PROGRESS TOWARDS THE SYNTHESIS OF TETRACYCLIC HETEROAROAROMATIC COMPOUNDS VIA TANDEM BENZANNULATION-CYCLIZATION STRATEGIES

By

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December 1, 2011

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ABSTRACT

A tandem benzannulation-cyclization strategy was successfully applied to the synthesis of a tetracyclic heteroaromatic compound expected to have interesting electronic properties. Benzannulation of a diazo ketone and a ynamide yielded a highly substituted aniline that was cyclized to indole according to protocols developed in our laboratory previously.

Thesis Supervisor: Rick L. Danheiser

Title: Arthur C. Cope Professor of Chemistry

Table of Contents

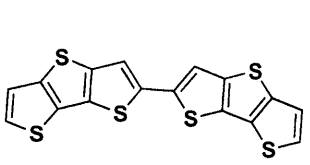
Part I

Introduction and Background

Chapter 1

Strategies for the Synthesis of Conjugated Tetracyclic Aromatic Compounds with Enhanced π-Electron Delocalization

Oligomeric compounds consisting of multiple aromatic moieties, such as compound **1,** feature very good π-electron delocalization. This property makes such compounds attractive for use as organic semiconductors in the manufacture of field-effect transistors, [1] light emitting diodes, [2] and photovoltaic cells. [3] Therefore, they have been the subject of increased interest from the research community over the past few decades. Compounds in which the aromatic units are joined around a central benzenoid core, such as **2**, have experienced surging interest as well, because they too possess very good, if not superior, π-electron delocalization in comparison with their linear derivatives. [4]



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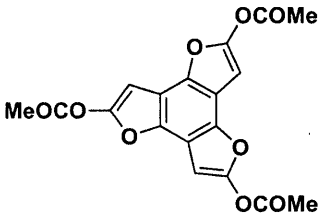

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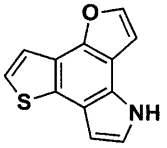

3

We became interested in synthesizing compound **3**, which we believed would have very interesting π-electron delocalization and electronic properties due to the

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[1] (a) Dimitrakopoulos, C. D.; Malenfant, P. *Adv. Mater.* **2002**, *14*, 9. (b) Katz, H. E.; Lovinger, A. J.; Laquindanum, J. G. *Chem. Mater.* **1998**, *10*, 457. (c) Garnier, F.; Yassar, A.; Hajlaoui, R.; Horowitz, G.; Deloffre, F.; Servet, B.; Ries, S.; Alnot, P. *J. Am. Chem. Soc.* **1993**, *115*, 8716. (d) Garnier, F.; Hajlaoui, R.; El Kassmi, A.; Horowitz, Laigre, L.; Porzio, W.; Armanini, M.; Provasoli, F. *Chem. Mater.* **1998**, *10*, 3334.

[2] (a) Mitschke, U.; Ba¨uerle, P. *J. Mater. Chem.* **2000**, *10*, 1471.

[3] (a) Videlot, C.; El Kassmi, A.; Fichou, D. *Solar Energy Mater. Solar Cells* **2000**, *63*, 69. (b) Fichou, D. *J. Mater. Chem.* **2000**, *10*, 571. (c) Noma, N.; Tsuzuki, T.; Shirota, Y. *AdV. Mater.* **1995**, *7*, 647.

[4] Yohann N.; Blanchard, P.; Levillain, E.; Allain, M.: Mercier, N.; Roncali, J. *Org. Lett.* **2004**, *6*, 273.

presence of the three different heteroaromatic moieties arrayed around the central benzene core.

A survey of the literature on the synthesis of tetracyclic compounds in which a central benzene is flanked by three heteroaromatic rings showed that in most cases all three heterocycles are of a single kind, or at most, are of two types of five-membered rings. To our knowledge, no compounds in which the central ring is surrounded by three different heterocycles have been reported previously.

One way of building heterocycles around a central benzene core is to ornament a benzene derivative with substituents that can undergo ring-closing reactions, resulting in the desired final product. This strategy requires the successive incorporation of the substituents to the benzene core, which results in a long linear synthetic sequence. In addition, such an approach is best suited for symmetric compounds in which all three moieties around the central benzene are the same. This is due to the fact that it is challenging to add substituents to a benzene ring one-by-one in a regioselective manner. This strategy is illustrated in Schemes 1, 2, and 3.

Perepichka[5] reported access to the terthienobenzene **10** via the reaction of the known trialdehyde precursor **7** with ethyl mercaptoacetate to give terthiophenobenzene–ester **8**. Following saponification of the triester and decarboxylation of the resulting triacid **9** by heating at elevated temperatures, terthienobenzene **10** was obtained in good yield. Trialdehyde **7** was obtained from 1,3,5-trichlorobenzene **5** in two steps. The commercially available 1,3,5-trichlorobenzene **5** undergoes a Friedel-Crafts alkylation with chloroform, followed by reaction with H_2SO_4 to yield the desired trialdehyde **7**.

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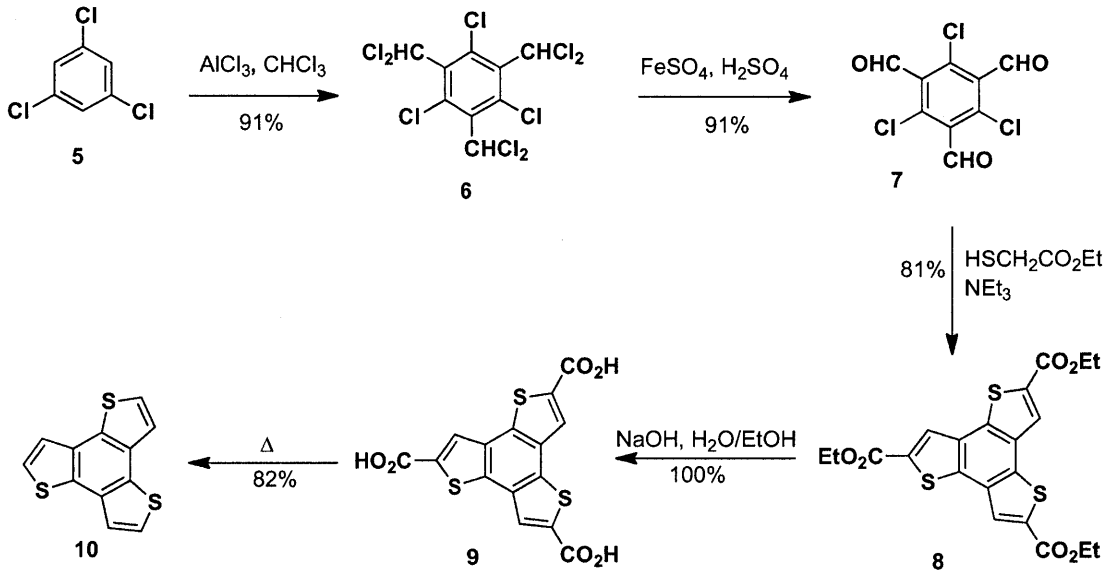
[5] Taerum, T.; Lukoyanova, O.; Wylie, R. G.; Perepichka, D. F. *Org. Lett.* **2009**, *11*, 3230.

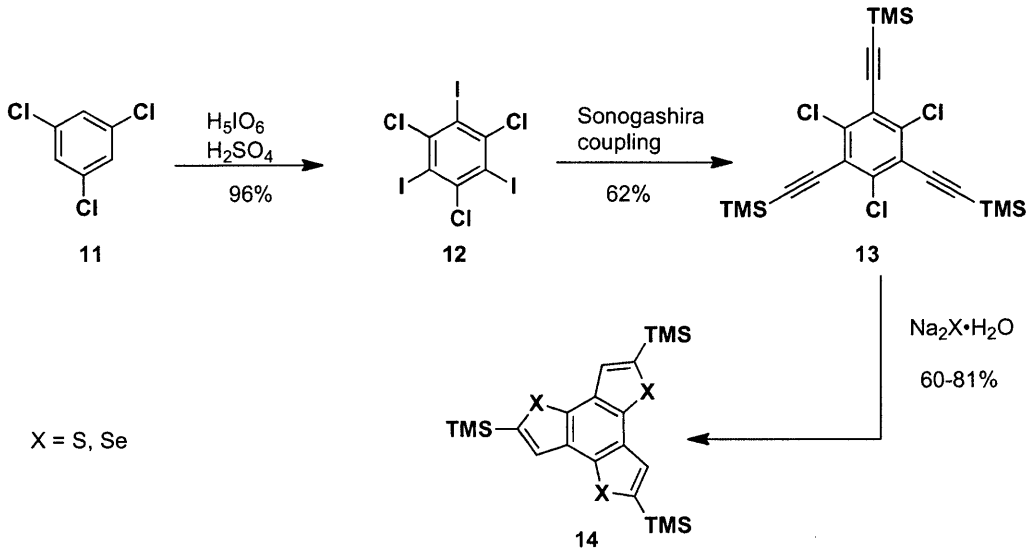
Scheme 1



An alternate route to a related terthiophenobenzene is shown in Scheme 2. In an aromatic nucleophilic substitution, sulfur, derived from inorganic sodium sulfide (Na_2S), displaces chloride to form a phenylthiolate intermediate, which then cyclized onto the acetylene functionality and results in the desired trithiophene **14**.[6] The precursor 1,3,5-trichloro-2,4,6-tris[(trimethylsilyl)ethynyl]benzene **13** was obtained by first treating 1,2,3-trichlorobenzene **11** with periodic acid, and then coupling the resulting halogenated benzene **12** with (trimethylsilyl)acetylene using Sonogashira conditions.[7]

[6] Kashiki, T.; Shinamura, S.; Kohara, M.; Miyazaki, E.; Takimiya, K.; Ikeda, M.; Kuwabara, H. *Org. Lett.* **2009**, *11*, 2473.
[7] Sonoda, M.; Inaba, A.; Itahashi, K.; Tobe, Y. *Org. Lett.* **2001**, *3*, 2419.

Scheme 2



Castellano exploited the O-acylation of benzotrifuranone **18** to obtain the aromatic benzotrifuran **19**.[8] The transformation consisted of deprotonation of benzotrifuranone **18** to form an enolate intermediate, which was immediately trapped with either methyl chloroformate or acetyl chloride to give compounds **19a** and **19b**, respectively. Benzotrifuranone **18** was obtained via dehydrative lactonization of triacid **17**, which in turned was synthesized from commercially available 1,3,5-trimethoxybenzene **15** in 5 steps.[9,10]

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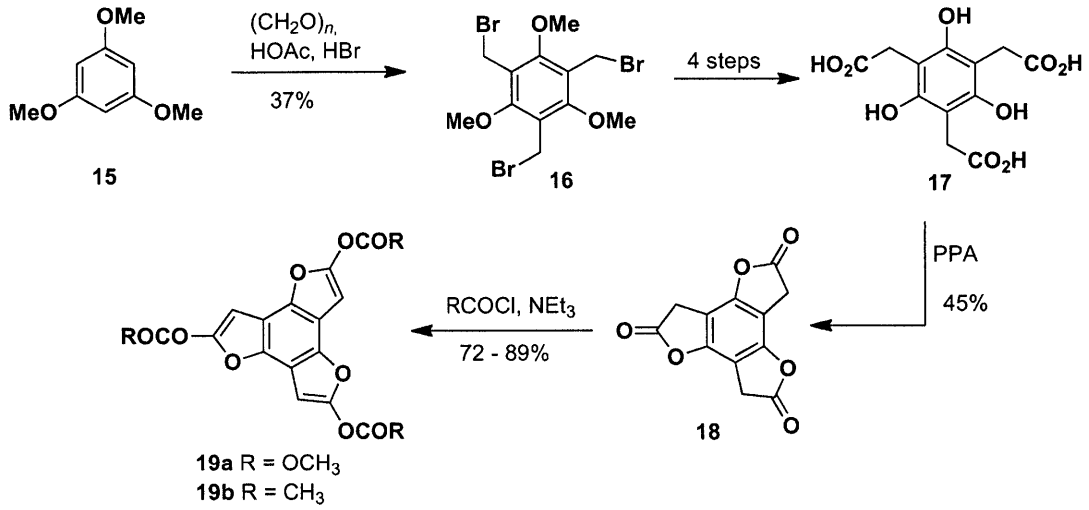
[8] Li, Y.; Lampkins, A. J.; Baker, M. B.; Sumpter, B. G.; Huang, J.; Abboud, K. A.; Castellano, R. K. *Org. Lett.* **2009**, *11*, 4314.

[9] Lampkins, A. J.; Li, Y.; Abbas, A. A.; Abboud, K. A.; Ghiviriga, I.; Castellano, R. K. *Chem. Eur. J.* **2008**, *14*, 1452.

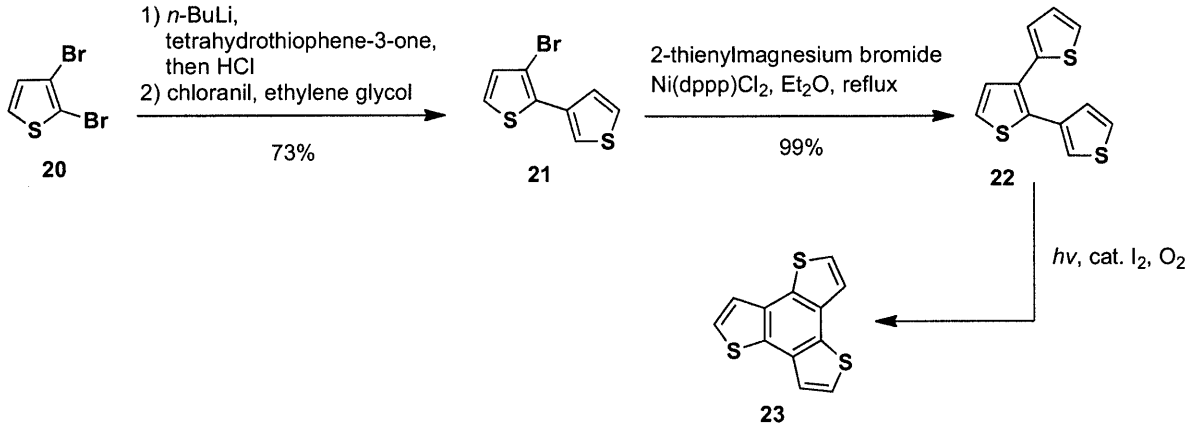
[10] Li, H.; Homan, E. A.; Lampkins, A. J.; Chiviriga, I.; Castellano, R. K. *Org. Lett.* **2005**, *7*, 443.

Scheme 3



A second approach to the synthesis of heterocyclic structures arrayed around a central benzene ring is to first link the desired heterocycles in the correct orientation, and then subject them to oxidative photocyclization to form the desired tetracycle. This strategy is illustrated in Scheme 4.

Scheme 4

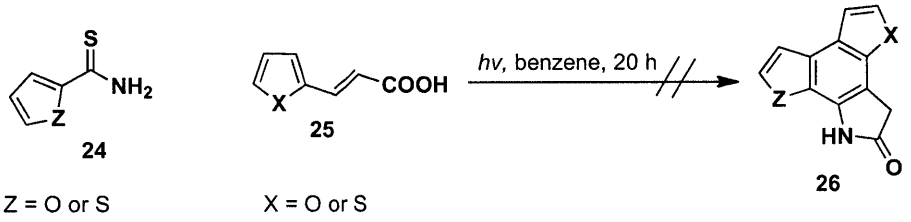


Bisthiophene **21** was obtained from 2,3-dibromothiophene **20** in two steps and was further reacted with 2-thienylmagnesium bromide in a nickel-catalyzed Kumada coupling reaction to give terthiophene **22**. This compound and a catalytic amount of

iodine were diluted in toluene and were irradiated in the presence of air to afford the desired benzo[1,2-*b*:3,4-*b*':5,6-*b*'']trithiophene **23**.[11]

Intramolecular cycloaddition reactions represent another class of strategies for the synthesis of this type of tetracyclic compounds. Oda attempted the intermolecular photoreaction of 5-membered heterocyclic carbohioamides **24a** and **24b** with furan- or thiopheneacrylic acid, but no tetracyclic compound was detected.[12] Interestingly, the annulation was successful and offered a moderate yield when the aromatic group in arenecarbothioamide was a phenyl group or a 4-pyridine, but not a 5-membered heterocycle.

Scheme 5



[11] Nicolas, Y.; Blanchard, P.; Levillain, E.; Allain, M.; Mercier, N.; Roncali, J. *Org. Lett.* **2004**, *6*, 273.
[12] Oda, K., Tsujita, H., Sakai M., Machida, M. *Chem Pharm. Bull.* **1998**, *46*, 1522.

Chapter 2

A Benzannulation Strategy for the Synthesis of Tetracycle 3

Our plan for the synthesis of tetracycle **3** revolved around the use of a benzannulation reaction to create a highly substituted benzene core intermediate. Highly substituted aromatic compounds are often obtained by employing linear substitution pathways involving nucleophilic and electrophilic aromatic substitutions, directed metalations, and metal-catalyzed coupling reactions. These strategies are often characterized by lengthy synthetic pathways, difficulties in obtaining the desired regiochemistry of substituents, and low overall yield. More effective are aromatic annulation strategies in which one or two compounds react in one step to form the benzenoid structure with all the desired substituents in place and in the desired regiochemistry.[13] Aromatic annulation strategies, including methods based on carbonyl condensations[14] and retro Diels-Alder reactions[15] are generally superior to linear substitution pathways because they allow for the efficient, convergent, and regiocontrolled synthesis of highly-substituted aromatic compounds.

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[13] For reviews, see: (a) Williams, A. C. *Comtemp. Org. Synth.* **1996**, *3*, 535. (b) Bamfield, P.; Gordon, P. F. *Chem. Soc. Rev.* **1984**, *13*, 441. (c) For a Symposium-in-Print on "Cycloaddition and benzannulation approaches to functionalized aromatic compounds", see: *Tetrahedron* **2008**, *64*, 767.

[14] For recent examples, see: (a) Langer, P.; Bose, G. *Angew. Chem. Int. Ed.* **2003**, *42*, 4033. (b) Barun, O.; Nandi, S.; Panda, K.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2002**, *67*, 5398.

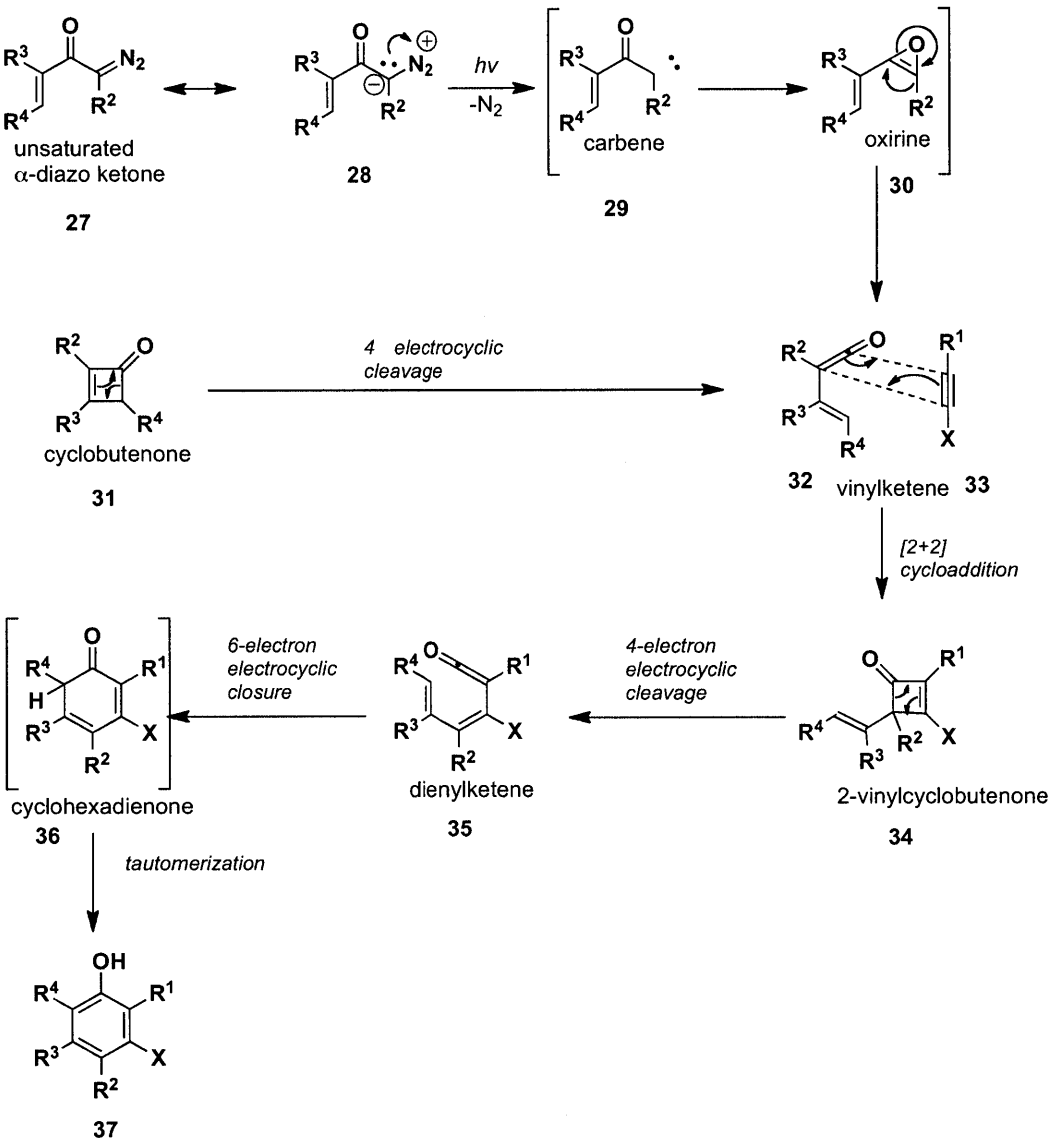
[15] For a review, see: Rickborn, B. *Org. React.* **1998**, *52*, 1.

Introduction to the Danheiser Benzannulation

The Danheiser laboratory has developed a highly efficient and convergent strategy for the formation of highly substituted benzenoid compounds. This strategy is often referred to as the Danheiser benzannulation and it was first reported in 1984, followed by a modified protocol, the "second-generation benzannulation," in 1990.[16] In benzannulation, a vinylketene **32** is formed in situ from either a cyclobutenone **31** or from a diazo ketone **27** (in the second-generation benzannulation). In the first generation benzannulation the vinylketene **32** is obtained from the thermal or light-triggered reversible 4π electrocyclic cleavage of the cyclobutenone. In the second-generation version of the benzannulation, the vinylketene is obtained from the Wolff rearrangement of a diazo ketone **27**. Once formed, the vinylketene rapidly reacts with the ketenophilic alkyne **33** in a regioselective [2+2] cycloaddition, resulting in cyclobutenone **34**, which further undergoes a reversible 4π electrocyclic cleavage to form dienylketene **35**. Intermediate **35** then undergoes a six-electron electrocyclization to afford cyclohexadienone **36**, which after tautomerization furnishes the desired aromatic product **37**.

[16] (a) Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1672. (b) Danheiser, R. L.; Nishida, A.; Savariar, S.; Trova, M. P. *Tetrahedron Lett.* **1988**, *29*, 4917. (c) Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc.* **1990**, *112*, 3093.

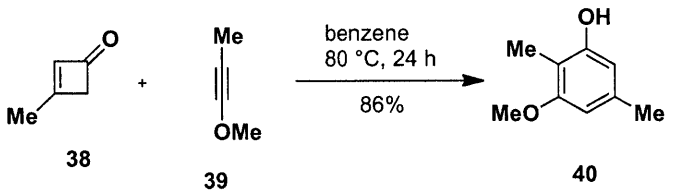
Scheme 6



Scope of the Danheiser Benzannulation

In the first generation benzannulation, cyclobutenones are either heated or irradiated to undergo a reversible 4π electrocyclic ring-opening and form vinylketene **32**. Activated alkynes such as arylacetylenes, alkynyl ethers, alkynyl thioethers, and alkynyl amines can serve as the ketenophilic partners in the benzannulation. In the course of the reaction, the vinylketene is only transient and reacts with its alkynyl partner as soon as it

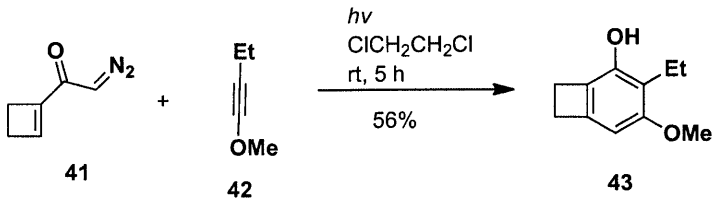
is formed. This ensures that almost no vinylketene polymerizes or undergoes other undesired transformations.



(1)

In the second-generation benzannulation, unsaturated (vinyl or aryl) α-diazo ketones are irradiated and undergo a photochemical Wolff rearrangement to generate the vinylketene intermediate, which then reacts with different activated alkynes. Through this modified protocol that uses unsaturated α-diazo ketones, one can make polycyclic aromatic and heteroaromatic systems that are not easily synthesized employing the first generation benzannulation. In addition, in the second-generation protocol, the photochemical transformation of the α-diazo ketone to vinylketene takes place at room temperature, broadening the scope of the reaction to include substrates and products that are unstable at elevated temperatures, as illustrated with the example in eq 2.

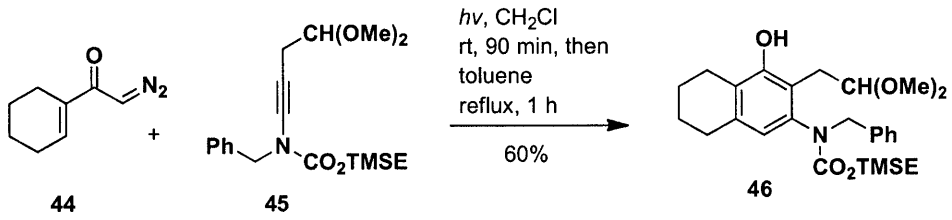
In the second-generation benzannulation, it is often desirable to run the reaction in two stages. First, irradiation of the reaction mixture effects the photo-Wolff rearrangement of the α-diazo ketone to form a vinylketene that undergoes [2+2] cycloaddition. The resulting 2-vinylcyclobutenone is then heated to complete the subsequent steps of the benzannulation. This is sometimes desirable because prolonged irradiation of the reaction mixture can lead to the formation of colored polymers. These polymers deposit on the walls of the reaction vessel and obstruct the light necessary to complete the transformation to the desired phenol.



(2)

Recent work in our laboratory focused on extending the benzannulation strategy to ynamine derivatives as the ketenophiles in the reaction since these reactions were envisioned to afford access to benzofused nitrogen heterocyclic compounds.[17]

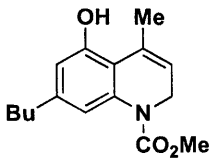
Early investigation of ynamines as substrates for the benzannulation showed that the reaction of these compounds often led to the formation of minor byproducts.[16a] Recently, ynamides, ynamine derivatives that contain an electron-withdrawing group on the nitrogen, were examined as alternative benzannulation partners.[18] Because ynamides are less nucleophilic than ynamines, it was believed that they would not undergo certain undesired side reactions when reacted with vinylketenes. Indeed, the use of ynamides in the benzannulation afforded the desired products in good yield without the formation of the byproducts. Ynamides have been used in the benzannulation reactions with cyclobutenones as well as with unsaturated α-diazo ketones.



(3)

[17] Mak, X. Y.; Crombie, A. L.; Danheiser, R. L. *J. Org. Chem.* **2011**, *76*, 4170.
[18] For recent reviews on the chemistry of ynamides, see: (a) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064. (b) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 2840.

The combination of benzannulation employing ynamides with various cyclization reactions was shown to provide efficient access to a range of benzofused nitrogen heterocyclic compounds.[17,19]



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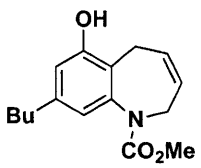

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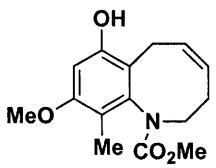

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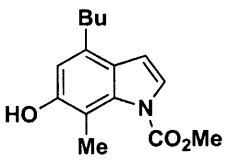

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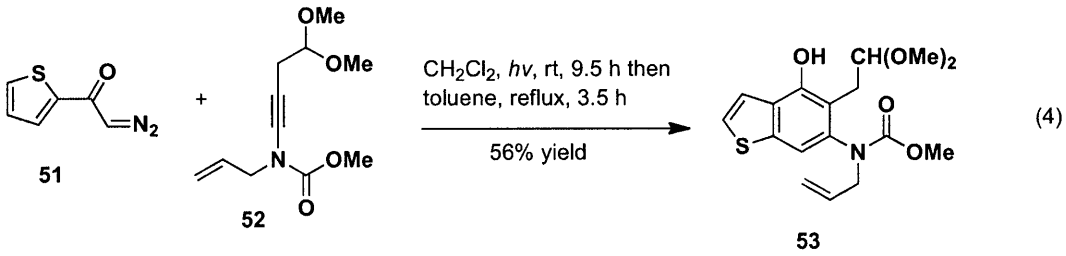
The successful application of this chemistry to the synthesis of indoles (e.g., eq 4) is especially significant for my project as our plan for the construction of the benzenoid core of the tetracycle **3** was envisioned to employ this strategy.



(4)

Methods for the Synthesis of Ynamides

There are several methods for the synthesis of ynamides.[20,21] The Danheiser laboratory developed and published a general and convenient copper-mediated protocol

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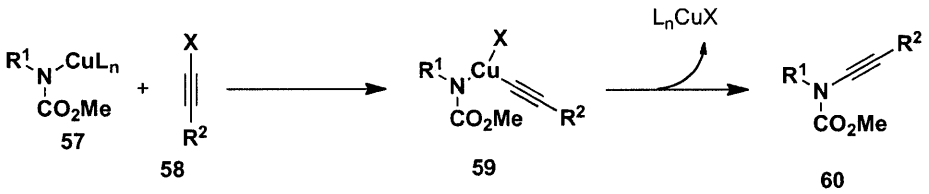
[19] Compounds **47**, **48**, and **49** were reported in reference 17; compound **50** was reported in Lam, T. Y. Synthesis of Indoles via a Tandem Benzannulation-Cyclization Strategy. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, September, 2008.

[20] For recent reviews of the synthesis and chemistry of ynamides, see: (a) Witulski, B.; Alayrac, C. In *Science of Synthesis*; de Meijere, A., Ed.; Thieme: Stuttgart, 2005; Vol 24, pp 1031. (b) Tracey, M. R.; Hsung, R. P.; Antoline, J.; Kurtz, K. C. M.; Shen, L.; Slafer, B. W.; Zhang, Y. In In *Science of Synthesis*;Weinreb, S. M., Ed.; Thieme: Stuttgart, 2005; Vol 21, pp 404. (c) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, 1379.

[21] For selected recent applications of ynamides, see: (a) Kohnen, A. L.; Mak, X. Y.; Lam, T. Y.; Dunetz, J. R.; Danheiser, R. L. *Tetrahedron* **2006**, *62*, 3815. (b) Couty, S.; Meyer, C.; Cossy, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6726. (c) Oppilliart, S.; Mousseau, G.; Zhang, L.; Jia, G.; Thuery, P.; Rousseau, B.; Cintrat, J.-C. *Tetrahedron* **2007**, *63*, 8094. (d) Oppenheimer, J.;

for ynamide synthesis in 2003.[22] A slightly modified version of this protocol was published in 2007.[23] In this method, an amide substrate is converted to its copper derivative **57** by deprotonation with a strong base (KHMDS) and reaction with a stoichiometric amount of CuI. Following the formation of copper amide **57**, alkynyl halide **58** is slowly added to the reaction mixture. The slow addition of the alkynyl halide is necessary because the copper-promoted dimerization of alkynyl halides is very facile and the slow addition greatly diminishes this undesired reaction.

Eq 6 outlines the proposed mechanism for the *N*-alkynylation reaction, which is believed to involve the oxidative addition of Cu(I) amide **57** to the alkynyl halide **58** to form copper(III) intermediate **59**. Copper intermediate **59**, in turn, undergoes reductive elimination to afford the ynamide **60**.



(6)

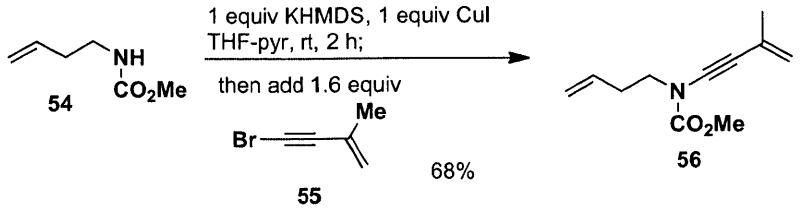
Amide substrates that react well under the alkynylation protocol developed in our laboratory include acyclic carbamates, acyclic sulfonamides, oxazolidinones, and cyclic ureas. Simple amides, on the other hand, are not reactive under these reaction conditions. The haloalkyne substrates used in this transformation can be either alkynyl bromides or alkynyl iodides.

An important feature of this protocol is that the reaction takes place at room temperature and therefore tolerates heat-sensitive substrates as shown in eq 5.

Johnson, W. L.; Tracey, M. R.; Hsung, R. P.; Yao, P.-Y.; Liu, R.; Zhao, K. *Org. Lett.* **2007**, *9*, 2361. (e) Al-Rashid, Z. F.; Hsung, R. P. *Org. Lett.* **2008**, *10*, 661. (f) Istrate, F. M.; Buzas, A. K.; Jurberg, I. D.; Odabachian, Y.; Gagosz, F. *Org. Lett.* **2008**, *10*, 925.

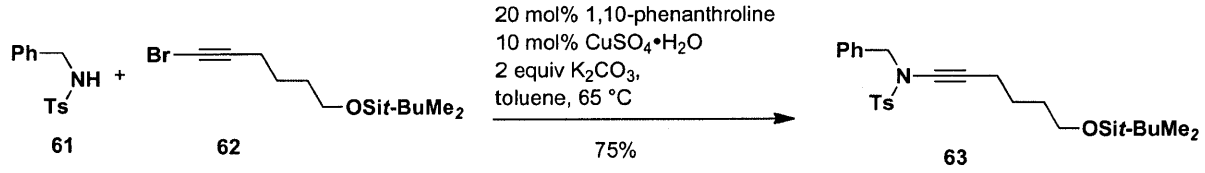
[22] Dunetz, J. R.; Danheiser, R. L. *Org. Lett.* **2003**, *5*, 4011.

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



(5)

An alternative way of synthesizing ynamides relevant to my project was developed in the Hsung laboratory at approximately the same time as the alkynylation protocol developed in our laboratory.[24] Eq 7 illustrates a typical alkynylation reaction under Hsung conditions. In the optimized protocol, the amide substrate is coupled to a bromoalkyne in the presence of a catalytic amount of copper sulfate hydrate, 1,10-phenanthroline, and either K_2CO_3 or K_3PO_4, depending on the amide substrate. In reactions with sulfonamides, K_2CO_3 is the base of choice, whereas in reactions with acyclic carbamates, K_3PO_4 works best. This reaction takes place at elevated temperatures, typically between 80-100 °C. Many amide substrates react well under these conditions, including acyclic sulfonamides, oxazolidinones, cyclic ureas, lactams, and acyclic carbamates. Acetamides and benzamides undergo alkynylation with only certain bromoalkynes.



(7)

[24] (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. (b) Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151. (c) 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. (d) Sagamanova, I. K.; Kurtz, K. C. M.; Hsung, R. P. *Org. Synth.* **2007**, *84*, 359.

Methods for the Synthesis of α-Diazo Ketones

In the context of our laboratory's work on the second-generation benzannulation, it became important to gain access to α,β-alkenyl α'-diazo ketones in an efficient and convenient manner.[25] The existing protocols did not offer efficient access to these compounds due to side reactions. Therefore, our laboratory has thoroughly examined existing conditions for this transformation and improved the protocol for the synthesis of α-diazo ketones via the method called "diazo group transfer".[26]

In the standard diazo group transfer strategy, a ketone is formylated to form an active 1,3-dicarbonyl compound that reacts with a sulfonyl azide to form an intermediate that undergoes cleavage to afford the desired α-diazo ketone. It was found that the Claisen condensation step employed in this transformation is sometimes detrimental to base-sensitive substrates such as α,β-enones. In addition, enones sometimes undergo dipolar cycloaddition with azide reagent. This causes the reaction to proceed in poor yield in certain cases.

Our lab found that modifying the conditions for the activating acylation step, by substituting trifluoroacetylation for the Claisen formylation step, improves the yield in most cases. In the modified protocol, a ketone **64** is treated with lithium hexamethyldisilazide to form the lithium enolate, and then with trifluoroethyl trifluoroacetate to form α-trifluoroacetyl ketone **65**. This compound then reacts with a sulfonyl azide reagent in acetonitrile in the presence of water and triethylamine to yield

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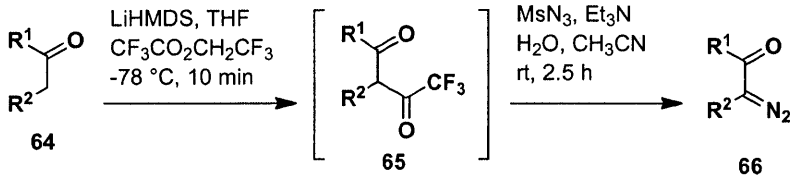
[25] For reviews of diazo ketone synthesis, see: (a) Doyle, M. P.; Mckervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley and Sons: New York, 1998; Chapter 1. (b) Regitz, M.; Maas, G. *Diazo Compounds: Properties and Synthesis*; Academic Press: Orlando, 1986.

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

diazo ketone **66**. This modified protocol affords higher or comparable yields in all diazo transfer reactions that were attempted.



(8)

Part II

Results and Discussion

Chapter 1

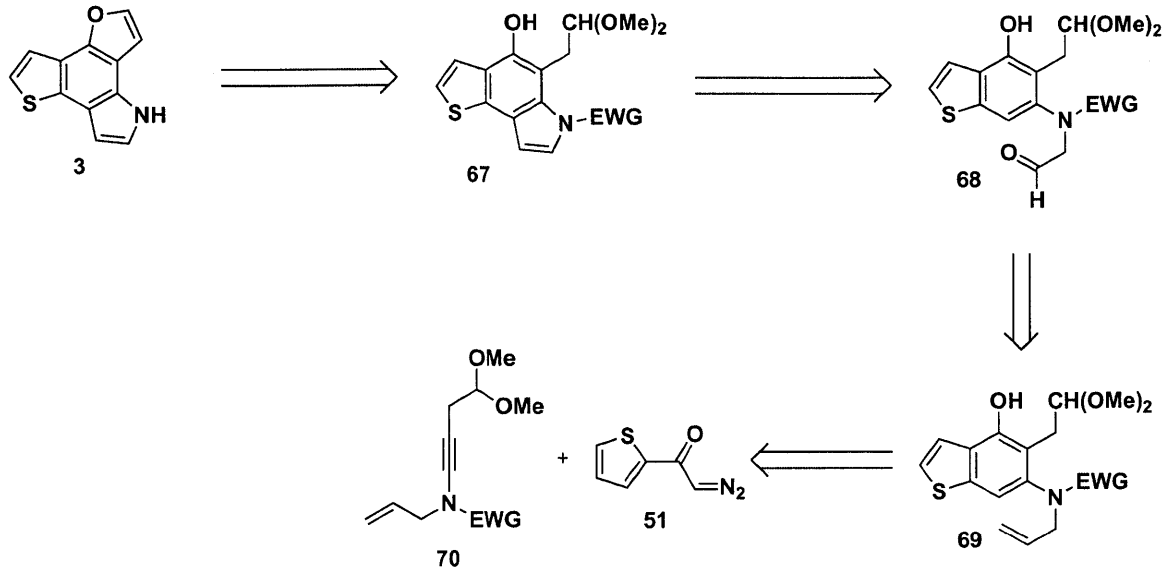
Synthesis of Tetracycle 3 via the *t*-Butoxy Carbamate Approach

Retrosynthetic Analysis

The previous chapter described a convenient one-step annulation strategy that offers access to highly substituted benzenoid cores. Recent work on the benzannulation strategy extended its scope to include the preparation of highly substituted aniline derivatives. These compounds were obtained from the reaction of α-diazo ketones or cyclobutenones with ynamides as the ketenophilic partner. The aniline derivatives can further participate in heterocyclization reactions to form different classes of benzofused nitrogen heterocyclic compounds such as indoles.

We envisioned that our target tetracycle **3** could be obtained through the cyclization of phenol **67** and elimination of methanol. As discussed below, indole **67** would be accessed by revealing the latent aldehyde **68** masked as a terminal olefin in the benzannulation product **69**. Compound **69** in turn would be derived from the benzannulation reaction of ynamide **70** and α-diazo ketone **51**, which would be obtained from commercially available compounds in 4 and 1 step, respectively.

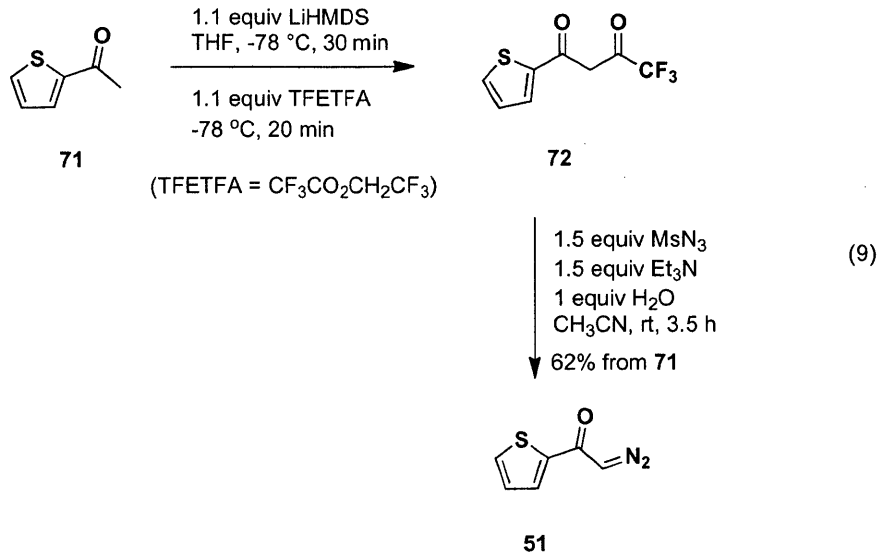
Scheme 7



Synthesis of α-Diazo Ketone 51

As discussed in the previous chapter, there are several ways to synthesize diazo ketones.[25] For this synthesis we obtained the requisite α',β'-unsaturated α-diazo ketone using the procedure developed in our laboratory.[26] The lithium enolate of the diazo ketone was obtained by treating **71** with LiHMDS and then reacted with 2,2,2-trifluoroethyl trifluoroacetate (TFETFA) to give the dicarbonyl compound **72** which was then allowed to react with methanesulfonyl azide (MsN_3). Diazo ketone **51** has been previously prepared by another route.[27]

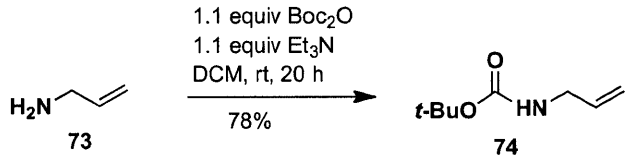
[27] (a) Ihara, E.; Inoue, K.; Tokimitsu, T. Carbonylmethylene polymers and their manufacture from α-diazo ketones. JP Patent 2004292556, October 21, 2004. (b) Ihmels, H.; Maggini, M.; Prato, M.; Scorrano, G. *Tetrahedron Lett.* **1991**, *32*, 6215.



71 72 51 (9)

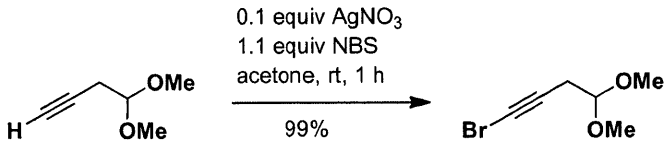
Synthesis of Ynamide 78

Carbamate **74** was prepared by protecting allylamine **73** as its Boc derivative by a previously published procedure.[28]



73 74 (10)

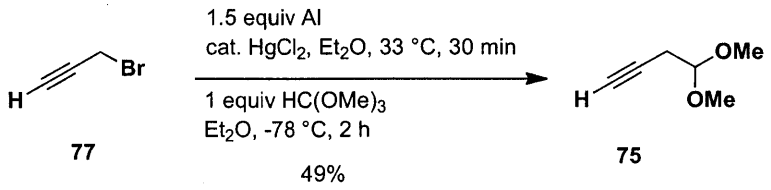
Alkyne **75** was brominated via the general procedure of Hofmeister[29] to afford bromoalkyne **78**, as shown in eq 11. Alkyne **75** reacted with catalytic silver(I) nitrate and *N*-bromosuccinimide to give **76** in high yield.



75 76 (11)

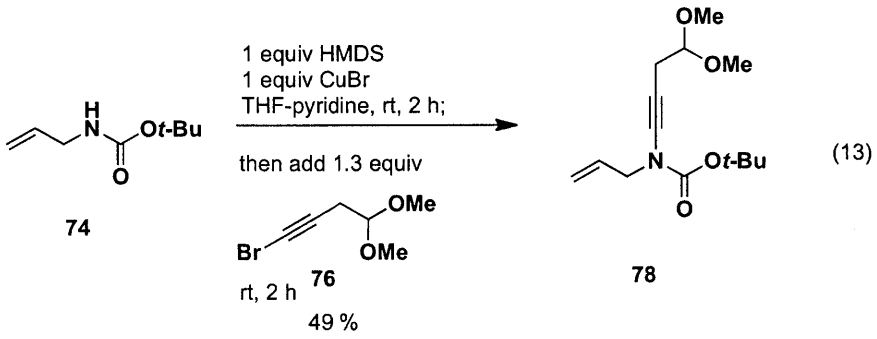
[28] Bischofberger, N.; Waldmann, H.; Saito, T.; Simon, E. S.; Lees, W.; Bednarski, M. D.; Whitesides, G. M. *J. Org. Chem.* **1988**, *53*, 3457.
[29] Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R. *Angew. Chem. Int. Ed.* **1984**, *23*, 727.

The alkyne **75** in turn was prepared from propargyl bromide as shown in eq 12.[30] Bromoalkyne **76** has been previously reported by Tammy Lam in her PhD thesis.[31]



77 75 (12)

Our key ynamide **78** was synthesized via the procedure developed in our laboratory as discussed in Chapter 2 of Part I.[22,23] The reaction worked in moderate yield forming the desired ynamide as well as a homocoupling product from the alkynyl bromide. Unfortunately, full conversion of the carbamate was not achieved. The carbamate **74** and the ynamide **78** have similar chromatographic properties on silica gel, which made it challenging to separate them using column chromatography. Separation on alumina was more effective, though both compounds still had a similar R_f. Fortunately, we found that carbamate **74** is volatile at 100 mmHg. Thus, it was convenient to remove the unreacted carbamate from the reaction mixture under reduced pressure, and then to separate the ynamide from the homocoupling dimer via column chromatography on silica gel.



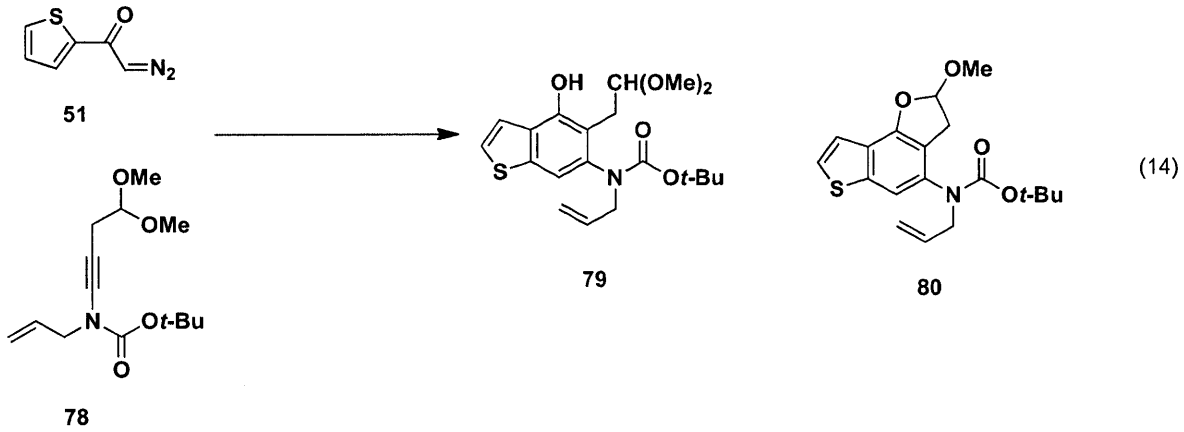
74 76 78 (13)

[30] Picotin, G.; Miginiac, P. *Chem. Ber.* **1986**, *119*, 1735.
[31] Lam, T. Y. Synthesis of Indoles via a Tandem Benzannulation-Cyclization Strategy. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, September, 2008.

Optimization of Benzannulation

We began our studies of the benzannulation step by irradiating ynamide **78** and an excess of diazo ketone **51** (2.1 equiv) in dichloromethane using a 450-W Hanovia mercury lamp. We found that upon prolonged irradiation, the diazo ketone formed an orange film on the reaction tube, which blocked the light coming from the lamp, slowing down the reaction rate. Decreasing the amount of diazo ketone from 2.1 equiv to 1.2 equiv led to less polymer build-up on the walls of the reaction tube and still resulted in an efficient reaction.

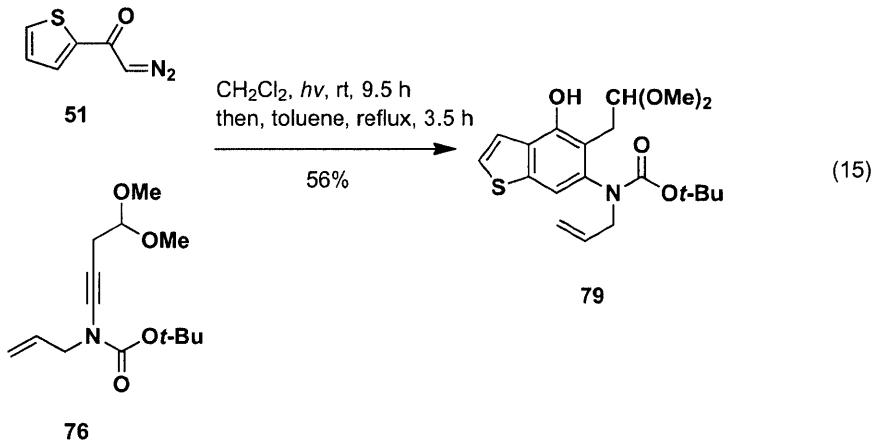
We performed the irradiation step in dichloromethane as well as in acetonitrile. We found that the formation of undesired polymer increased for reactions run in acetonitrile. In addition, reactions were generally slower when run in acetonitrile than when run in dichloromethane. Therefore, the optimized conditions use dichloromethane.



(14)

We discovered that along with the desired product **79**, the benzannulation also yielded an additional cyclized compound **80** (eq 14). We suspected that **80** formed through an S_N1 reaction, in which methanol was displaced by the phenolic hydroxyl group. The source of acidic protons necessary for this step could be the phenolic hydroxyl or a carboxylic acid generated by the reaction of traces of water with a ketene

intermediate in the reaction mixture. To correct for the presumed slightly acidic environment of the reaction mixture, in subsequent benzannulations the reaction flask was washed with a solution of potassium hydroxide and isopropanol. In addition, the diazo ketone was also dried via azeotropic removal of water with benzene. The treatment of glassware with base prior to running the reaction[32] and the use of dry diazo ketone eliminated the formation of compound **80** and the desired benzannulation product was then obtained in 56% yield (eq 15).



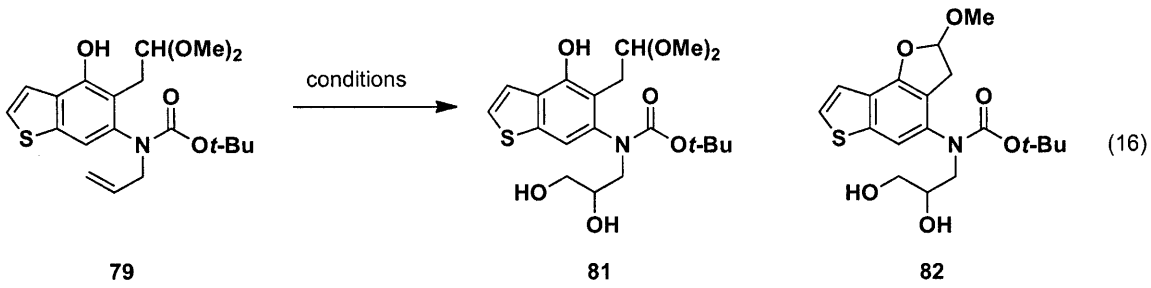
(15)

TES protection

With benzannulation product **79** in hand, we attempted to reveal the latent aldehyde masked as a terminal alkene by first dihydroxylating the double bond and then cleaving the resulting 1,2-diol to aldehyde as shown in eq 16. However, we discovered that the slightly acidic conditions required for the dihydroxylation led to the same undesired S_N1 transformation that took place in the previous benzannulation step.

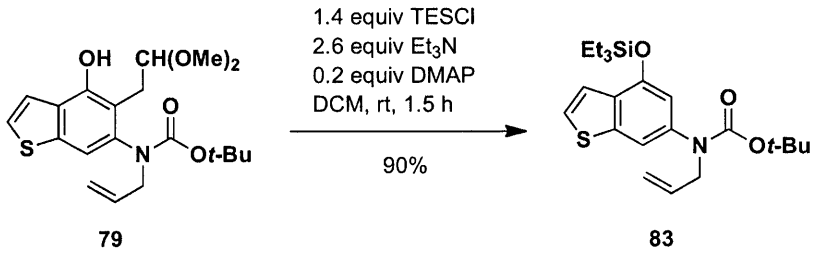
[32] The reaction tube was rinsed with a saturated solution of KOH and isopropyl alcohol by carefully adding the basic solution to the flask. After 10 min, the KOH-isopropyl alcohol solution was discarded, and the base-washed flask was rinsed with DI water and acetone.

Therefore, we decided to protect the phenol as a triethylsilyl ether to prevent this cyclization.



(16)

Silylation with triethylsilyl trifuoromethanesulfonate and 2,6-lutidine proceeded in poor yield.[33] We also attempted to effect the silylation with triethylsilyl chloride in the presence of excess triethylamine and a catalytic amount of DMAP.[34] This procedure was successful as shown in eq 17.



(17)

Oxidative Cleavage of the N-Allyl Group

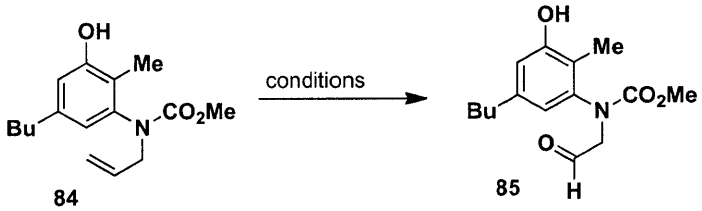
With the silylated phenol in hand, we proceeded to transform the terminal olefin **83** to aldehyde **87**. Tammy Lam worked extensively to find the best conditions for this type of transformation with compounds similar to **79** as illustrated in eq 18. To effect the oxidative cleavage of the *N*-allyl group, Tammy Lam reacted compound **84** with excess

[33] Goodacre, S. C.; Hallett, D. J.; Humphries, A. C.; Jones, P.; Kelly, S. M.; Merchant, K. J.; Moore, K. W.; Reader, M. Preparation of 8-fluoro-3-phenylimidazo[1,2-a]pyridine derivatives as ligands for gamma-aminobutyric acid (GABA) receptors. U.S. Patent WO 2003099816, December 4, 2003.

[34] Behloul, C.; Guijarro, D.; Yus, M. *Tetrahedron* **2005**, *61*, 6908.

ozone in a 20% solution of MeOH-CH_2Cl_2 followed by treatment with Me_2S. These oxidizing conditions led to many undesired oxidative transformations of phenol **79**, as is common for electron-rich aromatic systems.[35] Using more ozone led to a higher yield of the target aldehyde **85**, though a problematic purification process resulted in isolation of the product with only 80-85% purity.

Tammy Lam also attempted to cleave the *N*-allyl group employing the Lemieux-Johnson protocol which uses catalytic OsO_4 and excess $NaIO_4$.[36] She obtained aldehyde **85** in 66% yield under these conditions, but found that the product again was difficult to separate from impurities.



(18)

Tammy Lam found that the best protocol for the desired transformation was a two-step dihydroxylation-oxidative cleavage sequence. In this protocol, alkene **84** reacts with a catalytic amount of OsO_4 in the presence of a stoichiometric amount of NMO to yield a 1,2-diol. This compound is further oxidized without purification using sodium periodate supported on silica gel to give aldehyde **85** in high yield.[37] This two-step process works very well and affords an easily purified product.

We followed the two-step dihydroxylation-oxidative cleavage sequence to oxidatively cleave the *N*-allyl group to the desired aldehyde. Unfortunately, the desired

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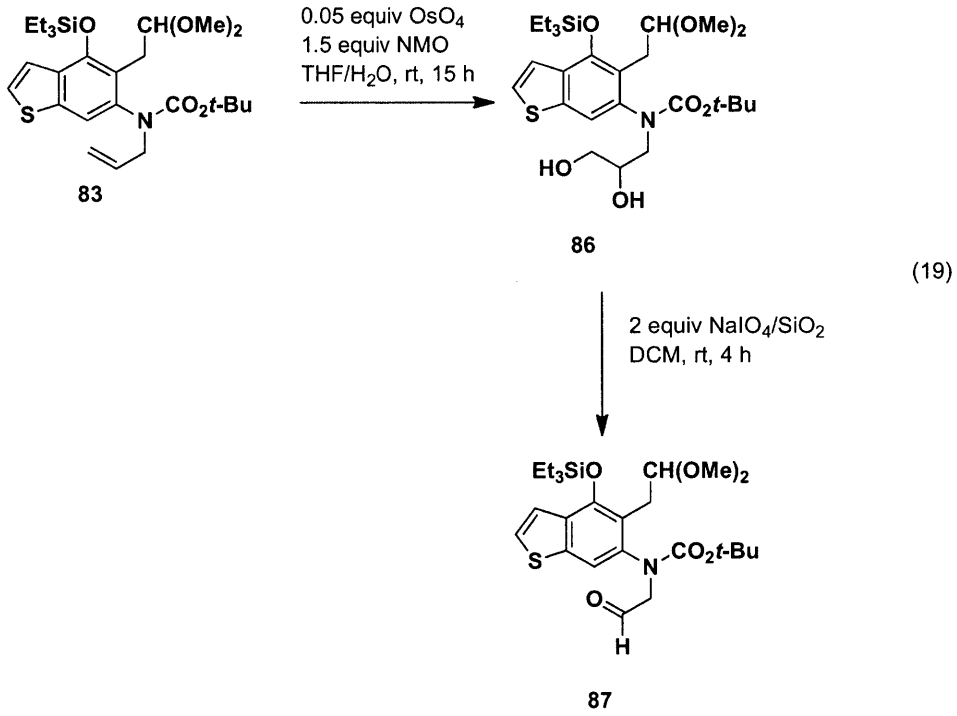
[35] For the prevention of over-oxidation during ozonolysis of electron-rich naphthalene systems by using controlled amount of ozone, see: Boger, D. L.; McKie, J. A.; Cai, H.; Cacciari, B.; Baraldi, P. G. *J. Org. Chem.* **1996**, *61*, 1710.
[36] Pappo, R.; Alen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.
[37] Zhong, Y-L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622.

aldehyde **87** proved unstable on silica gel or upon prolonged storage. Therefore, we carried the crude aldehyde onto the next step without purification.



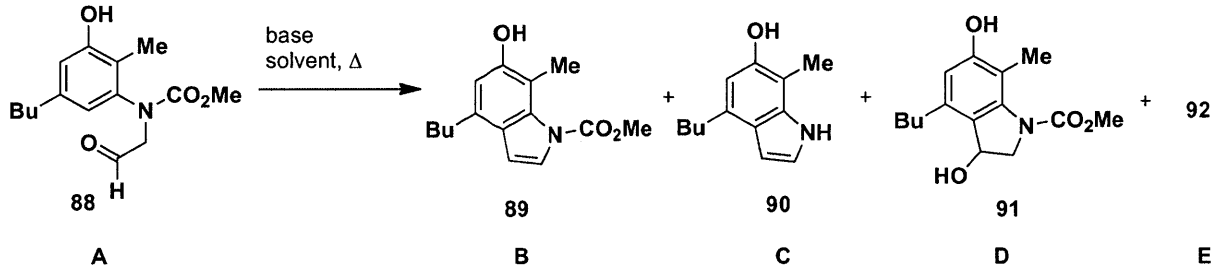
(19)

Cyclization to Indole

In her work on the synthesis of indoles via aromatic substitution, Tammy Lam screened many conditions for the transformation of aldehyde **88** to indole **89** as shown in Table 1.[31] She found that metal alkoxides did not promote the transformation, whereas $NaHSO_3$, Cs_2CO_3, and K_2CO_3 did bring about the desired cyclization. Initially, using K_2CO_3 in MeOH afforded the desired indole as well as the N-deprotected compound **90**. To avoid formation of compound **90**, she replaced the solvent with isopropyl alcohol. In addition, in order to prevent the formation of byproduct **92**, whose structure was not identified, but which probably formed as a result of the reaction between aldehyde **88** and indole **90**, a lower reaction concentration was required.

The cyclization was also examined using excess TBAF in isopropyl alcohol. However, because the reaction was quite slow, Tammy Lam did not pursue the optimization of a protocol using TBAF.

Table 1

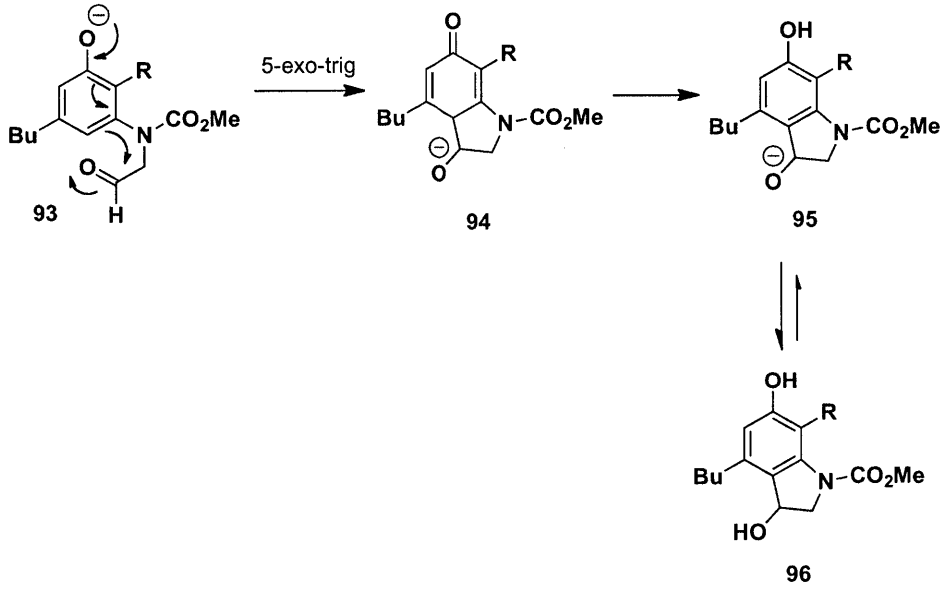


entry	base (equiv)	solvent	concn (M)	temp (°C)	time (h)	result
1	NaOMe (cat.)	MeOH	0.1	65	2	mixture of uncharacterized products
2	KO*t*-Bu	THF	0.1	65	18	mixture of **A** and uncharacterized products
3	$NaHCO_3$ (cat.)	MeOH	0.1	65	5.5	mixture of **B**, **C**, **D**, and **E**
4	K_2CO_3 (cat)	MeOH	0.1	65	5	mixture of **B**, **C**, and **E**
5	K_2CO_3 (5.0)	MeOH	0.01	50	1	mixture of **B**, **C**, and **D**
6	Cs_2CO_3 (1.0)	MeOH	0.01	50	4	mixture of **B**, **C**, and **D**
7	K_2CO_3 (5.0)	*i*-PrOH	0.01	50	1	**D**
8	DBU (10.0)	*i*-PrOH	0.01	50	1	**D**
9	Li_2CO_3 (5.0)	*i*-PrOH	0.01	55-80	6	mixture of **A** and decomposition
10	TBAF (5.0)	*i*-PrOH	0.01	55-80	6	mixture of **A** and **B**
11	Et_3N (10.0)	MeOH	0.01	50	2	mixture of **A** and **D**

[a]Concentration of aldehyde **88**. [b]For entries 1-4, products were isolated by column chromatography. For entries 5-11, results were based on TLC analysis of reaction mixtures.

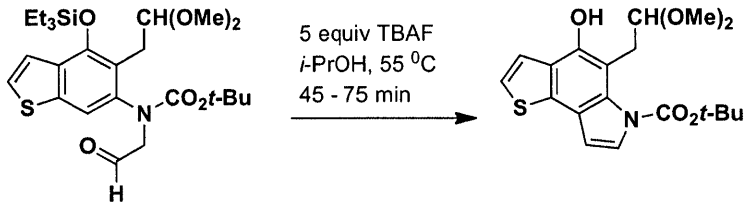
Eq 20 outlines the presumed mechanism for the cyclization of aldehyde **88** upon treatment with a base. It is believed that after deprotonation of the phenol, the resulting phenoxide **93** undergoes 5-exo-trig cyclization affording compound **94**, which tautomerizes to give **95** in equilibrium with compound **96**. Elimination of the secondary

alcohol to yield indole **89** requires treatment with acid. Therefore, after heating the aldehyde in presence of base in a dilute solution of isopropyl alcohol, the product is worked up with 1 M HCl to afford the desired indole **89**.



93 94 95 96 (20)

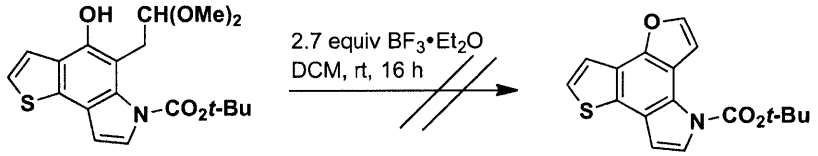
When we were contemplating the best conditions for our cyclization reaction, we had to take into consideration several important characteristics of our compound. In contrast to Tammy Lam's compounds, our phenol was protected as a triethylsilyl ether. Therefore, we required a protocol that would simultaneously deprotect the phenol and cyclize it to the desired indole. In addition, we wanted to avoid an acidic work-up because we were concerned that the Boc group might be unstable under these conditions. These considerations led us to use a protocol involving TBAF as the base. We found that TBAF effects the transformation well. However, indole **97** is unstable on silica gel as well as upon storage and was difficult to purify.



87 97 (21)

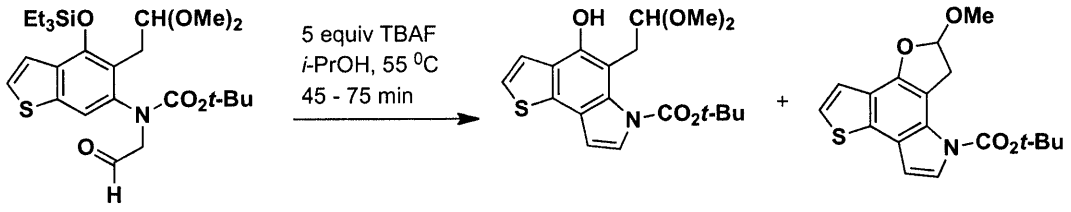
Cyclization to the Target Tetracycle 3

We attempted to carry out the cyclization of indole **97** to tetracycle **99** using excess $BF_3 \bullet Et_2O$ in CH_2Cl_2.[38] However, these conditions gave a mixture of compounds, among which the desired tetracycle was not observed.



97 99 (22)

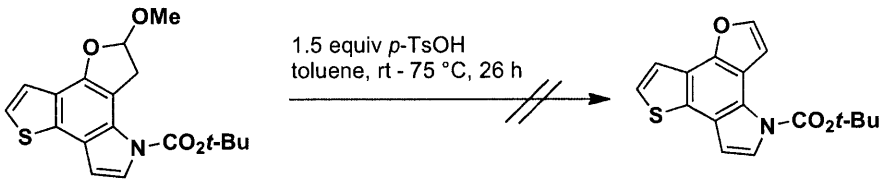
While preparing indole **97**, we observed the formation of another indole, **98**, in addition to **97**. This opened the opportunity of reaching **99** from **98**, which, we suspected, would form easily from **98** upon exposure of a trace of acid. Therefore, we attempted to cyclize indole **97** using silica gel in DCM with gentle heating at 40 °C overnight. The reaction proceeded cleanly, but afforded the product **98** in only 43% yield. This was most likely due to the fact that the starting material was somewhat impure, and the scale of the reaction was small.



87 97 98 (23)

[38] Samizu, K.; Ogasawara, K. *Heterocycles* **1994**, *38*, 1745.

With indole **98** in hand, we attempted to effect elimination of methanol with *p*-toluenesulfonic acid in toluene with heating at 75 °C. We observed the formation of two products by tlc analysis. However, we were unable to confirm the formation of the desired product due to the small scale of the reaction.



98 **99** (24)

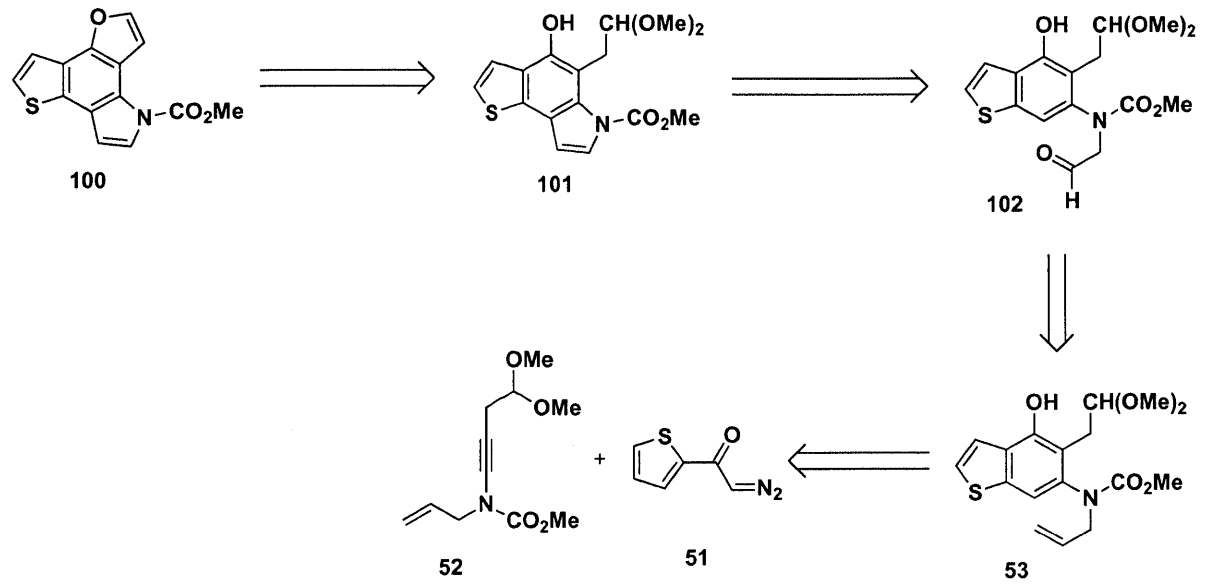
Chapter 2

Synthesis of Tetracycle 3 via the Methoxy Carbamate Route

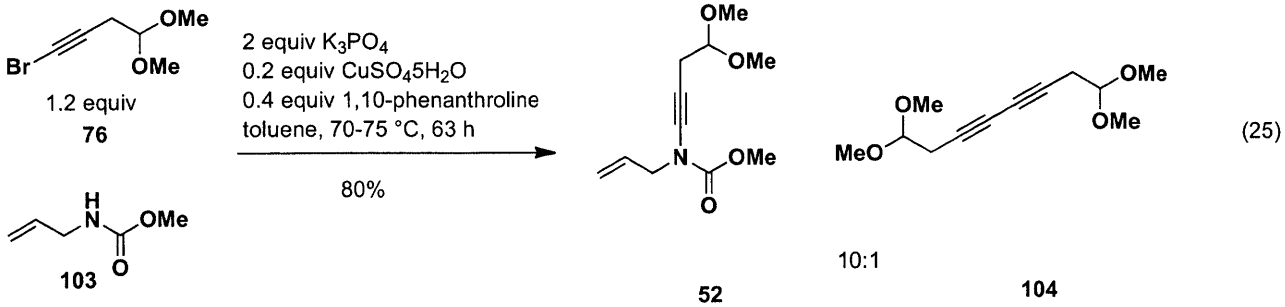
Manipulation of indole **97** proved challenging because it decomposed easily upon storage in DCM at 5-10 °C and during purification on silica gel. In addition, we were concerned that under the acidic conditions necessary for the cyclization to a furan, the Boc group might be cleaved, resulting in a very electron rich aromatic system with many potential routes for decomposition. Therefore, we desired to use an indole that would retain the nitrogen protecting group upon treatment with acid. We considered that a carbomethoxy protecting group on the nitrogen would be much better suited for this transformation under acidic conditions.

As in the synthesis route discussed above, we envisioned that the target tetracycle could be obtained from indole **101** under acidic conditions. The indole **101** would form under basic conditions via the 5-exo-trig cyclization of aldehyde **102**, which in turn could be obtained via the aldehyde derived from oxidative cleavage of the terminal olefin in benzannulation product **53**. The substrates for benzannulation would be ynamide **52** and α-diazo ketone **51**.

Scheme 8



Ynamide **52** was obtained using the *N*-alkynylation protocol developed in the Hsung laboratory (eq 25). Although the reaction did not proceed to completion even after heating the reaction mixture at 75 °C for 63 h, it afforded the ynamide in 80% yield. The unreacted starting materials, carbamate **103** and bromoalkyne **76,** are both volatile and could be removed under reduced pressure of 100 mmHg upon gentle heating at 30 °C overnight. In the course of the reaction, about a fifth of the bromoalkyne dimerizes to form side product **104**. The homodimer has an Rf similar to that of ynamide **52**. Nonetheless, it can be removed by column chromatography on silica gel.



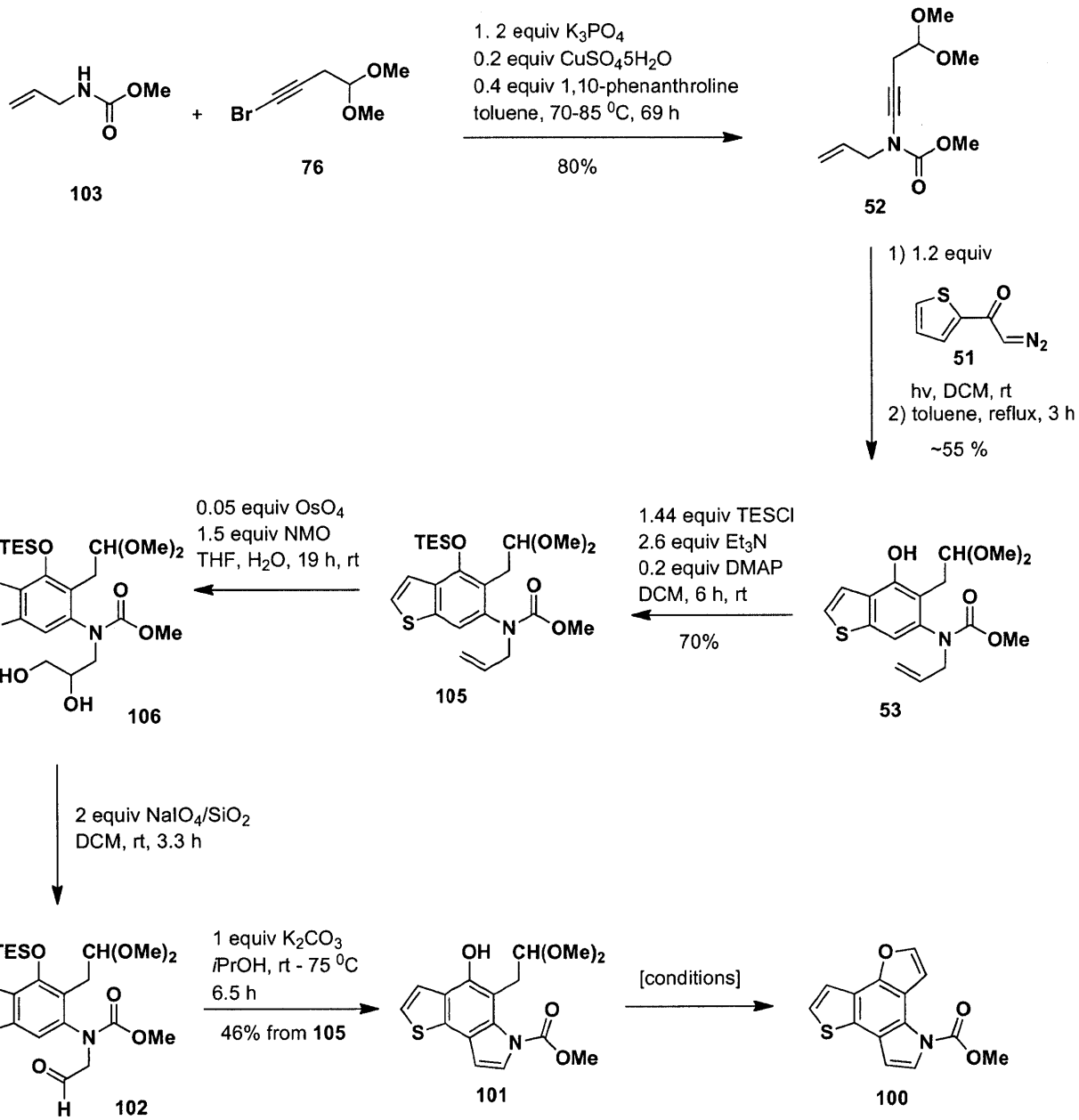
(25)

We also attempted the formation of ynamide **52** using the alkynylation protocol developed in our laboratory. However, the formation of homodimer **104** ocurred to a greater extent making the purification process considerably more challenging.

We subjected diazo ketone **51** together with ynamide **52** in dichloromethane to irradiation with a 450-W Hanovia mercury lamp, followed by heating in toluene. After purification on silica gel, the mostly pure aniline derivative **53** was obtained and silylated using TESCl according to the protocol discussed above. The product **105** was subjected to oxidative cleavage of the *N*-allyl group to afford an aldehyde **102**, which was cyclized to indole **101**. These three steps were effected without purification of intermediates and afforded indole **101** in 46% overall yield.

The reactions in this synthetic route have not been optimized. Because of time constraints my work on the project ended with the synthesis of indole **101**. However, Clarissa Forneris has continued the project and as of this writing, has been able to obtain the target tetracycle **100**. Treatment of indole **101** with 15 equivalents of trifluoroacetic acid in CH_2Cl_2 afforded tetracycle **100**. Clarissa is currently working on optimizing the route outlined in Scheme 9.

Scheme 9


1. 2 equiv K_3PO_4
0.2 equiv $CuSO_45H_2O$
0.4 equiv 1,10-phenanthroline
toluene, 70-85 ^{0}C, 69 h
80%
103
76
52
1) 1.2 equiv
51
hv, DCM, rt
2) toluene, reflux, 3 h
~55 %
0.05 equiv OsO_4
1.5 equiv NMO
THF, H_2O, 19 h, rt
1.44 equiv TESCl
2.6 equiv Et_3N
0.2 equiv DMAP
DCM, 6 h, rt
70%
106
105
53
2 equiv $NaIO_4/SiO_2$
DCM, rt, 3.3 h
1 equiv K_2CO_3
*i*PrOH, rt - 75 ^{0}C
6.5 h
46% from **105**
[conditions]
102
101
100

Part III

Experimental Procedures

Experimental Section

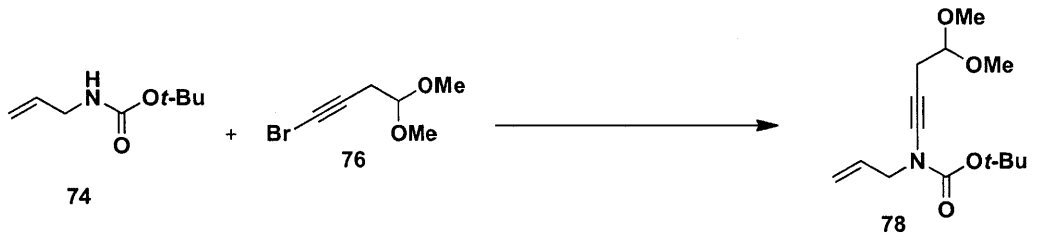
General Procedures. All reactions were performed in flame-dried or oven-dried glassware under a positive pressure of argon. Reactions were magnetically stirred unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred by syringe or cannula and introduced into reaction 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 (Merck) precoated glass-backed silica gel 60 F-254 250 'm plates or Baker-flex aluminum oxide IB-F precoated 200 'm flexible plastic sheets. Column chromatography was performed on Sorbent Technologies silica gel 60 (32-63 μm or 40-63 μm) or Aldrich aluminum oxide (activated, basic, Brockmann I, standard grade, ~ 150 mesh, 58Å). Slow addition from syringes were performed with an Orion M365 multi-range variable rate infusion pump manufactured by Thermo Electron Corporation.

Materials. Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane, diethyl ether, and tetrahydrofuran were purified by pressure filtration through activated alumina. Toluene was purified by pressure filtration through activated alumina and Cu(II) oxide. Triethylamine, trimethyl orthoformate, trifluoroethyl trifluoroacetate, and hexamethyldisilazane were distilled under argon from calcium hydride. Methanesulfonyl chloride was purchased from Alfa Aesar and used as received. CuBr was prepared from

$CuBr_2$ using the method of Townsend.[39] MsN_3 was prepared from MsCl.[16c] Carbamate **74**,[28] carbamate **103**,[23] alkyne **75**,[30] and bromoalkyne **76**[29] were prepared according to previously reported procedures.

Instrumentation. Infrared spectra were obtained using a Perkin Elmer 2000 FT-IR spectrophotometer. ^1H NMR spectra were recorded on Bruker Avance 400 (400 MHz) spectrometers. ^1H NMR chemical shifts are expressed in parts per million (δ) downfield relative to tetramethylsilane (with the chloroform resonance at 7.27 ppm). ^{13}C NMR spectra were recorded on Bruker Avance 400 (100 MHz) spectrometers. ^{13}C NMR chemical shifts are expressed in parts per million (δ) downfield relative to tetramethylsilane (with the chloroform resonance at 77.23 ppm used as a standard). High resolution mass spectra (HRMS) were measured on Bruker Daltonics APEXII 3 Tesla Fourier Transform and Bruker Daltonics APEXIV 4.7 Tesla mass spectrometers.

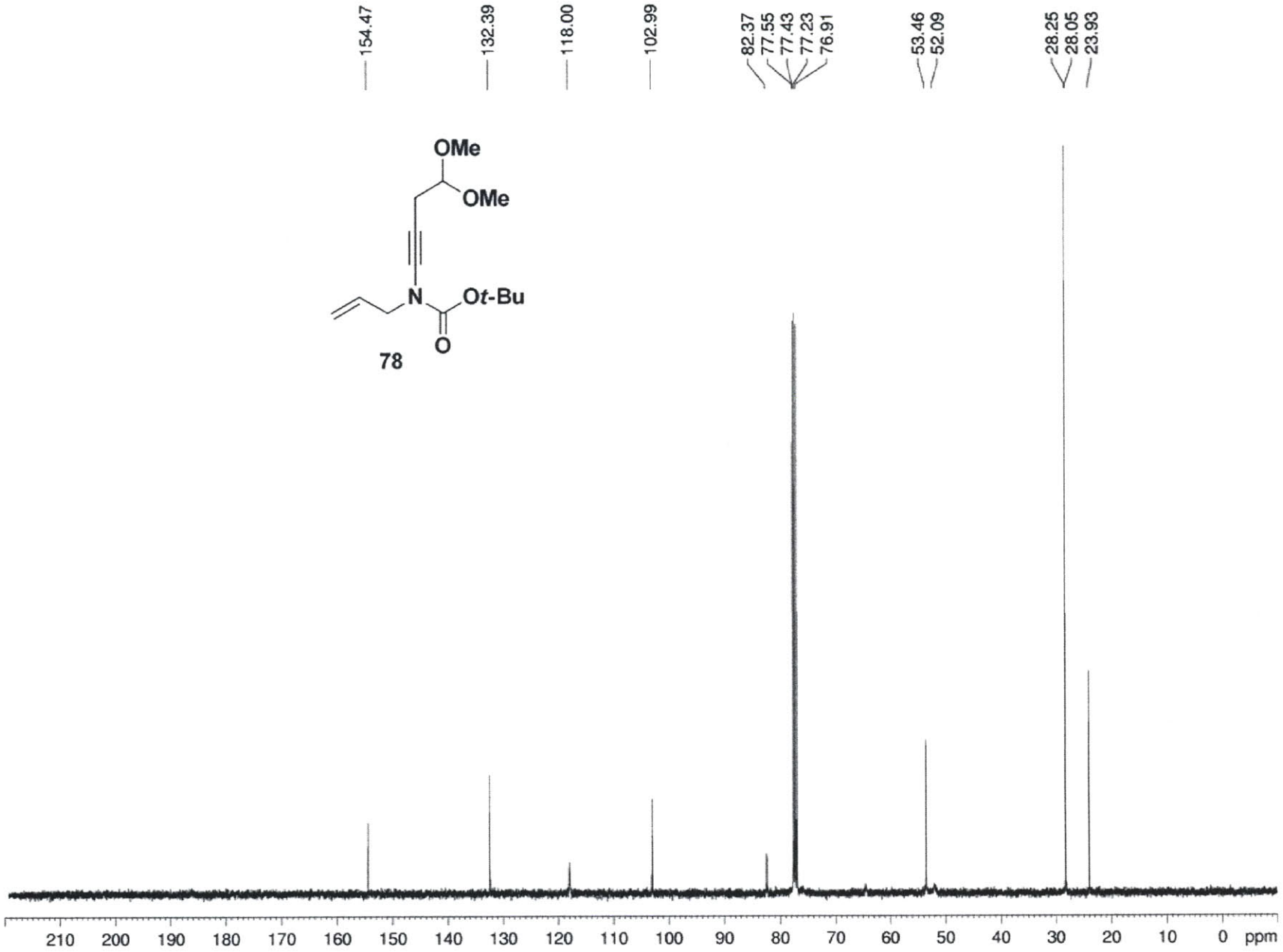
[39] (a) Theis, A. B.; Townsend, C. A. *Synth. Comm.* **1981**, *11*, 157. (b) Taylor, R. J. K. *Organocopper Reagents: A Practical Approach*; Oxford University Press: New York, 1984; pp. 38-39.



***N-tert*-Butoxycarbonyl-*N*-2-prop-2-enyl-4,4-dimethoxybut-1-ynylamine (78).** A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and an argon inlet needle was charged with carbamate **74** (0.304 g, 1.94 mmol, 1 equiv) and 7.7 mL of THF. The solution was cooled at 0 °C while 2.7 mL of KHMDS solution (0.91 M in THF, 1.90 mmol, 1 equiv) was added via syringe over 3 min. The resulting solution was stirred at 0 °C for 20 min, after which the ice bath was removed, and pyridine (4.7 mL, 4.6 g, 58 mmol, 30 equiv) was added. The reaction mixture was placed in a warm bath (ca. 40 °C), and CuBr (0.278 g, 1.94 mmol, 1 equiv) was added through temporary removal of the septum. The warm bath was removed, the reaction flask was covered in aluminum foil, and the reaction mixture was stirred at room temperature for 2.5 h. A solution of bromo alkyne **76** (0.510 g, 2.65 mmol, 1.4 equiv) in ca. 3 mL of THF was added via syringe pump over 45 min, and the resulting mixture was stirred at room temperature for 4 h. The reaction mixture was quenched with ca. 4 mL of a 2:1 mixture of saturated NaCl solution and concentrated NH_4OH solution, diluted with 80 mL of a 3:1 solution of Et_2O and pentane, and washed with three 20-mL portions of a 2:1 mixture of saturated NaCl solution and concentrated NH_4OH solution. The combined aqueous layers were extracted with two 40-mL portions of Et_2O, and the combined organic layers were washed with 40 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to provide 0.520 g of a dark brown oil. Column chromatography on ca. 25 g silica gel (elution with 10% EtOAc-hexanes) afforded 0.250 g (49%) of ynamide **78** as a colorless oil: IR (film)

3085, 2981, 2935, 2832, 2270, 1722, 1646, 1457, 1423, 1392, 1369, 1345, 1303, 1281, 1237, 1153, 1122, and 1068 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (ddt, J = 17.0, 10.4, 6.0 Hz, 1 H), 5.24 (dd, J = 18.8, 1.2 Hz, 1 H), 5.20 (dd, J = 10.2, 1.6 Hz, 1 H), 4.51 (t, J = 5.6 Hz, 1 H), 3.97 (d, J = 6.0 Hz, 2 H), 3.37 (s, 6 H), 2.62 (d, J = 6.0 Hz, 2 H), 1.49 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 132.4, 118.0, 103.0, 82.4, 77.4, 53.5, 52.1, 28.3, 28.1, and 23.9.

OMe
OMe
N
Ot-Bu
O
78
0.959
1.982
0.969
2.012
6.000
2.019
9.228
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


154.47
132.39
118.00
102.99
82.37
77.55
77.43
77.23
76.91
53.46
52.09
28.25
28.05
23.93
OMe
OMe
N
Ot-Bu
O
78
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

71 51

2-Diazo-l-(2-thienyl)-l-ethanone (51). A 100-mL, three-necked, round-bottomed flask equipped with a thermocouple, argon inlet adapter, and two rubber septa was charged with a solution of 1,1,1,3,3,3-hexamethyldisilazane (1.2 mL, 0.93 g, 5.5 mmol, 1.1 equiv) in 5.1 mL of THF and then cooled at 0 °C in an ice-water bath while *n*-butyllithium solution (2.53 M in hexanes, 2.2 mL, 0.36 g, 5.6 mmol, 1.1 equiv) was added dropwise over 9 min. After 10 min, the resulting solution was cooled at -78 °C in a dry ice-acetone bath while a solution of acetophenone **71** (0.54 mL, 0.63 g, 5.0 mmol, 1 equiv) in 5.1 mL of THF was added dropwise over 25 min via cannula (the flask was rinsed twice with 2 mL of THF). The reaction mixture was stirred at -78 °C for 30 min, and then 2,2,2-trifluoroethyl trifluoroacetate (1.1 mL, 1.6 g, 8.2 mmol, 1.1 equiv) was added rapidly by syringe in one portion. After 20 min, the reaction mixture was poured into a separatory funnel containing 10 mL of Et_2O and 20 mL of 5% aqueous HCl. The aqueous phase was extracted with 5 mL of Et_2O, and the combined organic phases were washed with 20 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to afford a yellow oil. This material was immediately dissolved in 17 mL of CH_3CN and transferred to a 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter and two rubber septa. Water (1.0 mL, 1.0 g, 1 equiv), Et_3N (1.0 mL, 13.8 mmol, 2.5 equiv), and a solution of methanesulfonyl azide (0.91 g, 7.52 mmol, 1.5 equiv) in 17 mL of CH_3CN were sequentially added via syringe. The resulting yellow solution was stirred at room temperature for 3.5 h, diluted with 30 mL of Et_2O, and washed with four 20-mL portions of 5% aqueous NaOH solution, three 20-mL portions of water, and two 20-mL

portions of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to afford 0.473 g of **51** as yellow crystals: IR (film) 3075, 3060, 2106, 1588, 1541, 1518, 1419, 1379, 1239, 1151, 854, 824, and 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 5.2 Hz, 1 H), 7.52 (d, J = 3.6 Hz, 1 H), 7.12 (dd, J = 4.0, 4.0 Hz, 1 H), 5.81 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1, 142.7, 132.4, 129.2, 128.2, and 54.4.

O
S
N2

51

1.000
1.036
1.002
1.012
0.184
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

179.07
142.71
132.37
129.20
128.21
77.55
77.23
76.91
54.42
O
S
N2
51
210
200
190
180
170
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150
140
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120
110
100
90
80
70
60
50
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30
20
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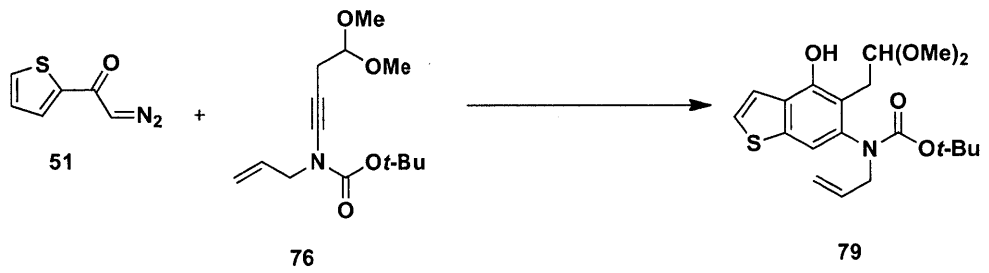
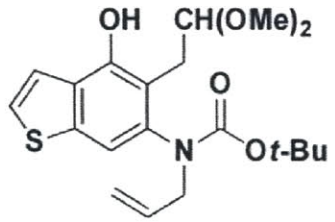
0
ppm



***N*-Allyl-*N*-2-*tert*-Butoxycarbonyl-[2-(2,2-dimethoxyethyl)-3-hydroxy-5*H*-thieno[2,3-e]phenyl]amine (79).** Ynamide **76** (0.501 g, 1.86 mmol, 1.0 equiv) was distributed equally between two base-washed[32] 20-cm quartz tubes (I.D.14 mm) equipped with rubber septa and argon inlet needles. The two tubes were charged with 9 ml each of a solution of diazo ketone **51** (0.334 g, 2.19 mmol, 1.2 equiv) in 18 ml of CH_2Cl_2 via temporary removal of the septa. The septa were secured with wires to the tubes to ensure a good seal, the tubes were covered in aluminum foil, and the mixtures were degassed by purging with argon for ca. 15 min. The aluminum foil was removed and the reaction tubes were positioned ca. 15 cm from a Hanovia 450W lamp cooled in a quartz immersion well. The reaction mixtures were irradiated for 22 h and then transferred to a base-washed 25-mL pear flask. The solution was concentrated, and the residue was dissolved in 18 mL of toluene. The flask was equipped with a cold-finger condenser with argon inlet side arm, and the solution was heated at reflux for 4 h, and then allowed to cool to room temperature and concentrated to give 0.930 g of a brown oil. Column chromatography on 90 g of silica gel (elution with 20% EtOAc-hexanes) provided an orange oil, which was triturated with pentane to afford 0.410 g of **79** as a beige solid: IR (film) 3271, 3083, 3935, 2977, 2836, 1698, 1615, 1551, 1454, 1418, 1392, 1367, 1342, 1304, 1252, 1159, 1117, and 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 1.1:1 mixture of rotamers) for major rotamer: δ 7.49 (d, J = 4.8 Hz, 1 H), 7.22 - 7.32 (m, 2 H), 5.88 - 5.95

(m, 1 H), 5.11 (d, J = 16.0 Hz, 1 H), 5.14 (d, J = 9.2 Hz, 1 H), 4.72 (br. s, 1 H) , 4.34 (m, 1 H), 3.91 (app. dd, J = 15.0, 6.8 Hz, 1 H), 3.47 (s, 6 H), 2.99 (d, J = 6.8 Hz, 2 H), 1.35 (br. s, 9 H); additional resonances appeared for the minor rotamer at: δ 4.59 (br. s, 1 H), 3.48 (s, 6 H), 1.53 (br. s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 151.8, 139.8, 133.6, 130.6, 125.2, 121.0, 118.2, 115.8, 114.7, 106.4, 80.6, 56.1, 54.7, 54.0, 31.4, and 28.6; HRMS $[M + Na]^+$ calcd for $C_{20}H_{27}NO_5S$: 416.1502, found 416.1513.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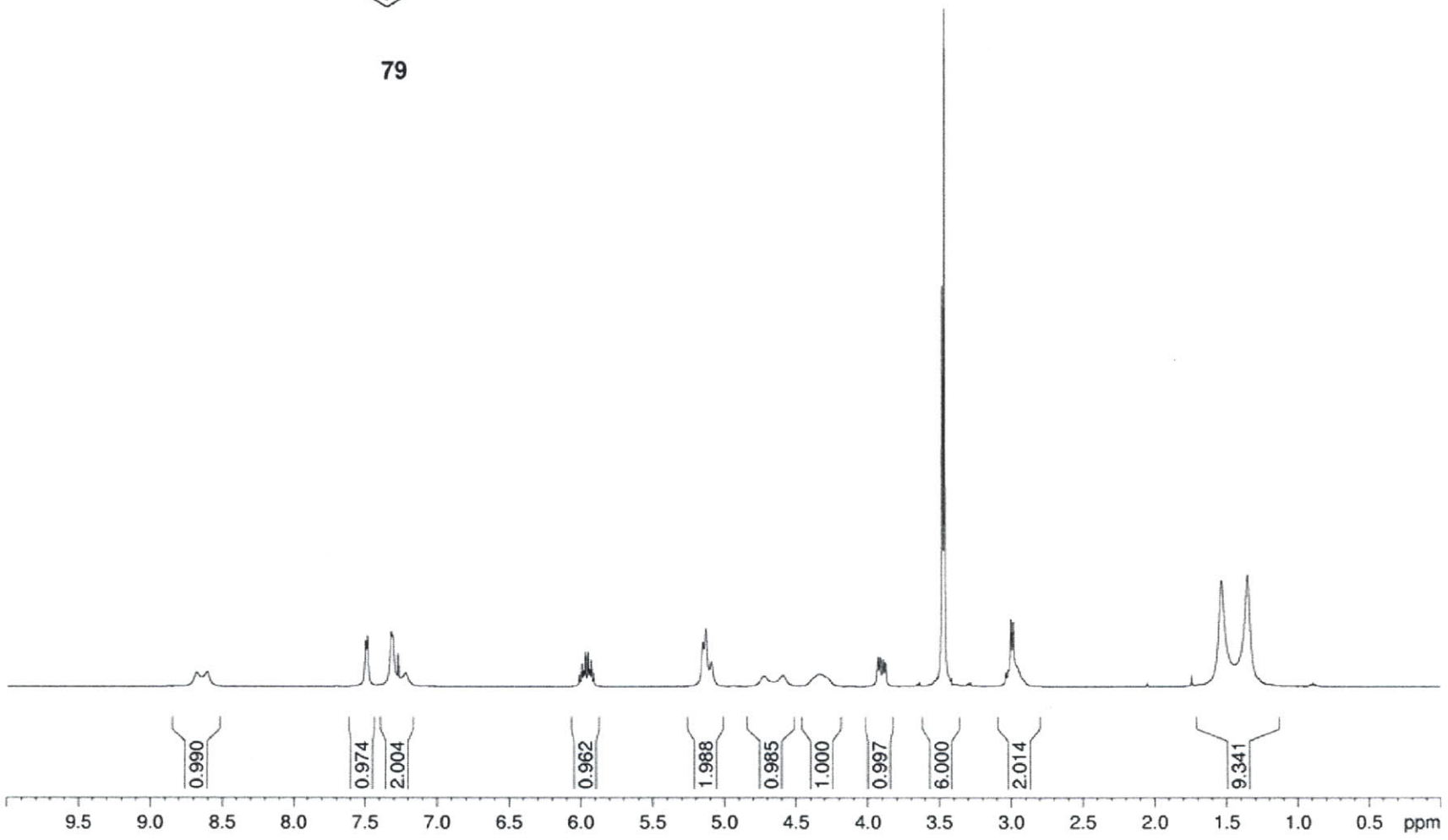
CH(OMe)2
O
S
N
Ot-Bu

79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0.962
1.988
0.985
1.000
0.997
6.000
2.014
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9.0
8.5
8.0
7.5
7.0
6.5
6.0
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2.0
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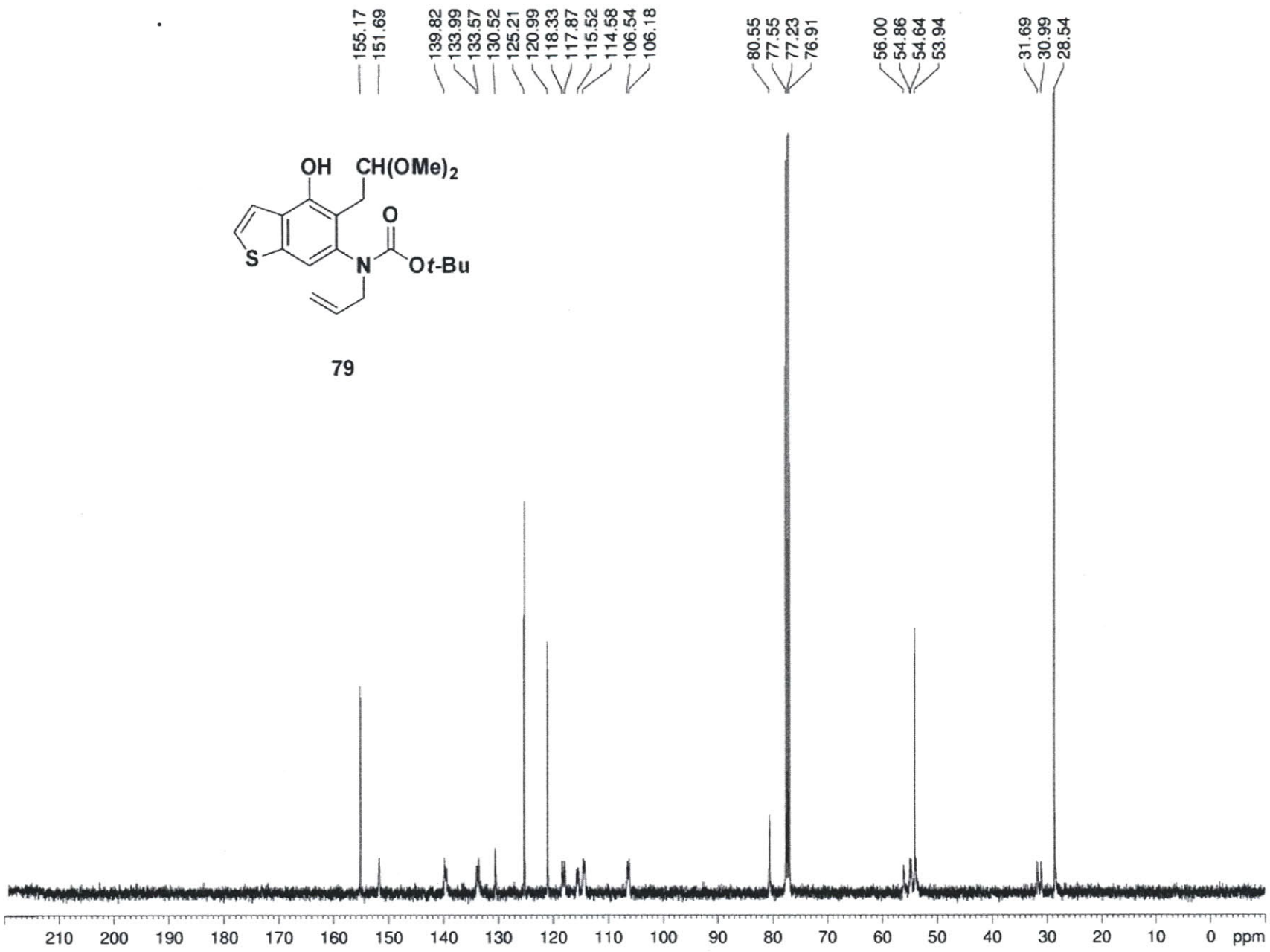
1.0
0.5
ppm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133.57
130.52
125.21
120.99
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117.87
115.52
114.58
106.54
106.18
80.55
77.55
77.23
76.91
56.00
54.86
54.64
53.94
31.69
30.99
28.54
OH
CH(OMe)2
O
S
N
Ot-Bu
79
210
200
190
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170
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110
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70
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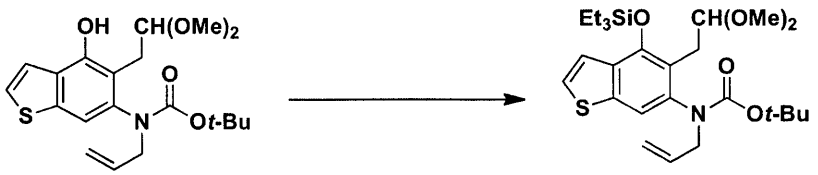
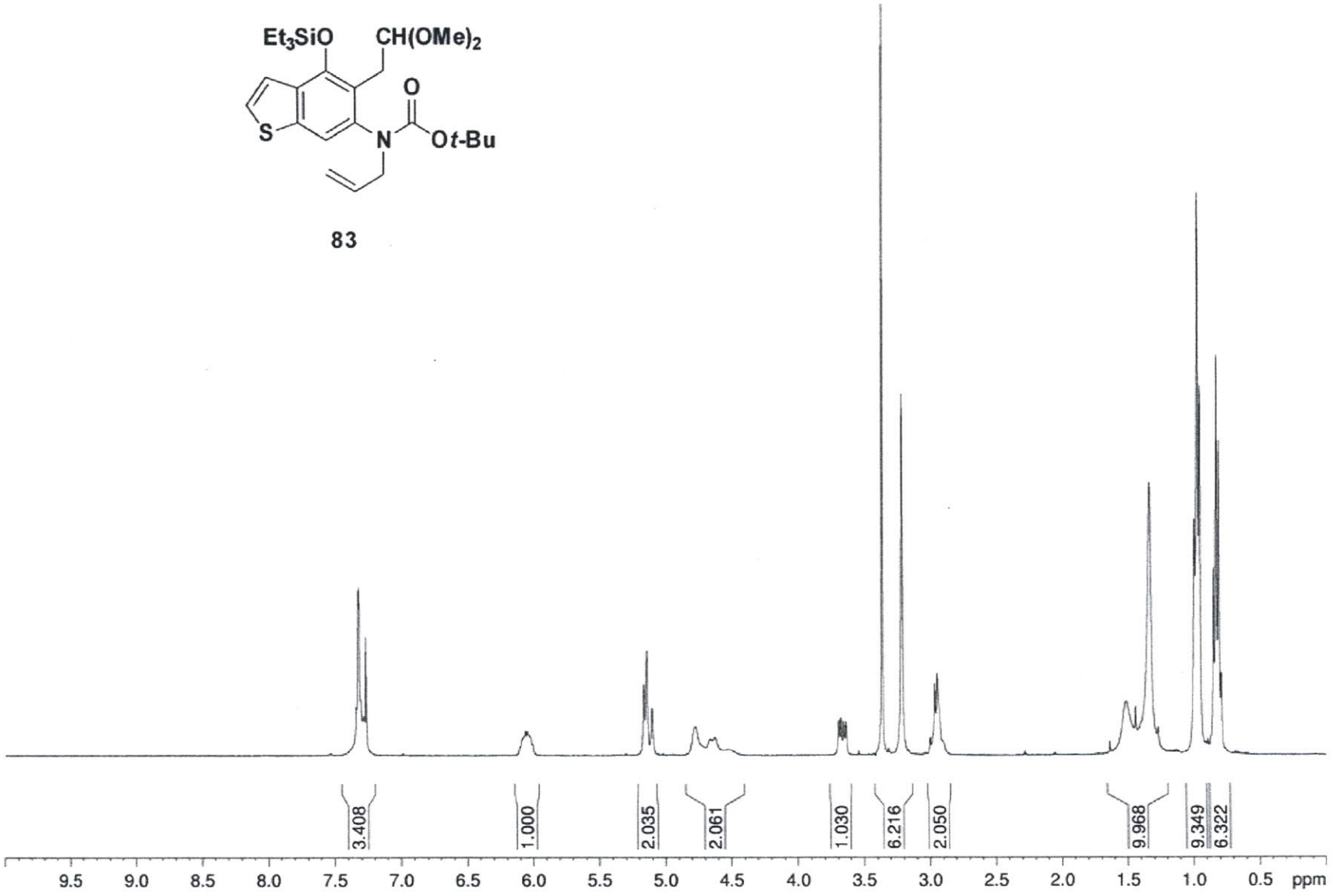
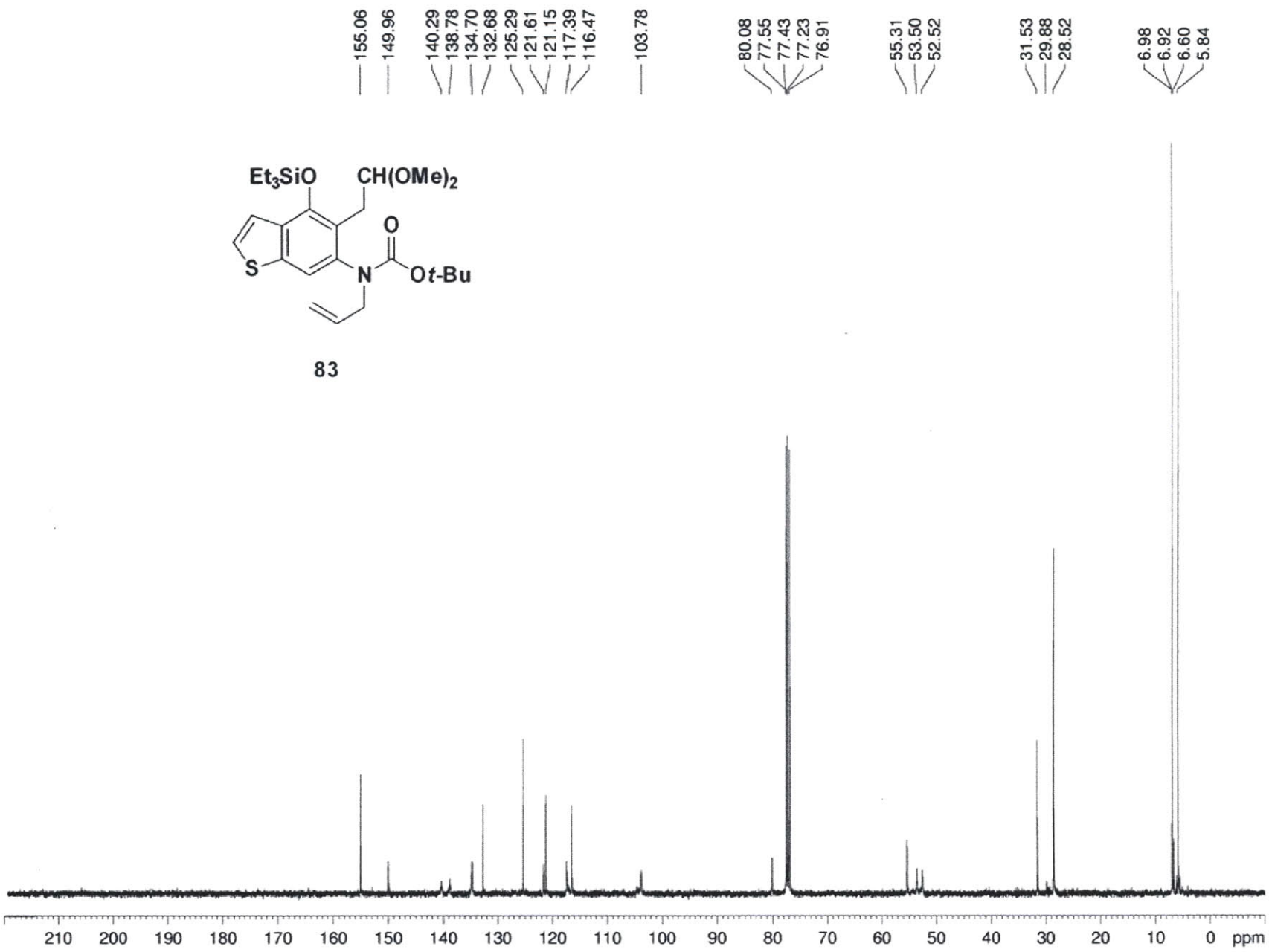
ppm



79 83

***N*-Allyl-*N*-2-*tert*-Butoxycarbonyl-[2-(2,2-dimethoxyethyl)-3-(triethylsilyl)oxy-5*H*-thieno[2,3-e]phenyl]amine (83).** A 10-mL, one-necked, round-bottomed flask equipped with a rubber septum and an argon inlet needle was charged with DMAP (0.014 g, 0.051 mmol, 0.2 equiv), 1 mL of CH_2Cl_2, TESCl (0.12 mL, 0.1 g, 0.7 mmol, 1.4 equiv), and Et_3N (0.18 mL, 0.13 g, 1.33 mmol, 2.6 equiv). The solution was stirred at room temperature for 30 min, and then phenol **79** (0.20 g, 0.51 mmol, 1 equiv) was added in one portion. The resulting mixture was stirred at rt for 1.5 h. The viscous orange slurry was washed with 3 mL of water and 3 mL of saturated NaCl solution, and the combined aqueous layers were extracted with three 3-mL portions of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 0.270 g of a yellow oil. Column chromatography on 55 g of silica gel (elution with 20% EtOAc-hexanes) and then on 47 g of silica gel (elution with 20% Et_2O-hexanes) gave 0.234 g (90%) of **83** as a colorless oil: IR (film) 3083, 2956, 2878, 2831, 1693, 1642, 1598, 1546, 1415, 1383, 1338, 1305, 1251, 1216, 1120, and 1067 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.34 (app. quintet, 3H), 6.01-6.10 (m, 1H), 5.15 (dd, J = 12.6, 4.6 Hz, 2 H), 4.78 (br s, 1H), 5.60 (app. br triplet, 1H), 3.67 (dd, J = 15.6, 3.6 Hz, 1H), 3.37 (s, 3H), 3.22 (s, 3H), 2.96 (d, J = 7.4 Hz, 2H), 1.51 (br s, 3H), 1.33 (br s, 6H), 0.97 (app triplet, J = 7.6 Hz, 9H), 0.82 (app. quartet, J = 7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 150.0, 140.3, 138.8, 134.7, 132.7, 125.3, 121.6, 117.4, 116.5, 103.8, 80.1, 77.4, 55.3, 53.5, 52.5, 31.5, 29.9, 28.5, 6.98, 6.92, 6.60, and 5.84.


Et3SiO
CH(OMe)2
O
S
N
Ot-Bu
83
3.408
1.000
2.035
2.061
1.030
6.216
2.050
9.968
9.349
6.322
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm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149.96
140.29
138.78
134.70
132.68
125.29
121.61
121.15
117.39
116.47
103.78
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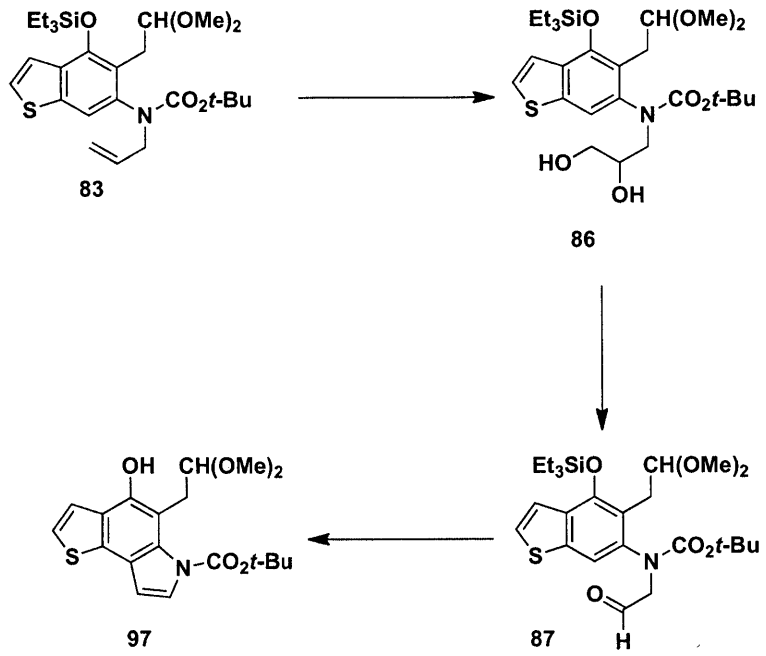
77.55
77.43
77.23
76.91
55.31
53.50
52.52
31.53
29.88
28.52
6.98
6.92
6.60
5.84
Et3SiO
CH(OMe)2
O
S
N
Ot-Bu
83
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

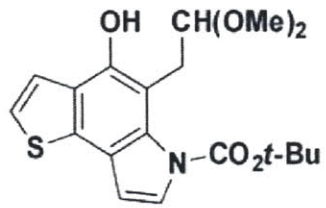


1-*tert*-Butoxycarbonyl-7-(2,2-dimethoxyethyl)-6-hydroxy--4*H*-thieno[2,3-e]indole (87). A 10-mL, one-necked, pear shaped flask equipped with a rubber septum and argon inlet needle was charged with alkene **83** (0.34 g, 0.67 mmol, 1 equiv), 5.2 mL of THF, 1.7 mL of water, OsO_4 (4 wt% in H_2O, 0.09 mL, 0.004 g, 0.014 mmol, 0.02 equiv), and NMO (0.117 g, 1.0 mmol, 1.5 equiv). The argon inlet needle was removed and the reaction mixture was stirred at room temperature for 22 h. A solution of $NaHSO_3$ (0.77 g, 7.37 mmol, 11 equiv) in 7.7 mL of water was added, and the resulting mixture was stirred at room temperature for 15 min. The mixture was diluted with 5 mL of saturated NaCl solution and extracted with three 8-mL portions of EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give 0.333 g of diol **86** as a brown oil used in the next step without purification.

A 10-mL, one-necked, pear shaped flask equipped with a rubber septum and argon inlet needle was charged with diol **86** (0.33 g, 1 equiv) and 3.5 mL of CH_2Cl_2. To this solution was added $NaIO_4$ supported on silica gel (1.97 g, 1.34 mmol, 2 equiv) and

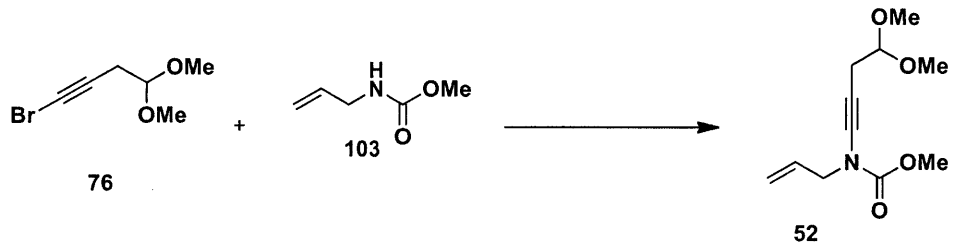
3.5 mL of CH_2Cl_2 via temporary removal of the septum. The orange suspension was stirred at room temperature for 2 h. The reaction mixture was filtered through a sintered glass funnel, and the residue was washed with five 10-mL portions of CH_2Cl_2. The filtrate was concentrated to provide 0.292 g of **87** as a brown oil used in the next step without purification.

A 100-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with aldehyde **87** (0.292 g, 1 equiv), 45 mL of isopropanol, and TBAF (1 M in THF, 3.35 mL, 0.88 g, 3.35 mmol, 5 equiv). The septum was replaced with a condenser fitted with an argon inlet adapter, and the reaction flask was heated in an oil bath at 55 °C for 75 min. The reaction mixture was allowed to cool to room temperature and then diluted with 20 mL of diethyl ether. The resulting solution was extracted with 10 mL of water and 10 mL of saturated NaCl solution and the combined aqueous phases were extracted with three 10-mL portions of diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 1.56 g of a brown oil. Purification by column chromatography on 80 g of silica gel (elution with 10% EtOAc-hexanes) and then on 26 g of silica gel (elution with 90 : 9 : 1 hexanes : EtOAc : Et_3N) afforded 0.092 g (36%, ca. 85% purity) of **97** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 7.59 (d, J = 5.4 Hz, 1H), 4.47 (d, J = 3.6 Hz, 1H), 7.28 (app. doublet, J = 5.7 Hz, 1H), 6.66 (d, J = 7.6 Hz, 1H), 5.18 (t, J = 5.2 Hz, 1H), 3.62 (s, 6H), 3.17 (d, J = 5.2 Hz, 2H).

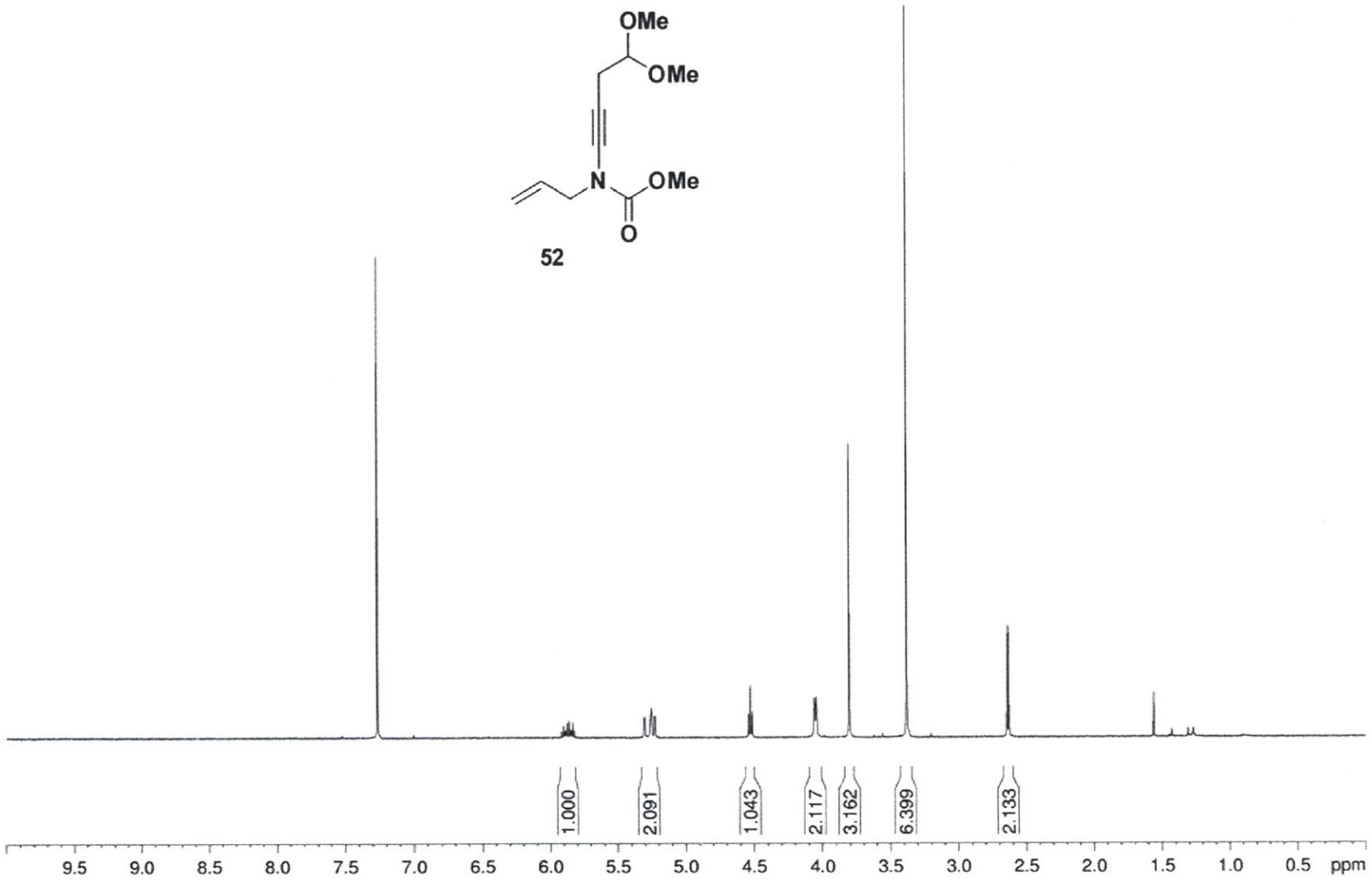

OH
CH(OMe)2
S
N–CO2t-Bu

97

1.000
1.022
1.077
1.890
0.991
1.039
6.354
2.133
9.265
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm



***N*-Methoxycarbonyl-*N*-2-prop-2-enyl-4,4-dimethoxybut-1-ynylamine (52).** A 25-mL, one-necked, round-bottomed flask equipped with a rubber septum was charged with carbamate **103** (0.206 g, 1.79 mmol, 1 equiv), a solution of bromo alkyne **76** (0.410 g, 2.12 mmol, 1.2 equiv) in ca. 2.5 mL of toluene, K_3PO_4 (0.739 g, 3.47 mmol, 2 equiv), 1,10-phenanthroline (0.125 g, 0.69 mmol, 0.4 equiv), and $CuSO_4 \cdot 5H_2O$ (0.088 g, 0.35 mmol, 0.2 equiv). The rubber septum was replaced with a reflux condenser equipped with an argon inlet adapter, and the reaction mixture was heated at 70–75 °C for 63 hours. After cooling to room temperature, the reaction mixture was diluted with ca. 10 mL of EtOAc, filtered through Celite with the aid of 100 mL of EtOAc, and then concentrated to afford 0.577 g of brown oil. Traces of starting materials still present were evaporated by gentle heating (ca. 30 °C at 0.3 mmHg) for 10 h. Column chromatography on 40 g of silica gel (elution with 15% EtOAc-hexanes) afforded 0.278 g of pure product in addition to some mixed fractions. The mixed fractions were chromatographed on 6 g of silica gel (elution with 25% Et_2O-hexanes) to afford 0.048 g of **52** as a colorless oil. The total yield for the reaction was 80%: IR (film) 3084, 2956, 2833, 2268, 1729, 1646, 1446, 1391, 1278, 1234, 1194, 1121, and 1067 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.84-5.90 (m, 1H), 5.26 (m, 2H), 4.53 (t, J = 5.6 Hz, 1H), 4.05 (d, J = 6 Hz, 2H), 3.38 (s, 6H), and 2.63 (d, J = 6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 131.9, 118.6, 103.0, 77.4, 54.2, 53.6, 52.7, and 24.0;


OMe
OMe
N
OMe
O
52
1.000
2.091
1.043
2.117
3.162
6.399
2.133
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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4.0
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3.0
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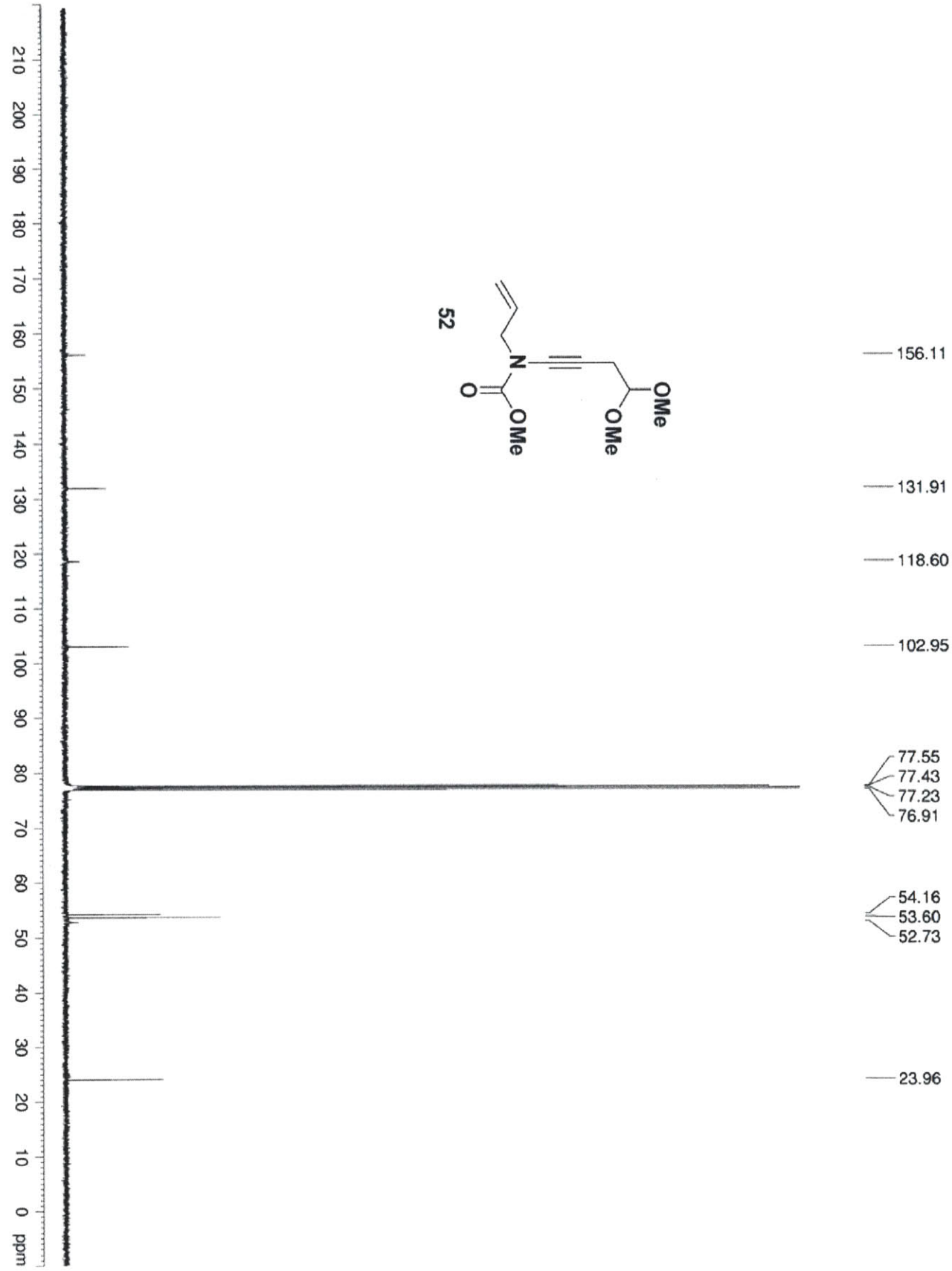
2.0
1.5
1.0
0.5
ppm


52
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O
OMe
OMe
OMe
156.11
131.91
118.60
102.95
77.55
77.43
77.23
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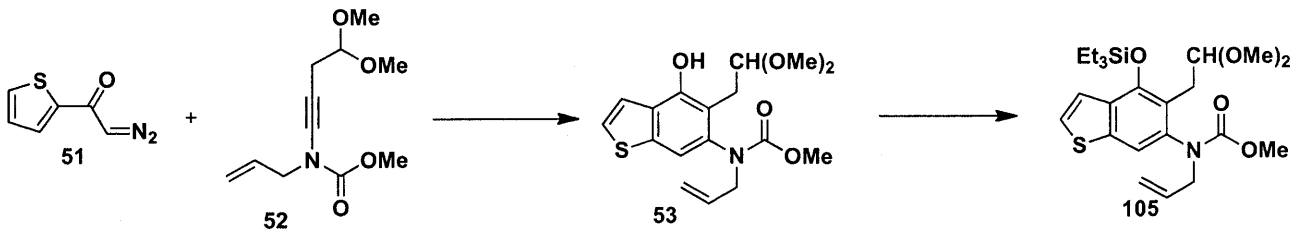
54.16
53.60
52.73
23.96
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



***N*-Allyl-*N*-2-Methoxycarbonyl-[2-(2,2-dimethoxyethyl)-3-(triethylsilyl)oxy-5*H*-thieno[2,3-e]phenyl]amine (105).** A base-washed[32] 20-cm quartz tube (I.D.14 mm) equipped with a magnetic stirrer, rubber septum and argon inlet needle was charged with ynamide **52** (0.259 g, 1.14 mmol, 1.0 equiv) and a solution of diazo **51** (0.208 g, 1.37 mmol, 1.2 equiv) in 11.4 mL of CH_2Cl_2. The septum was secured with wire to the tube to ensure a good seal, the tube was covered in aluminum foil, and the mixture was degassed by purging with argon for ca. 10 min. The aluminum foil was removed and the reaction tube was positioned ca. 15 cm from a Hanovia 450W lamp cooled in a quartz immersion well. The reaction mixture was irradiated for 9.5 h and then transferred to a base-washed 50-mL round-bottomed flask. The solution was concentrated, and the residue was dissolved in 12.5 mL of toluene. The flask was equipped with a magnetic stirrer, condenser, and argon inlet adapter, and the solution was heated at reflux for 3.5 h, and then allowed to cool to room temperature and concentrated to give a brown oil. Column chromatography on 45 g of silica gel (elution with 30% EtOAc-hexanes) provided 0.324 g of **53** as a yellow oil used in the next step without further purification.

A 50-mL one-necked, base-washed, round-bottomed flask equipped with a rubber septum and an argon inlet needle was charged with DMAP (0.04 g, 0.34 mmol, 0.2 equiv), TESCl (0.41 mL, 0.37 g, 2.46 mmol, 1.4 equiv), Et_3N (0.62 mL, 0.45 g, 4.45 mmol, 2.6 equiv), and 1 mL of CH_2Cl_2. The solution was stirred at room temperature for 30 min and then phenol **53** (0.690 g, 1.7 mmol, 1.0 equiv) prepared in the previous

reaction was added with ca. 2.5 mL of CH_2Cl_2, bringing the volume of solvent to a total of 3.4 mL. The argon inlet needle was removed, and the mixture was stirred at rt for 15.5 h. The resulting mixture was washed with 10 mL of water, the aqueous layer was separated and extracted with three 10-mL portions of CH_2Cl_2. The combined organic layers were washed with 10 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford a brown oil. Column chromatography on 40 g of silica gel (elution with 10% EtOAc-hexanes then 20% EtOAc-hexanes) afforded 0.243 g of pure product, as well as mixed fractions. The mixed fractions were concentrated and the residue was purified by column chromatography on 20 g silica gel (elution with 15% EtOAc-hexanes) to give 0.043 g of **105** as a colorless oil. The total yield of **105** was 0.286 g (54% overall from **52**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (s, 2H), 7.31 (s, 1H), 6.00-6.10 (m, 1H), 5.16 (dd, J = 13.0, 9.2 Hz, 2H), 4.66-4.74 (m, 2H), 3.75 (quadruplet, J = 5.7 Hz, 2H), 3.60 (s, 2H), 3.33 (s, 3H), 2.33 (s, 3H), 2.93 (app. triplet, J = 7.8 Hz, 2H), 0.97 (t, J = 7.5 Hz, 9H), 0.78-0.84 (m, 6H).

Et3SiO
CH(OMe)2
O
S
N
OMe
105
2.853
0.936
2.007
1.847
1.680
2.134
3.063
3.000
1.996
9.174
6.206
9.5
9.0
8.5
8.0
7.5
7.0
6.5
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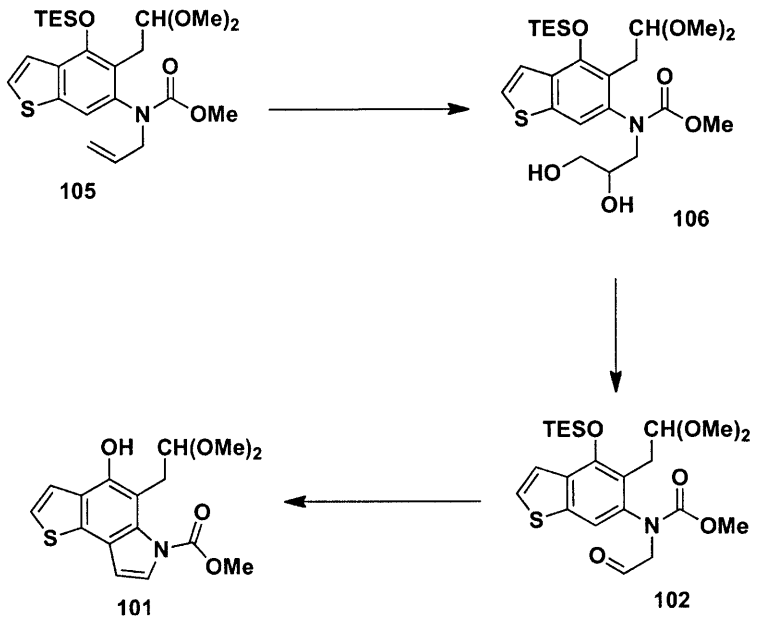
ppm



7-(2,2-dimethoxyethyl)-6-hydroxy-1-Methoxycarbonyl-4*H*-thieno[2,3-e]indole (101). A 50-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with carbamate **105** (0.163 g, 0.32 mmol, 1 equiv), 2.5 mL of THF, 0.8 mL of water, OsO_4 (4 wt% in H_2O, 0.09 mL, 0.004 g, 0.015 mmol, 0.05 equiv), and NMO (0.056 g, 0.48 mmol, 1.5 mmol). The argon inlet needle was removed and the reaction mixture was stirred at room temperature for 13 h. A solution of $NaHSO_3$ (0.605 g, 5.8 mmol, 11 equiv) in 5.5 mL of water was added, and the resulting mixture was stirred at room temperature for 10 min, and then transferred to a separatory funnel with ca. 8 mL of EtOAc. The aqueous layer was extracted with three 10-mL portions of EtOAc. The combined organic layers were washed with 10 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.243 g of diol **106** as a yellow oil used in the next step without purification.

A 25-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with diol **106** (0.243 g, 1.0 equiv) and 1.0 mL of CH_2Cl_2. $NaIO_4$ supported on silica gel (1.57 g, 1.04 mmol, 2.0 equiv) and 1.0 mL of CH_2Cl_2 were

added via temporary removal of the septum and the resulting orange suspension was stirred at room temperature for 4 h. The reaction mixture was filtered through a sintered glass funnel, and the residue was washed with five 10-mL portions of CH_2Cl_2. The filtrate was concentrated to provide 0.174 g of aldehyde **102** as a brown oil used in the next step without purification.

A 100-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with aldehyde **102** (0.174 g, 1.0 equiv), 35 mL of isopropanol (previously purged with a stream of argon), and TBAF (1 M in THF, 2.6 mL, 0.68 g, 2.6 mmol, 5 equiv). The rubber septum was replaced with a reflux condenser equipped with an argon inlet adapter and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with 30 mL of Et_2O and washed with three 10-mL portions of $NaHSO_3$ and 15 mL of saturated NaCl solution. The combined aqueous layers were extracted with three 10-mL portions of CH_2Cl_2, and the combined organic layers were washed with 10 ml of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford a brown oil. NMR analysis of this material indicated that considerable aldehyde **102** remained, so this material was reacted further with TBAF in isopropanol exactly as described above but at room temperature for 1 h, 60 °C for 1 h, and then at 45 °C for 1 h. After cooling to room temperature, the reaction mixture was diluted with 30 mL of Et_2O and washed with three 15-mL of $NaHSO_3$. The combined aqueous layers were washed with three 15-mL of portions of Et_2O, and the combined organic layers were washed with 65 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give a brown oil. Column chromatography on 18 g of silica gel (elution with 15% EtOAc-hexanes) afforded 0.079 g (46%, ca. 90% purity)

of indole **101** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 7.60 (d, J = 4.4 Hz, 1H), 7.56 (d, J = 3.8 Hz, 1H), 7.30 (d, J = 5.4 Hz, 1H), 6.71 (d, J = 3.8 Hz, 1H), 5.18 (t, J = 5.5 Hz, 1H), 4.02 (s, 3H), 3.59 (s, 6H), 3.23 (d, J = 5.2 Hz, 2H).


0.926
1.000
0.996
0.985
0.921
1.020
3.004
6.402
2.110
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
S
OH
CH(OMe)2
N
O
OMe
101