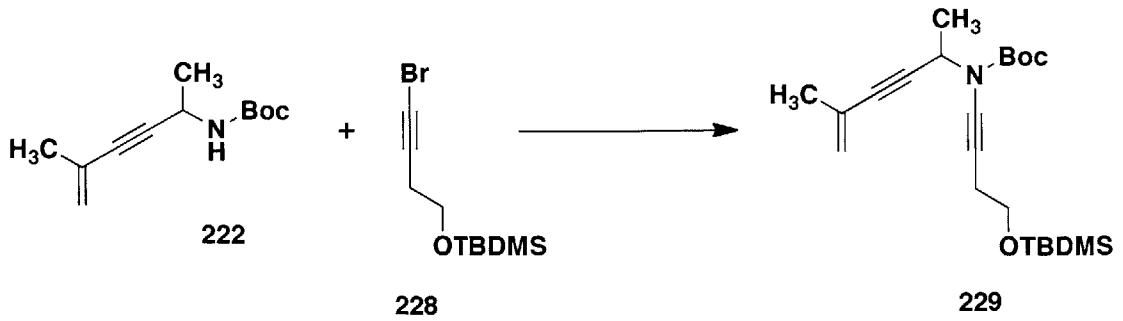
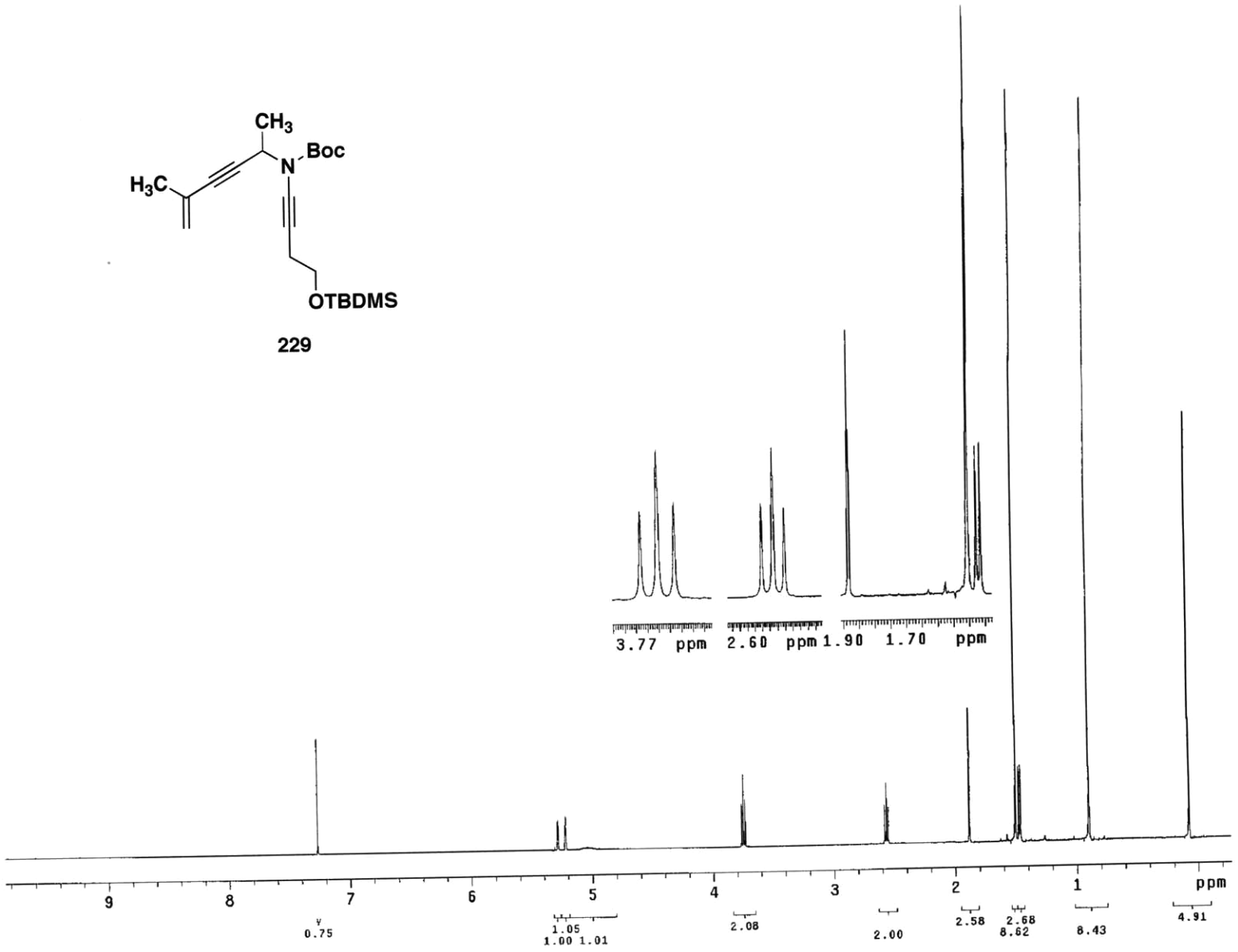
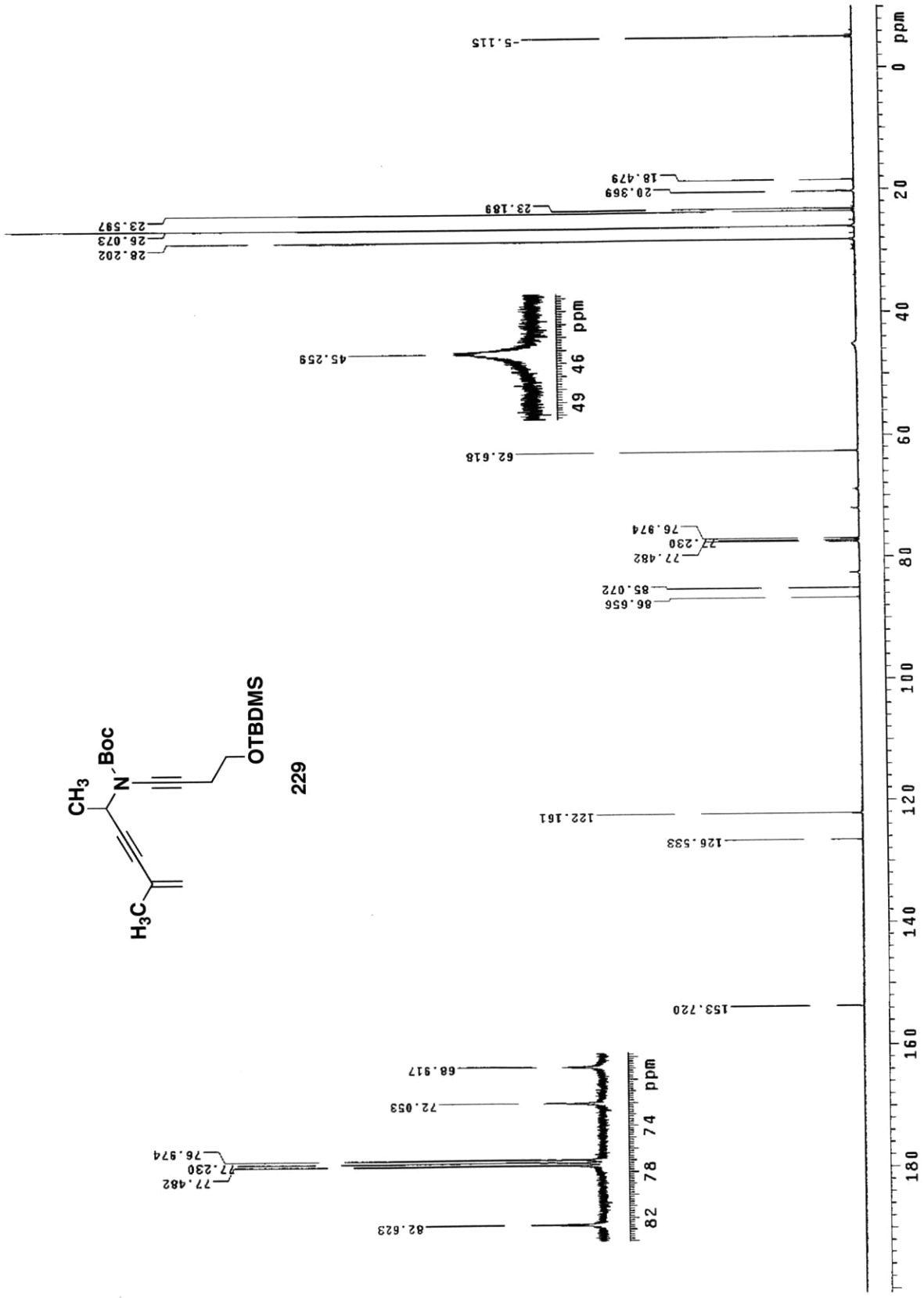
35.825
31.626
29.177
28.669
28.239
22.800
18.735
14.295
3.857
158 150 ppm
81 78 75 ppm
45 ppm
180 160 140 120 100 80 60 40 20 0 ppm



tert-Butyl (4-((tert-butyldimethylsilyl)oxy)but-1-yn-1-yl)(5-methylhex-5-en-3-yn-2-yl) carbamate (229). A 25-mL pear flask equipped with a rubber septum and argon inlet needle was charged with bromo alkyne **228**[114b] (3.0 g, 16 mmol, 1.1 equiv), carbamate **222** (0.209 g, 1.0 mmol, 1.0 equiv), K_3PO_4 (0.425 g, 2.0 mmol, 2.0 equiv), $CuSO_4 \cdot 5H_2O$ (0.025 g, 0.1 mmol, 0.10 equiv), 1,10-phenanthroline (0.036 g, 0.2 mmol, 0.20 equiv), and 1.4 mL of toluene. The septum was replaced with a cold-finger condenser fitted with an argon inlet adapter and the heterogeneous reaction mixture was stirred at 85 °C for 24 h. The resulting mixture was allowed to cool to rt and $CuSO_4 \cdot 5H_2O$ (0.025 g, 0.1 mmol, 0.10 equiv) and 1,10-phenanthroline (0.036 g, 0.2 mmol, 0.20 equiv) were added. The reaction mixture was stirred at 85 °C for 46 h, allowed to cool to rt, and diluted with 5 mL of EtOAc. The mixture was filtered through a ca. 2-g plug of Celite with the aid of five 5-mL portions of EtOAc, and the filtrate was concentrated to yield ca. 0.568 g of brown oil. Purification by column chromatography on 60 g of silica gel (elution with 2% EtOAc-hexanes) afforded 0.234 g (60%) of ynamide **229** as a yellow oil: IR (neat) 2955, 2931, 2857, 2262, 1720, 1305, 1166, 1106 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.26-5.29 (m, 1H), 5.20-5.22 (m, 1H), 5.03 (m, 1H), 3.74 (t, J = 7.5 Hz, 2H), 2.55 (t, J = 7.5 Hz, 2H), 1.87 (s, 3H), 1.49 (s, 9H), 1.46 (d, J = 7.0 Hz, 2H), 0.89 (s, 9H), 0.65 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 126.5, 122.2, 86.7, 85.1, 82.7, 72.0, 68.9, 62.6, 42.3, 28.2, 26.1, 23.6, 23.2, 20.4, 18.5, -5.1; HRMS-ESI (*m/z*) [M + Na] calculated for $C_{22}H_{37}NO_3Si$: 414.2435, found: 414.2447.


CH3
Boc
N
H3C
OTBDMS
229
3.77 ppm
2.60 ppm
1.90
1.70
ppm
9
8
7
6
5
4
3
2
1
ppm
0.75
1.05
1.00
1.01
2.08
2.00
2.58
2.68
8.62
8.43
4.91


OTBDMS
Boc
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CH3
H3C
229
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18.479
20.369
23.189
23.597
26.073
28.202
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72.053
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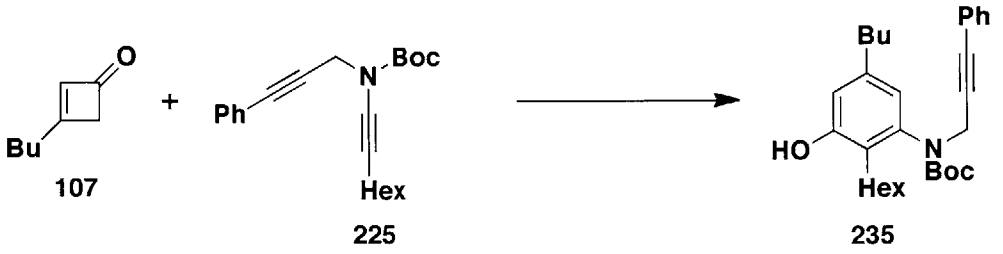
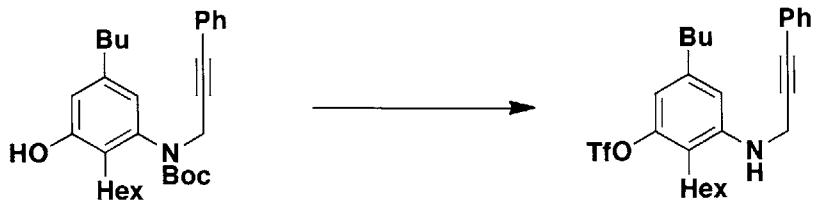
ppm



tert-Butyl 5-butyl-2-hexyl-3-hydroxyphenyl(3-phenylprop-2-ynyl) carbamate (235). A 25-mL pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with ynamide **225** (0.309 g, 0.92 mmol, 1.0 equiv), 3-butylcyclobut-2-enone (**107**)[117] (0.141 g, 1.1 mmol, 1.25 equiv), and 2.3 mL of toluene. The septum was replaced with a cold-finger condenser fitted with argon inlet adapter and the reaction mixture was heated at 80 °C for 1.5 h and then at reflux for 1 h. Concentration of the reaction mixture afforded 0.570 g of amber oil. Column chromatography on 60 g of silica gel (gradient elution with 5-10% EtOAc-hexanes) provided 0.378 g (89%) of carbamate **235** as an off-white solid: mp 90-91 °C; IR (neat) 3365 (broad), 2956, 2929, 2858, 1673, 1435, 1394, 1367, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 60:40 mixture of rotamers: δ 7.28-7.42 (m, 5H), 6.67 and 6.76 (rotamers, s, 1H), 6.61 and 6.49 (rotamers, s, 1H), 6.20 and 5.71 (rotamers, bs, 1H), 4.80 and 4.62 (rotamers, d, J = 17.5 Hz, 1H), 4.27 and 4.23 (d, J = 17.5 Hz, 1H), 2.34-2.62 (m, 4H), 1.49-1.63 (m, 4H), 1.61 and 1.39 (rotamers, s, 9H), 1.20-1.48 (m, 8H), 0.80-0.94 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6 and 155.5 (rotamers), 155.3 and 155.2 (rotamers), 141.5 and 141.0 (rotamers), 140.8 and 140.6 (rotamers), 131.8 and 131.6 (rotamers), 128.4 and 128.3 (rotamers), 128.2 and 128.1 (rotatmers), 125.3 and 124.7 (rotamers), 123.2, 120.5 and 120.0 (rotamers), 115.8 and 115.1 (rotamers), 85.7 and 85.2 (rotamers), 84.1 and 83.6 (rotamers), 81.2 and 80.6 (rotamers), 41.8 and 40.6 (rotamers), 35.2, 33.4 and 33.1 (rotamers), 32.0 and 31.9 (rotamers), 30.2 and 30.1 (rotamers), 29.6 and 29.2 (rotamers), 28.5 and 28.3 (rotamers), 26.1, 22.8 and 22.6 (rotamers), 22.2, 14.2, 14.0. Anal. Calcd for $C_{30}H_{41}NO_3$; C, 77.71; H, 8.91; N, 3.02. Found: C, 77.54; H, 8.93; N, 3.02.

Bu
Ph
HO
N
Boc
Hex
235
4.8
4.6
4.4
4.2
ppm
9
8
7
6
5
4
3
2
1
ppm
5.10
0.97
0.97
0.87
0.93
0.96
4.01
13.53
8.03
6.15

155.58
155.49
155.26
155.19
141.51
141.04
140.76
140.59
131.77
131.62
128.35
128.27
128.15
128.10
125.34
124.73
123.21
120.53
119.98
115.80
115.12
85.72
85.23
84.07
83.55
81.20
80.63
77.55
77.23
76.91
41.83
40.62
35.17
33.45
33.13
31.97
31.85
30.20
30.06
29.61
29.25
28.51
28.34
26.06
22.79
22.59
22.23
Bu
Ph
HO
N
Boc
Hex
235
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

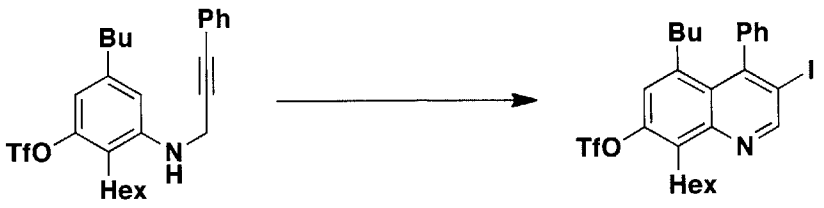


235 242

5-Butyl-2-hexyl-3-(3-phenylprop-2-ynylamino)phenyl trifluoromethanesulfonate (242). A 25-mL pear flask equipped with a rubber septum and argon inlet needle was charged with phenol **235** (0.487 g, 1.1 mmol, 1.0 equiv), 4-DMAP (0.206 g, 1.7 mmol, 1.6 equiv), and 5 mL of CH_2Cl_2. The yellow solution was cooled to 0 °C and triflic anhydride (0.25 mL, 1.5 mmol, 1.4 equiv) was added dropwise by syringe over ca. 3 min. The reaction mixture was allowed to warm to rt and stirred for 2 h. The resulting yellow slurry of white solid was cooled to 0 °C and trifluoroacetic acid (1.2 mL, 16 mmol, 15 equiv) was added dropwise over 5 min. The resulting golden orange solution was allowed to warm to rt and stirred for 1 h. The reaction mixture was then diluted with 25 mL of dichloromethane and washed with 25 mL of satd aq K_2CO_3 solution. The aqueous layer was extracted with three 10-mL portions of CH_2Cl_2, and the combined organic layers were washed with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.777 g of a dark red oil. Column chromatography on 19 g of silica gel (elution with 1% EtOAc-hexanes) afforded 0.480 g (92%) of triflate **242** as a pale yellow oil: IR (neat) 3449 (broad), 2958, 2931, 2860, 1416, 1213, 1141 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47-7.54 (m, 2H), 7.31-7.40 (m, 3H), 6.72 (s, 1H), 6.66 (s, 1H), 4.22-4.30 (m, 2H), 4.19 (bs, 1H), 2.61-2.74 (m, 4H), 1.59-1.75 (m, 4H), 1.34-1.55 (m, 8H), 0.93-1.06 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 146.4, 143.3, 131.9, 128.5, 128.4, 122.9, 118.8 (q, J = 318 Hz), 117.5, 111.2, 110.5, 85.9, 83.8, 35.8, 34.8, 33.5, 31.7, 29.6, 28.1, 24.8, 22.8, 22.5, 14.1, 14.0; HRMS-ESI (*m/z*) [M + H] calculated for $C_{26}H_{32}F_3NO_3S$, 496.2128; found 496.2111.

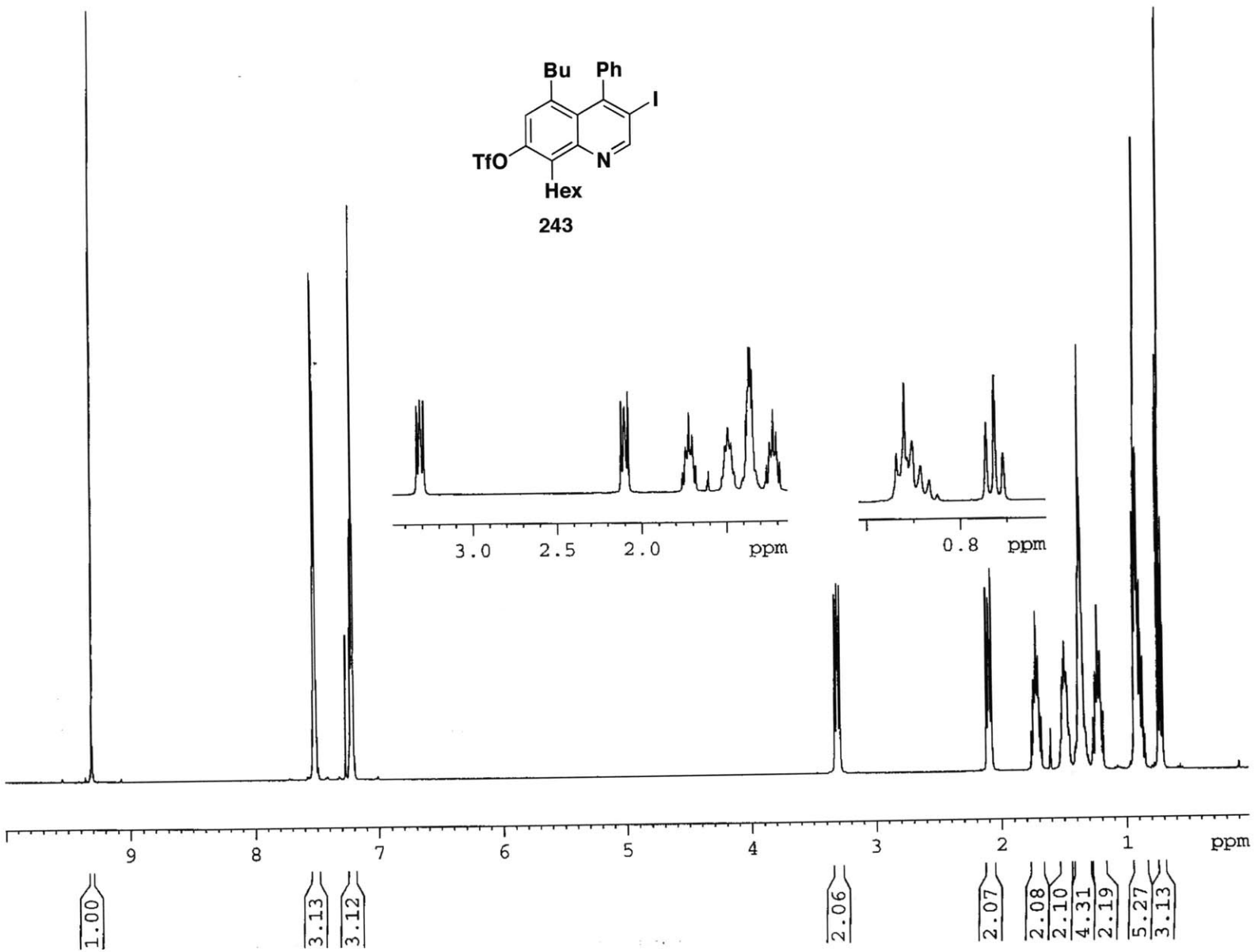
Bu
Ph
TfO
N
H
Hex
242
9
8
7
6
5
4
3
2
1
ppm
1.93
2.89
0.96
0.95
1.94
0.96
3.86
4.00
8.02
5.87

148.52
146.39
143.31
131.86
128.53
128.43
123.57
122.86
120.39
117.49
117.21
114.04
111.24
110.50
85.92
83.80
77.55
77.23
76.91
35.84
34.77
33.51
31.67
29.59
28.10
24.79
22.76
22.46
14.14
14.03
Bu
Ph
TfO
N
H
Hex
242
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



242 243

5-Butyl-8-hexyl-3-iodo-4-phenylquinolin-7-yl trifluoromethanesulfonate (243). A 25-mL pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with triflate **242** (0.480 g, 0.97 mmol, 1.0 equiv), $NaHCO_3$ (0.326 g, 3.9 mmol, 4.0 equiv), iodine (1.48 g, 5.8 mmol, 6.0 equiv), and 10 mL of CH_3CN. The reaction mixture was stirred at rt for 40 min, diluted with 30 mL of Et_2O, and then washed with two 15-mL portions of satd aq $Na_2S_2O_3$ solution. The aqueous layer was extracted with two 15-mL portions of Et_2O, and the combined organic layers were washed with 40 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.167 g of a yellow oil. Column chromatography on 42 g of silica gel (elution with 1% EtOAc-5% benzene-94% hexanes) yielded 0.522 g (87%) of quinoline **243** as a yellow oil: IR (neat) 2929, 1421, 1214, 1141 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 7.45-7.60 (m, 3H), 7.15-7.30 (m, 3H), 3.24-3.40 (m, 2 H), 2.02-2.19 (m, 2H), 1.66-1.76 (m, 2H), 1.43-1.53 (m, 2H), 1.30-1.41 (m, 4H), 1.17-1.26 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H) 0.83-0.93 (m, 2H), 0.72 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 151.8, 148.3, 147.0, 144.7, 141.2, 132.8, 128.9, 128.9, 128.7, 127.5, 122.6, 118.8 (d, J = 318 Hz), 102.0, 35.8, 34.3, 31.8, 30.4, 29.8, 26.2, 22.8, 22.6, 14.3, 13.9; HRMS-ESI (*m/z*) [M + H] calculated for $C_{26}H_{29}F_3INO_3S$, 620.0938; found 620.0917.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TfO
N
Hex
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ppm
0.8
ppm
9
8
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6
5
4
3
2
1
ppm
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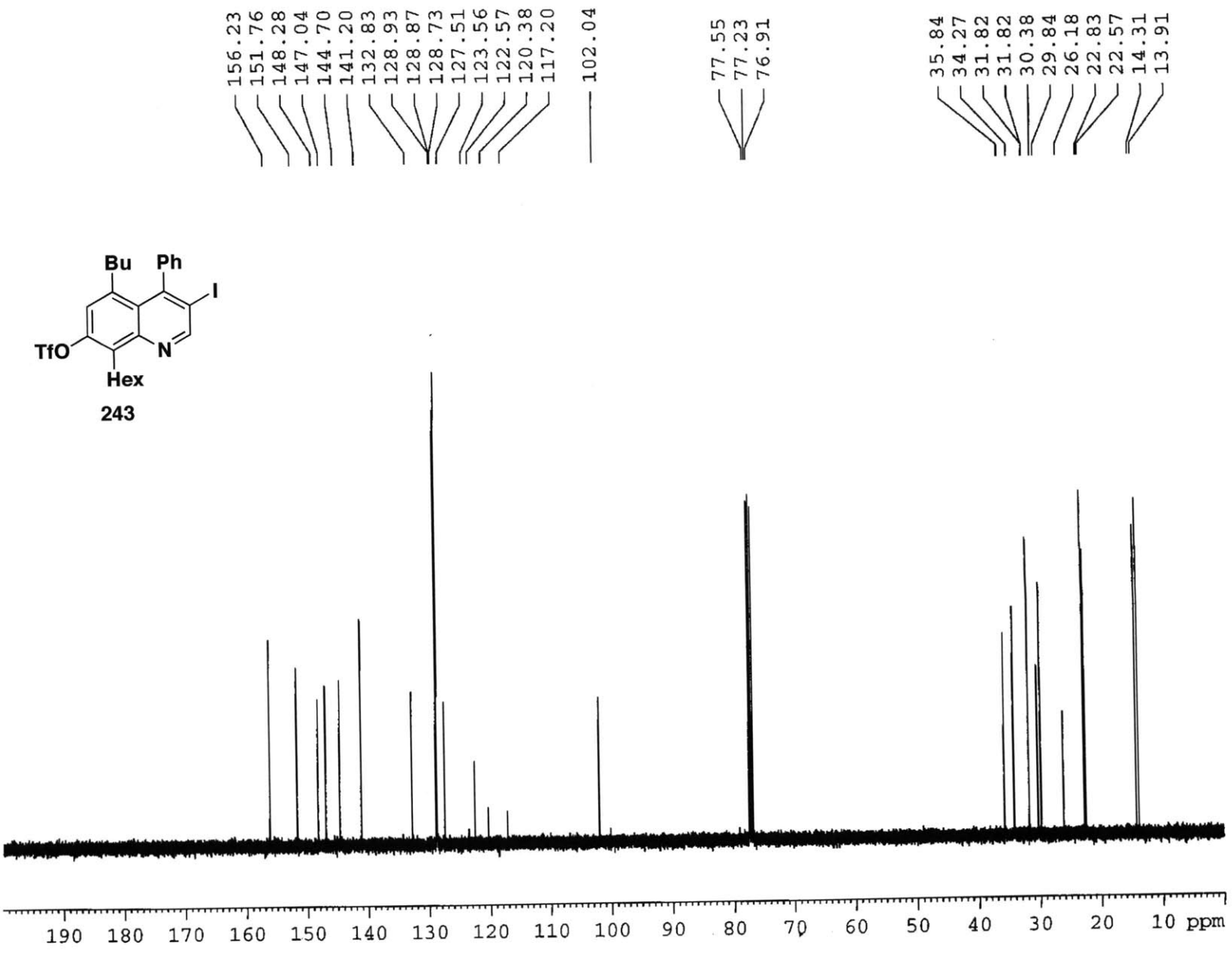
3.13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141.20
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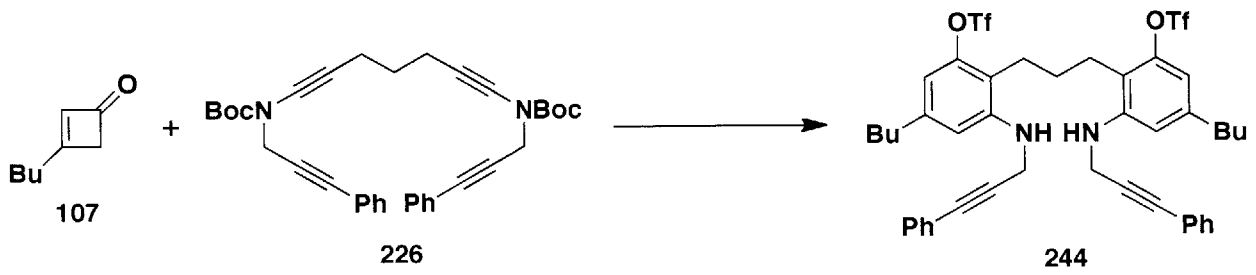
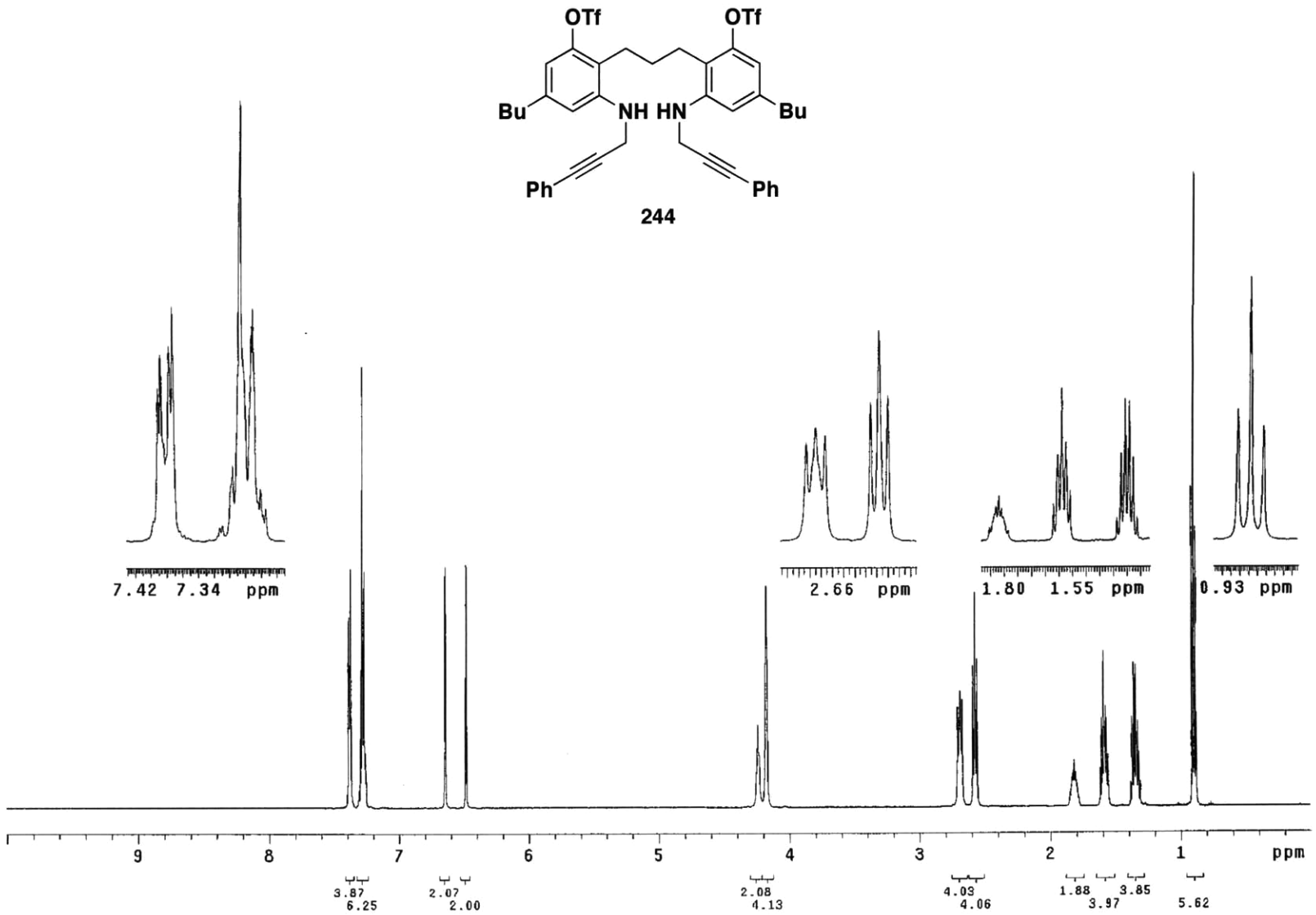
128.93
128.87
128.73
127.51
123.56
122.57
120.38
117.20
102.04
77.55
77.23
76.91
35.84
34.27
31.82
31.82
30.38
29.84
26.18
22.83
22.57
14.31
13.91
Bu
Ph
I
TfO
N
Hex
243
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



2,2'-(1,3-Propanedyil)bis-5,5'-butyl-3,3'-(3-phenylprop-2-ynylamino)phenyl trifluoromethanesulfonate, (244). A 25-mL pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with ynamide **226** (0.140 g, 0.25 mmol, 1.0 equiv), 3-butylcyclobut-2-enone (**107**)[117] (0.073 g, 0.58 mmol, 2.3 equiv), and 1.2 mL of toluene. The septum was replaced with a cold-finger condenser fitted with argon inlet adapter and the reaction mixture was heated at 80 °C for 2.5 h and then at reflux for 2.5 h. Concentration of the reaction mixture provided 0.243 g of an orange solid. 4-DMAP (0.155 g, 1.3 mmol, 5 equiv) and 1.7 mL dichloromethane were then added and the orange solution was cooled at 0 °C while triflic anhydride (0.10 mL, 0.58 mmol, 2.3 equiv) was added dropwise by syringe over ca. 5 min. The reaction mixture was allowed to warm to rt and stirred for 1 h. The resulting red slurry of white solid was cooled to 0 °C and trifluoroacetic acid (0.75 mL, 10 mmol, 40 equiv) was added dropwise over 10 min. The resulting red-brown solution was allowed to warm to rt and stirred for 1 h. The reaction mixture was then diluted with 20 mL of CH_2Cl_2 and washed with three 15-mL of satd aq K_2CO_3 solution, 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.386 g of a red-brown solid. Column chromatography on 39 g of silica gel (gradient elution 30-50% CH_2Cl_2-hexanes) furnished 0.136 g (62%) of triflate **244** as a white solid: mp 98-101 °C; IR (neat) 3446 (broad), 2959, 2933, 2862, 1406, 1222, 1141 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.40 (m, 4H), 7.25-7.32 (m, 6H), 6.65 (s, 2H), 6.49 (s, 2H), 4.21-4.27 (m, 2H), 4.15-4.20 (m, 4H), 2.62-2.76 (m, 4H), 2.57 (t, J = 7.5 Hz, 4H), 1.77-1.86 (m, 4H), 1.59 (quint, J = 7.5 Hz, 4H), 1.35 (app hex, J = 7.5 Hz, 4H), 0.90 (t, J = 7.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 146.5, 143.8, 131.9, 128.4, 128.4, 123.0, 118.7 (q, J = 318 Hz), 116.5, 111.4, 110.4, 85.9, 83.6, 35.9, 34.6, 33.5, 26.4, 24.9, 22.5, 14.1; Anal. Calcd for $C_{43}H_{44}F_6N_2O_6S_2$; C, 59.85; H, 5.14; N, 3.25. Found: C, 60.08; H, 5.29; N, 3.29.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OTf
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Bu
Ph
Ph
244
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2.66 ppm
1.80 1.55 ppm
0.93 ppm
9
8
7
6
5
4
3
2
1
ppm
3.87
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2.07
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2.08
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4.06
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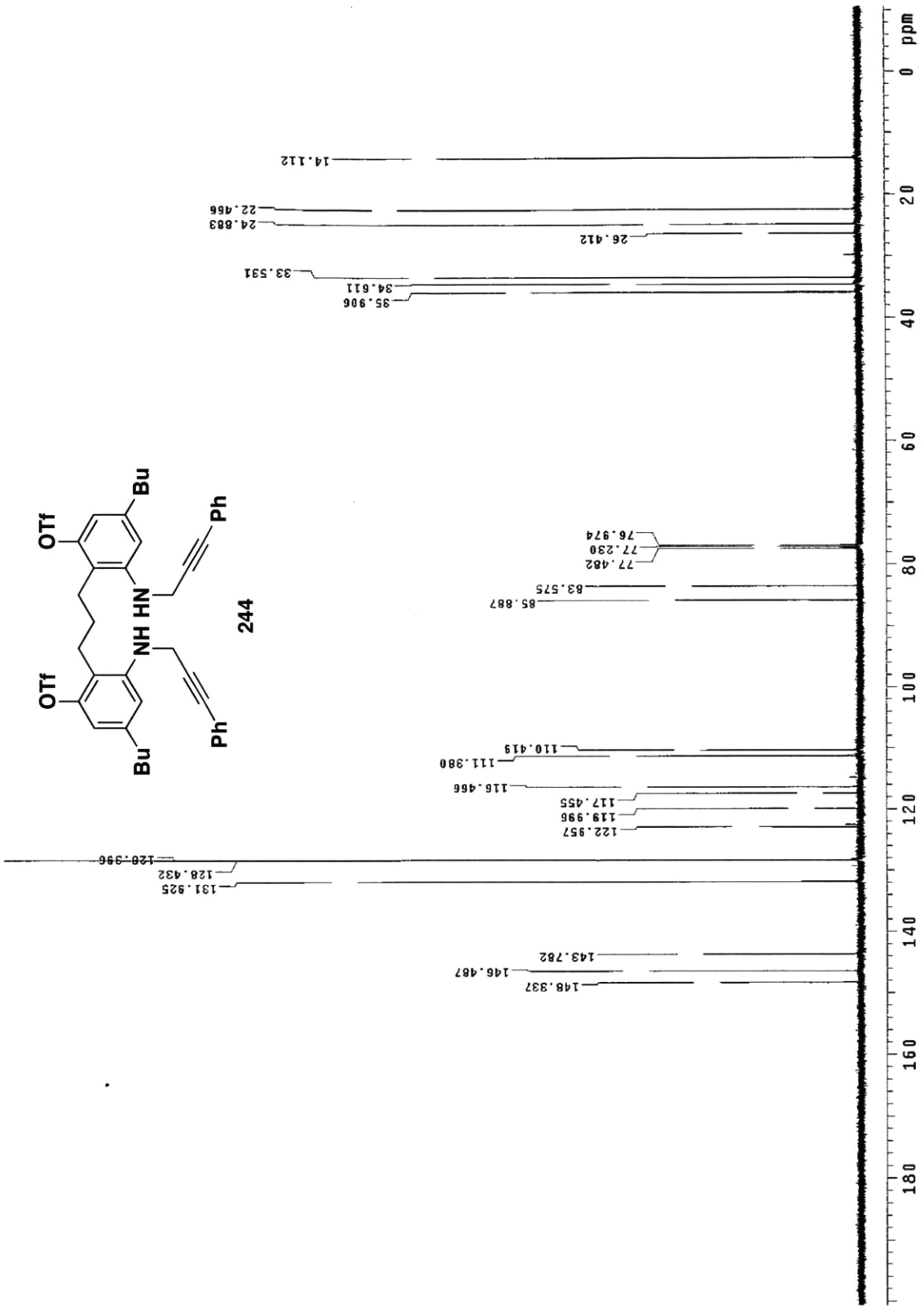
3.97
3.85
5.62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77.230
77.482
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85.887
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116.466
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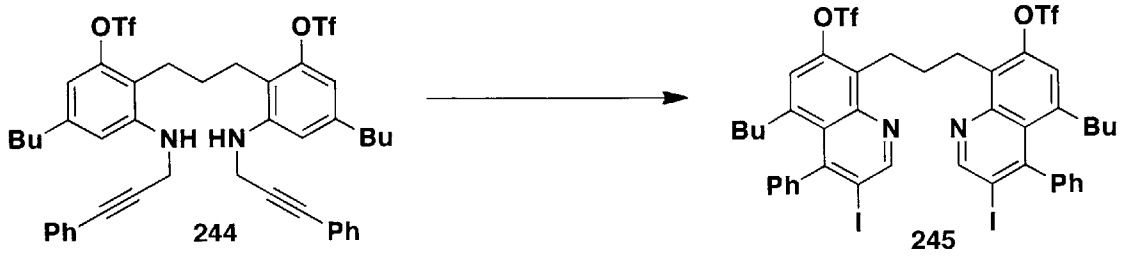
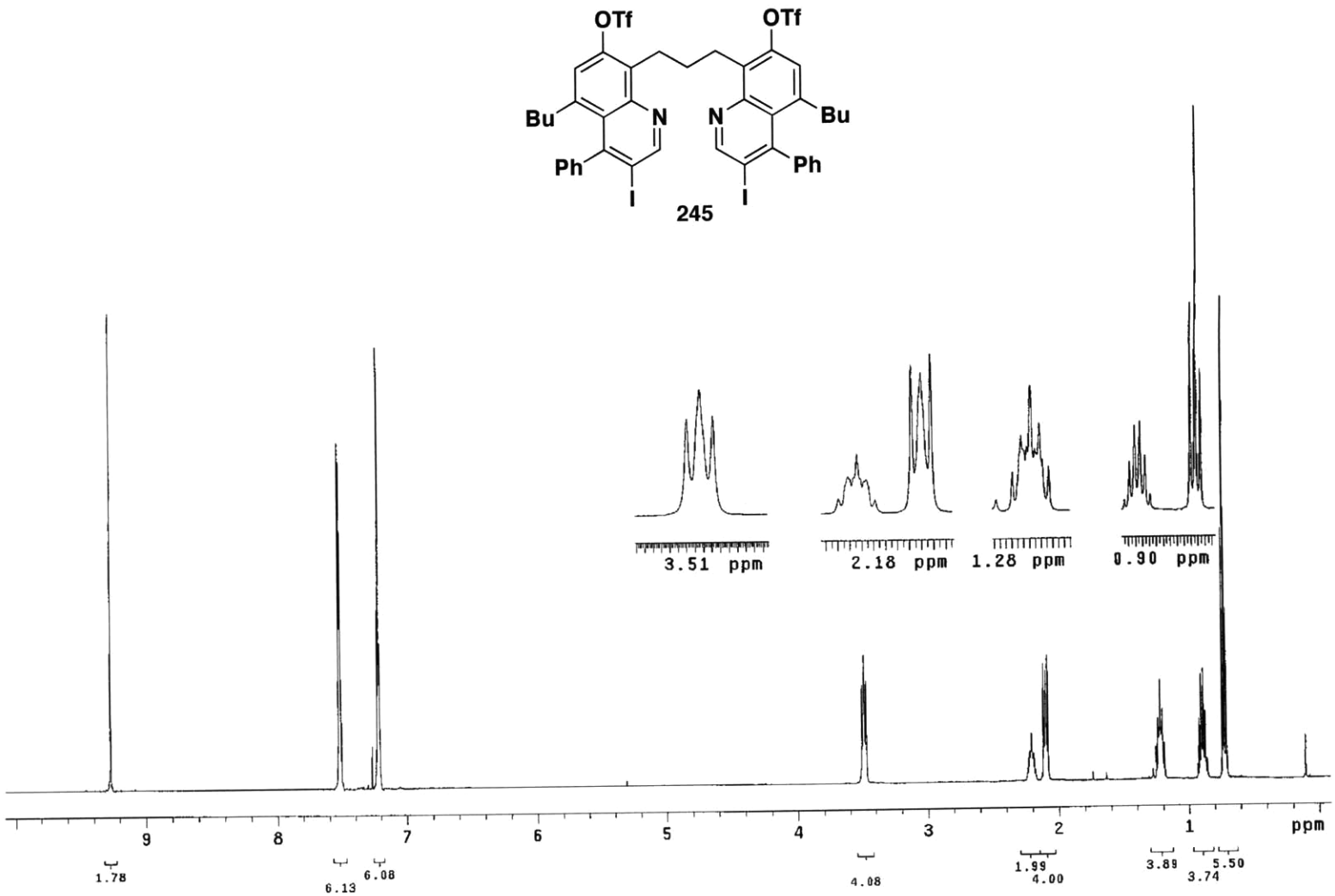
140
160
180



8,8'-(1,3-Propanedyil)bis-5,5'-butyl-3,3'-iodo-4,4'-phenylquinolin-7,7'-yl trifluoromethanesulfonate, (245). A 25-mL pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with triflate **244** (0.102 g, 0.12 mmol, 1.0 equiv), $NaHCO_3$ (0.079 g, 0.95 mmol, 8.0 equiv), iodine (0.360 g, 1.4 mmol, 12.0 equiv), and 2.4 mL of CH_3CN. The reaction mixture was stirred at rt for 1 h, diluted with 30 mL of Et_2O, and then washed with two 15-mL portions of satd aq $Na_2S_2O_3$ solution. The aqueous layer was extracted with two 15-mL portions of Et_2O, and the combined organic layers were washed with 60 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.137 g of a yellow oil. Column chromatography on 14 g of silica gel (elution with 2% EtOAc-hexanes) yielded 0.106 g (81%) of quinoline **245** as an off-white solid: mp 190-192 °C; IR (neat) 2959, 2931, 2873, 1420, 1217, 1141 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.27 (s, 2H), 7.49-7.54 (m, 6H), 7.20-7.24 (m, 6H), 3.45-3.54 (m, 4 H), 2.20 (quint, J = 7.5 Hz, 2H), 2.04-2.14 (m, 4 H), 1.22 (app quint, J = 7.5 Hz, 4H), 0.89 (app hex, J = 7.5 Hz, 4H), 0.72 (t, J = 7.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 151.7, 148.3, 147.1, 144.7, 141.4, 132.0, 128.9, 128.8, 128.7, 127.5, 122.6, 118.8 (d, J = 318 Hz), 102.0, 35.9, 34.3, 30.5, 26.0, 22.6, 13.9; Anal. Calcd for $C_{43}H_{38}F_6I_2N_2O_6S_2$; C, 46.50; H, 3.45; N, 2.52. Found: C, 46.48; H, 3.46; N, 2.42.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8
7
6
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ppm
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3.89
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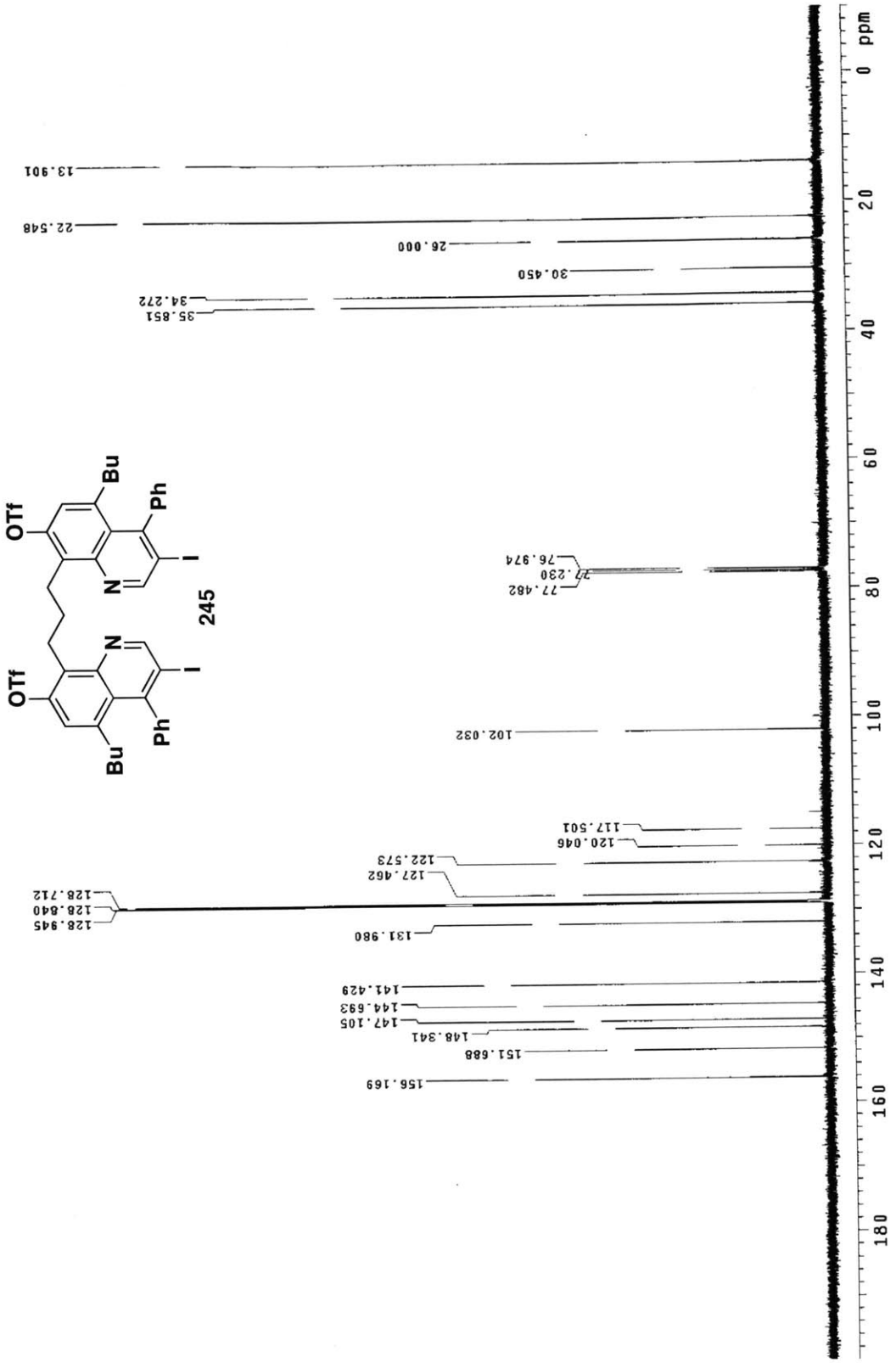
5.50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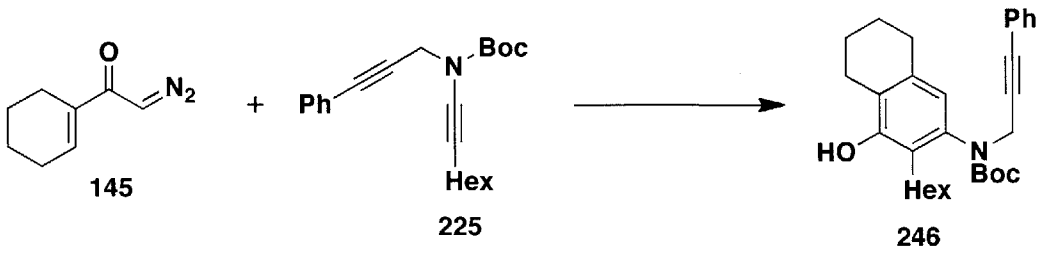
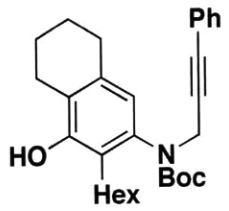


tert-Butyl 3-hexyl-4-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl(3-phenylprop-2-ynyl) carbamate (246). A 20-cm quartz tube (7 mm I.D., 10 mm O.D.) equipped with a rubber septum and argon inlet needle was charged with diazo ketone **145**[72a] (0.276 g, 1.8 mmol, 2.5 equiv), ynamide **225** (0.250 g, 0.74 mmol, 1.0 equiv), and 2.9 mL of CH_2Cl_2. The yellow solution was degassed for 10 min with a stream of argon. The quartz tube was placed ca. 20 cm from a 450-W Hanovia lamp (quartz immersion well, cooled by recirculating tap water) and irradiated under argon at 25 °C for 33 h. The reaction mixture was transferred to a 25-mL pear flask with the aid of two 4-mL portions of CH_2Cl_2 and concentrated to afford 0.507 g of an orange oil. This material was dissolved in 3.7 mL of toluene, the flask was equipped with a stir bar and cold-finger condenser, and the reaction mixture was heated at reflux for 2.5 h. The resulting mixture was concentrated to afford 0.515 g of a dark orange oil. Column chromatography on 52 g of silica gel (elution with 5% EtOAc-hexanes) provided 0.241 g of a yellow-orange foam. This material was dissolved in ca. 10 mL of hot hexanes and then cooled at -20 °C for 12 h. The resulting crystals were collected by filtration, washed with 20 mL of cold hexane, and then transferred to a 25-mL pear flask and dried overnight at 0.1 mmHg to provide 0.158 g (58%) of carbamate **246** as an off-white solid: mp 124-126 °C; IR (neat) 3428 (broad), 2929, 2858, 1685, 1490, 1436, 1394, 1367, 1307, 1246, 1162 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 50:50 mixture of rotamers δ 7.36-7.47 (m, 2H), 7.23-7.36 (m, 3H), 6.75 and 6.66 (rotamers, s, 1H), 5.13 and 4.94 (rotamers, s, 1H), 4.75 and 4.59 (rotamers, d, J = 18 Hz, 1H), 4.32 and 4.26 (rotamers, d, J = 18 Hz, 1H), 2.65-2.80 (m, 2H), 2.45-2.65 (m, 4H), 1.68-1.92 (m, 4H), 1.60 and 1.41 (rotamers, s, 9H), 1.35-1.58 (m, 4H), 1.22-1.35 (bs, 4H), 0.87 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2 and 154.8 (rotamers), 152.5 and 152.2 (rotamers), 138.8 and 138.2 (rotamers), 136.3 and 135.8 (rotamers), 131.8 and 131.7 (rotamers), 128.4 and 128.3 (rotamers), 128.2, 124.2 and 123.7 (rotamers), 123.3, 123.0 and 122.1 (rotamers), 121.2 and 121.0 (rotamers), 86.1 and 85.7 (rotamers), 83.9 and 83.4 (rotamers), 80.8 and 80.4 (rotamers), 41.9, 40.8, 32.0 and

31.9 (rotamers), 30.2, 29.5, 29.4, 28.6 and 28.5 (rotamers) , 26.3, 23.2 and 23.1 (rotamers), 22.9, 22.8, 14.3; Anal. Calcd for $C_{30}H_{39}NO_3$; C, 78.05; H, 8.52; N, 3.03. Found: C, 77.81; H, 8.71; N, 3.03.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Boc
Hex

246

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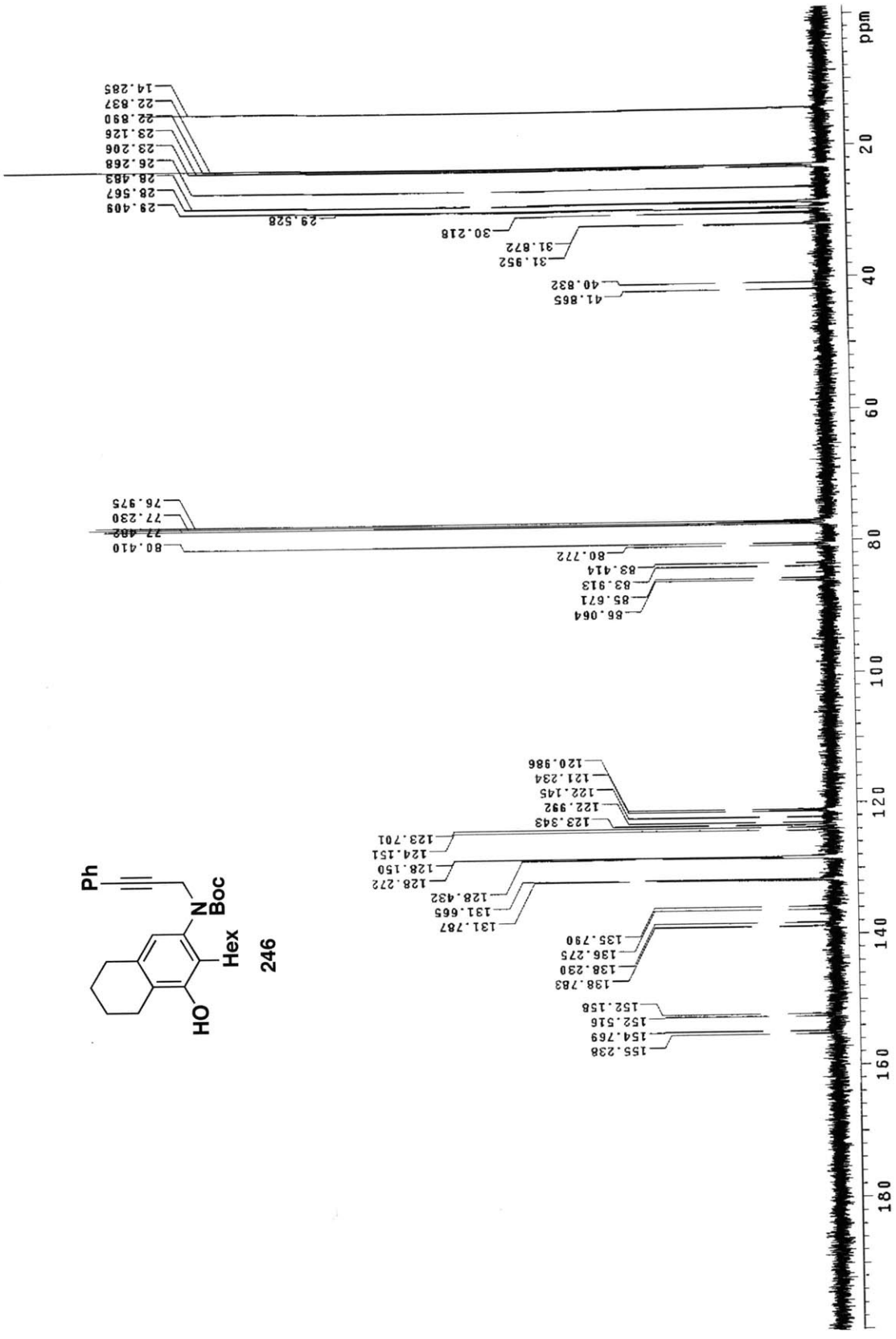
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Boc
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HO
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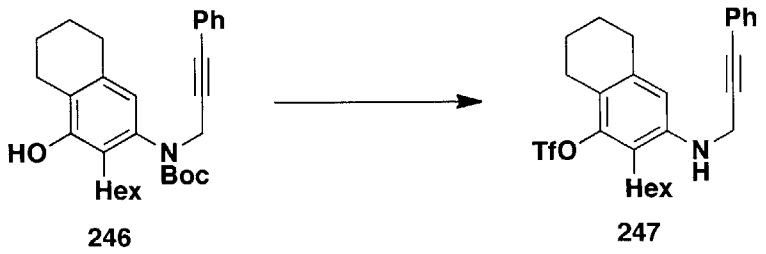
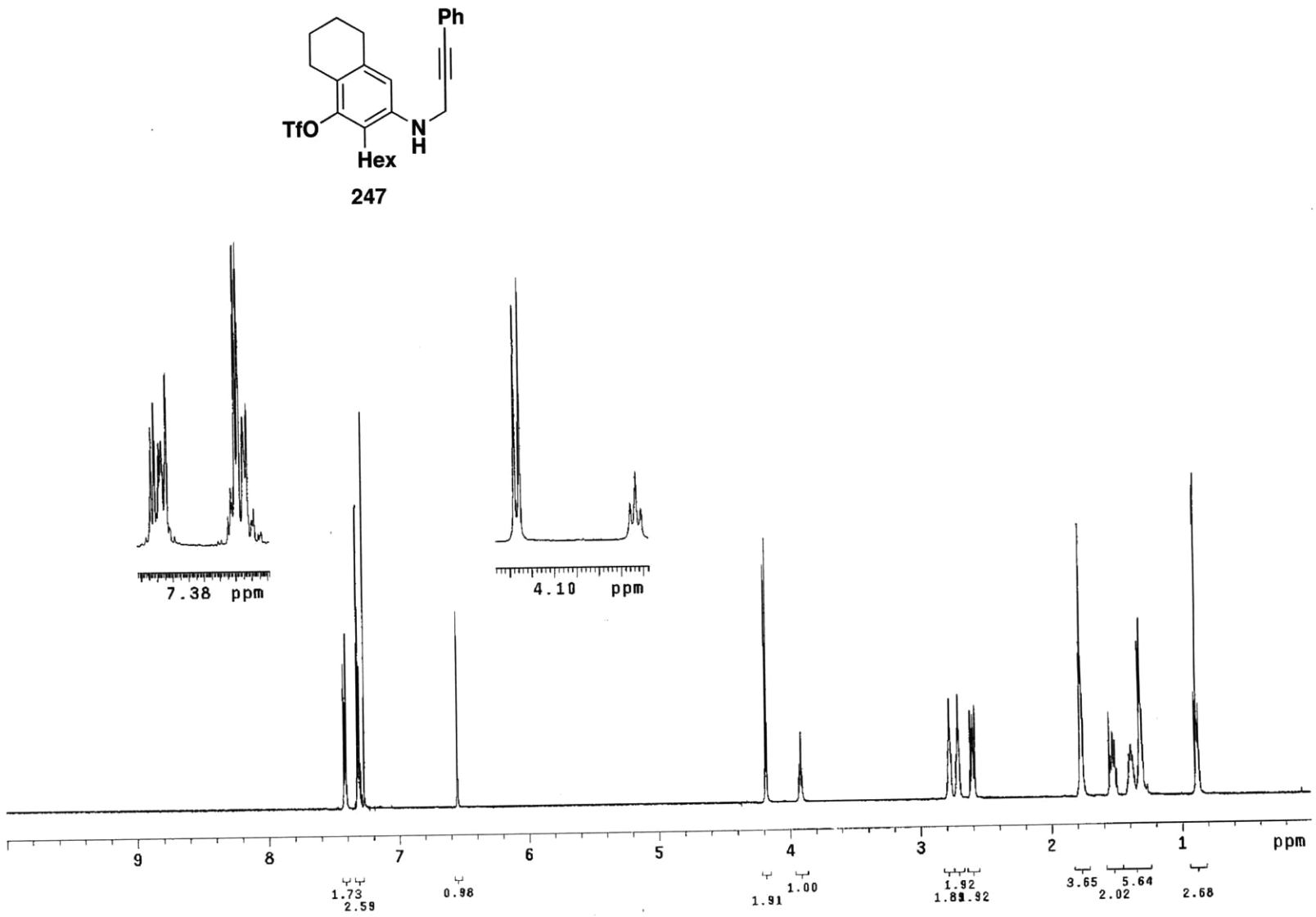


2-Hexyl-3-(3-phenylprop-2-ynylamino)-5,6,7,8-tetrahydronaphthalen-1-yl trifluoromethanesulfonate (247). A 25-mL pear equipped with a rubber septum and argon inlet needle was charged with phenol **246** (0.140 g, 0.30 mmol, 1.0 equiv), 4-DMAP (0.093 g, 0.76 mmol, 2.5 equiv), and 1.7 mL of CH_2Cl_2. The yellow solution was cooled to 0 °C and triflic anhydride (0.07 mL, 0.39 mmol, 1.3 equiv) was added dropwise by syringe over ca. 2 min. The reaction mixture was allowed to warm to rt and stirred for 1 h. The resulting yellow slurry of white solid was cooled to 0 °C and 2,2,2-trifluoroacetic acid (0.45 mL, 6.1 mmol, 20 equiv) was added dropwise over 6 min. The resulting golden orange solution was allowed to warm to rt and stirred for 1 h. The reaction mixture was then diluted with 15 mL of CH_2Cl_2 and washed with 15 mL of satd aq K_2CO_3 solution. The aqueous layer was extracted with two 10-mL portions of dichloromethane, and the combined organic layers were washed with 30 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.236 g of an orange semi-solid. Column chromatography on 5 g of silica gel (elution with 3% EtOAc-hexanes) afforded 0.137 g (91%) of triflate **247** as a yellow oil: IR (neat) 3442, 2932, 2860, 1402, 1243, 1212, 1140, 919 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-7.44 (m, 2H), 7.29-7.34 (m, 3H), 6.55 (s, 1H), 4.18 (d, J = 6 Hz, 2H), 3.92 (t, J = 6 Hz, 1H), 2.78 (m, 2H), 2.72 (m, 2H), 2.60 (m, 2H), 1.74-1.80 (m, 4H), 1.49-1.57 (m, 2H), 1.35-1.42 (m, 2H), 1.28-1.35 (m, 4H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.8, 143.9, 137.9, 131.9, 128.6, 128.5, 122.9, 120.3, 119.1, 118.9 (q, *J* = 318 Hz), 112.1, 86.2, 83.7, 35.1, 31.7, 29.9, 29.6, 28.4, 25.4, 24.0, 22.4, 22.8, 22.7, 14.3; HRMS-ESI (*m/z*) [M + H] calculated for $C_{26}H_{30}F_3NO_3S$, 494.1971; found 494.1980.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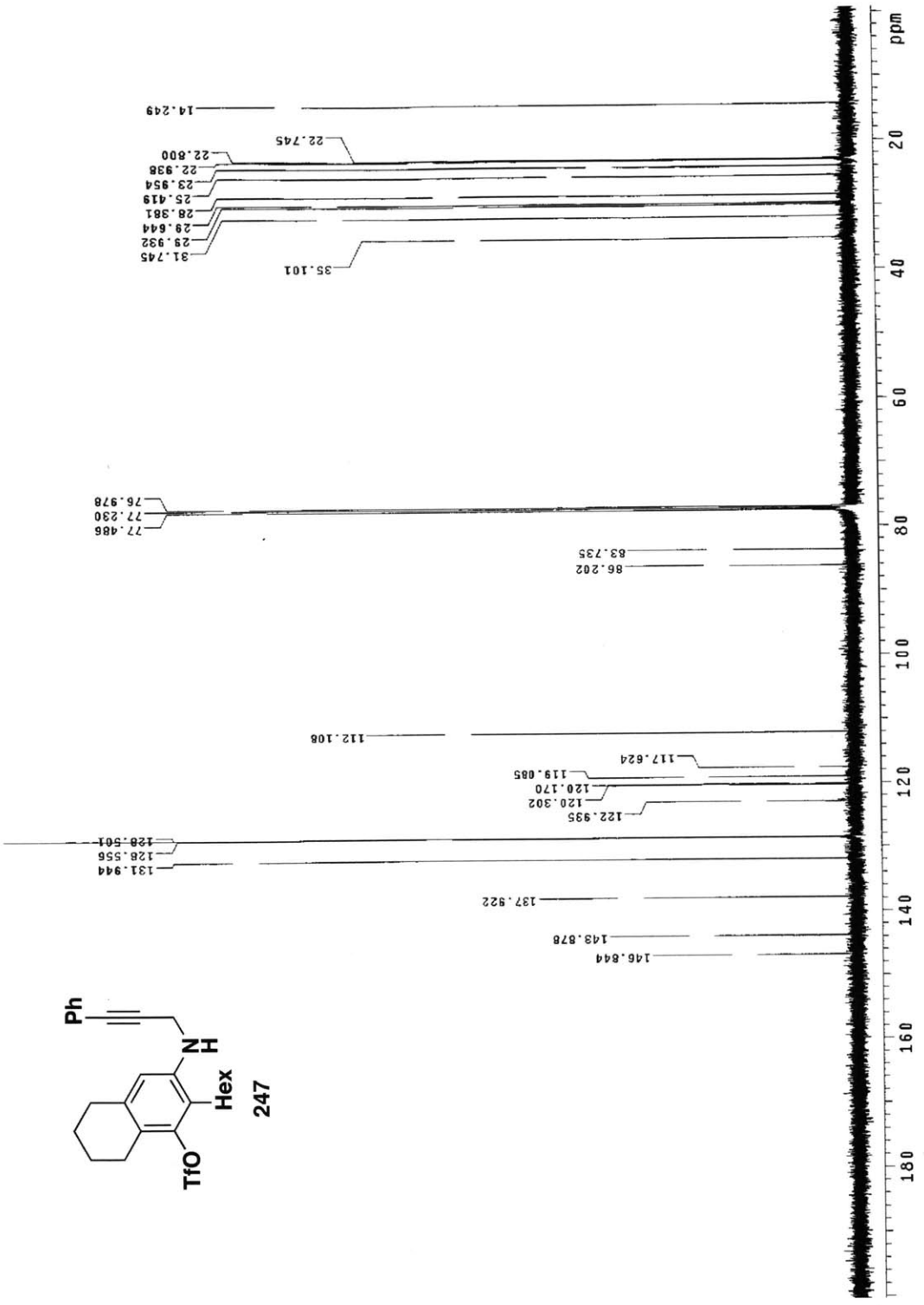
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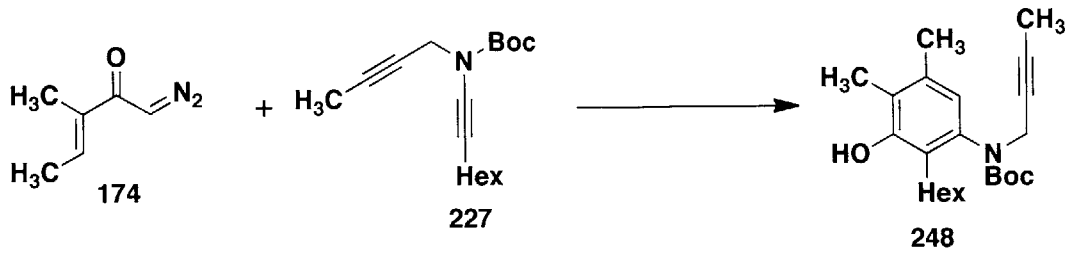
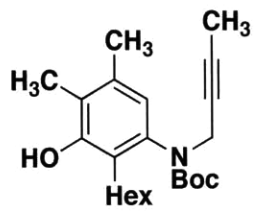


tert-Butyl but-2-yn-1-yl(2-hexyl-3-hydroxy-4,5-dimethylphenyl)carbamate (248). A 20-cm quartz tube (7 mm I.D., 10 mm O.D.) equipped with a rubber septum and argon inlet needle was charged with diazo ketone **174**[72a] (0.450 g, 3.6 mmol, 2.5 equiv), ynamide **227** (0.398 g, 1.4 mmol, 1.0 equiv), and 6 mL of CH_2Cl_2. The yellow solution was degassed for 10 min with a stream of argon. The quartz tube was placed ca. 20 cm from a 450-W Hanovia lamp (quartz immersion well, cooled by recirculating tap water) and irradiated under argon at 25 °C for 30 h. The reaction mixture was transferred to a 25-mL pear flask with the aid of two 4-mL portions of CH_2Cl_2 and concentrated to afford 0.81 g of an orange oil. This material was dissolved in 7 mL of toluene, the flask was equipped with a stir bar and cold-finger condenser, and the reaction mixture was heated at reflux for 2.5 h. The resulting mixture was concentrated to afford 0.832 g of a dark orange oil. Column chromatography on 85 g of silica gel (elution with 3% EtOAc-hexanes) provided 0.420 g of a yellow solid. This material was dissolved with 10 mL of pentane and then cooled at -20 °C for 12 h. The resulting crystals were collected by filtration, washed with 10 mL of cold pentane, and then transferred to a 25-mL pear flask and dried overnight at 0.1 mmHg to provide 0.290 g (55%) of carbamate **248** as an off-white solid: mp 89-91 °C; IR (neat) 3419 (broad), 2928, 2859, 1681, 1574, 1395, 1367, 1321, 1251, 1166 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 60:40 mixture of rotamers: δ 6.72 and 6.62 (rotamers, s, 1H), 5.06 and 4.81 (rotamers, s, 1H), 4.39 and 4.29 (rotamers, d, J = 17 Hz, 1H), 4.04 and 3.97 (rotamers, d, J = 17 Hz, 1H), 2.40-2.57 (m, 2H), 2.24 and 2.21 (rotamers, s, 3H), 2.14 and 2.08 (rotamers, s, 3H), 1.81 and 1.78 (rotamers, s, 3H), 1.54 and 1.35 (rotamers, s, 9H), 1.32-1.65 (m, 4H), 1.24-1.32 (m, 4H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2 and 154.8 (rotamers), 152.6 and 152.3 (rotamers), 138.4 and 138.3 (rotamers), 135.5 and 135.0 (rotamers), 124.6 and 124.1 (rotamers), 122.1, 121.4, 80.6 and 80.2 (rotamers), 79.6 and 79.1 (rotamers), 75.6 and 75.1 (rotamers), 41.3 and 40.5 (rotamers), 32.0 and 31.9 (rotamers), 30.2, 29.3, 28.5, 26.4, 22.9, 20.2, 14.3, 12.0, 3.9 and 3.7 (rotamers); HRMS-DART-ESI (*m/z*) [M - H]: calcd for $C_{23}H_{35}NO_3$,

372.2544; found: 372.2548. Anal. Calcd for $C_{23}H_{35}NO_3$; C, 73.96; H, 9.44; N, 3.75. Found: C, 74.18; H, 9.50; N, 3.70.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Boc
Hex

248

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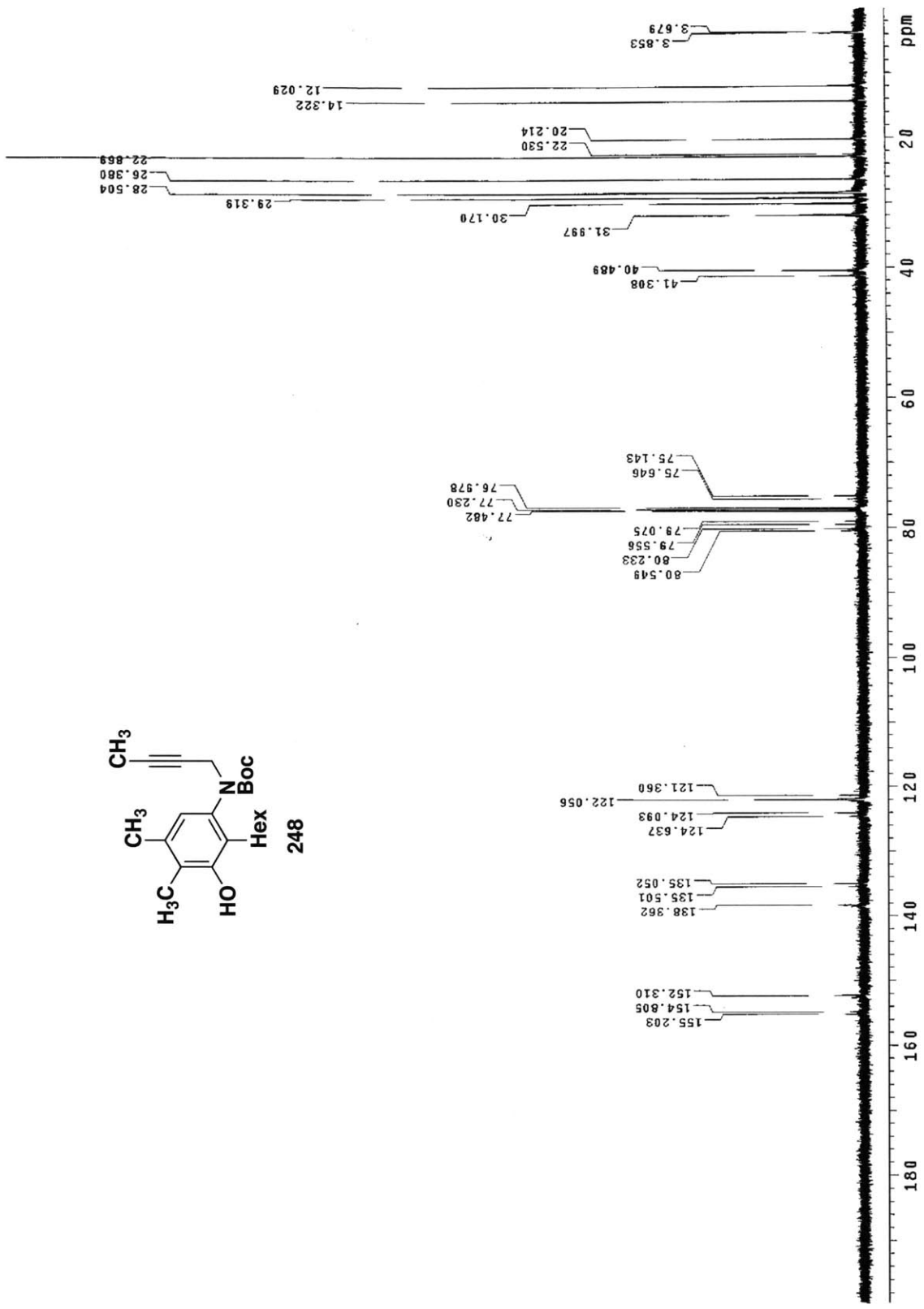
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Boc
CH3
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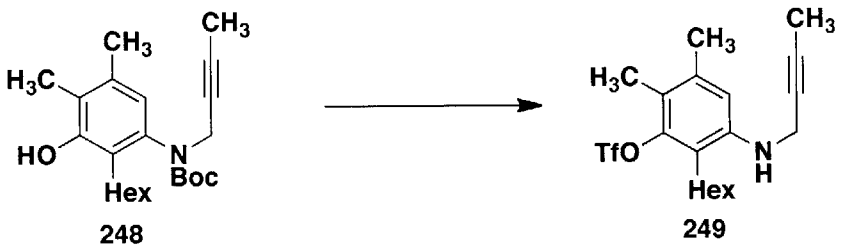
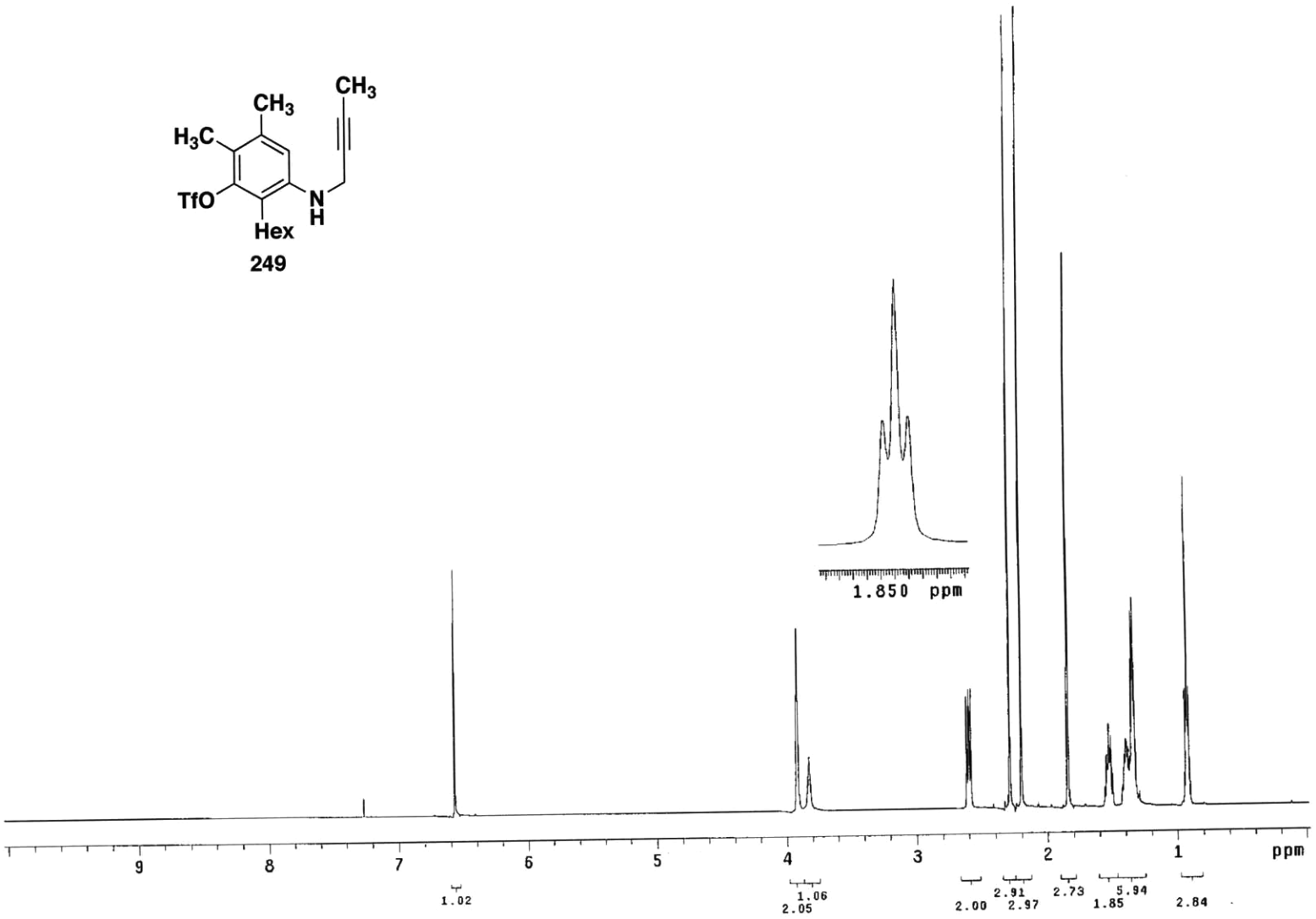
H3C
HO
248



3-(But-2-yn-1-ylamino)-2-hexyl-5,6-dimethylphenyl trifluoromethanesulfonate (249). A 25-mL pear flask equipped with a rubber septum and argon inlet needle was charged with phenol **248** (0.153 g, 0.41 mmol, 1.0 equiv), 4-DMAP (0.125 g, 1.0 mmol, 2.5 equiv), and 2.4 mL of CH_2Cl_2. The yellow solution was cooled to 0 °C and triflic anhydride (0.09 mL, 0.53 mmol, 1.3 equiv) was added dropwise by syringe over ca. 3 min. The reaction mixture was allowed to warm to rt and stirred for 1 h. The resulting yellow slurry of white solid was cooled to 0 °C and trifluoroacetic acid (0.61 mL, 8.2 mmol, 20 equiv) was added dropwise over 5 min. The resulting golden orange solution was allowed to warm to rt and stirred for 40 min. The reaction mixture was then diluted with 10 mL of dichloromethane and washed with two 10-mL portions of satd aq K_2CO_3 solution. The aqueous layer was extracted with two 10-mL portions of CH_2Cl_2, and the combined organic layers were washed with 30 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.303 g of a golden semi-solid. Column chromatography on 5 g of silica gel (elution with 3% EtOAc-hexanes) afforded 0.149 g (90%) of triflate **249** as a yellow oil: IR (neat) 3444, 2928, 2860, 1402, 1246, 1218, 1140, 909 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.57 (s, 1H), 3.90-3.94 (m, 2H), 3.83 (bs, 1H), 2.58-2.63 (m, 2H), 2.29 (s, 3H), 2.20 (s, 3H), 1.84 (t, J = 2 Hz, 3H), 1.49-1.57 (m, 2H), 1.36-1.44 (m, 2H), 1.31-1.38 (m, 4H), 0.92 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.9, 144.1, 137.2, 118.9 (q, J = 318 Hz), 118.8, 118.5, 113.0, 79.5, 76.0, 34.5, 31.7, 29.6, 28.2, 25.4, 22.8, 20.7, 14.2, 13.3, 3.6; HRMS-ESI (*m/z*) [M + H] calculated for $C_{19}H_{26}F_3NO_3S$, 406.1658; found: 406.1658.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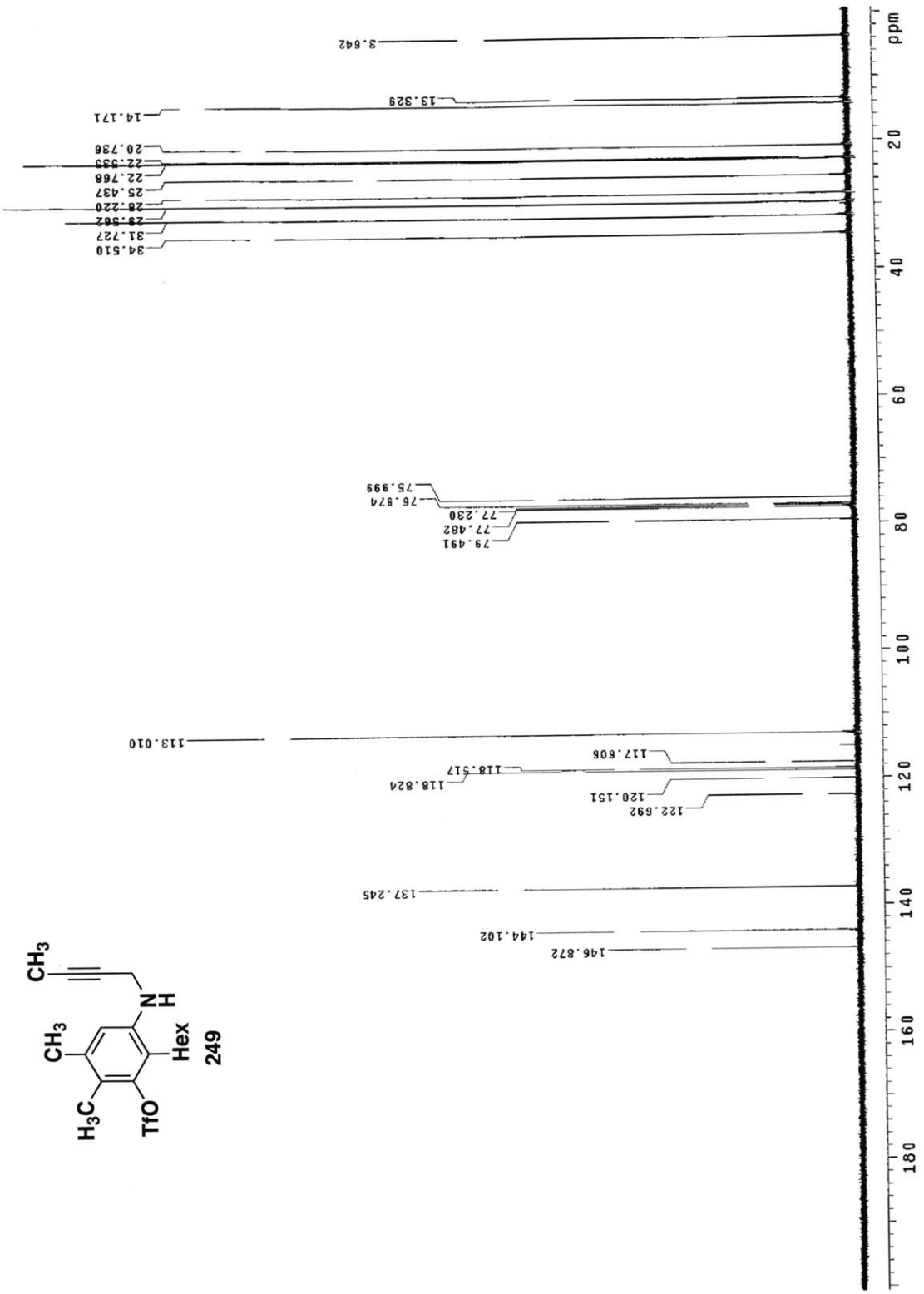
H3C
TfO
Hex
CH3
N
H
249
1.850 ppm
9
8
7
6
5
4
3
2
1
ppm
1.02
1.06
2.05
2.00
2.91
2.97
2.73
5.94
1.85
2.84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13.329
14.171
20.786
22.535
22.768
25.437
28.220
29.562
31.727
34.510
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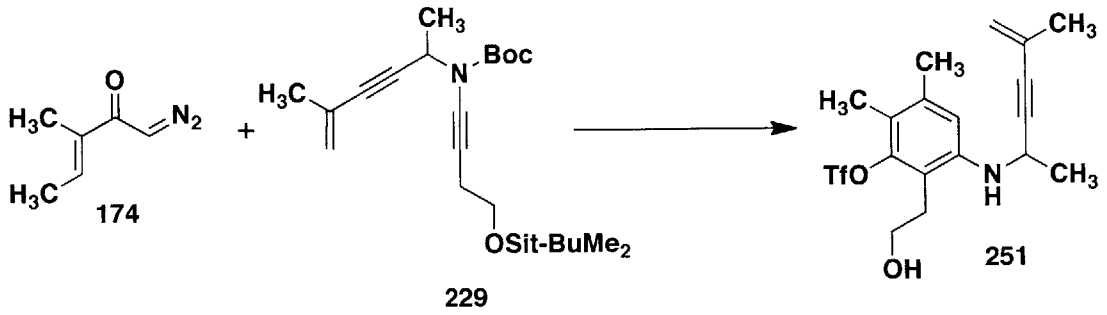
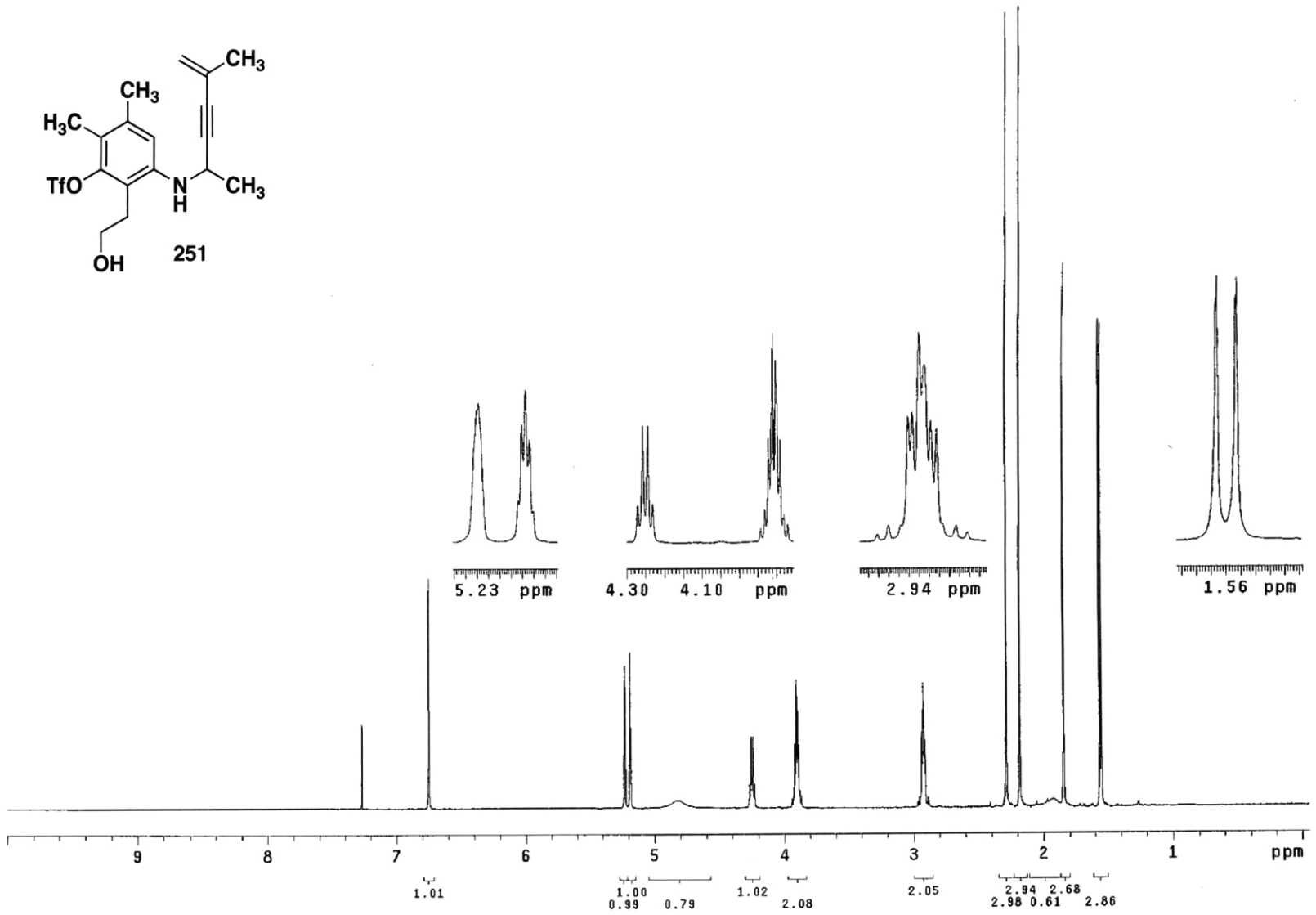
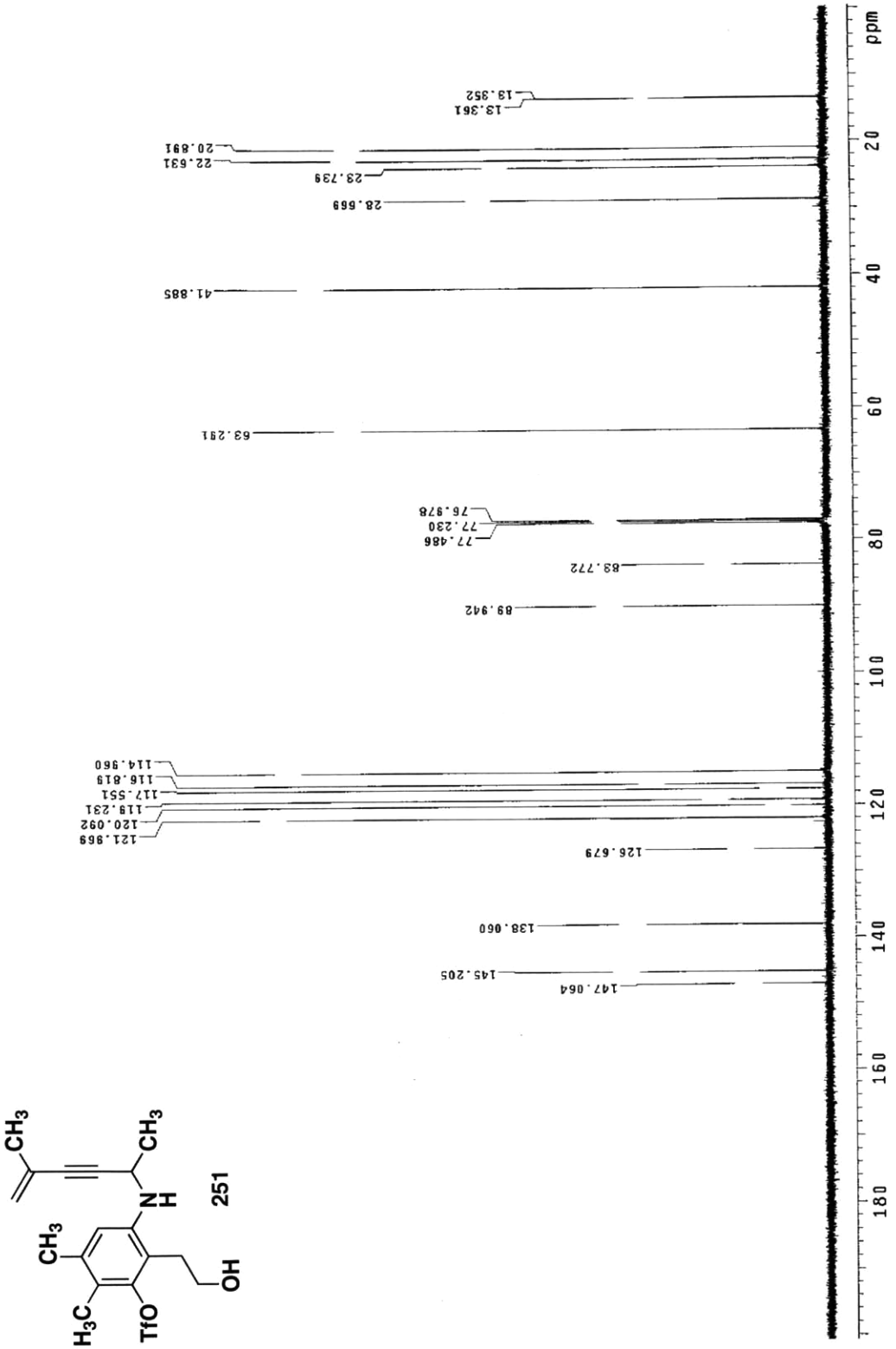
76.974
77.230
77.482
79.491
113.010
117.606
118.517
118.824
120.151
122.692
137.245
144.102
146.872
ppm
20
40
60
80
100
120
140
160
180
CH3
NH
CH3
Hex
H3C
TfO
249



2-(2-Hydroxyethyl)-5,6-dimethyl-3-((5-methylhex-5-en-3-yn-2-yl)amino)phenyl trifluoromethanesulfonate (251). A 20-cm quartz tube (7 mm I.D., 10 mm O.D.) equipped with a rubber septum and argon inlet needle was charged with diazo ketone **174**[72a] (0.177 g, 1.43 mmol, 2.5 equiv), ynamide **229** (0.224 g, 0.572 mmol, 1.0 equiv), and 2.4 mL of CH_2Cl_2. The yellow solution was degassed for 10 min with a stream of argon. The quartz tube was placed ca. 20 cm from a 450-W Hanovia lamp (quartz immersion well, cooled by recirculating tap water) and irradiated under argon at 25 °C for 38 h. The reaction mixture was transferred to a 25-mL pear flask with the aid of two 4-mL portions of CH_2Cl_2 and concentrated to afford 0.392 g of an orange oil. This material was dissolved in 3.0 mL of toluene, the flask was equipped with a stir bar and cold-finger condenser, and the reaction mixture was heated at reflux for 2 h. The resulting mixture was concentrated to afford 0.362 g of an orange oil. Filtration through a 4-g plug of silica gel (elution with 80 mL of 2% EtOAc-hexanes) afforded 0.220 g of a yellow oil. This oil was transferred to a 25-mL pear flask equipped with a rubber septum and argon inlet needle. 4-DMAP (0.165 g, 1.35 mmol, 3.0 equiv) and 4.5 mL of CH_2Cl_2 were added and the yellow solution was cooled to 0 °C while triflic anhydride (0.09 mL, 0.15 g, 0.54 mmol, 1.2 equiv) was added dropwise by syringe over ca. 5 min. The reaction mixture was allowed to warm to rt and stirred for 1.5 h. The resulting red slurry of white solid was cooled to 0 °C and trifluoroacetic acid (1.04 mL, 1.54 g, 13.5 mmol, 30 equiv) was added dropwise over 15 min. The resulting brown solution was allowed to warm to rt and stirred for 2 h. The reaction mixture was then diluted with 30 mL of dichloromethane and washed with three 20-mL portions of satd aq K_2CO_3 solution. The combined aqueous layers were extracted with two 10-mL portions of CH_2Cl_2, and the combined organic layers were washed with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.363 g of an orange-brown oil. Column chromatography on 40 g of silica gel (elution with CH_2Cl_2) afforded 0.125 g (54%) of triflate **251** as a yellow oil: IR

(neat) 3583, 3332, 2977, 2928, 2885, 1403, 1246, 1214, 1139, 913 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.75 (s, 1H), 5.22-5.24 (m, 1H), 5.18-5.20 (m, 1H), 4.82 (bs, 1H), 4.24 (q, J = 6.5 Hz, 1H), 3.86-3.95 (m, 2H), 2.88-2.97 (m, 2H), 2.29 (s, 3H), 2.18 (s, 3H), 1.93 (bs, 1H), 1.83-1.87 (m, 3H), 1.56 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.1, 145.2, 138.1, 126.7, 122.6, 122.0, 119.2, 118.8 (q, J = 318 Hz), 116.8, 115.0, 89.9, 83.8, 63.3, 41.9, 28.7, 23.7, 22.6, 20.9, 13.4; HRMS-ESI (*m/z*) [M + H] calculated for $C_{18}H_{22}F_3NO_4S$, 406.1294; found, 406.1294.


CH3
CH3
H3C
TfO
N
H
CH3
OH
251
5.23 ppm
4.30 4.10 ppm
2.94 ppm
1.56 ppm
9
8
7
6
5
4
3
2
1
ppm
1.01
1.00
0.99
0.79
1.02
2.08
2.05
2.94
2.98
2.68
0.61
2.86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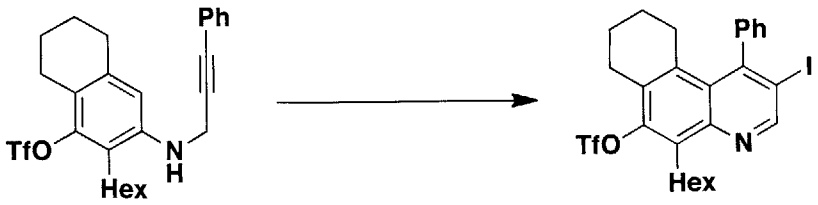
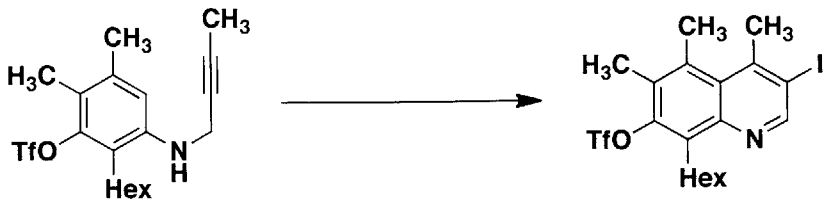
20.891
22.631
28.739
28.669
41.885
63.291
76.978
77.230
77.486
83.772
89.942
114.960
116.819
117.551
119.231
120.092
121.869
126.679
138.060
145.205
147.064
ppm
20
40
60
80
100
120
140
160
180
CH3
CH3
N
H
251
CH3
H3C
TfO
OH



5-Hexyl-2-iodo-1-phenyl-7,8,9,10-tetrahydrobenzo[f]quinolin-6-yl trifluoromethanesulfonate (252). A 25-mL pear flask equipped with a rubber septum and argon inlet needle was charged with triflate **247** (0.065 g, 0.13 mmol, 1.0 equiv), $NaHCO_3$ (0.044 g, 0.52 mmol, 4.0 equiv), iodine (0.199 g, 0.78 mmol, 6.0 equiv), and 1.3 mL of CH_3CN. The reaction mixture was stirred at rt for 45 min, diluted with 15 mL of Et_2O, and then washed with 15 mL of satd aq $Na_2S_2O_3$ solution. The aqueous layer was extracted with three 10-mL portions of Et_2O, and the combined organic layers were washed with 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.082 g of a yellow oil. Column chromatography on 20 g of silica gel (elution with 1% EtOAc-5% benzene-94% hexanes) provided 0.075 g (92%) of quinoline **252** as a pale yellow oil: IR (neat) 2932, 2861 1404, 1218, 1137 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 7.43-7.54 (m, 3H), 7.14-7.22 (m, 2H), 3.31-3.40 (m, 2H), 2.92 (t, J = 6.4 Hz, 2H), 2.14 (t, J = 6.2 Hz, 2H), 1.61-1.78 (m, 4H), 1.40-1.53 (m, 4H), 1.28-1.40 (m, 4H), 0.92 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 151.2, 147.0, 146.4, 145.9, 135.2, 133.4, 131.3, 129.4, 128.6, 128.5, 118.8 (q, J = 318 Hz), 102.4, 31.9, 31.6, 30.6, 29.9, 26.7, 25.8, 23.0, 22.8, 21.4, 14.3 (one carbon overlapped in the region 144-152); HRMS-ESI (*m/z*) [M + H] calculated for $C_{26}H_{27}O_3F_3INS$, 618.0781; found 618.0795.

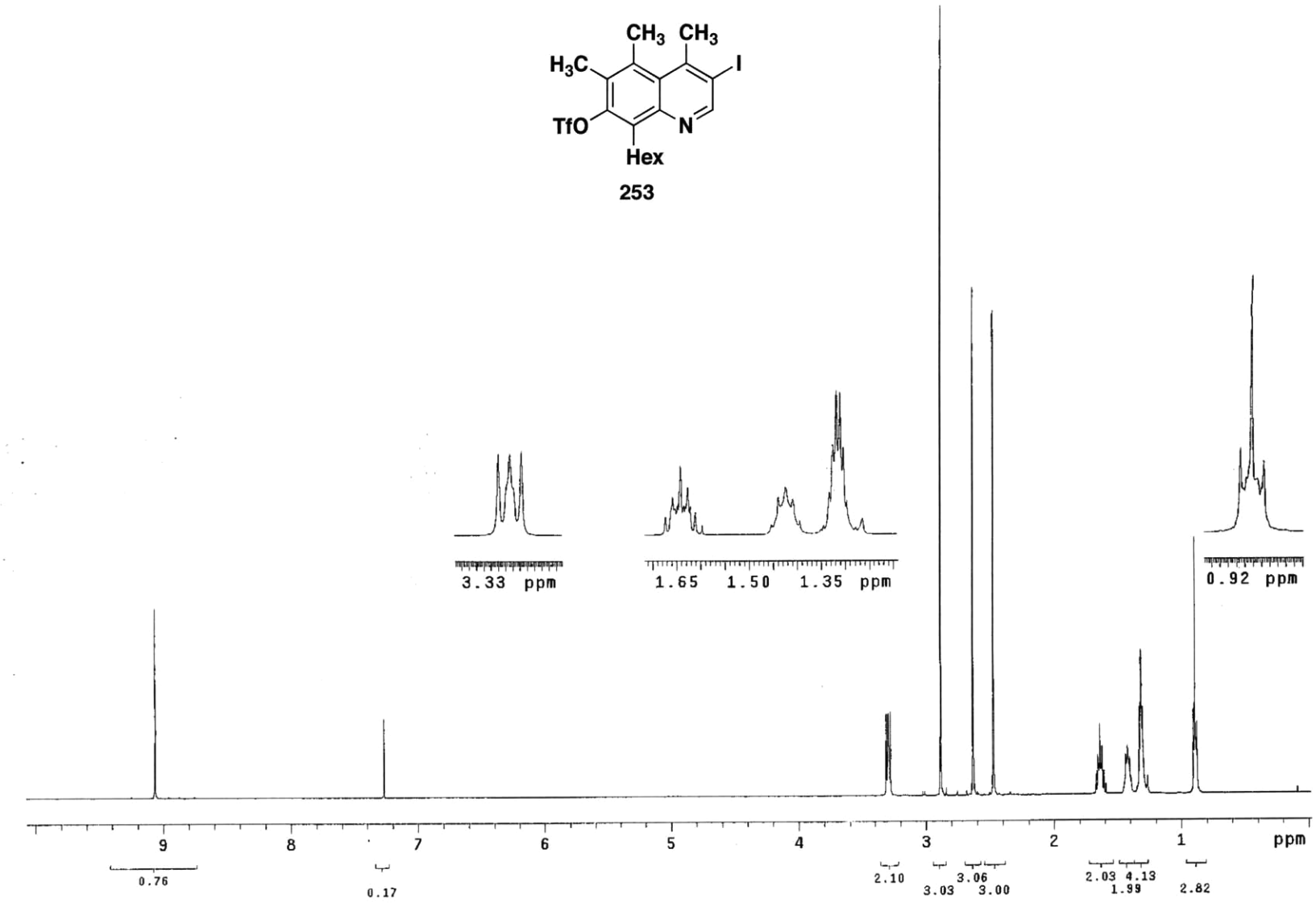
Ph
I
TfO
N
Hex
252
1.8
1.6
1.4
1.2
1.0
ppm
3.0
2.5
ppm
9
8
7
6
5
4
3
2
1
ppm
0.92
3.05
2.00
2.00
2.01
2.01
4.31
4.31
4.26
3.28

155.41
151.22
146.95
146.36
145.81
135.20
133.34
131.28
129.36
128.58
128.54
123.66
120.48
117.30
114.11
102.36
77.55
77.23
76.92
31.89
31.64
30.58
29.86
26.68
25.80
22.96
22.84
21.39
14.32
Ph
I
TfO
N
Hex
252
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



249 253

8-Hexyl-3-iodo-4,5,6-trimethylquinolin-7-yl trifluoromethanesulfonate (253). A 25-mL pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with triflate **249** (0.100 g, 0.25 mmol, 1.0 equiv), $NaHCO_3$ (0.084 g, 0.99 mmol, 4.0 equiv), iodine (0.376 g, 1.5 mmol, 6.0 equiv), and 2.5 mL of CH_3CN. The reaction mixture was stirred at rt for 30 min, diluted with 30 mL of Et_2O, and then washed with two 15-mL portions of satd aq $Na_2S_2O_3$ solution. The aqueous layer was extracted with two 15-mL portions of Et_2O, and the combined organic layers were washed with 40 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.167 g of a yellow oil. Column chromatography on 42 g of silica gel (elution with 10% benzene-hexanes) furnished 0.103 g (79%) of quinoline **253** as a off-white waxy solid: mp 36-38 °C; IR (neat) 2958, 2929, 2858 1406, 1217, 1138 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.07 (s, 1H), 3.27-3.32 (m, 2H), 2.88 (s, 3H), 2.63 (s, 3H), 2.47 (s, 3H), 1.59-1.68 (m, 2H), 1.38-1.46 (m, 2H), 1.27-1.36 (m, 4H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.7, 147.0, 146.1, 145.8, 133.3, 132.9, 131.2, 130.3, 118.9 (q, J = 318 Hz), 102.6, 31.9, 31.5, 30.5, 29.8, 26.6, 22.8, 21.8, 15.3, 14.3; Anal. Calcd for $C_{19}H_{23}F_3INO_3S$; C, 43.11; H, 4.38; N, 2.65. Found: C, 43.32; H, 4.33; N, 2.68.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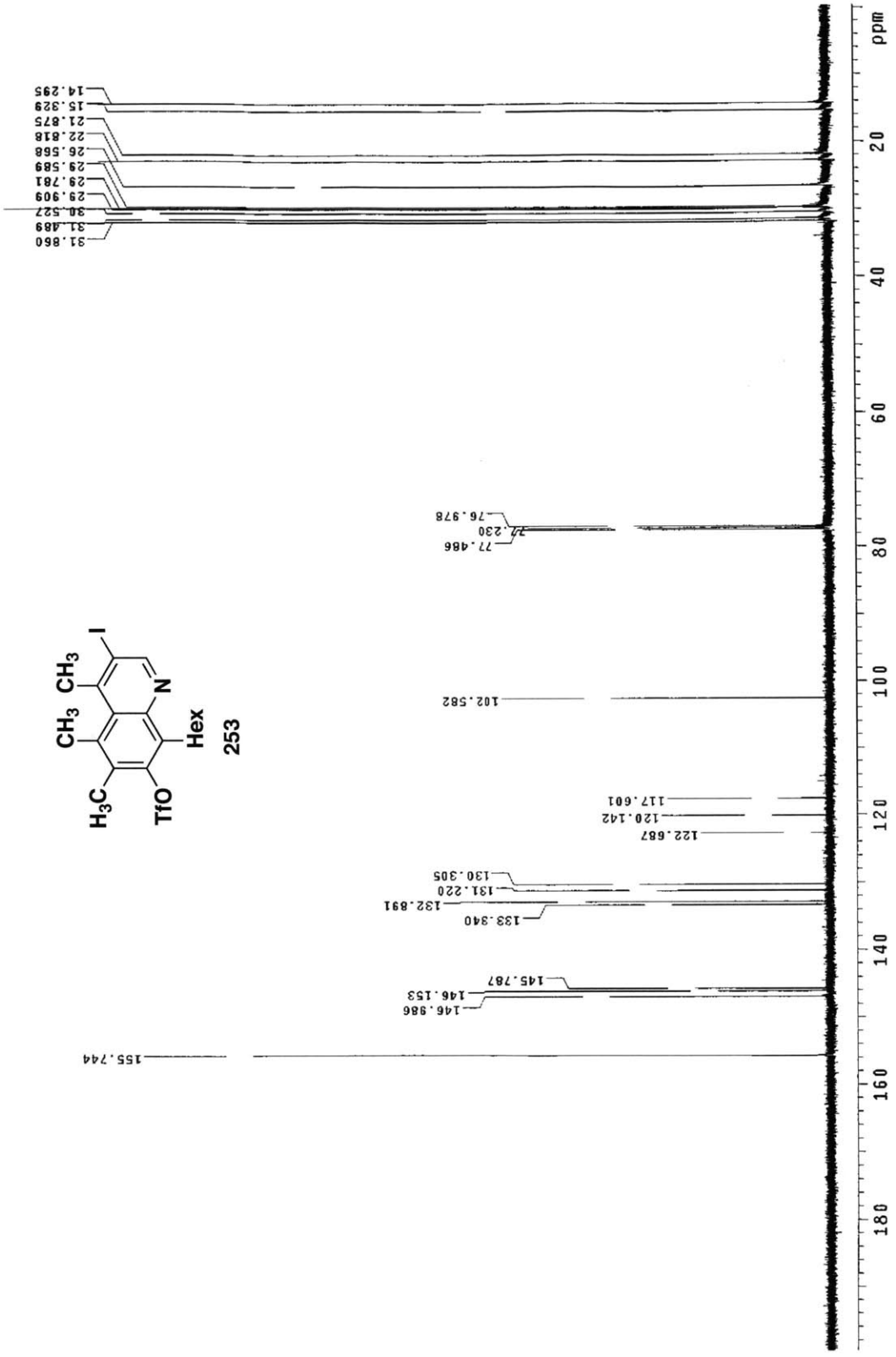
H3C
I
TfO
N
Hex
253
3.33 ppm
1.65 1.50 1.35 ppm
0.92 ppm
9 8 7 6 5 4 3 2 1 ppm
0.76
0.17
2.10
3.03
3.06
3.00
2.03
4.13
1.99
2.82


I
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CH3
N
Hex
H3C
TfO
253
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146.986
146.153
145.787
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132.891
131.220
130.305
122.687
120.142
117.601
102.582
77.486
77.230
76.978
31.860
31.489
30.527
29.909
29.781
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ppm
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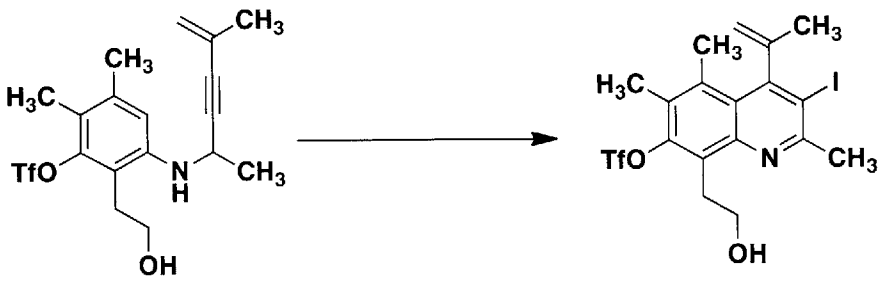
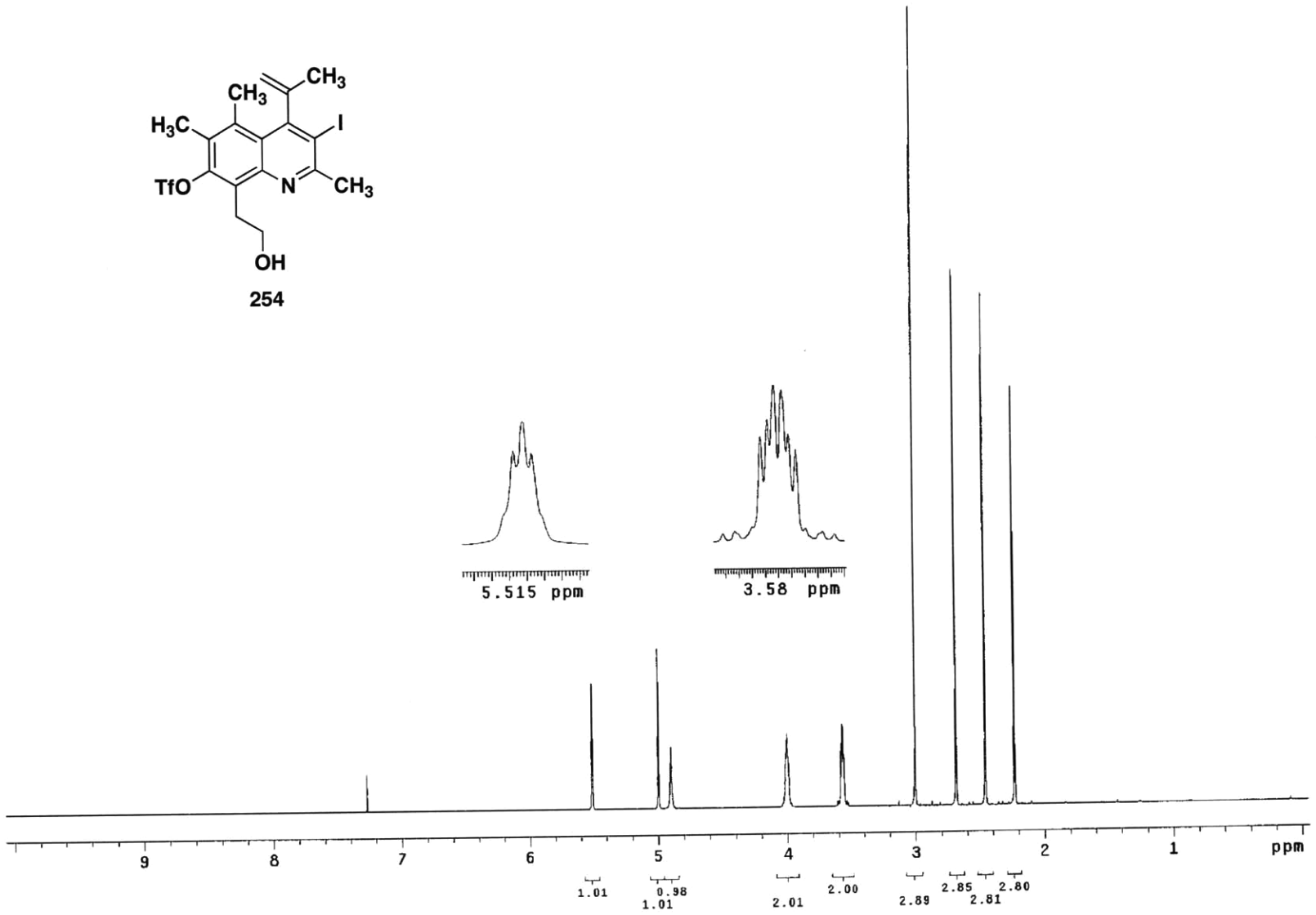
40
60
80
100
120
140
160
180



251 254

8-(2-Hydroxyethyl)-3-iodo-2,5,6-trimethyl-4-(prop-1-en-2-yl)quinolin-7-yl trifluoromethanesulfonate (254). A 25-mL pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with triflate **251** (0.107 g, 0.26 mmol, 1.0 equiv), $NaHCO_3$ (0.089 g, 1.1 mmol, 4.0 equiv), iodine (0.402 g, 1.6 mmol, 6.0 equiv), and 2.6 mL of CH_3CN. The reaction mixture was stirred at rt for 1 h, diluted with 25 mL of Et_2O, and then washed with three 10-mL portions of satd aq $Na_2S_2O_3$ solution. The combined aqueous layers were extracted with two 10-mL portions of Et_2O, and the combined organic layers were washed with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.140 g of a yellow oil. Column chromatography on 21 g of silica gel (elution with 2% Et_2O-CH_2Cl_2) furnished 0.110 g (79%) of quinoline **254** as a yellow oil: IR (neat) 3357, 2957, 2920, 2870 1406, 1214, 1140 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.50-5.53 (m, 1H), 4.98-5.01 (m, 1H), 4.90 (bs, 1H), 3.96-4.04 (m, 2H), 3.54-3.59 (m, 2H), 3.00 (s, 3H), 2.68 (s, 3H), 2.46 (s, 3H), 2.22-2.24 (m, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 159.8, 155.2, 149.2, 146.7, 146.1, 134.2, 130.2, 129.9, 125.9, 120.0, 118.8 (q, J = 318 Hz), 103.3, 63.4, 32.0, 30.1, 24.7, 20.3, 15.8; HRMS-ESI (*m/z*) [M + H] calculated for $C_{18}H_{19}F_3INO_4S$, 530.0104; found, 529.9998.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H3C
I
TfO
N
CH3
OH
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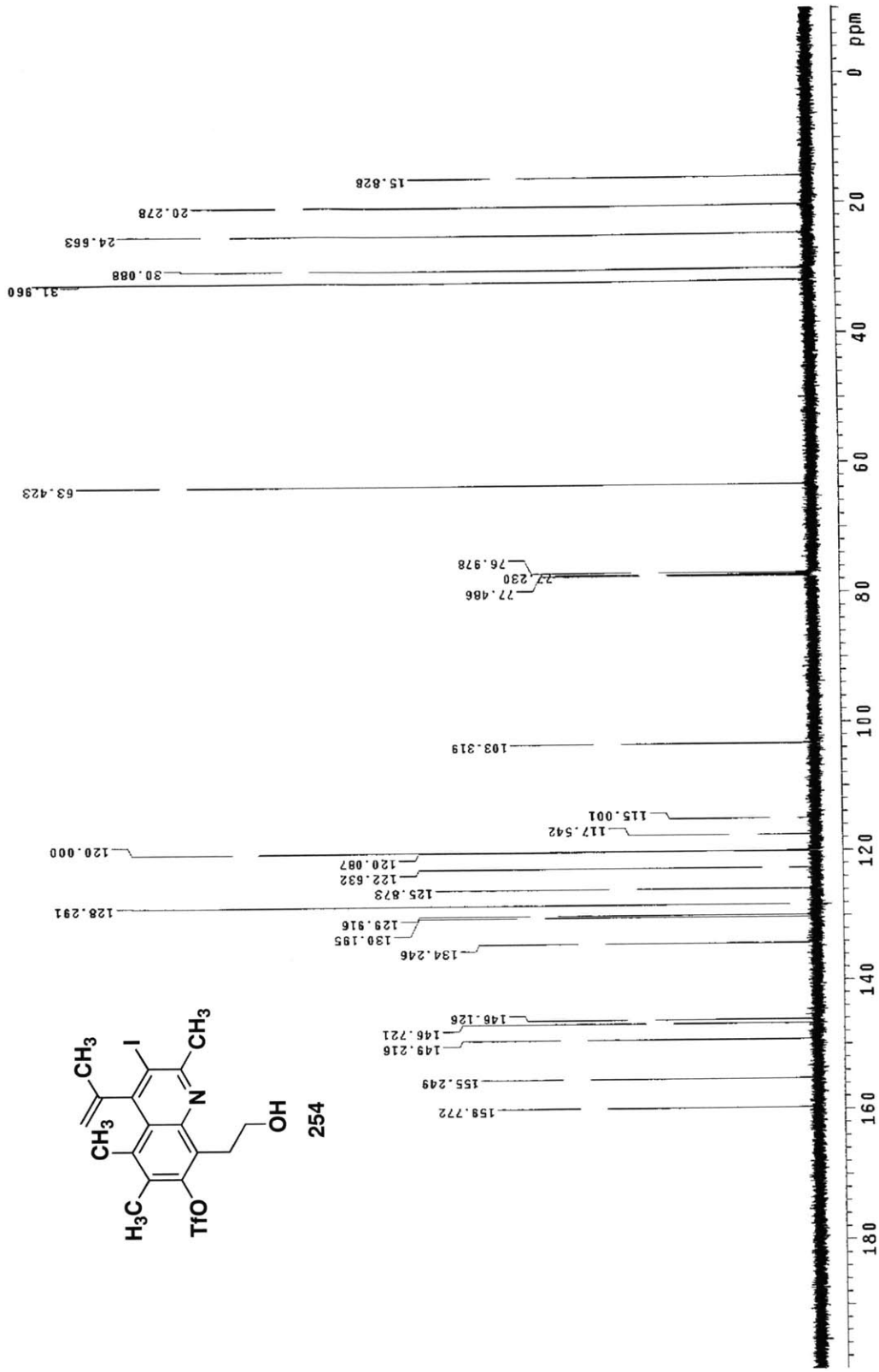
3.58 ppm
9
8
7
6
5
4
3
2
1
ppm
1.01
0.98
1.01
2.01
2.00
2.89
2.85
2.81
2.80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31.960
63.423
76.978
77.230
77.486
103.319
115.001
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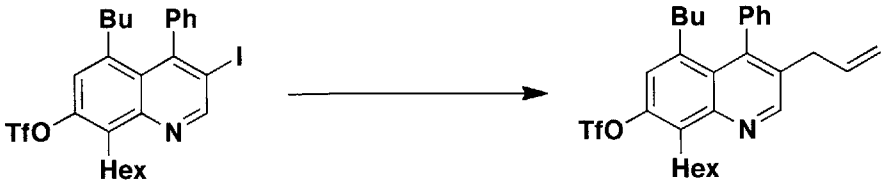
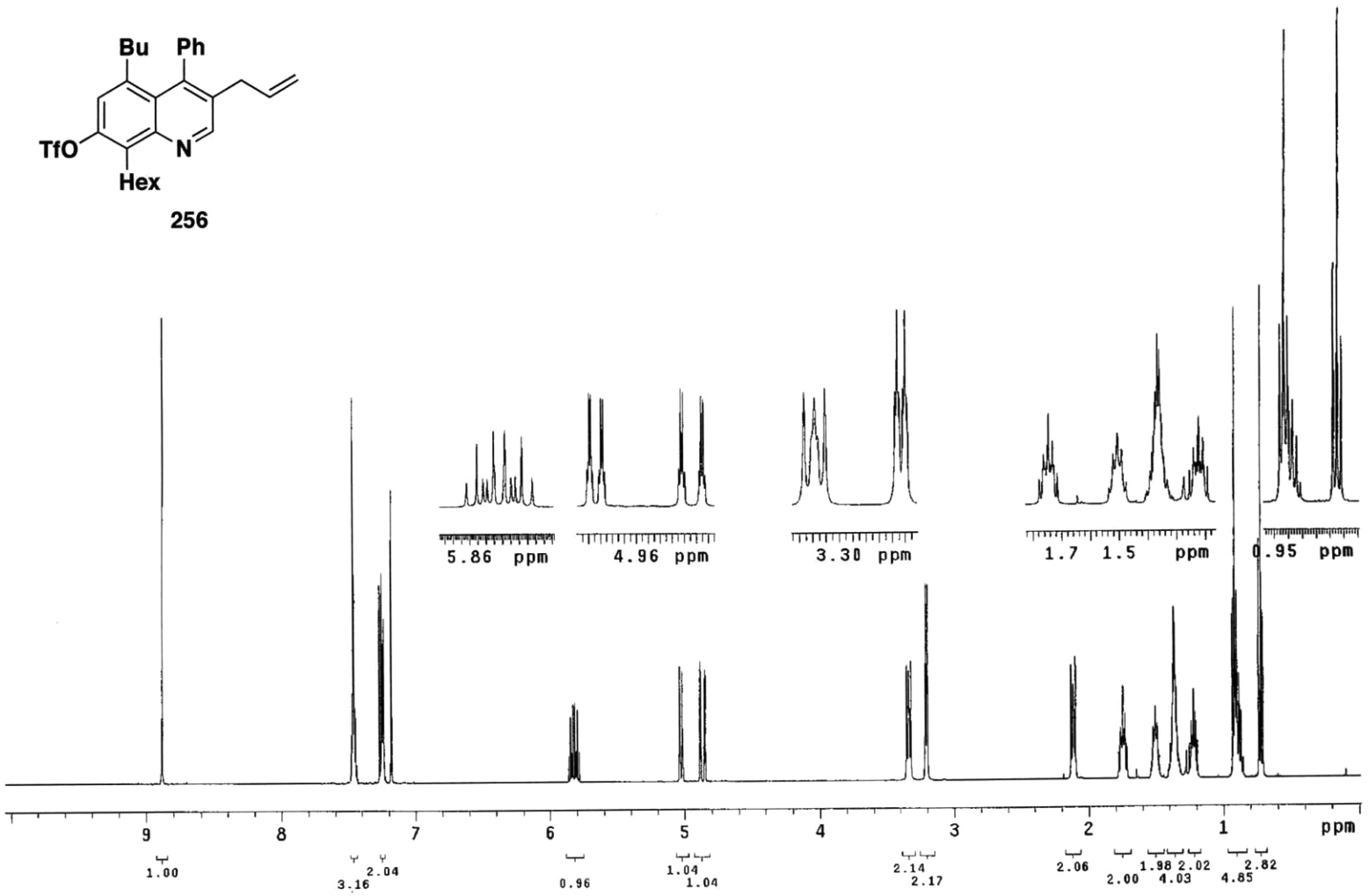
120.087
122.632
125.873
128.291
129.916
130.185
134.246
146.126
146.721
149.216
155.249
159.772
0 ppm
20
40
60
80
100
120
140
160
180
CH3
I
CH3
CH3
N
OH
H3C
TfO
254



243 256

5-Butyl-8-hexyl-3-(2-propenyl)-4-phenylquinolin-7-yl trifluoromethanesulfonate (256). A 10-mL 2-neck pear flask equipped with a rubber septum, argon inlet adapter, and thermocouple probe was charged with quinoline **243** (0.102 g, 0.16 mmol, 1.0 equiv) and 0.5 mL of THF. The reaction mixture was cooled to -30 °C, *i*-PrMgBr solution (0.47 M in THF, 0.37 mL, 0.17 mmol, 1.1 equiv) was added dropwise over 5 min, and the resulting gold-colored solution was stirred for 1 h at -30 °C. CuCN (2 mg, 0.016 mmol, 0.10 equiv) and then allyl bromide (0.018 mL, 0.025 g, 0.21 mmol, 1.2 equiv) were added, and the resulting yellow solution was stirred at -30 °C for 1 h and then allowed to warm to 0 °C and treated with 1 mL of brine. The resulting mixture was diluted with 4 mL of brine and the aqueous layer was separated and extracted with two 5-mL portions of EtOAc. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated to afford 0.086 g of an orange oil. Purification by column chromatography on 22 g of silica gel (elution with 1% EtOAc-hexanes) afforded 0.069 g of an orange oil which was further purified by column chromatography on 22 g of silica gel (elution with 10% benzene-hexanes) to afford 0.061 g (69%) of quinoline **256** as a yellow oil: IR (neat) 2958, 2931, 2859, 1582, 1421, 1215, 1142, 830 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.88 (s, 1H), 7.43-7.49 (m, 3H), 7.23-7.27 (m, 2H), 7.18 (s, 1H), 5.78-5.87 (m, 1H), 5.03 (dq, J = 1.5, 10.0 Hz, 1H), 4.87 (dq, J = 1.5, 17.0 Hz, 1H), 3.31-3.36 (m, 2H), 3.21 (dt, J = 1.5, 6.0 Hz, 2H), 2.09-2.15 (m, 2H), 1.71-1.79 (m, 2H), 1.47-1.54 (m, 2H), 1.30-1.41 (m, 4H), 1.18-1.27 (m, 2H), 0.72 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.7, 147.7, 146.6, 146.4, 141.3, 139.7, 136.6, 132.3, 131.8, 129.1, 128.4, 128.2, 125.7, 122.0, 118.9 (q, J = 318 Hz), 35.5, 35.3, 34.3, 31.9, 30.4, 29.9, 26.2, 22.9, 22.6, 14.3, 13.9; HRMS-ESI (*m/z*) [M + H] calculated for $C_{29}H_{34}F_3NO_3S$, 534.2284; found 534.2269.


Bu
Ph
TfO
N
Hex
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5.86 ppm
4.96 ppm
3.30 ppm
1.7 1.5 ppm
0.95 ppm
9
8
7
6
5
4
3
2
1
ppm
1.00
3.16
2.04
0.96
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2.00
1.98
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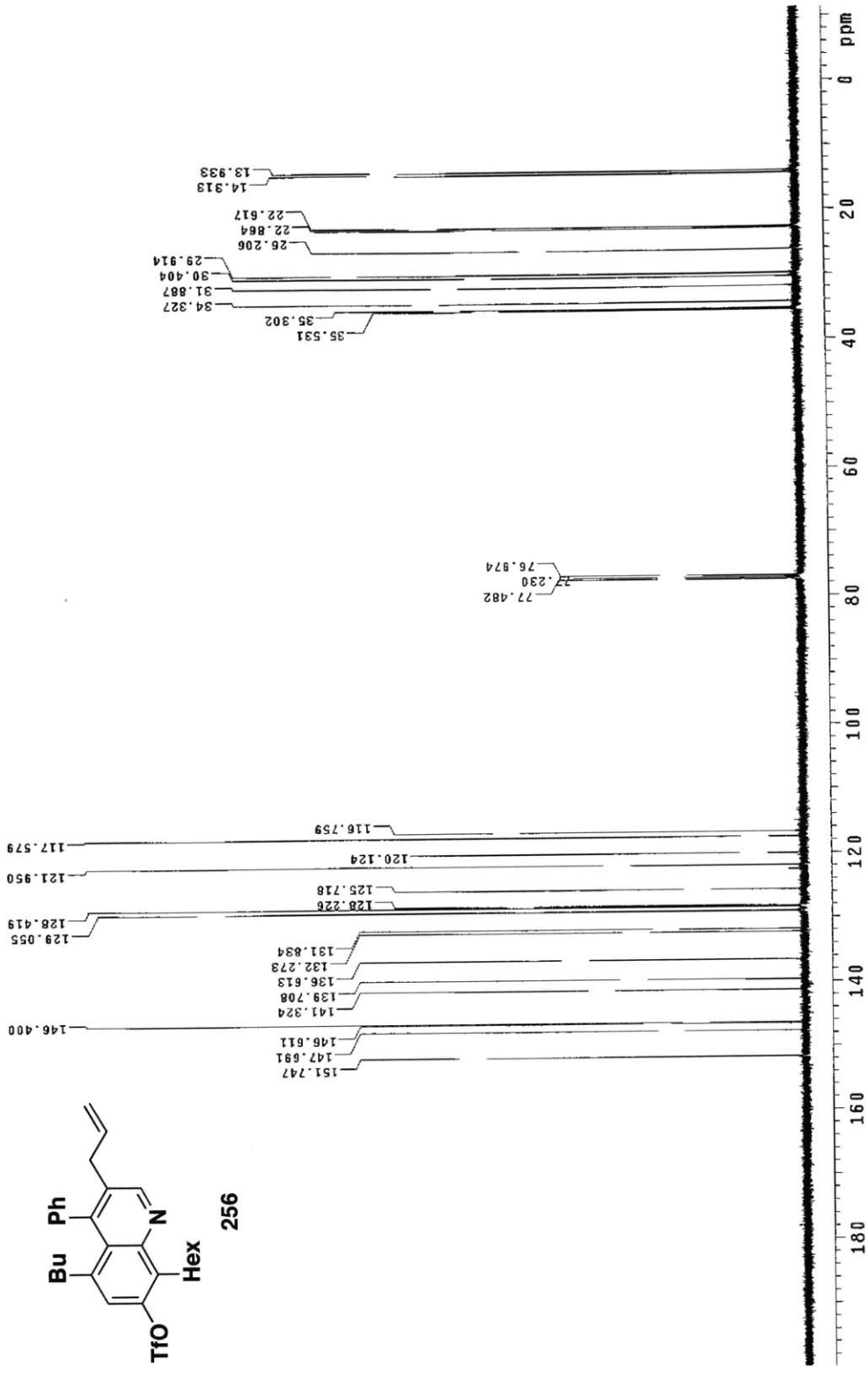
2.02
4.85
2.82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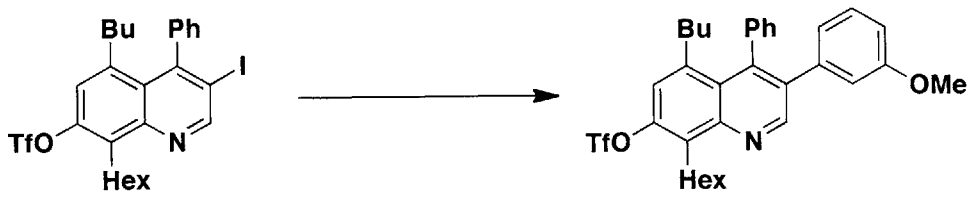
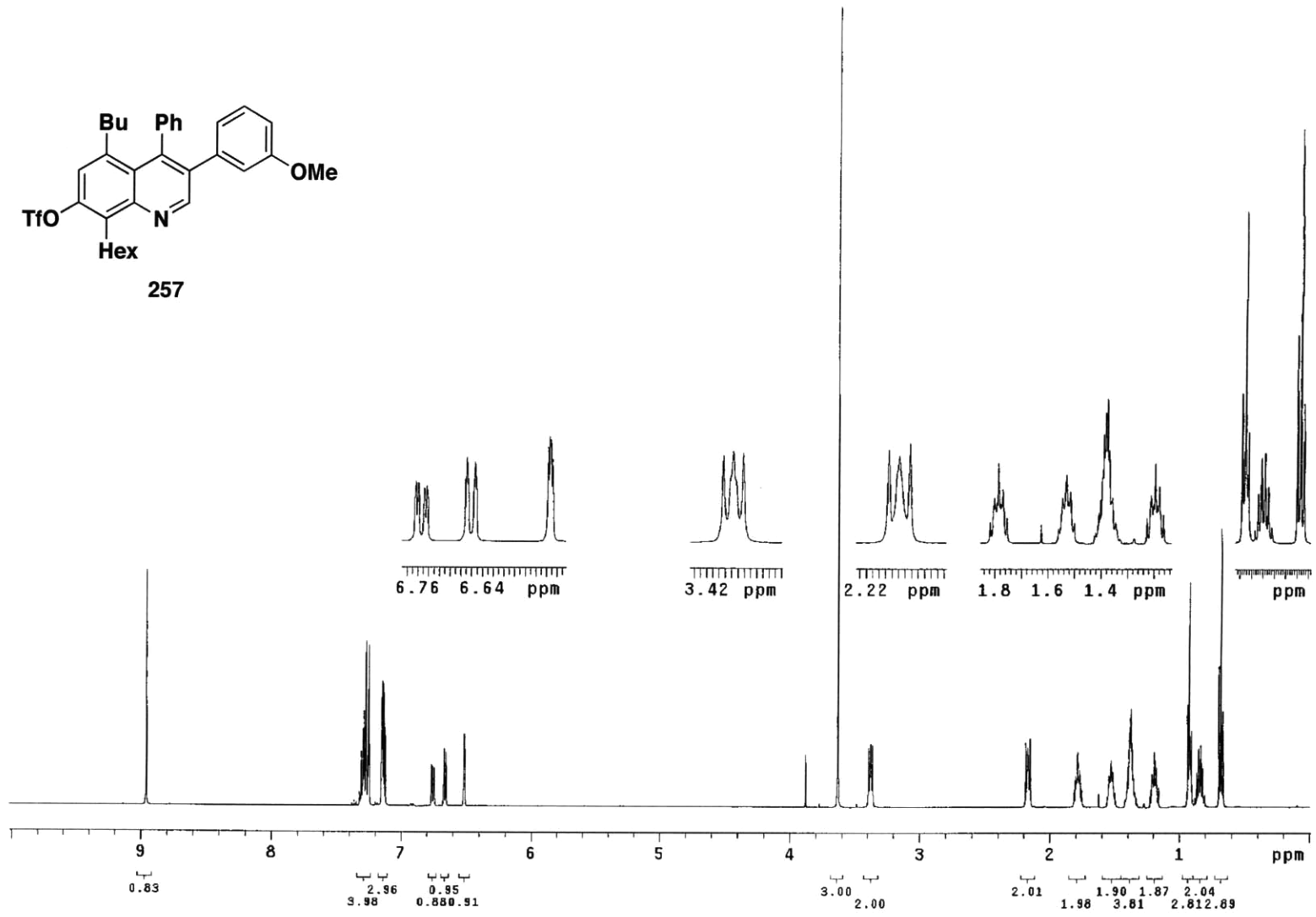
ppm



243 257

5-Butyl-8-hexyl-3-(3-methoxyphenyl)-4-phenylquinolin-7-yl trifluoromethanesulfonate (257). A 10-cm threaded Pyrex tube (12 mm I.D., 18 mm O.D.) equipped with a rubber septum and argon inlet needle was charged with 3-methoxyphenylboronic acid (0.065 g, 0.43 mmol, 1.2 equiv), $PdCl_2(dppf)•CH_2Cl_2$ (0.059 g, 0.07 mmol, 0.2 equiv), quinoline **243** (0.223 g, 0.36 mmol, 1.0 equiv), 2.8 mL of THF, and 0.7 mL of Cs_2CO_3 solution (1.0 M in water, 0.23 g Cs_2CO_3, 0.7 mmol, 2.0 equiv). The resulting mixture was degassed for 10 min with a stream of argon, the septum was replaced with a threaded Teflon cap, and the reaction mixture was heated at 45-50 °C for 20.5 h. The reaction mixture was then diluted with 30 mL of EtOAc, washed with two 15-mL portions of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.282 g of a brown oil. Column chromatography on 30 g of silica gel (elution with 1% EtOAc-hexanes) yielded 0.169 g (78%) of quinoline **257** as a white solid:[210] mp 69-71 °C; IR (neat) 2957, 2930, 2860, 1581, 1419, 1218, 1142 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.95 (s, 1H), 7.23-7.32 (m, 4H), 7.15-7.10 (m, 3H), 6.74 (dd, J = 2.5, 8.3 Hz, 1H), 6.65 (dt, J = 1, 8 Hz, 1H), 6.49-6.51 (m, 1H), 3.62 (s, 3H), 3.34-3.39 (m, 2H), 2.13-2.18 (m, 2H), 1.73-1.82 (m, 2H), 1.52 (app quint, J = 7.5 Hz, 2H), 1.31-1.42 (m, 4H), 1.14-1.22 (m, 2H), 0.91 (t, J = 7.0 Hz, 3H) 0.83 (app hex, J = 7.5 Hz, 2H), 0.67 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 150.9, 148.3, 147.0, 145.7, 141.9, 139.5, 139.3, 135.2, 132.3, 130.2, 129.0, 127.9, 127.9, 125.4, 122.8, 122.4, 118.8 (d, J = 318 Hz), 115.6, 113.2, 55.3 35.7, 34.3, 31.9, 30.4, 29.9, 26.2, 22.9, 22.6, 14.3, 13.9; HRMS-ESI (*m/z*) [M + H] calculated for $C_{33}H_{36}F_3NO_4S$, 600.2390; found 600.2369.

[210] The product is contaminated with a small amount (ca. 3 mol%) of 3,3'-dimethoxy-1,1'-biphenyl.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Ph
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TfO
N
Hex
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2.22 ppm
1.8 1.6 1.4 ppm
ppm
9
8
7
6
5
4
3
2
1
ppm
0.83
2.96
3.98
0.95
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3.00
2.00
2.01
1.98
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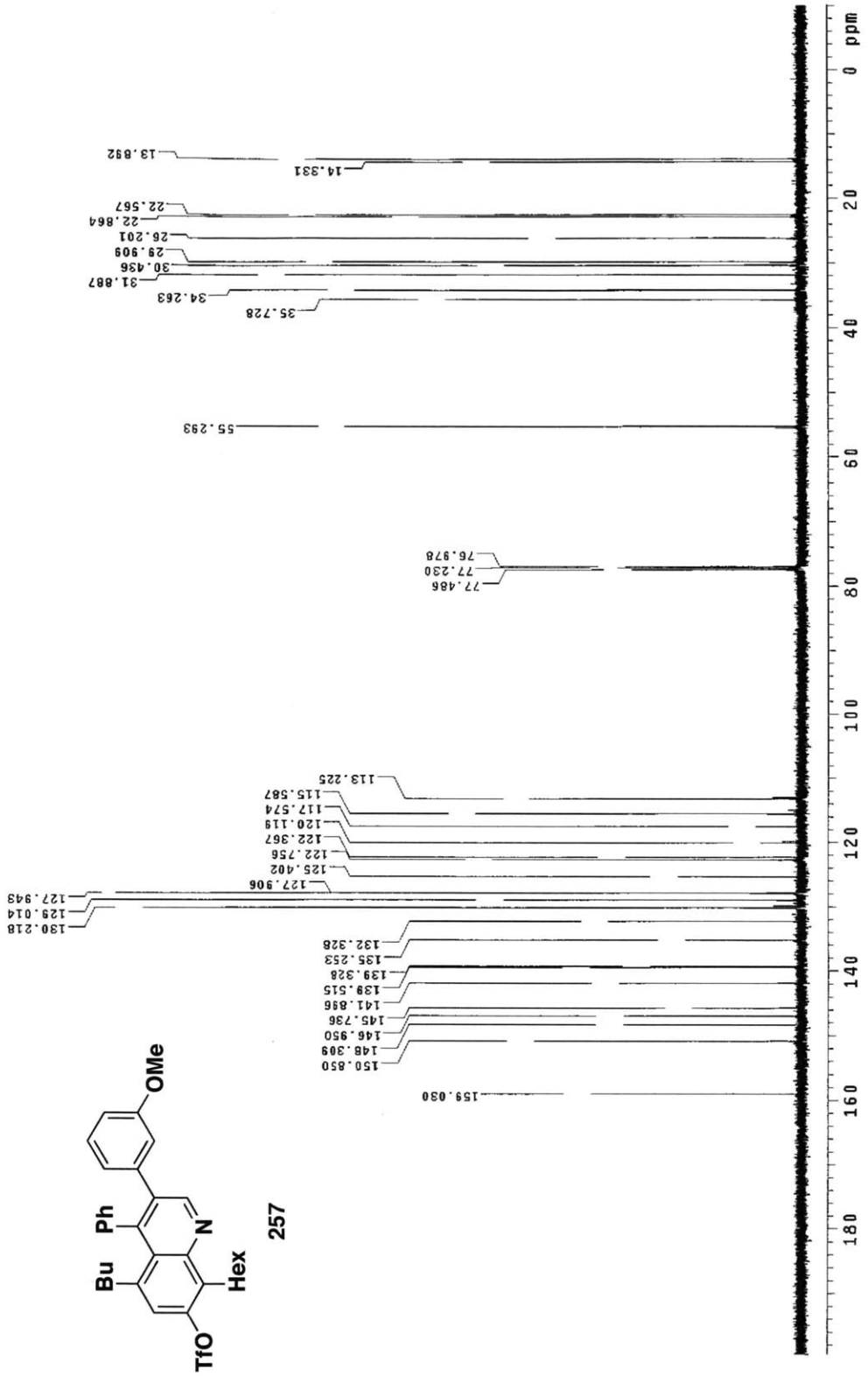
3.81
1.87
2.04
2.812.89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115.587
117.574
120.119
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122.756
125.402
127.906
127.943
129.014
130.218
132.328
135.253
139.328
139.515
141.896
145.736
146.950
148.309
150.850
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OMe
Ph
N
Bu
Hex
TfO
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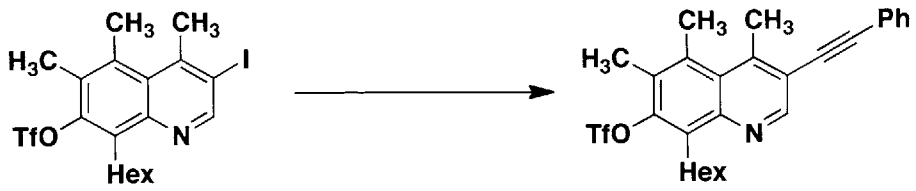
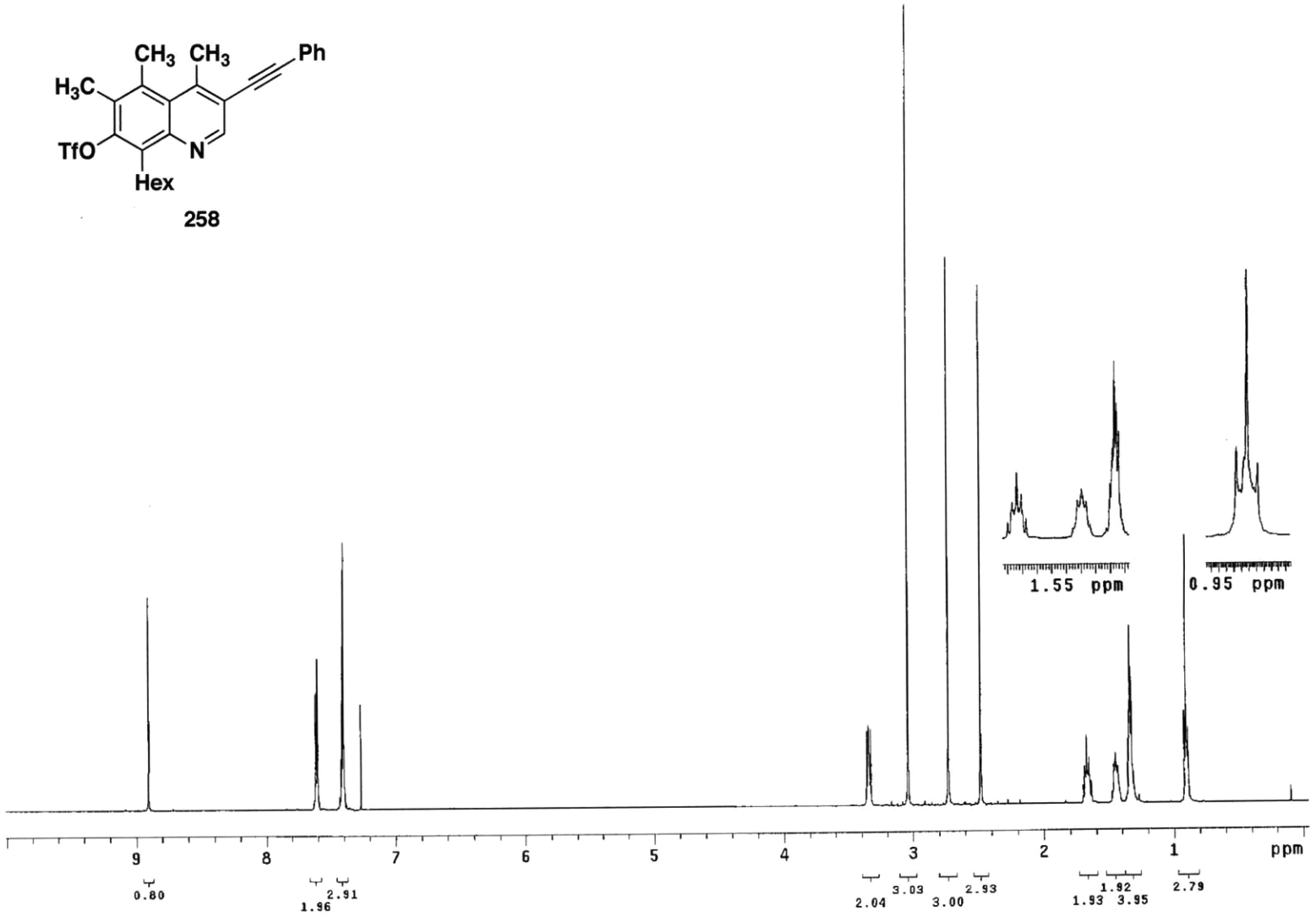
40
60
80
100
120
140
160
180



253 258

8-Hexyl-4,5,6-trimethyl-3-(phenylethynyl)quinolin-7-yl trifluoromethanesulfonate (258). A 25-mL pear flask equipped with a rubber septum and argon inlet needle was charged with quinoline **253** (0.110 g, 0.21 mmol, 1.0 equiv), $Pd(PPh_3)_2Cl_2$ (0.007 g, 0.01 mmol, 5 mol%), CuI (0.002 g, 0.01 mmol, 5 mol%), Et_3N (0.09 mL, 0.07 g, 0.62 mmol, 3.0 equiv), phenylacetylene (0.03 mL, 0.03 g, 0.27 mmol, 1.3 equiv) and 1.1 mL of THF, and the reaction mixture was stirred at rt for 1 h. The resulting brown solution was diluted with 20 mL of Et_2O, filtered through a ca. 2-g plug of Celite with the aid of five 5-mL portions of Et_2O, and concentrated to yield 0.134 g of a brown oil and solid. Column chromatography on 14 g of silica gel (elution with 2% EtOAc-hexanes) furnished 0.094 g (90%) of quinoline **258** as a yellow solid: mp 85-88 °C; IR (neat) 2959, 2930, 2859, 1405, 1217, 1138 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.90 (s, 1H), 7.59-7.63 (m, 2H), 7.38-7.44 (m, 3H), 3.37-3.31 (m, 2H), 3.04 (s, 3H), 2.73 (s, 3H), 2.48 (s, 3H), 1.62-1.71 (m, 2H), 1.41-1.48 (m, 2H), 1.29-1.36 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.8, 146.6, 146.5, 145.6, 133.7, 133.3, 131.8, 129.8, 129.0, 128.9, 128.7, 123.0, 119.9 118.9 (q, J = 318 Hz), 97.3, 86.7, 31.9, 30.5, 29.8, 26.7, 23.4, 22.8, 21.3, 15.4, 14.3; HRMS-DART-ESI (*m/z*) [M - H] calculated for $C_{27}H_{28}F_3NO_3S$, 502.1669; found, 502.1686.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TfO
N
Hex
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8
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6
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4
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2
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ppm
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3.00
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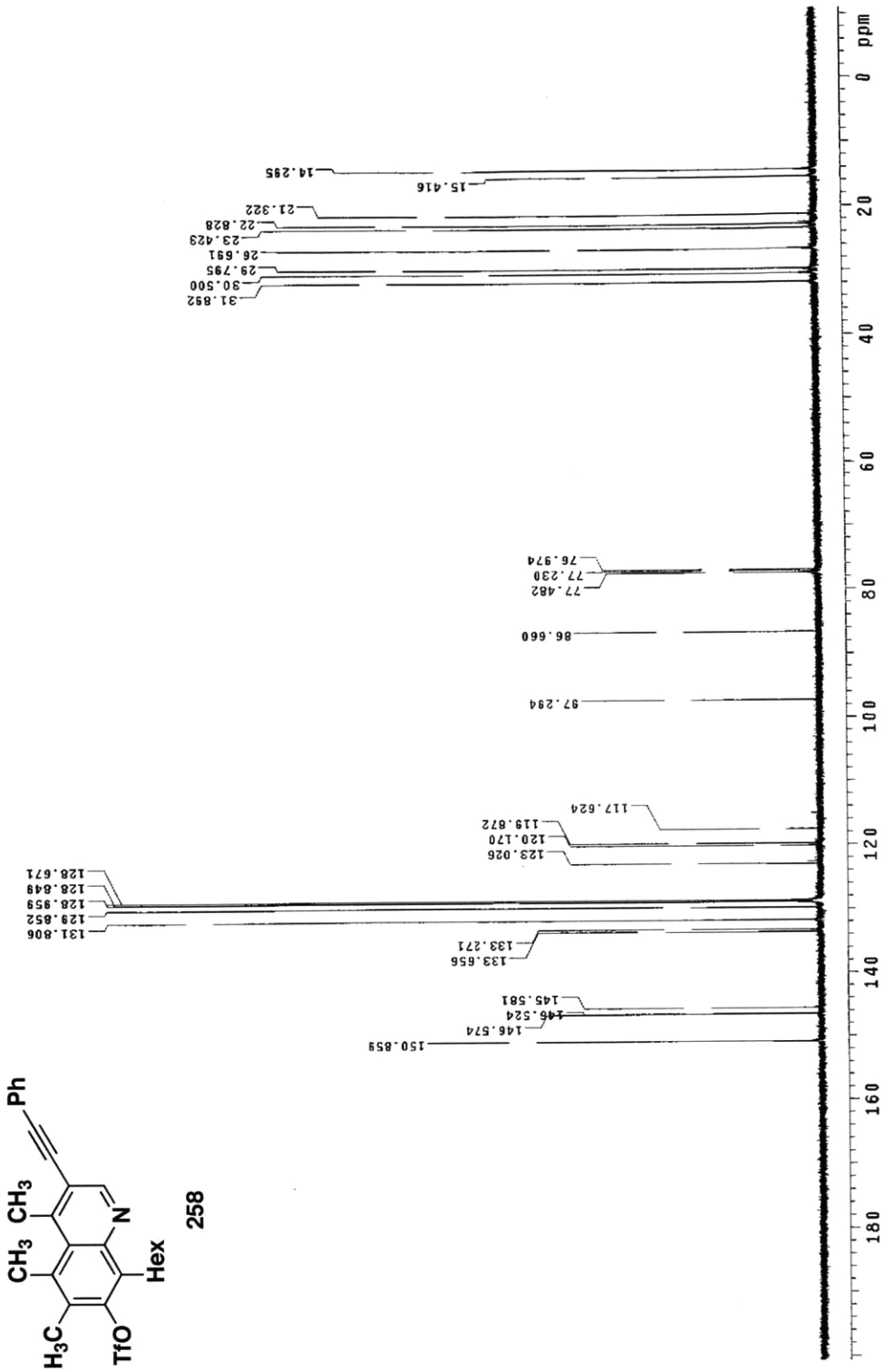
3.95
2.79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TfO
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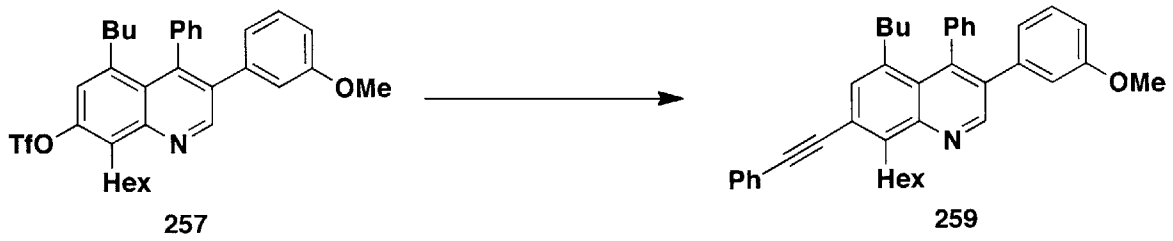
160
180



5-Butyl-8-hexyl-3-(3-methoxyphenyl)-4-phenyl-7-(phenylethynyl)quinoline (259). A 25-mL pear flask equipped with a rubber septum and argon inlet needle was charged with quinoline **257** (0.131 g, 0.22 mmol, 1.0 equiv), LiCl (0.03 g, 0.66 mmol, 3.0 equiv), $Pd(PPh_3)_2Cl_2$ (0.015 g, 0.02 mmol, 0.1 equiv), CuI (0.004 g, 0.02 mmol, 0.1 equiv), 1.4 mL of DMF, and 2.2 mL of Et_3N. The reaction mixture was stirred for 5 min, phenylacetylene (0.04 mL, 0.04 g, 0.36 mmol, 1.6 equiv) was added, and the solution was degassed for 10 min with a stream of argon. The septum was replaced with a cold-finger condenser fitted with an argon inlet adapter and the reaction mixture was stirred at 60 °C for 20 h. The resulting brown solution was allowed to cool to rt, diluted with 20 mL of H_2O and extracted with three 20-mL portions of EtOAc. The combined organic phases were washed with two 20-mL portions of H_2O, two 30-mL portions of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.142 g of a brown oil. Column chromatography on 20 g of silica gel (elution with 1% EtOAc-5% benzene-94% hexanes) yielded 0.093 g (78%) of quinoline **259** as a white solid: mp 78-80 °C; IR (neat) 2955, 2856, 2828, 1599, 1465, 1218, 1142 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.93 (s, 1H), 7.62 (dd, J = 1.5, 8.0 Hz, 2H), 7.47 (s, 1H) 7.35-7.44 (m, 4H), 7.23-7.31 (m, 3H), 7.10-7.17 (m, 3H), 6.75 (dd, J = 2.5, 8.5 Hz, 1H), 6.68 (d, J = 7.5 Hz), 6.51-6.53 (m, 1H), 3.62 (s, 3H), 3.57-3.64 (m, 2H), 2.18-2.11 (m, 2H), 1.87 (app quint, J = 7.5 Hz, 2H), 1.60 (app quint, J = 7.5 Hz, 2H), 1.32-1.47 (m, 4H), 1.15-1.23 (m, 2H), 0.90 (t, J = 7.5 Hz, 3H) 0.83 (app hex, J = 7.5 Hz, 2H), 0.68 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 150.0, 147.6, 145.3, 143.4, 140.1, 139.9, 138.9, 134.5, 132.1, 131.8, 130.3, 128.9, 128.6, 128.5, 127.8, 127.6, 125.7, 123.7, 122.8, 122.6, 115.6, 113.1, 94.5, 89.2, 55.3 35.6, 34.7, 32.2, 31.1, 30.7, 30.2, 23.0, 22.7, 14.4, 14.0; HRMS-ESI (*m/z*) [M + H] calculated for $C_{40}H_{41}NO$, 552.3261; found 552.3242.

Bu
Ph
OMe
N
Ph
Hex
259
7.65 ppm
6.72 6.62 ppm
2.0 1.7 1.4 1.1 ppm
ppm
9
8
7
6
5
4
3
2
1
ppm
0.91
0.92 8.28
1.88 2.83 3.03
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3.78
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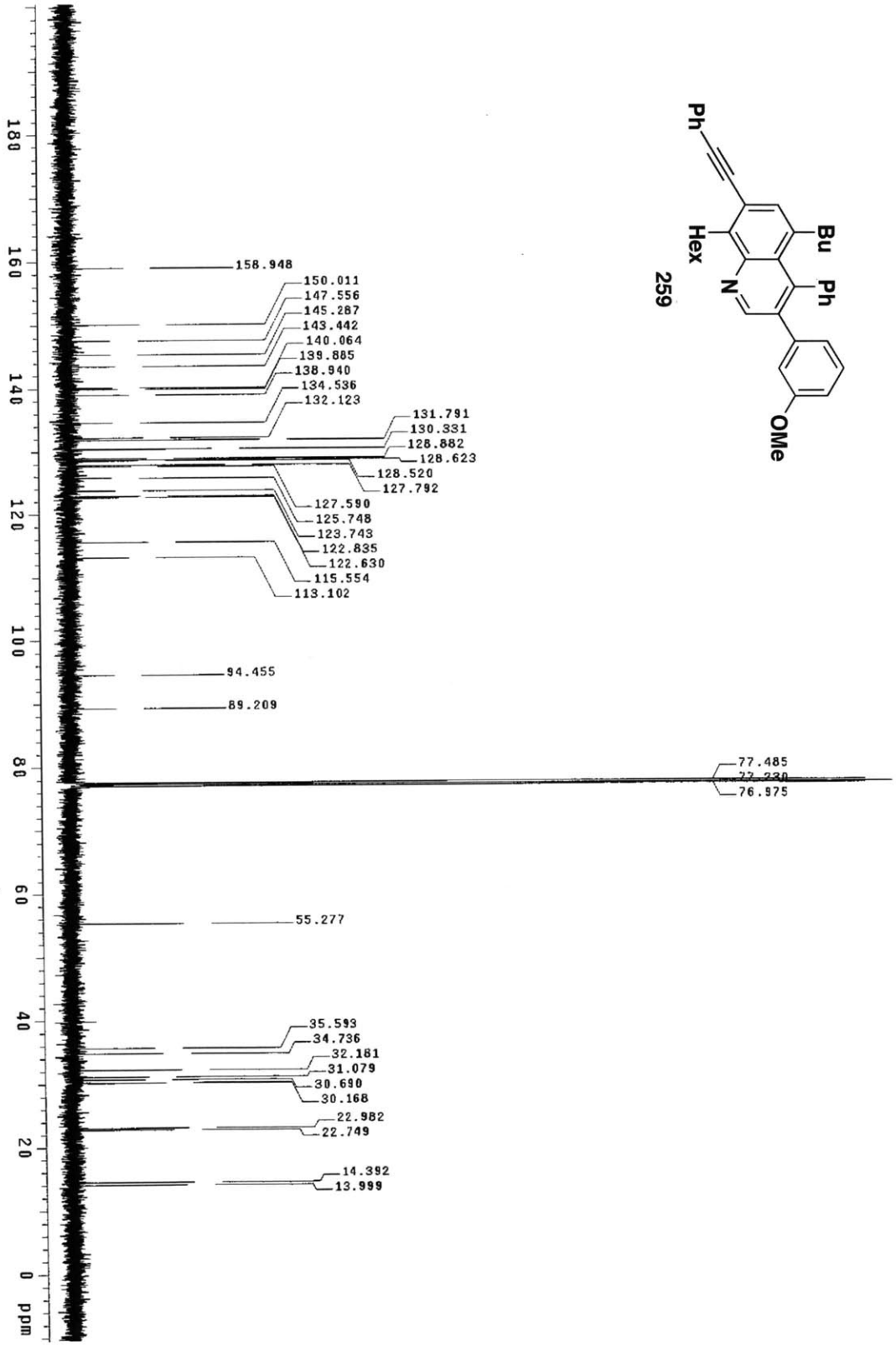
2.02
2.97 2.93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77.485
77.230
76.975
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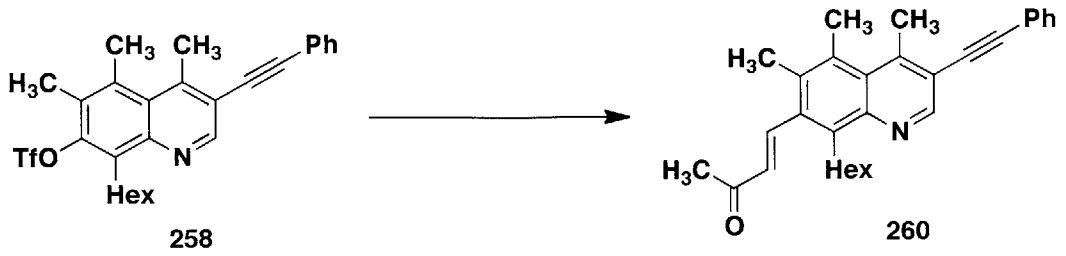
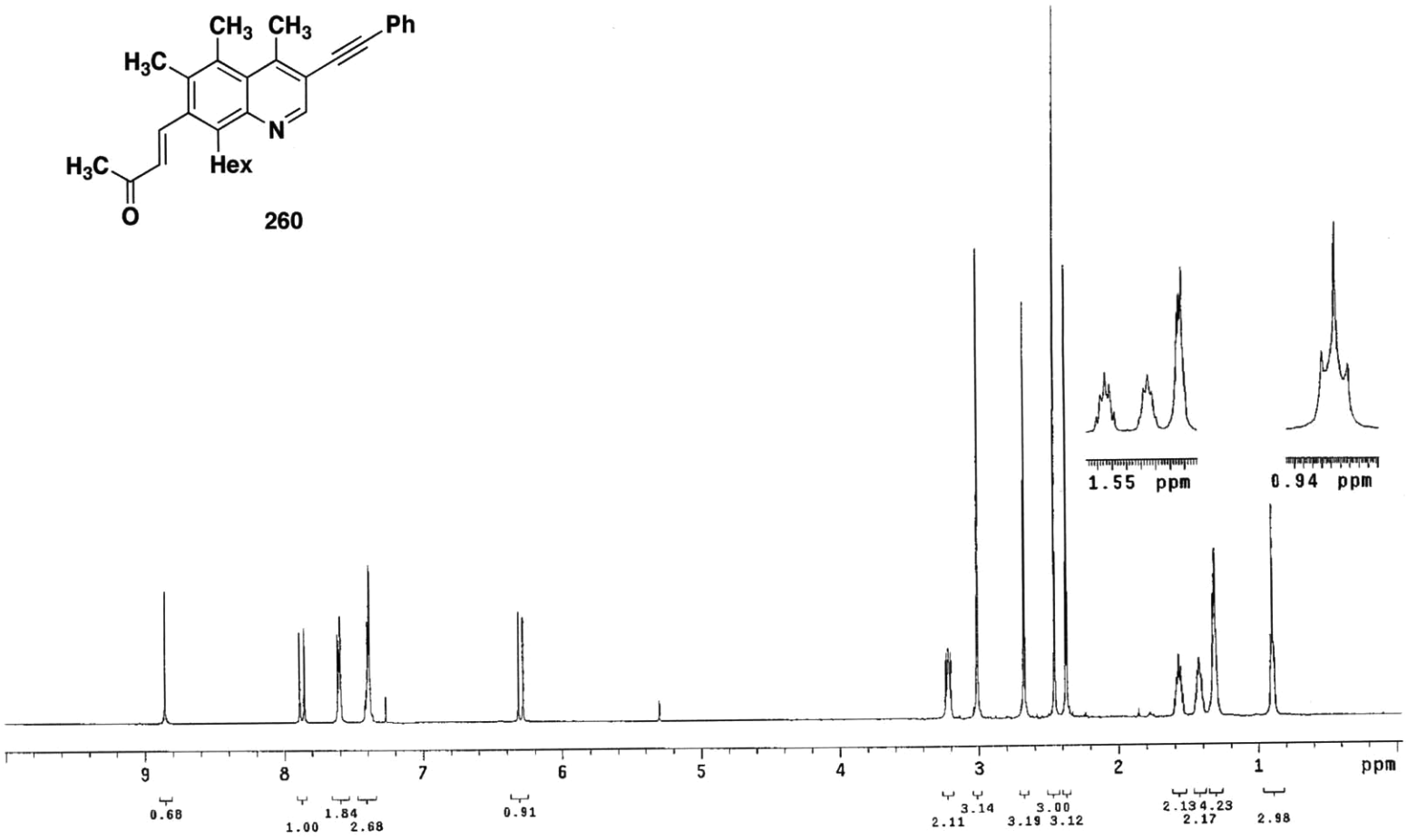


(E)-4-(8-Hexyl-4,5,6-trimethyl-3-(phenylethynyl)quinolin-7-yl)but-3-en-2-one (260). A 14-cm threaded Pyrex tube (1 cm I.D., 1.6 cm O.D.) equipped with a rubber septum and argon inlet needle was charged with quinoline **258** (0.070 g, 0.14 mmol, 1 equiv), MVK (0.06 mL, 0.05 g, 0.70 mmol, 5 equiv), Et_3N (0.06 mL, 0.04 g, 0.42 mmol, 3 equiv) and 1.4 mL of DMF. The golden reaction mixture was degassed for 10 min with a stream of argon and then 1 crystal of BHT and $(PPh_3)_4Pd$ (0.008 g, 0.07 mmol, 5 mol%) were added. The septum was replaced with a threaded Teflon cap and the tube was heated at 100 °C for 25 h. The resulting golden-orange reaction mixture was cooled to rt, diluted with 20 mL of EtOAc, washed with three 10-mL portions of H_2O and 30 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.068 g of a yellow oil. Column chromatography on 7 g of silica gel (elution with CH_2Cl_2) furnished 0.046 g (77%) of quinoline **260** as an off white solid: mp 133-135 °C; IR (neat) 3050, 2957, 2929, 2848, 1674, 1363 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.86 (s, 1H), 7.87 (d, J = 16.5 Hz, 1H), 7.57-7.63 (m, 2H), 7.36-7.42 (m, 3H), 6.30 (d, J = 16.5 Hz, 1H), 3.25-3.19 (m, 2H), 3.01 (s, 3H), 2.68 (s, 3H), 2.46 (s, 3H), 2.37 (s, 3H), 1.57-1.62 (m, 2H), 1.38-1.44 (m, 2H), 1.28-1.35 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.2, 150.0, 146.3, 144.9, 143.8, 138.0, 136.2, 134.1, 133.7, 131.8, 131.1, 128.8, 128.8, 128.7, 123.3, 119.0, 96.7, 87.2, 31.9, 31.2, 29.9, 29.2, 27.8, 23.4, 22.9, 21.3, 19.0, 14.3; HRMS-ESI (*m/z*) [M - H] calculated for $C_{30}H_{33}NO$, 424.2635; found, 424.2636.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ppm
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1.00
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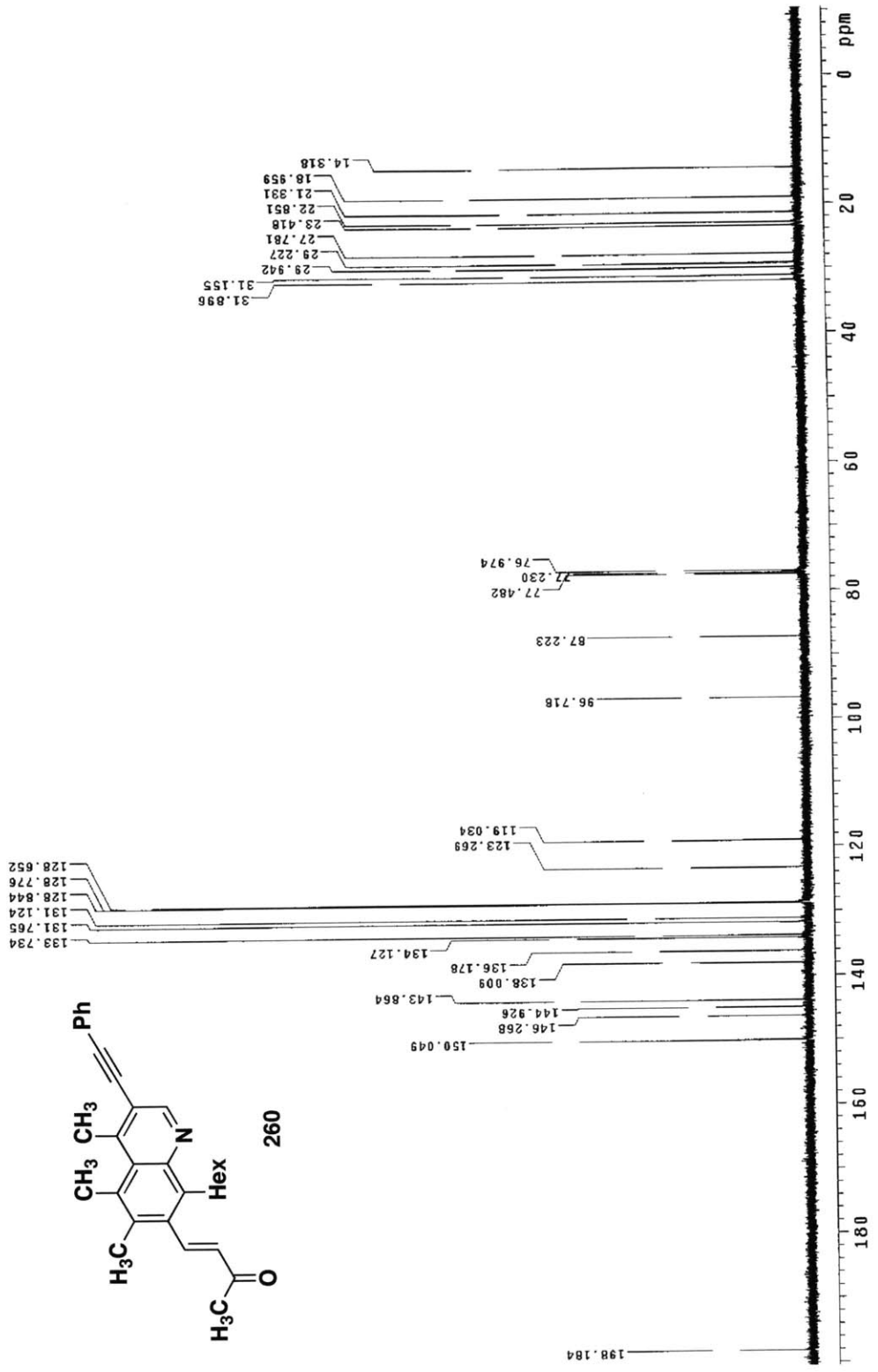
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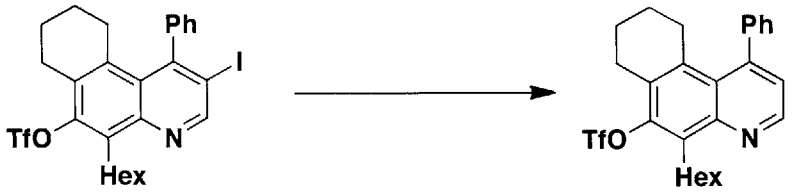
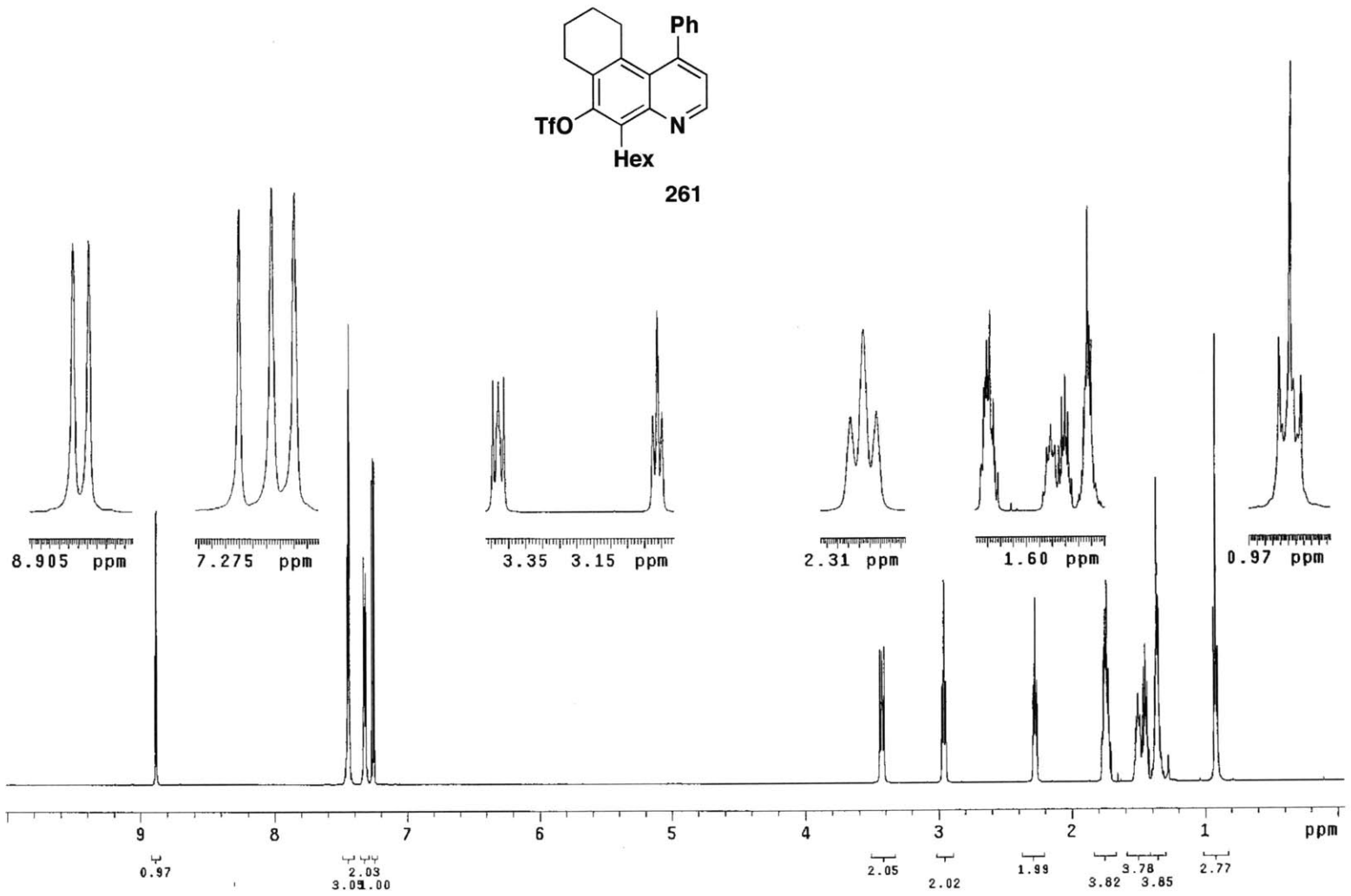


252 261

5-Hexyl-1-phenyl-7,8,9,10-tetrahydrobenzo[f]quinolin-6-yl trifluoromethanesulfonate (261). A 12-cm Pyrex tube (7 mm I.D., 12 mm O.D.) equipped with a rubber septum and argon inlet needle was charged with $Pd(OAc)_2$ (0.003 g, 0.013 mmol, 5 mol%), PPh_3 (0.007 g, 0.026 mmol, 10 mol%), quinoline **252** (0.158 g, 0.26 mmol, 1.0 equiv), Et_3N (65 μL, 47mg, 0.46 mmol, 1.8 equiv), and 1.0 mL of DMF. The resulting mixture was degassed for 10 min with a stream of argon, and then formic acid (13 μL, 16mg, 0.31 mmol, 1.2 equiv) was added and the reaction mixture was heated at 60-65 °C for 42 h. The tube was then cooled to room temperature, $Pd(OAc)_2$ (0.003 g, 0.013 mmol, 5 mol%), Ph_3P (0.007 g, 0.026 mmol, 10 mol%), and formic acid (4 μL, 5mg, 0.14 mmol, 0.5 equiv) were added and the resulting mixture was heated at 60-65 °C for 23 h. The reaction mixture was then cooled to room temperature, diluted with 10 mL of brine, and washed with two 10-mL portions of Et_2O. The combined organic phases were washed with two 10-mL portions of H_2O, 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.143 g of a brown oil. Column chromatography on 29 g of silica gel (elution with 30% benzene-hexanes) yielded 0.093 g (74%) of quinoline **261** as a pale yellow oil: IR (neat) 2932, 2860 1405, 1215, 1139, 909, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.88 (d, J = 4.0 Hz, 1H), 7.41-7.49 (m, 3H), 7.29-7.35 (m, 2H), 7.25 (d, J = 4.0 Hz, 1H), 3.40-3.46 (m, 2H), 2.96 (t, J = 6.8 Hz, 2H), 2.28 (t, J = 6.3 Hz, 2H), 1.70-1.78 (m, 4H), 1.42-1.55 (m, 4H), 1.32-1.41 (m, 4H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.6, 148.0, 147.3, 147.0, 143.2, 135.4, 133.1, 130.2, 128.7, 128.4, 128.0,126.6, 125.0, 119.0 (q, J = 318 Hz), 32.0, 31.9, 30.6, 29.9, 26.8, 25.4, 22.9, 22.8, 21.8, 14.3; HRMS-ESI (*m/z*) [M + H] calculated for $C_{26}H_{28}F_3NO_3S$, 492.1815; found, 492.1811.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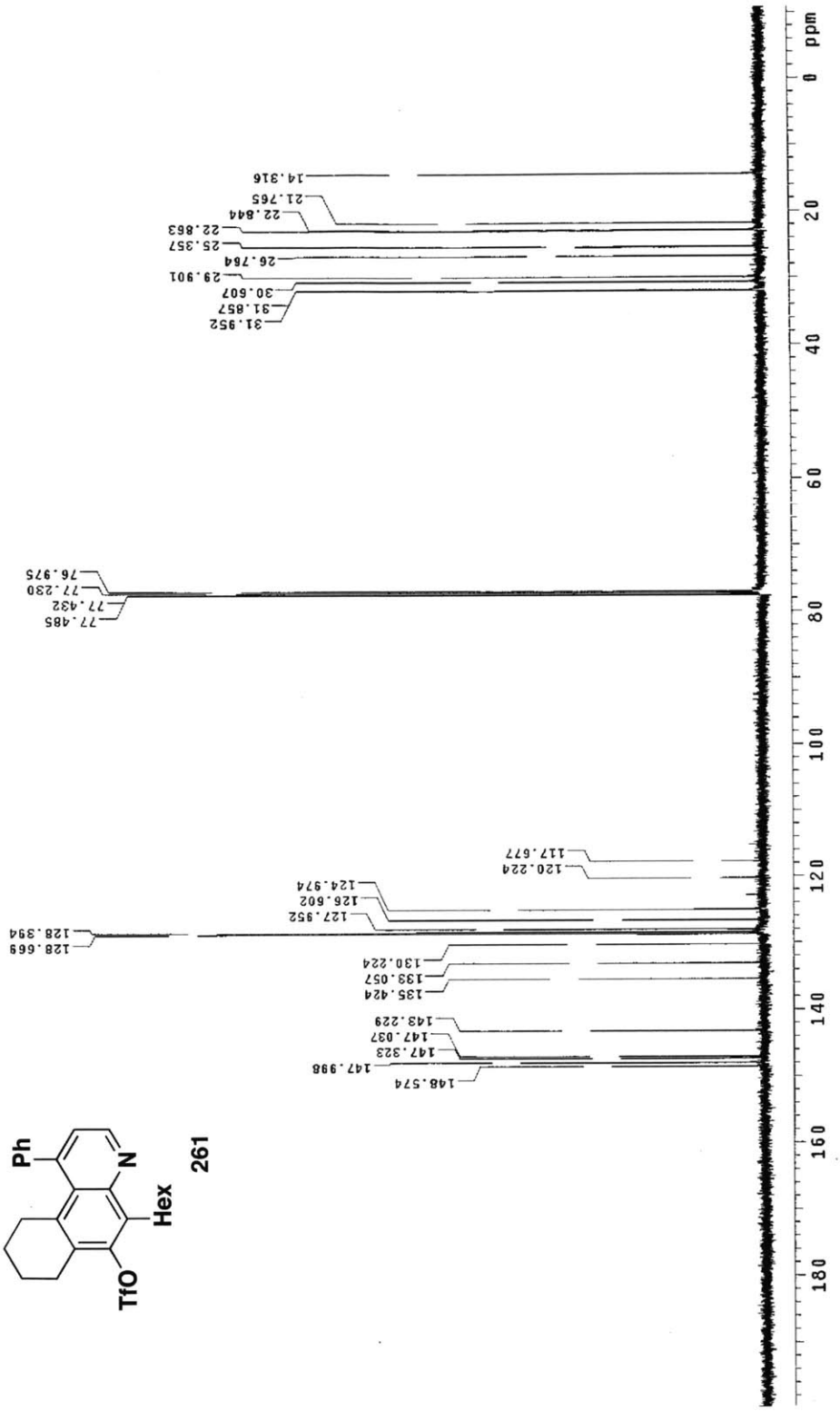
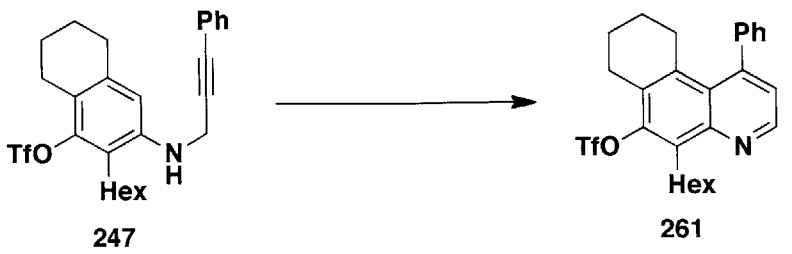
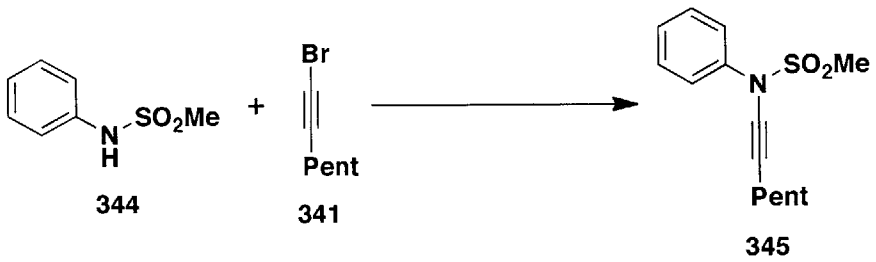
8
7
6
5
4
3
2
1
ppm
0.97
2.03
3.05
1.00
2.05
2.02
1.99
3.82
3.78
3.85
2.77


Ph
N
Hex
TfO
261
14.316
21.765
22.844
22.863
25.357
26.764
29.901
30.607
31.857
31.952
76.975
77.280
77.432
77.485
117.677
120.224
124.974
126.602
127.952
128.394
128.669
130.224
133.057
135.424
143.229
147.037
147.323
147.998
148.574
0
20
40
60
80
100
120
140
160
180
ppm

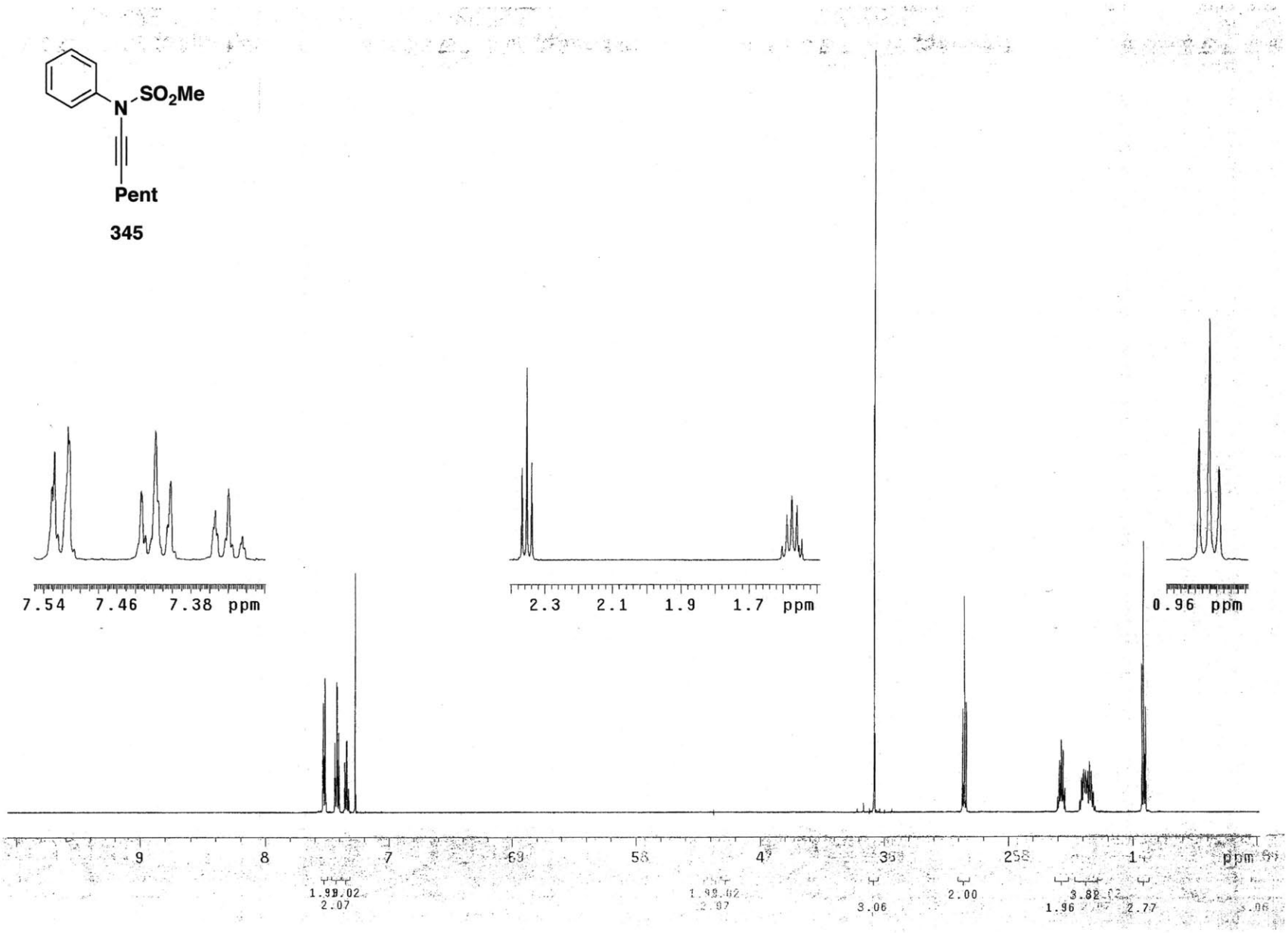


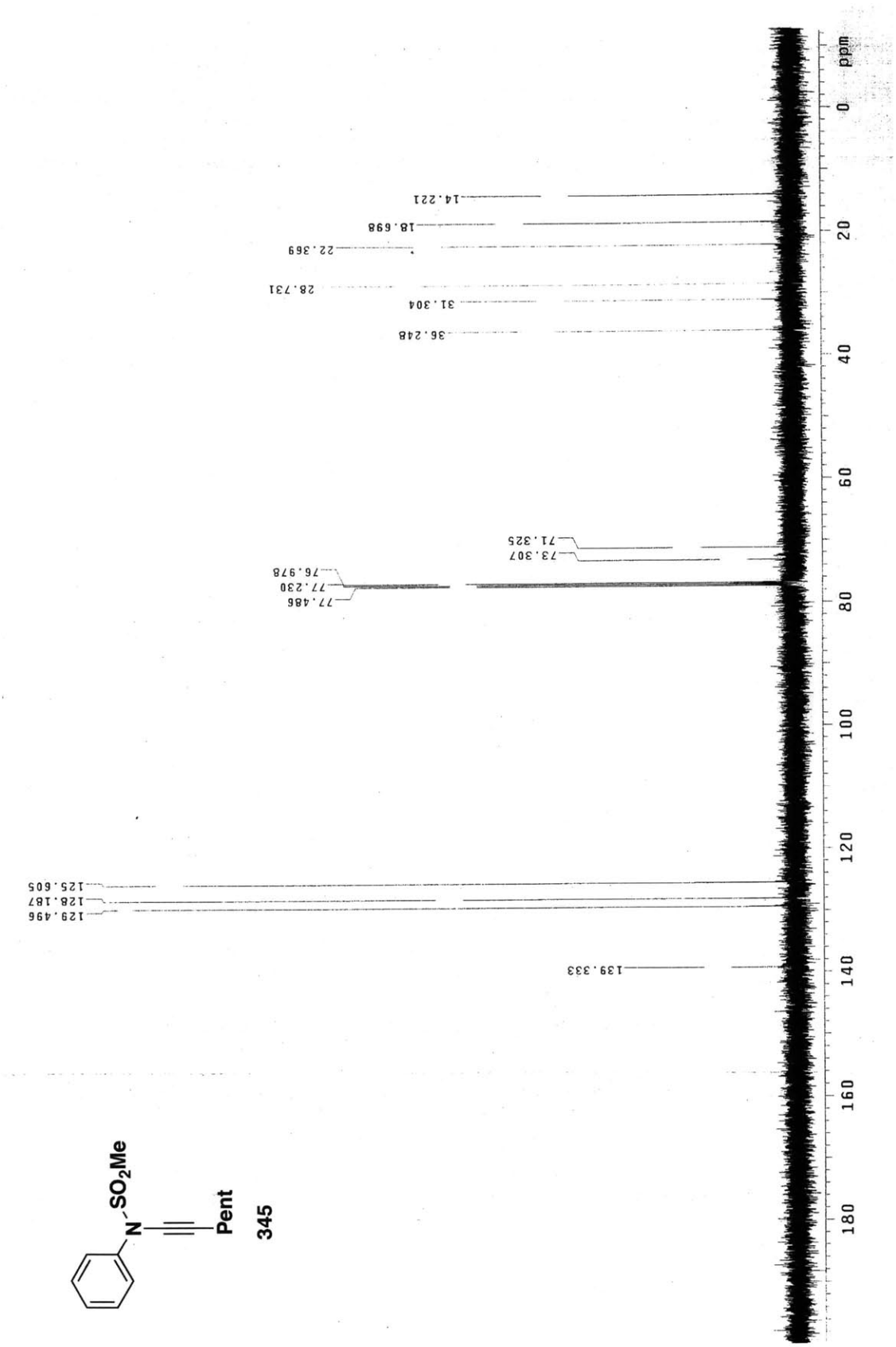
5-Hexyl-1-phenyl-7,8,9,10-tetrahydrobenzo[f]quinolin-6-yl trifluoromethanesulfonate (261). A 25-mL pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with triflate **247** (0.126 g, 0.26 mmol, 1.0 equiv), $Hg(OTf)_2$ (0.025 g, 0.05 mmol, 0.2 equiv), and 2.6 mL of CH_3CN. The reaction mixture was stirred under air at rt for 4 h, and then diluted with 20 mL of Et_2O and washed with two 10-mL portions of satd aq NaI solution. The combined aqueous washes were extracted with three 10-mL portions of Et_2O, and the combined organic layers were washed with 40 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.148 g of a yellow oil. Column chromatography on 30 g of silica gel (elution with 30% benzene-hexanes) furnished 0.098 g (78%) of quinoline **261** as a pale yellow oil.



***N*-(Methanesulfonyl)-*N*-(phenyl)-2-penylethynylamine (345).** A 25-mL round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with sulfonamide **344**[211] (0.750 g, 4.38 mmol, 1.0 equiv), K_2CO_3 (1.21 g, 8.76 mmol, 2.0 equ), $CuSO_4 \cdot 5H_2O$ (0.164 g, 0.657 mmol, 0.15 equiv), and 1,10-phenanthroline (0.236 g, 1.31 mmol, 0.30 equiv). The flask was then evacuated and backfilled with argon three times. A solution of 1-bromoheptyne **341**[160] (0.999 g, 5.71 mmol, 1.3 equiv) in 4.4 mL of DMF was added via cannula over 2 min (2 mL DMF rinse). The flask was then charged with 4 Å molecular sieves (0.375 g) and the septum was replaced with a cold-finger condenser fitted with an argon inlet adapter. The resulting heterogeneous reaction mixture was stirred at 65 °C for 48 h then cooled to rt, diluted with 60 mL of Et_2O, and washed with three 30-mL portions of a 2:1 mixture of brine and concd NH_4OH solution. The combined aqueous layers were extracted with two 30-mL portions of Et_2O, and the combined organic phases were washed with 60 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 1.31 g of orange oil. This material was dissolved in 25 mL of CH_2Cl_2 and concentrated onto 8 g of silica gel. The free-flowing powder was deposited on a column of 160 g of silica gel and eluted with 8% EtOAc-hexanes to afford 0.961 g (80%) of ynamide **345** as a faint yellow solid: mp 45-47 °C IR (neat) 3016, 2931, 2859, 2255, 1594, 1491, 1368, 1323, 1268, 1172 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52-7.56 (m, 2 H), 7.39-7.44 (m, 2 H), 7.32-7.36 (m, 1 H) 3.08 (s, 3 H), 2.35 (t, J = 7.3 Hz, 2 H), 1.57 (quint, J = 7.5 Hz, 2 H), 1.10-1.43 (m, 4 H), 0.91 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.8, 130.0, 128.7, 126.1, 73.8, 71.8, 36.7, 31.8, 29.2, 22.9, 19.2, 14.7; HRMS-ESI (*m/z*) [M + H] calculated for $C_{14}H_{19}NO_2S$: 266.1209, found: 266.1216.

[211] Prepared as described in Lis, R.; Marisca, A. J. *J. Org. Chem.* **1987**, *52*, 4377-4379.


SO2Me
N
Pent
345
7.54
7.46
7.38 ppm
2.3
2.1
1.9
1.7 ppm
0.96 ppm
ppm
2.07
3.06
2.00
1.96
2.77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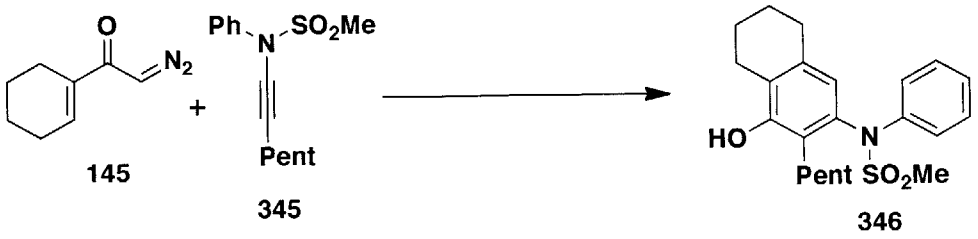
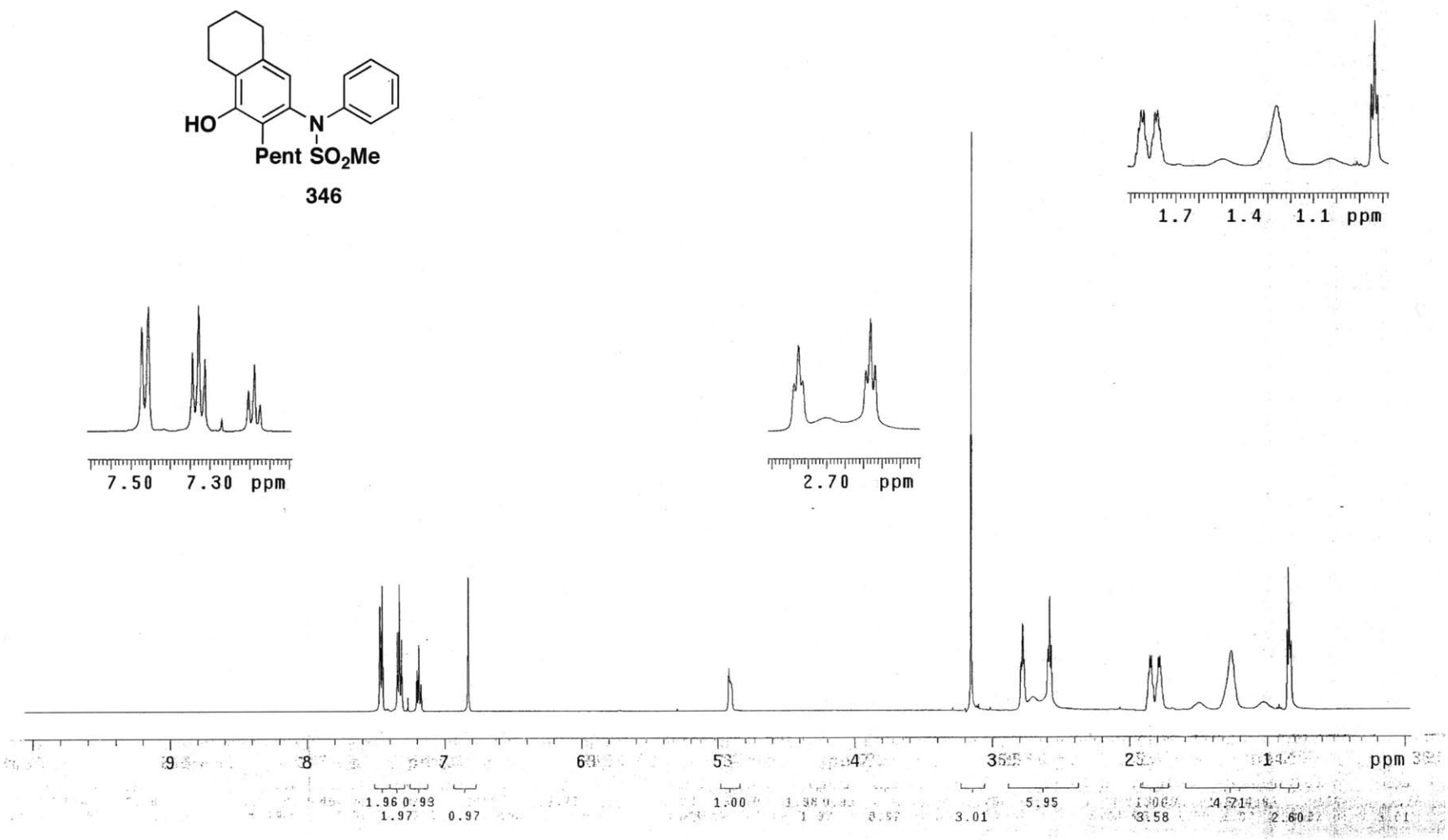
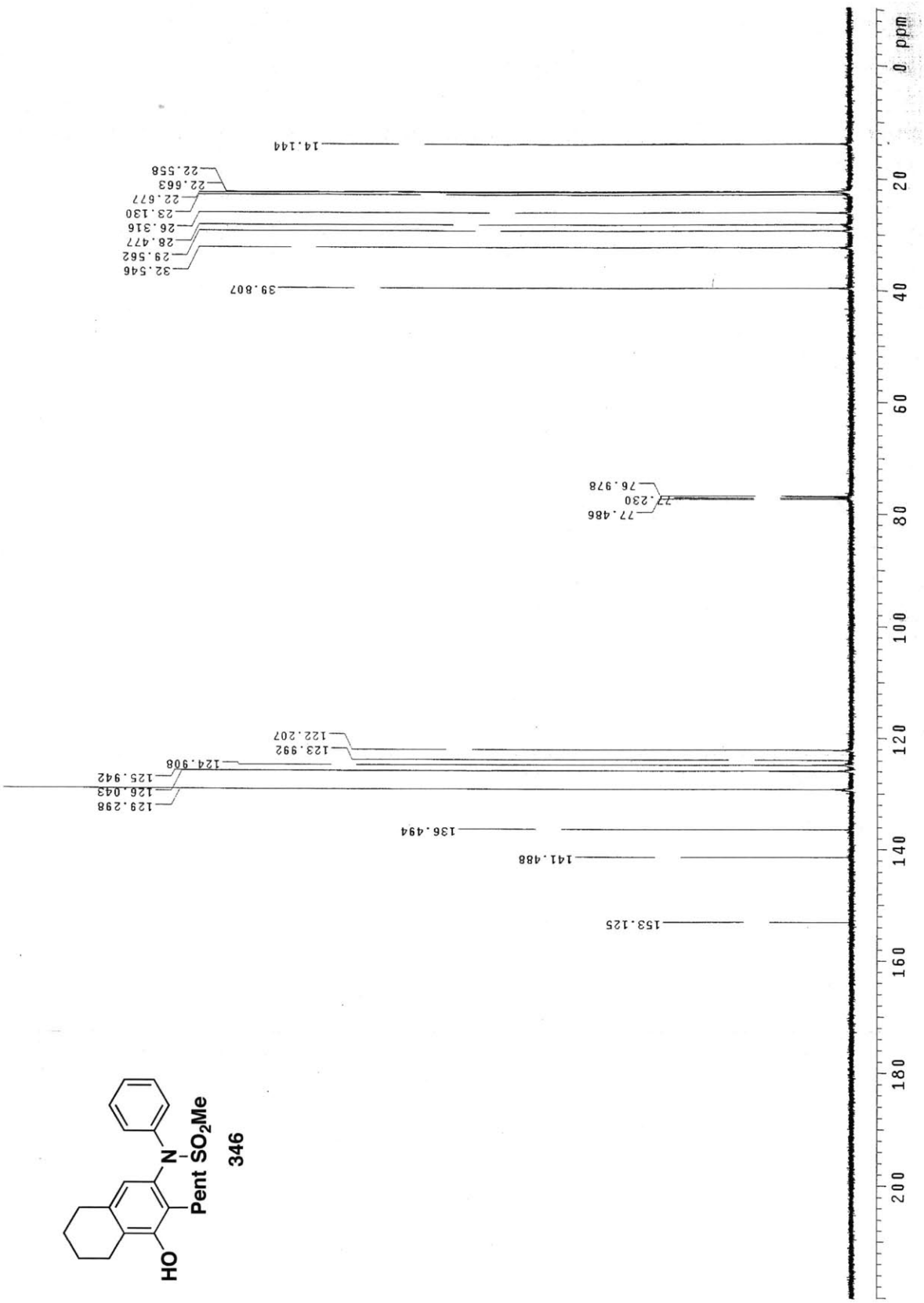
18.698
22.369
28.731
31.304
36.248
71.325
73.307
76.978
77.230
77.486
125.605
128.187
129.496
139.333
ppm
0
20
40
60
80
100
120
140
160
180
SO2Me
N
Pent
345



145 345 346

3-[*N*-(Methanesulfonyl)-*N*-(phenyl)amino]-2-pentyl-5, 6, 7, 8-tetrahydro-naphthalen-1-ol (346). A 20-cm quartz tube (12 mm I.D., 14 mm O.D.) equipped with a rubber septum and argon inlet needle was charged with diazo ketone **145**[72a] (0.075 g, 0.499 mmol, 1.0 equiv), ynamide **345** (0.530 g, 2.00 mmol, 4.0 equiv), and 13.4 mL of toluene, and the yellow solution was degassed by three freeze-pump-thaw cycles at -196 °C, 0.05 mmHg. The quartz tube was positioned ca. 20 cm from a Hanovia 450W lamp (quartz immersion well, uranium filter, cooled by recirculating tap water) and irradiated under argon at 25 °C for 22 h. The tube was then immersed in an oil bath and heated at 90 °C for 8 h. The resulting solution was concentrated to afford 0.612 g of yellow oil. Column chromatography on 60 g of silica gel (elution with 10% EtOAc-hexanes) provided 0.384 g (72%, 2.9 equiv) of ynamide **345** as a yellow oil and 0.122 g (63%) of sulfonamide **346** as a white solid: mp 128-130 °C; IR (neat) 3504 (broad), 2933, 2862, 1492, 1421, 1349, 1266, 1159 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J = 8.5 Hz, 2 H), 7.33 (t, J = 8.0 Hz, 2 H), 7.19 (t, J = 7.7 Hz, 1 H), 6.83 (s, 1 H), 4.91 (s, 1 H), 3.15 (s, 3 H), 2.52-2.82 (m, 6 H), 1.74-1.89 (m, 4 H), 1.41-1.57 (m, 1 H), 1.18-1.36 (m, 4 H), 0.94-1.11 (m, 1 H), 0.83 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1, 141.5, 136.5, 129.3, 126.0, 125.9, 124.9, 124.0, 122.2, 39.8, 32.5, 29.6, 28.5, 26.3, 23.1, 22.7, 22.7, 22.6, 14.1 (one carbon overlapped in the region 142-129); HRMS-ESI (*m/z*) [M + H] calculated for $C_{22}H_{29}NO_3S$, 388.1941; found 388.1932.


HO
N
Pent
SO2Me
346
1.7 1.4 1.1 ppm
7.50 7.30 ppm
2.70 ppm
9
8
7
6
5
4
3
2
1
ppm
1.96
0.93
0.97
1.00
3.01
5.95
3.58
2.60


14.144
22.558
22.663
22.677
23.130
26.316
28.477
29.562
32.546
39.807
76.978
77.230
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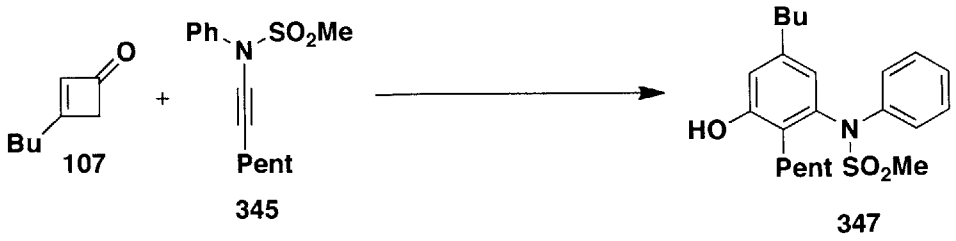
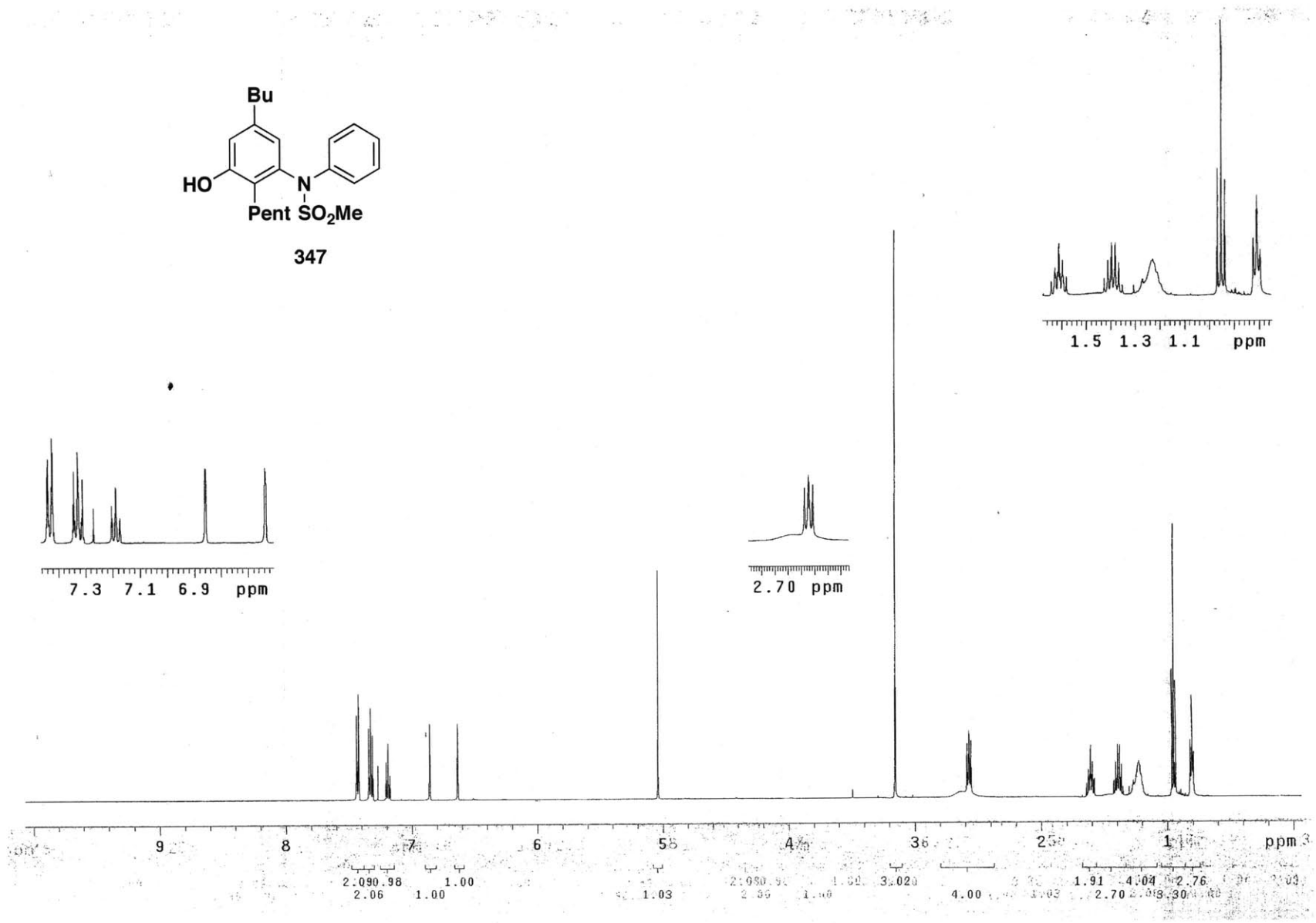
122.207
123.992
124.908
125.942
126.043
129.298
136.494
141.488
153.125
0 ppm
20
40
60
80
100
120
140
160
180
200
HO
N
Pent
SO2Me
346



***N*-(Methanesulfonyl)-*N*-(phenyl)-[5-butyl-3-hydroxy-2-pentylphenyl]amine (347).** A 50-mL round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with ynamide **345** (1.00 g, 3.77 mmol, 1.0 equiv), 3-butylcyclobut-2-enone (**107**)[117] (0.570 g, 4.52 mmol, 1.2 equiv), and 9.5 mL of toluene. The septum was replaced with a cold-finger condenser fitted with argon inlet adapter and the reaction mixture was heated at 80 °C for 2 h and then at reflux for 2 h. Concentration of the reaction mixture afforded 1.810 g of orange oil. Column chromatography on 180 g of silica gel (gradient elution with 10-20% EtOAc-hexanes) provided 1.315 g (90%) of sulfonamide **347** as an off-white solid: mp 73-75 °C; IR (neat) 3447 (broad), 2957, 2931, 2860, 1581, 1493, 1428, 1344, 1155, 1117 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.42 (d, J = 8.0 Hz, 2 H), 7.33 (t, J = 8.0 Hz, 2 H), 7.19 (t, J = 7.5 Hz, 1 H), 6.87 (s, 1 H), 6.66 (s, 1 H), 4.73 (s, 1 H), 3.15 (s, 3 H), 2.48-2.74 (m, 2 H), 2.54-2.62 (m, 2 H), 1.57-1.66 (m, 2 H), 1.34-1.55 (m, 1 H), 1.34-1.42 (m, 2 H), 1.18-1.32 (m, 4 H), 0.91-1.10 (m, 1 H), 0.95 (t, J = 7.5 Hz, 3 H), 0.82 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 142.2, 141.4, 139.2, 129.4, 127.3, 126.0, 124.8, 122.1, 116.3, 40.0, 35.3, 33.5, 32.6, 28.5, 26.2, 22.6, 22.6, 14.2, 14.2. HRMS-ESI (*m/z*) [M + H] calculated for $C_{22}H_{31}NO_3S$: 390.2097, found: 390.2107.

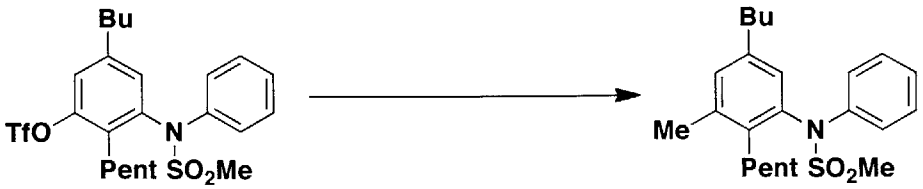

Bu
HO
N
Pent SO2Me
347
1.5 1.3 1.1 ppm
7.3 7.1 6.9 ppm
2.70 ppm
ppm
2.06
1.00
1.03
4.00
1.91
2.70

Bu
HO
N
Pent SO2Me
347
129.375
127.320
126.034
124.839
122.120
116.288
155.437
142.157
141.420
139.195
77.486
77.230
76.978
39.953
35.270
33.466
32.597
28.477
26.215
22.603
22.585
14.185
14.153
200
180
160
140
120
100
80
60
40
20
0
ppm

5-Butyl-2-pentyl-3-(*N*-phenylmethylsulfonamido)phenyl trifluoromethanesulfonate (352). A 25-mL pear flask equipped with a rubber septum and argon inlet needle was charged with phenol **347** (0.426 g, 1.09 mmol, 1.0 equiv), 4-DMAP (0.268 g, 2.19 mmol, 2.0 equiv), and 5.5 mL of CH_2Cl_2. The yellow solution was cooled to 0 °C and triflic anhydride (0.22 mL, 1.3 mmol, 1.2 equiv) was added dropwise by syringe over ca. 4 min. The reaction mixture was allowed to warm to rt, stirred for 2 h, and then diluted with 15 mL of CH_2Cl_2 and washed with two 20-mL portions of 1 M HCl. The combined aqueous layers were extracted with two 20-mL portions of CH_2Cl_2, and the combined organic layers were washed with 45 mL of satd aq $NaHCO_3$ solution and 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.569 g of orange oil. Column chromatography on 35 g of silica gel (elution with 50% CH_2Cl_2-hexanes) afforded 0.529 g (93%) of triflate **352** as an off-white solid: mp 48-50 °C; IR (neat) 2960, 2874, 1421, 1354, 1216, 1161, 1141 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.40 (m, 4 H), 7.32 (s, 1 H), 7.21-7.26 (m, 1 H), 7.17 (s, 1 H), 3.15 (s, 3 H), 2.64-2.72 (m, 4 H), 1.65 (quint, J = 7.5 Hz, 2 H), 1.35-1.54 (m, 1 H), 1.41 (sext, J = 7.5 Hz, 2 H) 1.19-1.33 (m, 4 H), 1.03-1.25 (m, 1 H), 0.97 (t, J = 7.0 Hz, 3 H), 0.83 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3, 143.2, 140.9, 140.4, 134.0, 130.3, 129.7, 126.6, 124.8, 121.9, 118.7 (q, J = 318 Hz), 40.2, 35.2, 33.3, 32.4, 28.8, 26.9, 22.5, 22.4, 14.1, 14.1; HRMS-ESI (*m/z*) [M + H] calculated for $C_{23}H_{30}F_3NO_5S_2$, 522.1590; found 522.1597.

Bu
TfO
N
Pent
SO2Me
352
7.34 7.24 ppm
4.03
1.04
0.98
0.95
1.7 1.5 1.3 1.1 ppm
2.84 ppm
ppm
4.00
1.00
3.11
3.99
1.98
7.39
2.66
3.11

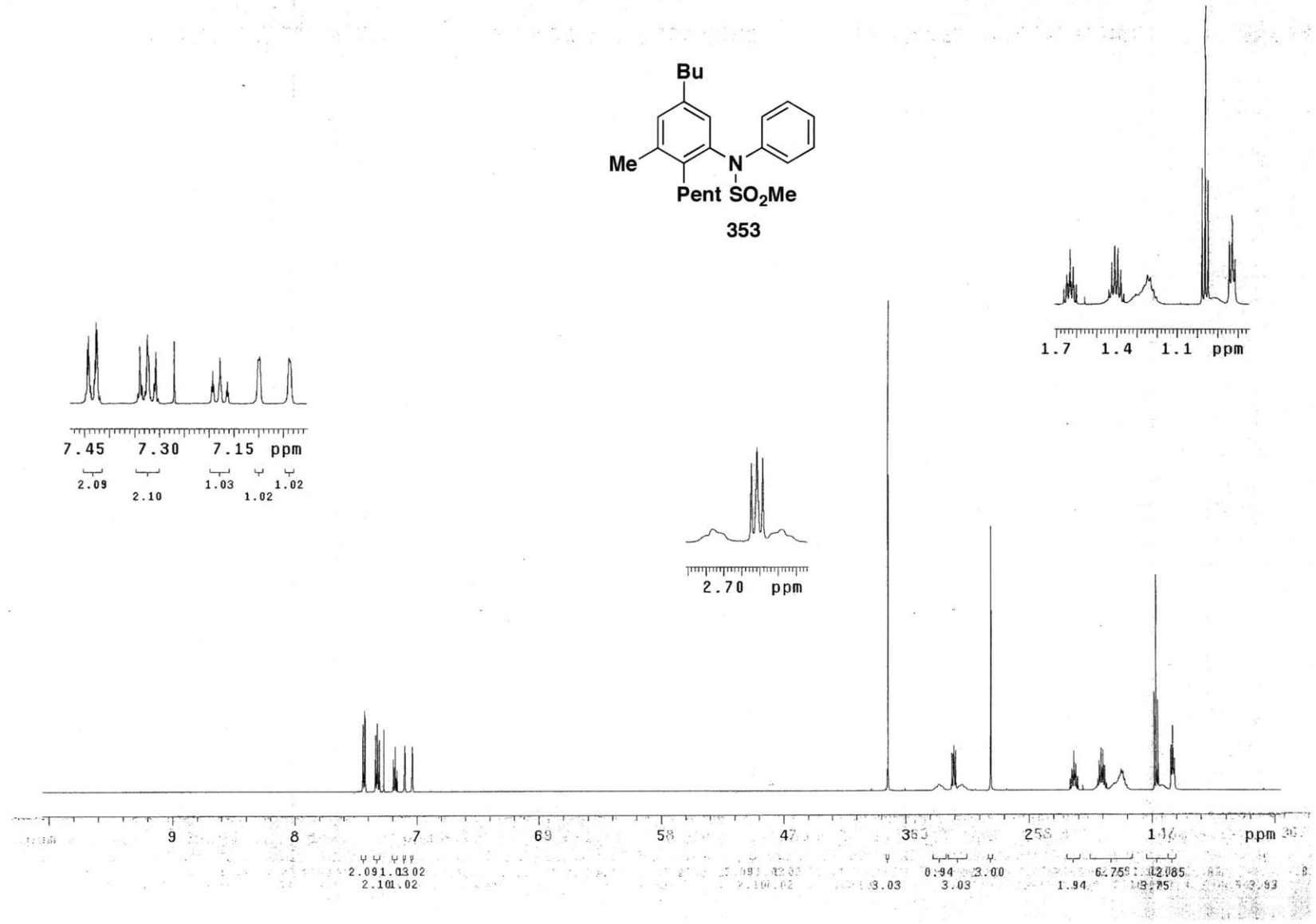
Bu
TfO
N
Pent
SO2Me
352
149.289
143.228
140.870
140.353
134.013
130.273
129.723
126.583
124.770
121.891
119.959
117.418
77.486
77.230
76.978
40.205
35.160
33.260
32.441
28.825
26.861
22.484
22.384
14.112
14.066
200
180
160
140
120
100
80
60
40
20
0 ppm

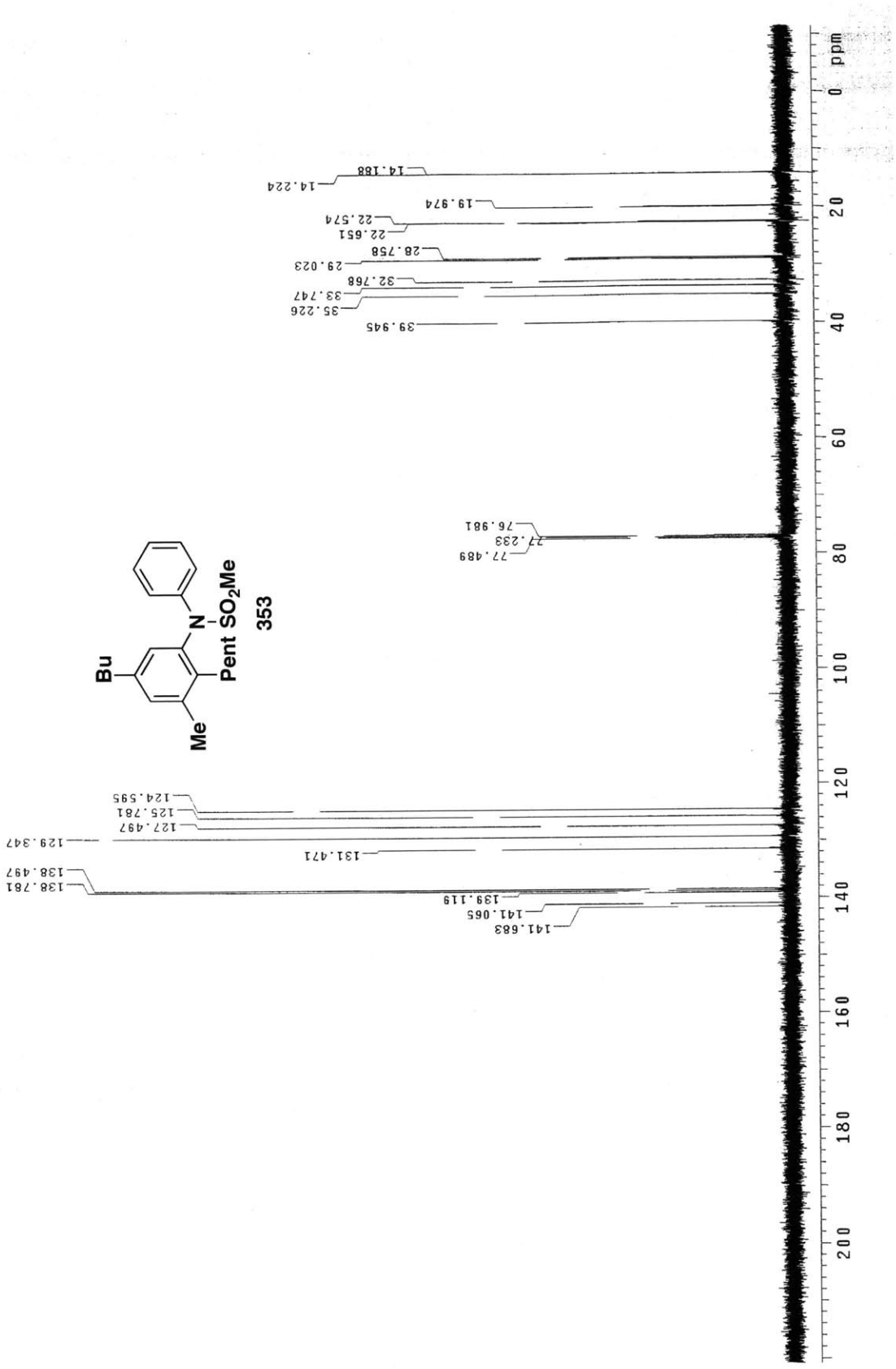


352 353

***N*-(Methanesulfonyl)-*N*-(phenyl)-[5-butyl-3-methyl-2-pentylphenyl]amine (353).** A 10-cm threaded Pyrex tube (14 mm I.D., 25 mm O.D.) equipped with a rubber septum and argon inlet needle was charged with triflate **352** (0.162 g, 0.31 mmol, 1 equiv), $Pd(OAc)_2$ (0.004 g, 0.02 mmol, 6 mol%), and SPhos (0.018 g, 0.04 mmol, 12 mol%). The tube was evacuated and backfilled with argon three times, and 1.8 mL of THF[212] and trimethylboroxine (0.05 mL, 0.045 g, 0.36 mmol, 1.2 equiv) were added. The tube was then charged with 1.7 mL of K_3PO_4 solution[3] (0.5 M in water, 0.85 mmol, 3.0 equiv), the septum was replaced with a threaded Teflon cap, and the tube was heated at 30 °C for 23 h. The resulting red reaction mixture was cooled to rt, diluted with 10 mL of Et_2O, and washed with 20 mL of H_2O. The aqueous layer was extracted with two 8-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 0.153 g of orange oil. Column chromatography on 18 g of silica gel (gradient elution with 3-5% EtOAc-hexanes) furnished 0.117 g (98%) of sulfonamide **353** as an off-white solid: mp 36-38 °C; IR (neat) 2930, 2859, 1596, 1494, 1351, 1160 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41-7.46 (m, 2 H), 7.30-7.35 (m, 2 H), 7.15-7.20 (m, 1 H), 7.10 (s, 1 H), 7.04 (s, 1 H), 3.14 (s, 3 H), 2.68-2.75 (m, 1 H), 2.57-2.64 (m, 2 H), 2.49-2.58 (m, 1 H), 2.31 (s, 3 H), 1.60-1.68 (m, 2 H), 1.35-1.48 (m, 1 H), 1.35-1.46 (m, 2 H), 1.19-1.35 (m, 4 H), 0.97 (t, J = 7.3 Hz, 3 H), 0.85-1.00 (m, 1 H), 0.83 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.7, 141.1, 139.1, 138.8, 138.5, 131.5, 129.3, 127.5, 125.8, 124.6, 39.9, 35.2, 33.7, 32.8, 29.0, 28.8, 22.7, 22.6, 20.0, 14.2, 14.2; HRMS-ESI (*m/z*) [M + Na] calculated for $C_{23}H_{33}NO_2S$, 410.2124; found, 410.2134.

[212] The THF and K_3PO_4 solution were degassed (three freeze-pump-thaw cycles at -196 °C, 0.05 mmHg) prior to addition.


Bu
Me
N
Pent SO2Me
353
7.45 7.30 7.15 ppm
2.09 2.10 1.03 1.02
1.02
1.7 1.4 1.1 ppm
2.70 ppm
ppm
2.09 1.03 0.94 3.00 6.75 12.85
2.10 1.02 3.03 3.03 1.94 3.75


353
Bu
Pent
SO2Me
Me
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14.224
19.974
22.574
22.651
28.758
29.023
32.768
33.747
35.226
39.945
76.981
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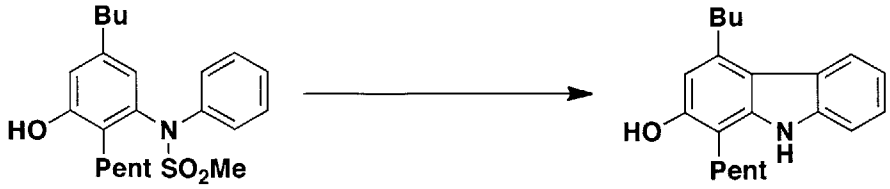
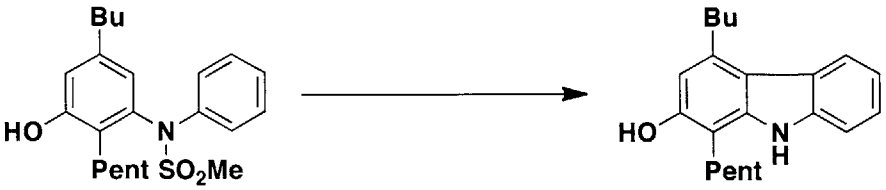
138.497
138.761
139.119
141.065
141.683
ppm



347 358

4-Butyl-1-pentyl-9*H*-carbazol-2-ol (358). A 20-cm quartz tube (12 mm I.D., 14 mm O.D.) equipped with a rubber septum and argon inlet needle was charged with sulfonamide **347** (0.078 g, 0.200 mmol, 1.0 equiv), triethylamine (0.06 mL, 0.400 mmol, 2.0 equiv), and 13.4 mL of ethanol. The reaction mixture was degassed with a stream of argon for 15 min and then positioned ca. 20 cm from a Hanovia 450W lamp (quartz immersion well, cooled by recirculating tap water) and irradiated under argon at 25 °C for 13 h. The solution was then diluted with 20 mL of Et_2O and washed two 15-mL portions of 1 M HCl. The combined aqueous layers were extracted with three 10-mL portions of Et_2O, and the combined organic layers were washed with 40 mL of satd aq $NaHCO_3$, 40 mL of brine, dried over Na_2SO_4, filtered, and concentrated to afford 0.070 g of a orange oil. This material was dissolved in 1 ml of CH_2Cl_2 and concentrated onto 0.8 g of silica gel. The free-flowing powder was deposited on a column of 8 g of silica gel and eluted with 5% EtOAc-hexanes to afford 0.031 g (48%) of carbazole **358** as a tan solid: mp 148-150 °C; IR (neat) 3420, 3329 (broad), 2954, 2928, 2856, 1600, 1402 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 8.0 Hz, 1 H), 7.92 (s, 1 H), 7.44 (d, J = 8.0 Hz, 1 H), 7.35 (t, J = 7.5 Hz, 1 H), 7.22 (t, J = 8.0 Hz, 1 H), 6.54 (s, 1 H), 4.68 (s, 1 H), 3.12 (t, J = 8.0 Hz, 2 H), 2.85 (t, J = 7.8 Hz, 2 H), 1.81 (quint, J = 7.8 Hz, 2 H), 1.71 (quint, J = 8.0 Hz, 2 H), 1.49-1.56 (m, 2 H), 1.35-1.49 (m, 4 H), 1.01 (t, J = 7.2 Hz, 3 H), 0.92 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.6, 140.5, 139.9, 136.9, 124.4, 124.1, 121.9, 119.7, 115.5, 110.4, 109.6, 107.5, 40.0, 32.3, 32.0, 29.2, 25.2, 23.1, 22.9, 14.3, 14.3; HRMS-ESI (*m/z*) [M + H] calculated for $C_{21}H_{27}NO$, 310.2165; found 310.2180.



347 358

4-Butyl-1-pentyl-9*H*-carbazol-2-ol (358). A 250-mL Pyrex photochemical reactor with a quartz immersion well fitted with a Corex filter sleeve, cooled by recirculating tap water, and equipped with an argon inlet and two septa was charged with sulfonamide **347** (0.330 g, 0.847 mmol, 1.0 equiv), triethylamine (5.9 mL, 42 mmol, 50 equiv), and 330 mL of ethanol. The solution was degassed with a stream of argon for 30 min then irradiated with a Hanovia 450W lamp at 25 °C for 2 h. The resulting orange solution was transferred to a 500-mL recovery flask, concentrated to a volume of ca. 50 mL, diluted with 65 mL of Et_2O, and washed with three 25-mL portions of 1 M HCl. The combined aqueous layers were extracted with two 20-mL portions of Et_2O, and the combined organic layers were washed with 70 mL of satd aq $NaHCO_3$ solution. The aqueous layer was then extracted with two 20-mL portions of Et_2O, and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated to afford 0.333 g of brown solid. Column chromatography on 40 g of silica gel (elution with 5% EtOAc-hexanes) provided 0.100 g (38%) of carbazole **358** as a faint yellow solid. Further purification of mixed fractions via column chromatography on 12 g of silica gel (elution with 5% EtOAc-hexanes) provided 0.016 g (6%) of carbazole **358** as a faint yellow solid; total yield: 0.116 g (44%).

347 358

4-Butyl-1-pentyl-9*H*-carbazol-2-ol (358). FEP tubing (ca. 50-ft length, 0.030 in. I.D., 0.0625 in. O.D., total internal volume ca. 6.3 mL) was wrapped around a quartz immersion well surrounding a water-jacketed, 450W Hanovia lamp equipped with a Pyrex filter and cooled by recirculating tap water. The top end of the tubing was fitted with a nut, a ferrule, and a thread to female Luer adapter. Approximately 2.5 ft of tubing was left at either end so that the length wrapped around the well was ca. 45 ft. The bottom end of the tubing was connected through a rubber septum to a 200-mL recovery flask equipped with an argon inlet needle and a needle vent.[213] The tubing was flushed with 10 mL of degassed EtOH, and then the lamp was turned on and degassed EtOH was pumped through the tubing for 5 min at a rate of 1.0 mL/min by syringe pump.

A 100-mL pear flask equipped with a rubber septum and argon inlet needle was charged with diaryl sulfonamide **347** (0.330 g, 0.847 mmol, 1.0 equiv), triethylamine (0.24 mL, 1.69 mmol, 2.0 equiv), and 60 mL of EtOH. The reaction mixture was degassed for 20 min with a stream of argon then pumped via syringe pump[214] through the tubing at a rate of 1.0 mL/min and collected in the 200-mL recovery flask. Once the addition was complete, 10 mL of degassed EtOH was pumped through the tubing at a rate of 1.0 mL/min. The resulting orange solution was concentrated to yield 0.420 g of an orange oil which was diluted with 50 mL of Et_2O, and washed with three 30-mL portions of 1 M HCl. The combined aqueous layers were extracted with two 20-mL portions of Et_2O and the combined organic layers were washed with 100 mL of satd aq $NaHCO_3$ solution, 100 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.311 g of orange oil. This material was dissolved in 15 mL of CH_2Cl_2 and concentrated onto 3 g of silica gel. The free-flowing powder was deposited on a column of 52 g of silica gel and eluted with 5% EtOAc-hexanes to afford 0.118 g (45%) of carbazole **358** as a pale yellow solid.

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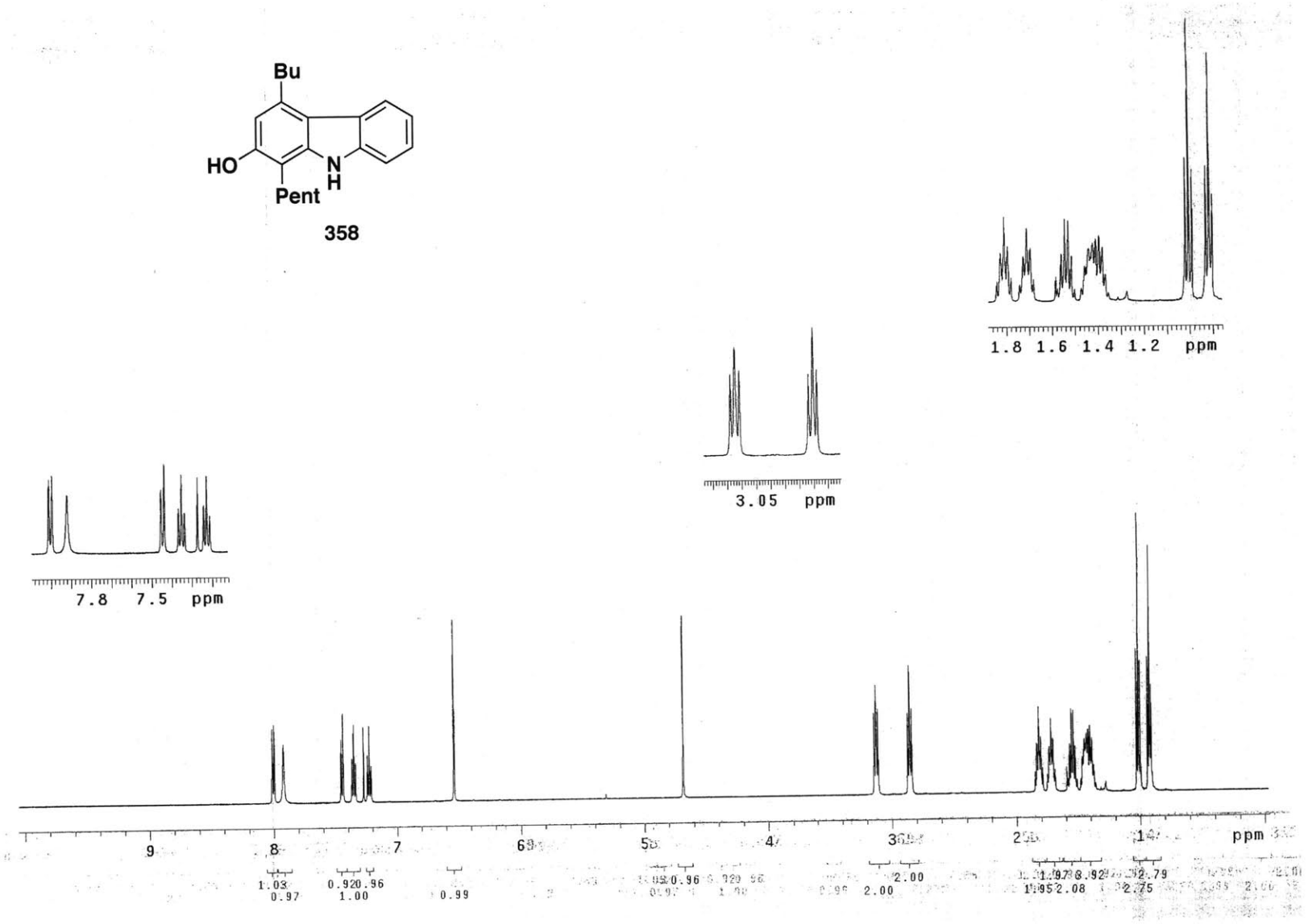
[213] For a more complete description of the construction of the continuous-flow reactor see pages 47-48 of this thesis.
[214] Addition in three 20-mL portions via a 24-mL NORM-JECT® plastic syringe


Bu
HO
N
H
Pent
358
1.8 1.6 1.4 1.2 ppm
3.05 ppm
7.8 7.5 ppm
9
8
7
6
5
4
3
2
1
ppm
1.03
0.97
0.92
0.96
1.00
0.99
0.96
2.00
2.00
1.97
8.92
2.08
2.79
2.75

Bu
HO
N
H
Pent
358
151.646
140.528
139.864
136.943
124.355
124.090
121.861
119.691
115.525
110.417
109.639
107.542
77.482
77.230
76.974
33.977
32.274
32.023
29.230
25.198
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22.932
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14.289
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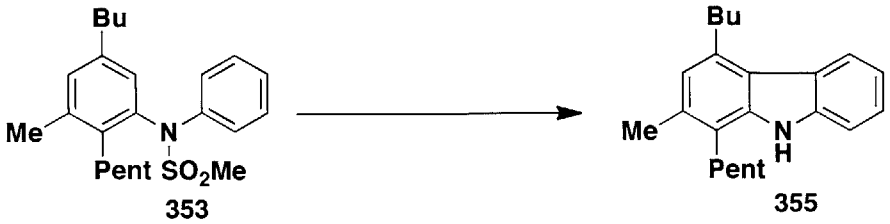
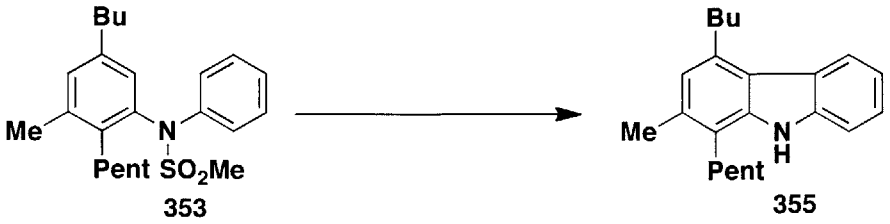
120
100
80
60
40
20
0
ppm



4-Butyl-2-methyl-1-pentyl-9*H*-carbazole (355). A 20-cm quartz tube (12 mm I.D., 14 mm O.D.) equipped with a rubber septum and argon inlet needle was charged with sulfonamide **353** (0.066 g, 0.170 mmol, 1.0 equiv), triethylamine (0.05 mL, 0.359 mmol, 2.1 equiv), and 12.2 mL of ethanol. The reaction mixture was degassed with stream of argon for 15 min and then positioned ca. 20 cm from a Hanovia 450W lamp (quartz immersion well, cooled by recirculating tap water) and irradiated under argon at 25 °C for 16.5 h. The solution was then diluted with 20 mL of Et_2O and washed two 15-mL portions of 1 M HCl. The combined aqueous layers were extracted with two 15-mL portions of Et_2O, and the combined organic layers were washed with 40 mL of satd aq $NaHCO_3$, 40 mL of brine, dried over Na_2SO_4, filtered, and concentrated to afford 0.090 g of orange oil. This material was dissolved in 1 ml of CH_2Cl_2 and concentrated onto 0.8 g of silica gel. The free-flowing powder was deposited on a column of 8 g of silica gel and eluted with 1% EtOAc-hexanes to afford 0.029 g (56%) of carbazole **355** as a faint yellow solid: mp 67-70 °C; IR (neat) 3429, 2950, 2929, 2859, 1612, 1460, 1397 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.0 Hz, 1 H), 7.95 (br s, 1 H), 7.48 (d, J = 8.0 Hz, 1 H), 7.40 (t, J = 7.5 Hz, 1 H), 7.25 (t, J = 8.0 Hz, 1 H), 6.88 (s, 1 H), 3.17 (t, J = 8.0 Hz, 2 H), 2.88 (t, J = 8.0 Hz, 2 H), 2.49 (s, 3 H), 1.80-1.89 (m, 2 H), 1.64-1.73 (m, 2 H), 1.52-1.62 (m, 2 H), 1.38-1.52 (m, 4 H), 1.03 (t, J = 7.5 Hz, 3 H), 0.95 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.7, 139.5, 135.6, 133.1, 124.7, 124.2, 123.1, 122.4, 120.4, 119.5, 119.4, 110.6, 34.1, 32.5, 32.3, 29.4, 28.3, 23.2, 22.9, 19.4, 14.3, 14.3; HRMS-ESI (*m/z*) [M + H] calculated for $C_{22}H_{29}N$, 308.2373; found 308.2382.



4-Butyl-2-methyl-1-pentyl-9*H*-carbazole (355). FEP tubing (ca. 50-ft length, 0.030 in. I.D., 0.0625 in. O.D., total internal volume ca. 6.3 mL) was wrapped around a quartz immersion well surrounding a water-jacketed, 450W Hanovia lamp equipped with a Pyrex filter and cooled by recirculating tap water. The top end of the tubing was fitted with a nut, a ferrule, and a thread to female Luer adapter. Approximately 2.5 ft of tubing was left at either end so that the length wrapped around the well was ca. 45 ft. The bottom end of the tubing was connected through a rubber septum to a 200-mL recovery flask equipped with an argon inlet needle and a needle vent.[215] The tubing was flushed with 10 mL of degassed EtOH, and then the lamp was turned on and degassed EtOH was pumped through the tubing for 5 min at a rate of 1.0 mL/min by syringe pump.

A 100-mL pear flask equipped with a rubber septum and argon inlet needle was charged with diaryl sulfonamide **353** (0.320 g, 0.826 mmol, 1.0 equiv), triethylamine (0.23 mL, 1.65 mmol, 2.0 equiv), and 60 mL of EtOH. The reaction mixture was degassed for 20 min with a stream of argon then pumped via syringe pump[216] through the tubing at a rate of 1.0 mL/min and collected in the 200-mL recovery flask. Once the addition was complete, 10 mL of degassed EtOH was pumped through the tubing at a rate of 1.0 mL/min. The resulting orange solution was concentrated to yield 0.603 g of an orange oil which was diluted with 50 mL of Et_2O, and washed with three 30-mL portions of 1 M HCl. The combined aqueous layers were extracted with two 20-mL portions of Et_2O and the combined organic layers were washed with 100 mL of satd aq $NaHCO_3$ solution, 100 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.255 g of orange oil. This material was dissolved in 15 mL of CH_2Cl_2 and concentrated onto 3 g of silica gel. The free-flowing powder was deposited on a column of 40 g of silica gel and eluted with 1% EtOAc-hexanes to afford 0.147 g (58%) of carbazole **355** as a pale yellow solid.

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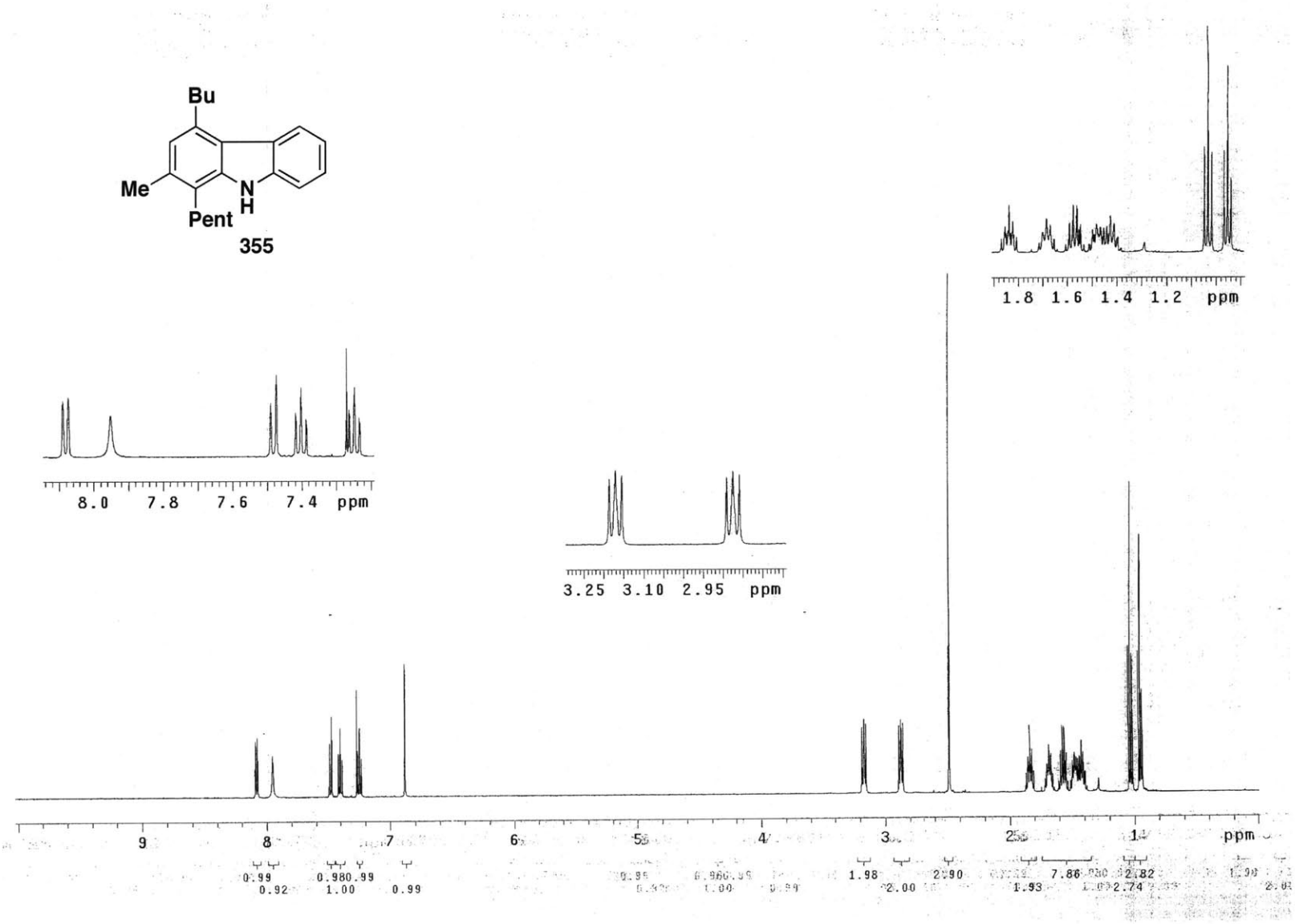
[215] For a more complete description of the construction of the continuous-flow reactor see pages 47-48 of this thesis.
[216] Addition in three 20-mL portions via a 24-mL NORM-JECT® plastic syringe


Bu
Me
N
H
Pent
355
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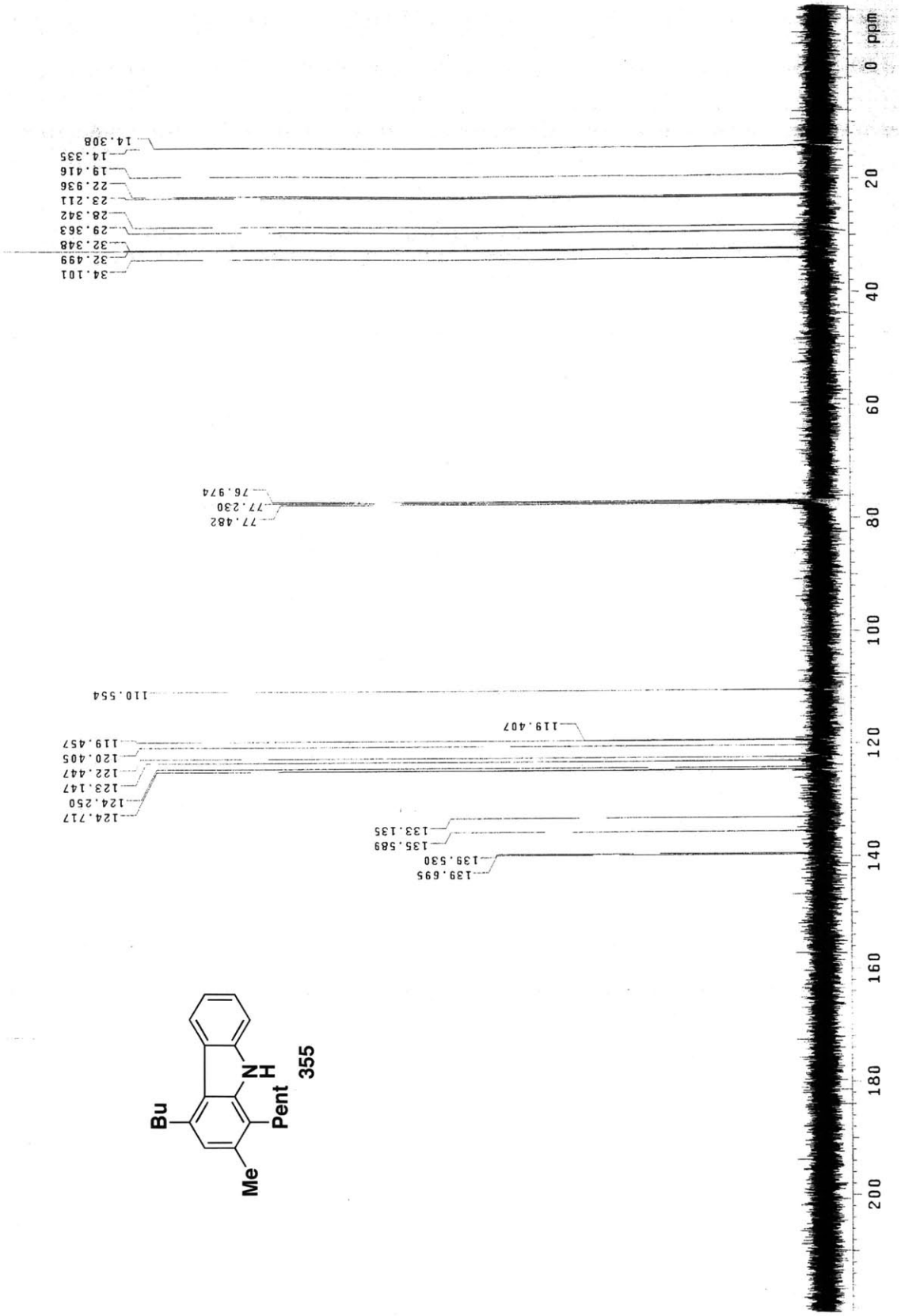
3.25 3.10 2.95 ppm
1.8 1.6 1.4 1.2 ppm
9 8 7 6 5 4 3 2 1 ppm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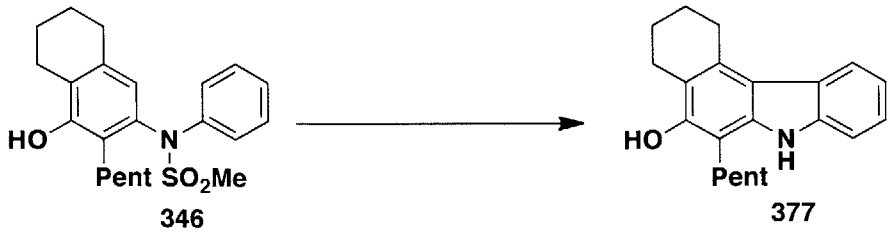
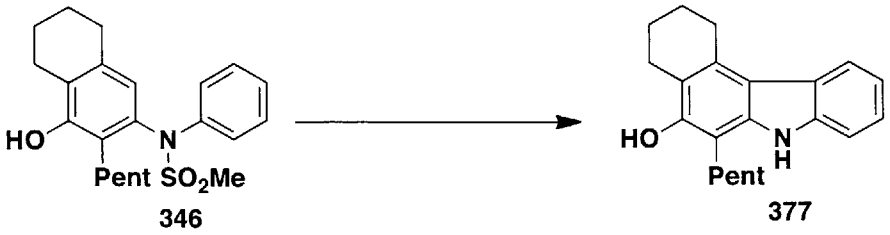
19.416
22.936
23.211
28.342
29.363
32.348
32.499
34.101
76.974
77.230
77.482
110.554
119.407
119.457
120.405
122.447
123.147
124.250
124.717
133.135
135.589
139.530
139.695
0 ppm
20
40
60
80
100
120
140
160
180
200
Bu
Me
Pent
N
H
355



6-Pentyl-2,3,4,7-tetrahydro-1*H*-benzo[*c*]carbazol-5-ol (377). A 20-cm quartz tube (12 mm I.D., 14 mm O.D.) equipped with a rubber septum and argon inlet needle was charged with sulfonamide **346** (0.075 g, 0.193 mmol, 1.0 equiv), triethylamine (0.05 mL, 0.359 mmol, 1.9 equiv), and 13 mL of ethanol. The reaction mixture was degassed with a stream of argon for 15 min and then positioned ca. 20 cm from a Hanovia 450W lamp (quartz immersion well, cooled by recirculating tap water) and irradiated under argon at 25 °C for 13.5 h. The solution was then diluted with 20 mL of Et_2O and washed two 15-mL portions of 1 M HCl. The combined aqueous layers were extracted with three 10-mL portions of Et_2O, and the combined organic layers were washed with 40 mL of satd aq $NaHCO_3$, 40 mL of brine, dried over Na_2SO_4, filtered, and concentrated to afford 0.047 g of a yellow oil. Column chromatography on 8 g of silica gel (elution with 5% EtOAc-hexanes) provided 0.035 g of a yellow solid. Further purification on 8 g of silica gel (elution with 50% dichloromethane-hexanes) provided 0.033 g (56%) of carbazole **377** as a white solid: mp 176-179 °C; IR (neat) 3417 (broad), 3055, 2928, 1607, 1455 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.0 Hz, 1 H), 7.87 (br s, 1 H), 7.44 (d, J = 8.0 Hz, 1 H), 7.34 (t, J = 7.0 Hz, 1 H), 7.21 (t, J = 8.0 Hz, 1 H), 4.78 (s, 1 H), 3.31-3.40 (m, 2 H), 2.87 (t, J = 7.8 Hz, 2 H), 2.70-2.81 (m, 2 H), 1.94-2.02 (m, 4 H), 1.72 (quint, J = 8.0 Hz, 2 H), 1.38-1.51 (m, 4 H), 0.93 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.1, 139.7, 137.9, 131.1, 124.9, 123.8, 122.2, 119.3, 115.6, 115.1, 110.2, 107.2, 32.3, 29.3, 28.2, 25.6, 23.7, 22.9, 22.9, 22.9, 14.3; HRMS-ESI (*m/z*) [M + H] calculated for $C_{21}H_{25}NO$, 308.2009; found 308.2004.



6-Pentyl-2,3,4,7-tetrahydro-1*H*-benzo[*c*]carbazol-5-ol (377). FEP tubing (ca. 50-ft length, 0.030 in. I.D., 0.0625 in. O.D., total internal volume ca. 6.3 mL) was wrapped around a quartz immersion well surrounding a water-jacketed, 450W Hanovia lamp equipped with a Pyrex filter and cooled by recirculating tap water. The top end of the tubing was fitted with a nut, a ferrule, and a thread to female Luer adapter. Approximately 2.5 ft of tubing was left at either end so that the length wrapped around the well was ca. 45 ft. The bottom end of the tubing was connected through a rubber septum to a 200-mL recovery flask equipped with an argon inlet needle and a needle vent.[217] The tubing was flushed with 10 mL of degassed EtOH, and then the lamp was turned on and degassed EtOH was pumped through the tubing for 5 min at a rate of 1.0 mL/min by syringe pump.

A 100-mL pear flask equipped with a rubber septum and argon inlet needle was charged with diaryl sulfonamide **346** (0.255 g, 0.658 mmol, 1.0 equiv), triethylamine (0.18 mL, 1.29 mmol, 2.0 equiv), and 48 mL of EtOH. The reaction mixture was degassed for 20 min with a stream of argon then pumped via syringe pump[218] through the tubing at a rate of 1.0 mL/min and collected in the 200-mL recovery flask. Once the addition was complete, 10 mL of degassed EtOH was pumped through the tubing at a rate of 1.0 mL/min. The resulting orange solution was concentrated to yield 0.501 g of an orange oil which was diluted with 50 mL of Et_2O, and washed with three 30-mL portions of 1 M HCl. The combined aqueous layers were extracted with two 20-mL portions of Et_2O and the combined organic layers were washed with 100 mL of satd aq $NaHCO_3$ solution, 100 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.206 g of orange oil. This material was dissolved in 15 mL of CH_2Cl_2 and concentrated onto 3 g of silica gel. The free-flowing powder was deposited on a column of 40 g of silica gel and eluted with 5% EtOAc-hexanes to afford 0.113 g (56%) of carbazole **377** as a pale yellow solid:.

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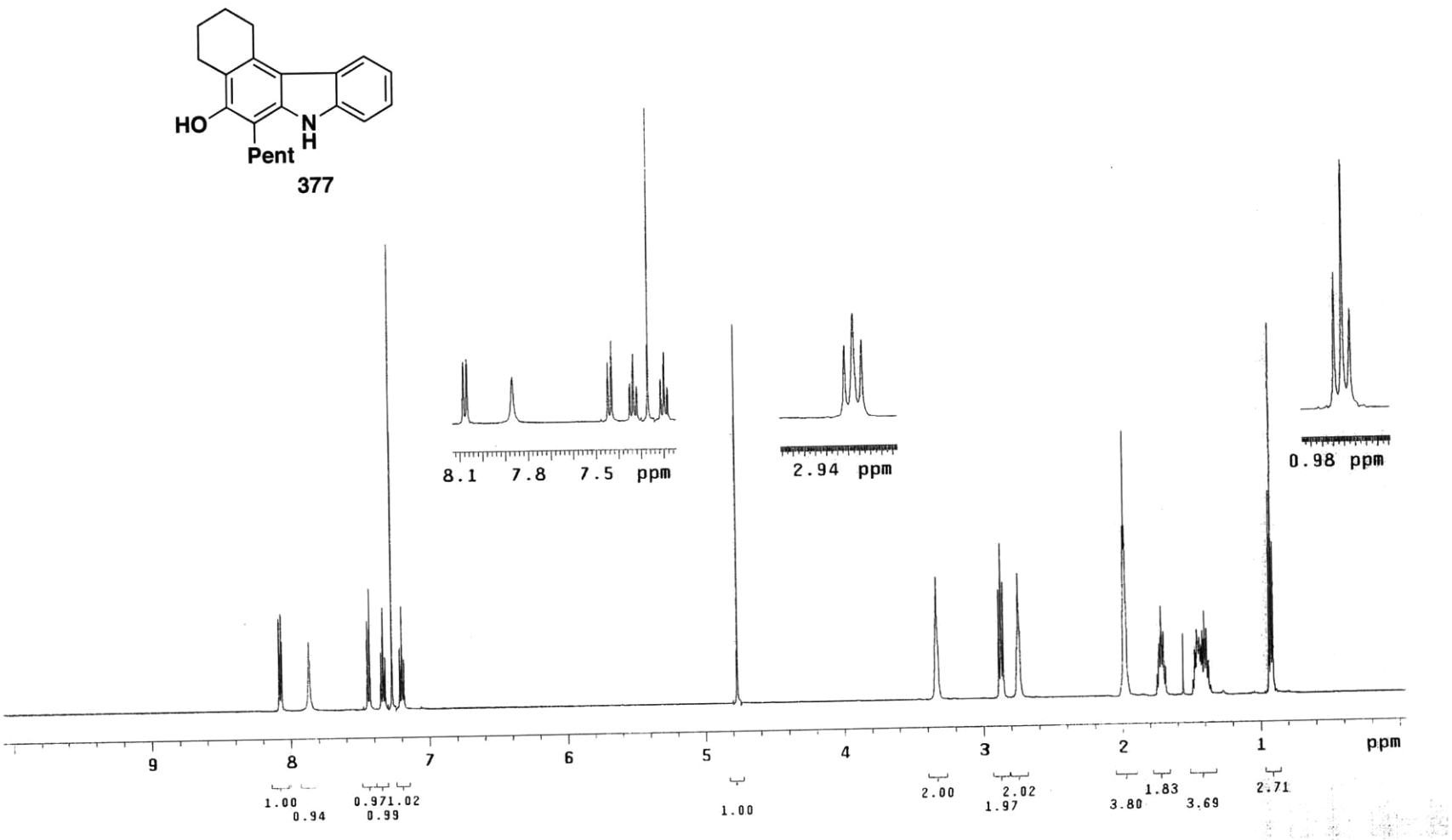
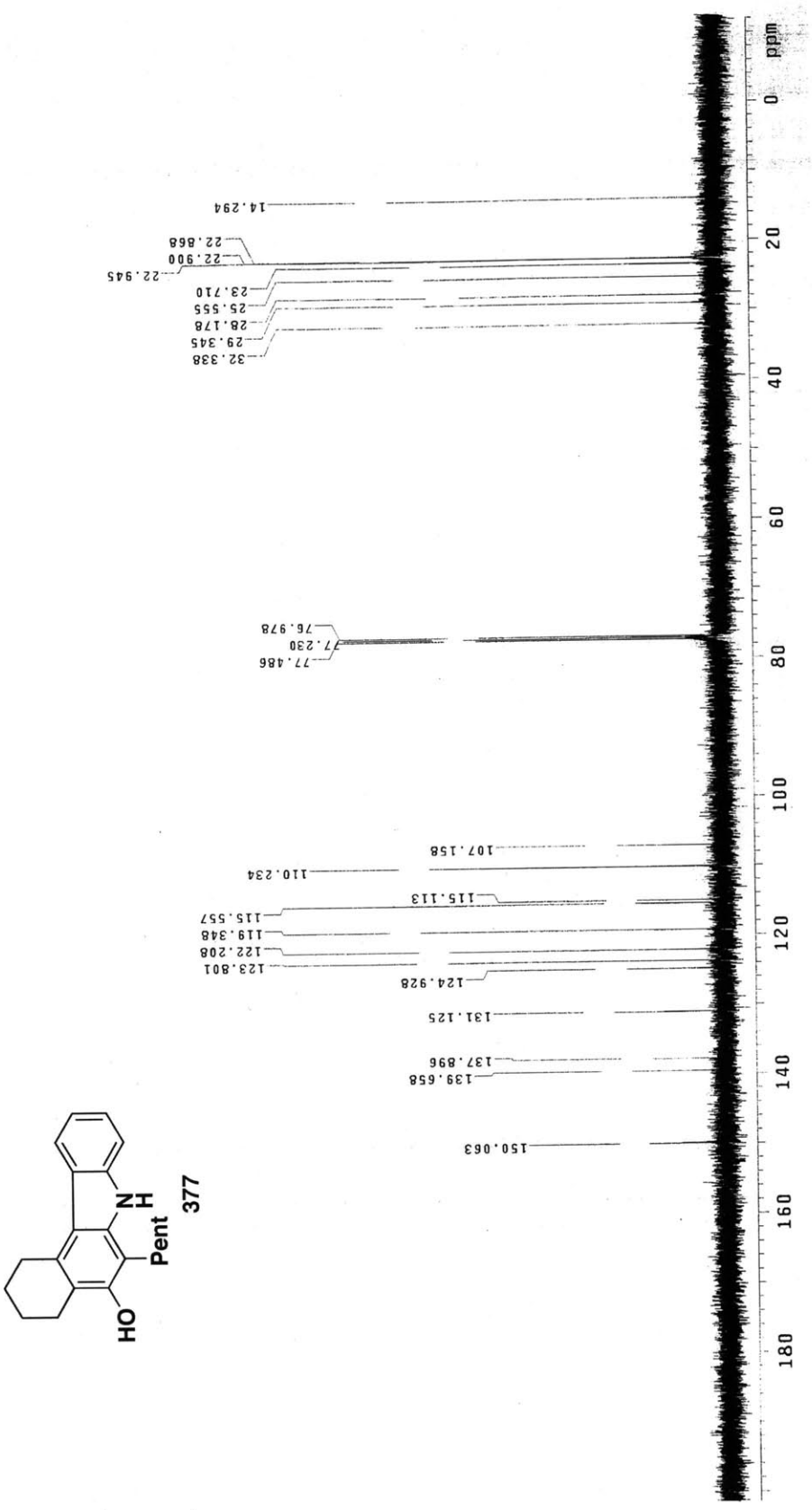
[217] For a more complete description of the construction of the continuous-flow reactor see pages 47-48 of this thesis.
[218] Addition in three 16-mL portions via a 24-mL NORM-JECT® plastic syringe


HO
N
H
Pent
377
8.1 7.8 7.5 ppm
2.94 ppm
0.98 ppm
9
8
7
6
5
4
3
2
1
ppm
1.00
0.94
0.97
1.02
0.99
1.00
2.00
2.02
1.97
3.80
1.83
3.69
2.71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22.868
22.900
22.945
23.710
25.555
28.178
29.345
32.338
76.978
77.230
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110.234
115.113
115.557
119.348
122.208
123.801
124.928
131.125
137.896
139.658
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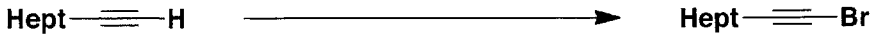
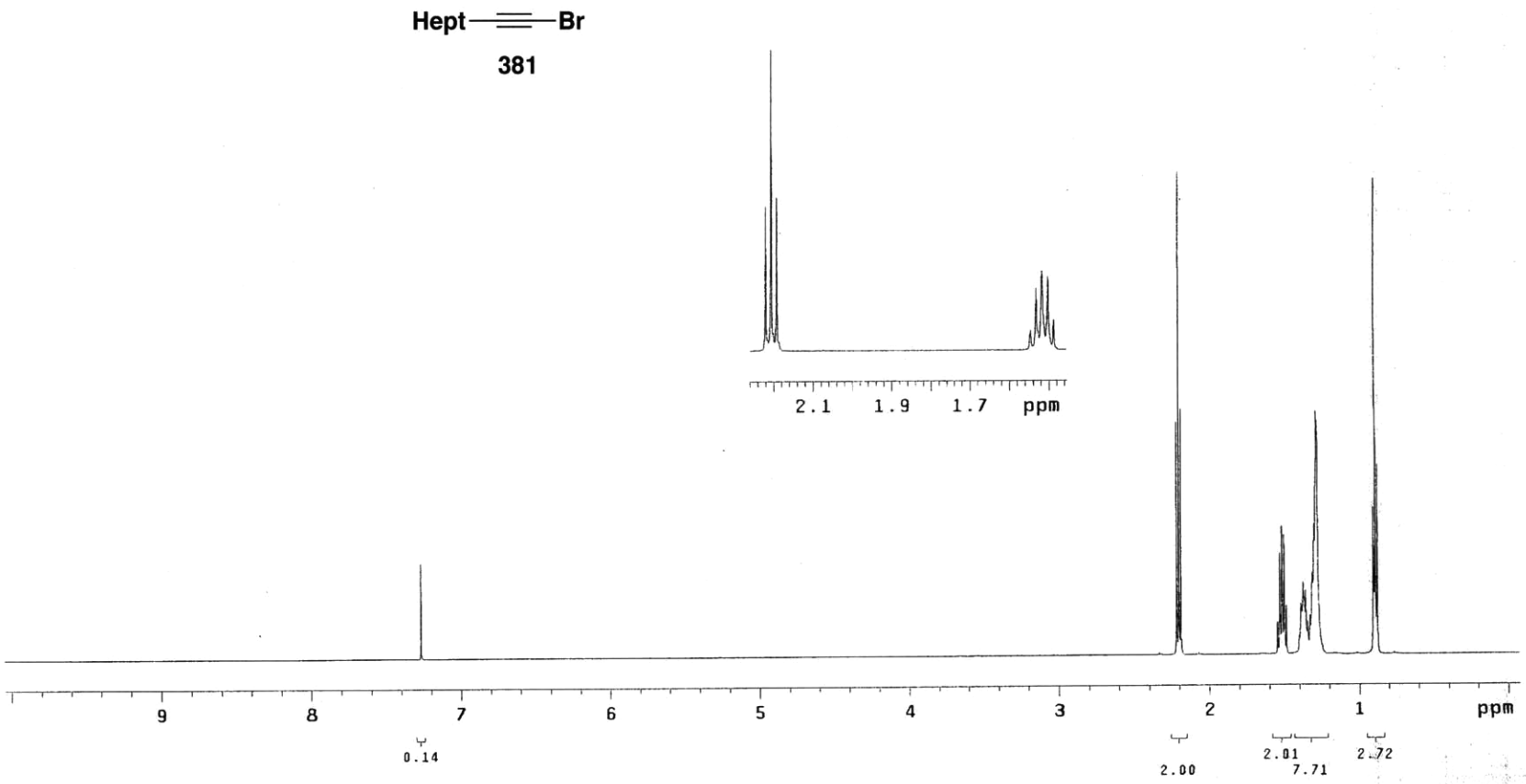
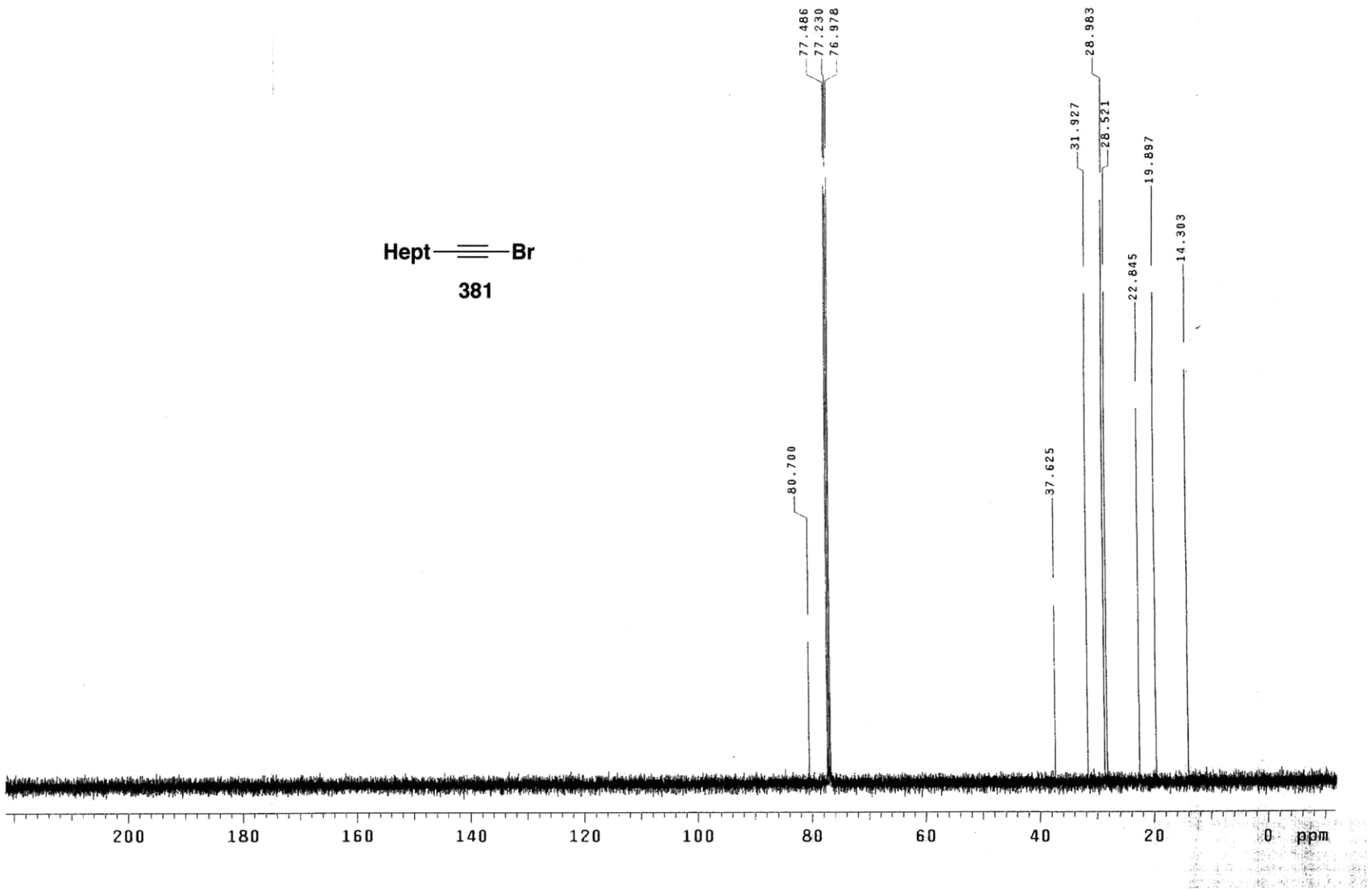
ppm
0
20
40
60
80
100
120
140
160
180
HO
Pent
N
H
377



381

1-Bromo-1-nonyne (381). A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, and glass stopper was charged with 1-nonyne (2.0 mL, 1.52 g, 12.1 mmol, 1.0 equiv), NBS (2.38 g, 13.3 mmol, 1.1 equiv), $AgNO_3$ (0.205 g, 1.20 mmol, 0.1 equiv), and 40 mL of acetone. The resulting mixture was stirred in the dark at rt for 3 h and then diluted with 80 mL of pentane and 60 mL of water. The organic layer was washed with four 20-mL portions of satd aq $Na_2S_2O_3$ solution and 80 mL of brine, dried over $MgSO_4$, filtered, and concentrated to yield 2.40 g (98%) of alkynyl bromide **381** as a clear oil: IR (thin film) 2930, 2857, 2219, 1466, 1430, 1378, 1328 cm^{-1}; ^1H NMR (500 MHz) δ 2.21 (t, J = 7.0 Hz, 2H) 1.52 (quintet, J = 7.5 Hz, 2H), 1.21-1.42 (m, 8H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz) δ 80.7, 37.6, 31.9, 29.0, 29.0, 28.5, 22.8, 19.9, 14.3.


Hept—≡—Br
381
2.1
1.9
1.7
ppm
9
8
7
6
5
4
3
2
1
ppm
0.14
2.00
2.01
7.71
2.72


Hept—≡—Br
381
77.486
77.230
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80.700
37.625
31.927
28.983
28.521
22.845
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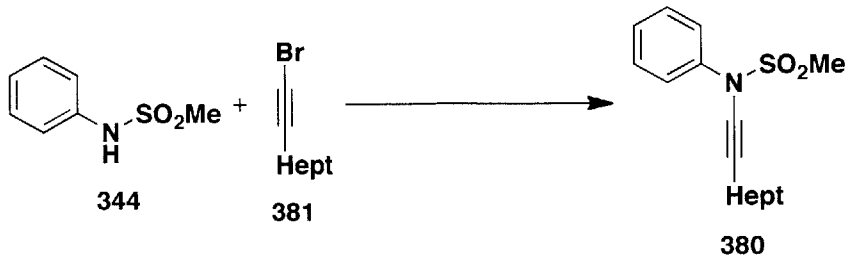
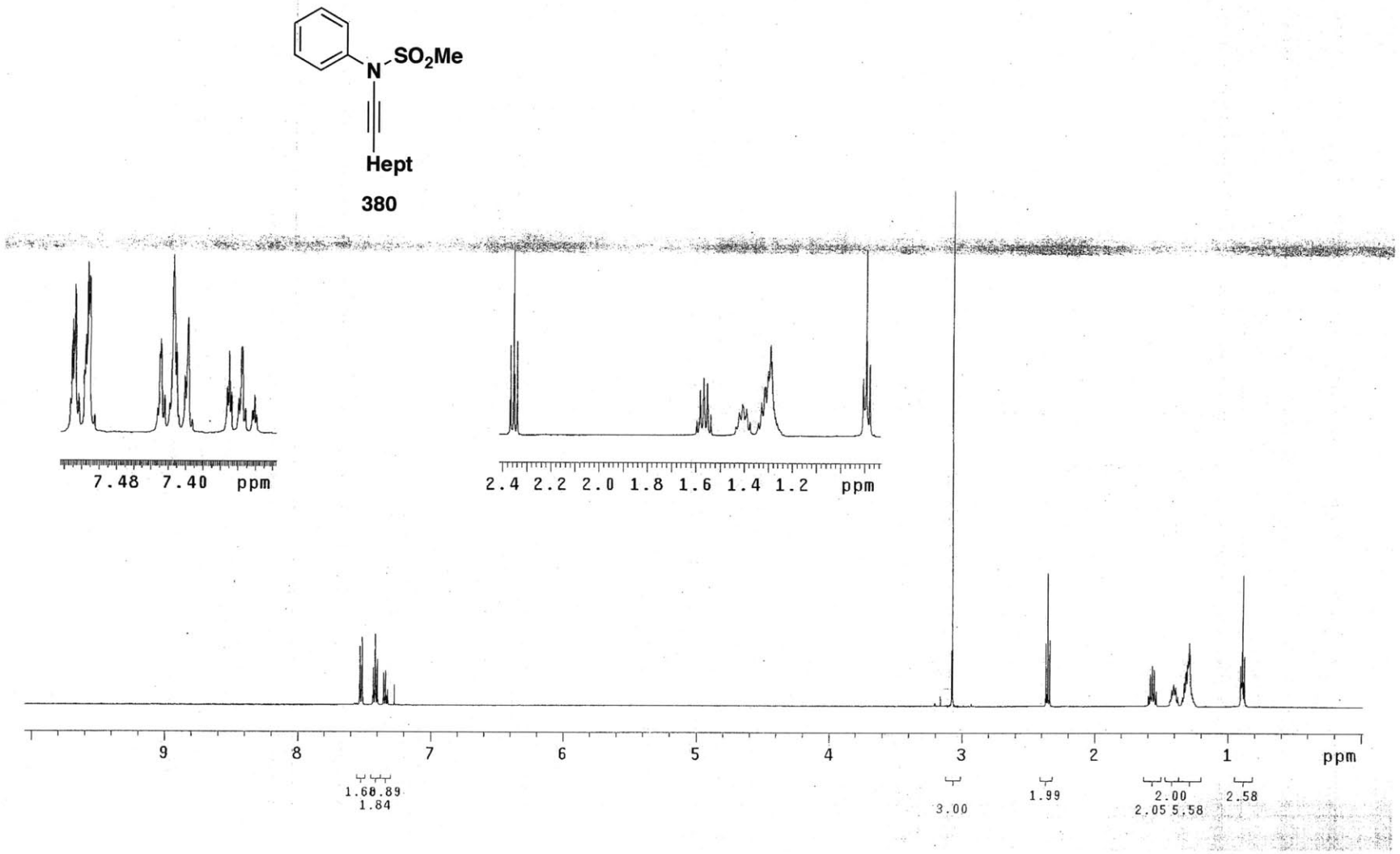
180
160
140
120
100
80
60
40
20
0 ppm



344 381 380

***N*-(Methanesulfonyl)-*N*-(phenyl)-2-heptylethynylamine (380).** A 25-mL round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with sulfonamide **344**[211] (1.26 g, 7.36 mmol, 1.0 equiv), K_2CO_3 (2.04 g, 14.8 mmol, 2.0 equiv), $CuSO_4 \cdot 5H_2O$ (0.279 g, 1.11 mmol, 0.15 equiv), and 1,10-phenanthroline (0.402 g, 2.23 mmol, 0.30 equiv). The flask was then evacuated and backfilled with argon three times. A solution of 1-bromoheptyne **381** (2.11 g, 10.4 mmol, 1.4 equiv) in 11 mL of DMF was added rapidly via cannula. The flask was then charged with 4 Å molecular sieves (0.600 g) and the septum was replaced with a cold-finger condenser fitted with an argon inlet adapter. The resulting heterogeneous reaction mixture was stirred at 65 °C for 47 h then cooled to rt, diluted with 70 mL of Et_2O, and washed with four 50-mL portions of a 2:1 mixture of brine and concd NH_4OH solution. The combined aqueous layers were extracted with 50 mL of Et_2O, and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated to afford 2.753 g of brown solid. This material was dissolved in 40 mL of CH_2Cl_2 and concentrated onto 15 g of silica gel. The free-flowing powder was deposited on a column of 210 g of silica gel and eluted with 8% to 15% EtOAc-hexanes to afford 1.782 g (83%) of ynamide **380** as a off-white solid: mp 54-56 °C; IR (KBr) 2928, 2857, 2255, 1593, 1490, 1356, 1274, 1158 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50-7.54 (m, 2 H), 7.39-7.44 (m, 2 H), 7.31-7.36 (m, 1 H) 3.07 (s, 3 H), 2.35 (t, J = 7.8 Hz, 2 H), 1.57 (quint, J = 7.5 Hz, 2 H), 1.38-1.48 (m, 2 H), 1.21-1.38 (m, 6 H), 0.89 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.3, 129.5, 128.2, 125.6, 73.3, 71.3, 36.3, 31.9, 29.1, 29.0, 29.0, 22.8, 18.7, 14.3; Anal. Calcd for $C_{16}H_{23}NO_2S$: C, 65.49; H, 7.90; N, 4.77; Found: C, 65.36; H, 7.80; N, 4.76.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Hept
380
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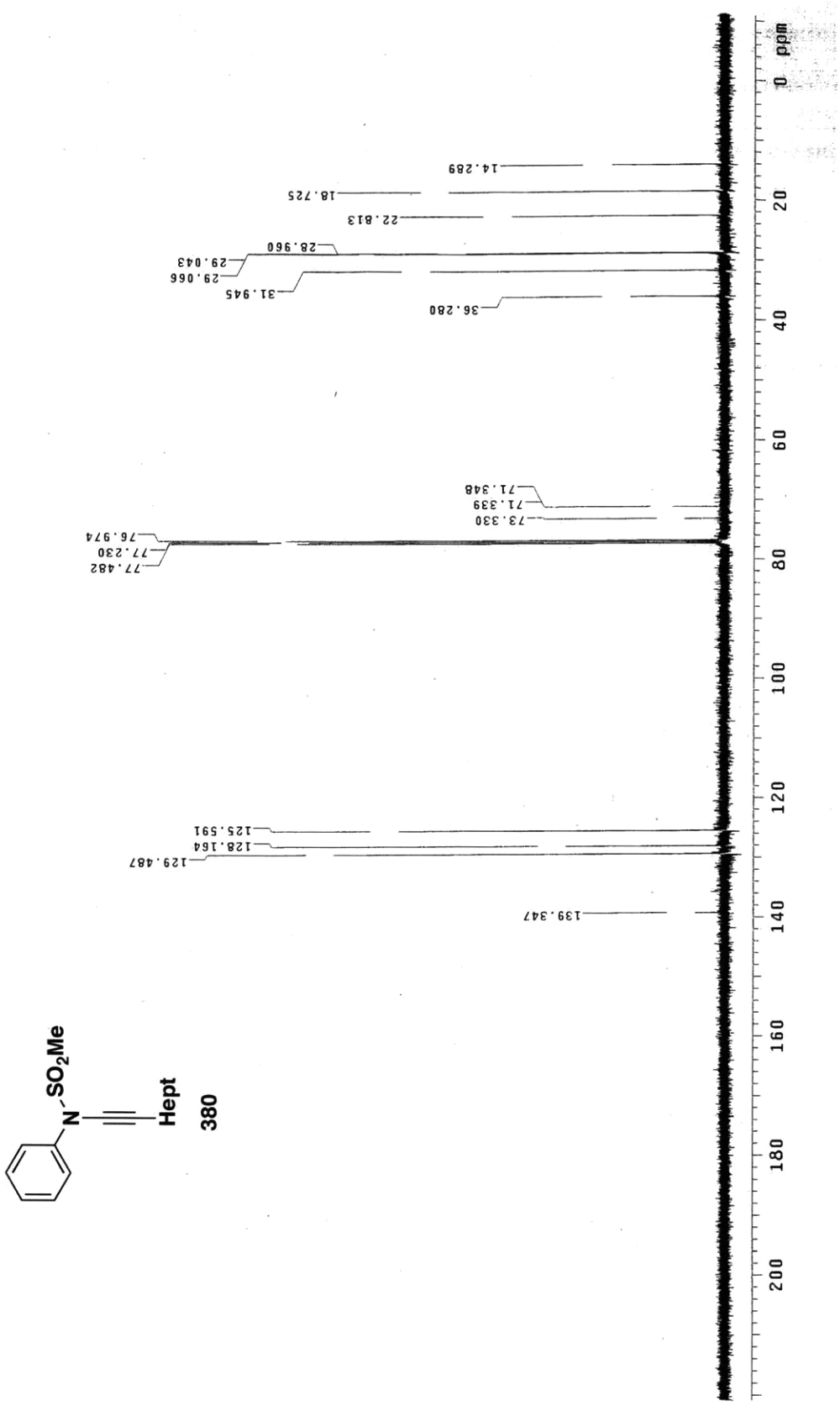
2.4 2.2 2.0 1.8 1.6 1.4 1.2 ppm
9 8 7 6 5 4 3 2 1 ppm
1.68
1.89
1.84
3.00
1.99
2.00
2.05
5.58
2.58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77.230
77.482
125.591
128.164
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20
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60
80
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160
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SO2Me
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Hept
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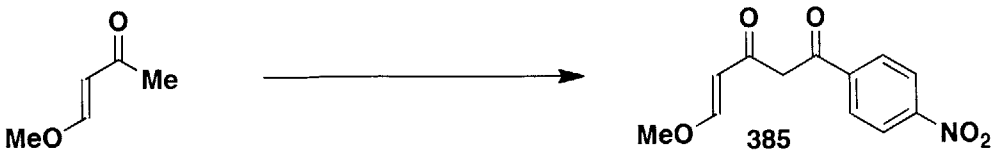
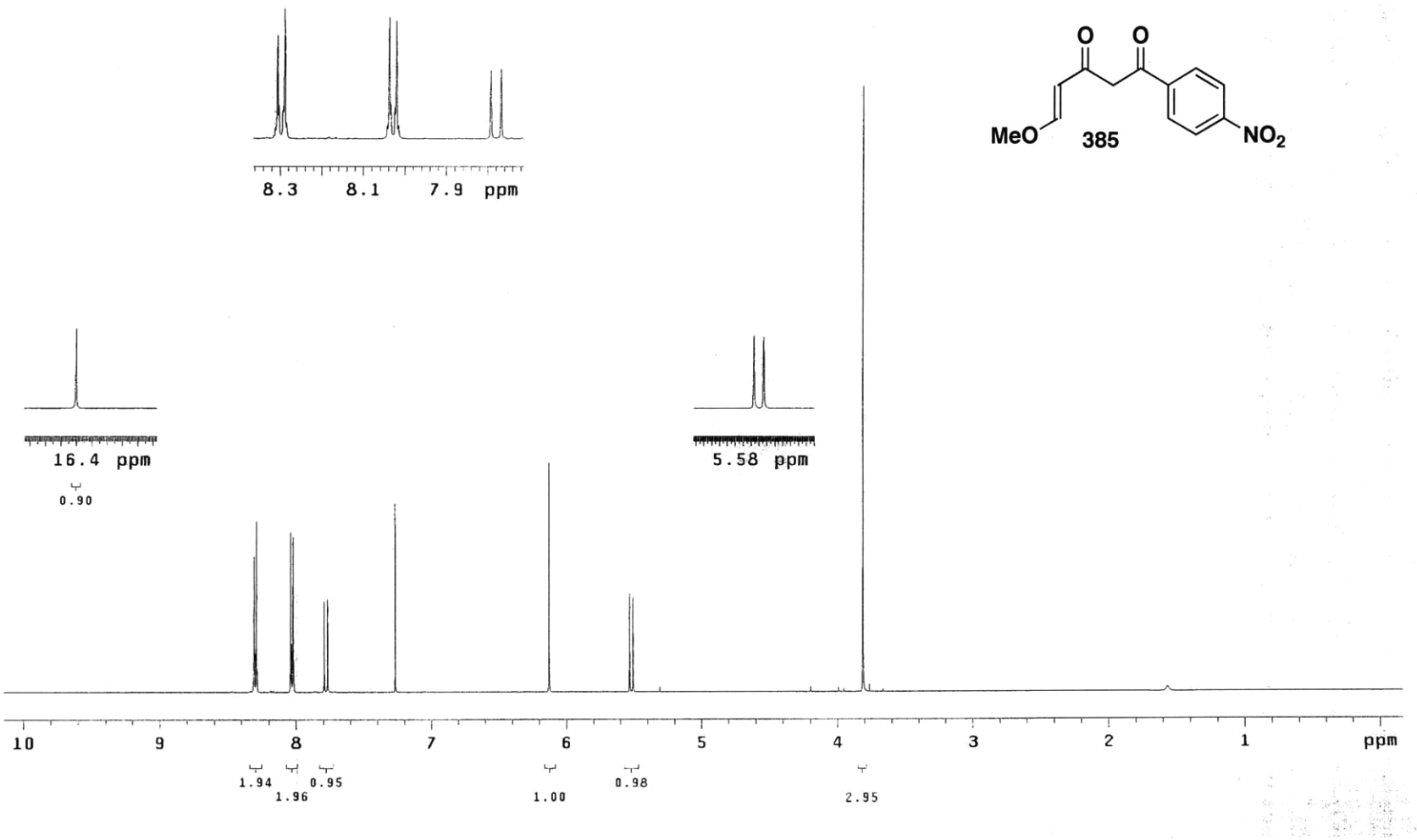


(*E*)-5-Methoxy-1-(4-nitrophenyl)pent-4-ene-1,3-dione (385). A 1-L, three-necked round bottomed flask equipped with an addition funnel, rubber septum, thermocouple and argon inlet adapter was charged with HMDS (9.0 mL, 42.9 mmol, 2.3 equiv), 16.4 mL of THF, and 50 mL of toluene and then cooled at 0 °C while *n*-BuLi (2.33 M in hexane, 17.6 mL, 41.1 mmol, 2.2 equiv) was added dropwise over 10 min. After 1 h, the resulting solution was cooled at -78 °C while a solution of ketone (4.0 mL, 3.9 g, 39 mmol, 2.1 equiv) in 50 mL of THF was added dropwise via the addition funnel over 45 min (1.0 mL toluene wash). After 1 h, a solution of 4-nitrophenylacetyl chloride (3.47 g, 18.7 mmol, 1.0 equiv) in 3.6 mL of THF and 15 mL of toluene was added dropwise via the addition funnel over 40 min. After 1 h, the reaction mixture was allowed to warm to rt, stirred for 1 h, then diluted with 150 mL of satd aq NH_4Cl solution and 150 mL of EtOAc. The aqueous phase was extracted with three 80-mL portions of EtOAc, and the combined organic phases were washed with 200 mL of brine, dried over Na_2SO_4, filtered, and concentrated to give 9.40 g of a brown solid. This material was dissolved in 50 mL of CH_2Cl_2 and concentrated onto 20 g of silica gel. The free-flowing powder was deposited on a column of 300 g of silica gel and eluted with CH_2Cl_2 to afford 2.58 g (55%) of diketone **385** as a bright yellow solid: mp 130-132 °C; IR (neat) 1653, 1523, 1345, 1271, 1129, 949, 842, 756, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 16.4 (s, 1 H), 8.30 (d, J = 9.0 Hz, 1 H), 8.03 (d, J = 9.0 Hz, 1 H), 7.78 (d, J = 17.0 Hz, 1 H), 6.13 (s, 1 H), 5.53 (d, J = 17.0 Hz, 1 H), 3.81 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.3, 180.0, 162.7, 149.8, 141,4, 127.9, 124.0, 102.7, 97.2, 58.3; HRMS-ESI (*m/z*) [M + H] calculated for $C_{12}H_{11}NO_5$, 250.0710; found 250.0706.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O
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385
NO2
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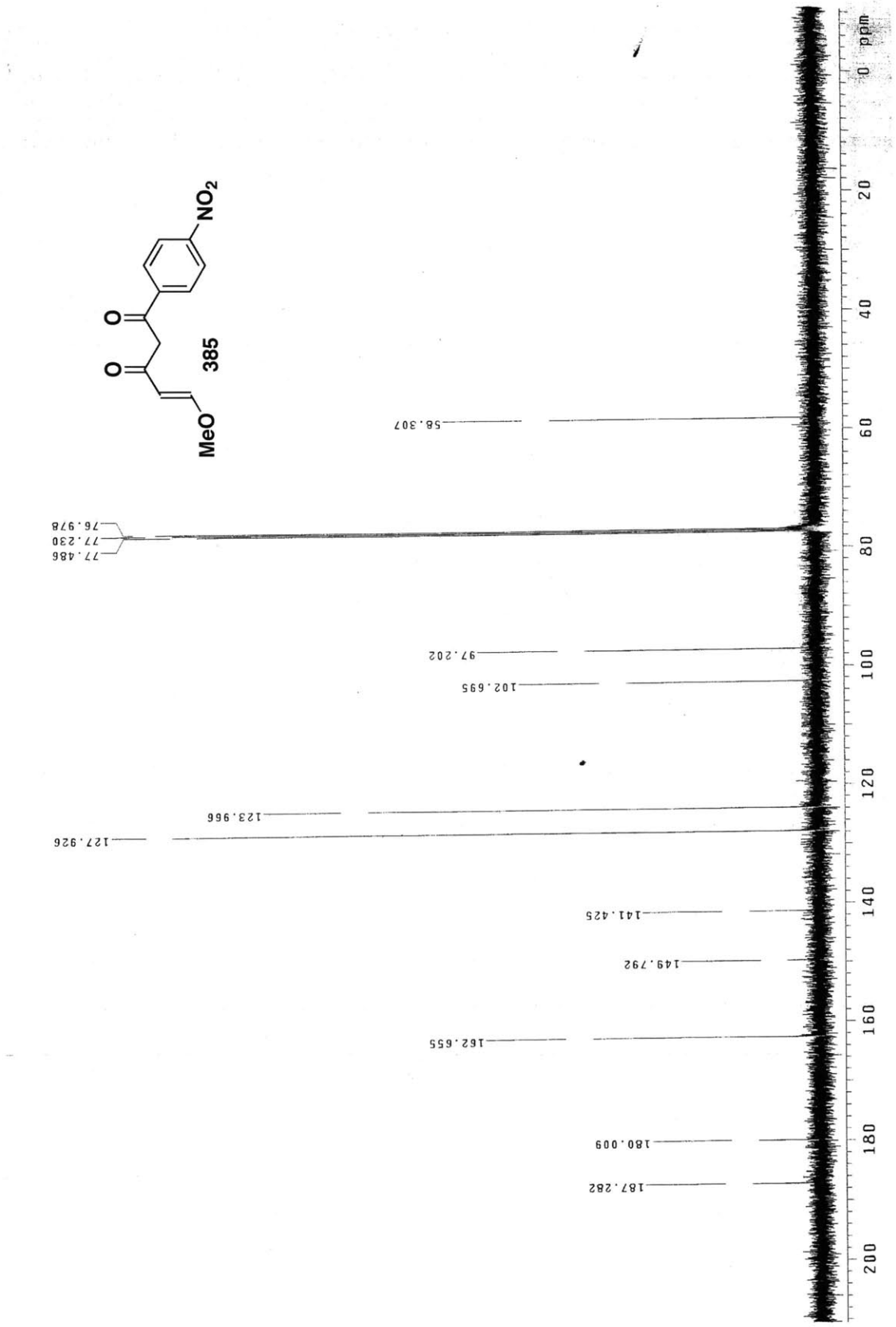
8.1
7.9
ppm
16.4 ppm
0.90
5.58 ppm
10
9
8
7
6
5
4
3
2
1
ppm
1.94
1.96
0.95
1.00
0.98
2.95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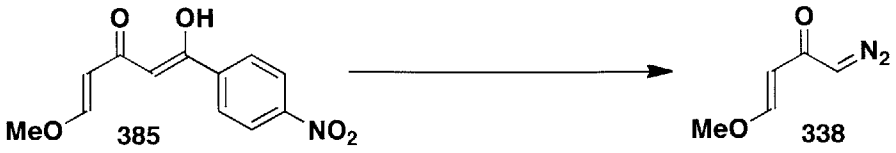
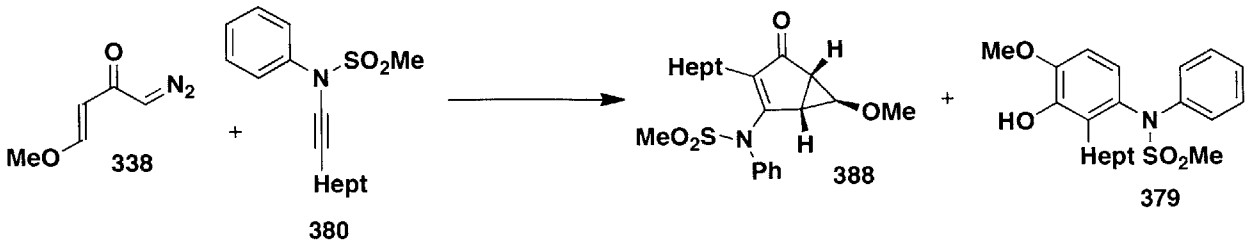
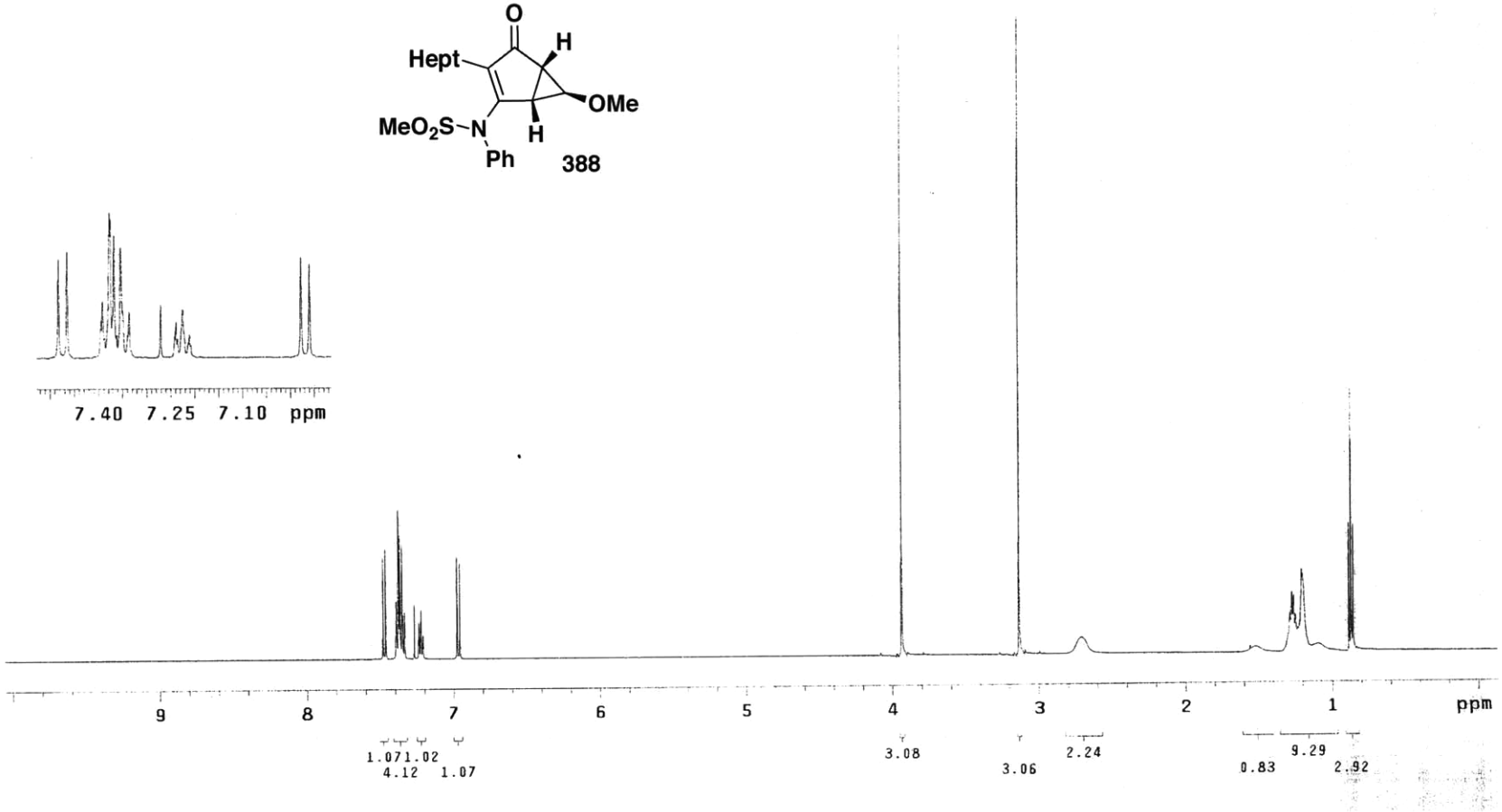
ppm



1-Diazo-4-methoxy-3-buten-2-one (338). A 200-mL recovery flask equipped with a rubber septum and argon inlet needle was charged with diketone **385** (1.00 g, 4.01 mmol, 1.0 equiv) and 28 mL of MeCN. The solution was cooled to 0 °C, Et_3N (0.84 mL, 6.02 mmol, 1.5 equiv) was added, and then a solution of methanesulfonyl azide (0.605 g, 5.00 mmol, 1.3 equiv) in 10 mL of CH_3CN was added dropwise via syringe over 10 min. The reaction mixture was allowed to warm to rt, stirred for 3 h, then transferred to a 1-L recovery flask and concentrated to afford ca. 2.5 g of an orange solid. The flask was equipped with a rubber septum and an argon inlet needle, and the solid was diluted with aq Li_2CO_3 solution (0.1 M in water, 12.0 mmol, 3.0 equiv) and 40 mL of Et_2O. The biphasic mixture was stirred vigorously for 26 h and then the aqueous layer was separated and washed with eight 50-mL portions of $CHCl_3$. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated to afford 0.860 g of an orange solid. Column chromatography on 70 g of silica gel (elution with 60% Et_2O-pentane) furnished 0.354 g (70%) of diazo ketone **338**[44a] as a bright yellow solid (mp 35-37 °C) with spectral characteristics identical to those previously reported.



***N*-(3-Heptyl-6-methoxy-4-oxobicyclo[3.1.0]hex-2-en-2-yl)-*N*-phenylmethanesulfonamide (388).** A 20-cm quartz tube (10 mm I.D., 12 mm O.D.) equipped with a rubber septum and argon inlet needle was charged with diazo ketone **338** (0.050 g, 0.396 mmol, 1.0 equiv), ynamide **380** (0.465 g, 1.58 mmol, 4.0 equiv), and 10.5 mL of toluene. The yellow reaction mixture was degassed with a stream of argon for 15 min. The quartz tube was positioned ca. 20 cm from a Hanovia 450W lamp (quartz immersion well, cooled by recirculating tap water) and irradiated under argon at 25 °C for 22 h. The reaction mixture was transferred to a 50-mL pear flask with the aid of two 1-mL portions of toluene. The flask was equipped with a stir bar and cold-finger condenser, and the reaction mixture was heated at reflux for 2 h. The resulting mixture was concentrated to afford 0.512 g of orange oil. Column chromatography on 50 g of silica gel (elution with 10-45% EtOAc-hexanes) provided 0.382 g (82%, 3.3 equiv) of ynamide **380** as an off-white solid, 0.061 g (39%) of ca. 80% pure phenol **379** as a yellow oil, and 0.038 g of a yellow oil that was further purified on 7 g of silica gel (elution with 30% EtOAc-hexanes) to afford 0.027 g (17%) of ketone **388** as a yellow oil: IR (neat) 2928, 2855, 1690, 1591, 1488, 1453, 1361, 1213, 1164, 960, 805, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.48 (m, 5 H), 3.46 (s, 3 H), 3.40-3.42 (m, 1H), 3.28 (dd, J = 6.0, 1.0 Hz, 1 H), 3.20 (s, 3 H), 2.47 (dd, J = 6.0, 1.0 Hz, 1 H), 1.52-1.60 (m, 1 H), 1.34-1.43 (m, 1 H), 1.18-1.28 (m, 2 H), 1.03-1.18 (m, 4 H), 0.89-1.01 (m, 3 H), 0.85 (t, J = 7.0 Hz, 3 H), 0.80-0.89 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.3, 161.3, 139.1, 131.7, 129.9, 129.3, 129.0, 78.5, 58.9, 40.5, 32.9, 31.9, 29.7, 29.2, 29.2, 27.6, 23.0, 22.8, 14.3; HRMS-ESI (*m/z*) [M + H] calculated for $C_{21}H_{29}NO_4S$, 392.1890; found 392.1883.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H
Hept
OMe
MeO2S
N
H
Ph
388
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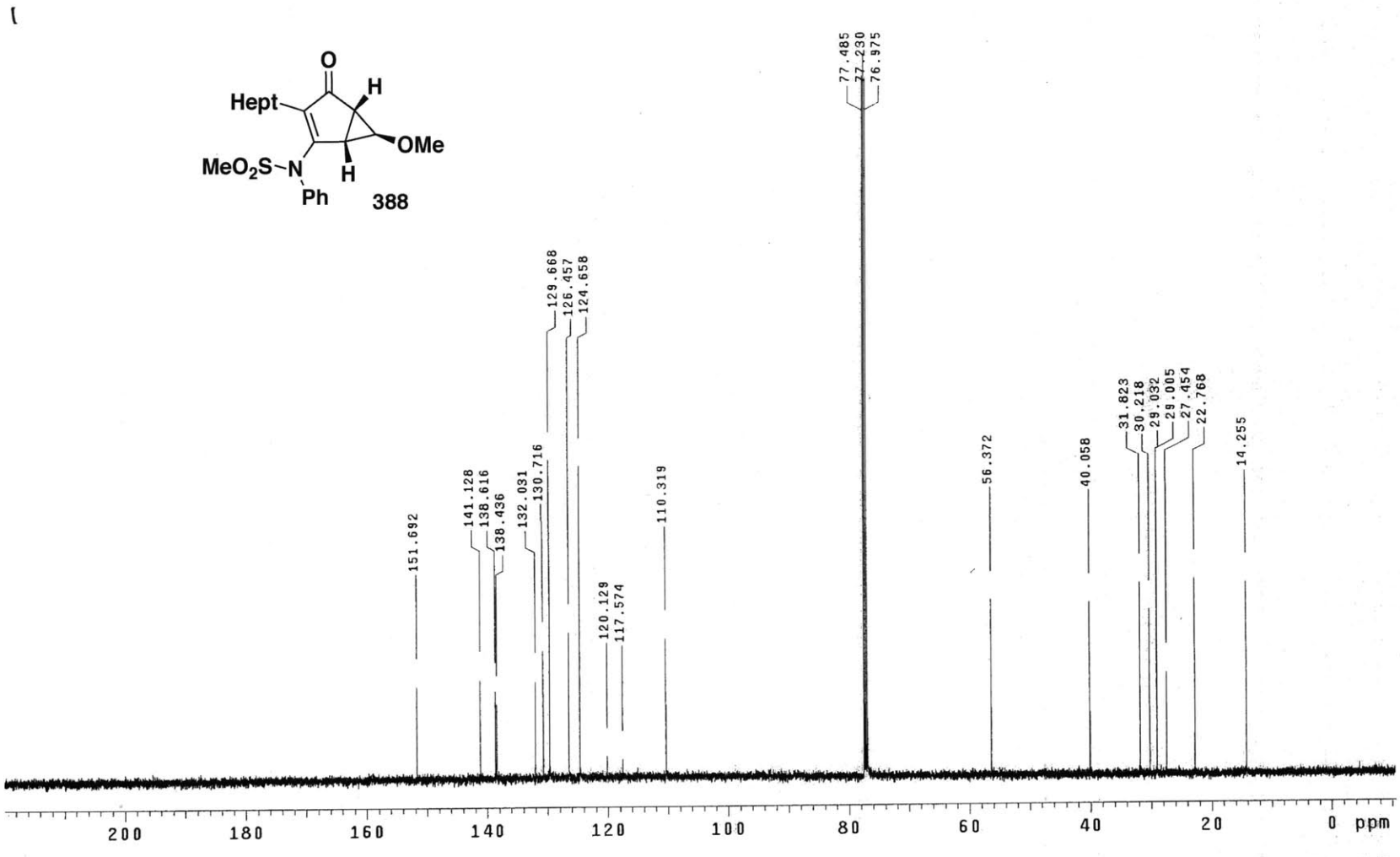
9 8 7 6 5 4 3 2 1 ppm
1.07 1.02
4.12 1.07
3.08
3.06
2.24
0.83
9.29
2.92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Hept
OMe
MeO2S
N
H
Ph
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31.823
30.218
29.032
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180
160
140
120
100
80
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20
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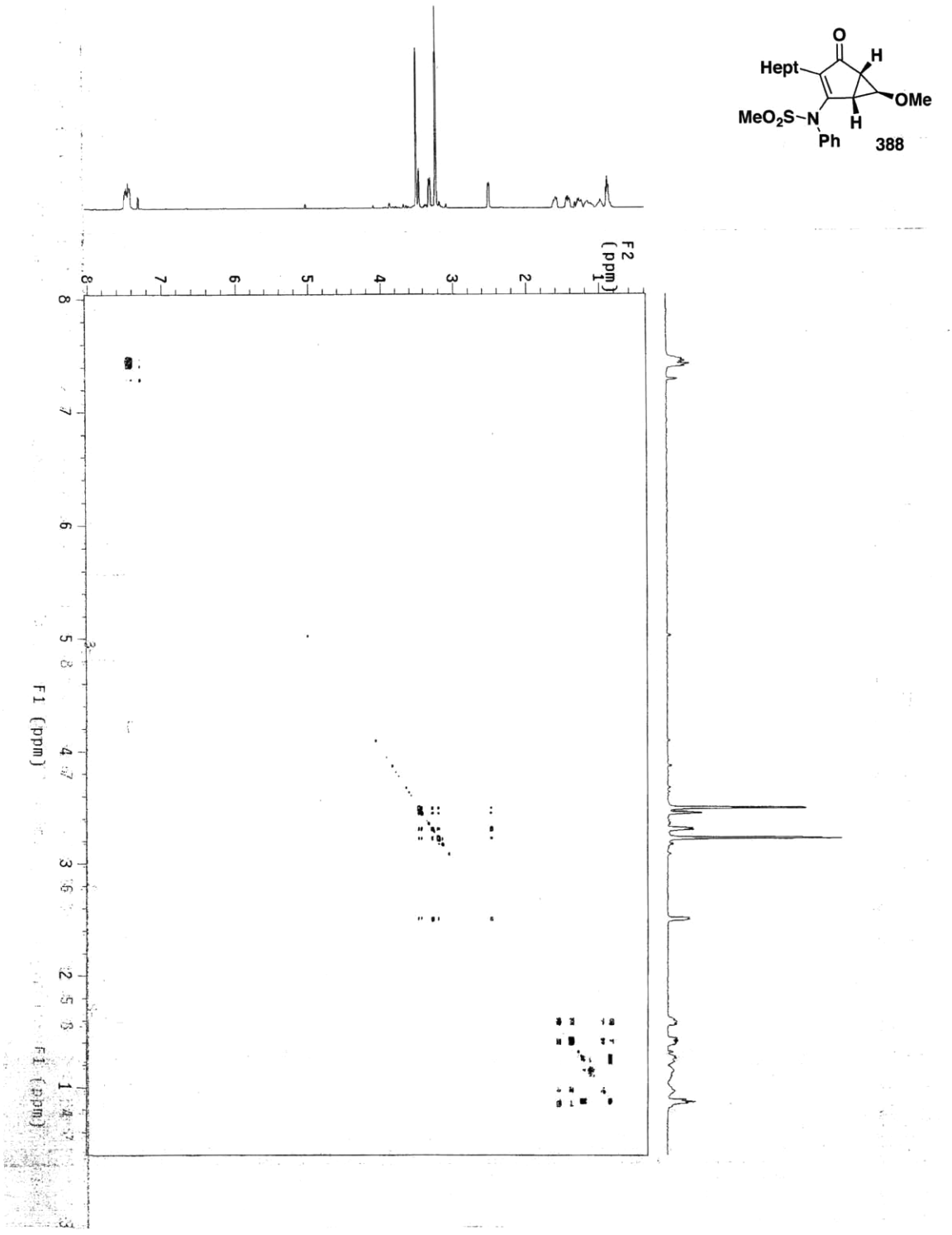
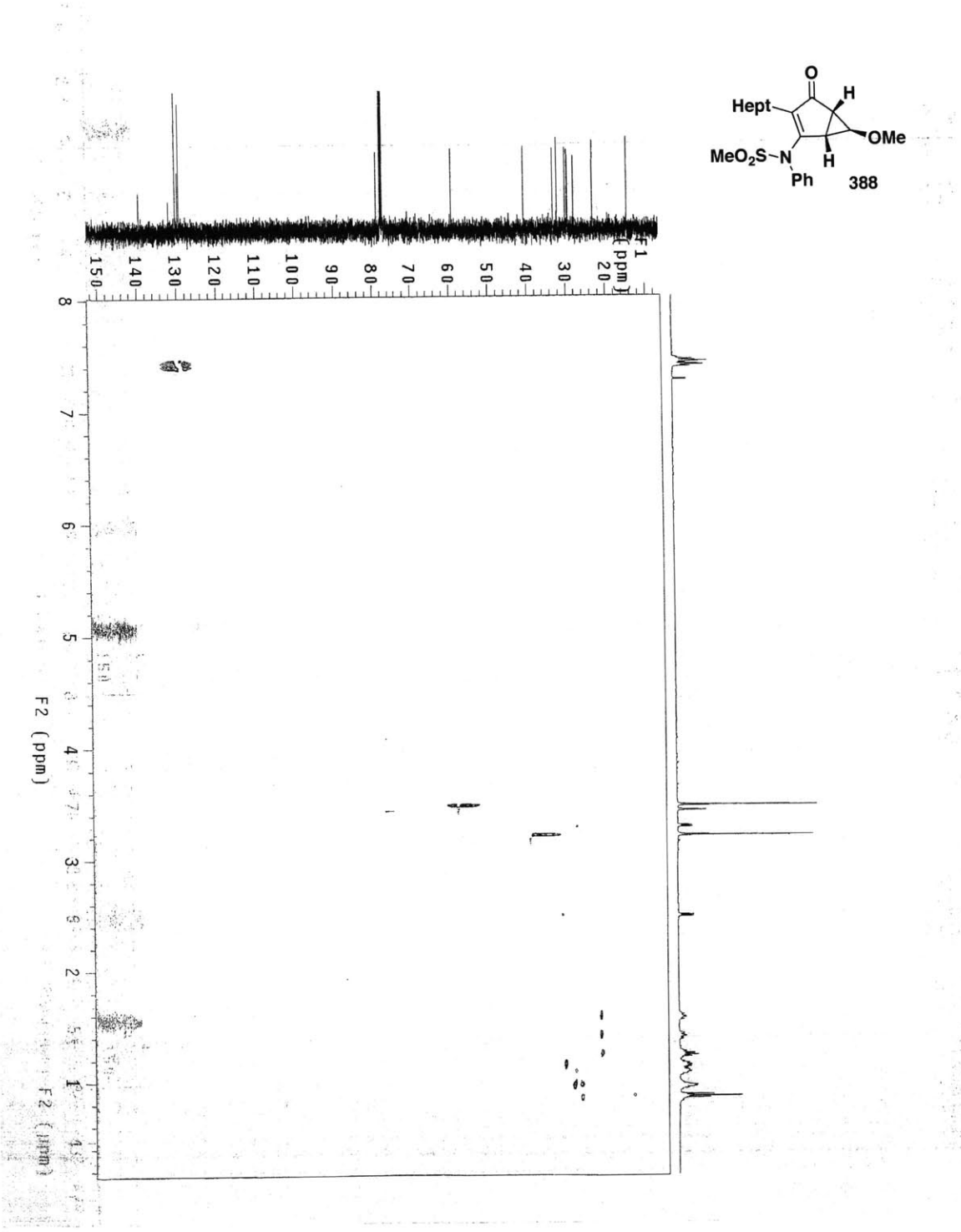
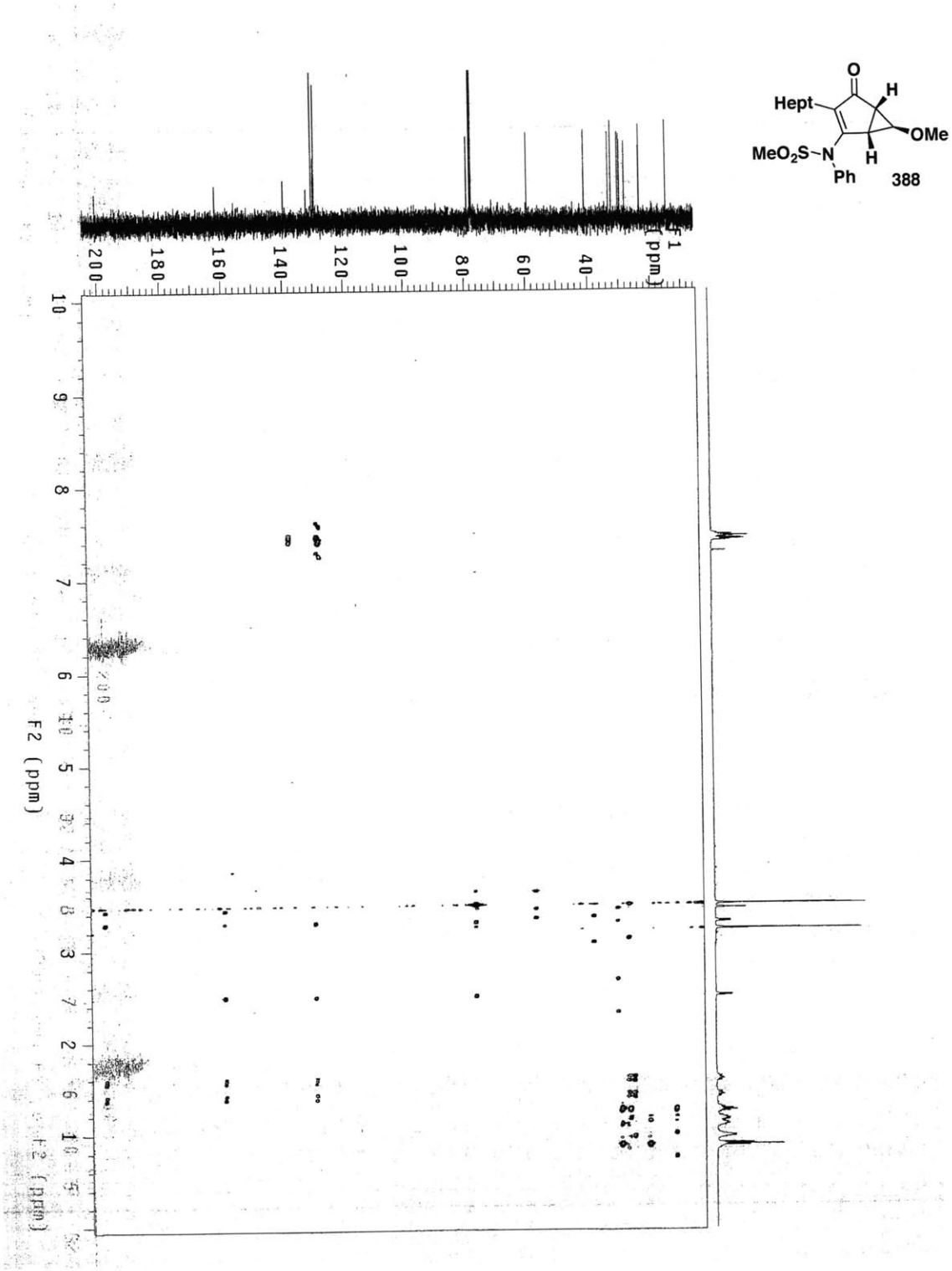
GCOSY

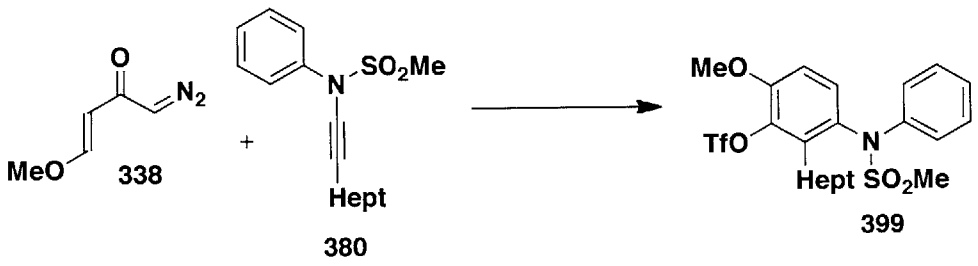


^{1}H, ^{13}C-HSQC



^{1}H, ^{13}C-HMBC

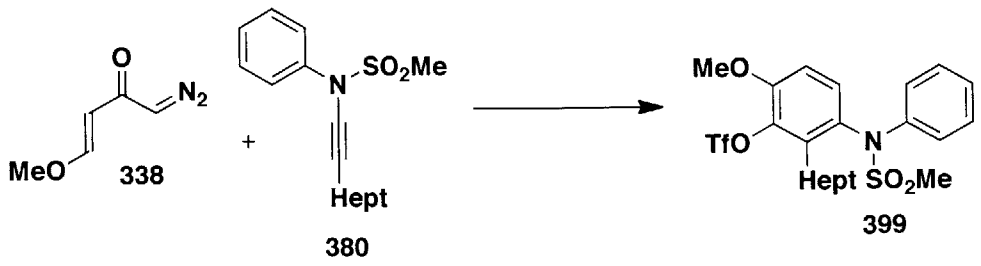




2-Heptyl-6-methoxy-3-(*N*-phenylmethylsulfonamido)phenyl trifluoromethanesulfonate (399). A solution of diazo ketone **338** (0.062 g, 0.491 mmol, 0.5 equiv) and ynamide **380** (1.16 g, 3.96 mmol, 4.0 equiv) in 25 mL of toluene was partitioned evenly between two 20-cm quartz tubes (10 mm I.D., 12 mm O.D.) fitted with rubber septa. Each solution was degassed with a stream of argon for 15 min and then positioned ca. 20 cm from a Hanovia 450W lamp (quartz immersion well, cooled by recirculating tap water) and irradiated under argon at 25 °C for 21 h. A second portion of diazo ketone **338** (0.062 g, 0.245 mmol per tube for a total of 0.124 g, 0.983 mmol) was added, the reaction flasks were again degassed with a stream of argon for 15 min, and then irradiated for another 23 h. The resulting solutions were transferred to a 100-mL round-bottomed flask with the aid of two 1-mL portions of toluene per tube. The flask was equipped with a stir bar and cold-finger condenser, and the reaction mixture was heated at reflux for 12 h. The resulting mixture was concentrated to afford 1.528 g of orange oil. Column chromatography on 140 g of silica gel (elution with 10-50% EtOAc-hexanes) provided 0.819 g (71%, 2.75 equiv) of ynamide **380** as an off-white solid and 0.257 g (67%) of ca. 90% pure phenol as an orange oil.

A 50-mL round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with phenol (0.257 g, 1.0 equiv), 4-DMAP (0.238 g, 1.95 mmol, 3.0 equiv), and 13 mL of CH_2Cl_2. The orange solution was cooled to 0 °C and triflic anhydride (0.17 mL, 1.01 mmol, 1.6 equiv) was added dropwise by syringe over ca. 3 min. The reaction mixture was allowed to warm to rt, stirred for 3 h, and then diluted with 25 mL of CH_2Cl_2 and washed with two 20-mL portions of 1 M HCl solution. The combined aqueous layers were extracted with 15 mL of CH_2Cl_2, and the combined organic layers were washed with 25 mL of satd aq $NaHCO_3$ solution and 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.401 g of orange oil. Column chromatography on 40 g of silica gel (elution with 25-35% EtOAc-hexanes) afforded 0.324 g (61% over two steps from the diazo ketone) of triflate **399** as a yellow oil: IR (neat) 2930, 2856, 1596, 1575, 1487, 1417, 1352, 1304, 1268, 1210, 1156, 1078, 999, 970, 874,

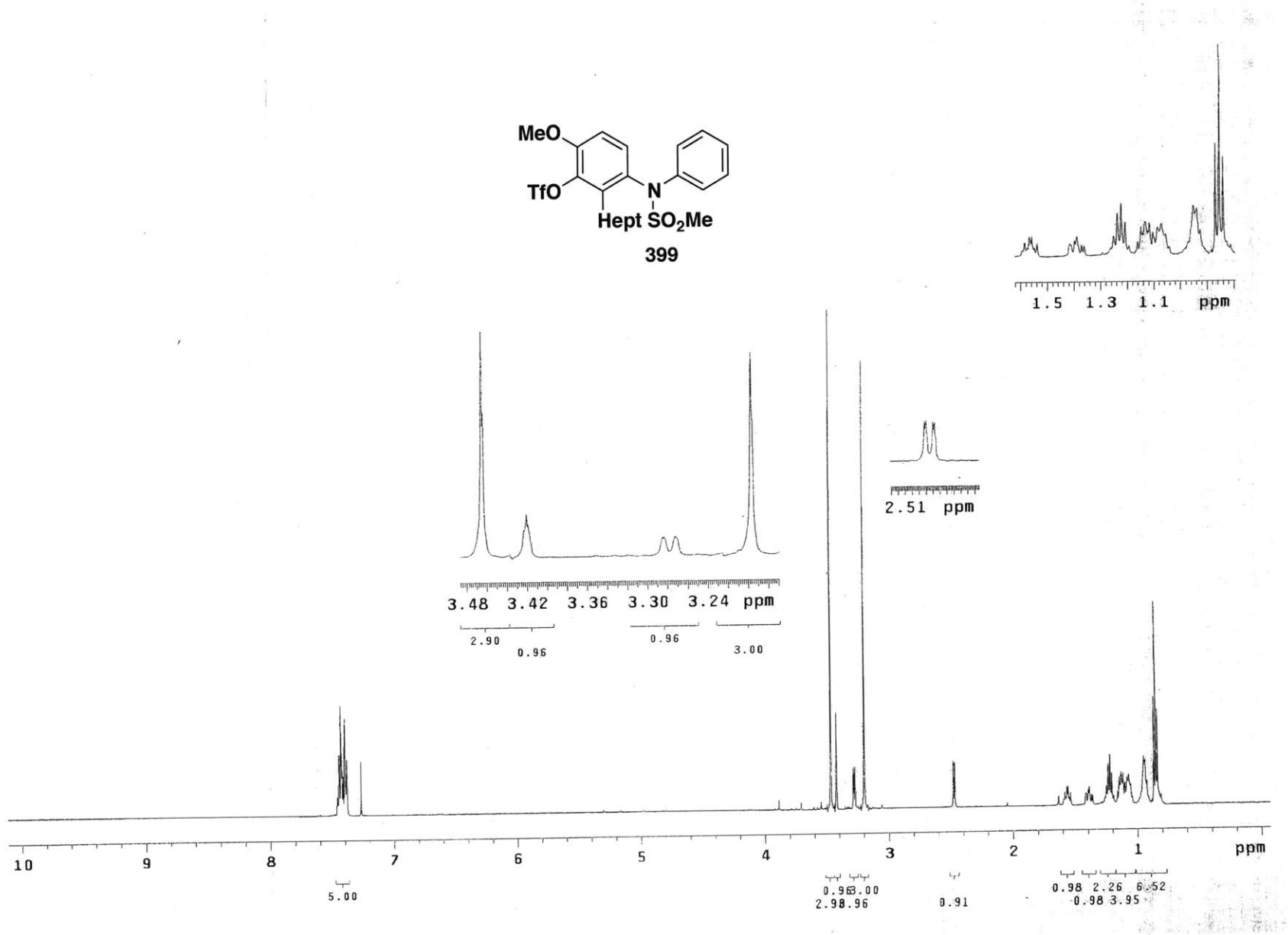
794, 762 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, J = 8.0 Hz, 1 H), 7.32-7.41 (m, 4 H), 7.22 (t, J = 8.0 Hz, 1 H), 6.96 (d, J = 9.0 Hz, 1 H), 3.94 (s, 3 H), 3.14 (s, 3 H), 2.63-2.80 (m, 2 H), 1.44-1.59 (m, 1 H), 1.16-1.34 (m, 8 H), 1.02-1.16 (m, 1 H), 0.87 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.7, 141.1, 138.6, 138.4, 132.0, 130.7, 129.7, 126.5, 124.7, 118.9 (q, J = 319 Hz), 110.3, 56.4, 40.1, 31.8, 30.2, 29.0, 29.0, 27.4, 22.8, 14.3; Anal. Calcd for $C_{22}H_{28}F_3NO_6S_2$: C, 50.47; H, 5.39; N, 2.68; Found: C, 50.61; H, 5.45; N, 2.68.



2-Heptyl-6-methoxy-3-(*N*-phenylmethylsulfonamido)phenyl trifluoromethanesulfonate (399). A 50-mL round-bottomed flask equipped with a condenser, rubber septum and argon inlet needle was charged with ynamide **380** (0.251 g, 0.855 mmol, 1.0 equiv) and 5.5 mL of toluene. A 25-mL pear flask fitted with a rubber septum and argon inlet needle was charged with diazo ketone **338** (0.270 g, 2.14 mmol, 2.5 equiv) and 8 mL of toluene. Both solutions were degassed with a stream of argon for 15 min. The solution of diazo ketone was taken up in a 10-mL glass syringe wrapped in aluminum foil and fitted with an 20-gauge, 20-cm long steel needle. The reaction mixture was heated at reflux and the diazo ketone solution was added through the condenser via syringe pump. After the addition was completed (ca. 14 h), the pear flask was rinsed with 0.5 mL of toluene and added with the same syringe in one portion to the reaction mixture. Heating was continued for 8 h. After cooling to rt, the reaction mixture was concentrated to afford 0.613 g of orange oil. Purification by column chromatography on 50 g of silica gel (elution with 30% EtOAc-hexanes) afforded 0.290 g (67%) of ca. 80% pure phenol as an orange solid.

A 50-mL pear flask equipped with a rubber septum and argon inlet needle was charged with phenol (0.290 g, 1.0 equiv), 4-DMAP (0.290 g, 2.37 mmol, 3.2 equiv), and 15 mL of CH_2Cl_2. The orange solution was cooled to 0 °C and triflic anhydride (0.20 mL, 1.19 mmol, 1.6 equiv) was added dropwise by syringe over ca. 5 min. The reaction mixture was allowed to warm to rt, stirred for 20 h, and then diluted with 30 mL of CH_2Cl_2 and washed with two 30-mL portions of 1 M HCl solution. The combined aqueous layers were extracted with 30 mL of CH_2Cl_2, and the combined organic layers were washed with 50 mL of satd aq $NaHCO_3$ solution and 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.370 g of orange oil. This material was dissolved in 25 mL of CH_2Cl_2 and concentrated onto 5 g of silica gel. The free-flowing powder was deposited on a column of 62 g of silica gel and eluted with 25-35%

EtOAc-hexanes to afford 0.260 g (58% over two steps from the diazo ketone) of triflate **399** as a yellow oil.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3.00
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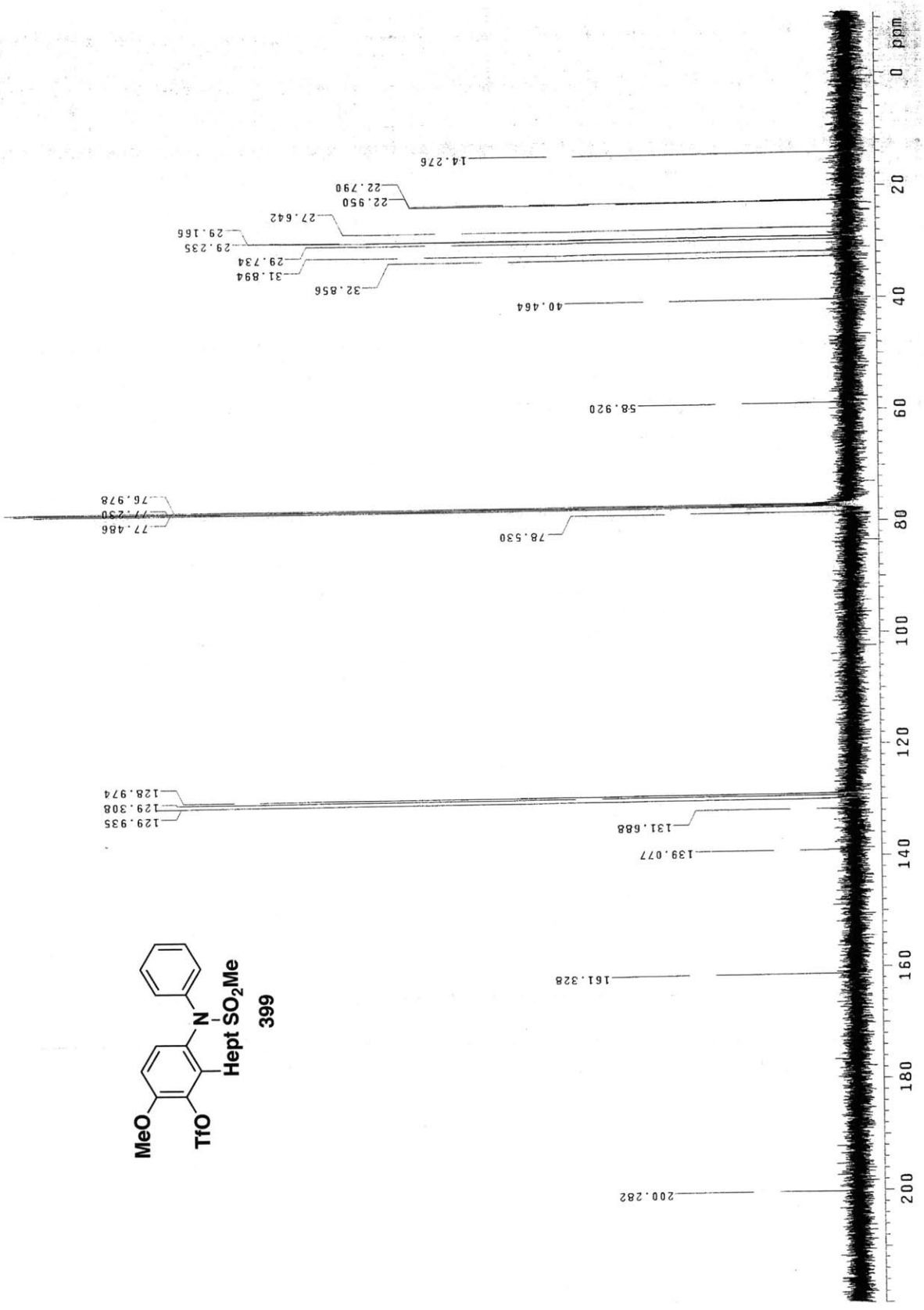
0.98 3.95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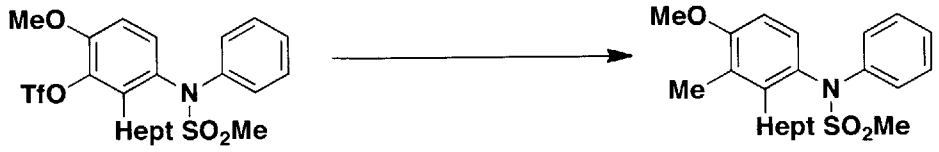
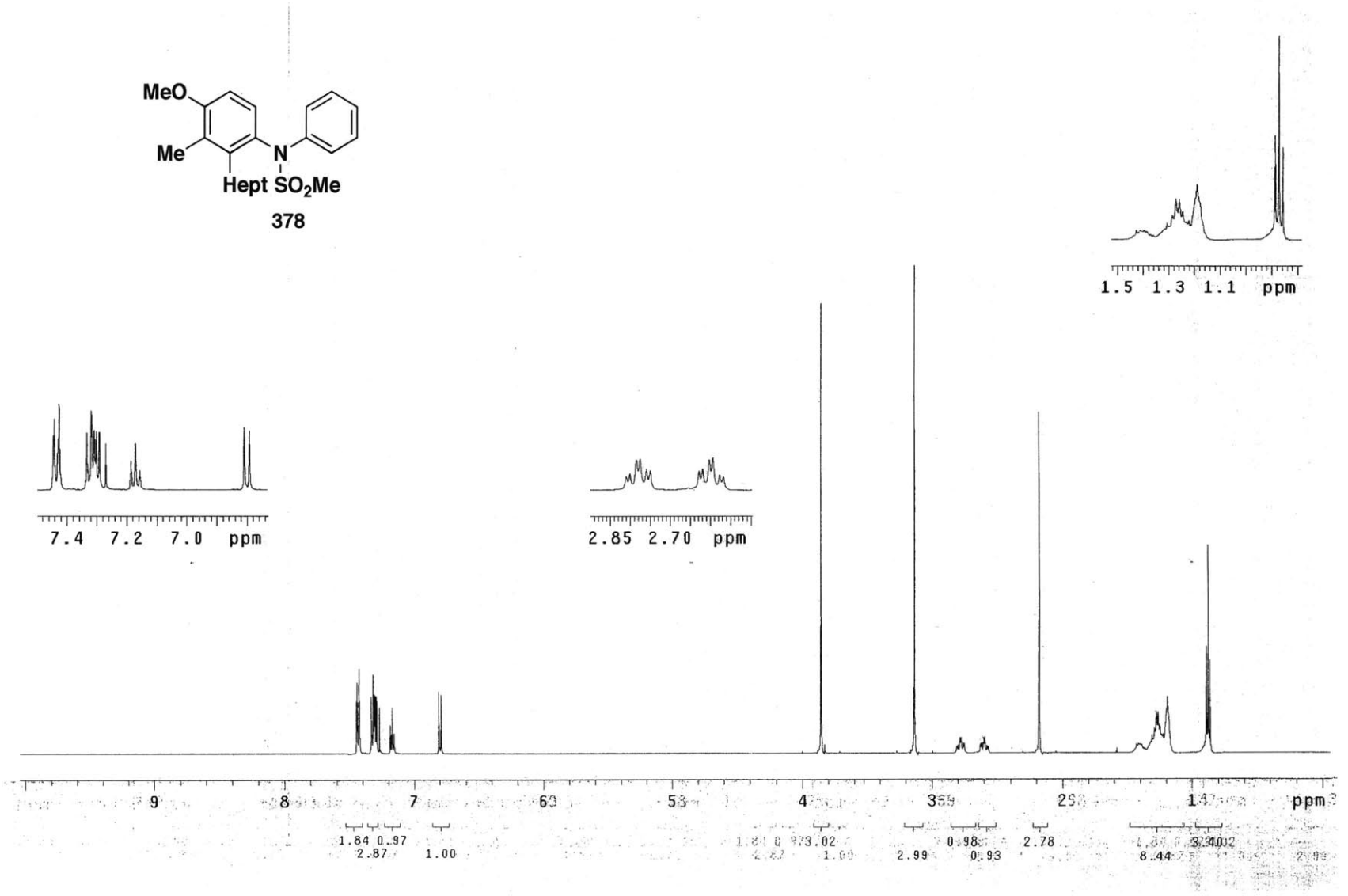
399

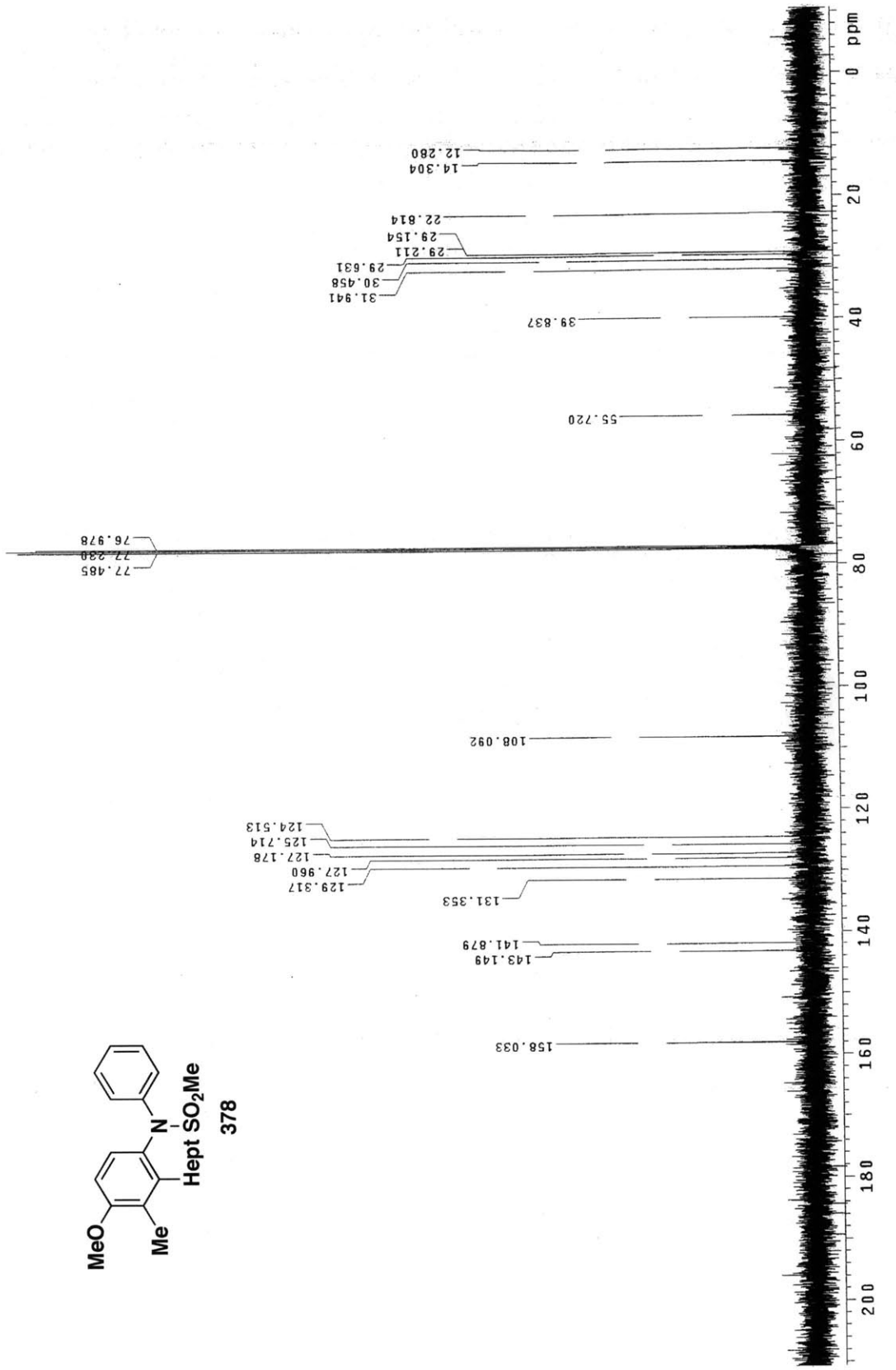


399 378

***N*-(2-Heptyl-4-methoxy-3-methylphenyl)-*N*-phenylmethanesulfonamide (378).** A 100-mL round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with triflate **399** (0.870 g, 1.65 mmol, 1.0 equiv), $Pd(OAc)_2$ (0.019 g, 0.09 mmol, 5 mol%), and SPhos (0.088 g, 0.21 mmol, 13 mol%). The tube was evacuated and backfilled with argon three times, and 9.2 mL of THF[219] and trimethylboroxine (0.28 mL, 0.251 g, 2.01 mmol, 1.2 equiv) were added. The tube was then charged with 10.0 mL of K_3PO_4 solution[5] (0.5 M in water, 4.95 mmol, 3.0 equiv) and heated at 30 °C for 23 h. The resulting red mixture was cooled to rt, diluted with 75 mL of Et_2O, and washed with 100 mL of H_2O. The aqueous layer was extracted with three 50-mL portions of Et_2O, and the combined organic phases were washed with 150 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.972 g of dark orange oil. Column chromatography on 65 g of silica gel (elution with 20% EtOAc-hexanes) furnished 0.619 g (96%) of sulfonamide **378** as a yellow oil: IR (neat) 2927, 2855, 1585, 1478, 1349, 1257, 1154, 1124, 1094, 968, 753, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 8.0 Hz, 2 H), 7.26-7.35 (m, 3 H), 7.17 (t, J = 7.5 Hz, 2 H), 6.80 (d, J = 8.5 Hz, 1 H), 3.86 (s, 3 H), 3.13 (s, 3 H), 2.78 (td, J = 12.5, 5 Hz, 1 H), 2.59 (td, J = 12.5, 5 Hz, 1 H), 2.17 (s, 3 H), 1.33-1.44 (m, 1 H), 1.13-1.34 (m, 9 H), 0.87 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0, 143.1, 141.9, 131.4, 129.3, 128.0, 127. 2, 125.7, 124.5, 108.1, 55.7, 39.8, 31.9, 30.5, 29.6, 29.2, 29.2, 22.8, 14.3, 12.3; Anal. Calcd for $C_{22}H_{31}NO_3S$: C, 67.83; H, 8.02; N, 3.60; Found: C, 67.75; H, 8.08; N, 3.55.

[219] The THF and K_3PO_4 solution were degassed (three freeze-pump-thaw cycles at -196 °C, 0.05 mmHg) prior to addition.


MeO
Me
N
Hept SO2Me
378
7.4 7.2 7.0 ppm
2.85 2.70 ppm
1.5 1.3 1.1 ppm
9
8
7
6
5
4
3
2
1
ppm
1.84 0.97
2.87
1.00
973.02
1.00
2.99
0.98
0.93
2.78
8.44


158.033
143.149
141.879
131.353
129.317
127.960
127.178
125.714
124.513
108.092
77.485
77.239
76.978
55.720
39.837
31.941
30.458
29.631
29.211
29.154
22.814
14.304
12.280
0 ppm
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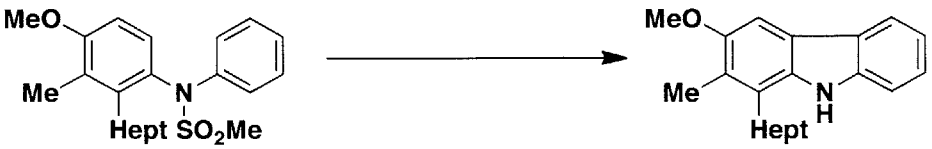
60
80
100
120
140
160
180
200
MeO
Me
N
Hept
SO2Me
378



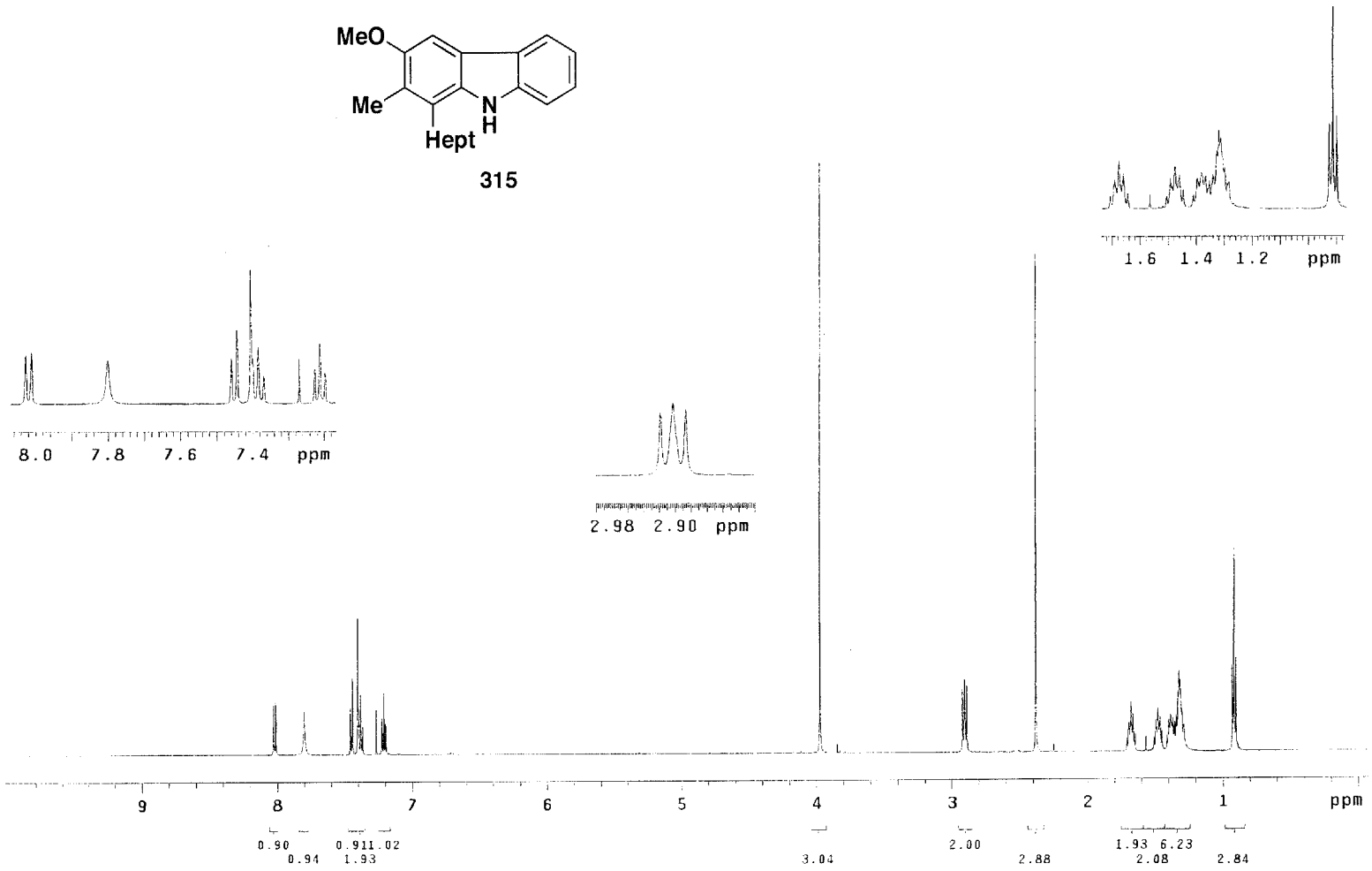
378 **315**

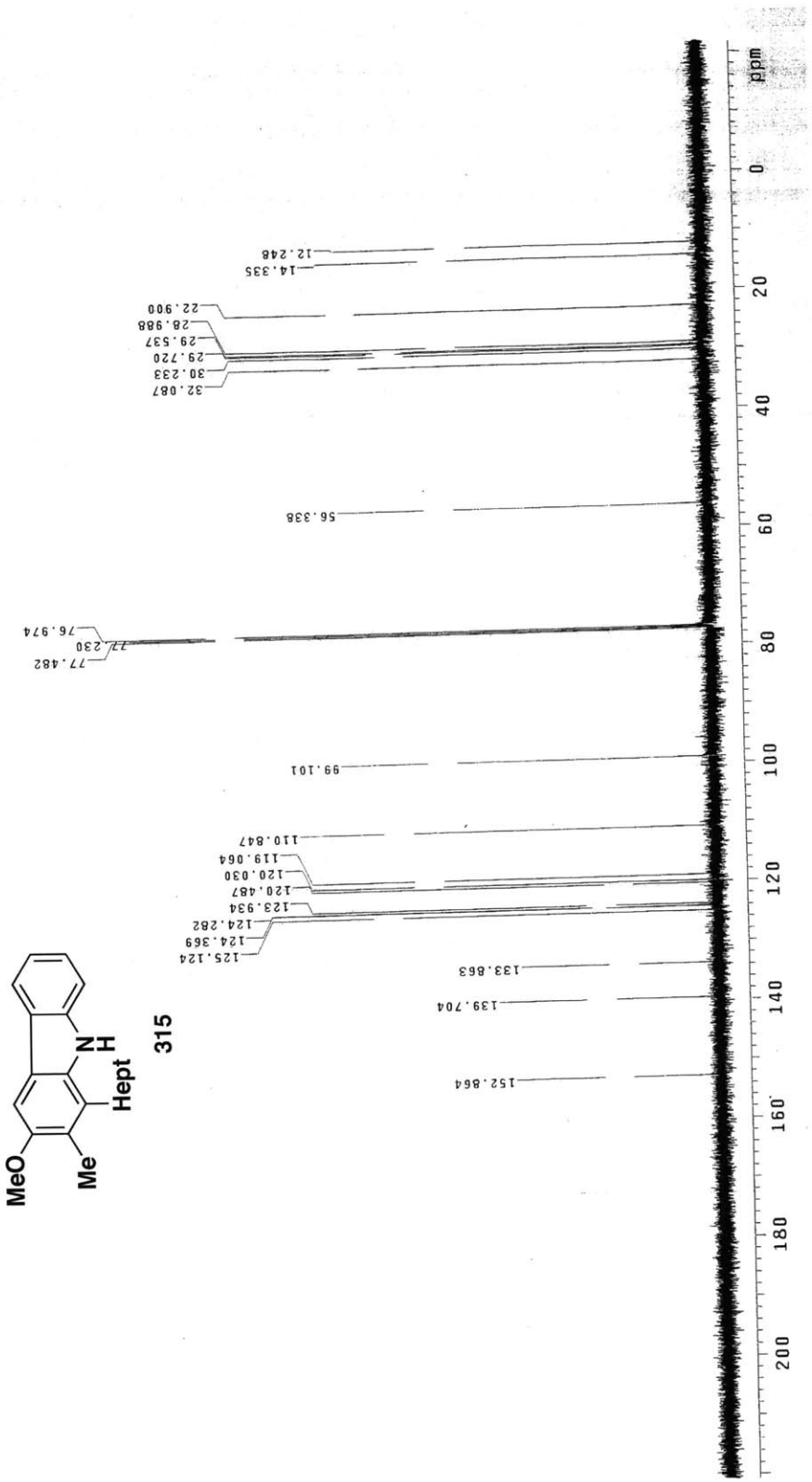
1-Heptyl-3-methoxy-2-methyl-9*H*-carbazole (315). FEP tubing (ca. 50-ft length, 0.030 in. I.D., 0.0625 in. O.D., total internal volume ca. 6.3 mL) was wrapped around a quartz immersion well surrounding a water-jacketed, 450W Hanovia lamp equipped with a Pyrex filter and cooled by recirculating tap water. The top end of the tubing was fitted with a nut, a ferrule, and a thread to female Luer adapter. Approximately 2.5 ft of tubing was left at either end so that the length wrapped around the well was ca. 45 ft. The bottom end of the tubing was connected through a rubber septum to a 500-mL round-bottomed flask equipped with an argon inlet needle and a needle vent.[220] The tubing was flushed with 10 mL of degassed EtOH, and then the lamp was turned on and degassed EtOH was pumped through the tubing for 5 min at a rate of 1.1 mL/min by syringe pump.

A 100-mL pear flask equipped with a rubber septum and argon inlet needle was charged with diaryl sulfonamide **378** (0.590 g, 1.51 mmol, 1.0 equiv), triethylamine (0.43 mL, 3.09 mmol, 2.0 equiv), and 108 mL of EtOH. The reaction mixture was degassed for 20 min with a stream of argon then pumped via syringe pump[221] through the tubing at a rate of 1.1 mL/min and collected in the 500-mL round-bottomed flask. Once the addition was complete, 10 mL of degassed EtOH was pumped through the tubing at a rate of 1.1 mL/min. The resulting orange solution was concentrated to yield 1.5 g of an orange oil which was diluted with 100 mL of Et_2O, and washed with four 50-mL portions of 1 M HCl. The combined aqueous layers were extracted with two 75-mL portions of Et_2O and the combined organic layers were washed with 200 mL of satd aq $NaHCO_3$ solution, 200 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.549 g of orange oil. This material was dissolved in 25 mL of CH_2Cl_2 and concentrated onto 5 g of silica gel. The free-flowing powder was deposited on a column of 80 g of silica gel and eluted with 35% toluene-hexanes to afford 0.209 g (45%) of carbazole **315** as a off-white solid: mp 100-102 °C; IR (neat) 3420, 2925, 2855, 1584, 1494, 1452, 1427, 1308, 1256, 1209, 1146, 1112, 1096, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 7.5 Hz, 1 H), 7.80 (s, 1 H), 7.45 (d, J = 8.0 Hz, 1 H), 7.41 (s, 1 H), 7.40 (t, J = 7.5 Hz, 1 H), 7.21 (t, J = 7.5 Hz, 1 H),

[220] For a more complete description of the construction of the continuous-flow reactor see pages 46-47 of this thesis.
[221] Addition in six 18-mL portions via a 24-mL NORM-JECT® plastic syringe

3.97 (s, 3 H), 2.90 (t, J = 8.0 Hz, 2 H), 2.36 (s, 3 H), 1.66 (quint, J = 8.0 Hz, 2 H), 1.46 (quint, J = 7.0 Hz, 2 H), 1.27-1.43 (m, 6 H), 0.91 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 139.7, 133.9, 125.1, 124.4, 124.3, 123.9, 120.5, 120.0, 119.1, 110.8, 99.1, 56.3, 32.1, 30.2, 29.7, 29.5, 29.0, 22.9, 14.3, 12.2; Anal. Calcd for $C_{21}H_{27}NO$: C, 81.51; H, 8.79; N, 4.53; Found: C, 81.38; H, 8.80; N, 4.49.


MeO
Me
N
H
Hept
315
8.0 7.8 7.6 7.4 ppm
2.98 2.90 ppm
1.6 1.4 1.2 ppm
9 8 7 6 5 4 3 2 1 ppm
0.90 0.94 0.91 1.93 1.02
3.04
2.00 2.88
1.93 2.08 6.23 2.84


315
MeO
Me
Hept
N
H
ppm
0
20
40
60
80
100
120
140
160
180
200
12.248
14.335
22.900
28.988
29.537
29.720
30.233
32.087
56.338
76.974
77.230
77.482
99.101
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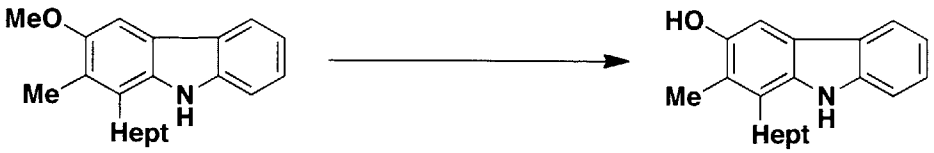
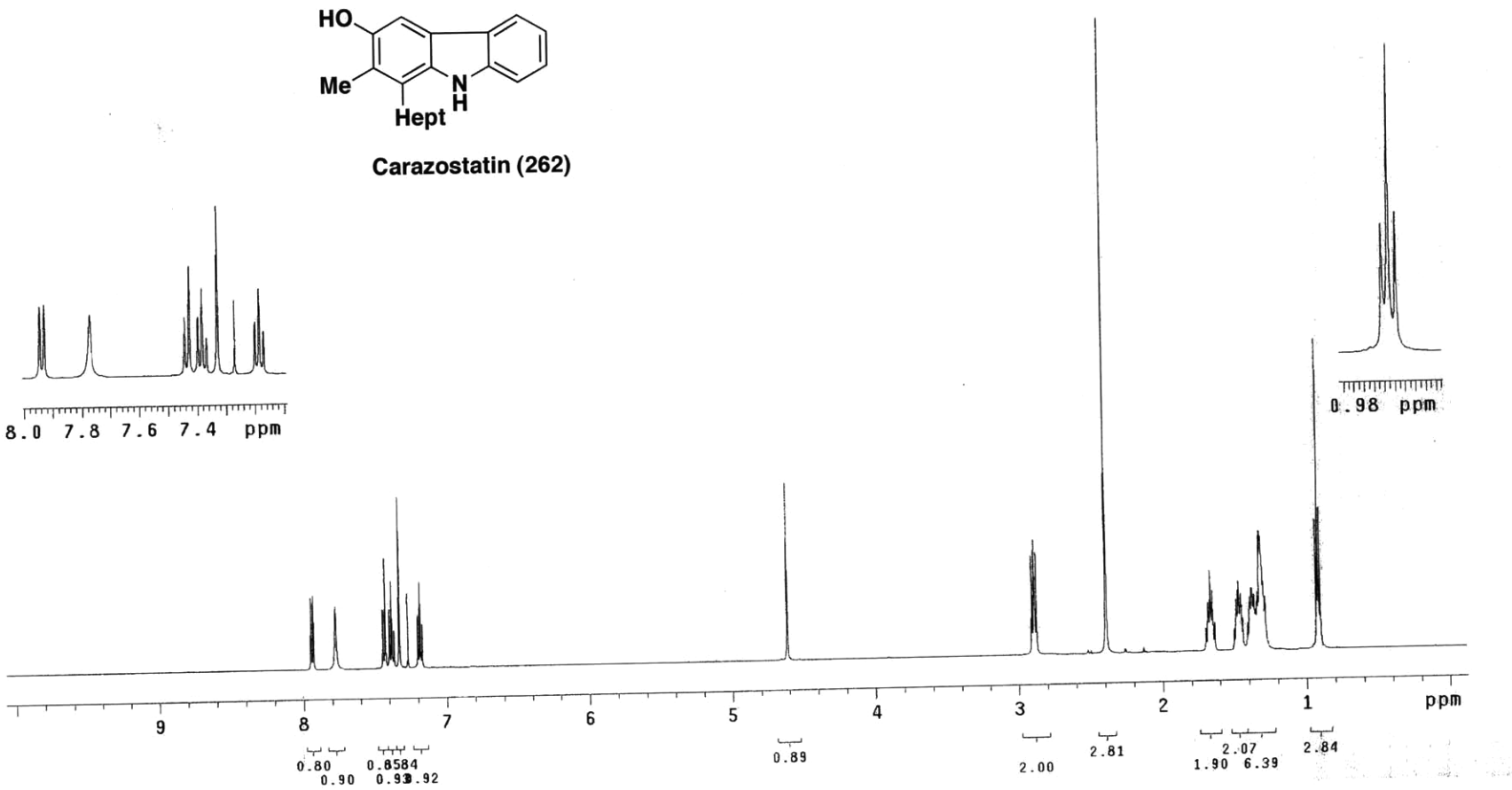
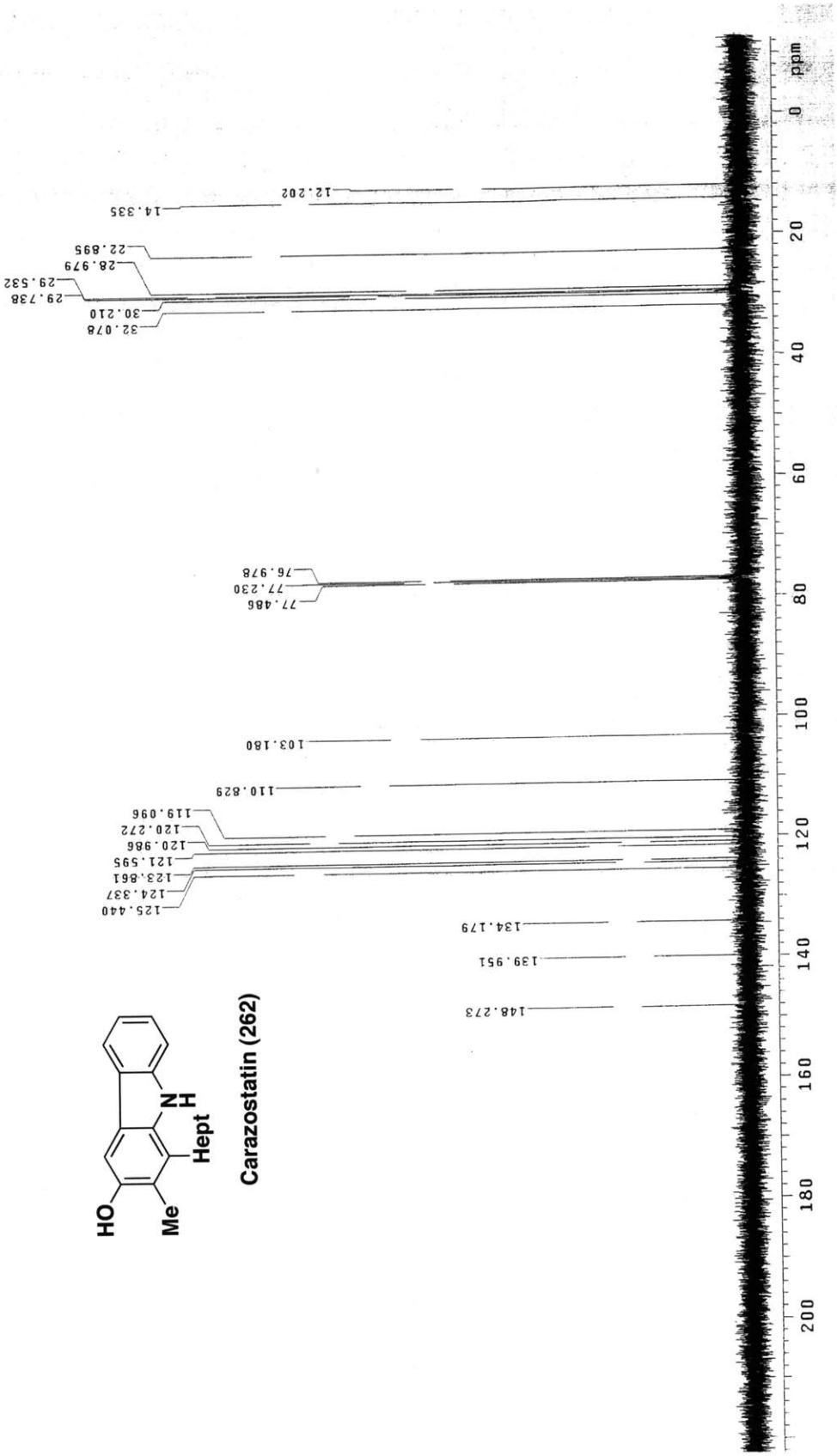
120.030
120.487
123.934
124.282
124.369
125.124
133.863
139.704
152.864



315 Carazostatin (262)

1-Heptyl-2-methyl-9*H*-carbazol-3-ol (Carazostatin) (362). A 100-mL, recovery flask equipped with a rubber septum and argon inlet needle was charged with carbazole **315** (0.207 g, 0.699 mmol, 1.0 equiv) and 13 mL of CH_2Cl_2. The solution was cooled to -78 °C and BBr_3 (1.0 M in CH_2Cl_2, 1.5 mL, 1.47 mmol, 2.2 equiv) was added dropwise over 15 min. The reaction mixture was allowed to warm to rt, stirred for 3.5 h, and then quenched with 30 mL of water. The aqueous layer was washed with two 30-mL portions of EtOAc, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give 0.209 g of a tan solid. Column chromatography on 30 g of silica gel (elution with 15% EtOAc-hexanes) provided 0.183 g (92%) of carazostatin **(262)** as a white solid: mp 156-158 °C; IR (neat) 3473 (broad), 3416, 2923, 2854, 1589, 1497, 1461, 1438, 1310, 1259, 1231, 1145, 1061, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, J = 7.5 Hz, 1H), 7.77 (br s, 1 H), 7.43 (d, J =8.0 Hz, 1H), 7.38 (t, J = 7.5 Hz, 1 H), 7.33 (s, 1 H), 7.17 (t, J = 7.5 Hz, 1H), 4.61 (s, 1 H), 2.89 (t, J = 7.5 Hz, 2 H), 2.39 (s, 3 H), 1.62-1.71 (m, 2 H), 1.51-1.42 (m, 2 H), 1.42-1.26 (m, 6 H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 140.0, 134.2, 125.4, 124.3, 123.9, 121.6, 121.0, 120.3, 119.1, 110.8, 103.2, 32.1, 30.2, 29.7, 29.5, 29.0, 22.9, 14.3, 12.2; Anal. Calcd for $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74; Found: C, 81.52; H, 8.46; N, 4.78.


HO
Me
N
H
Hept
Carazostatin (262)
8.0 7.8 7.6 7.4 ppm
0.98 ppm
9 8 7 6 5 4 3 2 1 ppm
0.80
0.90
0.89
2.00
2.81
1.90
2.07
6.39
2.84

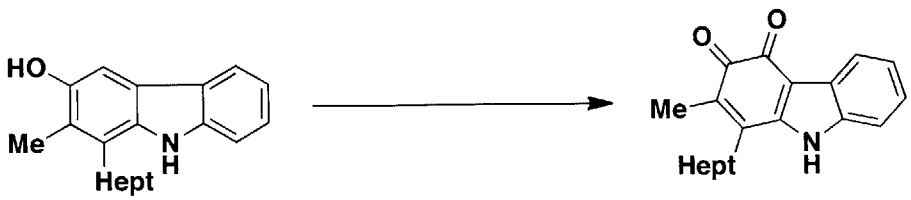

148.273
139.951
134.179
125.440
124.337
123.861
121.595
120.986
120.272
119.096
110.829
103.180
77.486
77.230
76.978
32.078
30.210
29.738
29.532
28.979
22.895
14.335
12.202
ppm
0
20
40
60
80
100
120
140
160
180
200
Carazostatin (262)
HO
Me
Hept
N
H

^{1}H NMR $CDCl_3$

Our Synthetic Carazostatin	Natural Carazostatin (ref 136)
7.94 (d, J = 7.5 Hz, 1H)	7.91 (dd, J = 8.0, 1.5 Hz, 1H)
7.77 (br s, 1H)	7.77 (br s, 1H)
7.43 (d, J = 8.0 Hz, 1H)	7.42 (dd, J = 8.0, 1.5 Hz, 1H)
7.38 (app t, J = 7.5 Hz, 1H)	7.37 (ddd, J = 8.0, 8.0, 1.5 Hz, 1H)
7.33 (s, 1H)	7.31 (s, 1H)
7.17 (app t, J = 7.5 Hz, 1H)	7.17 (ddd, J = 8.0, 8.0, 1.5 Hz, 1H)
4.61 (br s, 1H)	4.72 (br s, 1H)
2.89 (t, J = 7.5 Hz, 2H)	2.87 (t, J = 7.9 Hz, 2H)
2.39 (s, 3H)	2.38 (s, 3H)
1.62-1.71 (m, 2H)	1.65 (m, 2H)
1.51-1.42 (m, 2H)	1.30-1.46 (m, 8H)
1.42-1.26 (m, 6H)	
0.91 (t, J = 7.0 Hz, 3H)	0.91 (t, J = 7.0 Hz, 3H)

^{13}C NMR $CDCl_3$

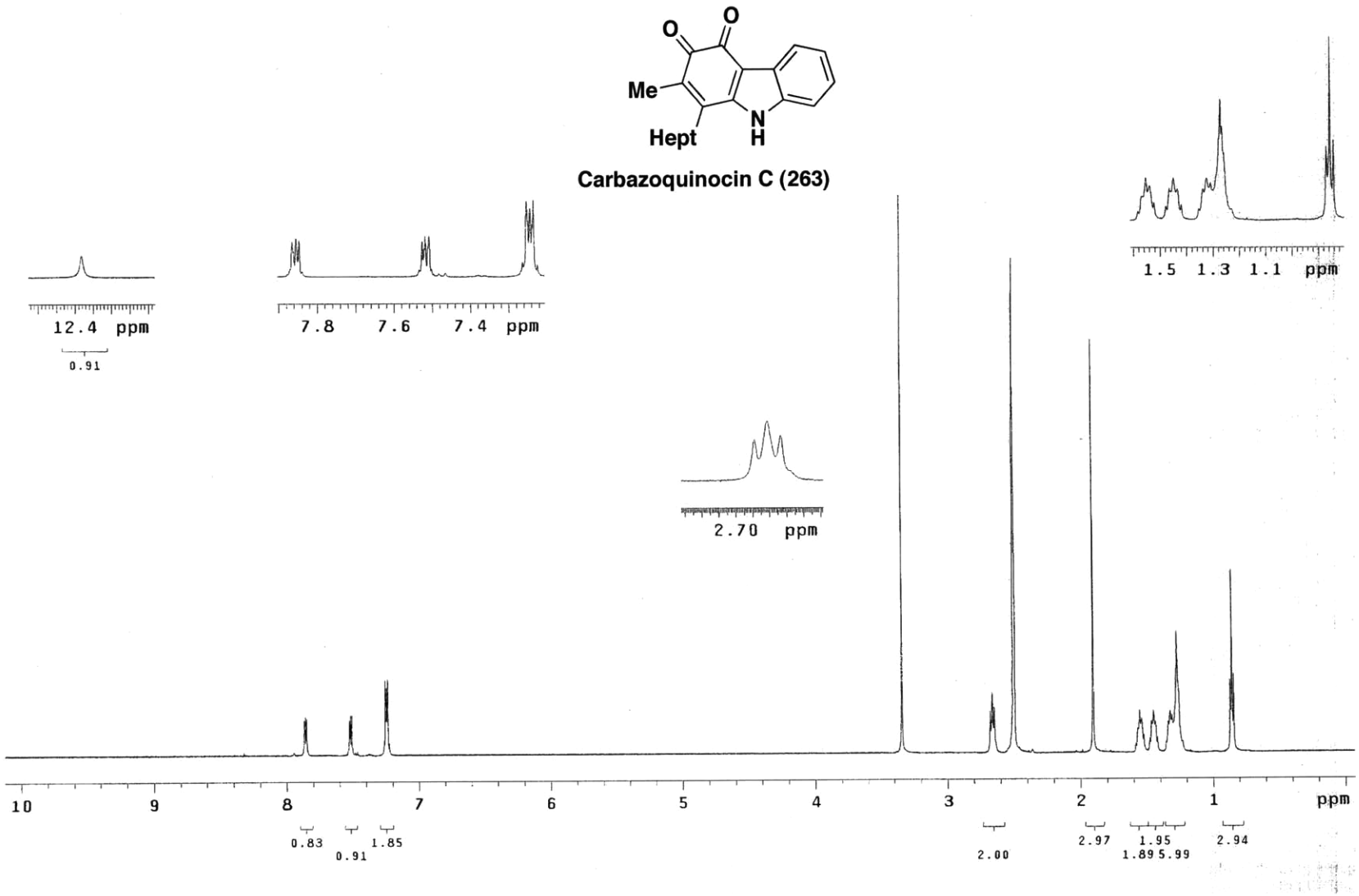
Our Synthetic Carazostatin	Natural Carazostatin (ref 136)
148.3	148.2
139.9	139.8
134.2	134.0
125.4	125.2
124.3	124.1
123.9	123.7
121.6	121.4
121.0	120.9
120.3	120.0
119.1	118.9
110.8	110.6
103.2	103.0
32.1	31.7
30.2	30.0
29.7	29.5
29.5	29.3
29.0	28.8
22.9	22.7
14.3	14.1
12.2	12.0

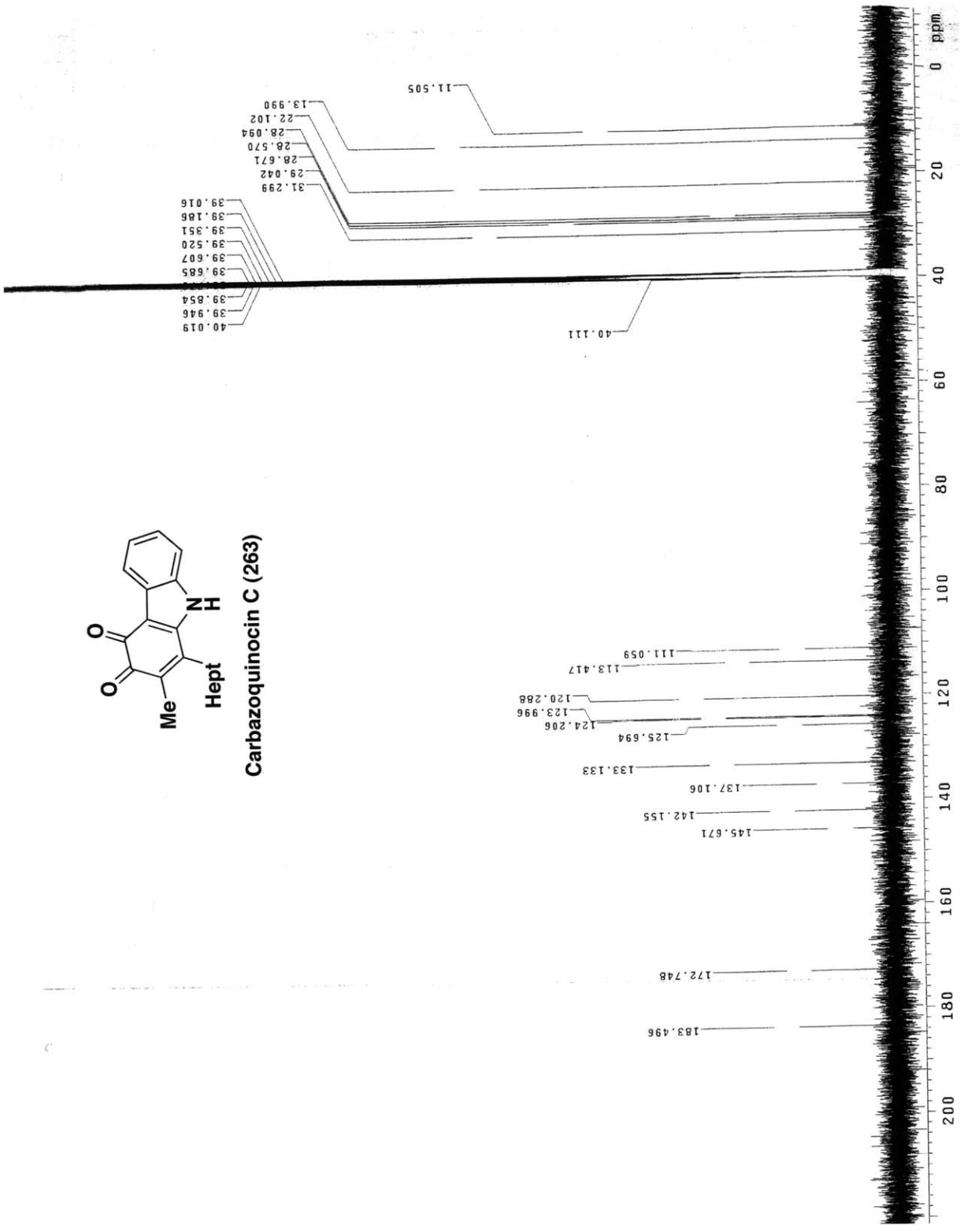


Carazostatin (262)

Carbazoquinocin C (263)

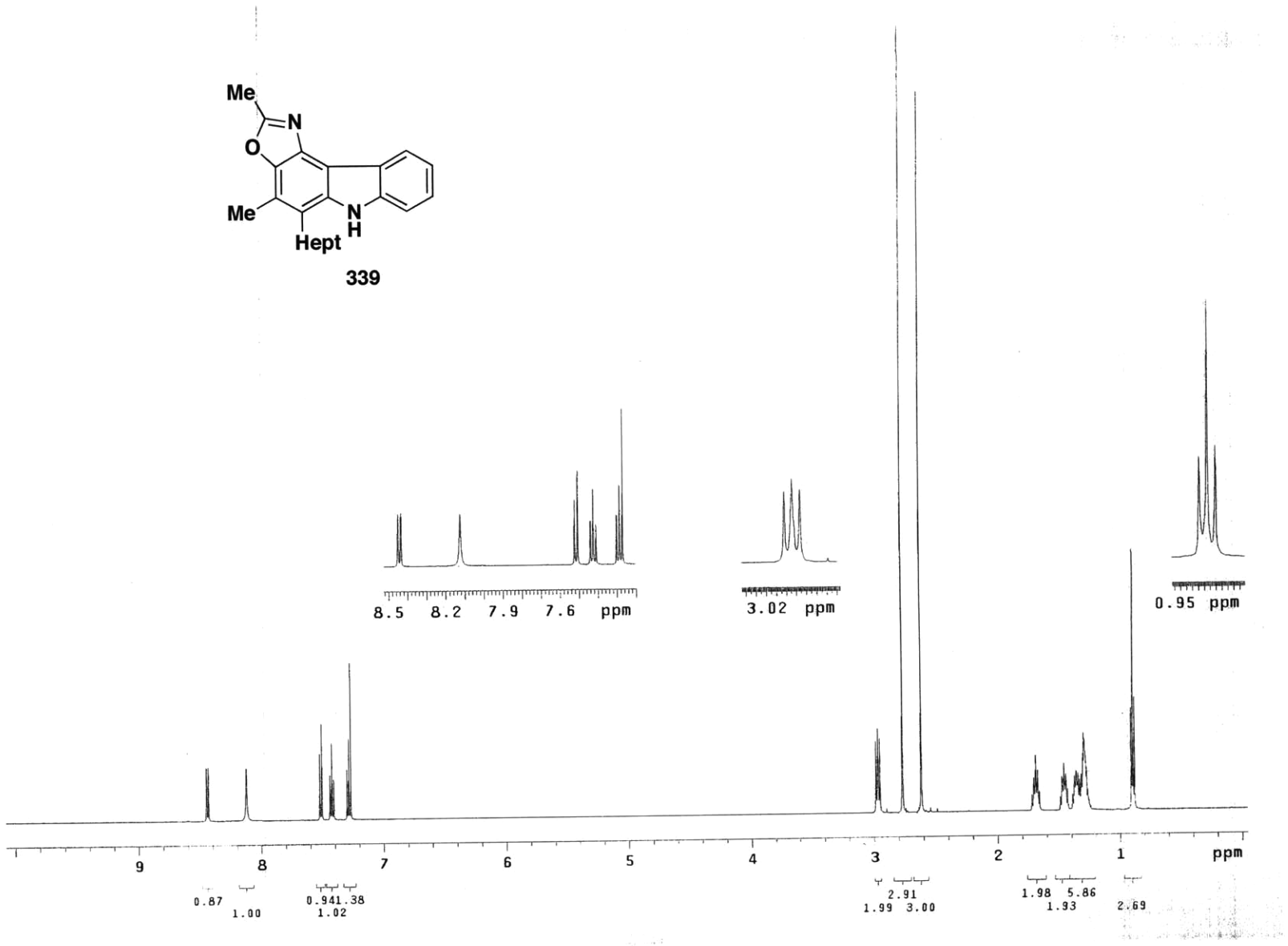
1-Heptyl-2-methyl-3H-carbazole-3,4(9H)-dione (Carbazoquinocin C) (263). A 25-mL recovery flask equipped with a rubber septum and argon inlet needle was charged with $(PhSeO)_2O$ (0.089 g, 0.247 mmol, 1.1 equiv) and 4.4 mL of THF. A solution of carazostatin (**262**) (0.068 g, 0.230 mmol, 1.0 equiv) in 4 mL of THF was added and the resulting dark red solution was heated at 50 °C for 30 min. The mixture was then cooled to rt and poured into 10 mL of MeOH and 90 mL of $CHCl_3$. The resulting solution was washed with two 50-mL portions of sat aq Na_2CO_3, 50 mL of water, 50 mL of brine, dried over Na_2SO_4, filtered and concentrated onto 3 g of silica gel. The free-flowing powder was deposited on a column of 39 g of silica gel and eluted with 25-100% EtOAc-hexanes to afford 0.064 g (90%) of carbazoquinocin C (**263**) as dark green solid: mp 211-213 °C; IR (KBr) 3214 (broad), 2958, 2926, 2855, 1637, 1625, 1466, 1249, 752 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 12.63 (br s, 1 H), 7.83-7.88 (m, 1 H), 7.49-7.55 (m, 1 H), 7.21-7.28 (m, 2 H), 2.66 (t, J = 7.5 Hz, 2 H), 1.91 (s, 3 H), 1.50-1.60 (m, 2 H), 1.41-1.49 (m, 2 H), 1.21-1.37 (m, 6 H), 0.86 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.5, 172.7, 145.7, 142.2, 137.1, 133.1, 125.7, 124.2, 124.0, 120.3, 113.4, 111.1, 31.3, 29.0, 28.7, 28.6, 28.1, 22.1, 14.0, 11.5; HRMS-ESI (*m/z*) [M + H] calculated for $C_{20}H_{23}NO_2$, 310.1802; found 310.1806.

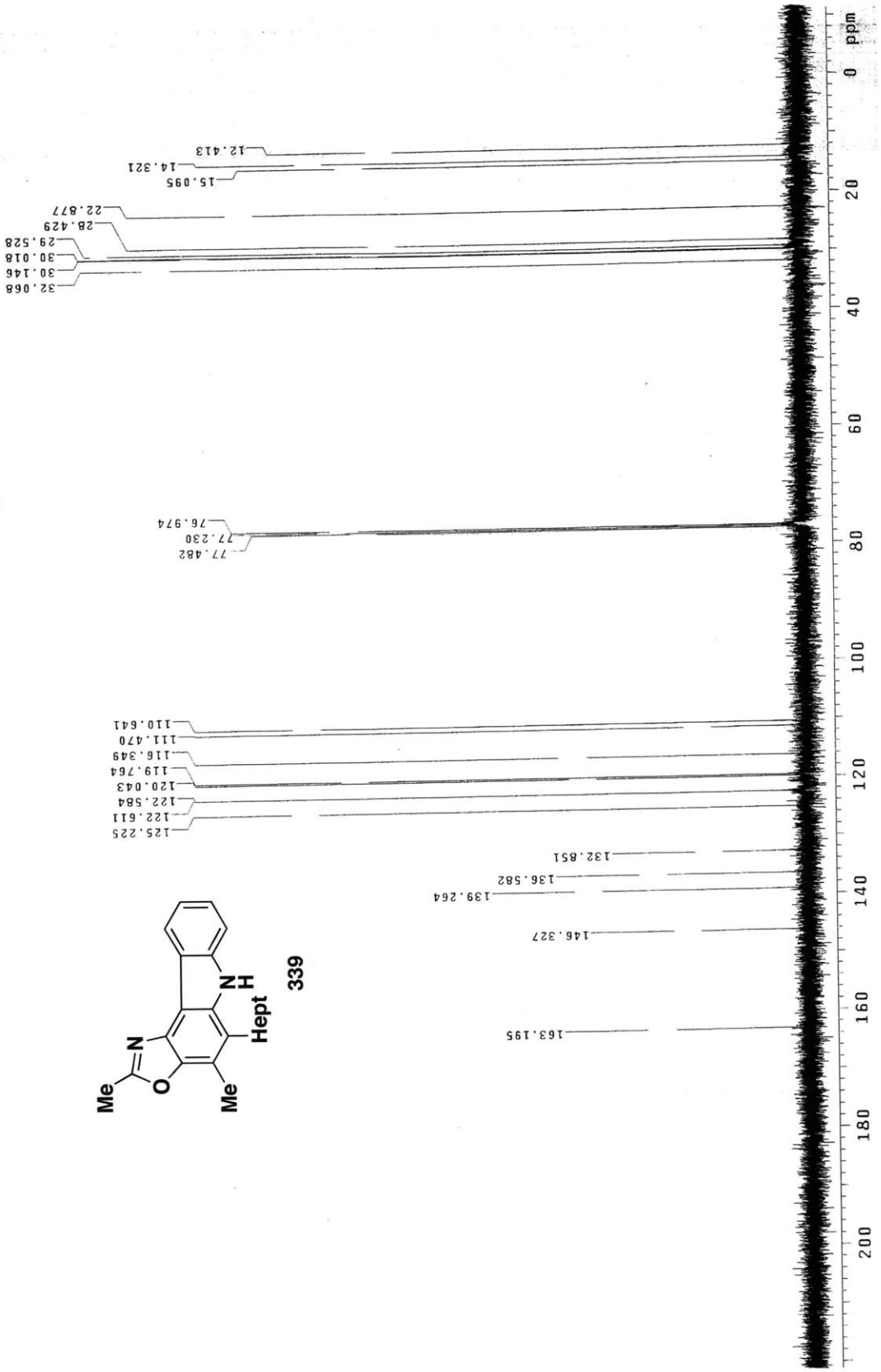

O
O
Me
N
H
Hept
Carbazoquinocin C (263)
12.4 ppm
0.91
7.8 7.6 7.4 ppm
2.70 ppm
1.5 1.3 1.1 ppm
10 9 8 7 6 5 4 3 2 1 ppm
0.83 0.91 1.85
2.00
2.97
1.89 1.95 5.99
2.94


Carbazoquinocin C (263)
Me
Hept
O
O
N
H
11.505
13.990
22.102
28.094
28.570
28.671
29.042
31.299
39.016
39.186
39.351
39.520
39.607
39.685
39.854
39.946
40.019
40.111
111.059
113.417
120.288
123.996
124.206
125.694
133.133
137.106
142.155
145.671
172.748
183.496
ppm
0
20
40
60
80
100
120
140
160
180
200

Carazostatin (262) 339

5-Heptyl-2,4-dimethyl-6*H*-oxazolo[5,4-*c*]carbazole (339). A 100-mL, three-necked round-bottomed flask equipped with a rubber septum, glass stopper, and argon inlet adapter was charged with carazostatin (**262**) (0.183 g, 0.619 mmol, 1.0 equiv), $EtNH_2$ (2.0 M in THF, 0.93 mL, 1.86 mmol, 3.0 equiv), and 21 mL of THF. The solution was cooled to 0 °C, and 3.66 g of manganese (IV) dioxide (20 wt equiv) was added in two portions over 5 min. The reaction mixture was allowed to warm to rt, stirred for 17 h, and then filtered through a ca. 4-g plug of Celite with the aid of five 40-mL portions of Et_2O. Concentration yielded ca. 0.230 g of red oil. Column chromatography on 30 g of silica gel (elution with CH_2Cl_2) provided 0.146 g (71%) of oxazole **339** as a tan solid: mp 152-154 °C; IR (neat) 3218 (broad), 2926, 2855, 1617, 1569, 1460, 1384, 1304, 1234, 1176 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.44 (d, J = 7.0 Hz, 1 H), 8.17 (br s, 1 H), 7.51 (d, J = 8.0 Hz, 1 H), 7.42 (td, J = 8.0, 1.0 Hz, 1 H), 7.28 (t, J = 8.0 Hz, 1 H), 2.96 (t, J = 8.0 Hz, 2 H), 2.77 (s, 3 H), 2.62 (s, 3 H), 1.65-1.74 (m, 2 H), 1.41-1.49 (m, 2 H), 1.23-1.40 (m, 6 H), 0.89 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2, 146.3, 139.3, 136.6, 132.9, 125.2, 122.6, 122.6, 120.0, 119.8, 116.3, 111.5, 110.6, 32.1, 30.1, 30.0, 29.5, 28.4, 22.9, 15.1, 14.3, 12.4; HRMS-ESI (*m/z*) [M + H] calculated for $C_{22}H_{26}N_2O$, 335.2118; found 335.2103.


Me
N
O
Me
N
H
Hept
339
8.5 8.2 7.9 7.6 ppm
3.02 ppm
0.95 ppm
9 8 7 6 5 4 3 2 1 ppm
0.87 1.00 0.94 1.38 1.02 2.91 1.99 3.00 1.98 5.86 1.93 2.69


12.413
14.321
15.095
22.877
28.429
29.528
30.018
30.146
32.068
76.974
77.230
77.482
110.641
111.470
116.349
119.764
120.043
122.584
122.611
125.225
132.851
136.582
139.264
146.327
163.195
Me
O
N
Me
Hept
N
H
339
ppm
0
20
40
60
80
100
120
140
160
180
200