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APPLICATION OF KETENES AND ALLENES IN THE TOTAL SYNTHESIS OF
DITERPENE QUINONES AND INDOLES

by
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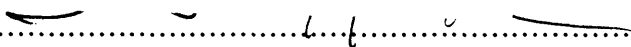
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*Dedicated to
Farkhondeh, Firooz, and Ziba Firooznia
for all their Unending Love and Support
and
In Memory of
Yousef and Ashraf Firooznia
and Reza Riazi-Nezhad*

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Submitted to the Department of Chemistry
on May 30, 1995 in partial fulfillment of the
requirements for the degree of Doctor of Philosophy

ABSTRACT

(+)-Neocryptotanshinone, (-)-cryptotanshinone, and tanshinone IIA, angularly fused Dan Shen diterpenoid quinones isolated from the dried roots of *Salvia miltorrhiza* Bunge, have been synthesized via a regiocontrolled aromatic annulation reaction based on the photochemical Wolff rearrangement. In this fashion, (+)-neocryptotanshinone was synthesized in enantiomerically pure form in only 5 steps from the known compound 1,1-dimethyl-5-tetralol via the reaction of a chiral acetylene and an α -diazo ketone. (+)-Neocryptotanshinone was then cyclized using concentrated sulfuric acid to produce (-)-cryptotanshinone in quantitative yield. Oxidation of (-)-cryptotanshinone afforded tanshinone IIA in excellent yield.

Synthetic approaches to the antitumor agent ellipticine have been investigated. Initial exploration of a synthetic route which relies on the base-catalyzed cyclization of 2-(allenyl)arylamines as the key step has been completed. A promising route to an advanced intermediate has been developed.

A convergent synthesis of substituted allenes based on the palladium-catalyzed reaction of propargylic carbonates and organoboron compounds has been developed. The requisite propargylic carbonates are prepared in a single step via the addition of acetylides to an aldehyde or ketone followed by *in situ* trapping with methyl chloroformate. Alkyl-, vinyl-, and aryl-substituted organoboron compounds participate in the reaction, which has been applied to the synthesis of a variety of substituted allenes. The reaction conditions tolerate a variety of functional groups, including alkyl ethers, nitrile and ketal functionalities.

Thesis Supervisor: Rick L. Danheiser

Title: Professor of Chemistry

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Part I:

Total Synthesis of Dan Shen Diterpenoid Quinones

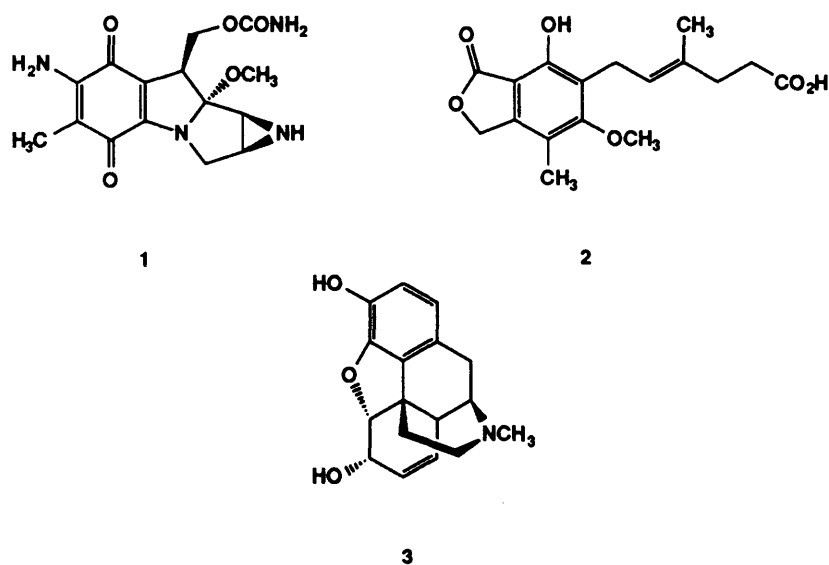
Chapter 1

Introduction and Background

Introduction

Highly substituted aromatic systems are common key structural features in a variety of biologically significant compounds.¹ The invention of efficient methods for the synthesis of such systems has been a worthy challenge for synthetic organic chemists since the late nineteenth century. Scheme 1 features mitomycin C (**1**), mycophenolic acid (**2**), and morphine (**3**) as selected examples of the numerous medicinally important natural products with highly substituted aromatic systems.

Scheme 1



Classical approaches to highly substituted aromatic compounds have relied on further functionalization of readily available, inexpensive benzene derivatives in stepwise fashion, appending substituents one at a time. Most such approaches are based on

1. Footnotes 2-15 in Koo, S.; Liebeskind, L. S.; *J. Am. Chem. Soc.* **1995**, *117*, 3389.

electrophilic² and nucleophilic substitution³ reactions. Recently, directed metalation reactions⁴ have been used as an alternative method for the introduction of substituents onto pre-existing aromatic systems. Despite their effectiveness for the preparation of simple aromatic derivatives, these classical approaches can suffer from a variety of complications when applied to the synthesis of highly substituted systems. For example, the control of the regioselectivity of substitution reactions becomes increasingly difficult as the number of substituents on the ring grows. Furthermore, the vigorous reaction conditions associated with the use of powerful electrophiles and nucleophiles are sometimes incompatible with many functional groups, thereby necessitating protection and deprotection steps. Finally, and most important, the inherent lack of convergence of such linear substitution strategies often leads to long, multistep syntheses with low overall efficiencies.

*Aromatic annulation methods*⁵ involve the application of convergent strategies for assembling the aromatic system from acyclic (or non-aromatic) precursors in a single step. These methods enjoy several advantages over classical linear substitution approaches. The regiochemical ambiguities associated with aromatic substitution reactions are frequently avoided as all (or most) of the substituents are generated in place in the annulation process. Annulation routes can thus provide access to substitution patterns that cannot be obtained easily via the more conventional strategies. Moreover, the intrinsic convergent nature of

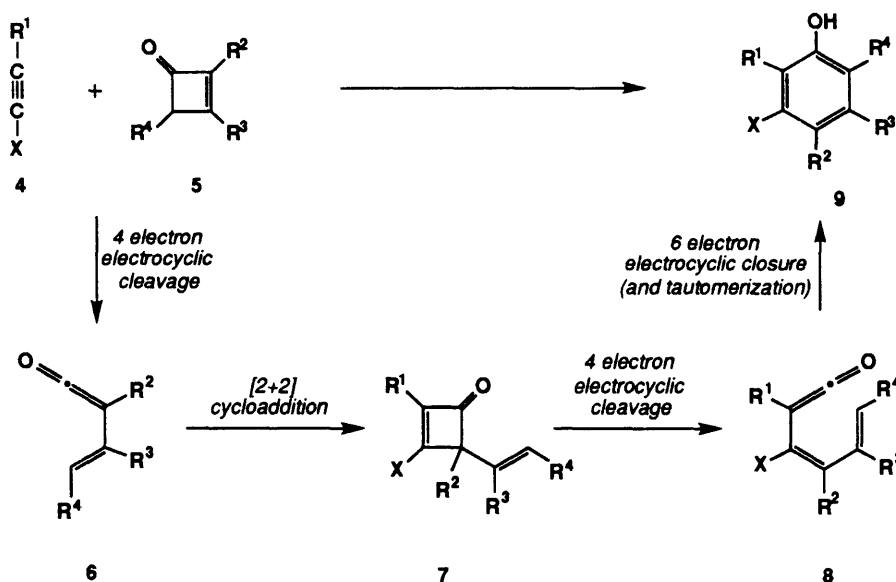
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2. For a recent review of Friedel-Crafts alkylation reactions, see (a) Olah, G. A.; Krishnamurti, R.; Surya, G. K. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 3, pp 293-339. (b) Olah, G. A. *Friedel-Crafts and Related Reactions*; Interscience: London, 1964, Vol. I-IV. (c) For a review of Friedel-Crafts acylations, see Heaney, H. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 2, pp 733-768.
 3. For a review of nucleophilic aromatic substitution reactions, see (a) Paradisi, C. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 4, pp 423-450. (b) Miller, J., *Aromatic Nucleophilic Substitution*; Elsevier: New York, 1968.
 4. (a) Gawly, R. E.; Rein, K. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. , pp 459-476. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (c) Gschwend, H. W.; Rodriguz, H. R. *Org. React.* **1979**, *26*, 1. (d) Townsend, C. A.; Davus, S. G.; Christensen, S. B.; Link, L. C.; Lewis, C. P. *J. Am. Chem. Soc.* **1981**, *103*, 6885. (e) Townsend, C. A.; Bloom, L. M. *Tetrahedron Lett.* **1981**, *22*, 3923. (f) Narasimhan, N. S.; Mali, R. S. *Top. Curr. Chem.* **1987**, *138*, 63.
 5. For reviews, see (a) Bamfield, P.; Gordon, P. F. *Chem. Soc. Rev.* **1984**, *13*, 441. (b) Wedenmeyer, K. F. In *Methoden der Organischen Chemie (Houben-Weyl)*; Muller, E., Ed.; George Thieme: Stuttgart, 1976; Vol. 6/1c, pp 853-924.

annulation strategies allows for the efficient assembly of highly substituted aromatic systems that would otherwise require long, multistep synthetic sequences.

The most important aromatic annulation strategies developed recently are based on the Diels-Alder reaction,⁶ carbonyl condensation reactions,⁷ and transition-metal mediated processes, most notably cobalt-mediated [2+2+2] acetylene cycloadditions⁸ and the Dötz reaction of Fischer carbene complexes.⁹

A powerful annulation strategy based on the reaction of acetylenes and vinylketenes has been developed in our laboratory.¹⁰ Scheme 2 outlines the pericyclic cascade of reactions involved in this process.

Scheme 2

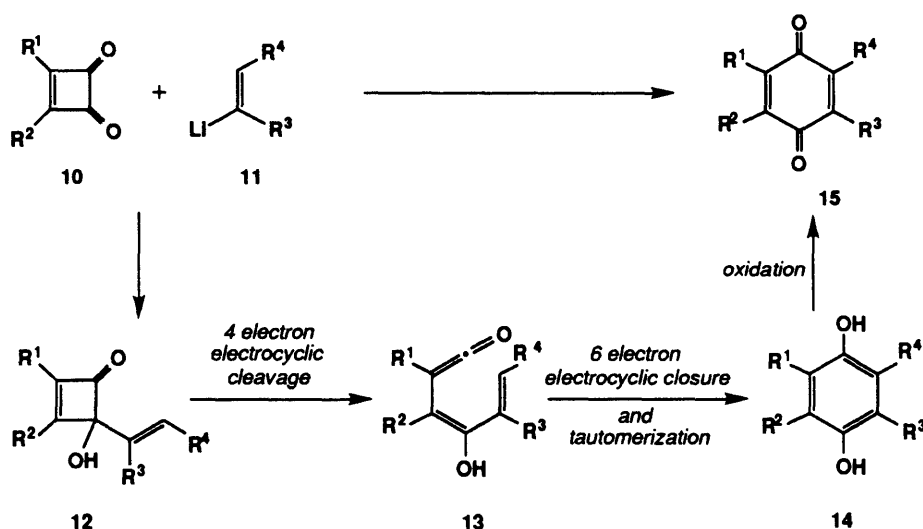


6. Recent examples: (a) Snowden, R. L.; Wüst, M. *Tetrahedron Lett.* **1986**, *27*, 703. (b) Boger, D. L.; Mullican, M. D. *Org. Synth.* **1987**, *65*, 98. (c) Ziegler, T.; Layh, M.; Effenberger, F. *Chem. Ber.* **1987**, *120*, 1347 and references cited therein.
7. Recent examples: (a) Tius, M. A.; Gomez-Galeno, J. *Tetrahedron Lett.* **1986**, *27*, 2571. (b) Chan, T. H.; Prasad, C. V. C. *J. Org. Chem.* **1986**, *51*, 3012.
8. Vollhardt, K. P. C. *Angew Chem., Int. Ed. Engl.* **1984**, *23*, 539.
9. Reviews: (a) Dötz, K. H.; Fischer, H.; Hofmann, P.; Kriessel, F. R.; Schubert, U.; Weiss, K. *Transition Metal Carbene Complexes*; Verlag Chemie International: Deerfield Beach, FL, 1984. (b) Dötz, K. H. *Angew Chem., Int. Ed. Engl.* **1984**, *23*, 587. (c) Wulff, W. D. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press, Inc.: Greenwich, CT, 1989; Vol. 1.
10. (a) Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1672, and references cited therein. (b) Danheiser, R. L.; Gee, S. K.; Perez, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 806. (c) Danheiser, R. L.; Nishida, A.; Savariar, S.; Trova, M. P. *Tetrahedron Lett.* **1988**, *29*, 4917. (d) See also Kowalski, C. J.; Lal, G. S. *J. Am. Chem. Soc.* **1988**, *110*, 3693.

Thermal four-electron electrocyclic ring opening of the cyclobutenone **5** produces the vinylketene **6**, and subsequent [2+2] cycloaddition with the ketenophilic acetylene **4** leads to the formation of the 4-vinylcyclobutenone intermediate **7**. Four-electron electrocyclic ring cleavage of **7** produces the dienylketene **8**, which then undergoes 6-electron electrocyclic closure (and subsequent tautomerization) to furnish the phenol **9**.

A related annulation method for the synthesis of quinones has been developed independently by Liebeskind¹¹ and Moore¹² in which the key intermediate 4-vinylcyclobutenone **12** is formed by the treatment of a squaric acid derivative **10** with an aryl- or vinyl-lithium compound (**11**) (Scheme 3). The 1,4-dihydroquinone product **14** is then converted by oxidation to the 1,4-benzoquinone **15**.

Scheme 3

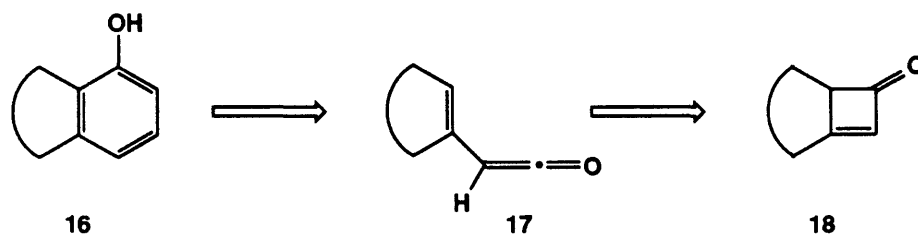


- (a) Liebeskind, L. S.; Iyer, S.; Jewell, C. F., Jr. *J. Org. Chem.* **1986**, *51*, 3065. (b) For the extension of this work to the synthesis of stannylquinones, see Edwards, J. P.; Krysan, D. J.; Liebeskind, L. S.; Foster, B. S. *J. Am. Chem. Soc.* **1990**, *112*, 8612. (c) For the synthesis of quinolinequinones and 1,2,3,4-tetrahydroquinolinequinones, see Liebeskind, L. S.; Zhang, J. *J. Org. Chem.* **1991**, *56*, 6379. (d) For the synthesis of pyridone-based azaheteroaromatics, see Gurski Birchler, A.; Liu, F.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 7737.
- (a) Moore, H. W.; Yerxa, B. R.; *Chem Tracts* **1992**, *5*, 273. (b) Perri, S. T.; Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1986**, *51*, 3067. (c) Perri, S. T.; Moore, H. W. *Tetrahedron Lett.* **1987**, *28*, 4507. (d) Moore, H. W.; Perri, S. T. *J. Org. Chem.* **1988**, *53*, 996. (e) Reed, M. W.; Moore, H. W. *J. Org. Chem.* **1988**, *53*, 4166. (f) Perri, S. T.; Moore, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 1897. (g) Heering, J. M.; Moore, H. W. *J. Org. Chem.* **1991**, *56*, 4048. (h) Xu, S. L.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 326. (i) Gayo, L. M.; Winters, M. P.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 6896. (j) Liu, H.; Gayo, L. M.; Sullivan, R. W.; Choi, A. Y. H.; Moore, H. W. *J. Org. Chem.* **1994**, *59*, 3284.

Liebeskind has devised several related annulation approaches to quinones and aromatic systems based on 4-vinylcyclobutenone intermediates. One approach involves the sequential introduction of substituents onto 3-isopropoxy-4-substituted-3-cyclobutene-1,2-diones.¹³ Later, Liebeskind developed versatile syntheses of cyclobutenones through the use of palladium-catalyzed cross coupling reactions of 4-chloro-2-cyclobutenone derivatives with organostannanes and organozirconium reagents,¹⁴ leading to the synthesis of highly substituted phenols,^{14b} resorcinols,^{14b,d} 2-pyrones,^{14e} naphthoquinones,^{14g} anthraquinones,^{14g} and angularly-fused polycyclic aromatic systems.^{14f,h} Catechols and other 1,2-dioxygenated aromatics were obtained via conjugate addition of vinyl-, aryl-, and heteroarylcuprates to cyclobutenediones followed by thermal rearrangement.¹⁵

The scope of the cyclobutenone-based aromatic annulation strategy developed in our laboratory and outlined above in Scheme 2 is limited to the construction of highly-substituted monocyclic aromatic systems. Polycyclic aromatic compounds would require the use of polycyclic cyclobutenones as vinylketene precursors, and such systems (e.g. **18**) are relatively difficult to prepare (Scheme 4).

Scheme 4

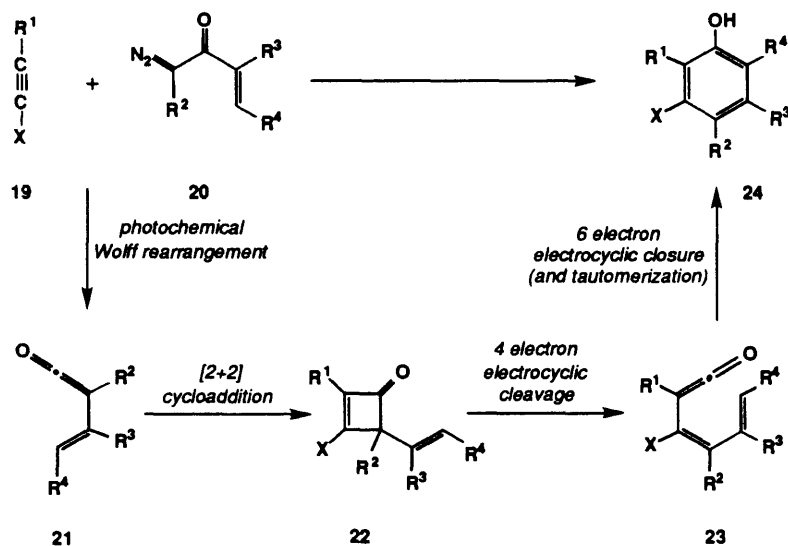


13. Liebeskind, L. S.; Granberg, K. L.; Zhang, J. *J. Org. Chem.* **1992**, *57*, 4345.
14. (a) Liebeskind, L. S.; Wang, J. *Tetrahedron Lett.* **1990**, *31*, 4293. (b) Krysan, D. J.; Gurski, A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1992**, *114*, 1412. (c) Liebeskind, L. S.; Yu, M. S.; Fengl, R. W. *J. Org. Chem.* **1993**, *58*, 3543. (d) Liebeskind, L. S.; Wang, J. *J. Org. Chem.* **1993**, *58*, 3550. (e) Liebeskind, L. S.; Wang, J. *Tetrahedron* **1993**, *49*, 5461. (f) Edwards, J. P.; Krysan, D. J.; Liebeskind, L. S. *J. Org. Chem.* **1993**, *58*, 3942. (g) Edwards, J. P.; Krysan, D. J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 9868. (h) Koo, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1995**, *117*, 3389.
15. Gurski, A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 6101.

An Aromatic Annulation Strategy Based on the Photochemical Wolff Rearrangement

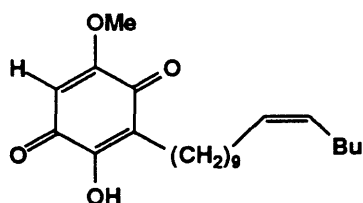
In order to surmount the limitations of the cyclobutenone-based aromatic annulation strategy, an alternative way of accessing the vinylketene intermediates was sought. Among several types of precursors examined, α -diazo ketones were found to function as particularly useful precursors to vinylketenes in this annulation chemistry. Thus, photochemical Wolff rearrangement¹⁶ of α -diazo ketones **20** efficiently generates the vinylketenes **21** which then participate in the previously described pericyclic cascade (Scheme 5). This "second generation" aromatic annulation strategy¹⁷ thus extends the scope of the original method to the synthesis of *polycyclic* aromatic compounds. A wide range of aryl and heteroaryl diazo ketones participate in this annulation reaction, providing an efficient route to substituted naphthalenes, benzofurans, benzothiophenes, indoles, and carbazoles.

Scheme 5



16. (a) Wolff, L. *Justus Liebigs Ann. Chem.* **1912**, 394, 23. For reviews, see: (b) Gill, G. B. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 3, pp 887-912. (c) Regitz, M.; Maas, G. *Diazo Compounds: Properties and Synthesis*; Academic Press: Orlando, FL, 1986, p 185. (d) Ando, W. In *The Chemistry of Diazonium and Diazo Groups*; Patai, S., Ed.; J. Wiley and Sons: New York, 1978, Part 1, p 458.
17. Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc.* **1990**, 112, 3093.

This second generation aromatic annulation strategy has a dual advantage over the original, cyclobutenone-based method. First, it provides access to a wider variety of aromatic systems, including polycyclic carboaromatic and heteroaromatic compounds. Moreover, the photochemical Wolff rearrangements can be carried out at considerably lower temperatures than the corresponding cyclobutenone ring-cleavage reactions. The total synthesis of the host defense stimulant maesanin¹⁸ (**25**) provided an early demonstration of the utility of this new annulation protocol.



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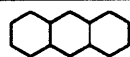
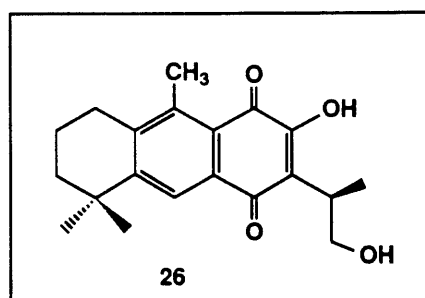
In order to further study the scope and limitations of the photochemical aromatic annulation, we chose to investigate the synthesis of several *polycyclic* diterpenoid quinones isolated from the dried roots of *Salvia miltorrhizia* Bunge, the source of a popular traditional Chinese drug (*vide infra*). This family of compounds provided us with the opportunity to examine the application of our method towards the synthesis of each of the three possible tricyclic arrangements of fused six-membered rings: linearly-fused systems such as that found in aegyptinone B (**26**),¹⁹ angularly-fused systems such as that of danshexinkun A (**27**),²⁰ and the condensed phenalenone system as found in the diterpene salvilenone (**28**).²¹

18. Danheiser, R. L.; Cha, D. D. *Tetrahedron Lett.* **1990**, *31*, 1527.

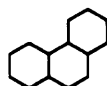
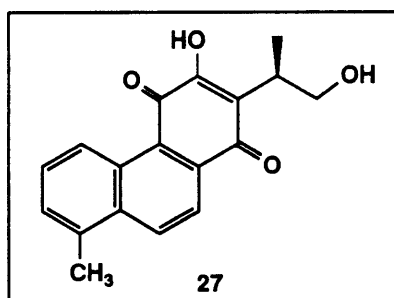
19. Danheiser, R. L.; Casebier, D. S.; Huboux, A. H. *J. Org. Chem.* **1994**, *59*, 4844.

20. Danheiser, R. L.; Casebier, D. S.; Loebach, J. L. *Tetrahedron Lett.* **1992**, *33*, 1149.

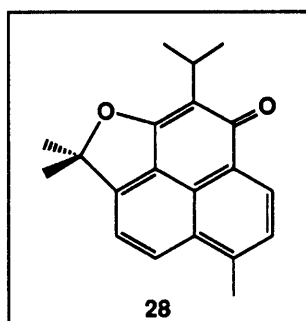
21. Danheiser, R. L.; Helgason, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 9471.



Aegyptinone B



Danshexinkun A



Salvilenone

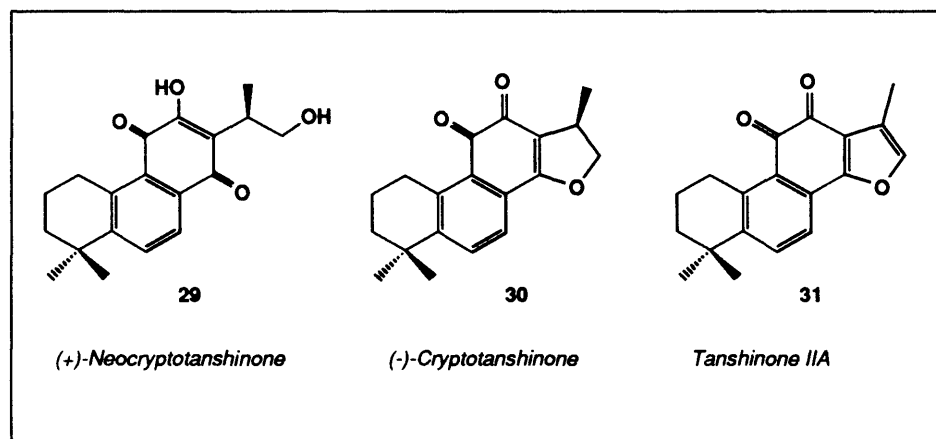
Dan Shen Diterpenoid Quinones

Dan Shen, obtained from the dried root of the Chinese red-rooted sage *Salvia miltorrhizia*, is an important drug in traditional Chinese medicine.²² It is currently used clinically for the treatment of heart disease, menstrual disorders, miscarriage, hypertension, and viral hepatitis. *Dan Shen* is also known to possess antipyretic, antineoplastic, antimicrobial, and anti-inflammatory properties.^{22b,23} It has been shown that *Dan Shen* consists of more than 50 interesting abietane diterpenoid quinones. The extreme scarcity of

22. (a) Duke, J. A.; Ayensu, E. S. *Medicinal Plants of China*; Reference Publications, Inc.: Algonac, MI, 1985; Vol. 2, p 381. (b) *Pharmacology and Applications of Chinese Materia Medica*; Chang, H. M.; But, P. P.; Eds.; World Scientific Publishing Co.: Singapore, 1986, Vol. 1, pp 255-268.
23. For additional references documenting the biological activity of *Dan Shen*, see: (a) Footnotes 3-5 in Lee, J.; Snyder, J. K. *J. Org. Chem.* **1990**, *55*, 4995. (b) Chang, H. M.; Cheng, K. P.; Choang, T. F.; Chow, H. F.; Chui, K. Y.; Hon, P. M.; Tan, F. W. L.; Yang, Y.; Zhong, Z. P.; Lee, C. M.; Sham, H. L.; Chan, C. F.; Cui, Y. X.; Wong, H. N. C. *J. Org. Chem.* **1990**, *55*, 3537, and references cited therein. (c) Thomson, R. H. *Naturally Occurring Quinones*; Chapman and Hall: London, 1987, Vol. 3, pp 624-629, and references cited therein.

some of these substances, however, has rendered the identification of the most active individual components in *Salvia miltorrhizia* problematic. Efficient chemical syntheses of these diterpenoid quinones thus appears to be the best approach towards the identification of their individual biological significance.

The first part of this thesis describes the total synthesis of three Dan Shen diterpenoid quinones: (+)-neocryptotanshinone (**29**), (-)-cryptotanshinone (**30**), and tanshinone IIA (**31**). This project served a threefold purpose. First, it provided a further test for the recently developed "second generation" version of our aromatic annulation strategy discussed above. A second objective of the project was to develop efficient syntheses of the target compounds practical enough to support the preparation of gram quantities of each diterpene, thus facilitating the evaluation of their biological activity. Finally, it provided the first unambiguous assignment of the absolute stereochemistry of neocryptotanshinone and cryptotanshinone (*vide infra*).



The tanshinones were first isolated by Nakao and Fukushima.²⁴ After some early confusion, the existence of four different compounds, namely tanshinones I, IIA, IIB, and cryptotanshinone, was finally established.²⁵ Extensive degradation studies by

24. Nakao, M. Fukushima, T. *J. Pharm. Soc. Japan* **1934**, *54*, 154.

25. (a) Takiura, K. *J. Pharm. Soc. Japan* **1941**, *61*, 475. (b) Takiura, K. *Chem. Pharm. Bull.* **1962**, *10*, 112.

Takiura,^{25a,26} Kakisawa,²⁷ and by Wessely and his co-workers²⁸ led to the structural assignments for tanshinones I²⁸ and IIA,^{25b,27} and cryptotanshinone.^{25a,26a}

Neocryptotanshinone was first reported by Takiura in his structure determination of tanshinone IIA.^{26a} It was not until recently, however, that neocryptotanshinone was isolated from the plant.²⁹

To our knowledge, there has been no unambiguous assignment of the absolute stereochemistry of neocryptotanshinone and cryptotanshinone to date. However, the optical rotations for these compounds have been reported.^{29,30}

The above diterpenoid quinones have all exhibited promising biological activity. Tanshinone IIA and cryptotanshinone have shown strong activity against carcinoma of the human nasopharynx (KB). It has been speculated that the saturated A ring possessing a *gem*-dimethyl group is required for this activity.³¹ Tanshinone IIA and cryptotanshinone have also shown antiplatelet aggregation activity.³⁰ Cryptotanshinone is known to be an effective coronary vasodilator,³² and has been found to be active against *Staphylococcus aureus* and gram positive bacteria.³³

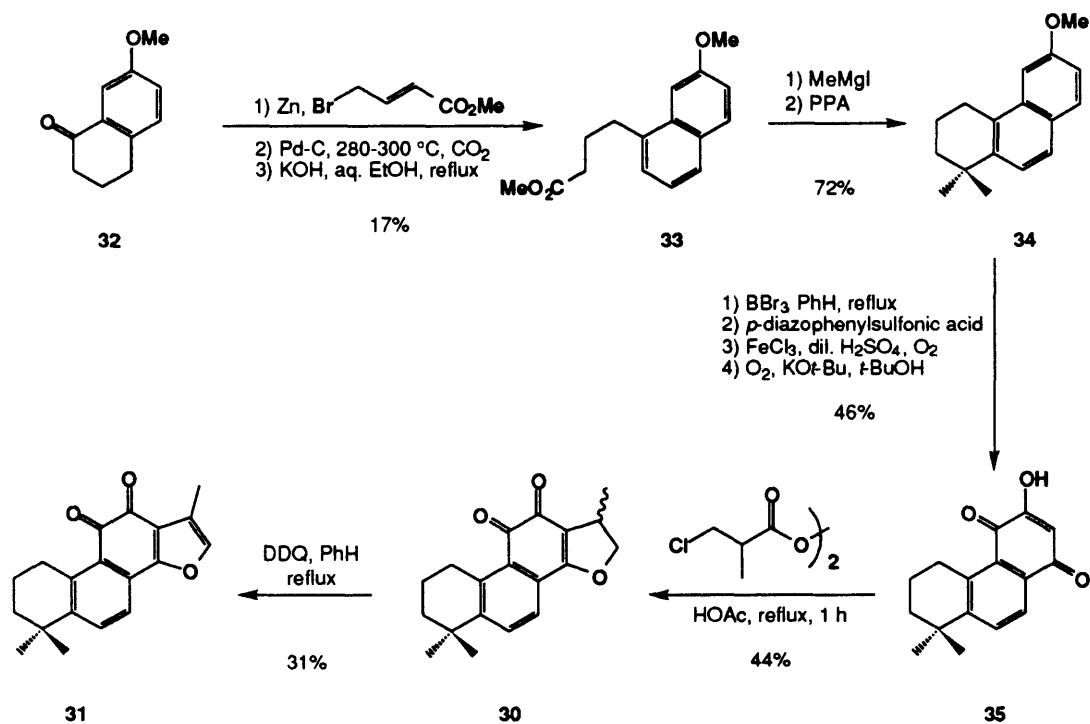
Previous Syntheses of Cryptotanshinone and Tanshinone IIA

Baillie and Thomson reported the first successful syntheses of racemic cryptotanshinone (**30**) and tanshinone IIA (**31**) in 1968.³⁴ They constructed the A ring of cryptotanshinone using a strategy that became the standard method for several later syntheses (Scheme 6). Reformatsky addition of methyl bromoacetate to the commercially

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26. (a) Takiura, K. *J. Pharm. Soc. Japan* **1941**, *61*, 482. (b) Takiura, K. *J. Pharm. Soc. Japan* **1943**, *63*, 40.
 27. (a) Okumura, Y.; Kakisawa, H.; Kato, M.; Hirata, Y. *Bull. Chem. Soc. Jpn.* **1961**, *34*, 895. (b) Okumura, Y.; Kakisawa, H.; Kato, M.; Hirata, Y. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 2061.
 28. (a) von Wessely F.; Wang, S. *Ber.* **1940**, *73*, 19. (b) von Wessely, F.; Bauer, A. *Ber.* **1942**, *75*, 617. (c) von Wessely, F.; Lauterbach, T. *Ber.* **1942**, *75*, 958.
 29. Lee, A.-R.; Wu, W.-L.; Chang, W.-L.; Lin, H.-C.; King, M.-L. *J. Nat. Prod.* **1987**, *50*, 157.
 30. Onitsuka, M.; Fujiu, M.; Shinma, N.; Maruyama, H. B. *Chem. Pharm. Bull.* **1983**, *31*, 1670.
 31. Wu, W.-L.; Chang, W.-L.; Lee, A.-R.; Lin, H.-C.; King, M.-L. *J. Med. Sci.* **1985**, *6*, 159.
 32. Chen, C.-C.; Chen, H.-T.; Chen, Y.-P.; Hsu, H.-Y.; Hsieh, T.-C. *Taiwan Pharm. Assoc.* **1986**, *38*, 226.
 33. Honda, G.; Koezuka, Y.; Tabata, M. *Chem. Pharm. Bull.* **1988**, *36*, 408.
 34. Baillie, A. C.; Thomson, R. H. *J. Chem. Soc. (C)* **1968**, 48.

available tetralone **32**, followed by dehydrogenation, produced the naphthalene **33**. Treatment of **33** with excess methyl Grignard reagent followed by intramolecular Friedel-Crafts alkylation then afforded the desired tetrahydrophenanthrol **34**.

Scheme 6



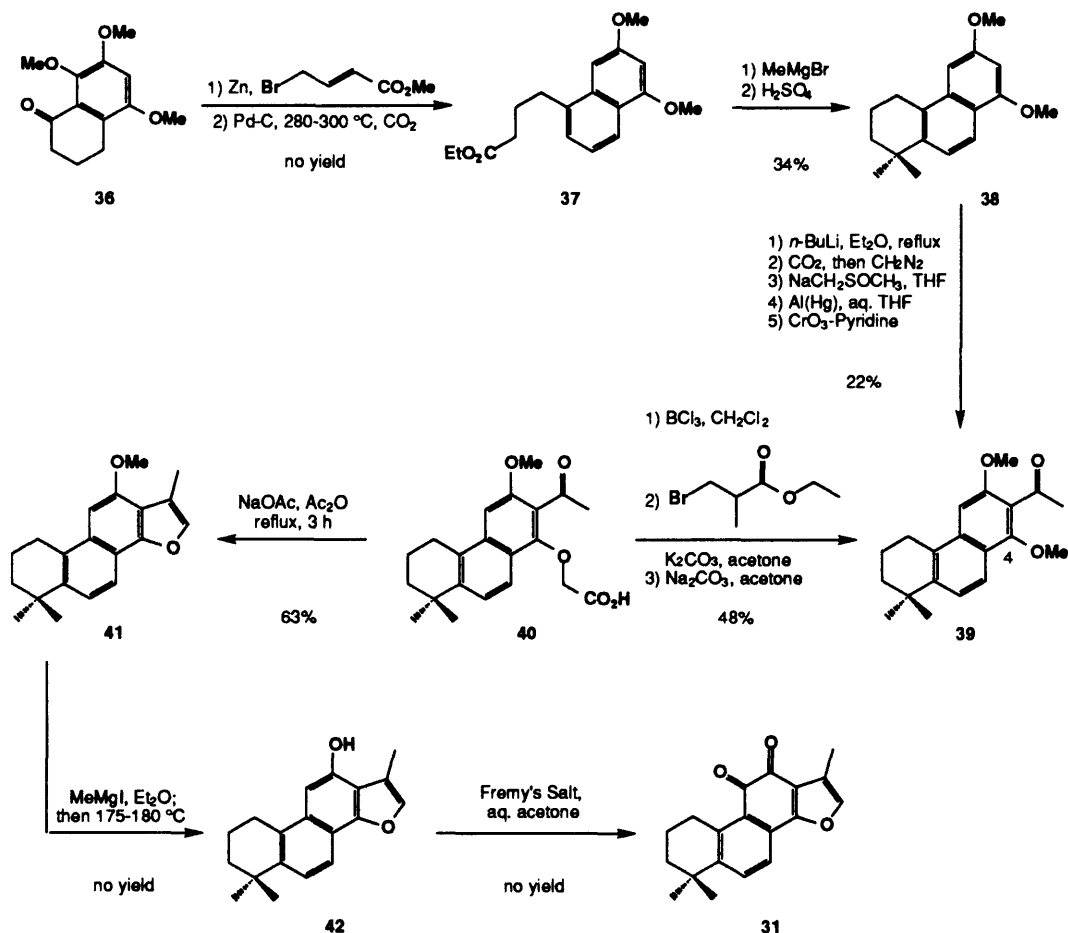
Tetrahydrophenanthrol **34** was then converted to racemic cryptotanshinone (**30**) in five steps. Oxidation with DDQ then afforded tanshinone IIA (**31**). The construction of tanshinone IIA (**31**) was thus completed in 11 steps, producing the natural product in 0.8% overall yield, whereas (\pm)-cryptotanshinone (**30**) was produced in ten steps with 2.5% overall yield.

The next synthesis of tanshinone IIA (**31**) was also published in 1968 by Kakisawa,³⁵ one of the most active scientists in this field. He employed the stepwise cyclization of each ring for the construction of the carbon skeleton of the compound

35. (a) Kakisawa, H.; Tateishi, M.; Kusumi, T. *Tetrahedron Lett.* **1968**, 3783. (b) Tateishi, M.; Kusumi, T.; Kakisawa, H. *Tetrahedron* **1971**, 27, 237.

(Scheme 7). Starting with the known tetralone **36** (available in three steps and 85% yield from 1,2,4-trimethoxybenzene), the saturated A ring was installed using Baillie and Thomson's strategy. Surprisingly, no explanation was offered about the "protodemethoxylation" reaction that takes place during the dehydrogenation leading to the ethyl ester **37**. Unfortunately, this unforeseen event necessitated an additional oxidation reaction as the final step of the synthesis, thereby rendering the choice of 1,2,4-trimethoxybenzene as starting material costly and futile. Starting with the much less expensive resorcinol dimethyl ether would have provided the same result.

Scheme 7



With the tricyclic intermediate **38** at hand, a heteroatom directed *ortho* metallation reaction was employed to install an acetyl group between the methoxy substituents to produce the ketone **39**. Selective deprotection of the 4-methyl ether, and treatment of the resulting phenol with ethyl bromoacetate afforded the keto acid **40**. A Perkin reaction was then used to form the furan moiety: treatment of the keto acid **40** with sodium acetate in acetic anhydride at reflux produced the furonaphthalene **41** in 63% yield. The remaining methyl ether was then cleaved by treating **41** with methylmagnesium iodide in ether. After the evaporation of the solvent, the residue was heated at 175-180 °C for 40 minutes. The resulting naphthol **42** was oxidized to tanshinone IIA (**31**) using Fremy's salt.

This total synthesis does not offer a great deal of novel and innovative chemistry. The synthetic sequence is lengthy (18 steps), and the overall yield of the penultimate intermediate **41** is only 1.6%.³⁶

The third synthesis of tanshinone IIA was also reported by Kakisawa, this time employing a Diels-Alder strategy (Scheme 8).³⁷ The furophenol **43**,³⁸ available in two steps and 48% yield from 2,6-dihydroxyacetophenone, was chosen as a key building block. This phenol was readily oxidized to the furoquinone **44** in quantitative yield. The Diels-Alder reaction of this quinone with the diene **45**³⁹ afforded, after dehydrogenation, the tetracyclic furoquinone **47**. Hydrogenation of the furan ring, followed by cleavage of the resulting dihydrofuran under basic conditions, provided neocryptotanshinone (**29**) (at that time not yet isolated from the natural source, and therefore not purified and characterized). Cyclization under acidic conditions provided (\pm)-cryptotanshinone (**30**), which was then dehydrogenated with DDQ to afford tanshinone IIA (**31**).

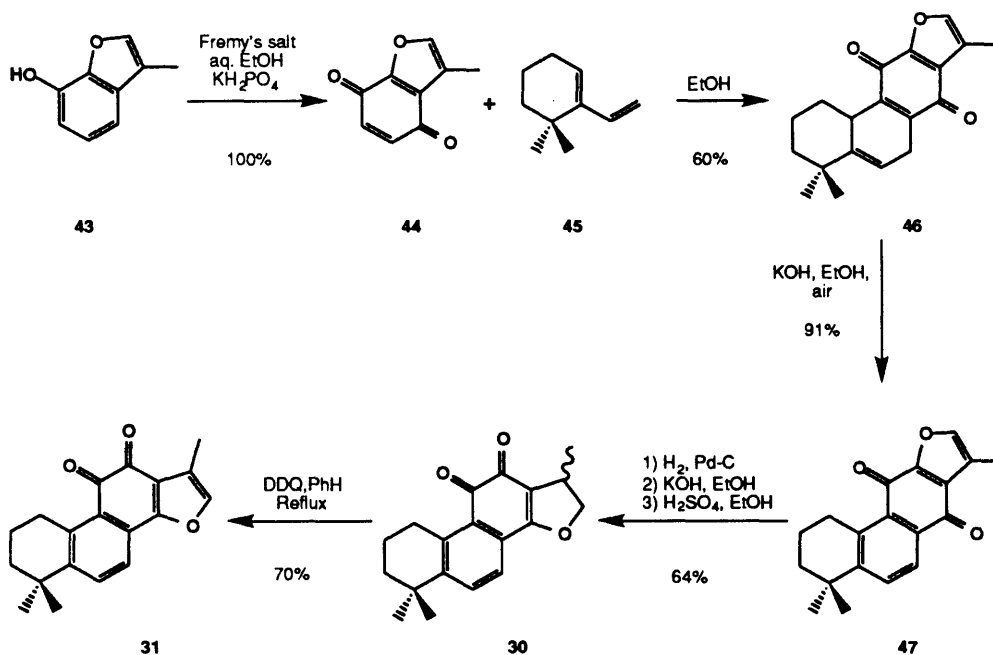
36. The overall yield for tanshinone IIA is unknown, since the yields for the final two reactions were not reported in the papers.

37. (a) Kakisawa, H.; Inouye, Y. *J. Chem. Soc., Chem. Commun.* **1968**, 1327. (b) Inouye, Y.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 3318.

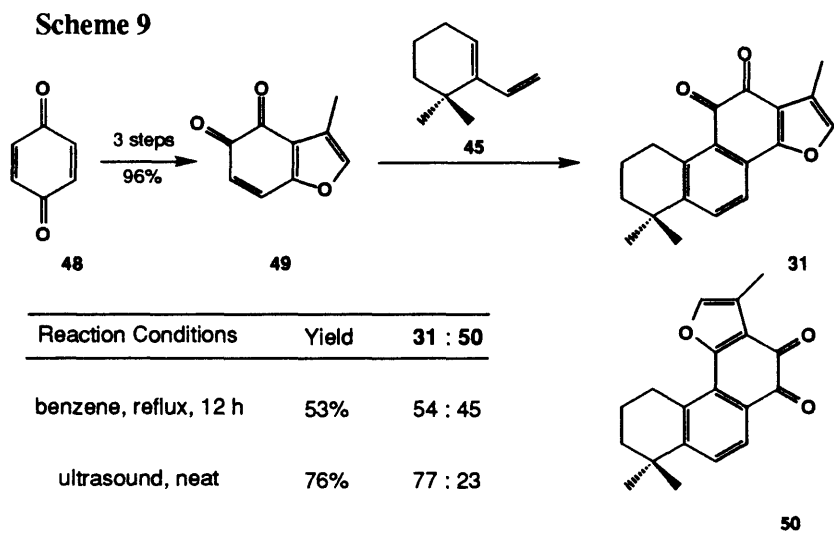
38. Whalley, W. B. *J. Chem. Soc.* **1951**, 3229.

39. Kakisawa, H.; Ikeda, M. *J. Chem. Soc. Jpn.* **1967**, *88*, 476.

Scheme 8



While investigating ultrasound promoted Diels-Alder cycloaddition reactions, Snyder developed the most convergent synthesis of tanshinone IIA reported to date (Scheme 9).⁴⁰



40. (a) Lee, J.; Snyder, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 1522. (b) Lee, J.; Snyder, J. K. *J. Org. Chem.* **1990**, *55*, 4995.

Snyder discovered that the ultrasound promoted Diels-Alder reaction of the diene **45** and the *o*-quinone **49**⁴¹ *in the absence of solvent* produced tanshinone IIA (**31**) in 76% yield, and with good regioselectivity.

With the exception of Snyder's work, the previous syntheses of tanshinone II A and cryptotanshinone are composed of lengthy linear sequences and proceed in low overall yield. Moreover, these prior syntheses were not designed to produce cryptotanshinone in enantiomerically pure form. The following chapter describes our efforts towards the total synthesis of the Dan Shen diterpenoid quinones using a convergent strategy based on the photochemical aromatic annulation.

41. For the synthesis of **49** in three steps (96% overall yield) from *p*-benzoquinone and 1-(*N*-morpholino)propene, see (a) Lee, J.; Tang, J.; Snyder, J. K. *Tetrahedron Lett.* **1987**, *28*, 3427. (b) Domschke, G. *J. Prakt. Chem.* **1966**, 144.

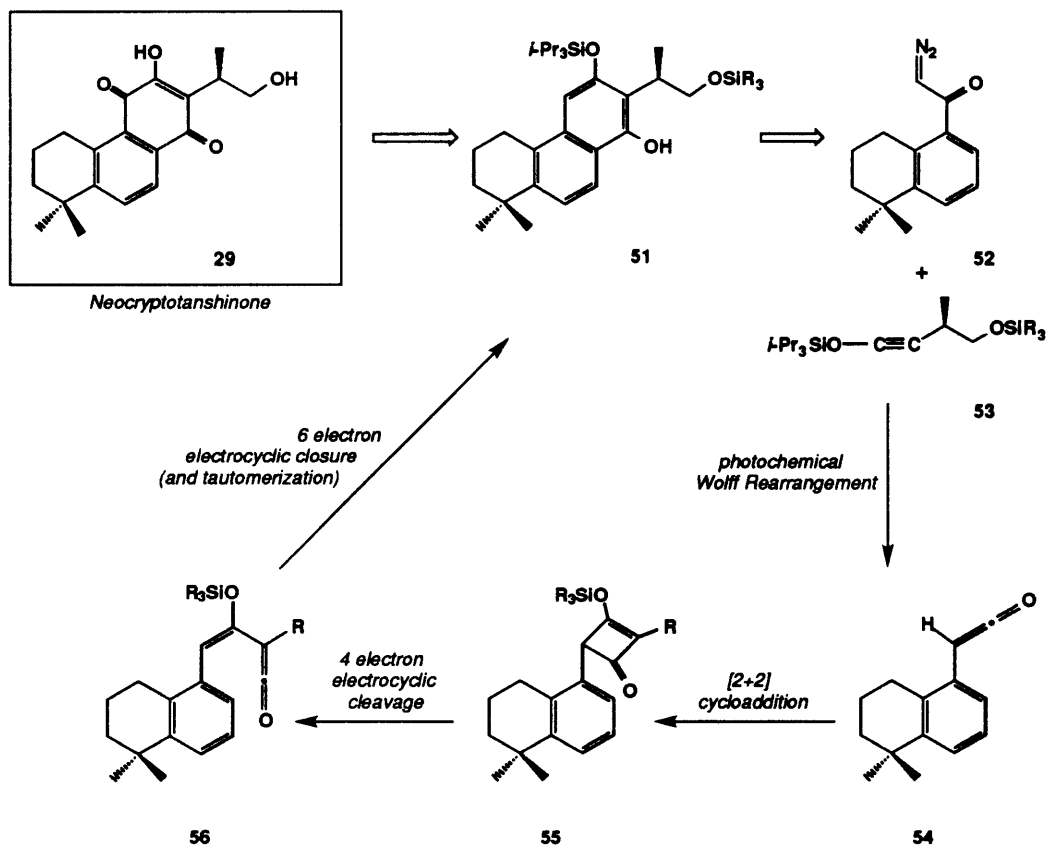
Chapter 2

Total Synthesis of (+)-Neocryptotanshinone, (-)-Cryptotanshinone, and Tanshinone IIA

Retrosynthetic Analysis

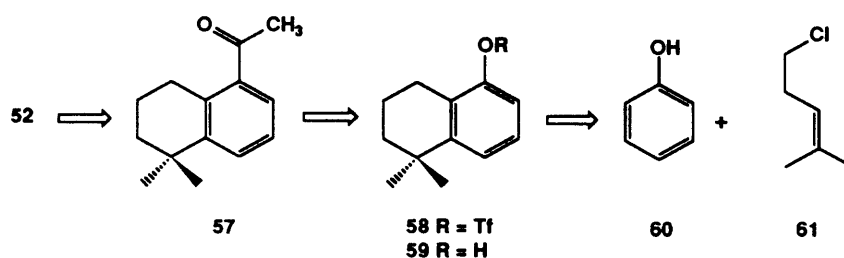
The application of our "second generation" aromatic annulation strategy to the assembly of the key tricyclic intermediate **51**, a precursor to (+)-neocryptotanshinone (**29**), (-)-cryptotanshinone (**30**), and tanshinone IIA (**31**) is outlined in the retrosynthetic scheme below (Scheme 10). The key reaction in our synthetic plan involved the reaction of the α -diazo ketone **52** with the siloxyacetylene **53**.

Scheme 10



The diazo ketone **52** was envisioned to be available via the aromatic ketone **57**, which in turn would be synthesized via a carbonylative Stille cross coupling reaction⁴² of the triflate **58**⁴³ (Scheme 11). The triflate would be obtained from the known tetralol **59**, previously prepared by Hart⁴⁴ in 30% yield simply by heating 2-methyl-5-chloro-2-pentene (**61**) with 5 equivalents of phenol at 150 °C for 24 h.

Scheme 11



Prior to the research described in this chapter, David Casebier carried out initial studies on the synthesis of Dan Shen diterpenes that resulted in successful routes to (+)-neocryptotanshinone, (-)-cryptotanshinone, and tanshinone IIA.⁴⁵ The aim of the research described here was to develop improved methods for preparing several key intermediates, to optimize all steps in the synthesis, and to prepare larger quantities of the target diterpenoid quinones for biological testing.

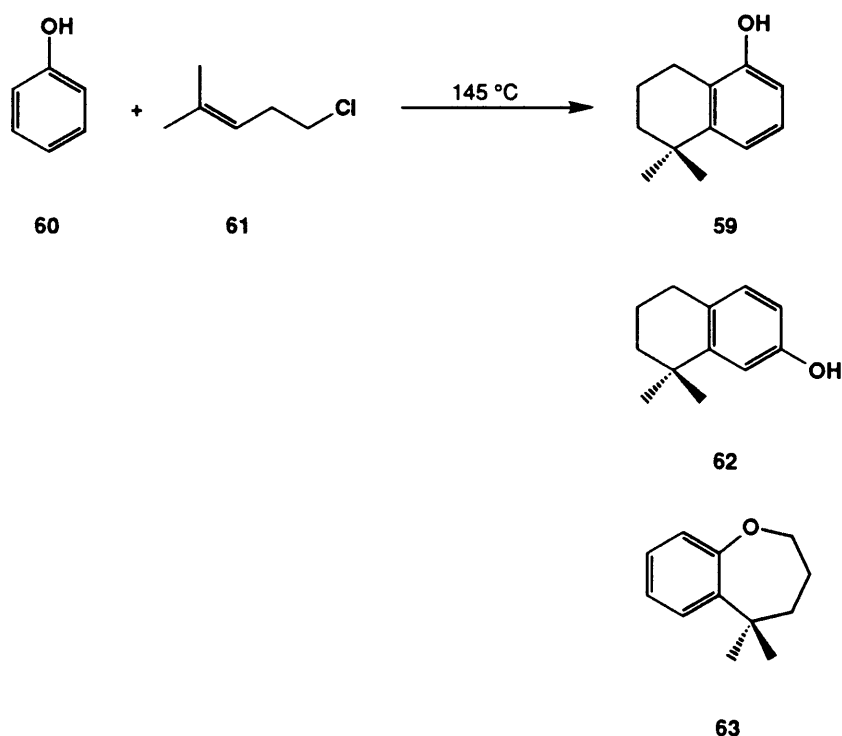
Synthesis of the Tetralol Intermediate **59**

Hart and coworkers had reported the isolation of three products from the reaction of phenol and homoprenyl chloride **61**.⁴⁴ Roughly equal amounts of the homochroman **63**,

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42. (a) For carbonylative Stille coupling of aryl triflates, see: Stille, J. K.; Echavarren, A. M. *J. Am. Chem. Soc.* **1988**, *110*, 1557. For reviews on the Stille coupling, see: (b) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (c) Mitchell, T. N. *Synthesis* **1992**, 803.
43. (a) For the synthesis of aryl triflates, see: Stang, P.J.; Hanack, M.; Sabramanian, L. R. *Synthesis* **1982**, 85. (b) For a recent review on synthetic transformations of vinyl and aryl triflates, see: Ritter, K. *Synthesis* **1993**, 735.
44. (a) Hart, H.; Corbin, J. L.; Wagner, C. R.; Wu, C.-Y. *J. Am. Chem. Soc.* **1963**, *85*, 3269. (b) Hart, H.; Corbin, J. L.; Wagner, C. R. *J. Am. Chem. Soc.* **1962**, *84*, 1740.
45. Casebier, D. S. Ph. D. Thesis, Massachusetts Institute of Technology, 1990.

and the two tetralols **59** and **62** were reported to be formed (Scheme 12). The homochroman **63** was then separated from the tetralols by partitioning the reaction mixture between methylene chloride and "Claisen's alkali".⁴⁶ The tetralols were then purified by distillation at reduced pressure, providing **59** as white crystals in 29% yield.

Scheme 12

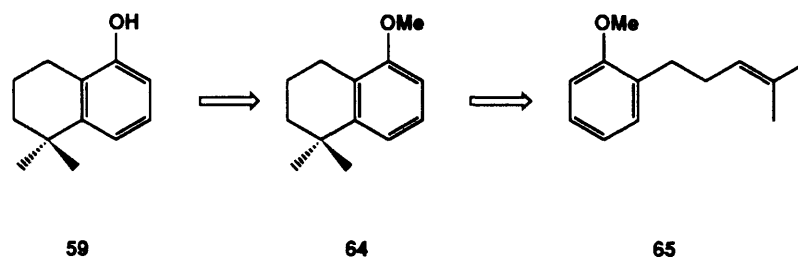


Unfortunately, none of Dr. Casebier's attempts to repeat the above reaction provided convenient access to the desired tetralol **59**. Although the desired compound was formed in the reaction, separation from the complex mixture of products proved impossible. We therefore chose to examine a different approach for the isolation and purification of **59** in place of the difficult fractional distillation procedure used by Hart. Thus, the alkaline extract from the Hart reaction was treated with 1.5 equiv of benzoyl

46. Prepared from 350 g of KOH in 250 g of water, diluted to one liter with MeOH. Stillson, G.H.; Sawyer, D. W.; Hunt, C. K. *J. Am. Chem. Soc.* **1945**, *67*, 303.

chloride in the presence of 3 equiv of pyridine and 0.2 equiv of DMAP, in the hope of selectively derivatizing the undesired tetralol **62** in the presence of the more hindered tetralol **59**. This reaction, however, resulted in the formation of a complex mixture of several products which were inseparable using the standard chromatographic techniques. It was therefore necessary to find a more reliable way to synthesize tetralol **59**. Consequently, we revised our plan and examined routes to **59** based on the stepwise approach outlined in Scheme 13. Thus, metalation and alkylation of anisole was expected to provide **65**, which we hoped would afford **64** by intramolecular Friedel-Crafts alkylation.⁴⁷ Cleavage of the methyl ether would provide the desired phenol. The methoxytetralin **64** has previously been prepared via a less attractive and efficient route by Winstein and Heck.⁴⁸

Scheme 13

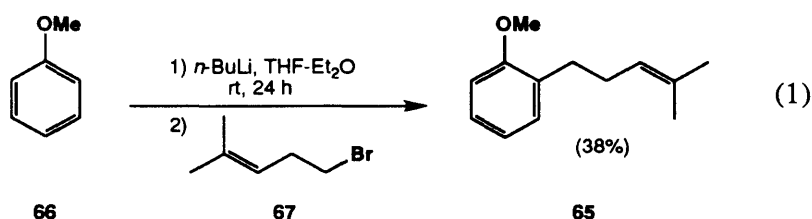


In Dr. Casebier's original investigation, **65** was prepared by *ortho* metalation⁴⁹ of anisole and its subsequent reaction with the bromide **67**, which was in turn synthesized according to the procedure of Julia.⁵⁰ The Julia method involves the treatment of cyclopropyl methyl ketone with 1.25 equiv of MeMgBr, followed by rearrangement of the

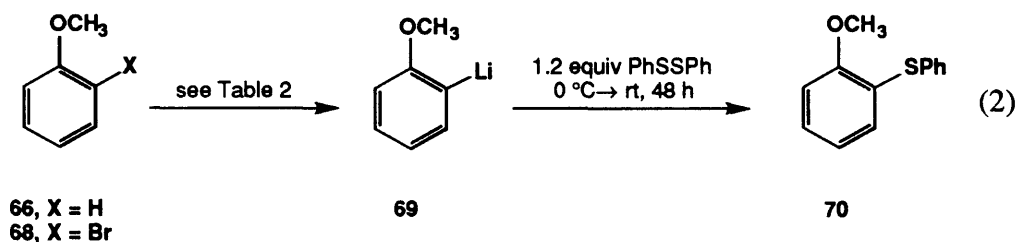
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47. For reviews, see Olah, G. A.; Krishnamurti, R.; Surya, G. K. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 3, pp 293-339, and references cited therein.
48. Winstein, S.; Heck, R. F. *J. Org. Chem.* **1972**, *37*, 825.
49. For reviews, see (a) Gawly, R. E.; Rein, K. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 1, pp 459-476. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (c) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1. (d) Narasimhan, N. S.; Mali, R. S. *Top. Curr. Chem.* **1987**, *138*, 63.
50. Julia, M.; Julia, S.; Guégan, R. *Bull. Soc. Chim. Fr.* **1960**, 1072.

resulting cyclopropyl carbanyl alcohol with aqueous HBr to produce **67** in 62% overall yield.

Dr. Casebier metalated anisole with 1.1 equiv of *n*-BuLi in Et₂O-THF (1:1) for 24 h, and then treated the resulting solution with 1.5 equiv of bromide **67** at -78 °C and then at room temperature for 24 h (eq 1). This reaction produced **65** in only 38% yield, and the separation of the desired product from unreacted anisole and excess bromide **67** was cumbersome.



In order to improve the yield of this reaction, we began a systematic investigation of the desired coupling. Our first goal was to optimize the *ortho* metalation of anisole. Three different methods previously known for *ortho* metalation of anisole were re-investigated.⁵¹ Table 1 summarizes the results of these investigations which involved quenching the aryllithium product **69** with phenyl disulfide and comparing the yields of the resulting aromatic sulfide **70** (eq 2).

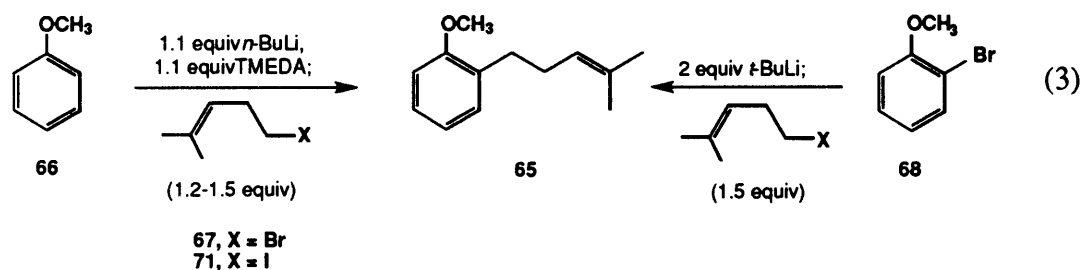


51. (a) Brandsma, L.; Verkuijsse, H. *Preparative Polar Organometallic Chemistry 1*; Springer-Verlag: New York, 1987. (b) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300.

Table 1. *Ortho* Metalation of Anisole

Method	Substrate	Metalation Conditions	Yield of 70
A	66	1.1 equiv <i>n</i> -BuLi, THF-Et ₂ O, rt, 24 h	70%
B	66	1.1 equiv <i>n</i> -BuLi, hexane 1.1 equiv TMEDA, 0 °C; then 40 °C, 30 min	94%
C	68	2.0 equiv <i>t</i> -BuLi, -78 °C, THF, 15 min	94%

Unfortunately, even though the latter two procedures for *ortho* metalation appeared to be superior to the one employed by Dr. Casebier, all three procedures gave virtually identical yields for the reaction of the aryllithium compound **69** with the bromide **67**. Method B was selected for the large scale synthesis of **65** (ca. 6.5 g scale), and in this fashion the alkylated product was obtained in 32-40% yield. The use of the iodide **71** (prepared from the corresponding bromide and excess NaI in refluxing acetone) did not improve the yield, and reducing the number of equivalents of **67** from 1.5 to 1.2 decreased the yield to 22% (eq 3).



Two other routes to **65** were also investigated. First, the formation of the Grignard reagent from 2-bromoanisole (**68**) and its Li₂CuCl₄-catalyzed coupling⁵² with **67** was studied. This reaction gave rise to a mixture of several products which could not be

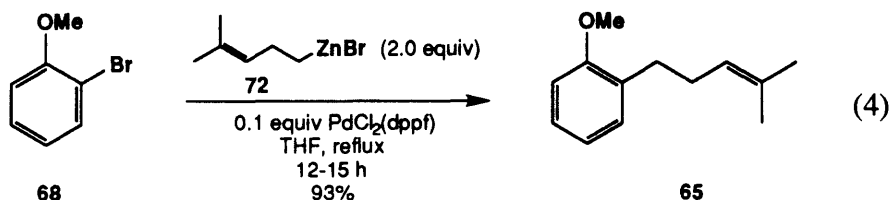
52. (a) Tamura, M.; Kochi, J. *Synthesis* 1971, 303. (b) Nunomoto, S.; Kawakami, Y.; Yamashita, Y. *J. Org. Chem.* 1983, 48, 1912. (c) For a review of the copper-catalyzed reactions of Grignard reagents, see Erdick, E. *Tetrahedron* 1984, 40, 641.

separated via chromatography. Second, the formation of a higher-order cyanocuprate reagent from 2-lithioanisole (**69**) and its subsequent coupling with the bromide **67** (according to the procedure by Lipshutz and co-workers for the coupling of arylcuprates and alkyl halides)⁵³ was investigated. In this case, the desired product **65** could not be separated from the product of homo-coupling of the cuprate reagent.

Finally, our attention was turned toward the formation of alkylzinc reagents and their Pd-catalyzed cross coupling with aryl halides,^{54,55} as reported by Kumada and by Rieke.⁵⁶ Earlier work on organozinc compounds was limited to the cross coupling reactions of aryl, alkenyl, and alkynyl organozinc reagents.⁵⁵ Kumada first introduced the Pd-catalyzed cross coupling reaction of secondary and primary *alkyl Grignard and alkylzinc reagents* with bromobenzene.^{56b,57} In these reactions, the organozinc compounds were prepared via a metathesis reaction with the corresponding Grignard or organolithium derivatives. Among several Pd catalysts examined for this coupling, PdCl₂(dppf)^{56b,57} was found to be by far the most active and selective. Later, Rieke developed a very mild method for the preparation of alkylzinc reagents via oxidative addition of *highly reactive zinc* with organic halides.^{56a} The alkylzinc halides thus prepared were then coupled with acid chlorides, α,β -unsaturated ketones, and allylic, aryl, and vinyl halides.

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53. (a) Lipshutz, B. H.; Parker, D.; Miller, R. D.; Kozlowski, J. A. *J. Org. Chem.* **1983**, *48*, 3334. For a review of higher-order cyano cuprates, see (b) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005.
54. For a review of transition metal catalyzed reactions of organozinc reagents, see Erdick, E. *Tetrahedron* **1992**, *48*, 9577.
55. For earlier work on the cross coupling of *aryl, alkenyl, and alkynyl organozinc reagents* and aryl halides, see (a) Dang, H. P.; Linstumelle, G. *Tetrahedron Lett.* **1978**, 191. (b) Fauvarque, J.-F.; Jutand, A. *J. Organomet. Chem.* **1977**, *132*, C17. (c) King, A. O.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1977**, 683. (d) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821. (e) King, A. O.; Negishi, E.; Villani, Jr., F. J.; Silveira, Jr., A. *J. Org. Chem.* **1978**, *43*, 358. (f) Negishi, E.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2254. (g) Russell, C. E.; Hegedus, L. S. *J. Am. Chem. Soc.* **1983**, *105*, 943.
56. (a) Zhu, L.; Vehemeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445. (b) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158.
57. For the preliminary report on the cross coupling reaction of secondary alkyl Grignard reagents with aryl- and vinyl halides, see Hayashi, T.; Konishi, M.; Kumada, M. *Tetrahedron Lett.* **1979**, 1871.

Using this methodology, a vastly improved synthesis of **65** was achieved. Treatment of 2-bromoanisole (**68**) with 2.0 equiv of the organozinc compound **72** along with 0.1 equiv of PdCl₂(dppf) in refluxing THF (12-15 h) produced **65** as a clear, colorless oil in 93% yield (eq 4). The alkylzinc reagent **72** was prepared by the addition of the bromide **67** to activated Zn, produced via the lithium naphthalenide reduction of ZnCl₂-dioxane.

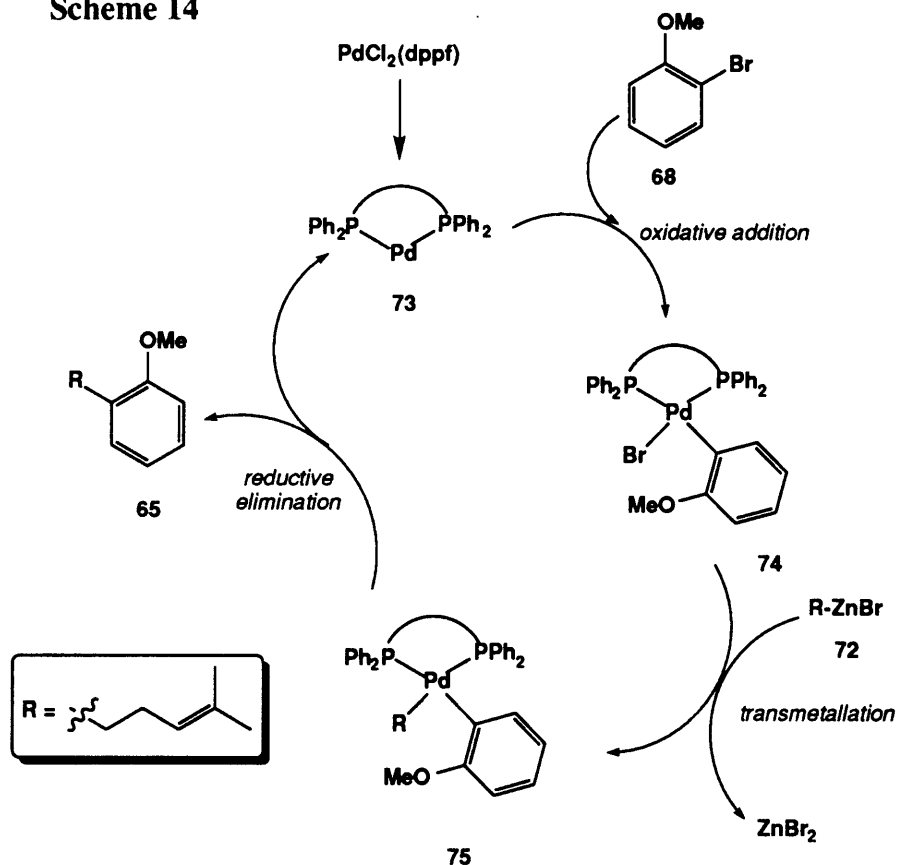


The mechanism for this coupling reaction is outlined in Scheme 14. Oxidative addition of 2-bromoanisole (**68**) to the Pd(0) catalyst **73** (generated *in situ*) leads to the formation of the Pd(II) intermediate **74** which then undergoes transmetalation and subsequent reductive elimination to produce **65**, while regenerating the active catalyst. The choice of PdCl₂(dppf) as the catalyst for this coupling reaction is *essential* for its success: triphenylphosphine-nickel or -palladium complexes are often inefficient for coupling reactions involving alkyl-metal species. This may be attributable to the dissociation of triphenylphosphine from the metal, which may promote β -elimination at **75** by forming coordinatively unsaturated species.⁵⁸ Bidentate phosphines are known to stabilize an alkyl-metal moiety against β -hydride elimination.^{58a} Consequently, catalysts complexed with a bidentate phosphine are more efficient when coupling reactions of alkyl-metal species are concerned. The catalytic activity of the palladium complexes with bidentate ligands is shown to be strongly dependent upon the molecular framework lying between the two diphenylphosphino groups in the ligand.^{56b} The phosphine ligand dppf, with its large P-

58. (a) Whitesides, G. M.; Gash, J. F.; Stedronsky, E. R.; *J. Am. Chem. Soc.* **1972**, *94*, 5258. (b) Reger, D. L.; Culbertson, E. C. *J. Am. Chem. Soc.* **1976**, *98*, 2789. (c) Grubbs, R. H.; Miyashita, A.; Liu, M.; Burk, P. *J. Am. Chem. Soc.* **1978**, *100*, 2418.

Pd-P and small Cl-Pd-Cl angles, accelerates reductive elimination to form the coupling product selectively.

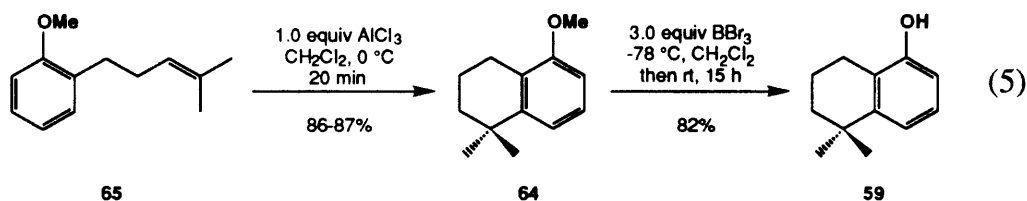
Scheme 14



With the alkylated anisole **65** in hand, the tetralol **59** was then prepared in two additional steps (eq 5). The intramolecular Friedel-Crafts alkylation⁴⁷ was achieved under standard conditions by treatment of **65** with 1.0 equiv of AlCl_3 in CH_2Cl_2 at 0 °C for 15 min. Chromatographic purification (elution with petroleum ether) afforded the known methoxytetralin **64**⁴⁸ as a clear, colorless oil in 86-87% yield. The aryl methyl ether was then cleaved upon treatment with 3.0 equiv of BBr_3 ⁵⁹ under standard conditions^{59c,d} (eq 5)

59. (a) Benton, F. L.; Dillon, T. E. *J. Am. Chem. Soc.* **1942**, *64*, 1128. (b) McOmie, J. F. W.; Watts, M. L. *Chem. & Ind.* **1963**, 1658. (c) McOmie, J. F. W.; Watts, M. L.; West, D. E. *Tetrahedron* **1968**, *24*, 2289. (d) McOmie, J. F. W.; West, D. E. *Org. Synth. Coll. Vol. V*, **1973**, 412.

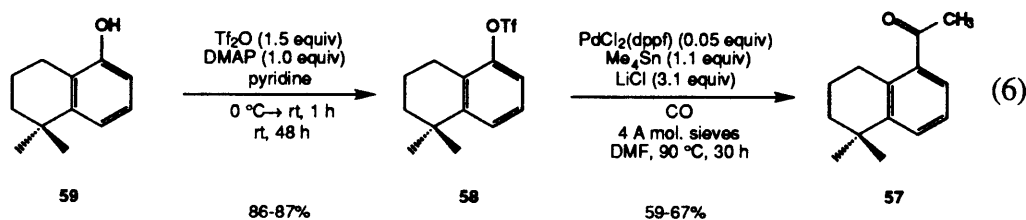
to furnish **59** as white crystals, mp 111-112 °C (lit. 112.5-113.5 °C),⁴⁴ in 82% yield after recrystallization from hexane.



Synthesis of the α -Diazo Ketone Intermediate **52**

The next step in the synthesis required the conversion of the tetralol **59** to the triflate **58**.⁴³ During the initial studies, Dr. Casebier treated a solution of **59** in pyridine with 1.0 equiv of DMAP and 1.5 equiv of Tf₂O at 0 °C for 1 h, followed by stirring at room temperature for 12 h to produce **58** in 67-74% yield. Our further research, however, has revealed that the yield can be increased significantly by employing a slow addition of Tf₂O (15-20 min) and increasing the reaction time to 48 h (eq 6). In this fashion, the desired triflate **58** was obtained in 86-87% yield as a yellow oil, which was used in the next step without further purification.

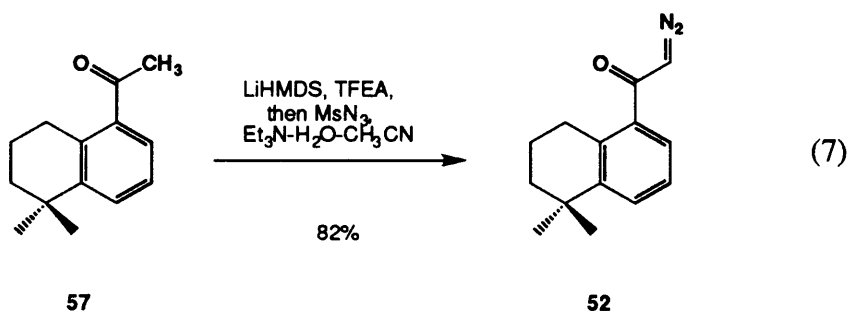
The triflate **58** was then converted to the aryl methyl ketone **57** via the carbonylative Stille cross coupling reaction.⁴² A solution of **58** in DMF was treated with 1.1 equiv of Me₄Sn, 0.05 equiv of PdCl₂(dppf), 3.1 equiv of LiCl, and then placed under ca. 3 atm of CO at 90 °C for 30 h to produce **57** as cream-colored crystals (mp 30-32 °C) in 59-67% yield (eq 6).⁶⁰



60. Yields decreased significantly when CO pressure was below 3 atm.

The α -diazo derivative **52** was next obtained by employing the improved "detrifluoroacetylative" diazo transfer method recently developed in our laboratory.⁶¹ This step was carried out by Maria Menichincheri. The original Casebier procedure for this reaction utilized only 1.2 equiv of Et₃N and MsN₃ as well as a saturated sodium bicarbonate wash in the final workup. Maria found that switching to 1.5 equiv of Et₃N and 2.0 equiv of MsN₃ provided the optimal reaction conditions. Also, she observed that 10% aqueous NaOH was necessary in the final workup in order to remove the remaining methane sulfonamide by-product which is not extracted when bicarbonate was used.

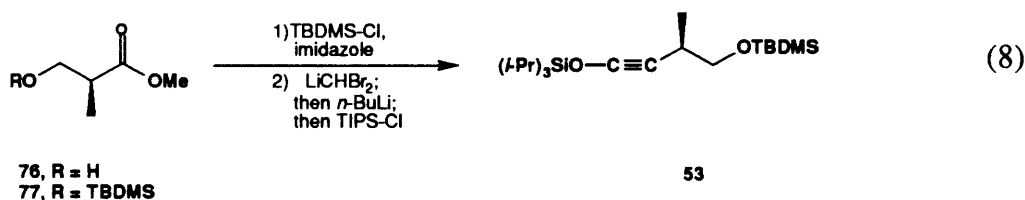
The α -diazo ketone **52** was thus obtained as bright yellow needles (mp 65-66 °C) in 82% yield (eq 7). The IR spectrum of the compound displayed the characteristic diazo stretch at 2100 cm⁻¹ and the ¹³C-NMR spectrum exhibited the diazo carbon at 56.5 ppm. The unusually broad signal at 5.52 ppm (corresponding to the α' -proton) in the ¹H-NMR spectrum is due to the coalescence of the signals from the *S-cis* and the *S-trans* rotamers of the diazo functionality.



61. (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.* **1995**, *73*, in press. For reviews of other methods for the synthesis of diazo ketones, see: (c) Regitz, M.; Maas, G. *Diazo Compounds, Properties and Synthesis*; Academic Press: New York, 1986. (d) Regitz, M. In *The Chemistry of Diazonium and Diazo Groups*; Patai, S., Ed.; Wiley: New York, 1978, Chapter 17. (e) McKervey, M. A.; Ye, T. *Chem. Rev.* **1994**, *94*, 1091.

The Pivotal Step: Aromatic Annulation

Siloxyalkynes, which can be prepared from carboxylic esters using the Kowalski method,⁶² are outstanding ketenophiles in the aromatic annulation reaction.^{10b,17-21,63} The requisite optically active siloxyacetylene **53**¹⁹⁻²⁰ was prepared from commercially available (S)-(+)-methyl-3-hydroxy-2-methyl propionate **76** according to the procedure described by our group earlier via (a) protection with *t*-butyldimethylsilyl chloride, followed by (b) sequential treatment of the ester in one flask with lithiodibromomethane, *n*-butyllithium, and triisopropylsilyl chloride (eq 8).^{64,65}



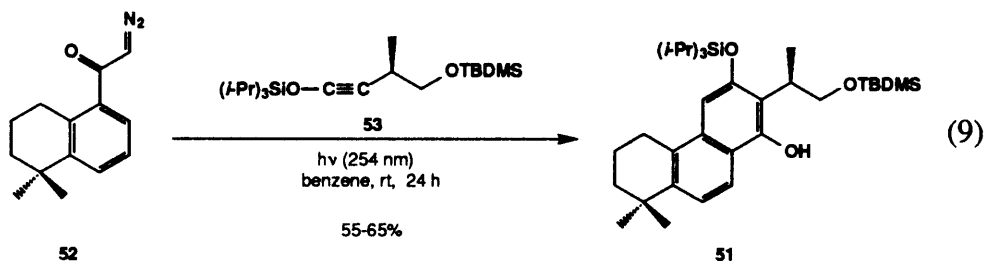
The key aromatic annulation reaction was originally carried out by Dr. Casebier by irradiating a degassed 0.3 M solution of the diazo ketone **52** and 2.0 equiv of the siloxyacetylene **53** in 1,2-dichloroethane in a Vycor tube using a low pressure mercury lamp (254 nm). After 5 h, a mixture of the desired annulation product **51** and the cyclobutenone intermediate **55** was produced. The formation of polymeric material, which covers the inner walls of the reaction vessel and thus impedes the transmittance of light, is believed to be the cause of the incomplete reaction. The remainder of the pericyclic cascade (4-electron cyclobutenone ring opening) thus had to be conducted thermally. This was achieved by diluting the reaction mixture with additional dichloroethane and heating it at

-
62. (a) Kowalski, C. J.; Lal, G. S.; Haque, M. S. *J. Am. Chem. Soc.* **1986**, *108*, 7127. For the mechanism of this reaction, see: (b) Kowalski, C. J.; Haque, M. S.; Fields, K. W. *J. Am. Chem. Soc.* **1985**, *107*, 1429. (c) Kowalski, C. J.; Haque, M. S. *J. Org. Chem.* **1985**, *50*, 5140. (d) Kowalski, C. J.; Reddy, R. E. *J. Org. Chem.* **1991**, *57*, 7194. (e) Reddy, R. E.; Kowalski, C. J. *Org. Synth.* **1992**, *71*, 146.
63. Kowalski, C. J.; Lal, G. S. *J. Am. Chem. Soc.* **1988**, *110*, 3693.
64. I would like to thank Dr. Alexandre H. Huboux for supplying me with a generous amount of the protected ester **77**.
65. The overall yield for this two-step sequence was ca. 30%. In other runs by Dr. Casebier and Dr. Huboux the overall yield for this two-step sequence ranged from 50-51%.

reflux for 3 h to complete the annulation. The phenol **51** was thus obtained as a yellow oil in 55-74% yield.

Upon reinvestigation and scale-up, however, the annulation reaction in 1,2-dichloroethane produced the desired tricyclic product in yields of <10%. Further study revealed that in benzene as solvent, the annulation proceeded in good yield, even on a large (1.3 g) scale, and the desired aromatic product could be isolated without the need for a separate thermolysis stage. After extensive study, it also became apparent that the aromatic annulation reaction proceeded in higher yields when conducted at lower concentrations.^{19,21} At 0.30 M concentration of diazo ketone **52**, the reaction produced the desired aromatic compound **51** in 49% yield. By conducting the reaction at concentrations of 0.15 M and 0.07 M, yields as high as 58-65% were achieved. The slight concentration-dependence of the aromatic annulation reaction can be explained by the fact that at lower concentrations of the diazo ketone **52**, the "desired" intramolecular reaction (Wolff rearrangement) takes precedence over the polymerization reactions that impede the annulation pathway.

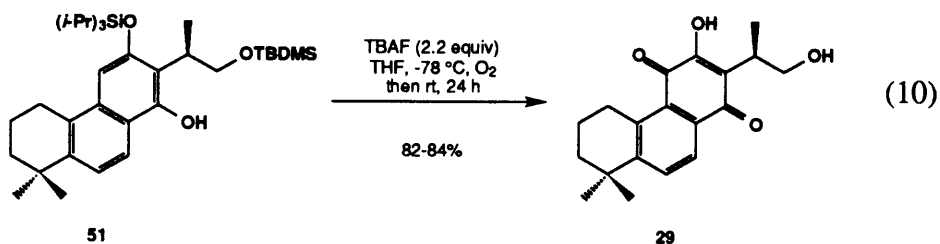
It was also found that the amount of acetylene **53** could be decreased from 2.0 to 1.5 equiv without affecting the yield. By modifying the solvent system for the chromatographic purification (gradient elution with 0-5% methylene chloride in hexane), **51** was obtained as an off-white solid (not a yellow oil as reported by Dr. Casebier), mp 145-147 °C, $[\alpha]_D -10.2^\circ$ (CHCl₃, *c* 1.34), in 55-65% yield (eq 9).⁶⁶



66. For a discussion of the stereochemical course of this aromatic annulation reaction, see reference 21.

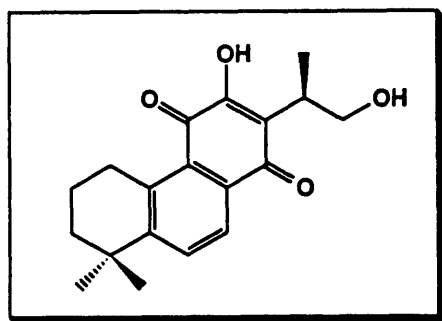
Synthesis of (+)-Neocryptotanshinone, (-)-Cryptotanshinone, and Tanshinone IIA

Cleavage of the silyl ether protective groups and oxidation to produce (+)-neocryptotanshinone (**29**) was achieved in a single operation (82-84%) by exposure of **51** to 2.2 equiv of tetra-*n*-butylammonium fluoride in THF (-78 °C to room temperature, 24 h) in the presence of oxygen (eq 10). Chromatographic purification on silica gel (gradient elution with 1-20% ethyl acetate in methylene chloride) furnished (+)-neocryptotanshinone as bright yellow needles, mp 163-165 °C, $[\alpha]_D^{25} +29.2^\circ$ (CHCl₃, *c* 0.91) (lit. 165-167 °C, $[\alpha]_D^{25} +29.8^\circ$, CHCl₃, *c* 0.84).²⁹ Synthetic (+)-neocryptotanshinone was characterized by ¹H NMR, ¹³C NMR, and IR spectroscopy. The ¹H NMR spectral data (300 MHz, CDCl₃) for our synthetic material (Figure 1) and that reported for the natural product (100 MHz, CDCl₃)²⁹ are summarized in Table 2. To our knowledge, no ¹³C NMR spectral data for (+)-neocryptotanshinone has been reported to date. The IR spectrum showed the expected absorptions corresponding to the OH (3330 cm⁻¹) and quinone (1770, 1660, and 1640 cm⁻¹) groups.

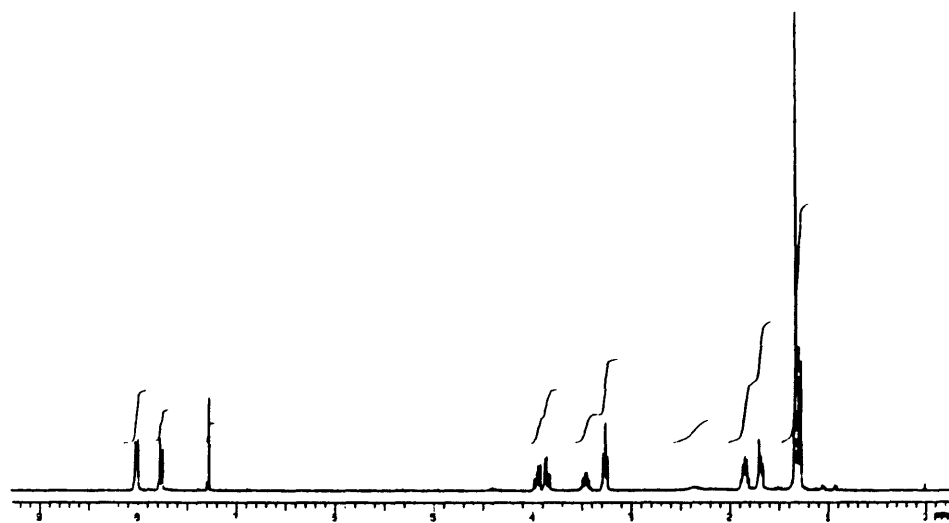


This efficient route to (+)-neocryptotanshinone thus furnished the target in only 5 steps from the known tetralol **59** in 19-26% overall yield. We were also able to establish the first unambiguous assignment of the absolute chemistry for (+)-neocryptotanshinone.

Figure 1. ^1H NMR Spectrum of (+)-Neocryptotanshinone in CDCl_3
(300 MHz)



(+)-neocryptotanshinone



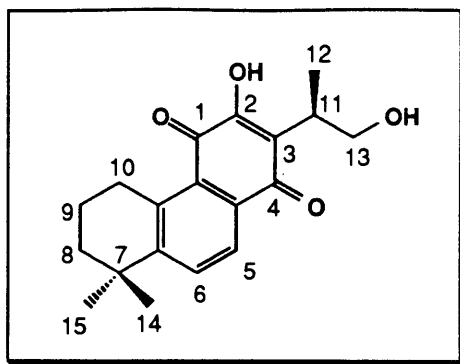
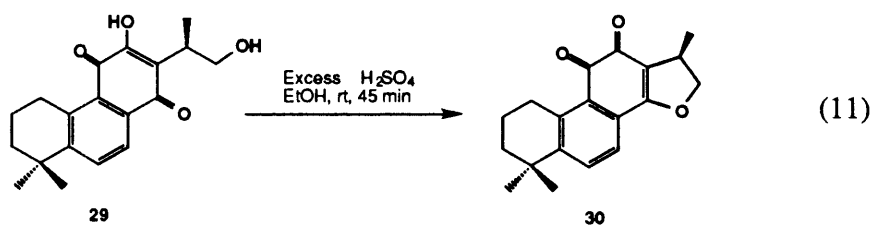


Table 2. ^1H NMR Spectral Data (CDCl_3) for (+)-Neocryptotanshinone

Atom #	Natural (100 MHz)	Synthetic (300 MHz)
1	-	-
2	7.20 (br s)	7.27 (s)
3	-	-
4	-	-
5	7.73 (d, 8)	7.75 (d, 8)
6	7.96 (d, 8)	8.00 (d, 8)
7	-	-
8	1.75 (m)	1.66-1.70 (m)
9	1.75 (m)	1.80-1.86 (m)
10	3.25 (t, 6)	3.25 (t, 6)
11	3.50 (ddq, 5, 7, 8)	3.45 (m)
12	1.24 (d, 7.8)	1.28 (d, 7)
13	3.88 (ddd, 4, 6, 10)	3.84 (dd, 5, 11)
13	3.88 (ddd, 4, 6, 10)	3.94 (dd, 8, 11)
14	1.30 (s)	1.32 (s)
15	1.30 (s)	1.32 (s)

Prior experience gained in the synthesis of Dan Shen diterpene quinones suggested that the *ortho*-quinone system of cryptotanshinone could be easily constructed via the acid-catalyzed cyclization of neocryptotanshinone.^{19,20,37,67} We decided to follow the procedure of Kakisawa³⁷ for the cyclization of neocryptotanshinone to cryptotanshinone via treatment with concentrated sulfuric acid. Thus, exposure of (+)-neocryptotanshinone to concentrated sulfuric acid in ethanol at 25 °C for 45 min afforded (-)-cryptotanshinone (**30**) in quantitative yield as orange-red needles, mp 188-189 °C (lit. 191-192 °C),³⁰ $[\alpha]_D^{25}$ -84.5° (CHCl₃, *c* 1.72) (lit. -79.9°, *c* 0.18).³⁰



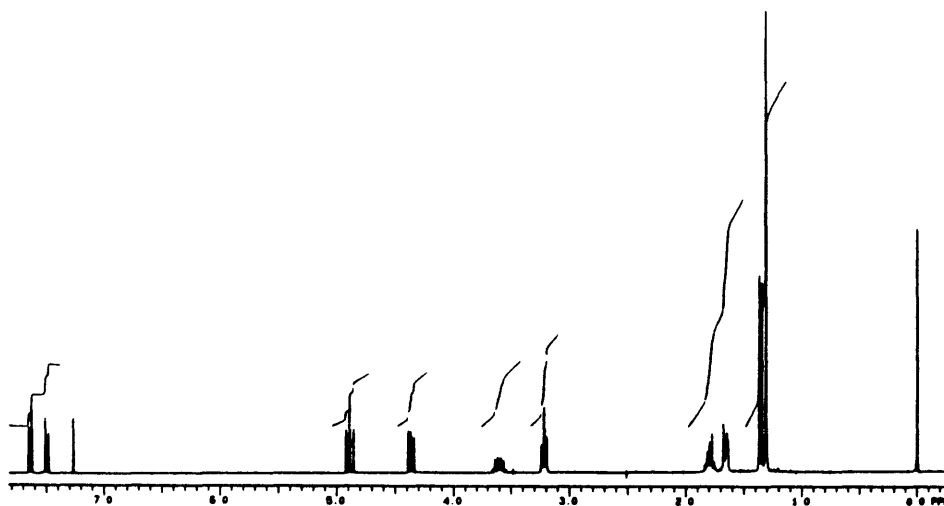
The ¹H NMR (300 MHz, CDCl₃) and ¹³C NMR spectra (75 MHz, CDCl₃) of synthetic (-)-cryptotanshinone were compared to spectra we measured at the same concentration for an authentic sample of the natural product (Figure 2, Tables 3 and 4).⁶⁸ The observed chemical shifts for the synthetic compound were in excellent agreement with those of the authentic natural product. The melting point of the natural (-)-cryptotanshinone was 190-191 °C, in close agreement with the value measured for our synthetic sample. A mixed sample of synthetic and natural (-)-cryptotanshinone was prepared by grinding equivalent amounts of each compound together. The melting point of this mixed sample was observed at 187-189 °C.

The unambiguous assignment of the absolute stereochemistry of (-)-cryptotanshinone was also established in our synthesis.

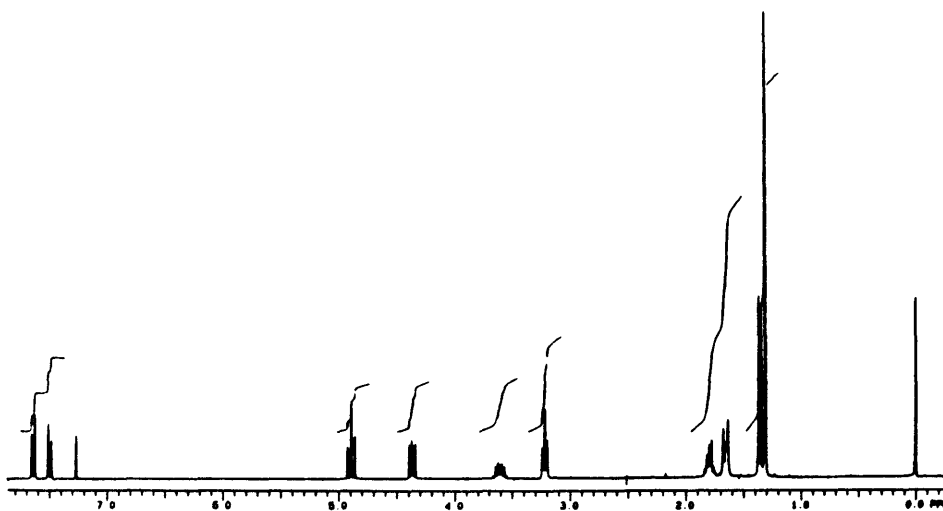
67. For a related cyclization involving the acid-catalyzed cyclization of danshexinkun A to dihydrotanshinone I, see Fang, C. N.; Chang, P.-L.; Hsu, T.-P. *Acta Chem. Sinica* **1976**, *34*, 197.

68. We are grateful to professor Henry N. C. Wong (Chinese University of Hong Kong) for providing us with an authentic sample of (-)-cryptotanshinone.

Figure 2. ^1H NMR Spectrum of Synthetic (-)-Cryptotanshinone in CDCl_3 (300MHz)



^1H NMR Spectrum of Authentic (-)-Cryptotanshinone in CDCl_3 (300MHz)



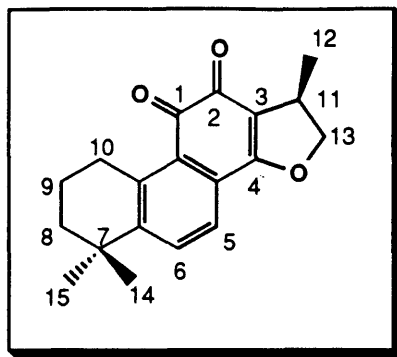


Table 3. ^1H NMR Spectral Data (CDCl_3 , 300 MHz) for (-)-Cryptotanshinone

Atom #	Natural	Synthetic
1	-	-
2	-	-
3	-	-
4	-	-
5	7.51 (d, 8)	7.51 (d, 8)
6	7.64 (d, 8)	7.64 (d, 8)
7	-	-
8	1.80 (m)	1.80 (m)
9	1.80 (m)	1.80 (m)
10	3.22 (t, 6)	3.22 (t, 6)
11	3.60 (ddq, 6, 7, 9)	3.60 (ddq, 6, 7, 9)
12	1.36 (d, 7)	1.36 (d, 7)
13	4.38 (dd, 6, 9)	4.37 (dd, 6, 9)
13	4.89 (t, 9)	4.89 (t, 9)
14	1.32 (s)	1.31 (s)
15	1.32 (s)	1.31 (s)

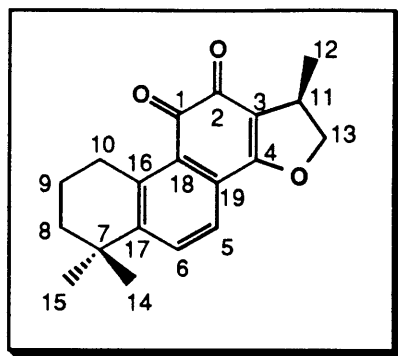


Table 4. ^{13}C NMR Spectral Data (CDCl_3 , 75 MHz) for (-)-Cryptotanshinone

Atom #	Natural	Synthetic
1	184.2	184.2
2	175.7	175.6
3	118.3	118.3
4	170.8	170.8
5	122.5	122.5
6	132.5	132.5
7	37.8	37.8
8	31.9	31.9
9	29.6	29.6
10	34.6	34.6
11	34.8	34.8
12	18.8	18.8
13	81.4	81.4
14	19.0	19.0
15	19.0	19.0
16	143.7	143.7
17	152.3	152.3
18	126.2	126.2
19	128.3	128.3

Previous reports on the synthesis of tanshinone IIA suggested that this compound could be easily obtained by the dehydrogenation of cryptotanshinone. Baillie and Thomson first reported the dehydrogenation of cryptotanshinone (**30**) to tanshinone IIA (**31**).³⁴ In their hands, treatment of cryptotanshinone with DDQ (refluxing benzene) produced tanshinone IIA in 31% yield (Scheme 6). Using the same procedure, Kakisawa and co-workers were able to oxidize cryptotanshinone to tanshinone IIA in 70% yield (Scheme 8).³⁷ Thus, we treated cryptotanshinone (**30**) with 2.5 equiv of DDQ in benzene at 25 °C for 24 h. Chromatographic purification on silica gel (gradient elution with 0-75% chloroform-benzene) provided tanshinone IIA (**31**) in 91% yield as dark red needles, mp 199-200 °C (lit. 196-198 °C).³⁰ The ¹H NMR spectral data (300 MHz, CDCl₃) for our synthetic material (Figure 3) and that measured by Dr. Casebier for an authentic sample of the natural product (300 MHz, CDCl₃) are summarized in Table 5.

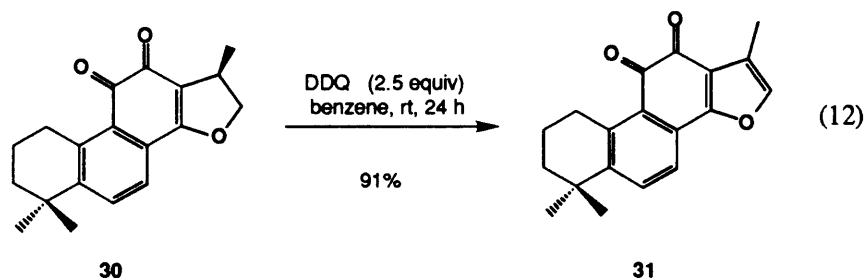
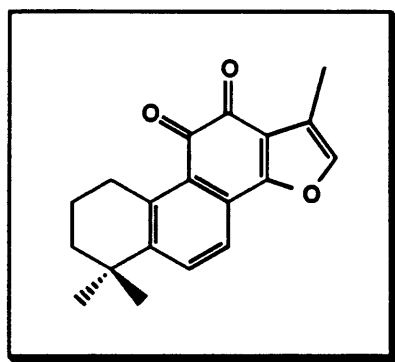
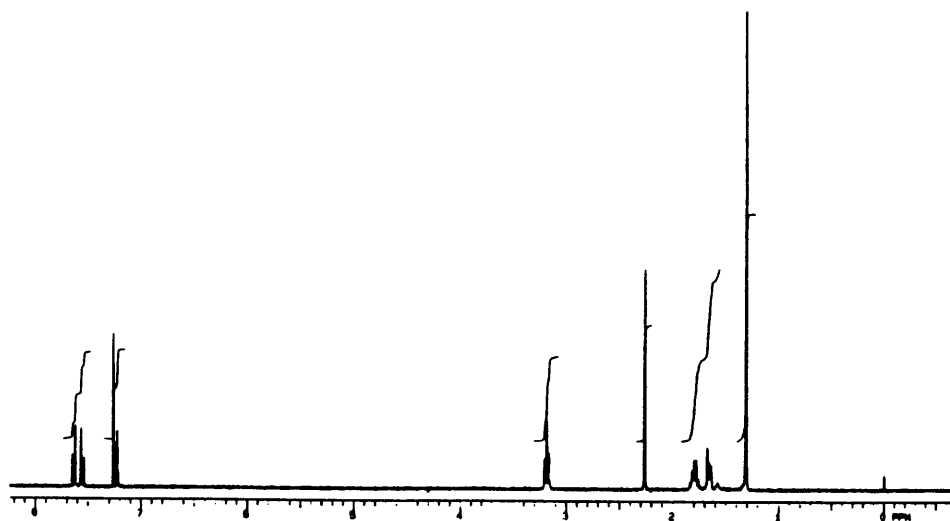


Figure 3. ^1H NMR spectrum of Tanshinone IIA in CDCl_3 (300 MHz)



tanshinone IIA



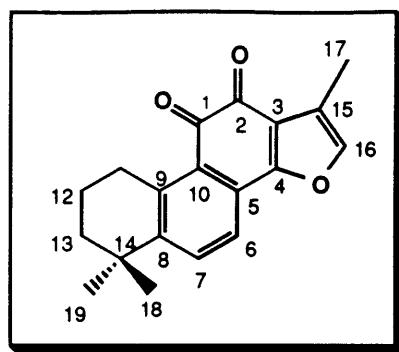


Table 5. ^1H NMR Spectral Data (CDCl_3 , 300 MHz) for Tanshinone IIA

Atom #	Natural	Synthetic
1	-	-
2	-	-
3	-	-
4	-	-
5	-	-
6	7.61 (d, 8.1)	7.63 (d, 8)
7	7.53 (d, 8.1)	7.55 (d, 8)
8	-	-
9	-	-
10	-	-
11	3.16 (t, 6.5)	3.18 (t, 6)
12	1.77 (m)	1.80 (m)
13	1.63 (m)	1.66 (m)
14	-	-
15	-	-
16	7.20 (d, 1.3)	7.22 (q, 1.3)
17	2.24 (d, 1.3)	2.26 (d, 1.3)
18	1.28 (s)	1.31 (s)
19	1.28 (s)	1.31 (s)

In summary, the synthetic route described in this thesis is the first synthesis of the target diterpenes *in enantiomerically pure form*. Using our methodology, either enantiomer of the target compounds are available. Our synthesis of tanshinone IIA provides this diterpene quinone in seven steps from the known tetralol **59** in 17-24% overall yield. (+)-Neocryptotanshinone and (-)-cryptotanshinone were made in five and six steps, respectively, in 19-26% overall yield for both products. The conclusive assignments for the absolute stereochemistry of (+)-neocryptotanshinone and (-)-cryptotanshinone were also established.

Part II:

Synthetic Approaches to Ellipticine

Chapter 1

Introduction and Background

Introduction

Indole and its derivatives have captured the imagination of organic chemists since the late nineteenth century, when von Baeyer and others first prepared indoles from indigo.^{69,70} The interest in these compounds now centers on their biological activity as well as their use as dyes. Indoles are key structural units in several clinically important drugs, including antitumor, antimicrobial, and anti-inflammatory agents, as well as in compounds regulating plant growth.

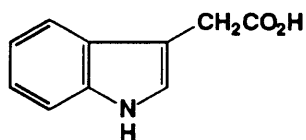
Shown below (Scheme 15) are several examples of biologically important indoles.⁷¹ Indoleacetic acid (**78**) is recognized as the principal auxin of higher plants, and is used as a plant growth regulator. The essential amino acid L-tryptophan (**79**) is the biosynthetic precursor for a variety of natural products including serotonin (**80**), the neurotransmitter involved in temperature regulation, sleep onset, and sensory perception. Reserpine (**81**) is a natural product with antihypertensive properties, but is no longer used as a drug due to its unwanted side effects. Vinblastine (**82**) and vincristine (**83**) are two very important antitumor drugs isolated from *Catharanthus roseus*. The semisynthetic indole LSD (**84**) is a well-known potent hallucinogen. Indomethacin (**85**), a synthetic drug developed at Merck, has antipyretic and analgesic properties, and is primarily used as an anti-inflammatory agent. These examples illustrate the broad spectrum of activity possessed by various indoles, as well as their structural diversity.

69. Baeyer, A. *Chem. Ber.* **1880**, *13*, 2254.

70. Baeyer, A. *Chem. Ber.* **1868**, *1*, 17.

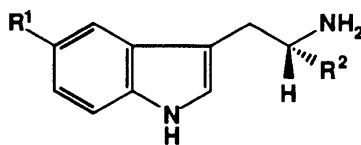
71. For leading references concerning the isolation, synthesis, and biological activity of these compounds refer to *The Merck Index*; 11th ed.; Budavari, S. Ed.; Merck and Co., Inc.: Rahway, NJ, 1989.

Scheme 15



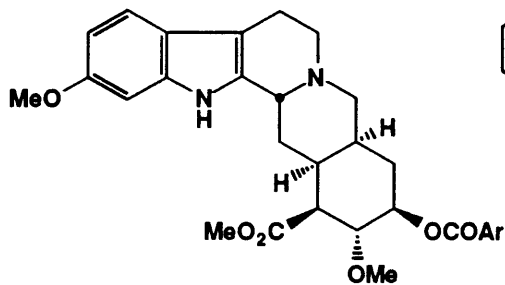
Indoleacetic Acid

78



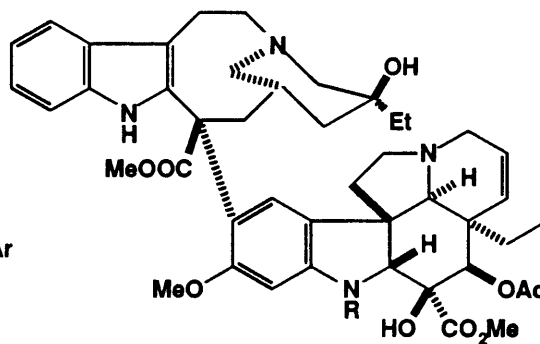
L-Tryptophan 79, R¹ = H R² = CO₂H

Serotonin 80, R¹ = OH R² = H

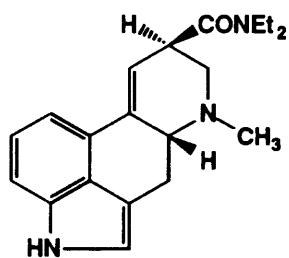


Reserpine

81

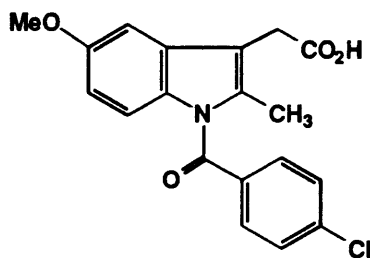


Vinblastine 82, R = Me
Vincristine 83, R = CHO



LSD

84



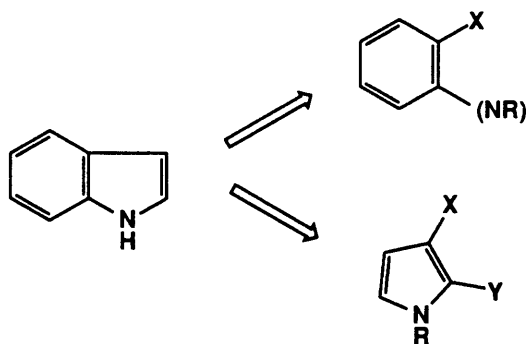
Indomethacin

85

Numerous synthetic strategies for the construction of indoles have been developed through the years. The majority of these methods involve the synthesis of indoles

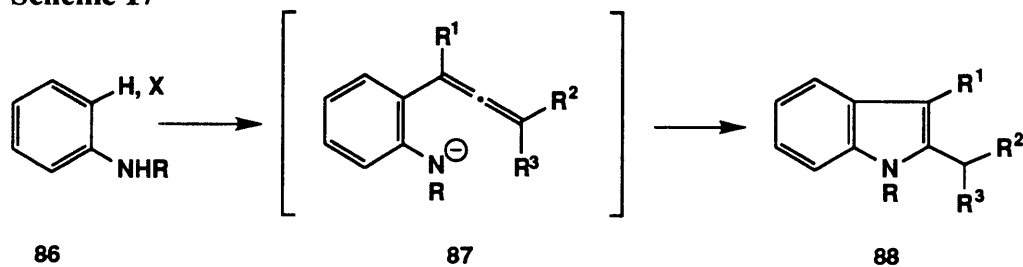
beginning from various benzene derivatives. Other strategies have employed pyrrole derivatives as starting materials (Scheme 16).

Scheme 16



Our research group has been interested in the chemistry of indoles for some time. Our studies have been directed toward the development of new synthetic strategies for the construction of indoles, as well as the application of those strategies to the total synthesis of biologically significant natural products. As a result of these efforts, a new annulation method for the synthesis of 2,3-disubstituted indoles has been recently developed in our laboratory (Scheme 17).⁷² The key step in this strategy involves a novel base-catalyzed cyclization of 2-(allenyl)arylamines, which are in turn synthesized from 2-haloanilines via transition-metal catalyzed reactions (*vide infra*). This methodology will be discussed in further detail in a later section.

Scheme 17



72. Danheiser, R. L.; Mori, I.; Romines, K. R. unpublished results.

The research described in this thesis had a twofold aim. The first objective was to further refine and extend the previously developed indole synthesis methodology, by discovering alternative ways to access the 2-(allenyl)arylamine intermediates. The second aim of the research described herein was to test the scope of our annulation methodology by examining its application in the total synthesis of natural products such as the antitumor agent ellipticine (*vide infra*).

In order to appreciate the potential utility of our indole annulation strategy, the existing synthetic approaches to indoles will be discussed briefly in the next section.

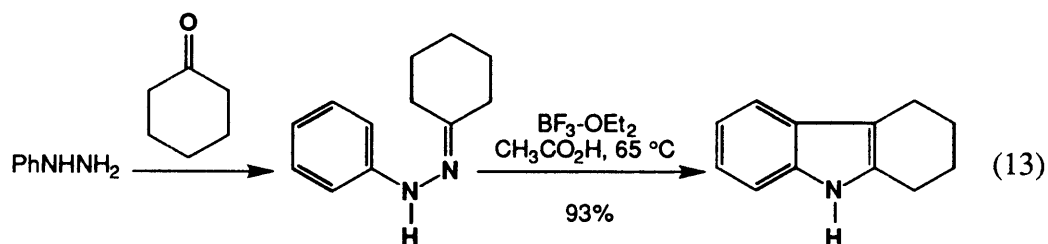
Strategies for the Synthesis of Indoles

Indoles were first prepared by von Baeyer from indigo in 1868.⁷⁰ A large number of synthetic methods for the construction of indoles have been developed since that time.⁷³ It is beyond the scope of this thesis to review all of these strategies. Instead, this section will focus on selected examples of general indole syntheses, with emphasis on those related to the methodology developed in our laboratory. As mentioned previously, the majority of these methods start with a readily available benzene derivative and focus on the synthesis of the five-membered ring. This is no doubt due to the wider availability of a range of substituted benzenes relative to pyrroles. Here, these methods are categorized according to the type of reaction involved in the key step. The indole syntheses using pyrroles as starting materials will not be discussed.

73. For reviews, see: (a) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970. (b) Brown, R. K. In *Indoles, The Chemistry of Heterocyclic Compounds*; Houlihan, Ed.; Wiley Interscience: New York, 1972. (c) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry*; Pergamon Press: Oxford, 1984, pp 313-376. (d) Yurovskaya, M. A. *Chem. Heterocyclic Comp.* **1987**, *23*, 919. (e) Hegedus, L. S. *Angew. Chem., Intl. Ed. Engl.* **1988**, *27*, 1113. (f) Pindur, U.; Adam, R. J. *Heterocycl. Chem.* **1988**, *25*, 1. (g) Ellis, G. P. In *The Chemistry of Heterocyclic Compounds*; Wiley: Chichester, 1992, Vol. 47, part 2. (h) Alvarez, M.; Salas, M.; Joule, J. A. *Heterocycles* **1991**, *32*, 1391. (i) Gribble, G. W. *Contemporary Organic Synthesis* **1994**, *1*, 145.

I. Sigmatropic Rearrangements

The best known indole synthesis involving a sigmatropic rearrangement is the Fischer indole synthesis,⁷⁴ which involves the cyclization of arylhydrazones in the presence of a Lewis or protic acid. The key step in the mechanism of this reaction is a [3,3]-sigmatropic rearrangement⁷⁵ (eq 13). Note that it is sometimes difficult to control the regiochemistry of unsymmetrical 2,3-disubstituted indoles using the Fischer indole synthesis. Recently, Yamamoto and co-workers reported the first example of a regioselective Fischer indole synthesis mediated by organoaluminum amides.⁷⁶



Other examples of indole syntheses involving sigmatropic rearrangements include Gassman's indole synthesis involving [2,3]-sigmatropic rearrangements of azasulfonium salts,⁷⁷ Bartoli's indole synthesis utilizing the reaction of nitro- and nitrosoarenes and Grignard reagents,⁷⁸ and Blechert's indole synthesis via amino vinyl ethers.⁷⁹ Parsons and co-workers have also reported an indole synthesis based on the cyclization of an allene intermediate produced via a [2,3]-sigmatropic rearrangement (Scheme 18).⁸⁰

74. For a review, see: Robinson, B. *The Fischer Indole Synthesis*; Wiley Interscience: New York, 1982.

75. Hughes, D. L.; Zhao, D. *J. Org. Chem.* **1993**, *58*, 228.

76. Maruoka, K.; Oishi, M.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 7638.

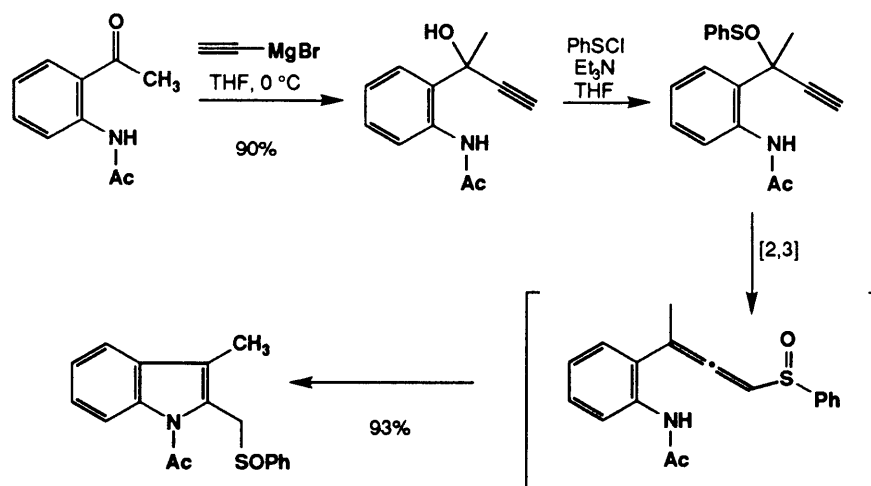
77. Gassman, P. G.; van Bergen, T. J.; Gilbert, D. P.; Cue, Jr., B. W. *J. Am. Chem. Soc.* **1974**, *96*, 5495.

78. (a) Bartoli, G.; Palmieri, G.; Bosco, M.; Dalpozzo, R. *Tetrahedron Lett.* **1989**, *30*, 2129. (b) Bartoli, G.; Bosco, M.; Dolpozzo, R.; Palmieri, G.; Marcantoni, E. *J. Chem. Soc., Perkin Trans. 1*, **1991**, 2757. (c) Bosco, M.; Dalpozzo, R.; Bartoli, G.; Palmieri, G.; Petrini, M. *J. Chem. Soc., Perkin Trans. 2*, **1991**, 657.

79. (a) Blechert, S. *Tetrahedron Lett.* **1984**, 1547. (b) Blechert, S. *Helv. Chim. Acta* **1985**, *68*, 1835.

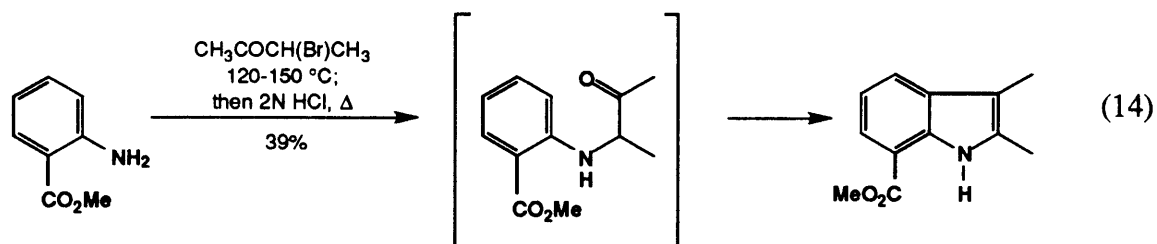
80. Gray, M.; Parsons, P. J.; Neary, A. P. *Synlett* **1993**, 281.

Scheme 18



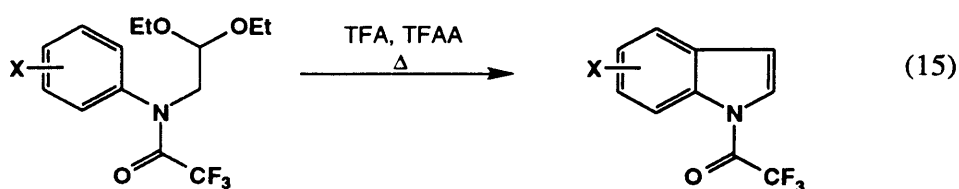
II. Electrophilic Cyclizations

The Bischler indole synthesis⁸¹ involves the electrophilic cyclization of α -arylamino ketones or their synthetic equivalents. These intermediates are usually prepared from the reaction of arylamines and α -halo ketones (eq 14).

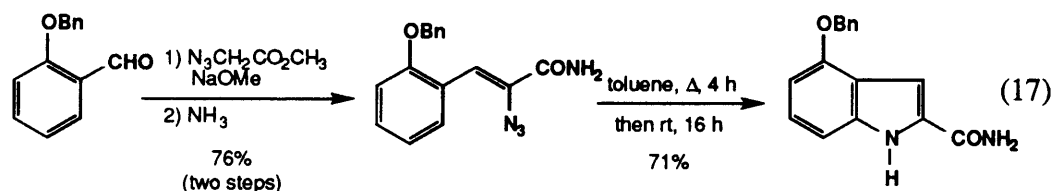
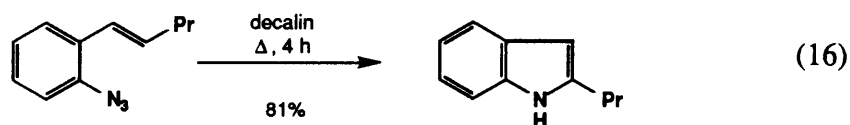


Nordlander modified Bischler's synthesis by using a combination of trifluoroacetic anhydride (TFAA) and trifluoroacetic acid (TFA) to effect the cyclization of N-trifluoroacetyl-2-anilino acetals (eq 15).⁸²

81. (a) Bischler, A.; Brion, H. *Chem. Ber.* **1892**, *25*, 2860. (b) Bischler, A.; Firemann, P. *Chem. Ber.* **1893**, *26*, 1336.
82. Nordlander, J. E.; Catalane, D. B.; Kotian, K. D.; Stevens, R. M.; Haky, J. E. *J. Org. Chem.* **1981**, *46*, 778.



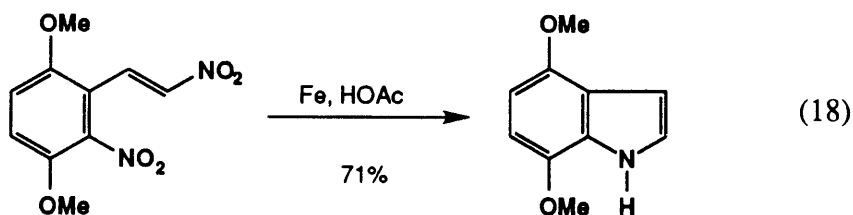
Several indole syntheses have been developed that utilize the electrophilic cyclization of nitrenes as the key step. Most noteworthy among these are the methods developed by Sundberg, Hemetsberger, and Moody. Sundberg reported the thermolysis of *o*-azidostyrenes which produce indoles via nitrene formation and insertion into the side chain C-H bond (eq 16).⁸³ Hemetsberger and Moody's approaches⁸⁴ involve the thermal decomposition of α -azidocinnamates, and the insertion of the resulting nitrene into the *ortho* Ar-H bond. The azide starting materials are prepared in moderate yields from the corresponding benzaldehydes by condensation with ethyl azidoacetate (eq 17).



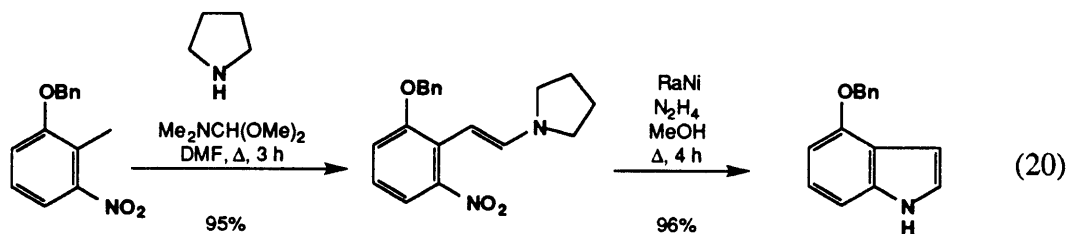
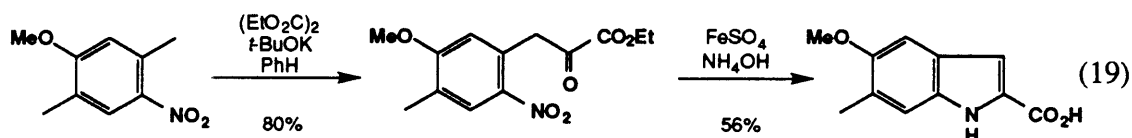
83. (a) Sundberg, R. J.; Russell, H. F.; Ligon, Jr., W. V.; Lin, L.-S. *J. Org. Chem.* **1972**, *37*, 719. For related methods, see: Cadogen, J. I. G.; Cameron-Wood, M.; Mackie, R. K.; Searle, R. J. G. *J. Chem. Soc.* **1965**, 4831. (c) Sundberg, R. J. *J. Org. Chem.* **1965**, *30*, 3604.
84. (a) Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1333. (b) Henn, L.; Hickey, D. M. B.; Moody, C. J.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2189. (c) Hickey, D. M. B.; Moody, C. J.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1113. (d) Hickey, D. M. B.; Moody, C. J.; Rees, C. W. *J. Chem. Soc., Chem. Commun.* **1982**, 1419. (e) Hemetsberger, H.; Knittel, D.; Wiedmann, H. *Montash. Chem.* **1970**, *101*, 161. (f) Adams, R. E.; Press, J. B.; Deegan, E. G. *Synth. Commun.* **1991**, *21*, 675.

III. Reductive Cyclizations

A method developed many years ago, and still popular as a route to many indoles, involves the reductive cyclization of *o*, β -dinitrostyrenes. Eq 18 shows an application of this strategy to the construction of methoxyindoles.⁸⁵



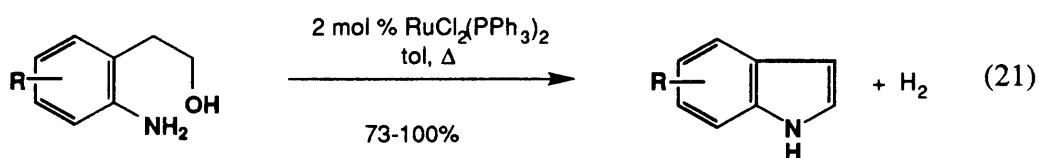
The classic Reissert indole synthesis involves the reductive cyclization of *o*-nitrophenyl pyruvic acid derivatives to form indole-2-carboxylic acid compounds (eq 19).⁸⁶ Subsequent modifications have greatly increased the utility of this strategy. The Leimgruber-Batcho synthesis (eq 20) is an example of later modifications of the Reissert indole synthesis.^{87,88}



85. Ijaz, A. S.; Parrick, J.; Yahya, A. *J. Chem. Res. (S)* **1990**, 116.
86. Reissert, A. *Chem. Ber.* **1897**, *30*, 1030.
87. (a) Batcho, A. D.; Leimgruber, W. *Org. Synth.* **1984**, *Coll. Vol. VII*, 34. (b) Clark, R D.; Repke, D. B. *Heterocycles* **1984**, *22*, 195. (c) Lloyd, D. H.; Nichols, D. E. *Tetrahedron Lett.* **1983**, *24*, 4561.
88. For other indole syntheses involving reductive cyclizations, see: (a) Makosza, M.; Danikiewicz, W.; Wojciechowski, K. *Liebigs Ann. Chem.* **1988**, 203. (b) Macor, J. E.; Newman, M. E. *Heterocycles* **1990**, *31*, 805. (c) Macor, J. E.; Wehner, J. M. *Heterocycles* **1993**, *35*, 349. (d) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1984**, *22*, 1347. (e) Akazome, M.; Kondo, T.; Watanabe, Y. *J. Org. Chem.* **1994**, *59*, 3375, and references cited therein. (f) Fürstner, A.; Hupperts, A. *J. Am. Chem. Soc.* **1995**, *117*, 4468.

IV. Oxidative Cyclizations

Watanabe and co-workers have reported a synthesis of indoles based on the ruthenium-catalyzed cyclization of 2-aminophenethyl alcohols, which are in turn synthesized via the condensation of 2-nitrotoluenes with formaldehyde (eq 21).⁸⁹

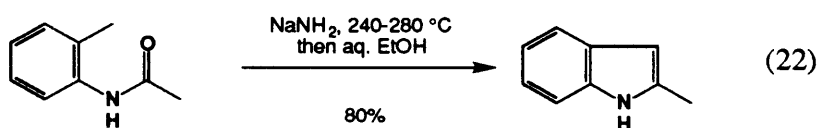


V. Radical Cyclizations

Most of the work involved in this area has resulted in the synthesis of dihydroindoles, and there are only a few methods that produce indoles directly. The most recent example is the work of Fukuyama and co-workers, utilizing the radical cyclization of *o*-isocyanostyrene derivatives.^{90,91}

VI. Nucleophilic Cyclizations

The Madelung indole synthesis is one of the oldest methods for the construction of indoles.⁹² This cyclization method in its classical form involves the reaction of *ortho*-alkylanilides with strong bases at high temperatures (eq 22).



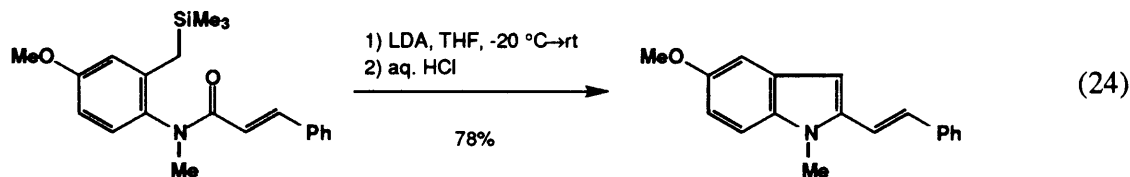
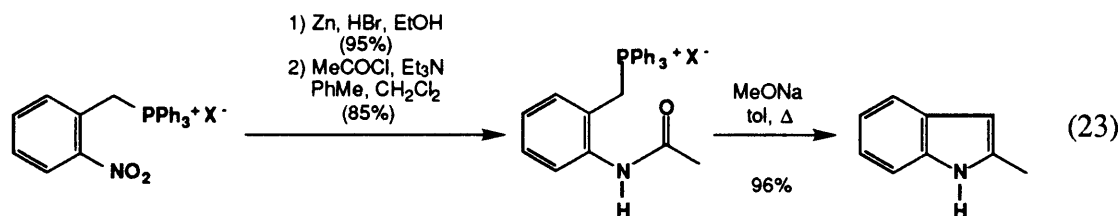
89. Tsuji, Y.; Kotachi, S.; Huh, K.; Watanabe, Y. *J. Org. Chem.* **1990**, *55*, 580.

90. Fukuyama, T.; Chen, X.; Peng, G. *J. Am. Chem. Soc.* **1994**, *116*, 3127.

91. For other examples of indole syntheses involving radical cyclizations, see: (a) Dittami, J. P.; Ramanathan, H. *Tetrahedron Lett.* **1988**, *29*, 45. (b) Inanaga, J.; Ujikawa, O.; Yamagushi, M. *Tetrahedron Lett.* **1991**, *32*, 1737. (c) Boger, D. L.; Yun, W.; Teegarden, B. R. *J. Org. Chem.* **1992**, *57*, 2873. (d) Ozlu, Y.; Cladingboel, D. E.; Parsons, P. J. *Synlett* **1993**, 357. (e) Cladingboel, D. E.; Parsons, P. J. *J. Chem. Soc., Chem. Commun.* **1990**, 1543. (f) Maquestiau, A.; Beugnies, D.; Flammang, R.; Katritzky, A. R.; Soleiman, M.; Davis, T.; Lam, J. N. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1071. (g) Barker, S. J.; Storr, R. *C. J. Chem. Soc., Perkin Trans. 1* **1990**, 485.

92. Madelung, W. *Chem. Ber.* **1912**, *45*, 1128.

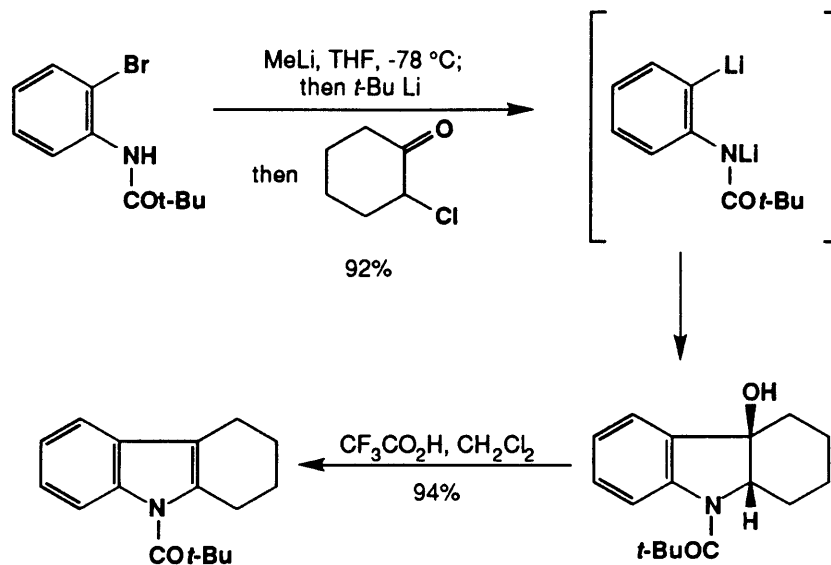
Houlihan⁹³ and Clark⁹⁴ have reported modifications of the original Madelung synthesis that use alkyllithium reagents instead of sodium amide for the metalation reaction. Other workers, such as LeCorre⁹⁵ (eq 23) and Bartoli (eq 24),⁹⁶ have improved upon the original procedure by activating the methyl group to facilitate the intramolecular olefination process. LeCorre uses a phosphonium salt, which is deprotonated with sodium methoxide and then cyclizes via an internal Wittig reaction. Bartoli's method, on the other hand, is based on an intramolecular Peterson olefination reaction of *ortho*-trimethylsilylmethyl anilides.



Other syntheses involving nucleophilic cyclizations have been developed by Schmid,⁹⁷ Wender,⁹⁸ and Coutre.⁹⁹ Wender's synthesis involves the *ortho*-lithiation of *N*-phenylamides followed by reaction with α -haloketones and subsequent ring closure and dehydration (Scheme 19).

93. Houlihan, W. J.; Parrino, V. A.; Uike, Y. *J. Org. Chem.* **1981**, *46*, 4511.
 94. Clark, R. D.; Muchowski, J. M.; Souchet, M.; Repke, D. B. *Synlett* **1990**, 207.
 95. (a) LeCorre, M.; Hercouet, A.; LeBaron, H. *J. Chem. Soc., Chem. Commun.* **1981**, 14. (b) LeCorre, M.; Hercouet, A.; LeStanc, Y.; LeBaron, H. *Tetrahedron* **1985**, *41*, 5313.
 96. (a) Bartoli, G.; Palmieri, G.; Petrini, M. *Tetrahedron* **1990**, *46*, 1379. (b) Bartoli, G.; Bosco, M.; Dalpozzo, R.; Todesco, P. E. *J. Chem. Soc., Chem. Commun.* **1988**, 807.
 97. Greuter, H.; Schmid, H. *Helv. Chim. Acta* **1974**, *57*, 281.
 98. Wender, P. A.; White, A. W. *Tetrahedron* **1983**, *39*, 3767.
 99. (a) Coutre, A.; Deniau, E.; Gimbert, Y.; Grandclaoudon, P. *Tetrahedron* **1993**, *49*, 1431. (b) Coutre, A.; Deniau, E.; Gimbert, Y.; Grandclaoudon, P. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2463.

Scheme 19



VII. Metal-Catalyzed Indole Syntheses¹⁰⁰

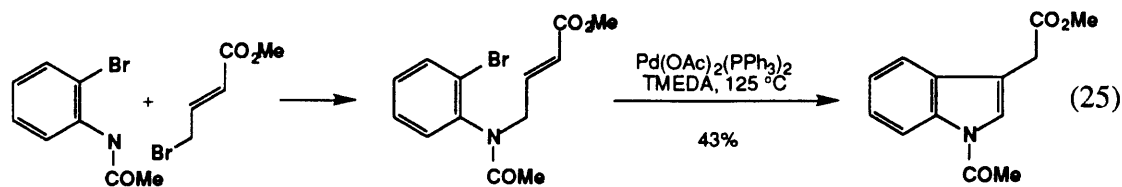
a. Palladium and Copper

It will be recalled that our approach to the synthesis of indoles involves the base-catalyzed cyclization of 2-(allenyl)arylamines, which are in turn prepared via transition metal-catalyzed coupling reactions of 2-haloanilines (Scheme 17). Prior to our work, and during the course of our studies, several methods have been developed based on Pd-catalyzed reactions that achieve a similar overall transformation.

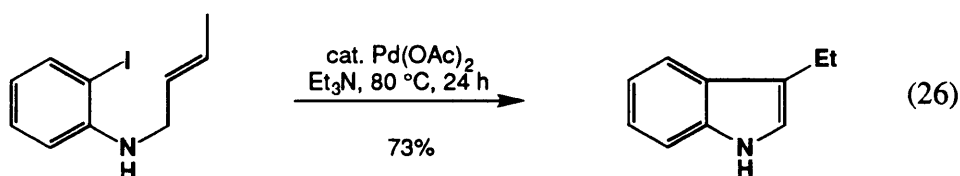
One of the most widely used strategies for the synthesis of indoles involves the use of the *intramolecular Heck reaction*. Mori and Ban were pioneers of this approach towards the synthesis of indoles. In their strategy, N-allyl-*o*-haloanilines are cyclized via an intramolecular Heck reaction using Pd(0). β -Hydride elimination and isomerization of the resulting double bond into the five-membered ring then furnishes the indole product (eq 25).¹⁰¹

100. For a review, see reference 67e.

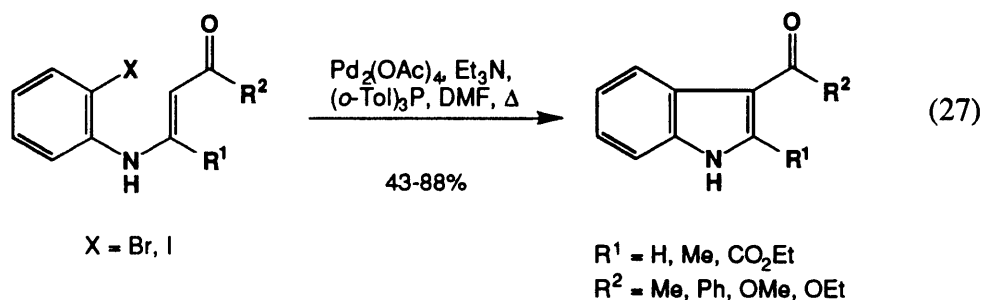
101. Mori, M.; Chiba, K.; Ban, Y. *Tetrahedron Lett.* 1977, 1037.



Larock has since extended the scope of this methodology to include "unactivated" olefins (eq 26).^{102,103} A carbonylative variation of the Mori-Ban method has been reported by Grigg and co-workers.¹⁰⁴



Yamanaka and co-workers have also reported the palladium-catalyzed cyclization of β -(2-halophenyl)amino substituted α,β -unsaturated ketones and esters to 2,3-disubstituted indoles (eq 27).¹⁰⁵



Another popular approach for the construction of indoles involves the *cyclization of 2-alkynylaniline derivatives*. In the first example of the use of this approach, Castro

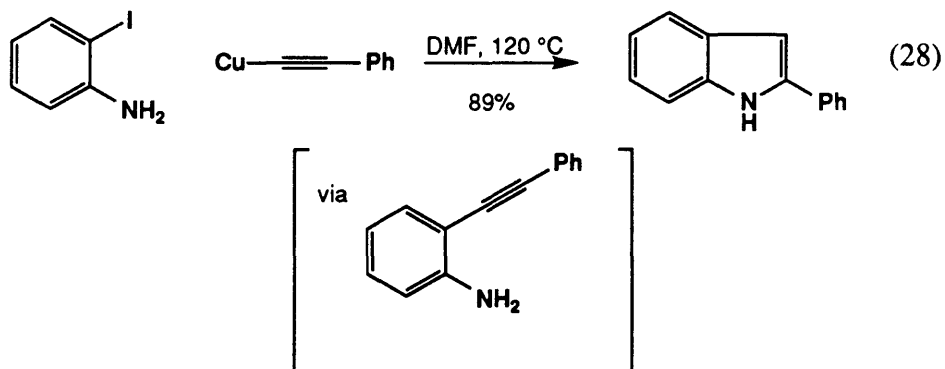
102. Larock, R. C.; Babu, S. *Tetrahedron Lett.* **1987**, *28*, 5291.

103. For other examples of the applications of this indole synthesis, see (a) Macor, J. E.; Blank, D. H.; Post, R. J.; Ryan, K. *Tetrahedron Lett.* **1992**, *33*, 8011. (b) Sakamoto, T.; Kondo, Y.; Uchiyama, M.; Yamanaka, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1941.

104. Grigg, R.; Kennewell, P.; Teasdale, A. J. *Tetrahedron Lett.* **1992**, *33*, 7789.

105. Sakamoto, T.; Nagano, T.; Kondo, Y.; Yamanaka, H. *Synthesis* **1990**, 215.

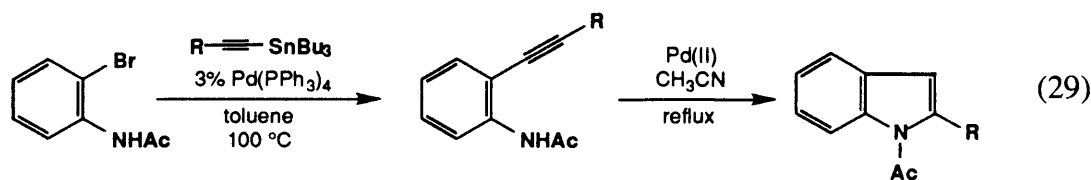
and Stephens used Cu(I) salts in their one-pot synthesis of indoles from *o*-haloanilines (eq 28).¹⁰⁶ This reaction is believed to proceed via the cyclization of a 2-alkynylaniline intermediate.



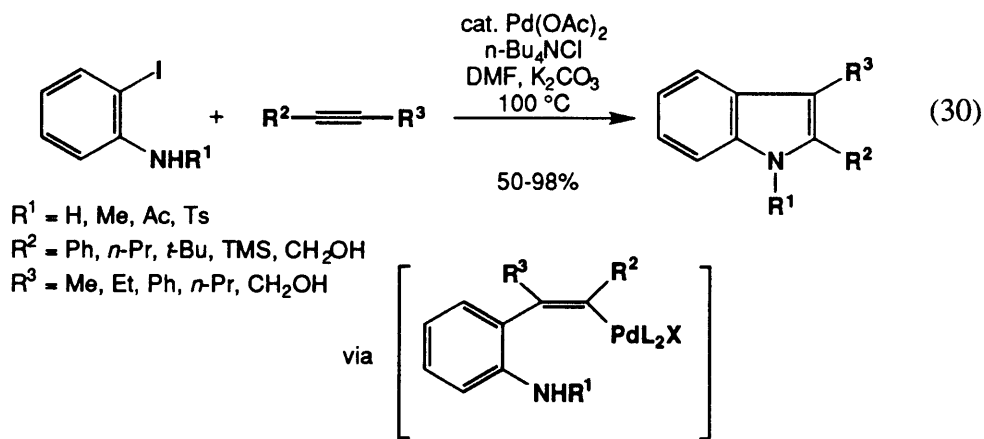
Several later syntheses of indoles have also been based on the cyclization reactions of 2-alkynylanilines. For example, Yamamoto¹⁰⁷ utilized the CuI-induced cyclization of 2-alkynylanilines (DMF, 120 °C), which were in turn prepared via the nucleophilic aromatic substitution reaction of organoaluminum reagents.

Stille reported an elegant variation of the Castro-Stephens method in which the requisite 2-alkynylanilines are prepared via the Pd(0)-catalyzed cross-coupling of alkynylstannanes with 2-bromoanilines (eq 29).¹⁰⁸ Other indole syntheses involving Pd(II)-catalyzed cyclizations of 2-alkynylanilines include Utimoto's synthesis of 3-allylindoles¹⁰⁹ and Taylor's synthesis of 2-phenylindoles.^{110,111}

106. (a) Castro, C. E.; Stephens, R. D. *J. Org. Chem.* **1963**, *28*, 2163. (b) Castro, C. E.; Gaughan, E. J.; Owsley, D. *C. J. Org. Chem.* **1966**, *31*, 4071.
107. Fujiwara, J.; Fukutani, Y.; Sano, H.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 7177.
108. Rudisill, D. E.; Stille, J. K. *J. Org. Chem.* **1989**, *54*, 5856.
109. Iritani, K.; Matsubara, S.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1799.
110. Taylor, E. C.; Katz, A. H.; Salgado-Zamora, H. *Tetrahedron Lett.* **1985**, *26*, 5963.
111. For related methods involving Pd(II)-catalyzed cyclizations of 2-alkynylanilines, see: (a) Hegedus, L. S.; Allen, G. F.; Waterman, E. L. *J. Am. Chem. Soc.* **1976**, *98*, 2674. (b) Hegedus, L. S.; Allen, G. F.; Olsen, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 3583.



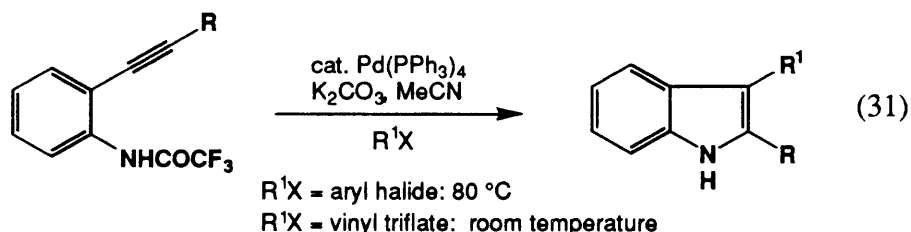
Larock has also reported an important new approach to indoles which involves the regioselective palladium-catalyzed heteroannulation of internal alkynes (eq 30).^{112,113} The mechanism of this reaction appears to involve (a) oxidative addition of Pd(0) into the Ar-I bond, (b) *syn* addition of the C-Pd bond to the alkyne to form a *Z*-styryl palladium intermediate, (c) displacement of halide from palladium by nitrogen to form a six-membered palladacycle, and finally (d) reductive elimination.



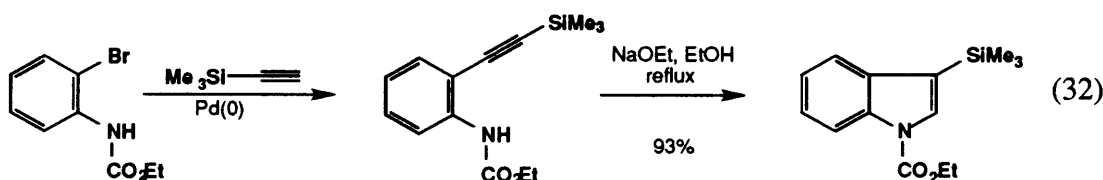
Another significant contribution to the synthesis of indoles has been reported by Cacchi and co-workers who have synthesized 2,3-disubstituted indoles through a palladium-catalyzed cyclization of 2-alkynylanilines^{114a} analogous to the Castro-

112. (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. For earlier work on the similar heteroannulation reactions of 1,3-dienes and 1,2-dienes, see (b) Larock, R. C.; Berrios-Peña, N. G.; Narayanan, K. *J. Org. Chem.* **1990**, *55*, 3447. (c) Larock, R. C.; Berrios-Peña, N. G.; Fried, C. A. *J. Org. Chem.* **1991**, *56*, 2615.
113. For examples of the applications of this methodology, see (a) Chen, C.-Y.; Lieberman, D. R.; Larsen, R. D.; Reamer, R. A.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1994**, *35*, 6981. (b) Wensbo, D.; Eriksson, A.; Jeschke, T.; Annby, U.; Gronowitz, S.; Cohen, L. A. *Tetrahedron Lett.* **1993**, *34*, 2823. (c) Jeschke, T.; Wensbo, D.; Annby, U.; Gronowitz, S.; Cohen, L. A. *Tetrahedron Lett.* **1993**, *34*, 6471.
114. (a) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1989**, *30*, 2581. (b) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1992**, *33*, 3915.

Stephens method discussed above. In a recent variant of this approach, these cyclizations have been promoted by aryl and vinylpalladium species generated *in situ* by oxidative addition reactions. Reductive elimination of palladium from the cyclized 3-palladaindole intermediate froms 2,3-disubstituted indoles (eq 31).^{114b}



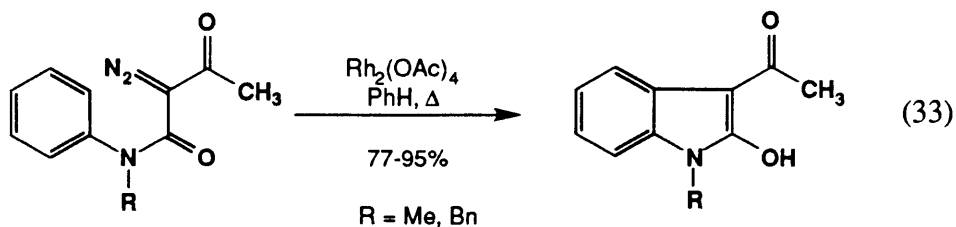
Finally, Yamanaka and co-workers have utilized a base-catalyzed cyclization of 2-alkynylanilines for the synthesis of indoles.^{115,116} The requisite 2-alkynylaniline precursors are prepared via the Pd-catalyzed coupling of 2-haloanilines and terminal alkynes. Treatment with NaOEt then provides the desired indoles in good yield (eq 32).



b. Rhodium

The synthesis of 3-acylindoles via the rhodium acetate-catalyzed reaction of the corresponding diazo compounds is another example of a transition-metal catalyzed indole synthesis (eq 33).¹¹⁷ This cyclization presumably involves insertion of a rhodium carbenoid into the *ortho* C-H bond of the aromatic ring.

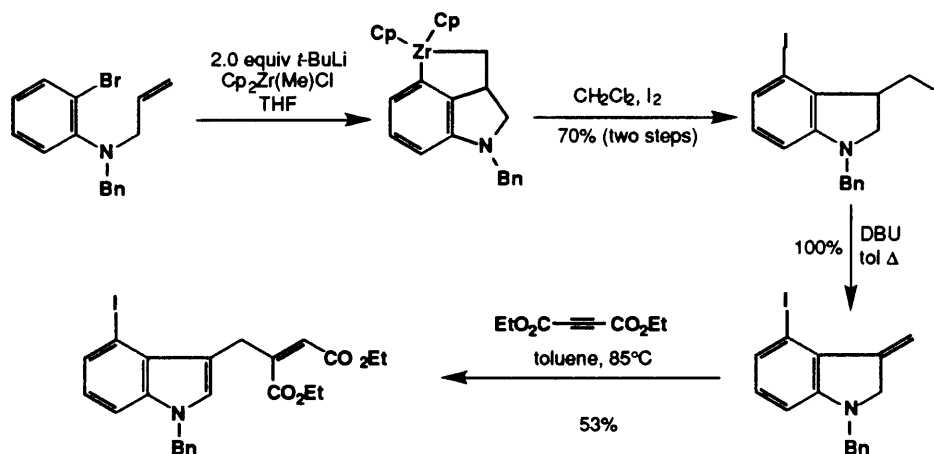
115. (a) Sakamoto, T.; Kondo, Y.; Yamanaka, H.; *Heterocycles* **1986**, *24*, 31. (b) Sakamoto, T.; Kondo, Y.; Iwashita, S.; Yamanaka, H. *Chem. Pharm. Bull.* **1987**, *35*, 1823. (c) Sakamoto, T.; Kondo, Y.; Iwashita, S.; Nagano, T.; Yamanaka, H. *Chem. Pharm. Bull.* **1988**, *36*, 1305.
116. For examples of the applications of this strategy, see (a) Takano, S.; Sato, T.; Inomata, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1991**, 462. (b) Villemin, D.; Goussu, D. *Heterocycles* **1989**, *29*, 1255.
117. Etkin, N.; Babu, S. D.; Fooks, C. J.; Durst, T. *J. Org. Chem.* **1990**, *55*, 1093.



c. Zirconium

Buchwald and co-workers have reported a novel indole synthesis involving zirconium complexes. The final ene reaction on the stable indole tautomer produces the indole product (Scheme 20).¹¹⁸

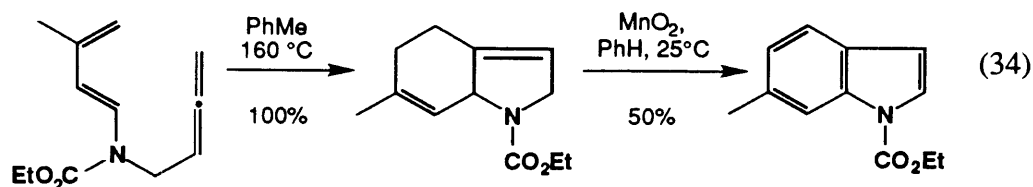
Scheme 20



VIII. Intramolecular Diels Alder Cycloadditions

Kanematsu¹¹⁹ and Ghosez¹²⁰ have employed intramolecular Diels-Alder reactions to simultaneously construct both rings of the indole nucleus. An example of Kanematsu's approach is shown in eq 34 below.

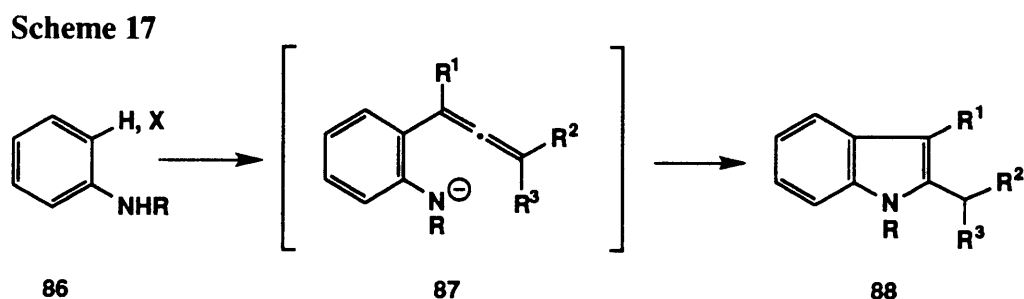
118. (a) Tidwell, J. H.; Senn, D. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 4685. (b) Tidwell, J. H.; Peat, A. J.; Buchwald, S. L. *J. Org. Chem.* **1994**, *59*, 7164. (c) Tidwell, J. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11797.
119. (a) Hayakawa, K.; Yasukouchi, T.; Kanematsu, K. *Tetrahedron Lett.* **1986**, 1837. (b) Hayakawa, K.; Yasukouchi, T.; Kanematsu, K. *Tetrahedron Lett.* **1987**, 5895.
120. Differding, E.; Ghosez, L. *Tetrahedron Lett.* **1985**, 1647.



Many of the numerous methods mentioned in the previous section suffer from a variety of limitations, and there still remains a need for new general approaches to the synthesis of indoles. The regiochemical control of the placement of substituents in the five-membered ring, and the development of mild reaction conditions which tolerate many functionalities are the key challenges that face the researchers in this important area of heterocyclic chemistry.

A New Synthesis of Indoles via Allene Cyclizations

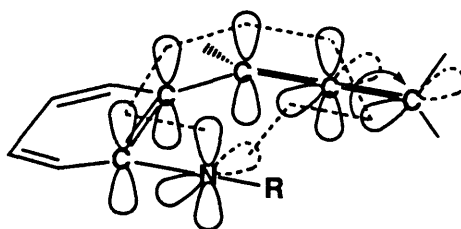
As mentioned previously, a new synthesis of indoles via a novel base-catalyzed cyclization of 2-(allenyl)arylamines was recently developed in our laboratory (Scheme 17).⁷² This strategy provides access to a variety of 2,3-disubstituted indoles via a short synthetic sequence starting with readily available *o*-haloaniline derivatives **86**.



One of the most attractive features of this strategy is the *very mild conditions* necessary for the cyclization reaction. Either a catalytic amount of DBU in DMF (2 h, room temperature) or potassium *t*-butoxide (2% base, 1-2 h, room temperature) is typically enough to effect the cyclization in >90% yield. Several mechanisms can

account for this unusual allene cyclization. The simplest interpretation involves nucleophilic addition of the deprotonated amine **87** to the central carbon of the allene. The absence of a strong electron-withdrawing group on the allene, however, would make this a surprising and remarkable nucleophilic addition. A second possible mechanism involves a 6π electrocyclic ring closure, a heteroatom variant of the pentadienyl anion ring closure reaction.¹²¹ It is believed that the additional orthogonal π -system of the allene might help enhance the orbital overlap in the transition state (Figure 4).¹²²

Figure 4. Transition State for Indole Cyclization

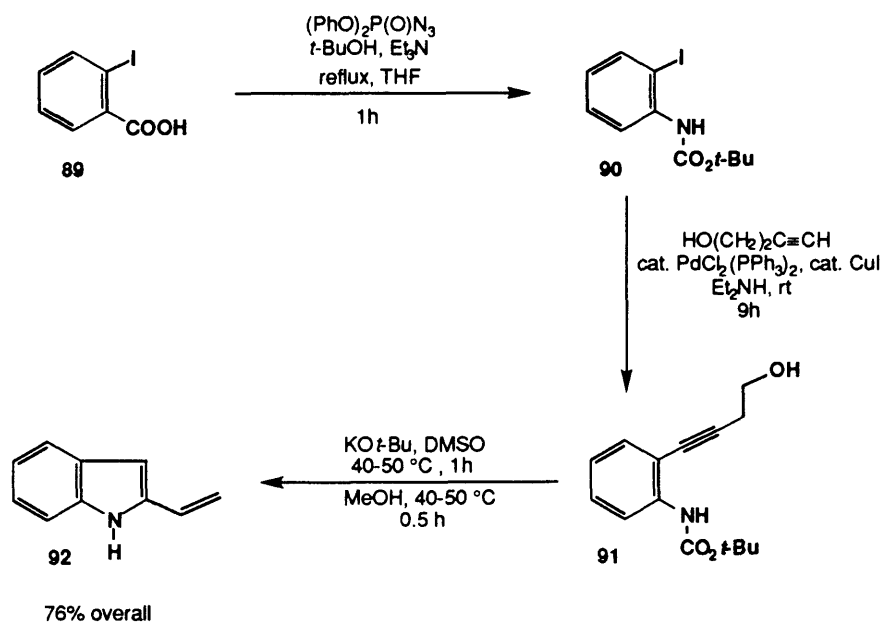


The key 2-(allenyl)arylamine intermediates for our synthesis have been prepared via two alternative routes. One of the most efficient ways to generate these intermediates involves their *in situ* generation via prototopic rearrangement of acetylenes. This tandem isomerization-cyclization strategy is especially effective for the synthesis of 2-substituted indoles. Scheme 21 below shows the application of this isomerization-cyclization strategy to an efficient synthesis of 2-vinylindole.¹²³ A Castro-Stephens coupling reaction under modified conditions¹²⁴ between the N-(*t*-butoxycarbonyl)aniline (**90**) and 3-butyne-1-ol leads to the formation of the acetylene intermediate **91** in high yield.

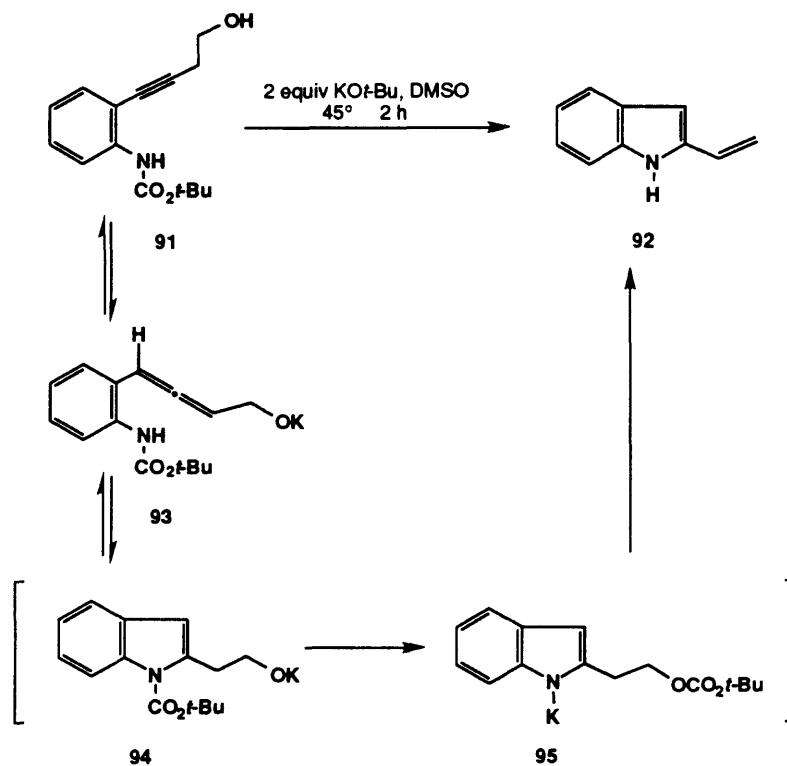
-
121. (a) Staley, S. W. In *Pericyclic Reactions*; Marchand, A. P., Lehr, R. E., Eds.; Academic Press: New York, 1977, Vol. I, pp 224-230. (b) Marvell, E. N. *Thermal Electrocyclic Reactions*; Academic Press: New York, 1980, pp 221-224. (c) Okamura, W. H.; De Lera, A. R. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford 1991, Vol. 5.
122. Similar arguments were used to explain regio- and stereochemical features of allene-olefin cycloaddition reactions: Pasto, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 37.
123. Danheiser, R. L.; Mori, I.; Romines, K. R.; Niger, R. J. unpublished results.
124. (a) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 3, pp 521-549. (b) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (c) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627.

Treatment of **91** with potassium *t*-butoxide then affords 2-vinylindole (**92**) in 76% overall yield (three steps). The mechanism of the key step is outlined in Scheme 22.

Scheme 21

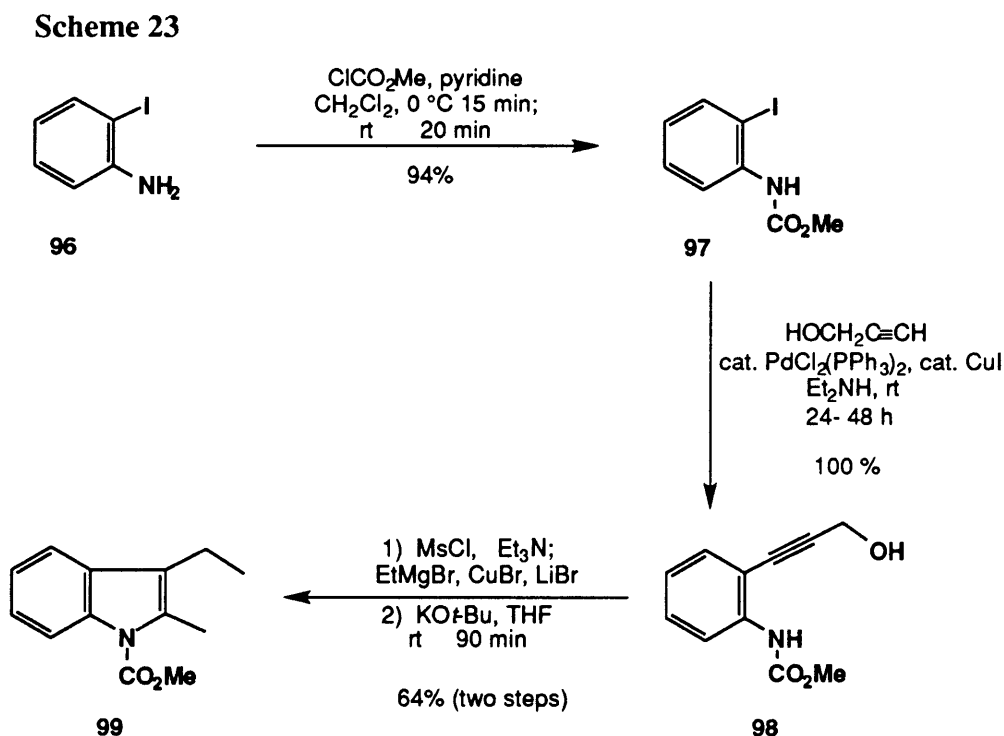


Scheme 22



An interesting aspect of this sequence is the intramolecular transfer of the *t*-butoxycarbonyl group to the alkoxide (**94** to **95**) via a 6-membered transition state. The indole **95** is now equipped with an excellent leaving group at the beta position of the ethyl side chain. The subsequent elimination reaction thus produces 2-vinylindole.

The S_N2' reaction of propargylic mesylates with organocopper compounds constitutes a second strategy for the synthesis of 2-(allenyl)arylamines.¹²⁵ The synthesis of *N*-(methoxycarbonyl)-2-ethyl-3-methylindole (**99**) is an example of the application of this strategy (Scheme 23).¹²⁶

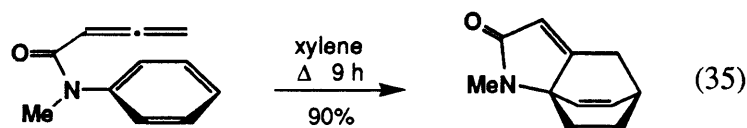


125. Chapter 1 of Part III of this thesis will further review various methods for the synthesis of allenes. For selected examples regarding this particular approach, see: (a) MacDonald, T. L.; Reagan, D. R.; Brinkmeyer, R. S. *J. Org. Chem.* **1980**, *45*, 4740 and references cited therein. (b) Vermeer, P.; Meijer, J.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **1975**, *94*, 112. (c) Vermeer, P.; Westmijze, H.; Klein, H.; van Dijck, L. A. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 56. (d) Westmijze, H.; Vermeer, P. *Synthesis* **1979**, 390. (e) Elsevier, C. J.; Vermeer, P. *J. Org. Chem.* **1989**, *54*, 3276. (f) Elsevier, C. J.; Meijer, J.; Westmijze, H.; Vermeer, P.; van Dijck, L. A. *J. Chem. Soc., Chem. Commun.* **1982**, 82.

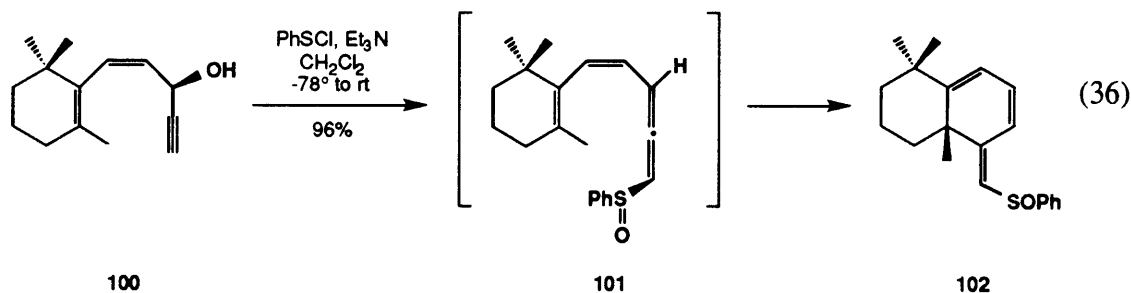
126. Romines, K. R. Ph. D. Thesis, Massachusetts Institute of Technology, 1993.

Previous Cyclization Reactions Involving Allenes

A remarkable feature of the new indole synthesis described above is the surprising facility of the base-promoted cyclization step. Allenes have previously exhibited unusual reactivity compared to the corresponding olefins in a variety of other important synthetic reactions. For example, they have been shown to be excellent dienophiles in Diels-Alder cycloadditions^{127,128} A remarkable intramolecular cycloaddition reaction of an allene with a monosubstituted *benzene ring* has been demonstrated by Himbert (eq 35).^{127a}



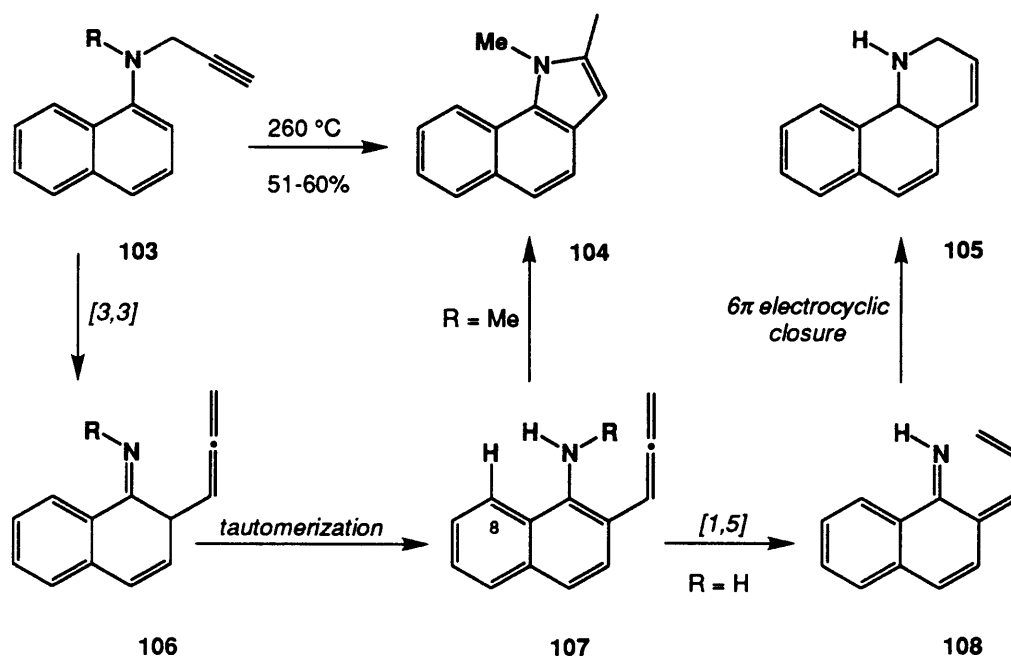
In addition, 6π electrocyclization reactions are more facile for allene systems as compared to simple alkenes.¹²⁹ Okamura^{129a} has shown that cyclization of the allene intermediate **84** has an activation barrier 15-20 kcal/mol lower than that of simple 1,3,5-hexatriene (eq 36).



127. (a) Himbert, G.; Henn, L. *Angew. Chem., Intl. Ed. Engl.* **1982**, *21*, 620. (b) Hayakawa, K.; Yodo, M.; Ohsuki, S.; Kanematsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 6735. (c) Hayakawa, K.; Ysukouchi, T.; Kanematsu, K. *Tetrahedron Lett.* **1986**, 1837.
128. For a review and additional references on the Diels-Alder reactions of allenes, see Huboux, A. H. Ph. D. Thesis, Massachusetts Institute of Technology, 1995.
129. (a) Okamura, W. H.; Peter, R.; Reischel, W. *J. Am. Chem. Soc.* **1985**, *107*, 1034. (b) Bowes, C. M.; Montecalvo, D. F.; Sondheimer, F. *Tetrahedron Lett.* **1973**, 3181. (c) Fleischhauer, I.; Brinker, U. H. *Tetrahedron Lett.* **1983**, 3205. (d) Brinker, U. H.; Wilk, G.; Gomann, K. *Angew. Chem., Intl. Ed. Engl.* **1983**, *22*, 868. (e) Muller, P.; Rodriguez, D. *Helv. Chim. Acta* **1985**, *68*, 975. (f) Barron, C. A.; Khan, N.; Sutherland, J. K. *J. Chem. Soc., Chem. Commun.* **1987**, 1728.

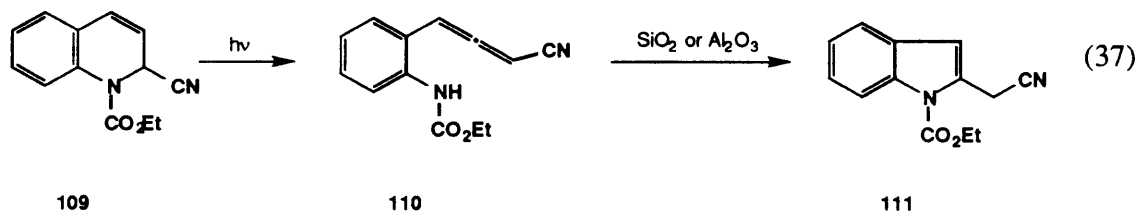
Another class of unusually facile allene cyclizations involves the addition of heteroatom nucleophiles to allene π -bonds. The naphthylamine cyclization shown in Scheme 24 below is an example of such a reaction. The naphthyl(propargyl)amine **103** undergoes a [3,3]-sigmatropic rearrangement under thermal conditions to form the allene **106**, which in turn produces **107** upon tautomerization. The allene **107** can then follow one of the two pathways shown, depending on the R group substituent on the amine. If R = H, a [1,5]-sigmatropic hydrogen shift occurs, followed by a 6π electrocyclic ring closure to form **105**. If R = Me, however, the hydrogen shift does not take place due to the peri interaction between the C-8 hydrogen on the naphthyl ring and the amine methyl group. This interaction leads to the conformation of amine shown in **107**, which cannot do a hydrogen shift. Compound **107** thus undergoes cyclization to form **104**.¹³⁰ Note that this process is related to the cyclization step in our new indole synthesis, although this is promoted by high temperature rather than by base catalysis.

Scheme 24



130. Scheurer, H.; Zsindely, J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 478.

Ikeda¹³¹ has shown that irradiation of ethyl-2-cyano-1,2-dihydroquinoline-1-carboxylates **109** gives rise to cyanoallenes **110**, which cyclize to indoles **111** upon chromatography on alumina or silica gel (eq 37).



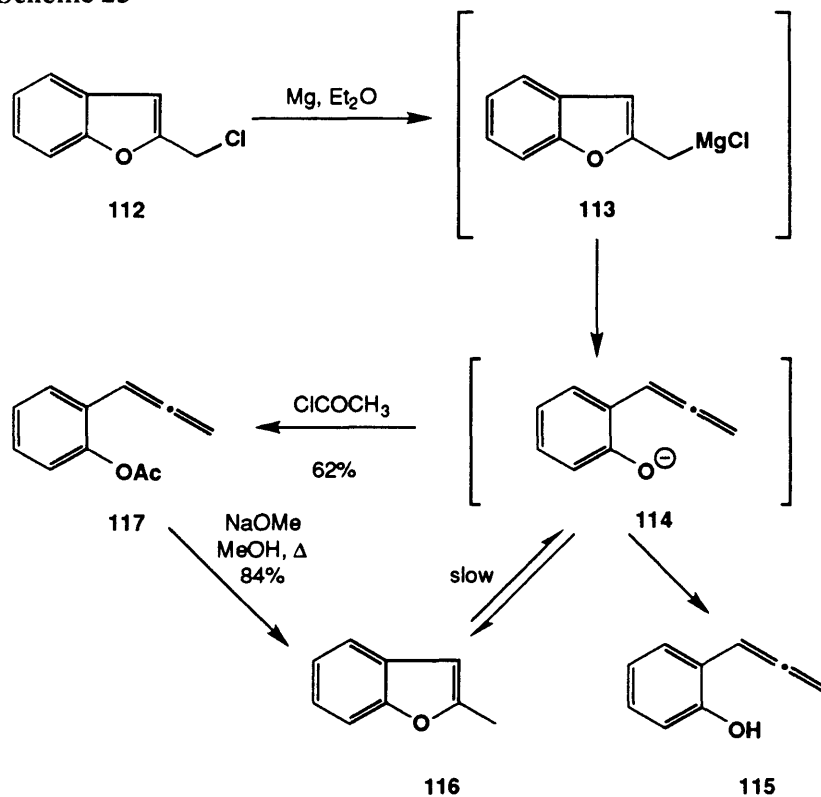
All of the reactions mentioned above¹³⁰⁻¹³² involve the generation of allenes *in situ* via rearrangement reactions. There have also been reports of thermal cyclizations of various stable allenes, and in most cases these compounds cyclize at lower temperatures than the allene intermediates generated *in situ*.¹³³

Several other allene cyclization reactions promoted by base have been described to date. Gaertner was among the first to utilize the cyclization of allenes to form benzofurans (Scheme 25).¹³⁴ Attempts to generate the Grignard reagent **113** resulted in the formation of 2-methylbenzofuran (**116**). Upon further investigation, the loss of Cl was attributed to the formation of allene **114** from **113**. The slow cyclization of this allene intermediate is responsible for the formation of **116**. The intermediacy of allene

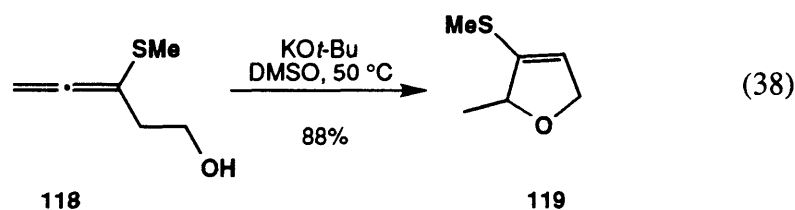
131. (a) Ikeda, M.; Matsugashita, S.; Ishibashi, H.; Tamura, Y. *J. Chem. Soc., Chem. Commun.* **1973**, 922. (b) Ikeda, M.; Matsugashita, S.; Tamura, Y. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2587. (c) Ikeda, M.; Matsugashita, S.; Tamura, Y. *Heterocycles* **1978**, *9*, 281.
132. For other examples of nucleophilic heteroatom-allene cyclizations, see: (a) Pryde, A.; Zsindely, J.; Schmid, H. *Helv. Chim. Acta* **1974**, *57*, 1598. (b) Bruhn, J.; Zsindely, J.; Schmid, H. *Helv. Chim. Acta* **1978**, *61*, 2542. (c) Sarcevic, N.; Zsindely, J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 1457. (d) Otte, B. A.; Saluja, S. S.; Foxm J. J. *J. Org. Chem.* **1972**, *37*, 2858. (e) Brown, G. R.; Elmore, N. F.; O'Donnell, G. M. *J. Chem. Soc., Chem. Commun.* **1972**, 896. (f) Attwood, M. R.; Churcher, I.; Dunsdon, R. M.; Hurst, D. N.; Jones, P. S. *Tetrahedron Lett.* **1991**, 811. (g) Thyagarajan, b. S.; Babasubramanian, K. K.; Rao, R. B. *Tetrahedron Lett.* **1963**, 1393. (h) Jullien, J.; Pechine, J. M.; Perez, F.; Paide, J. J. *Tetrahedron* **1982**, *38*, 1413. (i) Rao, U.; Babasubramanian, K. K. *Tetrahedron Lett.* **1983**, 5023. (j) Rehman, H.; Rao, J. M. *Synth. Commun.* **1987**, *17*, 1119. (k) Yadla, R.; Rao, J. M. *Heterocycles* **1987**, *26*, 329.
133. (a) Griecke, R.; Lues, I. *Tetrahedron Lett.* **1992**, 1871. (b) Mageswaran, S.; Ollis, W. D.; Sutherland, I. O.; Thebtranoth, Y. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1969.
134. (a) Gaertner, R. *J. Am. Chem. Soc.* **1951**, *73*, 4400. For other examples, see: (a) Bendz, G. *Ark. Kemi* **1959**, *15*, 131. (b) Bohlmann, F.; Herbst, P.; Gleinig, H. *Chem. Ber.* **1961**, *94*, 948.

114 was further established by its trapping with acetyl chloride to produce **117**, which under basic conditions cyclized to **116** in high yield.

Scheme 25

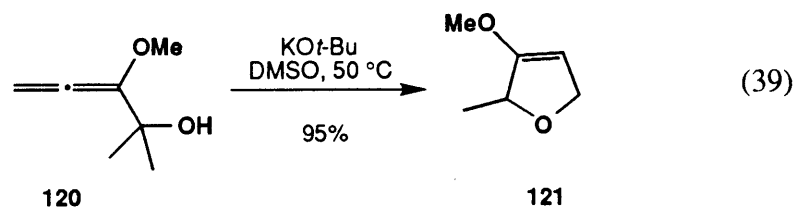


Later, the cyclization of α - and β -hydroxyallenes were investigated by Arens and co-workers (eq 38-39).¹³⁵ The presence of the thioether group on the β -hydroxyallene **118** is believed to accelerate the nucleophilic attack. The reaction in eq 39 was later used by Magnus¹³⁶ to make a series of dihydrofuranones, including an estrone precursor.

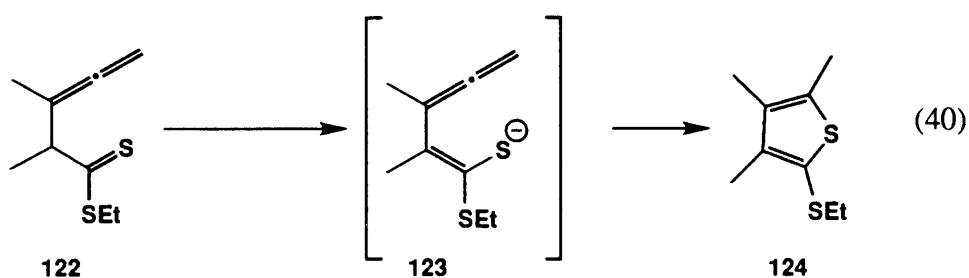


135. Hoff, S.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 609.

136. Grange, D.; Magnus, P. *J. Am. Chem. Soc.* **1978**, *100*, 7746.

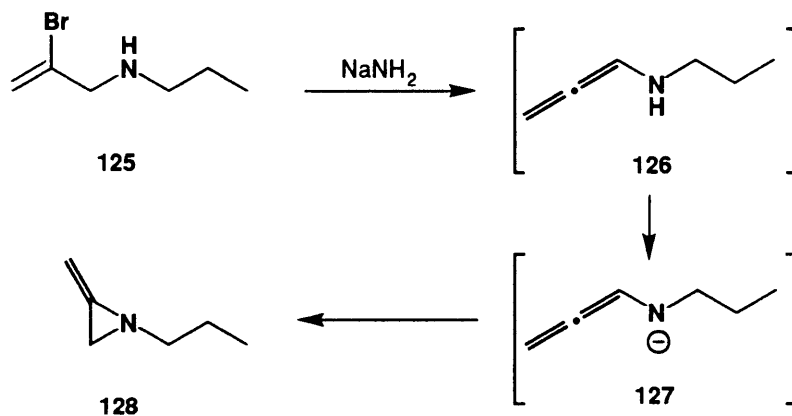


Brandsma has applied a similar strategy to the synthesis of thiophenes. Deprotonation alpha to the thionyl group in **122** promotes the attack of the resulting sulfide **123** and the formation of the tetrasubstituted thiophene ring **124** (eq 40).¹³⁷



Bottini investigated the synthesis of three-membered rings from allenylamines (Scheme 26).¹³⁸ The intermediacy of allene **126** was supported by radiolabelling experiments.

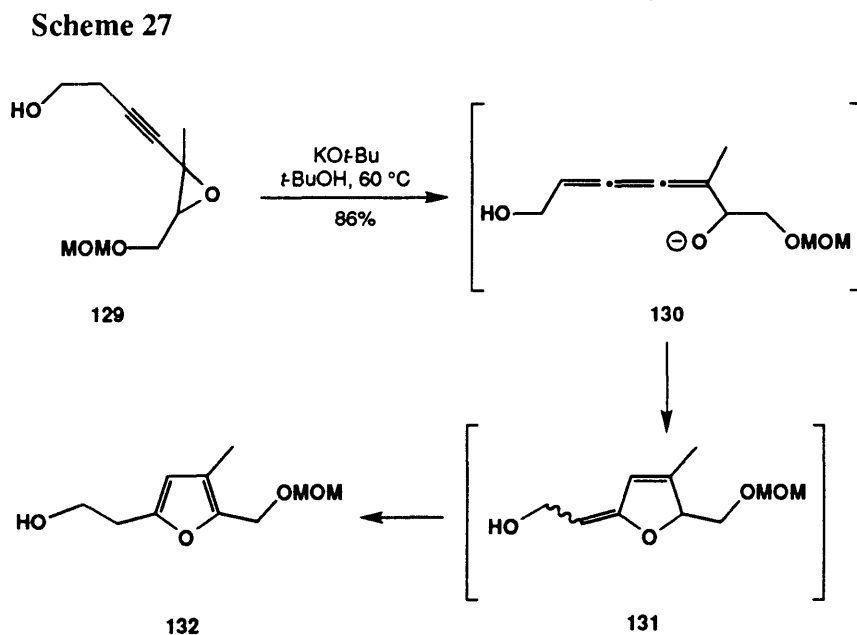
Scheme 26



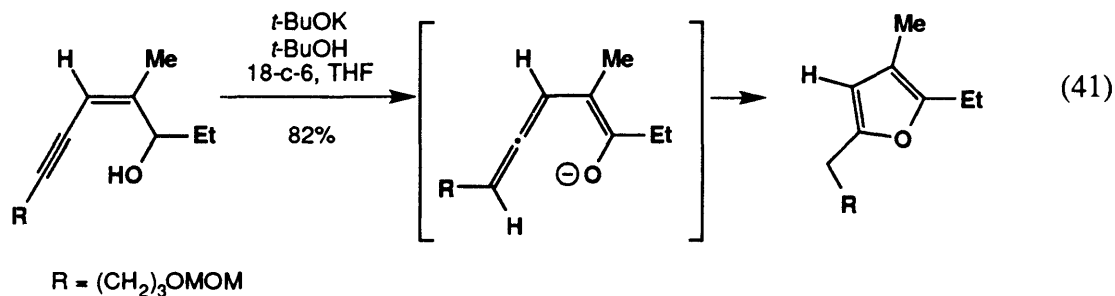
137. Schuijl-Laros, D.; Schuijl, P. J. W.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 1343.

138. Bottini, A. T.; Olsen, R. E. *J. Am. Chem. Soc.* **1962**, *84*, 195.

Recently, Marshall¹³⁹ has reported an example of heteroatom cyclization onto an extended π -system (Scheme 27). Deprotonation at the propargylic carbon in **129** leads to the formation of the cumulene **130**, which then undergoes cyclization to form **131**. The tautomerization of **131** then produces the final furan product **132**.



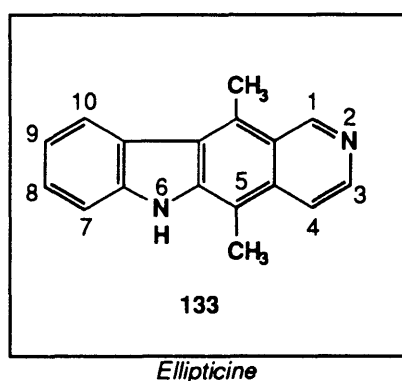
Marshall has also reported the synthesis of furans via base-catalyzed cyclization-isomerization of β - and γ -alkynyl allylic alcohols (eq 41).¹⁴⁰



139. (a) Marshall, J. A.; DuBay, W. J. *J. Am. Chem. Soc.* **1992**, *114*, 1450. (b) Marshall, J. A.; DuBay, W. J. *J. Org. Chem.* **1991**, *56*, 1685.
140. Marshall, J. A.; DuBay, W. J. *J. Org. Chem.* **1993**, *58*, 3435.

Total Synthesis of Ellipticine

In order to further study the scope and limitations of the allene-based indole annulation strategy developed in our laboratory, we chose to focus our efforts to the development of an efficient synthetic route to the carbazole ellipticine (**133**). This project served a twofold purpose: first, it provided a further test for our recently developed indole synthesis based on allene cyclizations. Second, it served as a vehicle to discover and investigate alternative ways to access the key 2-(allenyl)arylamine intermediates.

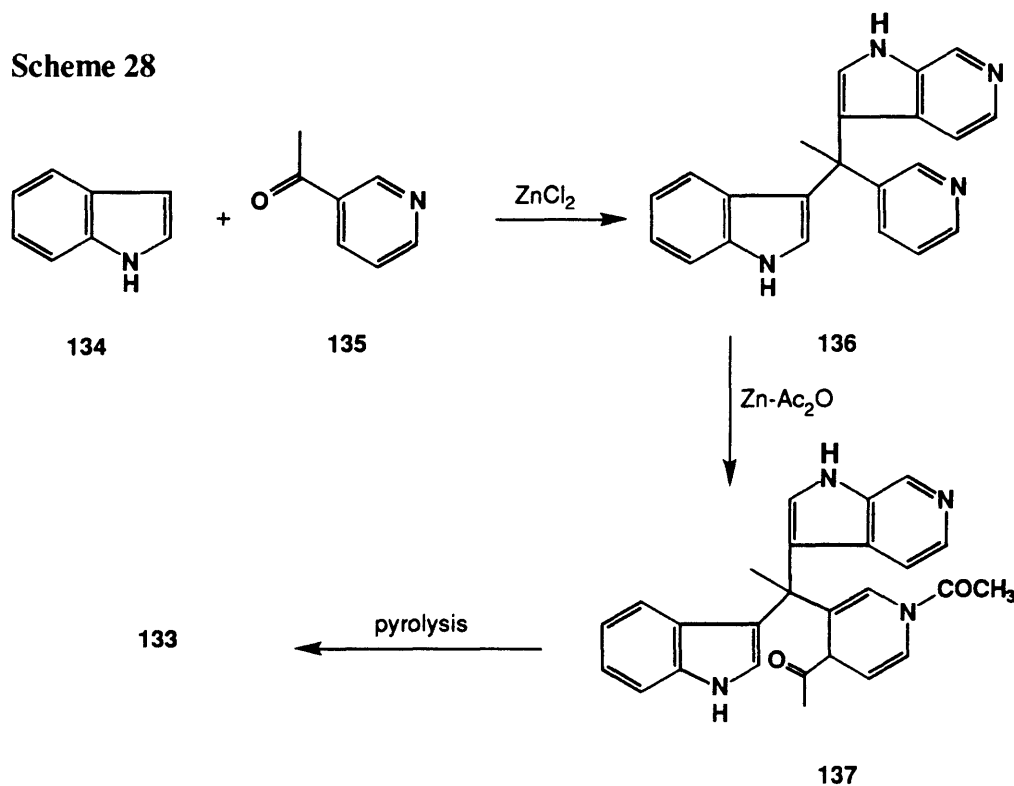


Ellipticine: Introduction and Background

The alkaloid ellipticine (5, 11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole) was first isolated in 1959 from the leaves of *Ochrosia elliptica* Labill, a plant harvested in Florida.¹⁴¹ Subsequently, ellipticine and its derivatives have been isolated from various other species of genera *Aspidosperma*, *Tabernaemontana*, and *Strychnos*.^{142,143} The

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141. Goodwin, S.; Smith, A. F.; Horning, E. C. *J. Am. Chem. Soc.* **1959**, *81*, 1903.
142. (a) Ohashi, M.; Joule, J. A.; Gilbert, B.; Djerassi, C. *Experientia*, **1964**, *20*, 363. (b) Gilbert, B.; Duarte, A. P.; Nakagawa, Y.; Joule, J. A.; Flores, S. E.; Brissolese, J. A.; Campello, J.; Carrazoni, E. P.; Owellen, R. J.; Blossy, E. C.; Brown, Jr., K. S.; Djerassi, C. *Tetrahedron* **1965**, *21*, 1141. (c) Büchi, G.; Mayo, D. W.; Hochstein, F. A. *Tetrahedron* **1961**, *15*, 167. (d) Schmutz, J.; Hunzicker, F. *Helv. Chim. Acta* **1958**, *4*, 288. (e) Brunell, R. H.; Della Casa, D. *Can. J. Chem.* **1967**, *45*, 89. (f) Goman, M.; Neuss, N.; Cone, N. J.; Deyrup, J. A. *J. Am. Chem. Soc.* **1960**, *82*, 1142. (g) Kilminster, K. N.; Sainsbury, M.; Webb, B. *Phytochemistry* **1972**, *11*, 389. (h) Michel, S.; Tillequin, F.; Koch, M. *J. Nat. Prod.* **1980**, *43*, 294. (i) Ahond, A.; Fernandez, H.; Moore, M. J.; Poupat, C.; Sanchez, V.; Potier, P.; Kan, S. K.; Sévenet, T. *J. Nat. Prod.* **1981**, *44*, 193.
143. For selected reviews on syntheses and biological activity of ellipticine, see: (a) Sainsbury, M. *Synthesis* **1977**, 437. (b) Paoletti, C.; Le Pecq, J.-B.; Dat-Xuong, N.; Juret, P.; Garnier, H.; Amiel, J.-L.; Rouesse, J. *Recent Results in Cancer Research* **1980**, *74*, 107. (c) Hewlins, M. J. E.; Oliveira-Campos, A.-M.; Shannon, P. V. R. *Synthesis* **1984**, 289. (d) Gribble, G. W.; Saulnier, M. G. *Heterocycles* **1985**, *23*, 1277. (e) Kansal, V. K.; Potier, P. *Tetrahedron* **1986**, *42*, 2389. (f) Gribble, G. W. In *The Alkaloids*; Academic Press: New York, 1990, Vol. 39, Chapter 7. (g) Gribble, G. W.; *Synlett* **1991**, 289.

unambiguous structural assignment of ellipticine was established as a result of its first total synthesis by Woodward and co-workers,¹⁴⁴ who synthesized ellipticine by the condensation of indole with 3-acetylpyridine to furnish **136**. Reduction of **136** with Zn and acetic anhydride, followed by pyrolysis produced ellipticine in 2% overall yield (Scheme 28).



The first report of antitumor activity of ellipticine was by Dalton and co-workers in 1967.¹⁴⁵ Since then, systematic studies have been conducted on the comparative antitumor activity of a wide range of ellipticine derivatives.¹⁴⁶ Ellipticine and its

144. Woodward, R. B.; Iacobucci, G. A.; Hochstein, F. A. *J. Am. Chem. Soc.* **1959**, *81*, 4434.
 145. Dalton, L. K.; Demerac, S.; Elmes, B. C.; Loder, J. W.; Swan, J. M.; Teitei, T. *Aust. J. Chem.* **1967**, *20*, 2715.
 146. (a) Guthrie, R. W.; Brossi, A.; Mennona, F. A.; Mullin, G. J.; Kierstad, R. W.; Grunberg, E. *J. Med. Chem.* **1975**, *18*, 755. (b) Hayat, M.; Mathé, G.; Janot, M. M.; Potier, P.; Dat-Xuong, N.; Cavé, A.; Sevenet, T.; Kanfan, C.; Poisson, J.; Miet, J.; Le Men, J.; Le Goffic, F.; Gouyette, A.; Ahond, A.; Dalton, L. K.; Connors, T. A. *Biomedicine* **1974**, *21*, 101. (c) Gouyette, A.; Reynaud, R.; Sadet, J.; Baillarge, M.; Gansser, C.; Cros, S.; Le Goffic, f.; Le Pecq, J.-B.; Paoletti, C.; Viel, C. *Eur. J. Med. Chem.* **1980**, *15*, 503. (d) Le Pecq, J.-B.; Dat-Xuong, N.; Gosse, C.; Paoletti, C. *Proc. Natl. Acad. Sci. (U. S. A.)* **1974**, *71*, 5078. (e) Dalton, L. K.; Demerac, S.; Teitei, T. *Aust. J. Chem.* **1969**, *22*, 185. (f) Lecointe, P.; Lesca, P.; Cros, S.; Paoletti, C. *Chem. Biol. Interact.* **1978**, *20*, 113. (g) Paoletti, C.; Cros, S.; Dat-Xuong, N.; Lecointe, P.; Moisand, A. *Chem. Biol.*

derivatives are especially interesting anticancer agents since in addition to having a broad spectrum of antitumor activity, they are effective by i.p., i.v., and oral routes.^{146b,147} The major mechanism of their antitumor activity is not well understood, but is believed to be through intercalation into DNA,¹⁴⁸ as evidenced by breaks in both single-strand and double-strand DNA.¹⁴⁹ Paoletti and co-workers postulated that for good *in vivo* activity, a compound in the ellipticine series must have either a hydrogen (which is readily oxidizable to a 9-hydroxy group) at C-9, or a 9-hydroxy group, or a derivatized 9-hydroxy group that is metabolically convertible to OH.¹⁵⁰ Ellipticine and some of its derivatives are currently used to treat myeloblastic leukemia, advanced breast cancer, and other solid tumors.

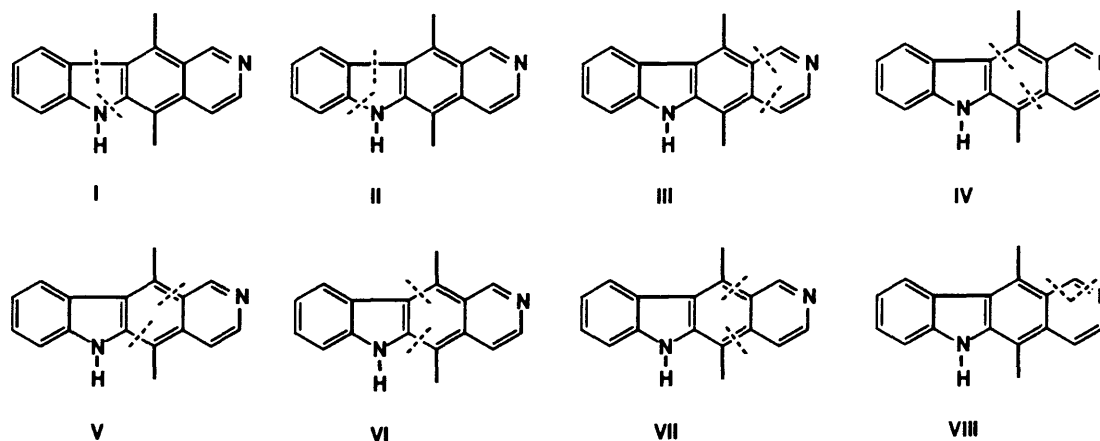
A variety of ellipticine derivatives with significant biological activity have been synthesized recently. Paoletti and co-workers have prepared a number of 1-(alkylamino)-9-methoxyellipticines,¹⁵¹ which have exhibited very high antitumor activity. Quaternary ellipticine glucosides have also shown promising antitumor activity in six different murine tumor systems with excellent therapeutic ratios.¹⁵² Koomen has synthesized 1-acetyl and 1-acetamido-6-methylellipticine¹⁵³ from 1-cyano-6-methylellipticine, and both compounds have shown cytostatic activity.

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- Interact.* 1979, 25, 45. (h) Paoletti, C.; Le Pecq, J.-B.; Dat-Xuong, N.; Lesca, P. *Curr. Chemother. Proc. Int. Congr. Chemother.* 10th. 1977, 2, 1195. (i) Rivalle, C.; Wendling, F.; Tambourin, P.; Lhoste, J.-M.; Chermann, J.-C. *J. Med. Chem.* 1983, 26, 181.
147. (a) Pelaprat, D.; Oberlin, R.; Roques, B.-P.; Le Pecq, J.-B. *C. R. Hebd. Seances Acad. Sci., Ser D* 1976, 283, 1109. (c) Svoboda, G. H.; Poore, G. A.; Montfort, M. L. *J. Pharm. Sci.* 1968, 57, 1720
148. (a) Kohn, K. W.; Waring, M. J.; Glaubiger, D.; Friedman, C. A. *Cancer Res.* 1975, 35, 71. (b) Ashby, J.; Elliott, B. M.; Styles, J. A. *Cancer Lett.* 1980, 9, 21.
149. For additional references on the biological activity of ellipticine, see Sinha, S.; Jain, S. *Progress in Drug Research* 1994, 42, 53.
150. (a) Paoletti, C.; Lecoite, P.; Lesca, P.; Cros, S.; Mansuy, D.; Dat-Xuong, N. *Biochimie* 1978, 60, 1003. (b) Meunier, B.; Auclair, C.; Bernadou, J.; Meunier, G.; Maftouh, M.; Cros, S.; Monsarrat, B.; Paoletti, C. *Dev. Pharmacol.* 1983, 3, 149.
151. Larue, L.; Rivalle, C.; Muzard, G.; Paoletti, C.; Bisagni, E.; Paoletti, J. *J. Med. Chem.* 1988, 31, 1951.
152. Honda, T.; Kato, M.; Inoue, M.; Shimamoto, T.; Shima, K.; Nakanishi, T.; Yoshida, T.; Noguchi, T. *J. Med. Chem.* 1988, 31, 1295.
153. Boogard, A. T.; Pandit, U. K.; Koomen, G.-J. *Tetrahedron* 1994, 50, 2551.

Previous Syntheses of Ellipticine

The promising antitumor activity of ellipticine and its derivatives has prompted numerous efforts to discover synthetic routes to the ellipticine nucleus. The key disconnection strategies are shown in Figure 5 below.^{143d} It is beyond the scope of this dissertation to review all of these synthetic approaches. The extensive review articles mentioned previously¹⁴³ have excellent detailed accounts of these previous syntheses. This section will instead focus only on some examples of those syntheses that involve a key disconnection similar to the one employed in our studies (disconnection V, Figure 5).

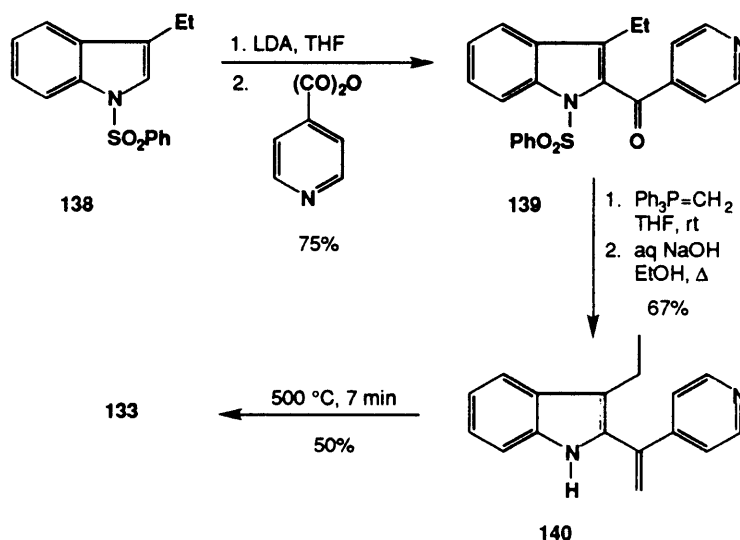
Figure 5. Key Strategic Disconnections for the Synthesis of Ellipticine



The most attractive and convergent disconnections break one of the two middle rings in ellipticine. Such disconnections would either produce a benzene derivative and an isoquinoline compound (e.g. disconnections I, II), or an indole derivative and a substituted pyridine (e. g. disconnection IV-VII). We chose the latter for our synthesis, since indoles and pyridines are more readily accessible than isoquinoline derivatives. Several previous syntheses of note have also chosen a similar disconnection strategy. The following are two examples of ellipticine syntheses that involve the cyclization of the C-ring as the final stage.

Kano's approach to ellipticine involved metallation of 1-(benzenesulfonyl)-3-ethylindole (**138**) with LDA followed by quenching the lithiated species with isonicotinic anhydride to produce the ketone **139**. A Wittig reaction and subsequent cleavage of the protective group gave alkene **140**, which upon thermolysis at 500 °C for 7 min produced ellipticine in modest yield (Scheme 29).¹⁵⁴

Scheme 29

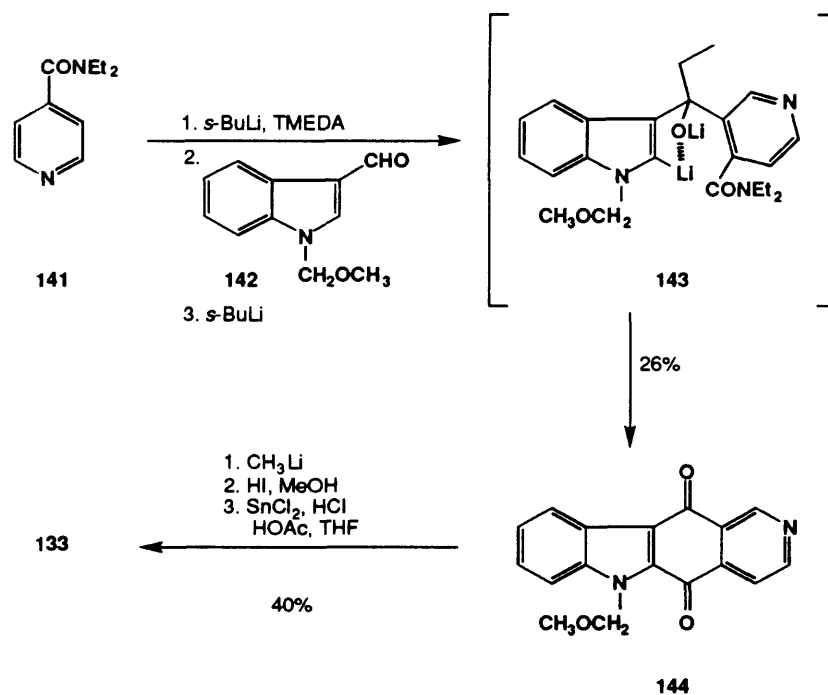


An exceptionally short and elegant synthesis of ellipticine was reported by Snieckus using "tandem metallation" (Scheme 30).¹⁵⁵ Lithiation of N,N-diethylisonicotinamide **141** with *s*-BuLi/TMEDA followed by addition of the indole-3-carboxaldehyde **142** generated the intermediate **143**, which underwent cyclization and spontaneous oxidation upon warming to room temperature. The resulting quinone **144** was then converted to ellipticine by sequential treatment with MeLi, 47% HI, and stannous chloride/hydrochloric acid.

154. Kano, S.; Sugino, E.; Shibuya, S.; Hibino, S. *J. Org. Chem.* **1981**, *46*, 2979.

155. Watanabe, M.; Snieckus, V. *J. Am. Chem. Soc.* **1980**, *102*, 1457.

Scheme 30



The above approaches used the cyclization of the C-ring of ellipticine as the final stage of the synthesis. In Kano's case (and in several other syntheses) very harsh reaction conditions were necessary to effect the desired cyclization. Our approach to ellipticine also involves the cyclization of the C-ring as the final step. However, we believed that the desired C-ring cyclization would proceed under very mild conditions in our synthesis (*vide infra*). The next chapter describes our efforts towards the total synthesis of ellipticine based on the indole annulation methodology discussed earlier.

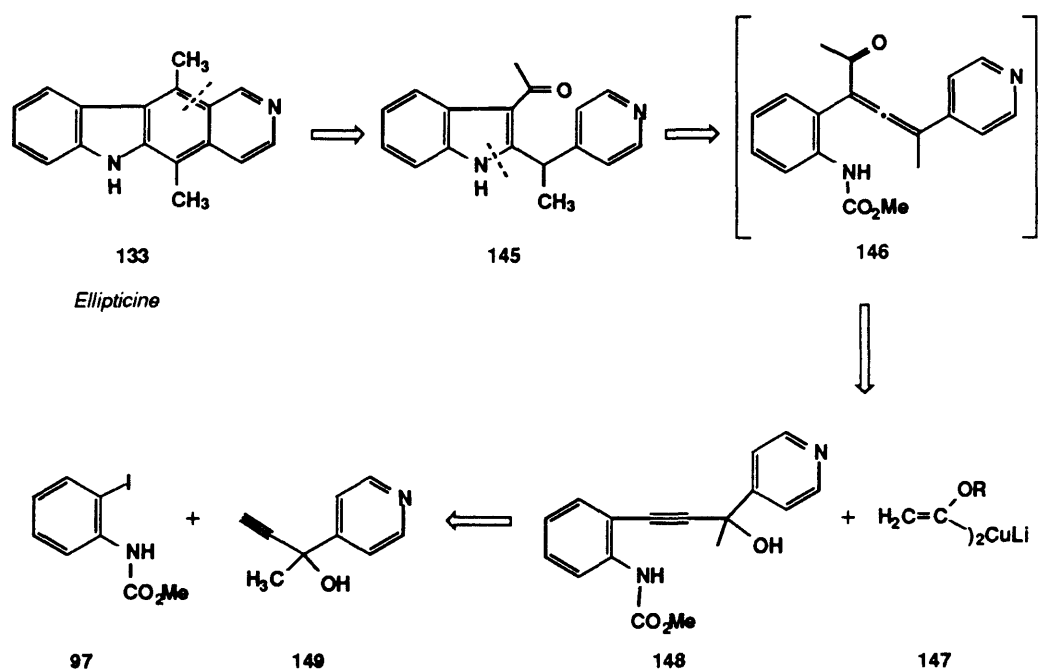
Chapter 2

Studies Directed Toward the Synthesis of Ellipticine

Retrosynthetic Analysis

The application of the base-catalyzed allene cyclization strategy developed in our laboratory to the assembly of the key 3-acetylindole derivative **145**, a precursor for ellipticine (**133**), is outlined in the retrosynthetic scheme below (Scheme 31). The pivotal step in the synthetic plan thus involves the base-catalyzed cyclization of the allenyl ketone **146** or a derivative incorporating a suitable precursor to the acetyl group.

Scheme 31

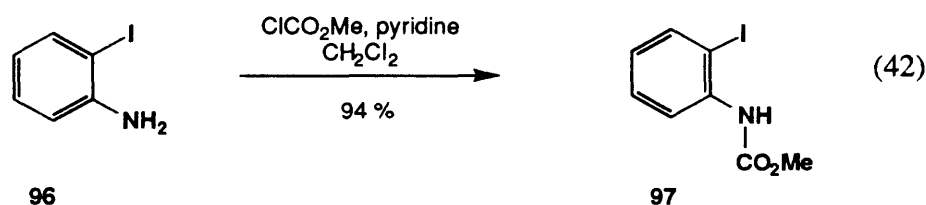


As discussed in the preceding chapter, one route we have employed for the synthesis of 2-(allenyl)arylamines involves the coupling of organocopper compounds with aryl-substituted propargylic alcohol derivatives. Scheme 31 shows how the allenyl

ketone **146** could be prepared from the S_N2' reaction of an acetyl anion equivalent¹⁵⁶ organocopper reagent (e.g. **147**) with a derivative of the propargylic alcohol **148**, which in turn would be synthesized via a Castro-Stephens coupling reaction^{106,124} between the propargylic alcohol **149** and N-(methoxycarbonyl)-2-iodoaniline (**97**).

Synthesis of the Propargylic Alcohol Intermediate **148**

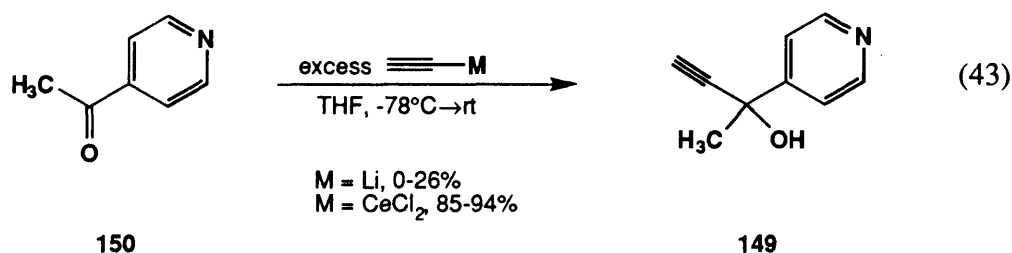
The starting material in the above scheme, N-(methoxycarbonyl)-2-iodoaniline (**97**), is a known compound¹⁵⁷ and was readily prepared according to the procedure developed by Dr. Karen Romines.¹²⁶ Thus, treatment of 2-iodoaniline with 1.5 equiv of methyl chloroformate in the presence of 1.2 equiv of pyridine (0 °C to room temperature) provided the protected aniline **97** in 88-94% yield (eq 42).



The synthesis of the second intermediate, the propargylic alcohol **149**, proved to be more difficult than originally imagined. Addition of monolithium acetylide (prepared according to Midland's procedure)¹⁵⁸ to commercially available 4-acetylpyridine produced the propargylic alcohol **149** in very low yield (eq 43). Presumably, proton transfer from the highly enolizable 4-acetylpyridine is the dominant pathway when this ketone reacts with lithium acetylide.

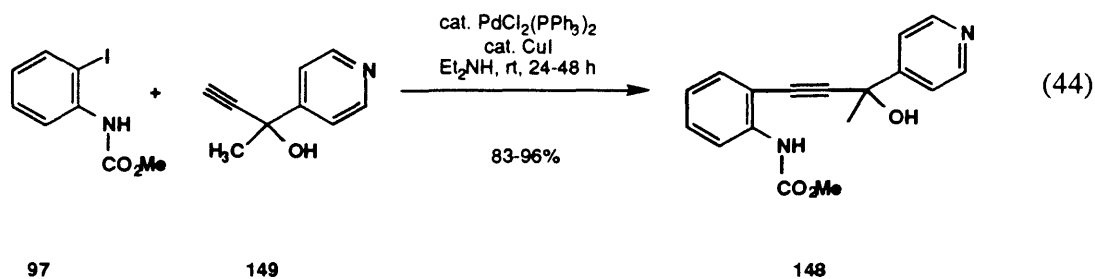
-
156. (a) For a review, see *Unpoled Synthons, A Survey of Sources and Uses in Synthesis*; Hase, T. A., Ed.; John Wiley & Sons: New York, 1987. For selected examples, see: (b) Baldwin, J. E.; Höfle, G. A.; Lever, O. W. *J. Am. Chem. Soc.* **1974**, *96*, 7125. (c) Levy, A. B.; Schwartz, S. J. *Tetrahedron Lett.* **1976**, 2201. (d) Chavdarian, C. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1975**, *97*, 3822. (e) Baldwin, J. E.; Lever, O. W.; Tzodikov, N. R. *J. Org. Chem.* **1976**, *41*, 2312. (f) Dexheimer, E. M.; Spialter, L. *J. Organomet. Chem.* **1976**, *107*, 229.
157. Takahashi, J.; Kirino, O.; Takayama, C.; Kamoshimta, K. *J. Chromatog.* **1988**, *436*, 316.
158. Midland, M. M. *J. Org. Chem.* **1975**, *40*, 2250.

We therefore chose to replace lithium acetylide with the corresponding organocerium reagent. It has been observed that the transmetalation of Grignard and organolithium reagents to cerium (III) derivatives dramatically enhances their reactivity in nucleophilic addition to enolizable ketones. This effect is presumably due to the high oxophilicity of the cerium (III) ion, which imparts stronger electrophilic character to the carbonyl group.¹⁵⁹ Thus, treatment of 4-acetylpyridine with 2.5 equiv of the organocerium reagent derived from lithium acetylide and cerium (III) chloride (-78 °C, 2-6 h, then rt) produced the desired propargylic alcohol **149** in 85-94% yield (eq 43).



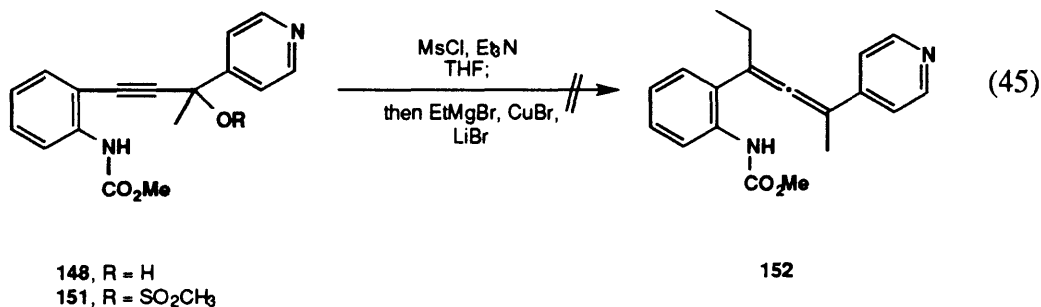
The aryl acetylene **148** was then prepared in 83-96% yield using the modified Castro-Stephens reaction conditions reported by Sonogashira and co-workers.^{124,160} Use of excess N-(methoxycarbonyl)-2-iodoaniline (**97**) was crucial to obtain the desired product in high yield and high purity. When only 1 equiv of **97** was used, the coupling reaction produced the desired product in <65% yield, and the separation of **148** from **149** by chromatography proved to be very difficult. Using 1.1 equiv of **97** increased the yield to 75%. With 1.2 equiv of **97**, yields ranging from 83-96% were achieved (eq 44).

159. (a) For a review on organocerium chemistry, see Imamoto, T. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 1, pp 231-250. (b) Imamoto, T.; Kusumoto, T.; Yokoyama, M. *J. Chem. Soc., Chem. Commun.* **1982**, 1042. (c) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, 4233. (d) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904. (e) Suzuki, M.; Kimura, Y.; Terashima, S. *Chem. Lett.* **1984**, 1543. (f) Suzuki, M.; Kimura, Y.; Terashima, S. *Chem. Pharm. Bull.* **1986**, *34*, 1531.
160. (a) For the preparation of CuI, see Kauffman, G. B.; Pinnell, R. P. *Inorg. Synth.* **1950**, *6*, 3. (b) For the preparation of PdCl₂(PPh₃)₂, see Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, 1985, p 18.



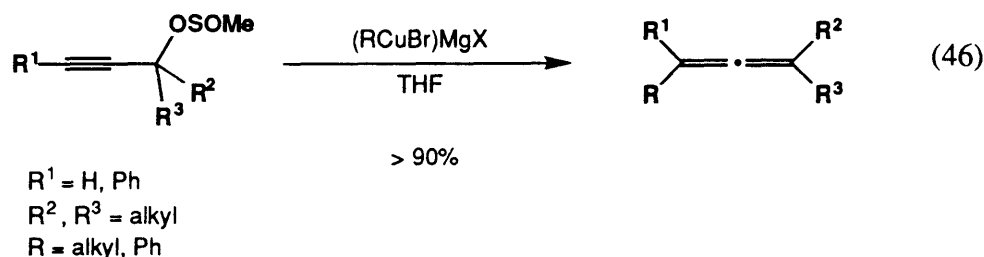
Synthesis of the Key Allene Intermediate via Organocopper Compounds

With the key intermediate **148** in hand, we next conducted a series of model studies directed at accomplishing the S_N2' reaction of organocopper reagents with various derivatives of the propargylic alcohol **148**. We selected the organocopper reagent prepared from ethylmagnesium bromide, CuBr,¹⁶¹ and LiBr as the initial model organocopper compound for this study. Unfortunately, our previous procedure involving the *in situ* generation of the mesylate **151**¹²⁵ failed to produce the desired allene **152** (eq 45). These reactions often led to the recovery of at least 60% of the starting propargylic alcohol, as well as a mixture of several unidentifiable products. It is well known that the formation of tertiary mesylates is often complicated due to the formation of the tertiary chlorides and elimination reactions. Furthermore, tertiary benzylic mesylates are expected to usually be very unstable compounds. We therefore decided to focus our attention on finding other leaving groups for this substitution reaction.



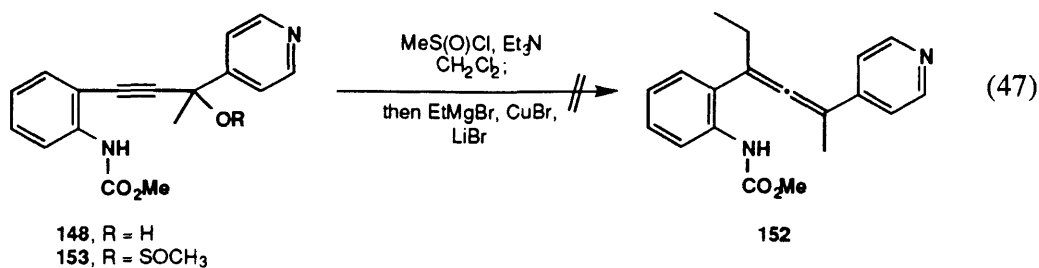
161. For an inexpensive preparation procedure for highly pure copper (I) bromide, see Theis, A. B.; Townsend, C. A. *Synth. Commun.* **1981**, *11*, 157.

In their work on the synthesis of tetrasubstituted allenes, Vermeer and co-workers¹⁶² discovered that *sulfinates* constitute a better leaving group than the corresponding sulfonate esters for substitution reactions involving organocopper reagents and tertiary propargylic compounds (eq 46). The sulfinates are easily accessible from the reaction of tertiary alcohols with methanesulfinyl chloride.¹⁶³



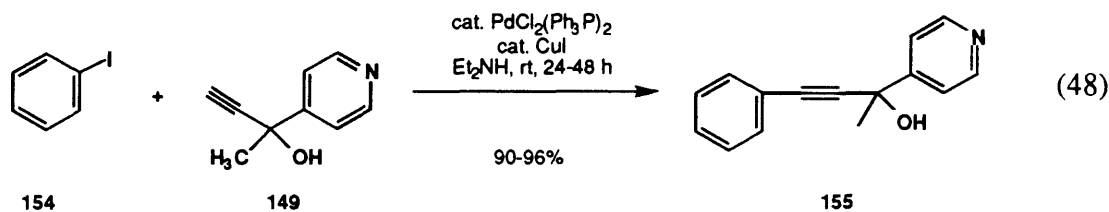
We decided to replace the sulfonate **151** with the sulfinate derivative **153** (which was prepared according to Vermeer's procedure)¹⁴² and repeat the model reaction with the same organocopper reagent as above (eq 47). Unfortunately, this reaction produced a complicated mixture of several products. It thus became clear that the $\text{S}_{\text{N}}2'$ substitution reaction with organocopper reagents was not the best method to access the desired allene **146** from our substrates. This may be attributed to the high reactivity of the tertiary, benzylic leaving groups in **151** and **153**, which results in the formation of several by-products via various substitution pathways ($\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2'$). Furthermore, the first equivalent of the organocopper reagent in these reactions is quenched by the acidic N-H proton in the substrate. The resulting deprotonated species might then participate in intramolecular or intermolecular side reactions, thus producing a mixture of by-products.

162. Vermeer, P.; Westmijze, H.; Kleijn, H.; van Dijck, L. A. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 56.
 163. (a) Mikolajczyk, M.; Drabowicz, J. *J. Chem. Soc.* **1974**, 547. For the preparation of methanesulfinyl chloride, see (b) Corey, E. J.; Durst, T. *J. Am. Chem. Soc.* **1968**, *90*, 5548. (c) Douglass, I. B.; Farah, B. S.; Thomas, E. *G. J. Org. Chem.* **1961**, *26*, 1996. (d) Douglass, I. B.; Farah, B. S. *Organic Syntheses* **1960**, *40*, 62.



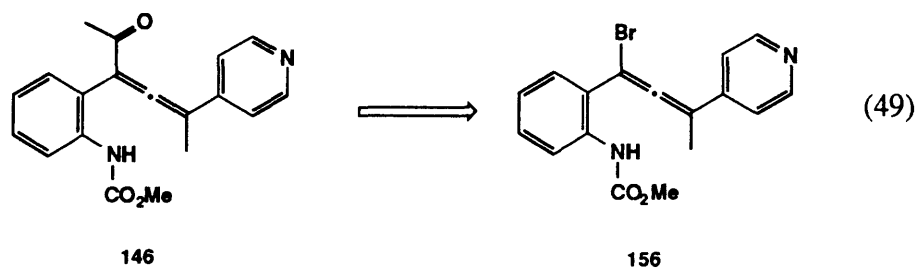
Rearrangement Approaches to the Key Allene Intermediate

At this point, we decided to investigate a variety of other allene-forming reactions using the model system **155** prepared from the coupling of the propargylic alcohol **149** with iodobenzene (**154**) according to the modified Castro-Stephens procedure of Sonogashira (eq 48).¹²⁴



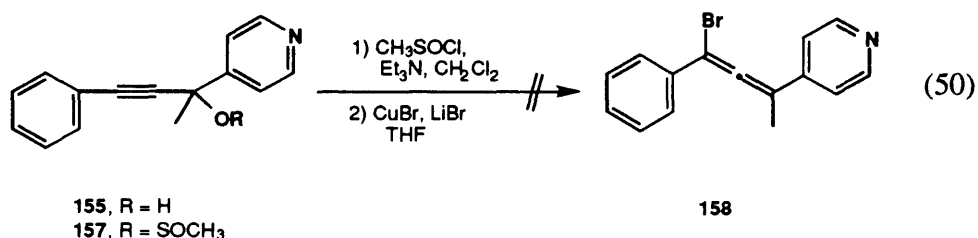
A. Bromoallenes

First, we investigated Goré's method for the preparation of bromoallenes from propargylic sulfonates.¹⁶⁴ We envisioned that with the bromoallene **156** in hand, we could readily access the desired allenyl ketone **146**, for example via a carbonylative Stille cross coupling reaction (eq 49).



164. Montury, M.; Goré, J. *Synth. Commun.* **1980**, *10*, 873.

Goré reported that a solution of CuBr and LiBr in THF (-60 °C) converts propargylic tosylates and mesylates to the corresponding 1-bromoallenes in good yield. In our hands, however, the reaction of the sulfinate derivative **157** with CuBr and LiBr in THF (-60 °C to room temperature) failed to produce any of the desired allene **158** in significant yield (eq 50). Instead, this reaction led to the formation of a mixture of several products, each in low yield, which were difficult to separate and isolate by chromatography.

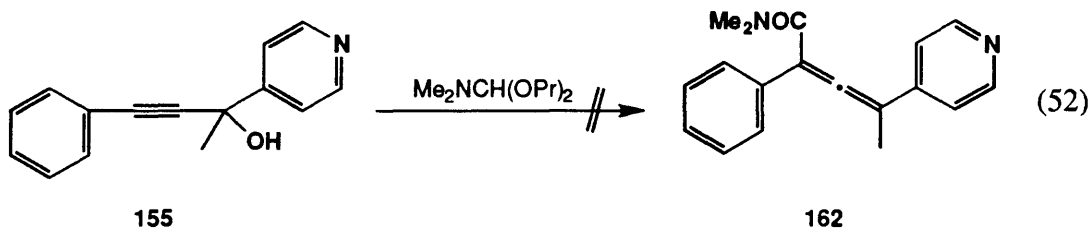
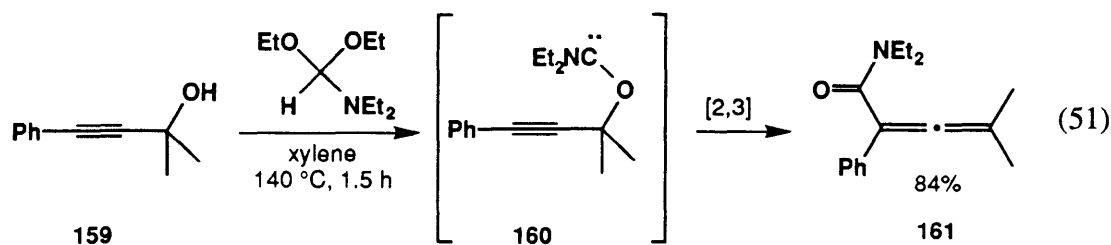


B. Allenic Amides

Parker has developed a synthesis of allenic amides from the reaction of propargylic alcohols with N,N-diethylformamide acetals (xylene or dichlorobenzene, 140-170 °C).¹⁶⁵ The key reaction (eq 51) involves a [2,3]-sigmatropic rearrangement (**160** to **161**) which is a variant of the Büchi [2,3]-sigmatropic rearrangement reaction of allylic alcohols.¹⁶⁶ Unfortunately, we were unable to successfully utilize this strategy for the synthesis of the key allene intermediate **162**. Reaction of the alcohol **155** with the commercially available N,N-dimethylformamide di-*n*-propyl acetal failed to produce **162** in good yield (eq 52). The majority of the starting material was recovered in these reactions. It is unclear why **155** fails to react since Parker has successfully applied this method to several related hindered tertiary alcohols.

165. (a) Parker, K. A.; Petraitis, J. J. *Tetrahedron Lett.* **1977**, 4561. (b) Parker, K. A.; Petraitis, J. J.; Kosley, R. W.; Buchwald, S. L. *J. Org. Chem.* **1982**, *47*, 389.

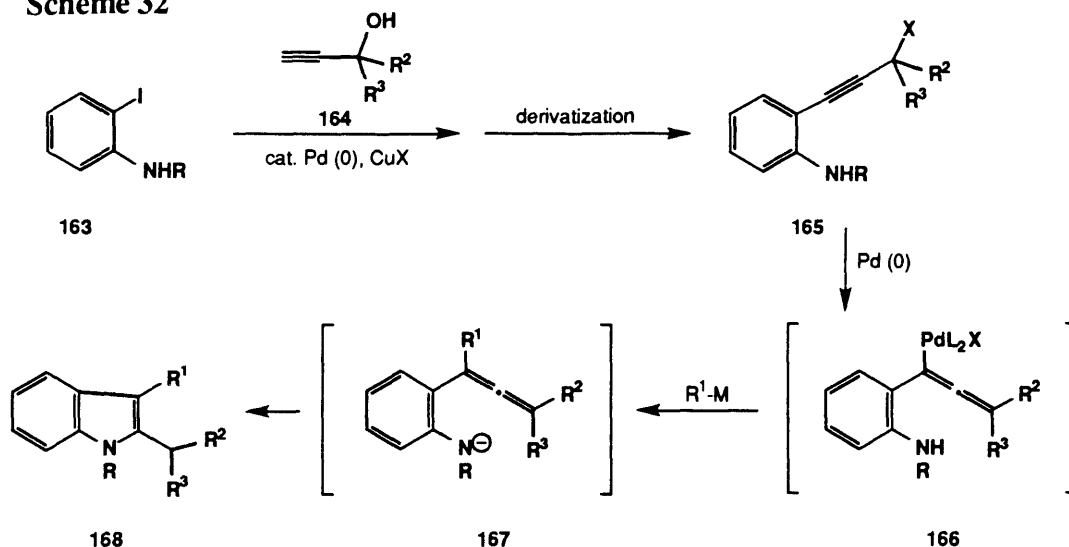
166. Büchi, G.; Gushman, M.; Wüest, H. *J. Am. Chem. Soc.* **1974**, *96*, 5563.



Synthesis of the Key Allene Intermediates via Organopalladium Compounds

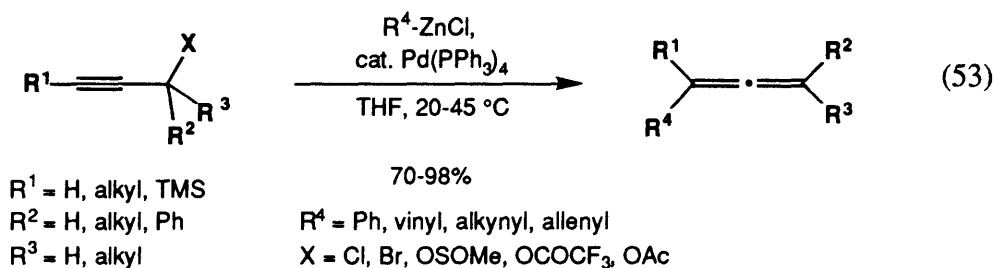
Many strategies for the synthesis of allenes have been developed that rely on the formation of *allenylpalladium species* from various propargylic derivatives as the key step. These strategies will be discussed in more detail in the following chapter. This section describes our efforts to apply some of these approaches to the synthesis of a key intermediate for our proposed total synthesis of the anticancer agent ellipticine. The following scheme summarizes our general strategy. Castro-Stephens type coupling of a propargylic alcohol **164** to **163** would afford **165** after conversion of the hydroxyl group to a suitable derivative. Oxidative addition of Pd(0) would be expected (see Chapter 1 of Part III) to then generate the allenylpalladium intermediate **166**. Transmetalation with an appropriate organometallic compound (e.g. M = Sn, Zn, B, etc.) and reductive elimination would afford the desired allene **167**, which ideally would undergo base-catalyzed cyclization to form the indole system in the same synthetic operation.

Scheme 32



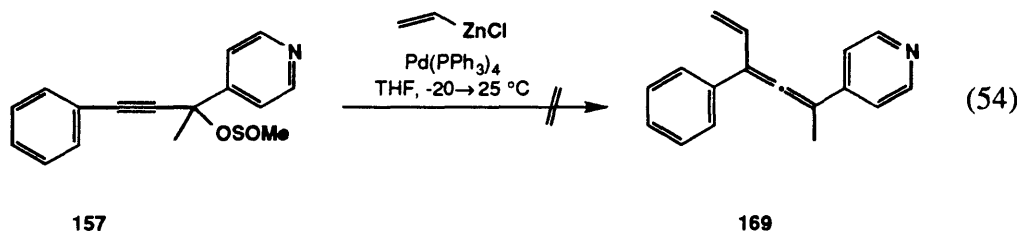
a. Pd-Catalyzed Reaction of Organozinc Compounds with Propargylic Derivatives

Linstrumelle was the first to report an allene synthesis involving palladium-catalyzed coupling reactions. Grignard reagents were found to react with propargylic and allenic halides in the presence of catalytic Pd(0).¹⁶⁷ Vermeer and co-workers¹⁶⁸ then studied the palladium(0)-catalyzed reaction of propargylic alcohol derivatives with *organozinc compounds* to form substituted allenes (eq 53). This reaction was further studied by Keinan and Bosch,¹⁶⁹ who investigated the relative reactivities of allylic and propargylic acetates towards palladium(0)-catalyzed substitution by various nucleophiles.



167. Jeffery-Luong, T.; Linstrumelle, G. *Tetrahedron Lett.* **1980**, 5019.
 168. (a) Ruitenbergh, K.; Kleijn, H.; Elsevier, C. J.; Meijer, J.; Vermeer, P. *Tetrahedron Lett.* **1981**, *22*, 1451. (b) Ruitenbergh, K.; Kleijn, H.; Westmijze, H.; Meijer, J.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 405. (c) Elsevier, C. J.; Stehouwer, P. M.; Westmijze, H.; Vermeer, P. *J. Org. Chem.* **1983**, *48*, 1103. (d) Elsevier, C. J.; Kleijn, H.; Boersma, J.; Vermeer, P. *Organometallics* **1986**, *5*, 716.
 169. Keinan, E.; Bosch, E. *J. Org. Chem.* **1986**, *51*, 4006.

As shown above, several propargylic alcohol derivatives participate in palladium-catalyzed coupling reactions with organozinc compounds. We chose to start our investigation of the application of this methodology to the synthesis of ellipticine by using the propargylic sulfinate **157** already prepared in connection with our organocopper reagent experiments. Unfortunately, the reaction of the sulfinate **157** with vinylzinc chloride (prepared from vinylmagnesium bromide and zinc chloride) under the conditions reported by Vermeer failed to produce a significant amount of the desired allene **169** (eq 54). This reaction instead led to the formation of a mixture of several products, which were difficult to separate by chromatography. At this point, further investigation of this strategy was suspended due to promising results we had obtained in exploratory studies on an alternative cross-coupling approach based on organoboron compounds (see Part III).

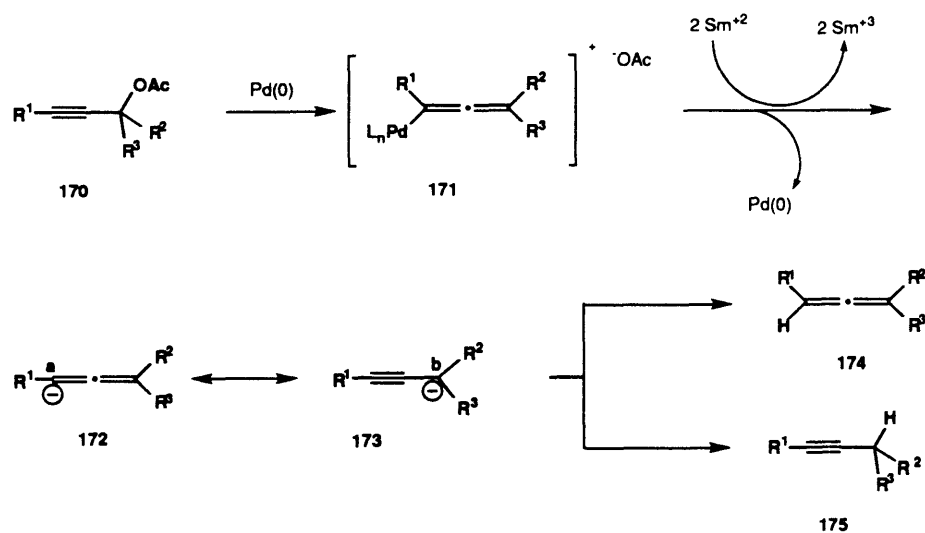


b. Strategies Based on Palladium-Catalyzed Reduction of Propargylic Alcohol Derivatives

Recently, several methods have been developed in which a propargylic alcohol derivative is converted (by way of allenylpalladium intermediates) to allene products via what is effectively an S_N2' displacement by hydride. Application of this methodology to **165** (Scheme 32) in our approach to ellipticine would generate an indole product **168** with $R^1 = \text{H}$; electrophilic substitution chemistry could then be used to install the requisite acetyl group at the C-3 position of the indole ring.

Inanaga and co-workers have reported a mild method for the reduction of propargylic acetates to allenes via a Pd(0)-catalyzed reaction with SmI₂ (THF, room temperature to 65 °C).¹⁷⁰ Tertiary and secondary acetates produce allenes almost exclusively when the hindered alcohol 2,4-dimethyl-3-pentanol is used as the proton source in the reaction (*vide infra*). However, primary acetates often lead to the formation of mixtures of allenes (minor products) and acetylenes (major products). The mechanism proposed for this reaction by Inanaga and co-workers is shown in Scheme 33 below.

Scheme 33

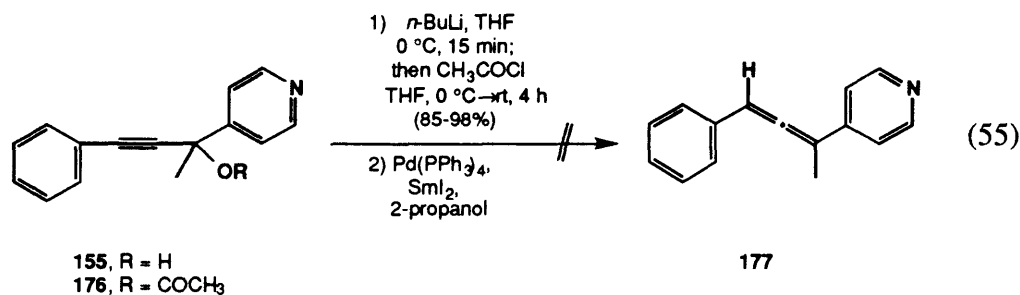


Oxidative addition of Pd(0) to the propargylic acetate **170** forms the allenylpalladium species **171**, which accepts two electrons from SmI₂ releasing Pd(0) and the allenyl anion **172** (which is a resonance form of the propargylic anion **173**). In the case of reactions beginning with secondary and tertiary acetates, protonation then occurs at the sterically less hindered carbon atom **a** (**172**) to produce allenes **174**. Primary

170. (a) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5237. (b) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Chem. Lett.* **1987**, 2275.

acetates ($R^2 = R^3 = H$), however, produce acetylenes **175** through protonation at carbon atom **b** (**173**).

The propargylic acetate **176** was prepared according to Kaiser's procedure¹⁷¹ in 85-98% yield by treating **155** with 1.1 equiv of *n*-BuLi (0 °C) and trapping the resulting alkoxide with 1.5 equiv of acetyl chloride (eq 55). Treatment of this acetate under Inanaga's conditions produced a mixture of several products (eq 55).



We next investigated another means of effecting the reductive conversion of propargylic alcohol **155** to allene **177** based on the hydrogenolysis of alk-2-ynyl carbonates with ammonium formate.¹⁷² Tsuji has reported that in the presence of 2 equiv of ammonium formate, alk-2-ynyl carbonates are converted into allenes at 20-30 °C in THF. Pd₂(dba)₃(CHCl₃):PBU₃ (1:4) was determined to be the optimum catalyst for this reaction. The reaction of secondary and tertiary propargylic carbonates produces allenes exclusively, while primary propargylic carbonates give rise to mixtures of allenes and acetylenes.

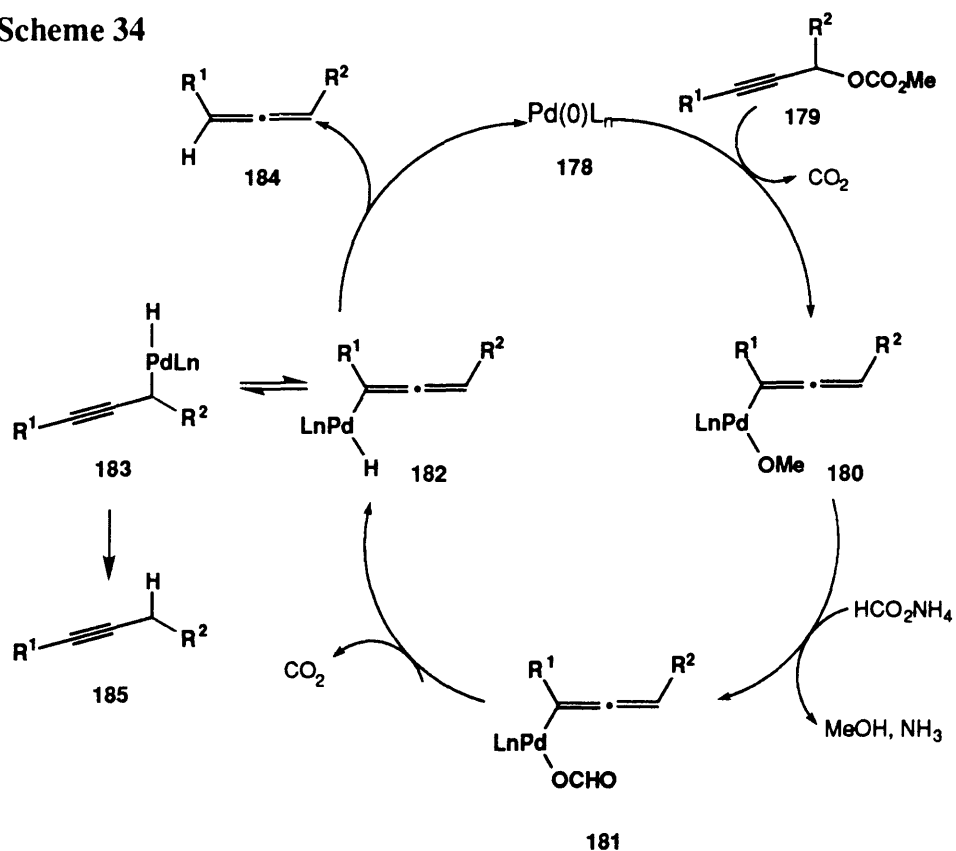
The proposed mechanism for this process is outlined in Scheme 34 below. Oxidative addition of the propargylic carbonate **179** with the palladium catalyst **178** and subsequent decarboxylation gives the allenylpalladium alkoxide complex **180**, which reacts with ammonium formate to afford the allenylpalladium formate complex **181**.

171. Kaiser, E. M.; Woodruff, R. A. *J. Org. Chem.* **1970**, *35*, 1198.

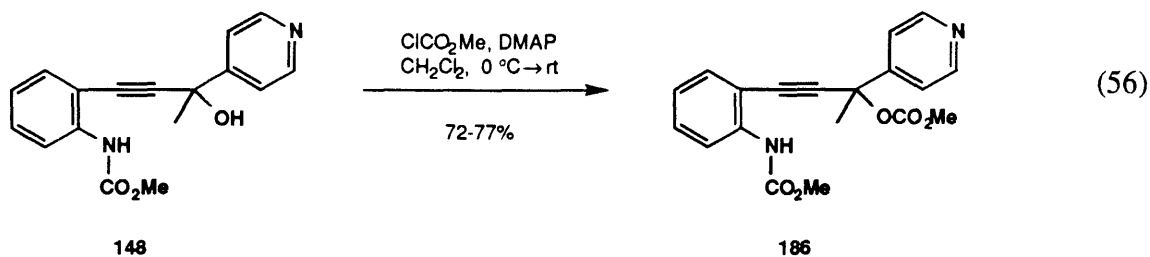
172. (a) Tsuji, J.; Sugiura, T.; Yuhara, M.; Minami, I. *J. Chem. Soc., Chem. Commun.* **1986**, 922. (b) Tsuji, T.; Sugiura, T.; Minami, I. *Synthesis* **1987**, 603. (c) For a review of synthetic methods involving transition metal-catalyzed reactions of allylic and propargylic carbonates, see Tsuji, J. *Tetrahedron* **1986**, *42*, 4361.

Decarboxylation of **181** produces the allenylpalladium hydride complex **182**, which upon reductive elimination produces the allene **184**. The acetylene by-product **185** is presumably obtained from the (propargylic)palladium hydride complex **183**, which is considered to be in equilibrium with **182**. It is believed that bulky R^1 groups lead to the preferential formation of the acetylene by-product by shifting this equilibrium toward the less sterically congested propargylic palladium species **183**.

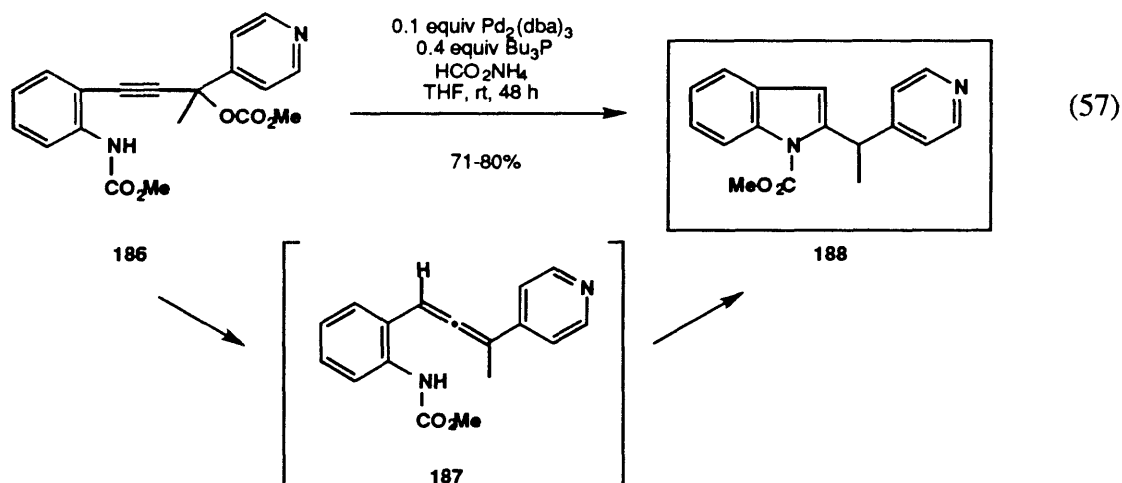
Scheme 34



Initially we elected to test the application of this strategy on the ellipticine synthesis intermediate **148**. Treatment of this alcohol with 1.5 equiv of methyl chloroformate and 2.0 equiv of DMAP provided the desired tertiary propargylic carbonate substrate **186** for the Tsuji reaction in 72-77% yield (eq 56).



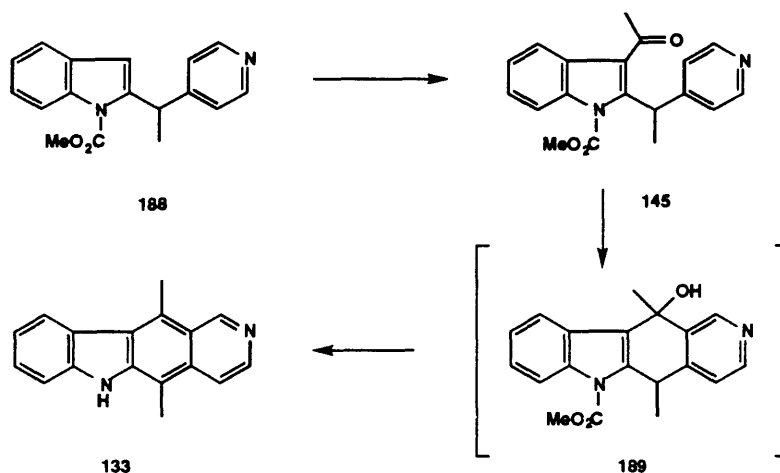
Treatment of the propargylic carbonate **186** with 2 equiv of ammonium formate in the presence of a catalytic amount of $\text{Pd}_2(\text{dba})_3 \cdot \text{PBu}_3$ (1:4) in THF at room temperature according to the procedure of Tsuji produced the desired indole **188** *in one pot* in 71-80% yield. As hoped, the intermediate allene **187** is generated and then cyclizes *in situ* to form the indole **188** without the need for an additional base-catalyzed cyclization step (eq 57).



The indole **188** was characterized by ^1H NMR, ^{13}C NMR, and IR spectroscopy. The ^1H NMR spectrum of this indole features a characteristic singlet at 6.67 ppm for the C-3 proton (the C-2 proton would appear at ca. 7.2 ppm). The ^{13}C NMR includes characteristic signals at 142.7 ppm (C-2 of the indole ring), and 108.9 (C-3 of the indole ring) which are consistent with the proposed structure.

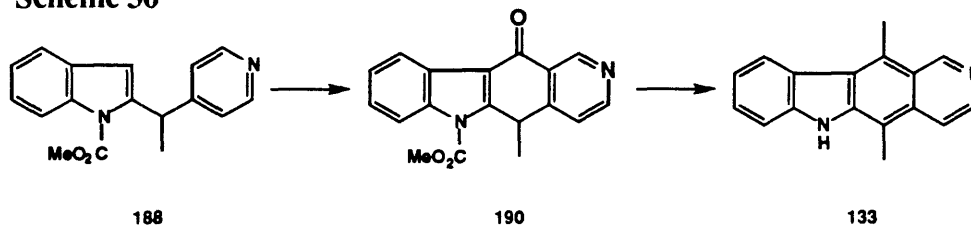
The synthesis of indole **188** was a major breakthrough. All that remains to complete the total synthesis is acylation of indole **188** at the 3-position to form the key 3-acetylindole derivative **145**, and its subsequent cyclization and dehydration to produce ellipticine (Scheme 35).

Scheme 35



Alternatively, treatment of **188** with phosgene would produce the indole **190**, a compound very similar to "ellipticine quinone", a common intermediate in many previous syntheses of ellipticine (Scheme 36)¹⁷³.

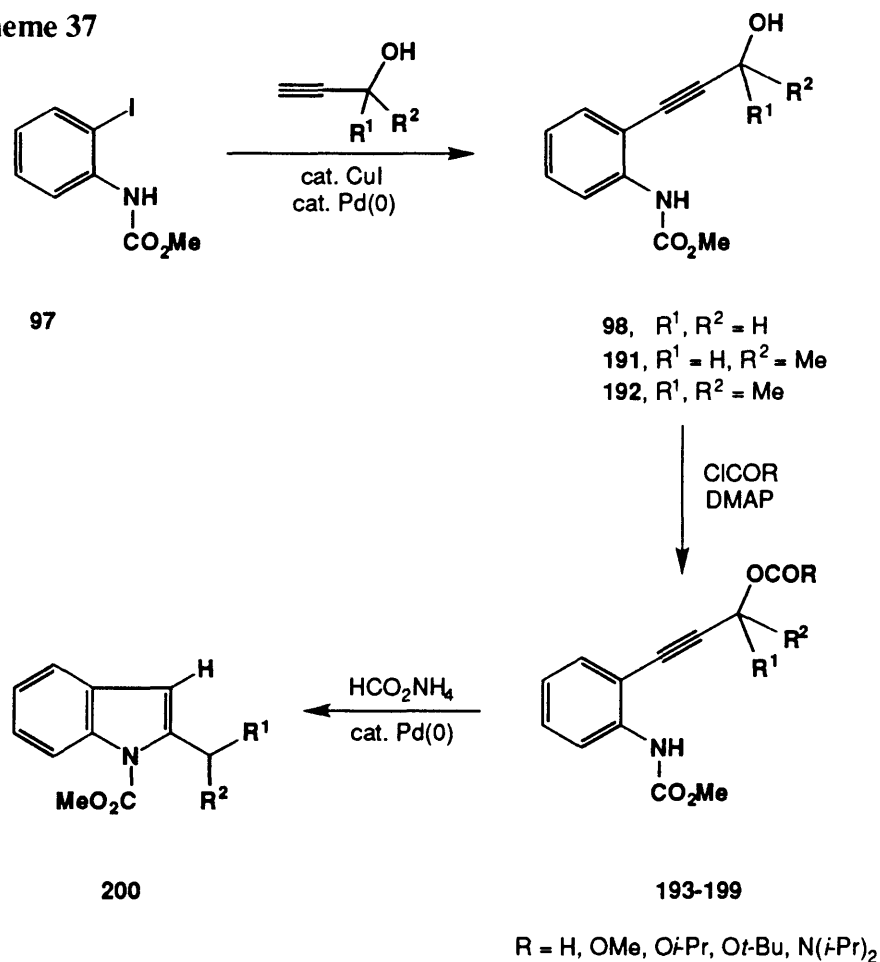
Scheme 36



173. For selected examples of ellipticine syntheses via this quinone, see (a) Taylor, D. A.; Baradarani, M. H.; Martinez, S. J.; Joule, J. A. *J. Chem. Res. (S)* **1979**, 387. (b) Watanabe, M.; Snieckus, V. *J. Am. Chem. Soc.* **1980**, *102*, 1457. (c) Ashcroft, W. R.; Beal, M. G.; Joule, J. A. *J. Chem. Soc., Chem. Commun.* **1981**, 994. (d) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 2810. (e) Ketcha, D. M.; Gribble, G. W. *J. Org. Chem.* **1985**, *50*, 5451.

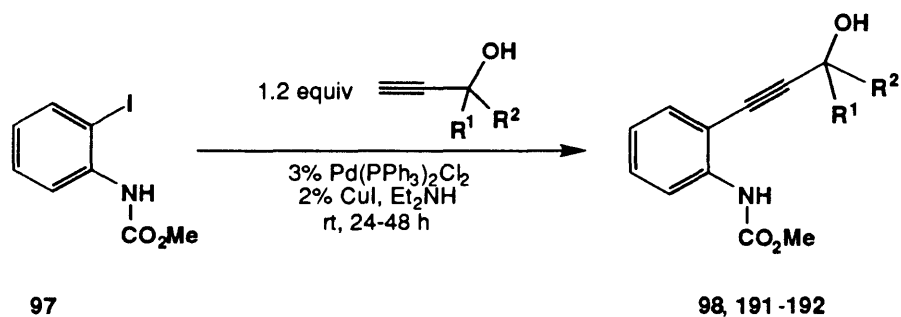
After obtaining these successful results in the context of our proposed ellipticine synthesis, we considered it worthwhile to further investigate the scope of this new strategy for the synthesis of substituted indoles (Scheme 37).

Scheme 37



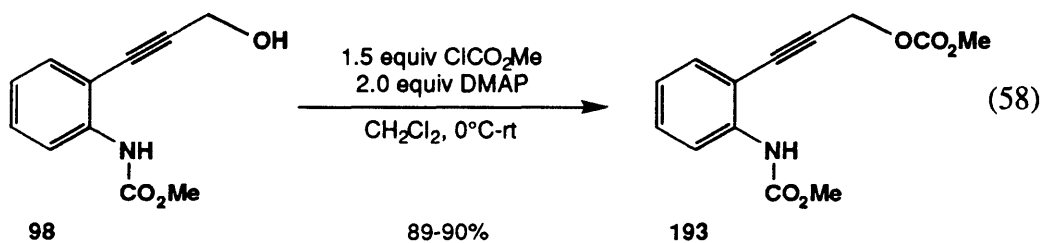
To investigate the generality of this strategy, we chose the known propargylic alcohols **98**, **191** and **192**,¹²⁶ (Table 6) and their derivatives (*vide infra*) as representative substrates. These alcohols were synthesized using the Castro-Stephens coupling of N-(methoxycarbonyl)-2-iodoaniline (**97**) with various propargylic alcohols under the standard Sonogashira conditions.¹²⁴

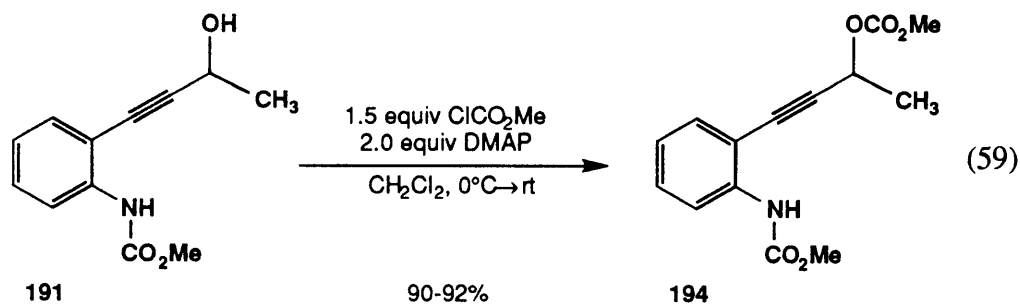
Table 6. Synthesis of the Model Propargylic Alcohols



entry	R ¹	R ²	compound	yield
1	H	H	98	95-100%
2	H	Me	191	92-100%
3	Me	Me	192	96%

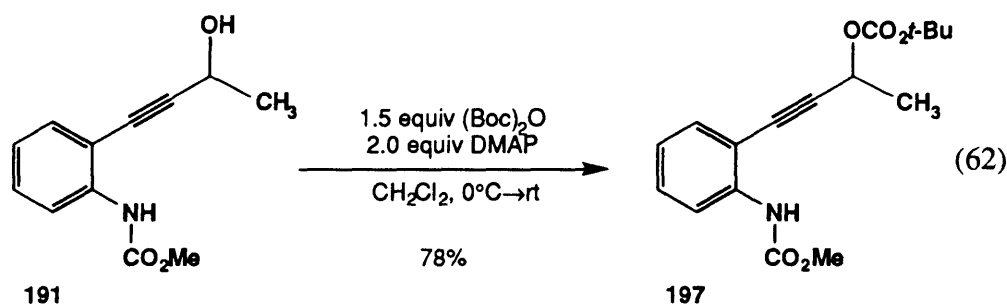
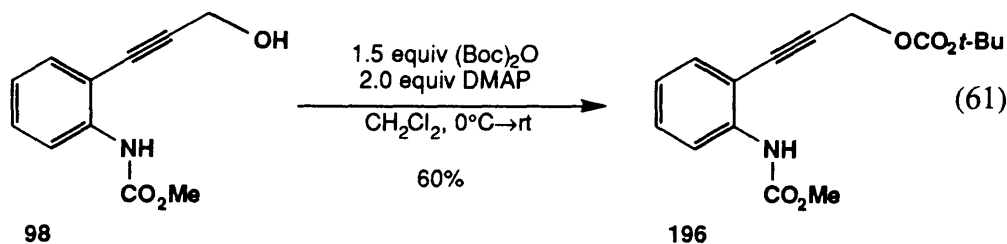
The propargylic carbonates **193** and **194** were synthesized in good yield (eq 58-59) via the treatment of the propargylic alcohols **98** and **191** with methyl chloroformate (1.5 equiv) in the presence of 2 equiv of DMAP (CH_2Cl_2 , 0 °C to room temperature). Treatment of the hindered propargylic alcohol **192** under similar conditions, however, failed to produce the desired propargylic carbonate **195** (eq 60). In this case, a mixture of starting material **186** and the *N,N*-diacylated aniline was produced.



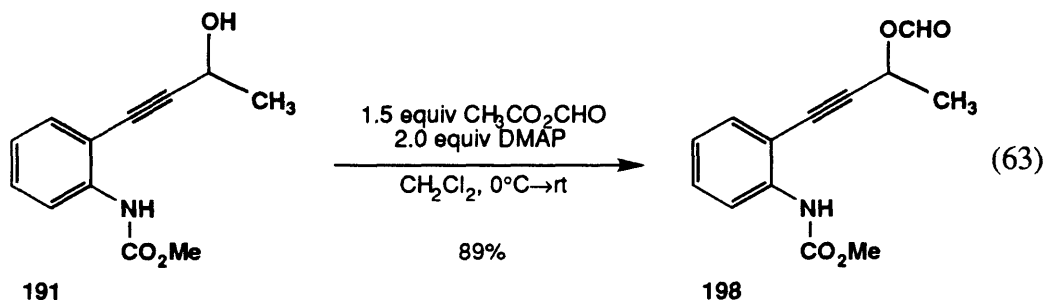


We also decided to prepare a number of other propargylic derivatives in order to investigate the effect of leaving groups on the Pd-catalyzed reaction with ammonium formate. This served another purpose as well. As outlined in Scheme 34 above, the mechanism of the reaction is believed to involve a decarboxylation step which leads to the formation of ammonia and methanol as by-products. We felt that by changing the methyl carbonate leaving group to *t*-butyl carbonate or a *carbamate*, we could produce a more basic by-product *in situ* (*t*-BuOH and/or an amine) which would hopefully help promote the cyclization of the allene products to indoles in the same synthetic operation.

The *t*-butyl carbonates **196** and **197** were prepared in good yield (eq 61-62) via treatment of the propargylic alcohols **98** and **191** with 1.5 equiv of (*t*-BuO₂C)₂O in the presence of 2.0 equiv of DMAP (CH₂Cl₂, 0 °C to room temperature).



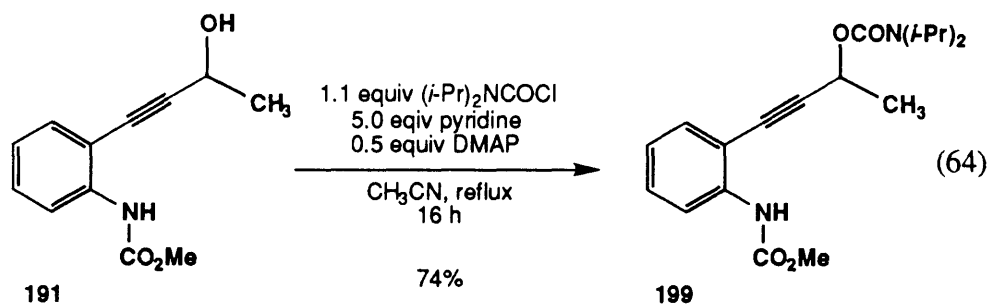
The formate **198** was synthesized according to the procedure of Muramatsu and co-workers.¹⁷⁴ Thus, treatment of the propargylic alcohol **191** with 1.5 equiv of acetic formic anhydride in the presence of 2.0 equiv of DMAP (0 °C to room temperature) produced the propargylic formate **198** in 89% yield (eq 63).



Finally, the carbamate **199** was synthesized via treatment of the propargylic alcohol **191** with 1.1 equiv of *N,N*-diisopropylcarbamoyl chloride¹⁷⁵ (eq 64) in the

174. (a) Muramatsu, I.; Murakami, M.; Yoneda, T.; Hagitani, A. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 244. (b) For the preparation of acetic formic anhydride, see Krinen, L. I. *Organic Syntheses* **1972**, *50*, 1.
175. Prepared from the reaction of diisopropylamine with 0.33 equiv of triphosgene in the presence of 2.0 equiv of triethylamine (THF, 0 °C to room temperature, 83%). For the preparation of carbamoyl chlorides and carbamates, see (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X. L. *J. Org. Chem.* **1992**, *57*, 2768, and references cited therein. (b) Ghosh, A. K.; Duong, T. T.; McKee, S. P. *Tetrahedron Lett.* **1991**, *32*, 4251. (c) Hoshino, O.;

presence of 5 equiv of pyridine and 0.5 equiv of DMAP in refluxing acetonitrile (16 h, 74%).

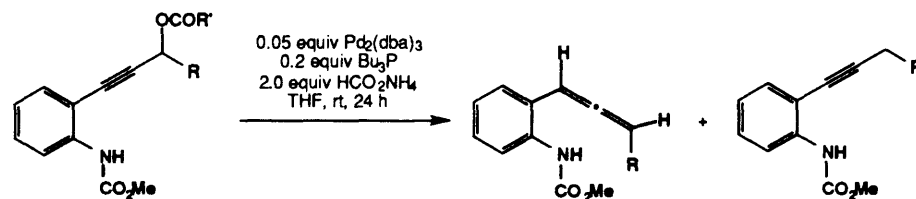


The propargylic derivatives discussed above were then treated with 2.0 equiv of ammonium formate according to Tsuji's procedure.^{157a,b} The results are summarized in Table 7 below. Unfortunately, none of the propargylic derivatives provided direct access to an indole derivative. Moreover, only the primary propargylic carbonate **193** produced the desired 2-(allenyl)arylamine product (**201**) exclusively. The secondary propargylic carbonate **194** afforded a 1:1 mixture of the desired allene **203** and the acetylene **204**. The separation of these two compounds proved to be very difficult by chromatography. Consequently, we were not able to isolate the allene **203** in pure form.

In contrast to the methyl carbonates, the *t*-butyl carbonates **196** and **197** produced the acetylenes **202** and **204** (respectively) as the major products. In these cases, the reactions were sluggish, and substantial quantities (ca. 40%) of the starting materials were recovered. The formate derivative **198** produced only the acetylene **204**. Later on, Tsuji and co-workers¹⁷⁶ reported the formation of disubstituted acetylenes from the Pd-catalyzed decarboxylation-hydrogenolysis of propargylic formates. The reaction with the propargylic carbamate **199** was also very sluggish, and resulted only in the formation of a trace amount of the acetylene **204**.

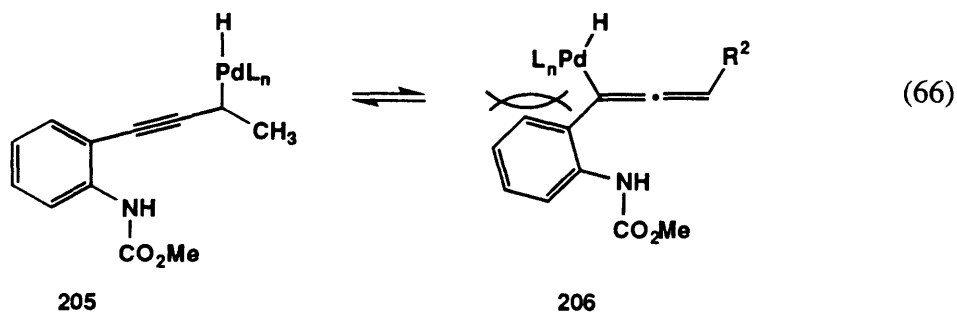
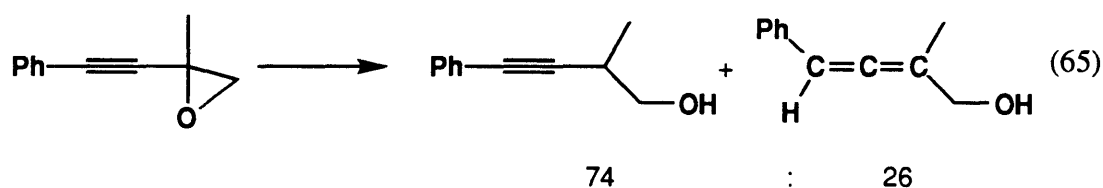
Saito, K.; Ishizaki, M.; Umezawa, B. *Synth. Commun.* **1987**, *17*, 1887. (d) Sicker, D. *Synthesis* **1989**, 875. (e) Eckert, H.; Forster, B. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 894. (e) Itoh, M.; Hagiwara, D.; Kamiya, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 718.
176. Mandai, T.; Matsumoto, T.; Kawada, M.; Tsuji, J. *Tetrahedron Lett.* **1993**, *34*, 2161.

Table 7. Model Studies for the Synthesis of Indoles via Pd(0)-Catalyzed Reaction of Propargylic Carbonates and Ammonium Formate



entry	starting material	R	R'	products	
1	193	H	OMe	 201 81%	
2	196	H	O <i>t</i> -Bu	 201 15%	 202 50%
3	194	Me	OMe	 203 31%	 204 33%
4	197	Me	O <i>t</i> -Bu	 203 Not observed	 204 34%
5	198	Me	H	 203 Not observed	 204 36%
6	199	Me	N(<i>i</i> -Pr) ₂	 203 Not observed	 204 Trace

At this point, we do not have a detailed understanding of the mechanism of this reaction and cannot account for the results presented in Table 7 above. As shown above in Scheme 34, the Pd(0)-catalyzed reaction of ammonium formate and propargylic carbonates is believed to proceed via an equilibrium between allenylpalladium and propargylic palladium species **182** and **183**. It appears, however, that the equilibrium ratios of the two palladium compounds are governed by several factors in addition to steric congestion at the allenyl position α to palladium as suggested by Tsuji.^{172a,b} Most of the cases examined by Tsuji involve terminal acetylenic substrates. Our substrates are different in that they contain *internal aryl acetylenes*. In addition, the reaction of our substrates might be complicated by the coordination of the carbamate group to Pd. Tsuji has reported only one example involving an aryl acetylene similar to those investigated by us. In this case, a mixture of allene (minor product) and acetylene (major product) is formed (eq 65). In the case of our substrates, the steric interaction between the aryl moiety and the Pd group in the allenylpalladium species **206** (eq 66) cannot explain the results in Table 7.



It is important to note that Vermeer and co-workers^{168d} have observed that even mixtures of propargylic and allenylpalladium species can give rise to allenes as the only products of certain coupling reactions. This observation suggests that the rate of ligand exchange (or reductive elimination) may be drastically different for propargylic and allenylpalladium species. Consequently, the ratio of allene to acetylene in the products may be determined by the relative reactivity for the allenylpalladium and propargylic palladium species, and not their original equilibrium ratios.

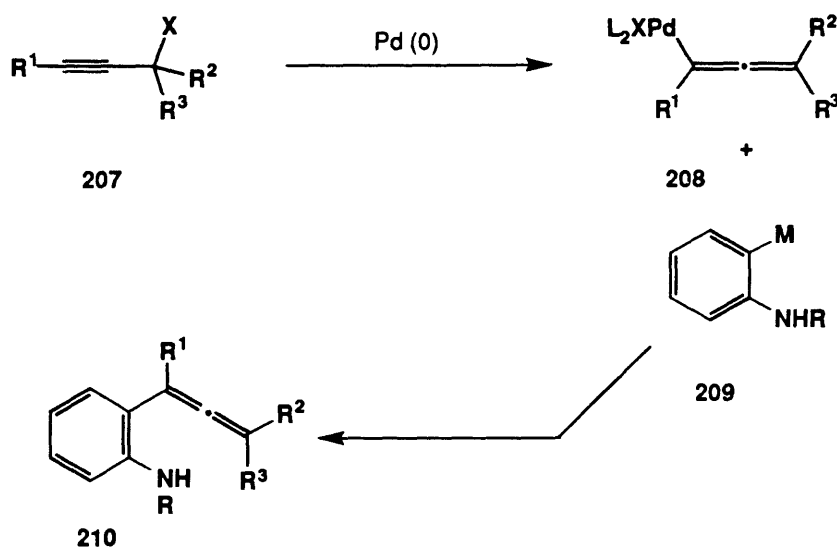
In order to gain a better understanding of this reaction, we have conducted a number of experiments. Some of our significant observations include:

1. In order to determine whether we could cyclize the mixture of allene and acetylene products to produce the desired indole, we treated a mixture of **203** and **204** (see Table 7) with *t*-BuOK in the presence of Pd₂(dba)₃ and Bu₃P. Under these conditions the allene **203** cyclized to the indole, but acetylene **204** was recovered unchanged.
2. To determine whether Pd(II) species were responsible for the cyclization in the ellipticine synthesis, **203** and **204** were treated with Pd(OAc)₂ in THF at room temperature for 3 h. No cyclization of acetylene **204** was observed, and only partial cyclization of allene **203** was observed to take place.
3. To determine whether the allenyl product was formed first, and then converted to the propargylic compound via palladium-catalyzed isomerization, we treated **203** and **204** with Pd₂(dba)₃. No interconversion between the two was observed.

It thus became apparent that the palladium-catalyzed reaction of propargylic derivatives with ammonium formate does not provide a general method for the preparation of 2-(allenyl)arylamines and indoles. We therefore decided to subsequently

focus our attention on the more attractive strategy outlined in Scheme 38 below. Reaction of a propargylic alcohol derivative with a catalytic amount of Pd(0) complex would give rise to the allenylpalladium compound **208**. Transmetalation with a suitable arylmetal compound **209** and reductive elimination would then provide the 2-(allenyl)arylamine **210**. We considered this approach to be superior to our earlier strategy in that it is more convergent and might also be applicable to the synthesis of a wide range of substituted systems.

Scheme 38



There are several possible choices for the metal M in the aniline derivative **209**. We chose to investigate cross coupling reactions involving organoboron compounds (M = B). There have been numerous reports in the literature concerning the Suzuki coupling reaction¹⁷⁷ of organoboron compounds and a variety of aryl, vinyl, and allyl derivatives (vide infra). Through the work of Snieckus,¹⁷⁸ arylboronic acids and their derivatives

177. For a detailed review, see the following chapter.

178. For reviews, see (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (b) Snieckus, V. *Pure Appl. Chem.* **1990**, *62*, 671. For some examples, see (c) Alo, B. I.; Kandil, A.; Patil, P. A.; Sharp, M. J.; Siddiqui, M. A.; Snieckus, V. *J. Org. Chem.* **1991**, *56*, 3763. (d) Sharp, M. J.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 5997. (e) Sharp, M. J.; Cheng, W.; Snieckus, V. *Tetrahedron Lett.* **1987**, *28*, 5093. (f) Cheng, W.; Snieckus, V. *Tetrahedron Lett.* **1987**, *28*, 5097. (g) Fu, J.-M.; Sharp, M. J.; Snieckus, V. *Tetrahedron Lett.* **1988**, *29*, 5459. (h) Siddiqui, M.

have emerged as very useful synthetic building blocks for a variety of coupling reactions. Part III of this dissertation describes our systematic studies on this new strategy for the synthesis of allenes based on the palladium-catalyzed cross coupling of organoboron compounds and propargylic carbonates.

A.; Snieckus, V. *Tetrahedron Lett.* **1988**, *29*, 5463. (i) Fu, J.-M.; Snieckus, V. *Tetrahedron Lett.* **1990**, *31*, 1665. (j) Unrau, C. M.; Campbell, M. G.; Snieckus, V. *Tetrahedron Lett.* **1992**, *33*, 2773. (k) Brandão, M. A. F.; de Oliveira A. B.; Snieckus, V. *Tetrahedron Lett.* **1993**, *34*, 2437.

Part III:

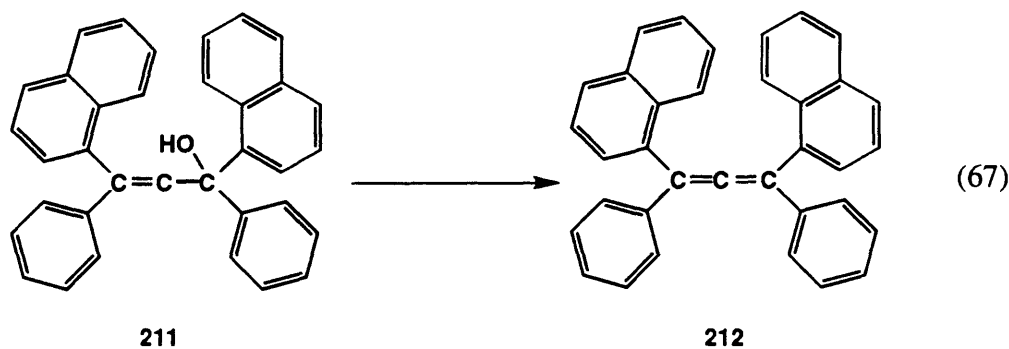
A New Synthesis of Allenes Based on the Palladium-Catalyzed Coupling of Organoboron Compounds and Propargylic Carbonates

Chapter 1

Recent Developments in the Synthesis of Allenes

Introduction

The study of allenes has been a rapidly growing field in the recent past, in part due to their utility as versatile intermediates in synthetic strategies. The first allene was prepared by Burton and Pechmann in 1887.¹⁷⁹ This accomplishment gave rise to a significant theoretical interest in the properties of the unusual unsaturated system of allenes. van't Hoff first predicted the existence of two enantiomeric forms for an unsymmetrically substituted allene,¹⁸⁰ but his prediction was not confirmed until 1935 when Maitland and Mills¹⁸¹ obtained the first optically active allene **212** by dehydrating racemic **211** with (+)-camphor-10-sulfonic acid (eq 67).



Relatively few allenes have been isolated from natural sources.¹⁸² The presence of naturally occurring allenes was not observed until 1952, when mycomycin (**213**) was isolated by Celmer and Solomons.¹⁸³ Since then, many other optically active allenes have been discovered in nature, principally among fungal metabolites, pigments of brown

179. Burton, B. S.; Pechmann, H. V. *Chem. Ber.* **1887**, *20*, 145.

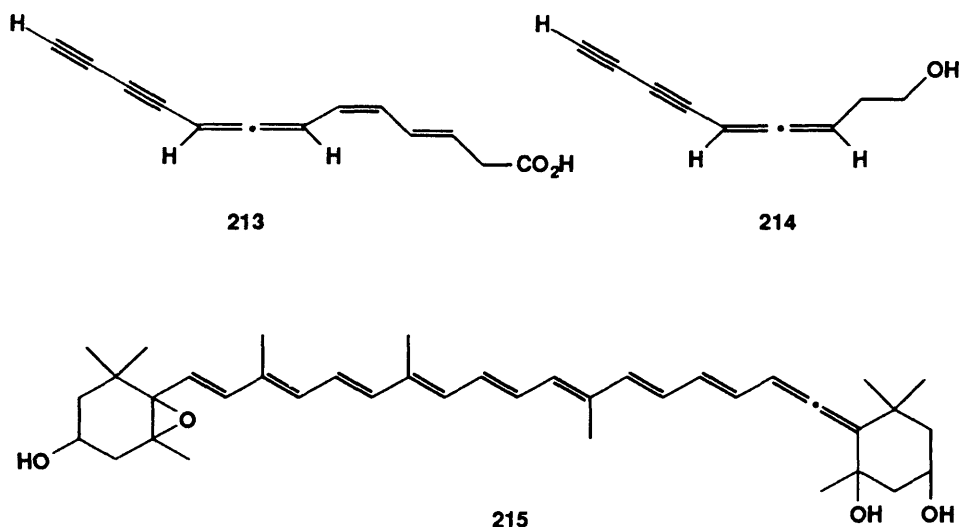
180. van't Hoff, J. H., *La Chimie dans l'Espace*, P. M. Bazendijk: Rotterdam, 1875, p 29.

181. (a) Maitland, P.; Mills, W. H. *Nature* **1935**, *135*, 994. (b) Maitland, P.; Mills, W. H. *J. Chem. Soc.* **1936**, 987.

182. For a review of naturally occurring allenes, see Landor, S. R. In *The Chemistry of Allenes*; Landor, S. R., Ed.; Academic Press: New York, 1982, Vol 3, pp 679-708.

183. (a) Celmer, W. C.; Solomons, I. A. *J. Am. Chem. Soc.* **1952**, *74*, 1870, 2245, 3838. (b) Celmer, W. C.; Solomons, I. A. *J. Am. Chem. Soc.* **1953**, *75*, 1372, 3430.

algae and sea urchins, diatoms, and leaves.¹⁸⁴ Marasin (**214**)¹⁸⁵ and neoxanthin (**215**)¹⁸⁶ are two other examples of naturally occurring allenes.

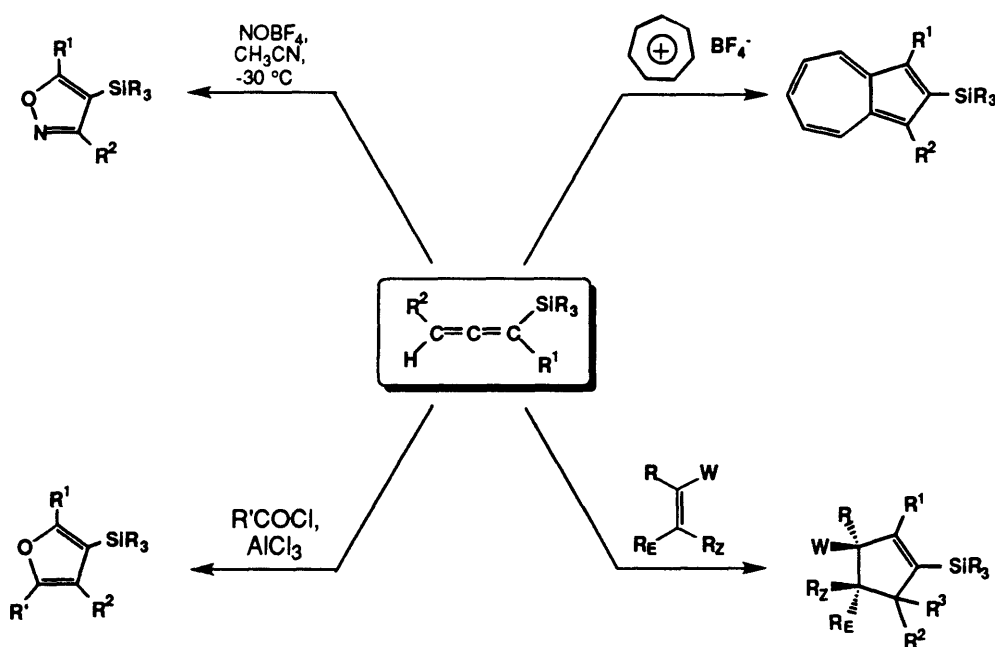


The biological activity of allenes, and consequently their use as pharmaceuticals, has been limited.¹⁸⁷ The interest in allenes has therefore been mainly theoretical and due to their application in synthesis. The perpendicular adjacent π -systems of allenes allows for their participation in many reactions that could not be carried out using olefins. Several useful synthetic methods have been developed based on the unusual reactions of allenes with a variety of electrophiles¹⁸⁸ and nucleophiles.¹⁸⁹ Allenes also readily participate in a number of pericyclic processes, such as cycloadditions and sigmatropic rearrangements.¹⁹⁰

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184. References 5-15 in R. Rossi, Diversi, P. *Synthesis* **1973**, 25.
 185. (a) Cambie, R. C.; Hirschberg, A.; Jones, E. R. H.; Lowe, G. *J. Chem. Soc.* **1963**, 4210. (b) Benz, G. *Arkiv för Kemi* **1959**, *14*, 305, 574.
 186. Cholnoky, J. *J. Chem. Soc. (C)* **1969**, 1256.
 187. For a review of biologically active allenes, see Claesson, A. In *The Chemistry of Allenes*; Landor, S. R., Ed.; Academic Press: New York, 1982, Vol 3, pp 711-732.
 188. For a review, see Blake, P. In *The Chemistry of Ketenes, Allenes and Related Compounds*; Patai, S., Ed.; Wiley: New York, 1980, Part 1, pp 348-352.
 189. For selected examples, see (a) Brühn, J.; Zsindely, J.; Schmid, H.; Frater, G. *Helv. Chim. Acta* **1978**, *61*, 2542. (b) Hoff, S.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 609. (c) Gange, D.; Magnus, P. *J. Am. Chem. Soc.* **1978**, *100*, 7746. (d) Gaertner, R. *J. Am. Chem. Soc.* **1951**, *73*, 4400.
 190. For reviews on the reactions of allenes, see (a) Schuster, H. F.; Coppola, G. M. In *Allenenes in Organic Synthesis*; Wiley-Interscience: New York, 1984. (b) Landor, S. R.; Hopf, H.; Jacobs, T. L. In *The Chemistry of Allenes*; Landor, S. R., Ed.; Academic Press: New York, 1982, Vol 2. (c) Rutledge, T. F. *Acetylenes and Allenes*; Reinhold: New York, 1969. (d) Zimmer, R. *Synthesis* **1993**, 165.

Our research group has been interested in the chemistry of allenes and their application in the synthesis of carbocycles and heterocycles for some time. For example, a general [3+2] annulation method has been developed in which allenylsilanes react with nitrosonium ions, tropylium ions, acylium ions, and α,β -unsaturated carbonyl compounds to form a variety of five-membered ring systems such as isoxazoles,¹⁹¹ azulenes,¹⁹² furans,¹⁹³ and cyclopentenones,¹⁹⁴ respectively (Scheme 39).

Scheme 39



The studies described in Part III of this thesis were aimed at the development of a new convergent synthetic route to allenes based on the palladium-catalyzed coupling of organoboron compounds and propargylic alcohol derivatives. In order to appreciate the potential utility of this new strategy, the existing synthetic approaches to allenes will be

191. Danheiser, R. L.; Becker, D. A. *Heterocycles* **1987**, *25*, 227.
 192. Danheiser, R. L.; Becker, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 389.
 193. Danheiser, R. L.; Stoner, E. J.; Koyama, H.; Yamashita, D. S.; Klade, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 4407.
 194. (a) Danheiser, R. L.; Carini, D. J.; Basak, A. *J. Am. Chem. Soc.* **1981**, *103*, 1604. (b) Danheiser, R. L.; Carini, D. J.; Fink, D. M.; Basak, A. *Tetrahedron* **1983**, *39*, 935. (c) Danheiser, R. L.; Fink, D. M. *Tetrahedron Lett.* **1985**, *26*, 2513. (d) Danheiser, R. L.; Fink, D. M.; Tsai, Y. - M. *Org. Synth.* **1988**, *66*, 8.

discussed briefly in this chapter. It is beyond the scope of this dissertation to review all of the synthetic routes to allenes, and only a summary of the most important existing methods will be presented.¹⁹⁵ Special emphasis will be placed on those strategies which most closely resemble the one employed in our approach.

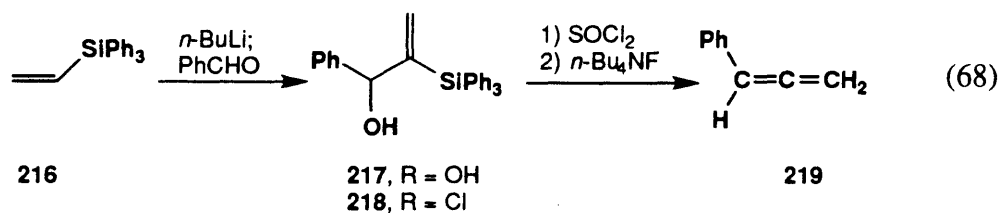
Synthesis of Allenes: An Overview

The synthetic approaches to allenes can be divided into several categories depending on the type of chemistry employed in the key step.

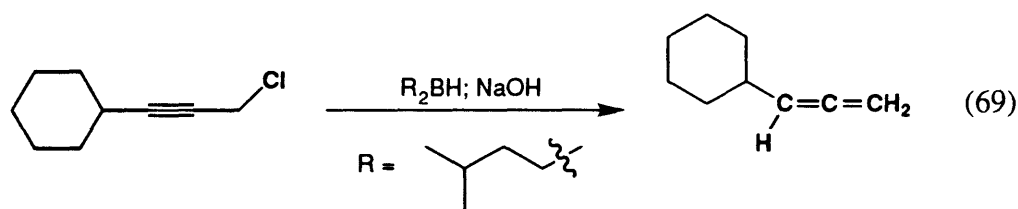
A. 1,2-Eliminations

The traditional methods for forming double bonds such as dehydrohalogenation and dehalogenation frequently involve harsh reaction conditions, and when applied to the synthesis of allenes, lead to the formation of acetylenic by-products.^{195a} Recent developments have involved the use of milder and more selective methods to effect eliminations. For example, Chan and co-workers^{196a} have utilized a version of the Peterson olefination¹⁹⁷ that involves the fluoride induced elimination of α -chloromethyl vinylsilanes **218** to generate terminal allenes (eq 68). The requisite allylic chloride substrates are prepared in two steps via the addition of α -silylvinyllithium reagents to aldehydes and ketones and reaction of the resulting allylic alcohols with thionyl chloride.

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195. For reviews on the synthetic approaches to allenes, see (a) Landor, P. D. In *The Chemistry of Allenes*; Landor, S. R., Ed.; Academic Press: New York, 1982, Vol 1. (b) Pasto, D. J. *Tetrahedron* **1984**, *40*, 2805. (c) *The Chemistry of Ketenes, Allenes, and Related Compounds, Parts 1-2*; Patai, S., Ed.; Wiley: New York, 1980. (d) Brandsma, L.; Verkrujse, H. D. *Synthesis of Acetylenes, Allenes, and Cumulenes*; Elsevier: New York, 1980. (e) Sandler, S. R.; Karo, W. *Organic Functional Group Preparations, 2nd ed.*; Academic Press: New York, 1986, Chapter 1. (f) Rossi, R.; Diversi, P. *Synthesis* **1973**, 25.
196. (a) Chan, T. H.; Mychajlowski, W. *Tetrahedron Lett.* **1974**, 171. For a related method involving Peterson olefination for the synthesis of allenes, see (b) Hudrlik, P. F.; Kassim, A. M.; Agwarambo, E. L. O.; Doonquah, K. A.; Roberts, R. R.; Hudrlik, A. M. *Organometallics* **1993**, *12*, 2367. For an allene synthesis via 1,2-elimination reactions of stannyl allylic alcohols, see (c) Konoike, T.; Araki, Y. *Tetrahedron Lett.* **1992**, *33*, 5093.
197. For a review, see Ager, D. J. *Org. React.* **1990**, *38*, 1.



A related method is based on the 1,2-elimination of α -chloromethylvinylboranes, which are prepared via the reaction of propargylic chlorides and disiamylborane (eq 69).¹⁹⁸

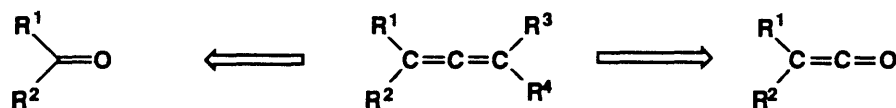


Another elimination approach involves the conversion of ketones to their corresponding vinyl triflates, followed by base-induced elimination to the allene.¹⁹⁹

B. Wittig Olefination and Related Methods

There are two possible ways to disconnect an allene when applying the Wittig olefination strategy,²⁰⁰ resulting in ketenes or ketones (or aldehydes) as starting materials (Scheme 40).

Scheme 40



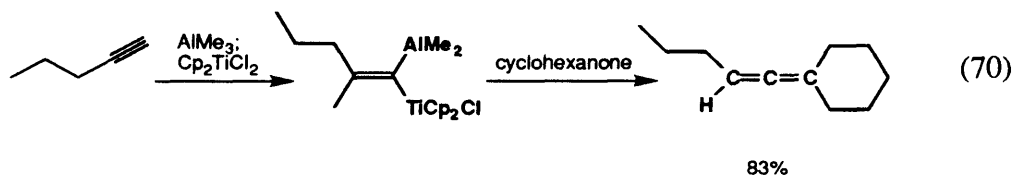
198. Zweifel, G.; Hornig, A.; Snow, J. T. *J. Am. Chem. Soc.* **1970**, *92*, 1427.

199. Stang, P. J.; Hargrove, R. J. *J. Org. Chem.* **1975**, *40*, 657.

200. For a review of this reaction, see Maercker, A. *Org. React.* **1965**, *14*, 270.

The limited availability and high reactivity of most ketenes renders their use as allene precursors somewhat difficult.²⁰¹ Nevertheless, a useful method for the synthesis of allenes has been developed via the trapping of ketenes generated *in situ* from the decomposition of acyl chlorides.²⁰² In addition, symmetrical allenes have been prepared from the reaction of 2 equiv of an alkylidetriphenylphosphorane with CO₂. One possible pathway for this transformation proceeds via ketene intermediates.²⁰³

The Tebbe reagent has also been applied for the synthesis of olefins from carbonyl compounds.²⁰⁴ Negishi has developed a highly convergent method for the synthesis of allenes (eq 70)²⁰⁵ which utilizes "Tebbe-style" reagents prepared by the successive treatment of a terminal acetylene with a mixture of Me₃Al and Cp₂TiCl₂.²⁰⁶ A related method developed by Grubbs and Buchwald utilizes a titanium-mediated olefin metathesis reaction.^{207,208}



C. Prototypic Rearrangement of Acetylenes, and Related Methods

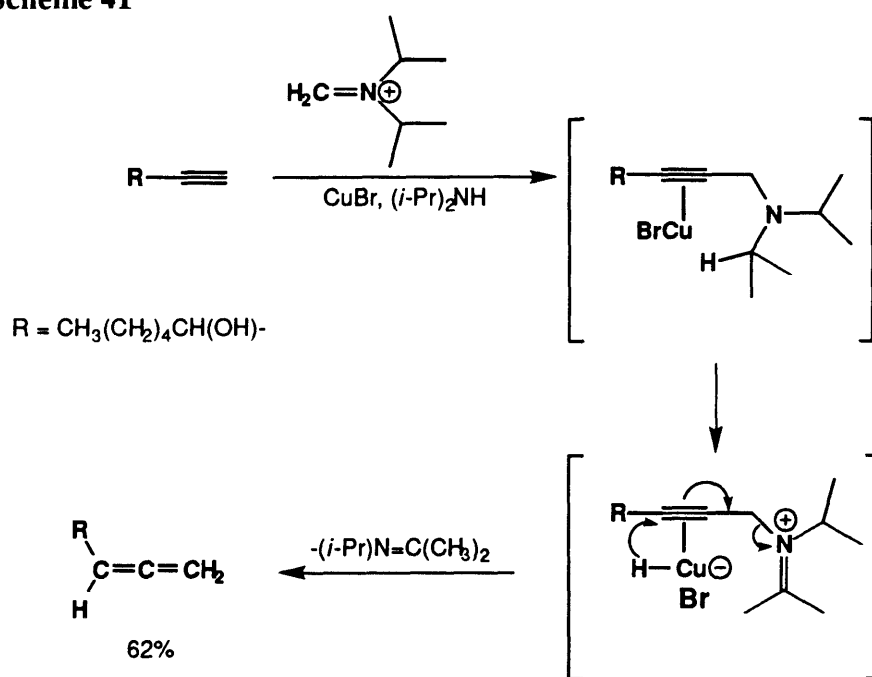
The isomerization of acetylenes often leads to the formation of several products that are in equilibrium. The nature of the substituents on the acetylene determines the

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201. (a) Wittig, G.; Haag, A. *Chem. Ber.* **1963**, *96*, 1535. (b) Baron-Marszak, M.; Silalty, M.; Seuleman, A. *Tetrahedron Lett.* **1974**, *22*, 1905.
202. (a) Lang, R. W.; Hansen, H.-J. *Helv. Chim. Acta* **1979**, *62*, 1025. (b) Lang, R.W.; Hansen, H.-J. *Org. Synth.* **1990**, *Coll. Vol. VII*, 232.
203. Besrman, H. J.; Denzel, T.; Salbaum, H. *Tetrahedron Lett.* **1974**, 1275.
204. (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611. (b) Tebbe, F. N.; Parshall, G. W.; Ovenall, D. W. *J. Am. Chem. Soc.* **1979**, *101*, 5074.
205. Yoshida, T.; Negishi, E. *J. Am. Chem. Soc.* **1981**, *103*, 1276.
206. van Horn, D. E.; Valente, L. F.; Idacavage, M. J.; Negishi, E. *J. Organomet. Chem.* **1978**, *156*, C20.
207. Buchwald, S. L.; Grubbs, R. *J. Am. Chem. Soc.* **1983**, *105*, 5490.
208. For other related methods, see (a) Reynolds, K. A.; Dopico, P. G.; Sundermann, M. J.; Hughes, K. A.; Finn, M. G. *J. Org. Chem.* **1993**, *58*, 1298. (b) Tucker, C. E.; Greve, B.; Klein, W.; Knochel, P. *Organometallics* **1994**, *13*, 94-101.

equilibrium ratio. A favorable ratio of allene to acetylene is obtained when a conjugated system such as an allenyl ketone is produced.^{209,210}

The Crabbé reaction²¹¹ provides a reliable approach for the synthesis of allenes from acetylenes. Treatment of a terminal acetylene with a Mannich reagent (generated *in situ* from diisopropylamine and formaldehyde) in the presence of catalytic CuBr produces a homologated allene in good to excellent yield. The mechanism of this reaction is believed to proceed via a propargylic imminium ion intermediate as shown in Scheme 41.^{211b}

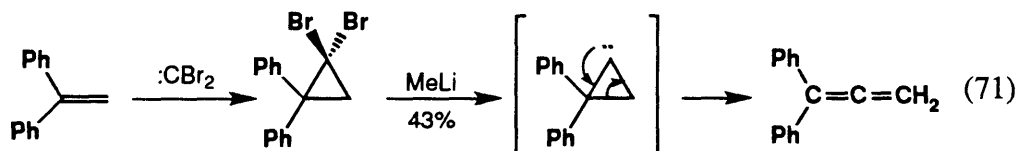
Scheme 41



209. (a) Leroux, Y.; Montaine, R. *J. Organomet. Chem.* **1971**, *30*, 295. (b) Russell, C. E.; Hegedus, L. S. *J. Am. Chem. Soc.* **1983**, *105*, 943.
210. Huntsman, W. D. In *The Chemistry of Ketenes, Allenes, and Related Compounds*; Patai, S., Ed.; Wiley: New York, 1980, Vol2, Chapter 15, pp 523-657.
211. (a) Crabbé, P.; Fillion, H.; André, D.; Luche, J.-L. *J. Chem. Soc., Chem. Commun.* **1979**, 859. (b) Crabbé, P.; Nassim, B.; Robert-Lopes, M.-T. *Org. Synth.* **1985**, *63*, 203. (c) Searles, S.; Yushun, L.; Nassim, B.; Robert-Lopes, M.-T.; Tran, P. T.; Crabbé, P. *J. Chem. Soc., Perkin Trans. I* **1984**, 747.

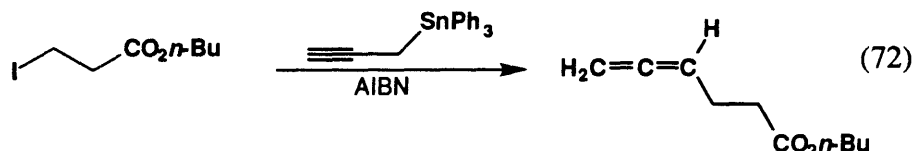
D. Rearrangement of Carbenes

The Doering-Moore-Skatteböl rearrangement²¹² of cyclopropyl carbenoids (eq 71) is one of the most widely used methods for the preparation of substituted allenes, especially strained cyclic derivatives.²¹³



E. Radical Additions

A radical allenyl-transfer reaction involving propargylic stannanes has been reported by Baldwin and co-workers.^{214,215} In this reaction, triphenylprop-2-ynylstannane is treated with an alkyl halide in the presence of AIBN (80 °C) to afford monosubstituted allenes (eq 72).

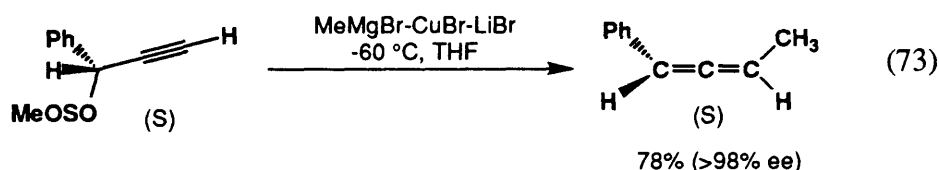


A novel method for the synthesis of allenes reported by Ando relies on the Norrish Type I cleavage of exomethylene cyclopropyl ketones upon photolysis. The requisite ketones are prepared via the rearrangement of allenyl epoxides, which are in turn produced from the epoxidation of cumulenes.²¹⁶

212. (a) Doering, W. vE.; LaFlamme, P. M. *Tetrahedron* **1958**, *2*, 75. (b) Moore, W. R.; Ward, H. R. *J. Org. Chem.* **1960**, *25*, 2073. (c) Skatteböl, L. *Tetrahedron Lett.* **1961**, 167.
213. For examples, see (a) Johnson, R. P. *Chem. Rev.* **1989**, *89*, 111. (b) Dehnlow, E. V.; Stiehm, T. *Tetrahedron Lett.* **1990**, *31*, 1841. (c) Untch, K. G.; Martin, D. J.; Castelluchi, N. T. *J. Org. Chem.* **1965**, *30*, 3572.
214. Baldwin, J. E.; Adlington, R. M.; Basak, A. *J. Chem. Soc., Chem. Commun.* **1981**, 1284.
215. For earlier work involving allyl transfer reactions based on an analogous allylstannane reagent, see Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron*, **1985**, *41*, 4079.
216. Ando, w.; Hayakawa, H.; Tokitoh, N. *Tetrahedron Lett.* **1986**, *27*, 6357.

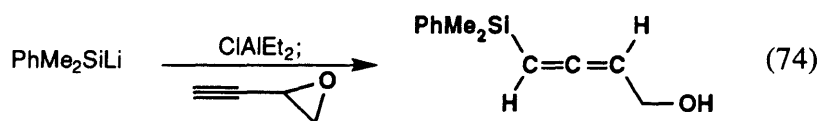
F. Reactions of Propargylic Derivatives with Nucleophiles²¹⁷

This approach is by far the most widely used method for the synthesis of allenes. For example, a number of substituted allenes have been produced from the reaction of a variety of organocopper reagents (generated *in situ* from the corresponding Grignard or lithium compounds) with propargylic halides,²¹⁸ sulfonates,²¹⁹ sulfonates,²²⁰ acetates,²²¹ alcohols,²²² ethers,^{218b,223} carbamates,²²⁴ and epoxides.^{225,226} In some cases, acetylenes have been observed as the by-products of these reactions.²²⁷ These reactions are generally believed to proceed via *anti* addition of the cuprates to the propargylic derivatives, thus allowing for the conversion of enantiomerically pure propargylic derivatives to allenes with high enantiomeric purity (eq 73).²²⁸

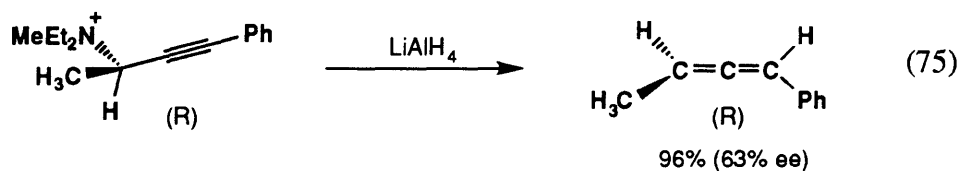


217. Brandsma, L.; Verkruisje, H. D. *Synthesis of Acetylenes, Allenes and Cumulenes*; Elsevier: New York, 1981, pp.151-196.
218. Kalli, M.; Landor, P. D.; Landor, S. R. *J. Chem. Soc. Perkin Trans. I* 1973, 1347.
219. (a) Boudouy, R.; Goré, J. *J. Chem. Res. (M)* 1981, 278. (b) Vermeer, P.; Meijer, J.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* 1975, 94, 112. For the synthesis of allenylsilanes, see (c) Vermeer, P.; Westmijze, H. *Synthesis* 1979, 390.
220. Vermeer, P.; Westmijze, H.; Kleijn, H.; van Dijck, L. A. *Recl. Trav. Chim. Pays-Bas* 1978, 97, 56.
221. (a) Luche, J. L.; Barreiro, E.; Dollat, J. M.; Crabbé, P. *Tetrahedron Lett.* 1975, 4615. For a discussion of the mechanism of this reaction, see (b) Sahlberg, C.; Claesson, A. *J. Org. Chem.* 1984, 49, 4120.
222. Tanigawa, Y.; Murahashi, S. *J. Org. Chem.* 1980, 45, 4538.
223. Alexakis, A.; Marek, I.; Normant, J. F. *J. Am. Chem. Soc.* 1990, 112, 8042.
224. (a) Pirkle, W.H.; Boeder, C. W. *J. Org. Chem.* 1978, 43, 1950. (b) Pirkle, W.H.; Boeder, C. W. *J. Org. Chem.* 1978, 43, 2091.
225. (a) Ortiz de Montellano, P. R. *J. Chem. Soc., Chem. Commun.* 1973, 709. (b) Vermeer, P.; Meijer, J.; de Graaf, C.; Schreurs, H. *Recl. Trav. Chim. Pays-Bas* 1974, 93, 46. (c) Oehlschlager, A. C.; Czyzewska, E. *Tetrahedron Lett.* 1983, 5587. (d) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *Tetrahedron Lett.* 1989, 30, 2387. (e) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *Tetrahedron Lett.* 1989, 30, 2391. (f) Marshall, J. A.; Pinney, K. G. *J. Org. Chem.* 1993, 58, 7180. For a review on the diastereoselective syn or anti opening of propargylic epoxides, see (g) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *Tetrahedron* 1991, 47, 1677.
226. For a review of the effects of various organocopper reagents and propargylic substrates in nucleophilic addition reactions, see (a) Macdonald, T. L.; Reagan, D. R.; Brinkmeyer, R. S. *J. Org. Chem.* 1980, 45, 4740. (b) Ruitenbergh, K.; Kleijn, H.; Westmijze, H.; Meijer, J.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* 1982, 101, 405.
227. For a discussion of the regioselectivity in the addition of alkylcopper-magnesium bromide reagents to propargylic derivatives, see Alexakis, A.; Normant, J. F. *J. Molecular Catalysis* 1975, 1, 43.
228. (a) Elsevier, C. J.; Vermeer, P. *J. Org. Chem.* 1989, 54, 3726. (b) Tadema, G.; Everhardus, R. H.; Westmijze, H.; Vermeer, P. *Tetrahedron Lett.* 1978, 3935.

Trost has reported the synthesis of allenylsilanes via the reaction of silylalanines to propargylic epoxides (eq 74).²²⁹



Several other examples of nucleophilic additions to propargylic derivatives have been reported. The reaction of LiCu_2Br_3 with propargylic mesylates is reported to produce 1-bromoallenes.²³⁰ The copper enolate derivative of ethyl acetate was treated with propargylic sulfonates to afford allenes in moderate yields.²³¹ Hydride reducing agents such as LiAlH_4 and LiEt_3BH have also been shown to produce allenes upon reaction with propargylic derivatives (eq 75).²³²

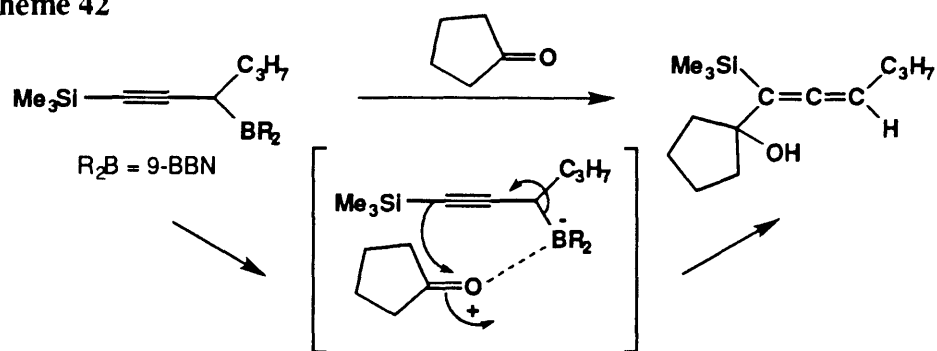


G. Reaction of Propargylic Derivatives with Electrophiles

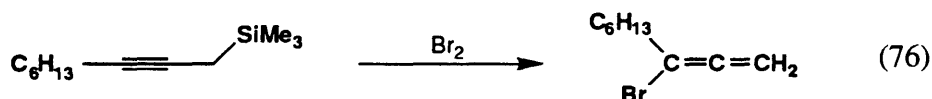
The reaction of propargylic boranes with aldehydes and ketones has been extensively studied by Wang and co-workers.²³³ The mechanism of this reaction is outlined in Scheme 42 below. A six-membered transition state leads to the formation of a borate ester, which is hydrolyzed during the workup to produce an allenyl alcohol.

229. Trost, B. M.; Tour, J. M. *J. Org. Chem.* **1989**, *54*, 484.
 230. (a) Caporusso, A. M.; Consoloni, C.; Lardicci, L. *Gazz. Chim. Ital.* **1988**, *118*, 857. (b) Caporusso, A. M.; Polizzi, C.; Lardicci, L. *J. Org. Chem.* **1987**, *52*, 3920.
 231. Amos, R. A.; Katzenellenbogen, J. A. *J. Org. Chem.* **1978**, *43*, 555.
 232. (a) Claesson, A.; Olsson, L.-I. *J. Am. Chem. Soc.* **1979**, *101*, 7302. (b) Claesson, A.; Olsson, L.-I.; Bogentoft, C. *Acta Chem. Scand.* **1973**, *27*, 2941. (c) Colas, Y.; Cazes, B.; Gore, G. *Tetrahedron Lett.* **1984**, *25*, 845.
 233. (a) Wang, K. K.; Chin, L. *J. Org. Chem.* **1985**, *50*, 2578. (b) Wang, K. K.; Nikan, S. S.; Ho, C. D. *J. Org. Chem.* **1983**, *48*, 5376. (c) Wang, K. K.; Andemichael, Y. W.; Dhumrongvaraporn, S. *Tetrahedron Lett.* **1989**, *30*, 1311.

Scheme 42

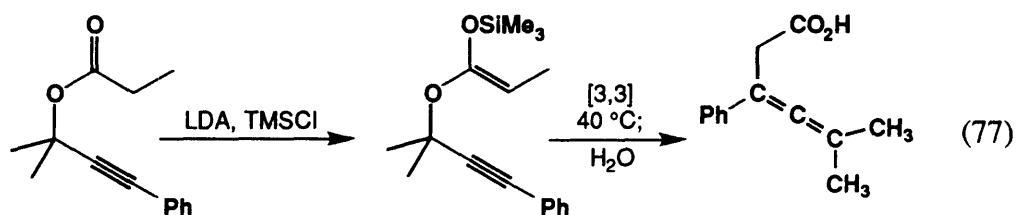


The reaction of propargylsilanes with electrophiles to produce allenes is limited to the preparation of terminal allenes, as propargylsilanes are difficult to prepare (eq 76).²³⁴



H. Pericyclic Processes

The Claisen rearrangement of propargyl vinyl ethers was first investigated by Landor and co-workers.²³⁵ Using this methodology, homoallenyl ketones were produced in high yield. Later, Baldwin and co-workers²³⁶ utilized the rearrangement of TMS enol ethers of propargylic esters to prepare allenyl acetic acids (eq 77).²³⁷



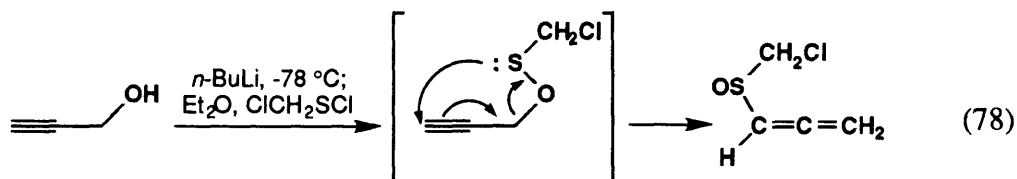
234. Flood, T.; Peterson, P. E. *J. Org. Chem.* **1980**, *45*, 5006.

235. Black, D. K.; Fomum, Z. T.; Landor, P. D.; Landor, S. R. *J. Chem. Soc. Perkin Trans. I* **1973**, 1349.

236. Baldwin, J. E.; Bennett, P. A.; Forrest, A. K. *J. Chem. Soc., Chem. Commun.* **1987**, 250.

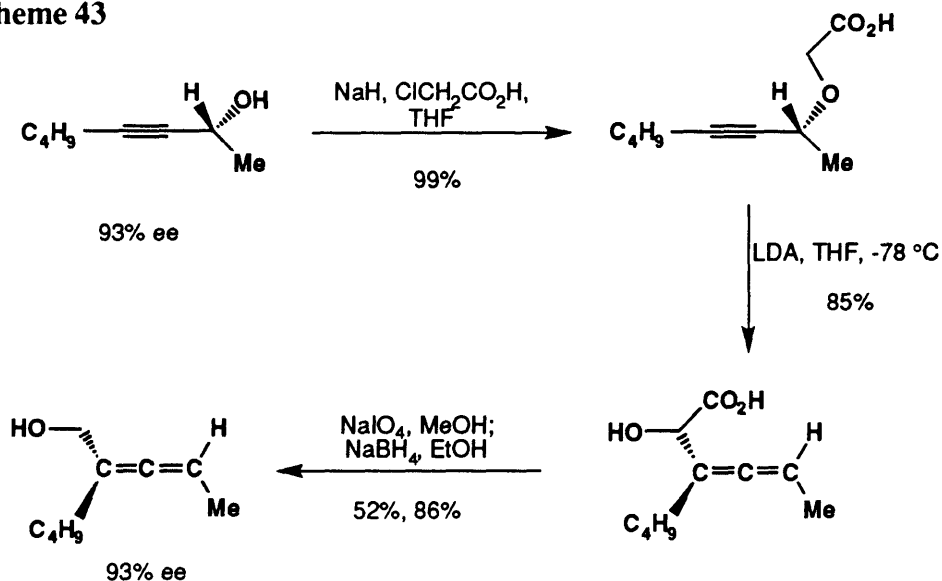
237. For a related method using the rearrangement of propargylic acetates, see Oelberg, D. G.; Shiawelli, M. D. *J. Org. Chem.* **1977**, *42*, 1805.

The [2,3]-sigmatropic rearrangement has been exploited by several groups for the synthesis of allenes. For example, Block and co-workers used the rearrangement of S-chloromethyl propargyl sulfenates to produce allenyl chloromethyl sulfoxides (eq 78).²³⁸



Marshall's novel dihydrofuran synthesis utilizes allenyl alcohols that are prepared via a Wittig [2,3] sigmatropic rearrangement,²³⁹ which proceeds with a high degree of stereoselectivity (Scheme 43).²⁴⁰

Scheme 43



Allenes have also been successfully synthesized via the reduction of propargylic tosylhydrazones. This method is similar to the reductive deoxygenation strategy

238. Block, E.; Putman, D. *J. Am. Chem. Soc.* **1990**, *112*, 4072.

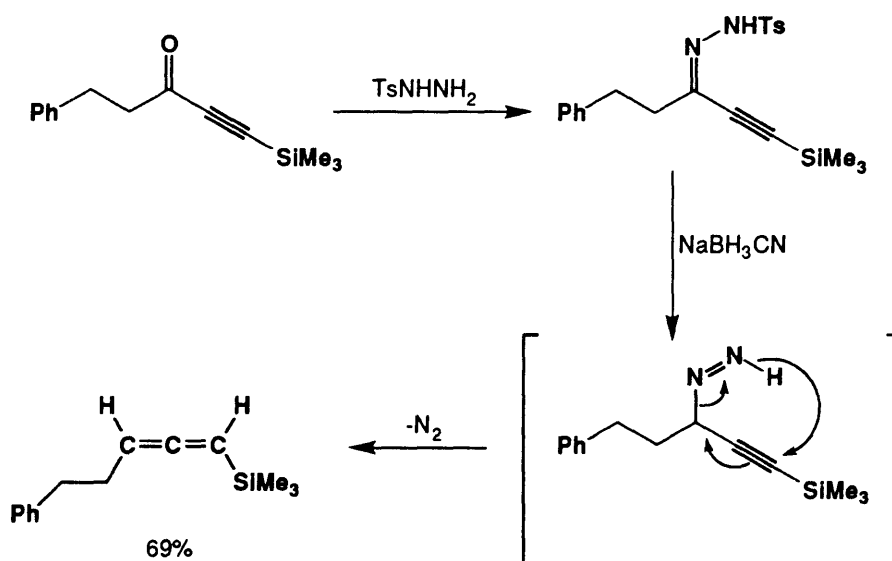
239. Marshall, J. A.; Wang, X.-J. *J. Org. Chem.* **1990**, *55*, 2995.

240. (a) Marshall, J. A.; Robinson, E. D.; Zapata, A. *J. Org. Chem.* **1989**, *54*, 5854. (b) Marshall, J. A.; Wang, X.-J. *J. Org. Chem.* **1991**, *56*, 4913. (c) Marshall, J. A.; Wang, X.-J. *J. Org. Chem.* **1992**, *57*, 2747.

developed by Hutchins.²⁴¹ The formation of a diazene derivative is followed by a retro-ene reaction with loss of N₂.²⁴²

Our research group has applied this strategy to the synthesis of allenylsilanes (Scheme 44).²⁴³ The requisite propargylic tosylhydrazones are prepared from the corresponding TMS-substituted propargylic ketones and aldehydes. Reduction of the hydrazones to the diazenes, followed by the retro ene reaction, produces the allenes.

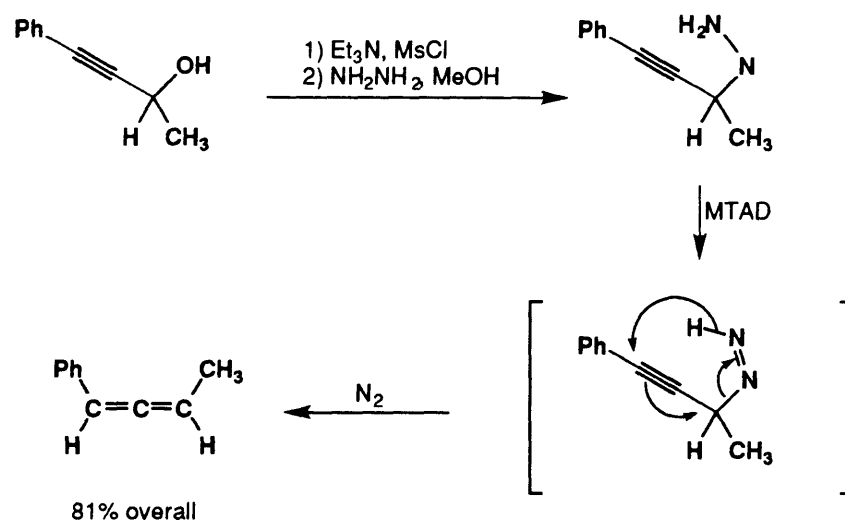
Scheme 44



Myers and co-workers have reported a similar strategy for the generation of allenes under very mild conditions (Scheme 45).²⁴⁴ In this case, the diazene derivatives are synthesized in two steps via the reaction of propargylic mesylates with hydrazine, and subsequent oxidation with DEAD or 4-methyl-1,2,4-triazoline-3,5-dione (MTAD).

241. (a) Hutchins, R. O.; Kacher, M.; Rua, L. *J. Org. Chem.* **1975**, *40*, 923. (b) Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662.
 242. Kabalka, G. W.; Newton, R. J.; Chandler, J. H. *J. Chem. Soc., Chem. Commun.* **1978**, 726.
 243. Danheiser, R. L.; Carini, D. J. *J. Org. Chem.* **1980**, *45*, 3295.
 244. Myers, A. G.; Finney, N. S.; Kuo, E. Y. *Tetrahedron Lett.* **1989**, *30*, 5747.

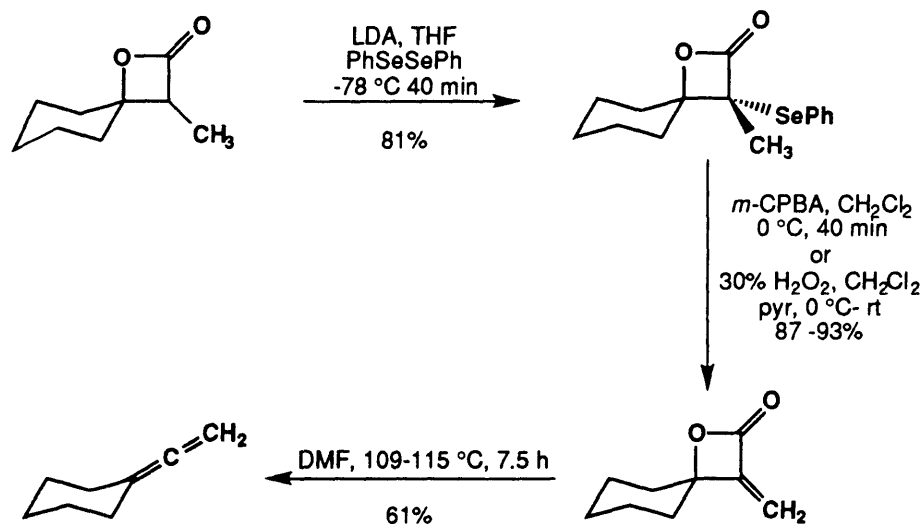
Scheme 45



Cycloreversions have not been frequently used for the synthesis of allenes.²⁴⁵

Our research group has recently developed a triply convergent synthesis of allenes based on the decarboxylation of α -alkylidene- β -lactones (Scheme 46).^{246,247}

Scheme 46



245. For some examples involving ketene dimers, see (a) Baba, A.; Kitano, S.; Ohshiro, Y.; Agawa, T. *Synthesis* **1975**, 537. (b) Moore, H. W.; Duncan, W. G. *J. Org. Chem.* **1973**, *38*, 156. (c) Gompper, R.; Wolf, U. *Liebigs Ann. Chem.* **1979**, 1388. For examples involving alkylidene-cyclobutenes, see (d) Knoth, H.; Coffman, D. D. *J. Am. Chem. Soc.* **1960**, *82*, 3873. (e) Stevenson, H. B.; Sharkey, W. H. *Org. Synth. Coll. Vol. V* **1973**, 734.

246. Danheiser, R. L.; Choi, Y. M.; Menichincheri, M.; Stoner, E. J. *J. Org. Chem.* **1993**, *58*, 322.

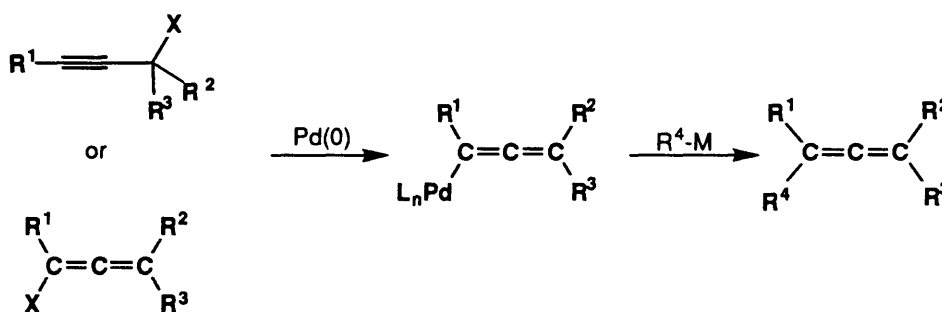
247. For the synthesis of β -lactones, see Danheiser, R. L.; Nowick, J. S. *J. Org. Chem.* **1991**, *56*, 1176.

I. Allenyl Metal Derivatives

Although propargyl and allenyl Grignard and lithium reagents are very useful for making some allene derivatives, they sometimes afford mixtures of allenes and acetylenes when treated with various electrophiles. The ratios of allenes to acetylenes in these reactions often depend upon the nature of the organometallic compound and the temperature of the reaction.

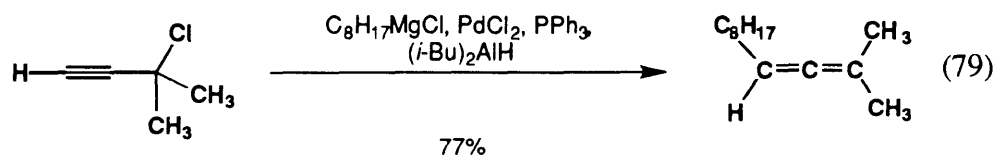
Allenylpalladium compounds, on the other hand, have been shown to be excellent precursors for the formation of various allenyl derivatives (*vide infra*). The past few years have witnessed an explosion of interest in the field of allenylpalladium chemistry, and numerous methods have been developed based on the Pd-catalyzed cross coupling reactions of various organometallic compounds and propargylic derivatives. The general strategy is outlined in Scheme 47 below.

Scheme 47

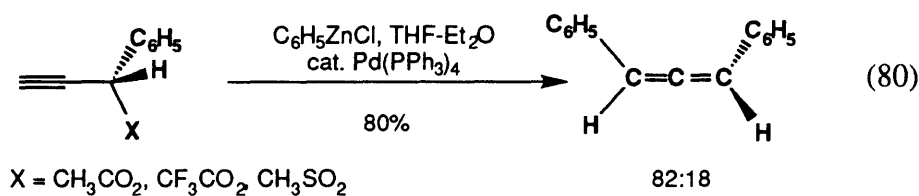


Linstrumelle reported the first example of the palladium-catalyzed synthesis of allenes via this strategy in 1980 (eq 79).²⁴⁸ Grignard reagents were found to react with propargylic or allenic halides in the presence of catalytic amounts of palladium chloride, triphenylphosphine, and diisobutylaluminum hydride (THF, room temperature).

248. Jeffery-Luong, T.; Linstrumelle, G. *Tetrahedron Lett.* **1980**, 5019.



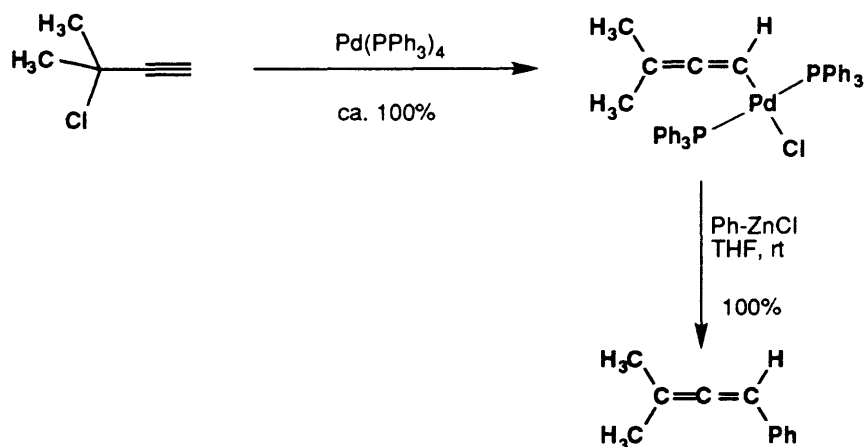
Vermeer and co-workers reported the Pd-catalyzed cross coupling of organozinc compounds with propargylic halides and acetates²⁴⁹ and allenic halides.^{246a,250} These reactions proceed in a stereoselective manner, producing the *anti* substitution products (eq 80).^{246c} The mechanism of this transformation is believed to involve (a) formation of an allenylpalladium species with inversion of configuration via an $\text{S}_{\text{N}}2'$ substitution, (b) transmetallation with retention, and (c) reductive elimination with retention of configuration.



The intermediacy of allenylpalladium species in these reactions was established by Vermeer and co-workers when they treated a propargylic chloride with 1.0 equiv of $\text{Pd}(\text{PPh}_3)_4$ in THF to obtain a σ -allenylpalladium (II) compound as a yellow solid. Treatment of the isolated allenylpalladium species with phenyl- and (trimethylsilyl)-ethynylzinc chloride in THF produced the corresponding allenes in quantitative yield (Scheme 48).²⁵¹

249. (a) Ruitenbergh, K.; Kleijn, H.; Elsevier, C. J.; Meijer, J.; Vermeer, P. *Tetrahedron Lett.* **1981**, 1451. (b) Kleijn, H.; Meijer, J.; Overbeek, G. C.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 97. For a discussion of the stereochemical course of this reaction, see (c) Elsevier, C. J.; Stehouwer, P. M.; Westmijze, H.; Vermeer, P. *J. Org. Chem.* **1983**, *48*, 1103. For a comparison of cross coupling reactions with propargylic vs. allylic acetates, see (d) Keinan, E.; Bosch, E. *J. Org. Chem.* **1986**, *51*, 4006.
250. For a discussion of the stereochemical course of this reaction, see Elsevier, C. J.; Vermeer, P. *J. Org. Chem.* **1985**, *50*, 3042.
251. (a) Elsevier, C. J.; Kleijn, H.; Ruitenbergh, K.; Vermeer, P. *J. Chem. Soc., Chem. Commun.* **1983**, 1529. (b) Elsevier, C. J.; Kleijn, H.; Boersma, J.; Vermeer, P. *Organometallics* **1986**, *5*, 716. For related studies on the interconversion of propargylic and allenic platinum species, see Blosser, P. W.; Schimpff, D. G.; Gallucci, J. C.; Wojcicki, A. *Organometallics*, **1993**, *12*, 1993.

Scheme 48



In addition to Pd, other transition metals such as Ni²⁵² and Fe²⁵³ have also been used to promote the cross coupling reactions of Grignard reagents with propargylic derivatives.

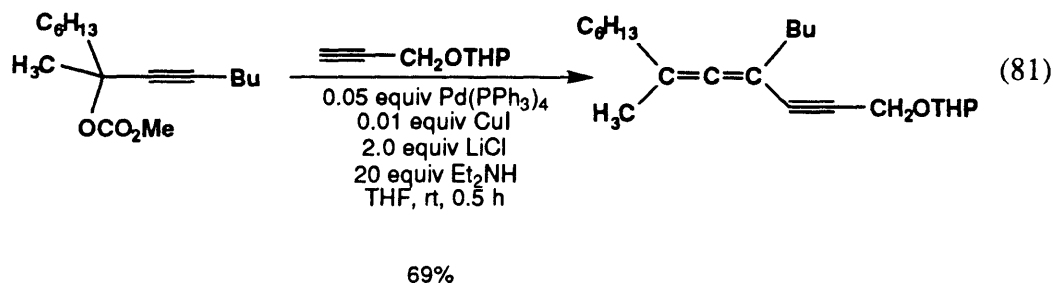
While investigating palladium-catalyzed reactions of allylic derivatives, Tsuji, Mandai, and their co-workers discovered that carbonates constitute more reactive leaving groups than acetates.^{172c} These workers have also extensively studied the palladium-catalyzed cross coupling reactions of *propargylic carbonates*.^{172c} The palladium-catalyzed reaction of these compounds with ammonium formate^{172a,b} was discussed in detail in the previous chapter of this dissertation. Another useful application of this chemistry is the synthesis of 1,2-dien-4-yne (allene-yne) via the palladium-catalyzed reaction of propargylic carbonates with terminal acetylenes.²⁵⁴ In the presence of catalytic amounts of $\text{Pd}(\text{PPh}_3)_4$ and CuI, along with 2 equiv of LiCl and excess diethylamine, terminal acetylenes react with propargylic carbonates (THF, room temperature, 30 min) to produce 1,2-dien-4-yne in good yield (eq 81). The mechanism

252. Wenkert, E.; Leftin, M. H.; Michelotti, E. L. *J. Org. Chem.* **1985**, *50*, 1122.

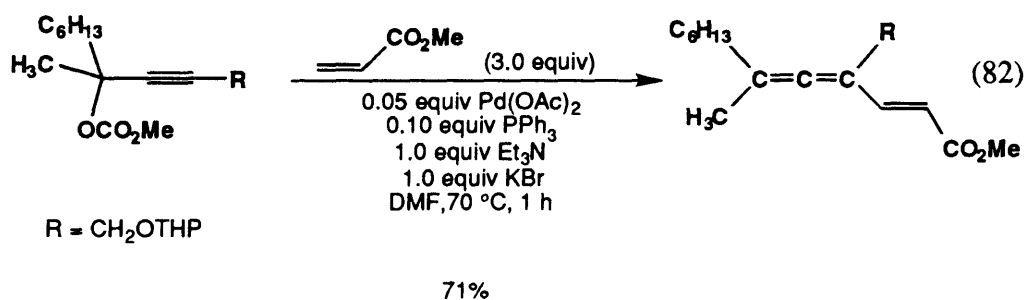
253. Pasto, D. J.; Chau, S.-K.; Waterhouse, A.; Shults, R. H.; Hennion, G. F. *J. Org. Chem.* **1978**, *43*, 1385.

254. (a) Mandai, T.; Nakata, T.; Murayama, H.; Yamaoki, H.; Ogawa, M.; Kawada, M.; Tsuji, J. *Tetrahedron Lett.* **1990**, *31*, 7179. (b) Mandai, T.; Murayama, H.; Nakata, T.; Yamaoki, H.; Ogawa, M.; Kawada, M.; Tsuji, J. *J. Organomet. Chem.* **1991**, *417*, 305.

of this reaction is believed to involve transmetalation of an allenylpalladium species with a copper acetylide (R^4-M in Scheme 47).



A similar strategy was also used for the synthesis of vinylallenes (eq 82).²⁵⁵ α,β -unsaturated carbonyl compounds (3 equiv) were thus coupled with propargylic carbonates in the presence of 1-2 equiv of Et_3N , 1-2 equiv of KBr , water, and catalytic amounts of $Pd(OAc)_2$ and PPh_3 (DMF, 70 °C, 1 h) to produce vinylallenes in good yield. In this reaction, the allenylpalladium intermediate undergoes a Heck reaction with the electron deficient olefin to produce the vinylallene product.

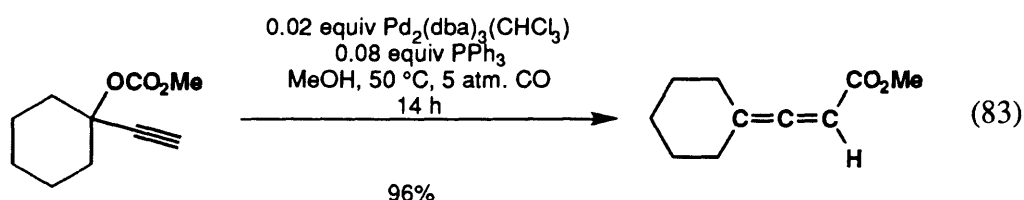


The palladium-catalyzed carbonylation of propargylic carbonates is a useful method for the preparation of allenyl esters (eq 83).²⁵⁶ In the presence of 0.02 equiv of $Pd_2(dba)_3 \cdot CHCl_3$, 0.08 equiv of PPh_3 , and an alcoholic solvent, propargylic carbonates are converted to allenyl esters (10-35 atm CO pressure, room temperature, 5-44 h). In

255. Mandai, T.; Ogawa, M.; Yamaoki, H.; Nakata, T.; Murayama, H.; Kawada, M.; Tsuji, J. *Tetrahedron Lett.* **1991**, 32, 3397.

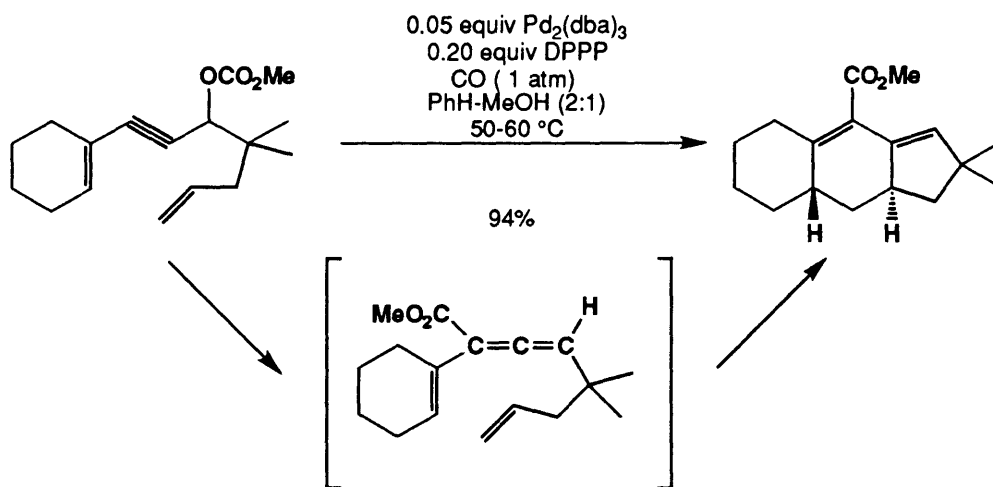
256. Tsuji, J.; Sugiura, T.; Minami, I. *Tetrahedron Lett.* **1986**, 27, 731.

some cases, acetylenic by-products are also formed in the reaction. The mechanism of this reaction is believed to involve carbonylation of the allenylpalladium intermediate via (a) ligand exchange with carbon monoxide, (b) migratory insertion, and (c) reductive elimination of the acylpalladium species.



The same strategy was applied in a tandem carbonylation-intramolecular Diels-Alder approach to the synthesis of polycyclic compounds.²⁵⁷ An example of the application of this strategy is shown in Scheme 49 below.

Scheme 49

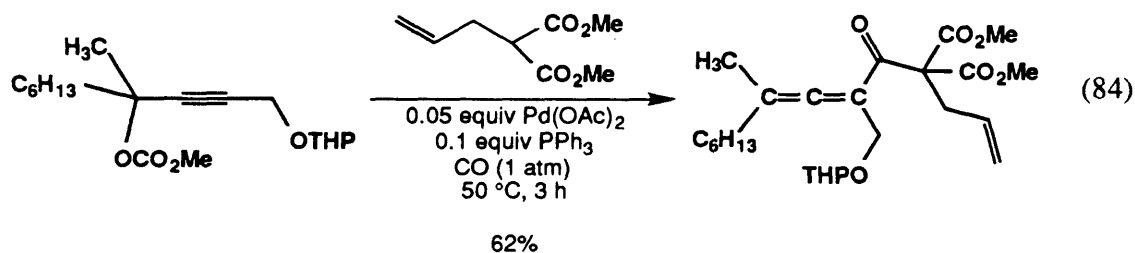


Allenyl ketones have also been prepared using a similar carbonylative strategy.²⁵⁸ Palladium-catalyzed coupling of propargylic carbonates and active methylene and

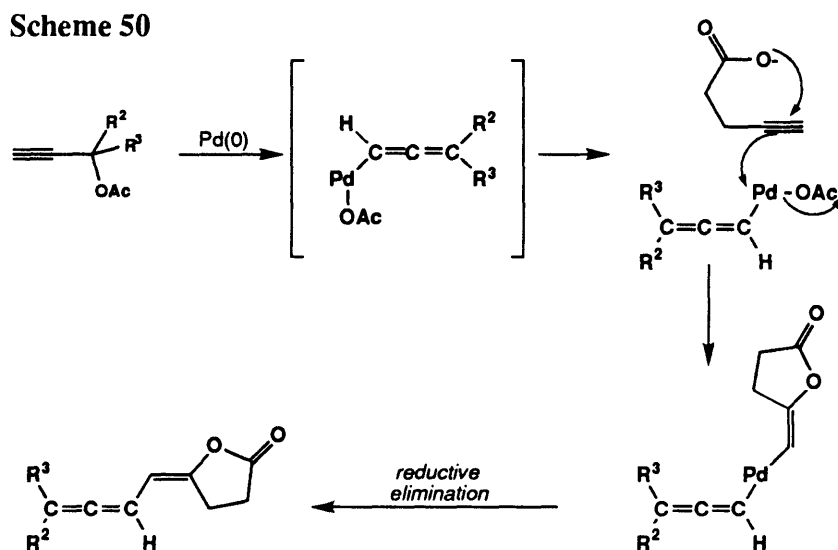
257. Mandai, T.; Suzuki, S.; Ikawa, A.; Murakami, T.; Kawada, M.; Tsuji, J. *Tetrahedron Lett.* **1991**, 32, 7687.

258. Mandai, T.; Kunitomi, H.; Higashi, K.; Kawada, M.; Tsuji, J. *Synlett* **1991**, 697.

methine compounds under an atmosphere of CO and in the presence of sodium hydride, (THF, 50 °C, 3 h) produced allenyl ketones in moderate yields (eq 84).



Finally, an interesting application of allenylpalladium chemistry has been reported recently by Bouyssi and co-workers.²⁵⁹ Various γ -allenylidene γ -lactones [(5(E)-(2-allenylidene)-tetrahydro-2-furanones)] were synthesized in moderate yield (50-62%) via the Pd-catalyzed coupling of 4-pentynoic acid and propargylic acetates in the presence of K_2CO_3 , and catalytic amounts of $Pd(OAc)_2$ and tri(2-furyl) phosphine (DMSO, 20 °C, 7-22 h). Scheme 50 below outlines the mechanism for this reaction.



259. Bouyssi, D.; Core, J.; Balme, G.; Louis, D.; Wallach, J. *Tetrahedron Lett.* 1993, 34, 3129.

The previous section described a variety of methods for the synthesis of allenes based on palladium-catalyzed cross coupling reactions of propargylic derivatives. The following chapter will describe our efforts towards the synthesis of allenes based on the palladium-catalyzed coupling reactions of propargylic carbonates and organoboron compounds.

Chapter 2

Results and Discussion

As described in Part II of this dissertation, we next decided to focus our attention on the convergent strategy outlined in Scheme 38 for the synthesis of 2-(allenyl)arylamines and indoles. In particular, we chose to investigate cross coupling reactions involving organoboron reagents ($M = B$, Scheme 38). As a result of these efforts, we have developed a new method for the synthesis of substituted allenes via palladium-catalyzed coupling reactions of propargylic carbonates and organoboron compounds. Before discussing our results, the following section briefly reviews important features of the Suzuki cross-coupling methodology.

The Suzuki Coupling Reaction: Background

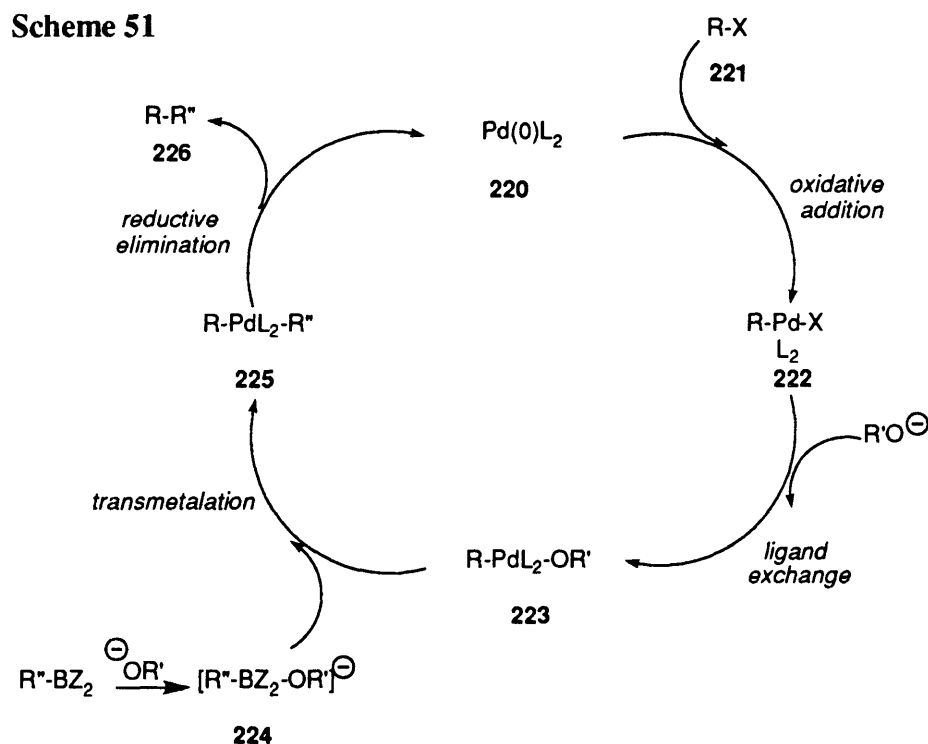
The Suzuki coupling reaction²⁶⁰ has become one of the most useful procedures for carbon-carbon bond formation in organic synthesis. Suzuki first observed that activation of organoboranes as "ate" complexes by common bases such as hydroxide and alkoxide promotes the coupling of these compounds with alkyl, vinyl and aryl halide and triflate derivatives in the presence of Ni or Pd catalysts. The generality of this reaction has since been demonstrated in numerous applications to the synthesis of a wide range of organic compounds.

There are several attractive features that distinguish the Suzuki reaction from similar coupling protocols employing various other organometallic compounds. For example, the necessary use of tin in stoichiometric amounts in the Stille coupling of organostannanes makes it less attractive than the Suzuki methodology for application in the fine chemical and pharmaceutical industry. Moreover, organoboron compounds are

260. For reviews, see (a) Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419. (b) Suzuki, A. *Pure Appl. Chem.* **1985**, *57*, 1749. (c) Suzuki, A. *Acc. Chem. Res.* **1982**, *15*, 178.

frequently more accessible and less sensitive to air and moisture than their magnesium, zinc, and zirconium counterparts. Finally, although the Suzuki coupling procedure was originally carried out in the presence of strong bases, it can now be carried out under modified and rather mild conditions compatible with many functional groups.²⁶¹

Until recently, very little was known about the mechanistic details of the Suzuki reaction. Scheme 51 outlines the mechanism proposed by Suzuki and co-workers.²⁶²



Organoboron compounds do not participate in direct transmetalation with organopalladium(II) halide and triflate complexes. However, such transmetalations readily take place when strong bases are added to the reaction mixture. Suzuki therefore suggested that the base plays a dual role in these reactions. First, it is believed that the nucleophilic base forms a reactive "ate" complex 224 at boron, which is then capable of

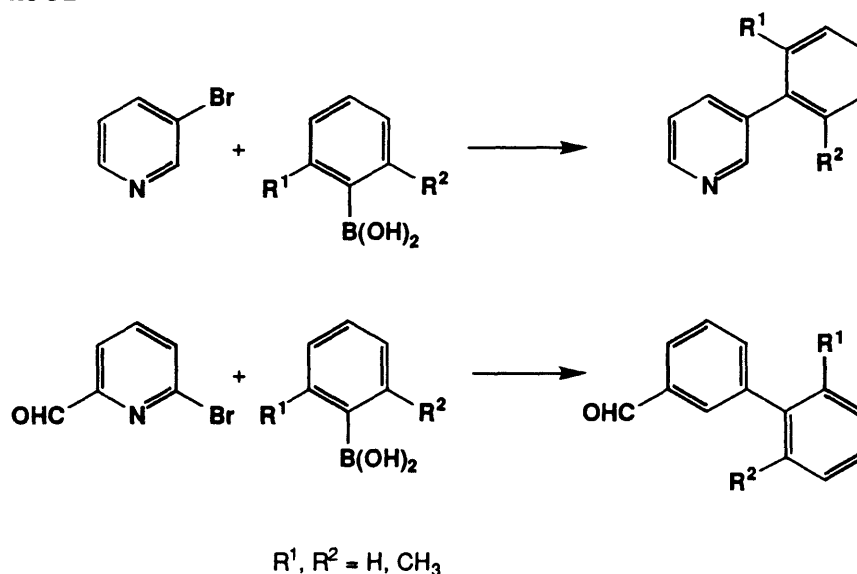
261. For selected examples, see (a) Hoshino, Y.; Miyaura, N.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3008. (b) Sato, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1989**, 1405.

262. Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972.

engaging in transmetalation. It has been speculated that the base may also coordinate to Pd(II) by displacing the halide ligand, and convert the initial oxidative addition intermediate **222** into a more electrophilic species such as **223**. The evidence supporting this latter role is scant, however.

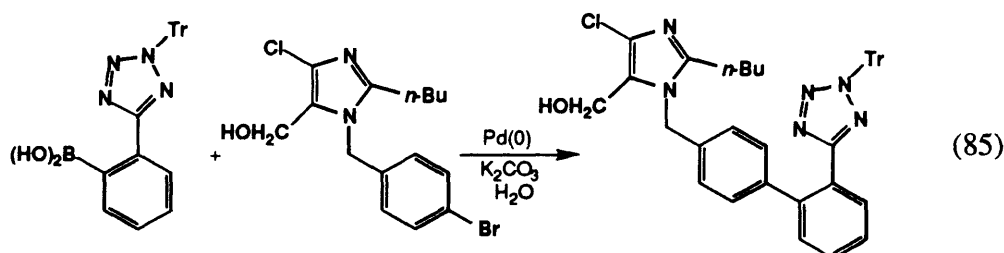
Canary and Aliprantis²⁶³ attempted to observe the intermediates of the Suzuki reaction by electrospray mass spectrometry, investigating the coupling reactions of various phenylboronic acids with pyridyl bromides (Scheme 52). Although [(pyrH) Pd(PPh₃)₂Br]⁺ (corresponding to **222**) and [(pyrH) (R¹R²Ph) Pd(PPh₃)₂]⁺ (corresponding to **225**) were readily observed, no peaks corresponding to [(pyrH) PdL₂OH] or [(pyrH) PdL₂OCH₃] (corresponding to **223**) were detected. It should be noted, however, that the mere non-detection of such intermediates does not necessarily prove their absence from the catalytic cycle. The species **223** might be very reactive and short-lived in the reaction process, and thus escape detection.

Scheme 52

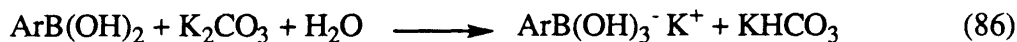


263. Aliprantis, A. O.; Canary, J. W. *J. Am. Chem. Soc.* **1994**, *116*, 6985.

While investigating the synthesis of Losartan potassium, an angiotensin II receptor antagonist developed for the treatment of high blood pressure and heart failure, a group of scientists at Merck extensively investigated the mechanism for the Suzuki cross-coupling reaction shown in eq 85.²⁶⁴



This investigation led to the conclusion that 2 equiv of water and carbonate each are required for the overall stoichiometry of the reaction. It is believed that one equiv of water and one equiv of carbonate are required initially to activate the boronic acid (eq 86), and that another equiv of each is needed to neutralize the boric acid produced as the reaction by-product (eq 87).



The reaction rate was not affected when sodium or cesium carbonate were used instead of K_2CO_3 , but virtually no coupling occurred when potassium bicarbonate was used as the base. This is consistent with the necessity to form $\text{ArB(OH)}_3^- \text{K}^+$ to initiate the coupling reaction. Carbonate ($\text{p}K_a$ 10.3) is basic enough to form the "ate" complex with ArB(OH)_2 , whereas bicarbonate ($\text{p}K_a$ 6.35) is too weak to do so.²⁶⁵

264. Smith, G. B.; Dezeny, G. C.; Hughes, D. L.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1994**, *59*, 8151.

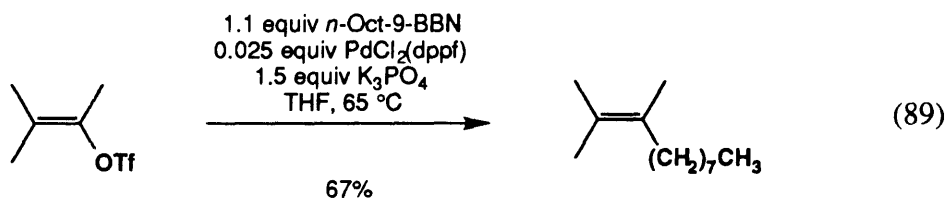
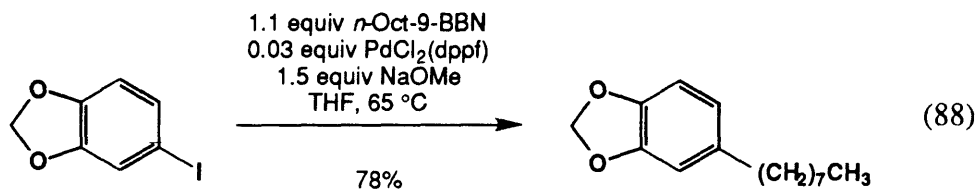
265. The $\text{p}K_a$ of phenylboronic acid is 8.8. See reference 264.

A key observation in these studies was made by varying the halide group on the aryl halide component of the coupling reactions. It was determined that *the slow step of this Suzuki coupling reaction depends on the identity of the halide*. With the aryl bromide, the slow step was the oxidative addition. With the aryl iodide, however, transmetalation was the rate-determining step. It was also observed that the transmetalation step is sensitive to steric hindrance, since the *ortho*-substituted aryl bromide corresponding to the intermediate shown in eq 85 was found to be a catalyst poison.

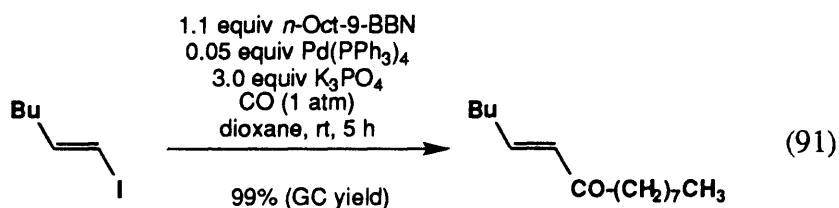
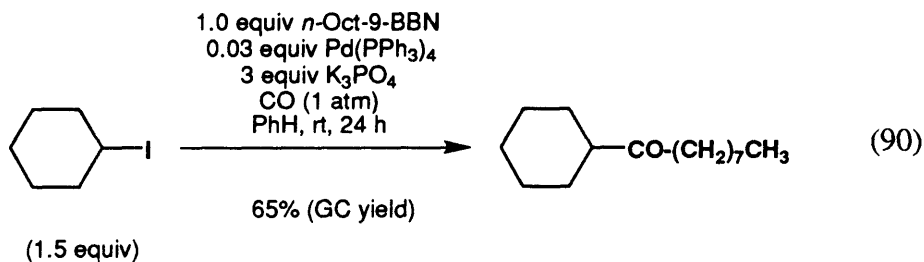
I. Scope of the Suzuki Coupling Reaction: Alkylboron Compounds²⁶⁶

9-BBN derivatives have become the most popular boron compounds for the transfer of alkyl moieties. They are readily available via hydroboration of alkenes (0 °C-room temperature) and can be treated *in situ* with base to promote smooth coupling with vinyl and aryl halides²⁶⁷ (eq 88) and triflates²⁶⁸ (eq 89). The 9-BBN residue behaves as a "dummy ligand" in these reactions, and no selectivity problems have been observed. Soderquist has recently introduced an interesting modification, involving the partial oxidation of the BBN moiety, which allows the organoboron compound to be isolated and stored prior to use in the coupling reaction.²⁶⁹ Arylboronic acids and esters, as well as catecholborane derivatives, have also been utilized in similar coupling reactions with aryl and vinyl iodides.²⁷⁰

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266. For reviews, see (a) Brown, H. C. *Organic Synthesis via Boranes*; Wiley: New York, 1975. (b) Cragg, G. M. L. *Organoboranes in Organic Synthesis*; Marcel Dekker: New York, 1973.
267. Miyaura, N.; Ishiyama, T.; Sasaki, M.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314.
268. Oh-e T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201.
269. Soderquist, J. A.; Santiago, B. *Tetrahedron Lett.* **1990**, *31*, 5541.
270. (a) Sato, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1989**, 1405. For the hydroboration of alkenes with catecholborane, see (b) Männig, D.; Nöth, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 878. (c) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 6917. (d) Sato, M.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1990**, *31*, 231. (e) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1992**, *114*, 6671, 6679.



9-Alkyl-9-BBN derivatives have also found use in *carbonylative* cross coupling reactions with iodoalkanes²⁷¹ (eq 90) and vinyl iodides²⁷² (eq 91) to produce ketones and α,β -unsaturated ketones, respectively.



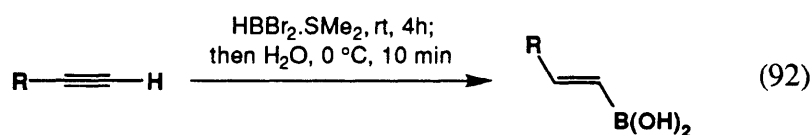
II. Scope of the Suzuki Reaction: Alkenylboron Compounds

Alkenylboronic acids are readily available via the hydroboration of alkynes with dibromoborane-dimethylsulfide (HBBR₂·SMe₂) and subsequent hydrolysis with water.

271. Ishiyama, T.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1991**, *32*, 6923.

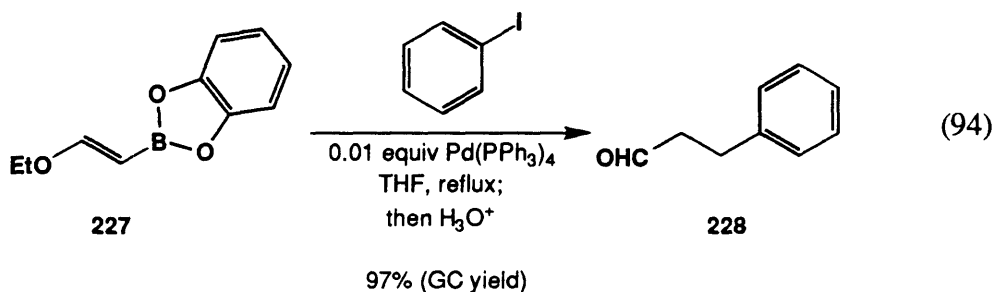
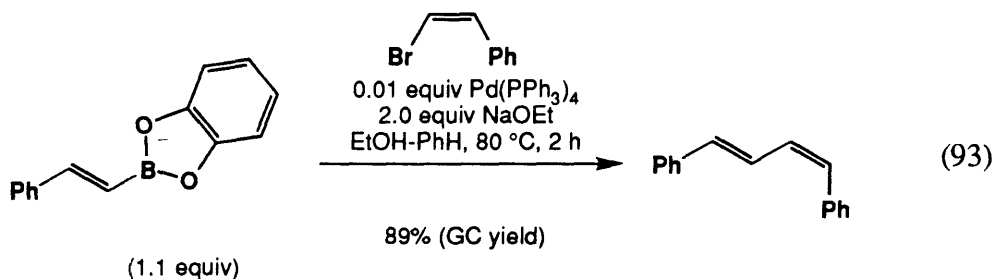
272. Ishiyama, T.; Miyaura, N.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1999.

The corresponding alkenylboronic esters are prepared via the reaction of the alkenyldibromoborane-dimethylsulfide complexes with alcohols and glycols (eq 92).^{273,274}

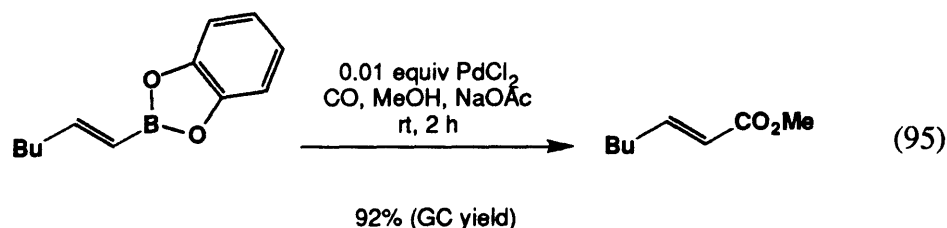


In a similar fashion, (*E*)-1-alkenyl-1,3,2-benzodioxaboroles are prepared via the hydroboration of alkynes with catecholborane.²⁷⁵ These catecholborane derivatives have been used extensively for Suzuki coupling reactions. For example, they have been treated with bromoalkenes^{276,277} and vinyl triflates,²⁶⁸ as well as aryl halides,²⁷⁸ to produce conjugated dienes (eq 93) and styrene derivatives. An interesting application of this methodology involves the coupling of the (2-ethoxyvinyl)borane derivative **227** with aryl and benzyl halides in a homologation strategy for the synthesis of aldehydes (**228**) (eq 94).²⁷⁹

273. For the preparation of (*E*)-1-alkenylboronic acids and esters, see (a) Brown, H. C.; Bhat, N. G.; Somayaji, V. *Organometallics* **1983**, *2*, 1311. For the synthesis of (*Z*)-1-alkenylboronic esters, see Brown, H. C.; Imai, T. *Organometallics* **1984**, *3*, 1392.
274. For related methods for the synthesis of alkenylboronic acids and esters, see (a) Mazal, C.; Vaultier, M. *Tetrahedron Lett.* **1994**, *35*, 3089. (b) Kamabuchi, A.; Moriya, T.; Miyaura, N.; Suzuki, A. *Synth. Commun.* **1993**, *23*, 2851.
275. (a) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1971**, *93*, 1816. (b) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 4370. (c) Gridnev, I. D.; Miyaura, N.; Suzuki, A. *Organometallics* **1993**, *12*, 589. (c) Miyaura, N.; Suzuki, A. *Org. Synth.* **1990**, *68*, 130.
276. (a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, 3437. (b) Miyaura, N.; Suginome, H.; Suzuki, A. *Tetrahedron Lett.* **1981**, *22*, 127. For the synthesis of alkenyl sulfides, see (c) Ishiyama, T.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1987**, 25. (d) Hoshino, Y.; Ishiyama, T.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1988**, *29*, 3983. (e) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972. For an interesting application of this coupling to the synthesis of conjugated dienones, see (f) Satoh, M.; Ishiyama, T.; Miyaura, N.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3471.
277. For similar reactions with diisopropyl (*E*)-(1-alkyl-1-alkenyl)boronates, see (a) Satoh, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1986**, 1329. (b) Miyaura, N.; Satoh, M.; Suzuki, A. *Tetrahedron Lett.* **1986**, *27*, 3745.
278. (a) Gridnev, I. D.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, 5351. (b) Miyaura, N.; Suzuki, A. *J. Organometallic Chem.* **1981**, *213*, C53.
279. (a) Miyaura, N.; Maeda, K.; Suginome, H.; Suzuki, A. *J. Org. Chem.* **1982**, *47*, 2117. For the application of this approach to the synthesis of benzo-fused heteroaromatic compounds, see Satoh, M.; Miyaura, N.; Suzuki, A. *Synthesis* **1987**, 373.



The Pd-catalyzed carbonylation of alkenylborane derivatives has been utilized in the synthesis of α,β -unsaturated esters (eq 95).²⁸⁰



III. Scope of the Suzuki Reaction: Arylboron Compounds

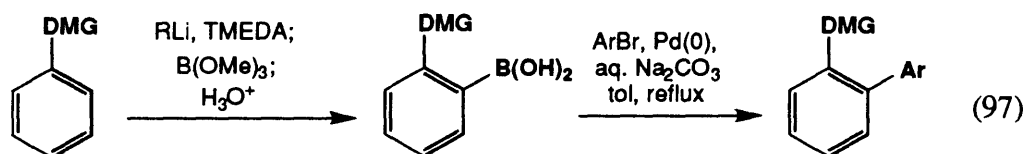
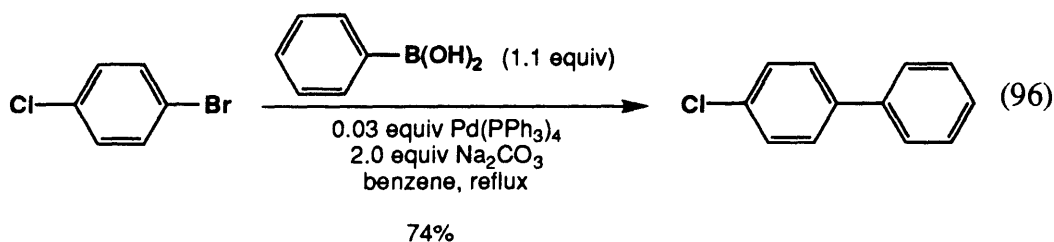
The palladium-catalyzed cross coupling of phenylboronic acid with haloarenes was first introduced by Suzuki in 1981 (eq 96).^{281,282} Later, phenylboronic acids and

280. Miyaura, N.; Suzuki, A. *Chem. Lett.* **1981**, 879.

281. Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513.

282. For the synthesis of Isoflavones via the cross coupling of arylboronic acids and 3-bromochromones, see (a) Hoshino, Y.; Miyaura, N.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3008. For the synthesis of sterically hindered biaryls, see (b) Watanabe, T.; miyaura, N.; Suzuki, A. *Synlett* **1992**, 207. For the synthesis of unsymmetrical mononitrobiphenyls, see (c) Miller, R. B.; Dugar, S. *Organometallics* **1984**, 1261. For the synthesis of 5-arylnicotinates, see (d) Thompson, W. J.; Gaudino, J. *J. Org. Chem.* **1984**, *49*, 5237.

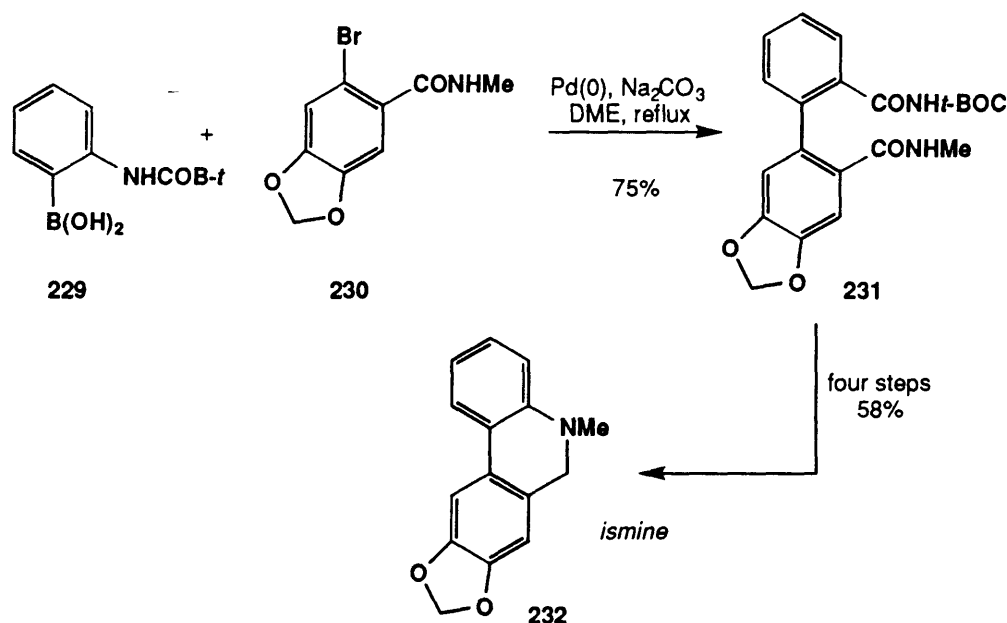
their esters were used in cross coupling reactions with vinyl and aryl triflates.^{268,283} Since then, arylboronic acids and their Pd-catalyzed coupling reactions have been extensively studied by Snieckus and co-workers,¹⁷⁸ who have combined the powerful *ortho* metalation strategy with the Suzuki coupling reaction (eq 97) to synthesize a variety of substituted aromatic systems and natural products, such as the biphenyl alkaloid ismine (*vide infra*)^{178h} and the antitumor, antimalarial agent β -lapachone.^{178k}



The key step in the synthesis of ismine^{178h} (**232**) is shown in Scheme 53 below. The cross coupling of the boronic acid **229** with the aryl bromide **230** produced the key intermediate **231** in 75% yield. Four additional steps were necessary to produce ismine in 58% yield from **231**.

283. For selected examples, see (a) Huth, A.; Beetz, I.; Schumann, I. *Tetrahedron* **1989**, *45*, 6679. (b) Wustrow, D. J.; Wise, L. D. *Synthesis* **1991**, 993. (c) Shieh, W.-C.; Carlson, J. A. *J. Org. Chem.* **1992**, *57*, 379.

Scheme 53



The scope of the Suzuki reaction of arylboron compounds has been greatly expanded over the past few years. A variety of heteroaryl boronic acids and esters²⁸⁴ have been synthesized and used in Pd-catalyzed cross coupling reactions.²⁸⁵ In addition, tetraarylborates have been utilized as substitutes for arylboronic acid derivatives.²⁸⁶ In a recent development, heterogeneous catalysis conditions associated with hydrogenation have been successfully employed for the Pd-catalyzed coupling of arylboronic acids with aryl halides and triflates.²⁸⁷ Although the reaction times are remarkably longer than the times usually reported for the conventional Pd(PPh₃)₄-catalyzed reactions, the isolated yields are generally the same.

284. For a review on the preparation and cross coupling reactions of heteroarylboronic acids, see Terashima, M.; Ishikura, M. *Adv. Heterocycl. Chem.* **1989**, *46*, 143.

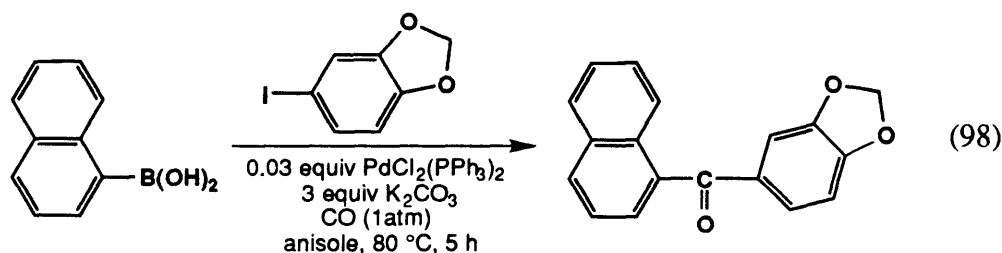
285. For the synthesis of Furo[2,3-C]quinolines, see (a) Yang, Y. *Synth. Commun.* **1989**, *19*, 1001. For the synthesis of indole derivatives, see (b) Zheng, Q.; Yang, Y.; Martin, A. *Tetrahedron Lett.* **1993**, *34*, 2235. For the cross coupling reaction of furylborates and organohalides, see (c) Cristofoli, W. A.; Keay, B. A. *Tetrahedron Lett.* **1991**, *32*, 5881.

286. For examples, see (a) Catellani, M.; Chiusoli, G. P.; Fornasari, V. *Gazz. Chim. Ital.* **1990**, *120*, 779. (b) Legros, J.-Y.; Fiaud, J.-C. *Tetrahedron Lett.* **1990**, *31*, 7453. (c) Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1992**, *33*, 4815.

287. Marck, G.; Villiger, A.; Buchecker, R. *Tetrahedron Lett.* **1994**, *35*, 3277.

It has been demonstrated that phosphine inhibition plays a key role in limiting the catalytic efficiency in Suzuki aryl couplings, and extraordinarily mild, efficient, and clean catalysis occurs in the complete absence of phosphines.²⁸⁸

The carbonylative cross coupling reaction of arylboronic acids with aryl iodides has also been reported. In this manner, unsymmetrical biaryl ketones are prepared in good yields (eq 98).²⁸⁹



Finally, Tour and co-workers have introduced acylated diethanolamine complexes of arylboron reagents as very effective partners in cross coupling reactions.²⁹⁰

IV. General Conditions for the Suzuki Reaction

A variety of bases have been used for the Suzuki coupling reaction. The most commonly used bases include NaOH and Na₂CO₃, usually in mixed solvent systems (THF, DME, or dioxane in water). Hydrolytic deboronation is a major side reaction in some Suzuki couplings. Non-protic conditions, using bases such as K₃PO₄ in dry organic solvents like DMF, have been developed to circumvent this problem.²⁹¹ Thallium salts were introduced by Kishi,²⁹² and are claimed to make possible a 10³-fold increase in the

288. (a) Wallow, T. I.; Novak, B. M. *J. Org. Chem.* **1994**, *59*, 5034. (b) Moreno-Mañas, M.; Pajuelo, F.; Pleixats, R. *J. Org. Chem.* **1995**, *60*, 2396.

289. Ishiyama, T.; Kizaki, H.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1993**, *34*, 7595.

290. Lamba, J. S.; Tour, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 11723.

291. Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207.

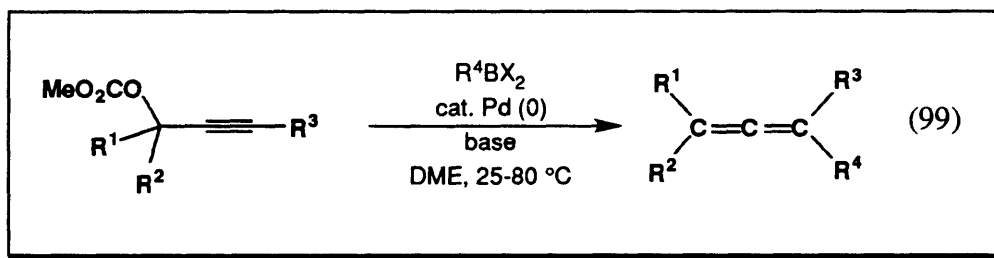
292. Uenishi, J.; Beau, J.-M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4756.

coupling rate. Recently, there have been reports of accelerated transmetalations when a stoichiometric amount of Cu(I) salts were added to the reaction.²⁹³

The traditional Pd(PPh₃)₄ complex is the catalyst most often used for Suzuki reactions, but PdCl₂(dppf) has also been employed when 9-BBN derivatives are concerned.

Synthesis of Allenes via Pd-Catalyzed Coupling of Organoboron Compounds

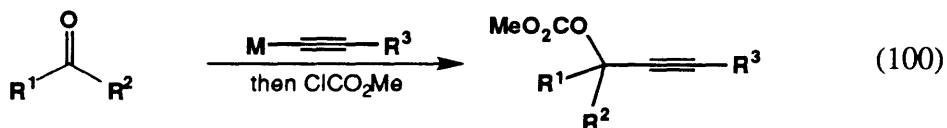
As mentioned in the previous chapter, our laboratory has been interested in the chemistry of allenes and their application in the synthesis of carbocycles and heterocycles for some time.^{191-194,243,246} In connection with several allene-based annulation methods under study in our laboratory, we required an improved route to highly substituted allene derivatives. The reports on the palladium-catalyzed coupling of propargylic halides and carbonates with organozinc and organocopper species (see Chapter 1 of Part III) prompted us to investigate the synthesis of allenes via the reaction of organoboron compounds with propargylic carbonates as outlined in eq 99.



We believed that there would be several advantages in employing this strategy for the synthesis of allenes. First, this method could provide access to *a wide variety of functionalized allenes*. The coupling partners employed in this chemistry should be easily prepared in gram quantities. As mentioned earlier in this chapter, a variety of

293. Ichikawa, J.; Ikeura, C.; Minami, T. *Synlett* 1992, 739.

organoboron compounds are readily available from aromatic precursors, alkynes, and alkenes. In addition, a large number of propargylic carbonates can be easily prepared from the reaction of the appropriate acetylides with aldehydes or ketones, and subsequent trapping (one pot) of the alkoxide intermediate with methyl chloroformate (eq 100).



Furthermore, we hoped that this methodology could ultimately be applied to the synthesis of *allenes in enantiomerically pure form*^{294,295} through the use of enantiomerically pure propargylic carbonates. As discussed previously (see page 124) the Pd-catalyzed reaction is expected to proceed stereoselectively in an *anti* fashion, as observed by Vermeer and co-workers for the coupling of organozinc compounds and propargylic acetates.^{251c}

Several methods for the synthesis of propargylic alcohols in enantiomerically pure form have been reported to date. Most of these methods rely on the enantioselective reduction of α,β -acetylenic ketones.²⁹⁶ Noyori has employed binaphthol-modified lithium aluminum hydride reagents for the enantioselective reduction of propargylic ketones.²⁹⁷ Using this methodology, acetylenic ketones can be reduced to either enantiomer of the corresponding propargylic alcohols in good yield, and with high

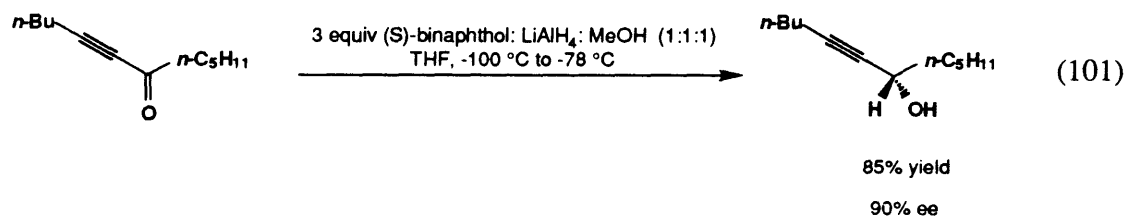
294. For reviews on the synthesis of chiral allenes, see (a) Pasto, D. J. *Tetrahedron* **1984**, *40*, 2805. (b) Rossi, R.; Diversi, P. *Synthesis* **1973**, 25. For selected examples, see chapter 5 of this dissertation.

295. For methods for the determination of the enantiomeric purity of allenes, see (a) Uccello-Barretta, G.; Balzano, F.; Caporusso, A. M.; Salvadori, P. *J. Org. Chem.* **1994**, *59*, 836. (b) Krause, N.; Handke, G. *Tetrahedron Lett.* **1991**, *32*, 7225. (c) Pietuszka, J.; Hochmuth, D. H.; Gehrcke, B.; Icheln, D.; Runge, T.; König, W. A. *Tetrahedron. Asym.* **1992**, *3*, 661. (d) Goering, H. L.; Eikenberry, J. N.; Koerner, G. S. *J. Am. Chem. Soc.* **1971**, *93*, 5913. (e) Fraser, R. R.; Petit, M. A.; Saunders, J. K. *J. Chem. Soc., Chem. Commun.* **1971**, 1450. (f) Claesson, A.; Olsson, L.-I.; Sullivan, G. R.; Mosher, H. S.; *J. Am. Chem. Soc.* **1975**, *97*, 2919. (g) Parker, D.; Taylor, R. J. *Tetrahedron* **1988**, *44*, 2241. (h) Lang, R. W.; Hansen, H.-J. *Helv. Chim. Acta* **1979**, *62*, 1025. (i) Mannschreck, A.; Munninger, W.; Burgemeister, T.; Gore, J.; Cazes, B. *Tetrahedron* **1986**, *42*, 399. (j) Schurig, V.; Nowotny, H.-P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 939.

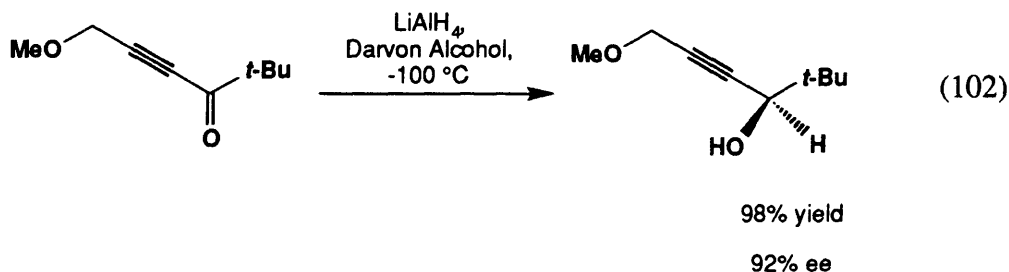
296. For a review, see Singh, V. K. *Synthesis* **1992**, 605.

297. Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717.

enantioselectivity (eq 101). This reduction has been utilized as the key step for the asymmetric synthesis of several insect pheromones.²⁹⁸



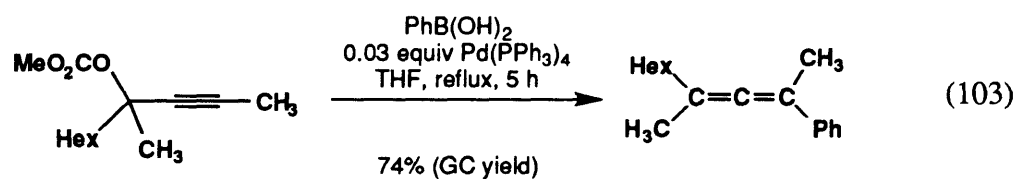
The chiral LiAlH_4 /Darvon alcohol complex was introduced by Mosher²⁹⁹ for the enantioselective reduction of ynones. Lautens³⁰⁰ and Marshall³⁰¹ have extensively used this reaction to synthesize a variety of chiral propargylic alcohols in high enantiomeric purity (eq 102).³⁰² Alpine borane has also been used for the enantioselective reduction of propargylic ketones.³⁰³ Finally, propargylic alcohols have been synthesized in high enantioselectivity via the oxidative C-Si cleavage of propargylic silanes.^{304,305}



298. Nishizawa, M.; Yamada, M.; Noyori, R. *Tetrahedron Lett.* **1981**, *22*, 247.
299. (a) Yamaguchi, S.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 1870. (b) Yamaguchi, S.; Mosher, H. S.; Pohland, A. *J. Am. Chem. Soc.* **1972**, *94*, 9254.
300. Lautens, M.; Delanghe, P. H. M. *J. Am. Chem. Soc.* **1994**, *116*, 8526.
301. (a) Marshall, J. A.; Wang, X.-J. *J. Org. Chem.* **1991**, *56*, 3211. (b) Marshall, J. A.; Wang, X.-J. *J. Org. Chem.* **1992**, *57*, 1242. (c) Marshall, J. A.; Tang, Y. *J. Org. Chem.* **1993**, *58*, 3233.
302. For other applications of this reaction, see (a) Johnson, W. S.; Brinkmeyer, R. S.; Kapoor, V. M.; Yarnell, T. M. *J. Am. Chem. Soc.* **1977**, *99*, 8341. (b) Cohen, N.; Lopresti, R. J.; Neuom, C.; Saucy, G. *J. Org. Chem.* **1980**, *45*, 582. (c) Wender, P. A.; Ihle, N. C.; Correia, C. R. D. *J. Am. Chem. Soc.* **1988**, *110*, 5904. (d) Trost, B. M.; Hipskind, P. A.; Chung, J. Y. L.; Chan, C. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1502. (e) Heathcock, C. H.; Stafford, J. A. *J. Org. Chem.* **1992**, *57*, 2566.
303. For examples, see (a) Midland, M. M.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1977**, *99*, 5211. (b) Carreira, E. M.; Hastings, C. A.; Shepard, M. S.; Yerkey, L. A.; Millward, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 6622.
304. Hartley, R. C.; Lamothe, S.; Chan, T. H. *Tetrahedron Lett.* **1993**, 1449.
305. An alternative method for the synthesis of propargylic alcohols in enantiomerically pure form has been reported by Corey. This strategy involves highly enantioselective alkynylation of aldehydes promoted by chiral oxazaborolidines. The alkynylation reagents are generated *in situ* from bromodimethylborane and alkynylstannanes: Corey, E. J.; Cimprich, K. A. *J. Am. Chem. Soc.* **1994**, *116*, 3151.

Propargylic carbonates were chosen as the substrates for our reaction because of their ability to generate methoxide *in situ* upon oxidative addition to Pd(0) (*vide infra*).^{172c} The initial palladium carbonate complexes resulting from the oxidative addition of propargylic carbonates readily undergo decarboxylation to form palladium methoxide species. We were hoping that this *catalytic* generation of base *in situ* would eliminate the need for additional base to help with the transmetalation step in the desired coupling reaction.³⁰⁶

During the course of our studies, a paper by Suzuki and co-workers³⁰⁷ appeared describing a similar method for the synthesis of allenes (eq 103). They reported that the (alkoxo)palladium complexes resulting from the oxidative addition of *tertiary* propargylic carbonates undergo transmetalation with organoboron compounds under neutral conditions, without the need for external base.

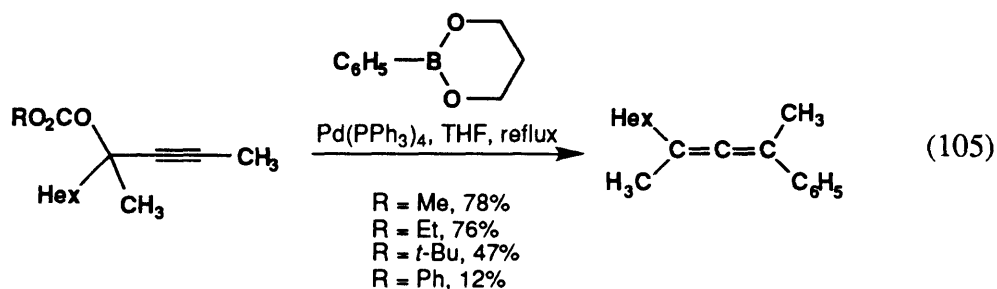
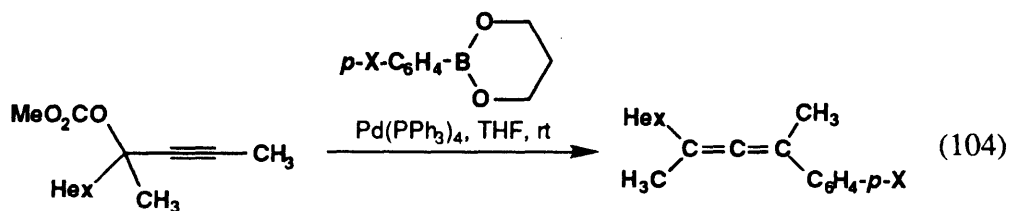


Suzuki reported that the choice of solvents (THF, benzene, or DMF) does not appear to affect the yield of these coupling reactions. The ratio of phosphine ligand per palladium, however, does affect both the yields and selectivities. Better results were always obtained when Pd complexes with high numbers of phosphine ligands were used. It was also determined through a linear free energy study that electron-withdrawing substituents on the arylboronic compounds accelerate the reaction (eq 104). Less bulky

306. For transmetalations of organoboron compounds with (alkoxo)palladium species, see (a) Sato, N.; Ishiyama, T.; Miyaura, N.; Suzuki, A. *Bull. Chem. Soc. Jpn* **1987**, *60*, 3471. (b) Sasaya, F.; Miyaura, N.; Suzuki, A. *Bull. Korean. Chem. Soc.* **1987**, *8*, 329. (c) Wakita, Y.; Yasunaga, T.; Akita, M. *J. Organomet. Chem.* **1986**, *301*, C17.

307. Moriya, T.; Miyaura, N.; Suzuki, A. *Synlett* **1994**, 149.

and more nucleophilic carbonate alkoxy groups were shown to accelerate the coupling reaction (eq 105).



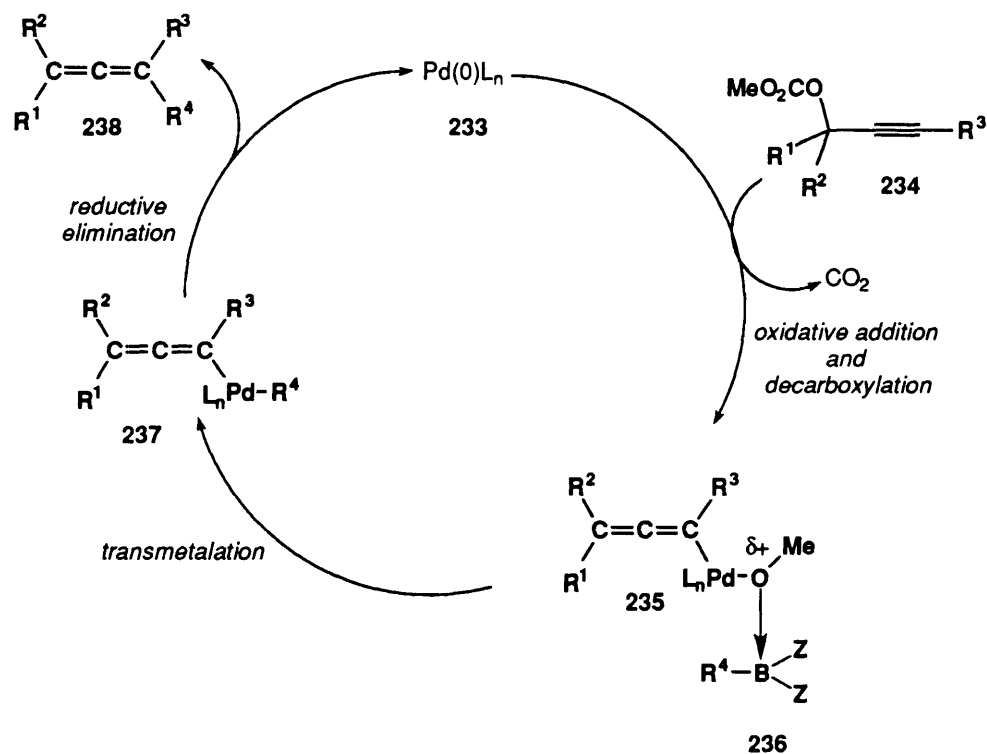
Suzuki suggests that these observations are consistent with a mechanism that proceeds through coordination of the boron atom to an alkoxy oxygen on the allenylpalladium intermediate (235 and 236, Scheme 54). The transfer of the activated organic group from boron to the palladium center then follows. A similar transmetalation process between (methoxy)platinum(II) complexes and arylboronic acids has been reported.³⁰⁸

In contrast to our results (*vide infra*), Suzuki reported that his coupling reaction could be successfully applied only to *tertiary* propargylic carbonates. Carbonates derived from secondary and primary propargylic alcohols react to form the desired allenes in very low yield accompanied by several minor by-products. It was also observed that even though unsaturated (aryl, vinyl, and alkynyl) organoboron compounds undergo transmetalation without the need for additional base, trialkylborane derivatives do not

308. Siegmann, K.; Pregosin, P. S.; Venanzi, L. M. *Organometallics* 1989, 8, 2659.

participate in the reaction unless potassium phosphate or similar bases are added to the reaction mixture.

Scheme 54



As discussed in the remainder of this chapter, simultaneous with Suzuki, we have developed a very similar allene synthesis based on the coupling of organoboron compounds and propargylic carbonates. Significantly, we have found that under our somewhat different reaction conditions, the reaction is applicable to the synthesis of a broader range of allenes than reported by Suzuki.

Synthesis of Propargylic Carbonates

As mentioned previously, propargylic carbonates can be easily prepared from the reaction of the appropriate acetylides (generated *in situ* from deprotonation with *n*-BuLi,

THF, -78 °C or 0 °C) with aldehydes and ketones, and subsequent trapping (one pot) of the alkoxide intermediates with methyl chloroformate (eq 100). In this manner, a number of primary, secondary, and tertiary propargylic carbonates can be conveniently prepared. A typical procedure involves the reaction of 1.2-1.25 equiv of the acetylide with an aldehyde or ketone at -78 °C for 3 h, followed by trapping with 1.25 equiv of methyl chloroformate at 0 °C (15 min), and subsequent warming to room temperature. Table 8 below summarizes the synthesis of the propargylic carbonates used in our studies.

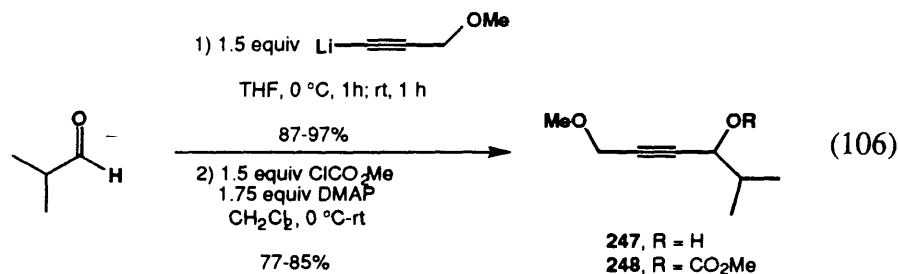
Table 8. Synthesis of Propargylic Carbonates

$\text{R}^3-\text{C}(=\text{O})-\text{R}^4 \xrightarrow[\text{then ClCO}_2\text{Me (1.25 equiv)}]{(1.2 - 1.25 \text{ equiv}) \text{ R}^2-\text{C}\equiv\text{C}-\text{M}} \text{THF, -78 }^\circ\text{C, 3 h}$ $\text{R}^2-\text{C}\equiv\text{C}-\text{C}(\text{R}^3)(\text{R}^4)\text{OCO}_2\text{Me}$				
entry	$\text{R}^3-\text{C}(=\text{O})-\text{R}^4$	$\text{R}^2-\text{C}\equiv\text{C}-\text{M}$	$\text{R}^2-\text{C}\equiv\text{C}-\text{C}(\text{R}^3)(\text{R}^4)\text{OCO}_2\text{Me}$	yield
1		$t\text{-BuMe}_2\text{Si}-\text{C}\equiv\text{C}-\text{Li}$		67%
2		$\text{Me}_3\text{Si}-\text{C}\equiv\text{C}-\text{Li}$		75-89%
3		$\text{MeO}-\text{CH}_2-\text{CH}_2-\text{C}\equiv\text{C}-\text{Li}$		73%
4		$\text{H}-\text{C}\equiv\text{C}-\text{MgBr}$		80%

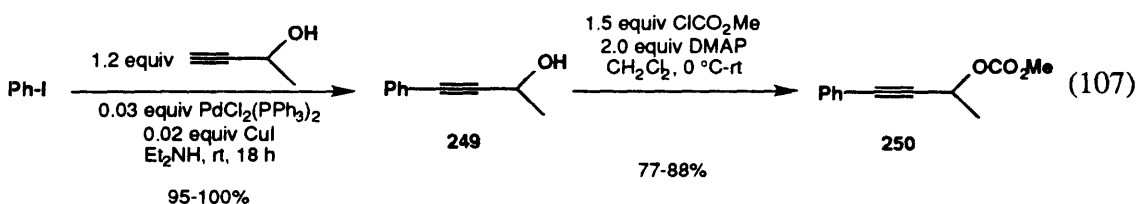
entry		$R^2-C\equiv C-M$		yield
5		$H-C\equiv C-MgBr$		64-74%
6		$MeO-CH_2-C\equiv C-Li$		83-86%
7		$MeO-CH_2-C\equiv C-Li$		84%
8	paraformaldehyde (reaction carried out in refluxing THF)	$MeO-CH_2-C\equiv C-Li$		74%

In addition to the propargylic carbonates in Table 8, three other propargylic carbonates were prepared by using alternative procedures. The propargylic carbonate **248** was prepared by a two-step version of our standard procedure as outlined in eq 106.³⁰⁹ In this case, the propargylic alcohol intermediate **247** was isolated (87-97% yield) and then treated separately with 1.5 equiv of methyl chloroformate in the presence of 1.75 equiv of DMAP to produce **248** in 77-85% yield.

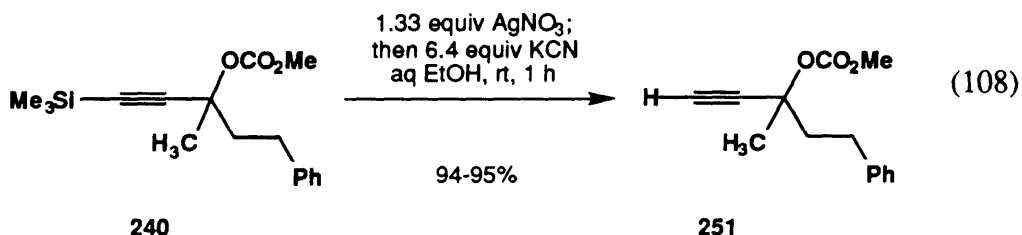
309. This reaction was carried out prior to the development of the more convenient one-pot procedure described above.



The propargylic carbonate **250** was prepared by the treatment of the propargylic alcohol **249** with 1.5 equiv of methyl chloroformate in the presence of 2 equiv of DMAP (CH_2Cl_2 , 0 °C→room temperature, 77-88%). The propargylic alcohol **249** was itself prepared via the Castro-Stephens coupling of commercially available 3-butyn-2-ol and iodobenzene in 95-100% yield (eq 107).

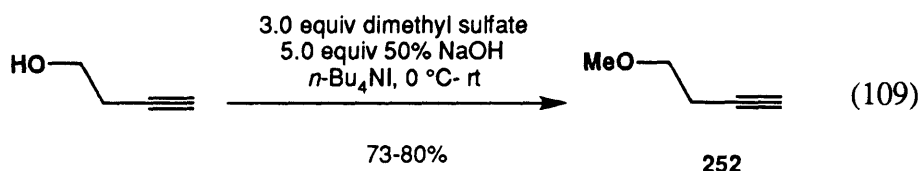


Finally, the propargylic carbonate **251** was prepared via the desilylation of the propargylic carbonate **240** using the conditions developed by Schmidt and Arens.³¹⁰ Thus, treatment of **240** with 1.33 equiv of AgNO_3 , followed by 6.4 equiv of KCN (aqueous EtOH , rt, 1 h) produced the terminal acetylene **251** in 94-95% yield (eq 108).



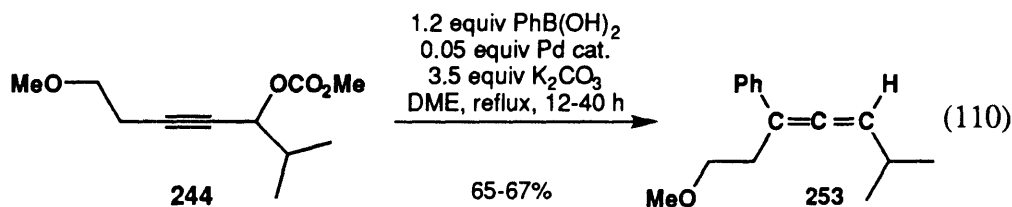
310. Schmidt, H. M.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 1138.

The known homopropargylic ether **252**³¹¹ which was used to synthesize some of the propargylic carbonates mentioned above was prepared via the phase-transfer-catalyzed *O*-methylation of 3-butyn-1-ol with dimethyl sulfate according to the procedure reported by Merz.³¹² Thus, treatment of 3-butyn-1-ol with 5.0 equiv of 50% NaOH solution and 3.0 equiv of dimethyl sulfate in the presence of tetra-*n*-butylammonium iodide produced the methyl ether **252** in 73-80% yield (eq 109).



Optimization of the Allene Synthesis

In order to test the feasibility of the proposed coupling reaction, we decided to investigate the coupling of the secondary propargylic carbonate **244** with commercially available phenylboronic acid. Thus, **244** was treated with 1.2 equiv of PhB(OH)₂ in the presence of 2.0 equiv of K₂CO₃ in refluxing DME³¹³ to produce the allene **253** in 65-67% yield after chromatographic purification (eq 110).



This first result was very encouraging, and we next set out to determine the optimal conditions for the coupling reaction.

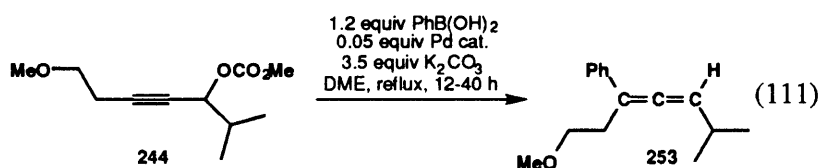
311. McCusker, P. A.; Kroeger, J. W. *J. Am. Chem. Soc.* **1937**, *59*, 213.

312. Merz, A. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 846.

313. These non-aqueous reaction conditions were selected because in a model study, the propargylic carbonate **234** was hydrolyzed to form the corresponding propargylic alcohol when heated in the presence of 2 M NaOH or Ba(OH)₂ solution in refluxing DME.

The propargylic carbonate **244** was chosen as the model system for our studies to determine the optimal reaction conditions for the palladium-catalyzed coupling reaction. First, the effect of varying the palladium catalyst was investigated. In a series of small-scale runs, the carbonate **244** was treated with 1.2 equiv of phenylboronic acid and 0.05 equiv of a palladium catalyst in refluxing DME in the presence of 3.5 equiv of K_2CO_3 (eq 111). The progress of these reactions was then monitored by TLC at regular intervals. Table 9 summarizes the results of these investigations.³¹⁴

Table 9. Effect of Pd Catalyst on the Coupling Reaction

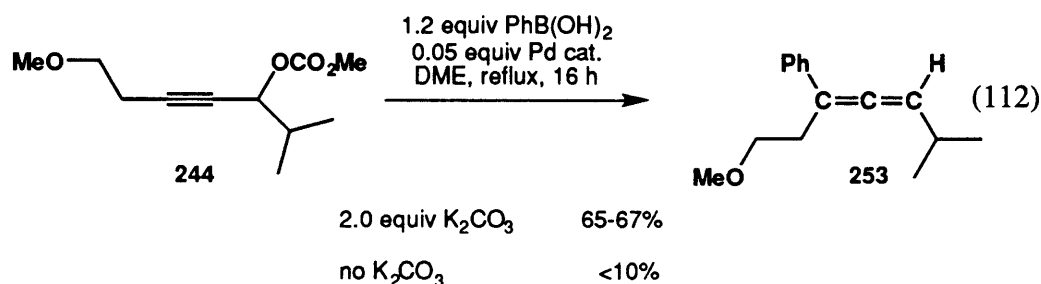


entry	Pd catalyst	comments
1	$Pd_2(dba)_3$: PPh_3 (1:4)	SM disappeared, 60% allene product (12 h)
2	$Pd_2(dba)_3$: PPh_3 (1:2)	incomplete reaction, 30% allene product (16 h)
3	$Pd_2(dba)_3$: tri-2-furylphosphine (1:4)	very sluggish reaction, mostly SM after 40 h
4	$Pd_2(dba)_3$: tri-2-furylphosphine (1:2)	sluggish reaction mostly SM after 12 h
5	$Pd_2(dba)_3$: Bu_3P (1:2)	no SM after 4 h, mixture of several products formed
6	$Pd_2(dba)_3$, no ligand	>80% of SM recovered

314. For the synthesis and reactivity of $Pd_2(dba)_3$ complexes, see (a) Ukai, T.; Kuwazura, H.; Ishii, Y.; Bonnet, J. J.; Ibers, J. A. *J. Organometallic Chem.* **1974**, *65*, 253. (b) Ito, T.; Hasegawa, S.; Takahashi, Y.; Ishii, Y. *J. Organomet. Chem.* **1974**, *73*, 401. (c) Ishii, Y.; Hasegawa, S.; Kimura, S.; Itoh, K. *J. Organomet. Chem.* **1974**, *73*, 411.

The results of our studies are consistent with the findings subsequently reported by Suzuki.³⁰⁷ Better results were obtained when Pd complexes with higher phosphine to Pd ratios were used. In addition, use of the electron-withdrawing ligand tri-2-furylphosphine³¹⁵ was shown to impede our coupling reaction. This electronic effect can be explained by the mechanism outlined in Scheme 54, which involves the coordination of the boron atom to the alkoxy oxygen on the allenylpalladium intermediate **235**. The electrophilic partial positive character on **235** would be better accommodated by electron rich palladium species. Electron-withdrawing ligands on palladium may inhibit the formation of this coordinated complex, which is essential for transmetalation, the rate-limiting step of the catalytic cycle. Therefore, electron-withdrawing ligands will retard the rate of the coupling reaction.

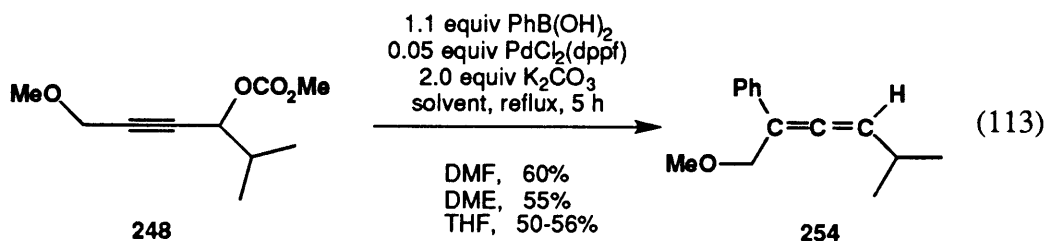
We were not able to effect the coupling of the secondary propargylic carbonate **244** with phenylboronic acid in the absence of added base. The reaction of **244** with 1.2 equiv of PhB(OH)₂ and 0.05 equiv of PdCl₂(dppf) in refluxing DME produced only a trace amount of the desired allene **253**. Most (75%) of the propargylic carbonate was recovered unchanged from this reaction (eq 112). Note that although Suzuki reported successful couplings in the absence of base, all of his examples involved *tertiary* propargylic alcohol derivatives. In our hands, the tertiary propargylic carbonate **241** did undergo the coupling reaction in the absence of base, although at a much slower rate than in the presence of K₂CO₃.



³¹⁵. (a) Farina, V.; Baker, S. R.; Benigni, D. A.; Hauck, S. I.; Sapino, Jr., C. *J. Org. Chem.* **1990**, *55*, 5833. (b) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.

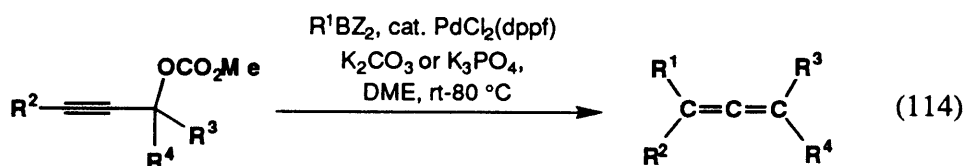
Next, we examined the effect of varying the added base on the coupling reaction of the propargylic carbonate **244** with phenylboronic acid. When K_2CO_3 was used, the reaction proceeded smoothly to provide the allene **253** in 65-67% yield. With Cs_2CO_3 and Tl_2CO_3 , however, the coupling reactions were very sluggish and produced the allene **253** in <20% yield. This effect may be due to the high insolubility of the latter two bases in DME. Later, it was discovered that K_3PO_4 is superior to all of the above bases in these coupling reactions.

The effect of varying the solvent was briefly examined. As illustrated in eq 113, in the case of propargylic carbonate **248**, DMF, THF, and DME are all suitable solvents. Finally, the effect of added H_2O was investigated. In the presence of water, the propargylic carbonates hydrolyzed to propargylic alcohols.



Scope of the Coupling Reaction

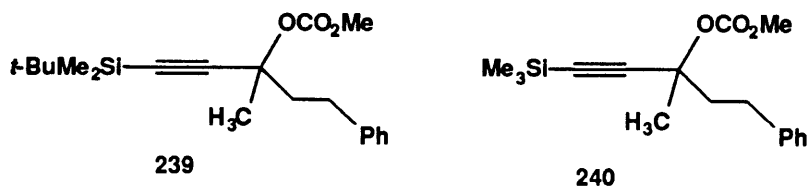
Table 10 summarizes the scope of the coupling of propargylic carbonates and organoboron compounds to form allenes according to the reaction formulated in eq 114.



As shown in the Table, aryl-, vinyl-, and alkyl-substituted organoboron compounds all participate in this reaction. *Both secondary and tertiary propargylic carbonates are good substrates in our palladium-catalyzed coupling* (entries 1-12), but

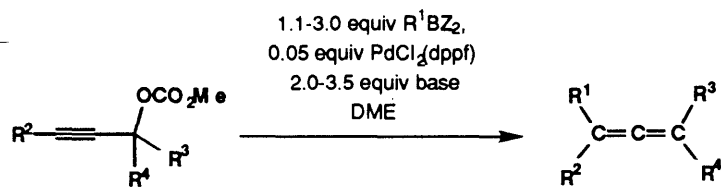
the reaction of primary propargylic carbonates leads to a mixture of products (entry 13). The coupling reaction of tertiary propargylic carbonates is much faster than the coupling reaction of secondary propargylic carbonates (compare entries 6 and 8), and can even be carried out at *room temperature* (entries 4-5).

To our dismay, the silyl-substituted propargylic carbonates **239** and **240** did not undergo the coupling reaction with phenylboronic acid to produce the desired allenylsilanes (entries 14-15). In the case of the trimethylsilyl-substituted derivative **240**, desilylation was a major problem. With the bulkier *tert*-butyldimethylsilyl-substituted derivative **239**, enyne formation was the major reaction pathway. Presumably, the bulky silyl group drives the equilibrium between the allenylpalladium and propargylic palladium intermediates toward the propargylic palladium complex which subsequently undergoes β -hydride elimination (*vide infra*).

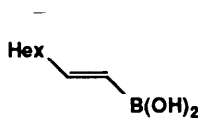
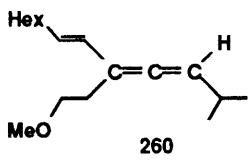
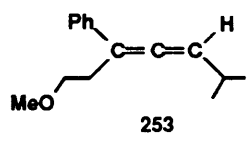
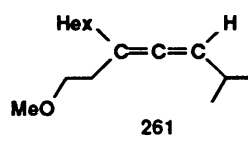
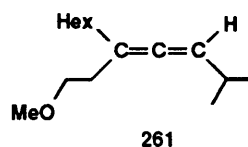
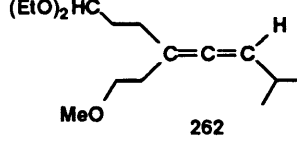
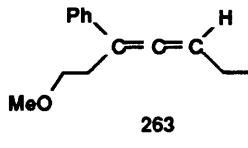


Arylboronic acids undergo the coupling much faster than the corresponding alkyl- or vinyl-substituted organoboron compounds when K_2CO_3 is used as the base. By substituting K_3PO_4 for K_2CO_3 , however, the coupling reactions of alkyl- and vinyl-substituted organoboron compounds can be carried out at much shorter reaction times (compare entries 9 and 10). This observation is consistent with the results reported by the Merck scientists.²⁶⁴ The more basic phosphate ($\text{p}K_{\text{a}}$ 12.7) accelerates the transmetalation reaction more than carbonate ($\text{p}K_{\text{a}}$ 10.3).

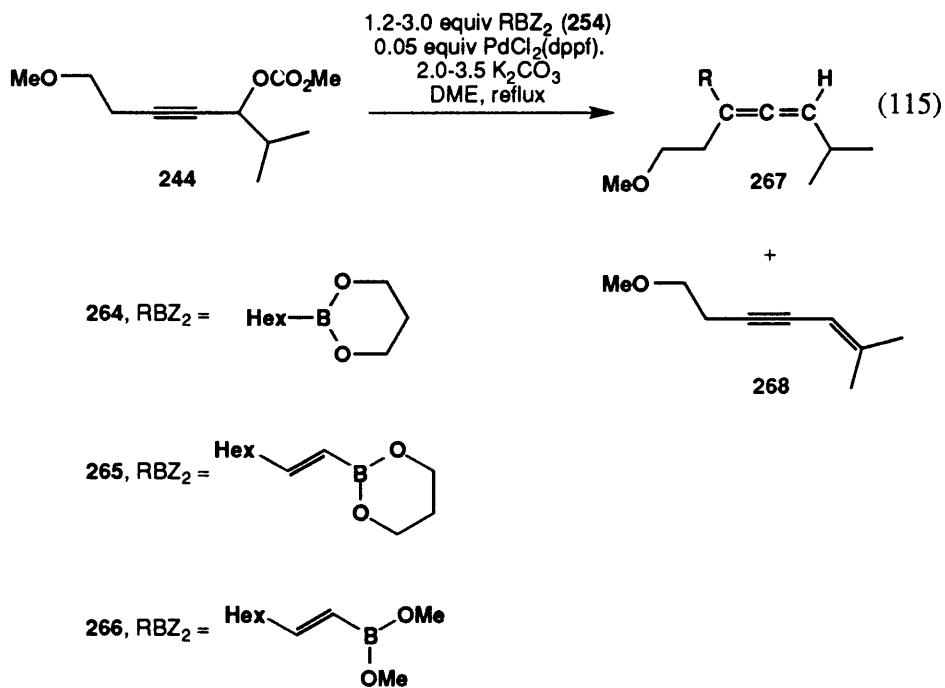
Table 10. Results of Coupling Reactions



entry	propargylic carbonate	R ¹ -BZ ₂	time (h)	temp (°C)	base (equiv)	product	yield (%)
1	251	Hex-CH=CH-B(OH) ₂	12	80	K ₂ CO ₃ (2.5)	Hex-CH=CH-C=C(CH ₃)-CH ₂ -Ph 255	51
2	251	Hex-CH=CH-B(OH) ₂	3	80	K ₃ PO ₄ (2.0)	Hex-CH=CH-C=C(CH ₃)-CH ₂ -Ph 255	54
3	251	NC(CH ₂) ₃ -9-BBN	3	80	K ₃ PO ₄ (2.0)	NC(CH ₂) ₃ -CH=CH-C=C(CH ₃)-CH ₂ -Ph 256	69
4	241	PhB(OH) ₂	48	25	K ₂ CO ₃ (2.0)	MeO-CH ₂ -CH ₂ -C=C(CH ₃)-CH ₂ -Ph 257	74-78
5	241	<i>n</i> -Hex-9-BBN	20	25	K ₂ CO ₃ (3.0)	MeO-CH ₂ -CH ₂ -C=C(CH ₃)-CH ₂ -Ph 258	34
6	242	PhB(OH) ₂	1.5	80	K ₂ CO ₃ (1.5)	Ph-C=C(CH ₃)-C=C(CH ₃)-CH ₂ -Ph 259	60

entry	propargylic carbonate	R ¹ -BZ ₂	time (h)	temp (°C)	base (# equiv)	product	yield (%)
7	244		12	80	K ₂ CO ₃ (2.5)		53
8	244	PhB(OH) ₂	5	80	K ₃ PO ₄ (2.0)		65-67
9	244	<i>n</i> -Hex-9-BBN	12	80	K ₂ CO ₃ (2.0)		63
10	244	<i>n</i> -Hex-9-BBN	3	80	K ₃ PO ₄ (3.0)		65
11	244	(EtO) ₂ CH(CH ₂) ₂ -9-BBN	3	80	K ₃ PO ₄ (3.0)		71
12	245	PhB(OH) ₂	12	80	K ₂ CO ₃ (2.0)		65
13	246	PhB(OH) ₂	12	80	K ₂ CO ₃ (2.0)	inseparable mixture of two products	
14	239	PhB(OH) ₂	12	80	K ₂ CO ₃ (2.0)	inseparable mixture of several products	
15	240	PhB(OH) ₂	12	80	K ₂ CO ₃ (2.0)	inseparable mixture of several products	

Boronate esters do not appear to participate in our coupling reaction. In contrast to the successful reactions of *n*-hexyl-9-BBN and (*E*)-1-octenylboronic acid, the esters **264-266** did not produce the allene **267** exclusively when treated with the propargylic carbonate **244** (eq 115). The conjugated enyne **268** was the major product in these sluggish reactions. However, note that Suzuki reported the successful coupling of vinyl and aryl boronates, although these reactions all involved *tertiary* propargylic carbonates.³⁰⁷

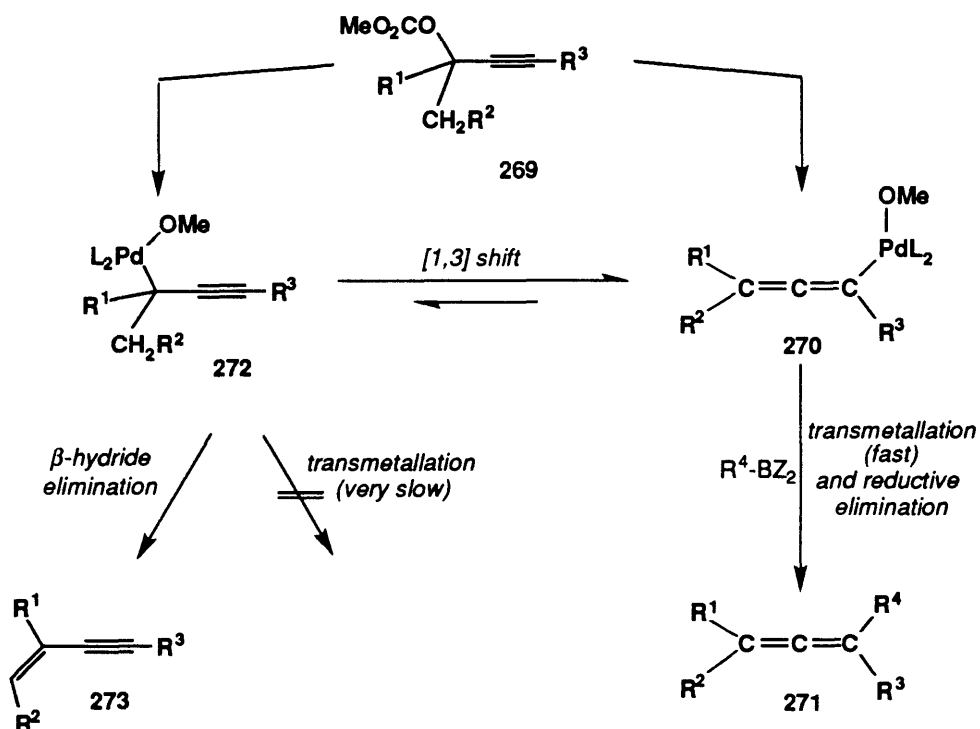


The formation of enyne by-products such as **268** in these reactions can be accounted for by a modification of Suzuki's mechanism for the Pd-catalyzed coupling reaction. This revised mechanism (Scheme 55) is consistent with Tsuji's observation that allenylpalladium species are in equilibrium with propargylic palladium compounds.^{172,316} Thus, oxidative addition could initially produce either the allenylpalladium intermediate **270**, the propargyl derivative **272**, or both. The ratio of these species most likely depends

316. Mandai, T.; Tsujiguchi, Y.; Matsuoka, S.; Tsuji, J. *Tetrahedron Lett.* **1993**, *34*, 7615.

on the nature of the substituents R^1 , R^2 , and R^3 . In the case of tertiary propargylic carbonates, this equilibrium, for example, presumably lies entirely on the side of the allenyl species **270**. When R^3 is very bulky (e.g. *Sit*-BuMe₂), the propargyl species **272** may be favored.

Scheme 55



When transmetalation is fast, the propargyl- and allenylpalladium species **270** and **272** do not have a significant lifetime. However, when transmetalation is slow (as in the case of reactions involving the boronate esters), the propargylic palladium species have a longer lifetime and undergo β -hydride elimination reactions to produce the conjugated enynes **273**.

Conclusions and Summary

In this chapter we have described a new and general method for the synthesis of substituted allenes via the palladium-catalyzed coupling of organoboron compounds and propargylic carbonates. *Both secondary and tertiary propargylic carbonates* are good substrates for our reaction, which has been applied toward the synthesis of a variety of aryl-, vinyl, and alkyl-substituted allene derivatives. The investigation of the effects of various catalysts, substrates, and bases has led to a deeper understanding of the mechanism of this coupling reaction. Work is currently underway to apply this methodology to the synthesis of allenes in enantiomerically pure form. The application of this strategy to the synthesis of 2-(allenyl)arylamine derivatives, and ultimately the synthesis of indoles, will also be investigated.

Part IV:

Experimental Section

General Procedures

All reactions were performed in flame-dried glassware under a positive pressure of argon or nitrogen. Reaction mixtures were stirred magnetically unless otherwise indicated, except for photochemical reactions which were *not stirred* unless otherwise indicated. Air and/or moisture sensitive reagents and solutions were transferred via syringe or cannula and were introduced into reaction vessels through rubber septa. Reaction product solutions were concentrated with the use of a Büchi rotary evaporator at approximately 20 mmHg unless otherwise indicated.

Materials

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

Distilled under nitrogen, argon or vacuum from calcium hydride: acetonitrile, dichloromethane, diethylamine, diisopropylamine, dibromomethane, 1,2-dichloroethane, triethylamine, 2,2,2-trifluoroethyl trifluoroacetate, 1,1,1,3,3,3-hexamethyldisilazane, anisole, pyridine, dimethylformamide, and triisopropylsilyl chloride.

Distilled under nitrogen or argon from sodium: 1,2-dimethoxyethane

Distilled under nitrogen or argon from sodium benzophenone ketyl or dianion: benzene, diethyl ether, and tetrahydrofuran.

Distilled under argon or nitrogen from lithium aluminum hydride: methyl propargyl ether.

Purification of other reagents was accomplished in the following manner; lithium chloride was dried at 140 °C (ca. 0.05 mmHg) for 24 h. Molecular sieves were heated under vacuum with a Bunsen burner and then stored at 140 °C in an oven until use. Methanesulfonyl chloride was distilled at reduced pressure. Methyl chloroformate was distilled under argon atmosphere

Alkyl lithium reagents were titrated in tetrahydrofuran or hexane at 0 °C with *sec*-butanol using 1,10-phenanthroline as an indicator.³¹⁶

Chromatography

Analytical thin-layer chromatography (TLC) was performed on Merck pre-coated glass-backed silica gel 60 F-254 0.25 mm plates. Visualization of spots was effected by one or more of the following techniques: (a) ultraviolet irradiation, (b) exposure to iodine vapor, (c) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating to ca. 200 °C, (d) immersion of the plate in an ethanolic solution of 3% *p*-anisaldehyde containing 0.5% concentrated sulfuric acid followed by heating to ca. 200 °C, and (e) immersion of the plate in an ethanolic solution of 3% *p*-vanillin containing 0.5% concentrated sulfuric acid followed by heating to ca. 200 °C.

Column chromatography was performed by using 230-400 mesh Merck or Baker silica gel.

Instrumentation

Photolyses were performed in a Rayonet Photochemical Reactor Model RPR-100 or RPR-200, both produced by the Southern New England Ultraviolet Company, or by using a medium pressure Hanovia lamp. The reactors each contained sixteen low pressure mercury bulbs or 253.7 nm ultraviolet light. The photolyses were conducted

316. Watson, S. C.; Eastham, J. F. J. *Organomet. Chem.* 1967, 9, 165.

with an internal fan in operation, and the internal temperature of the chamber was never higher than 35 °C.

Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected.

Infrared spectra (IR) were recorded using a Perkin-Elmer 1320 grating spectrophotometer.

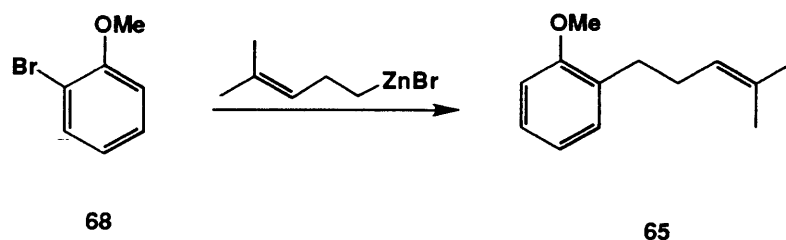
¹H NMR spectra were recorded with a Varian XL-300 (300 MHz) and a Varian Unity 300 (300 MHz) spectrophotometer. Chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane.

¹³C NMR spectra were determined on a Varian XL-300 (75 MHz) spectrophotometer. Chemical shifts are reported in parts per million (δ), relative to tetramethylsilane (with the central peak of CDCl₃ at 77.0 ppm used as a standard).

Ultraviolet-visible spectra were recorded with a Perkin-Elmer 552 UV-vis spectrophotometer, and absorbances are reported in nanometers (nm).

High resolution mass spectra (HRMS) were measured on a Finnegan MATT-8200 spectrometer.

Elemental analyses were performed by Robertson Microlit Laboratories, Inc., of Madison, New Jersey.



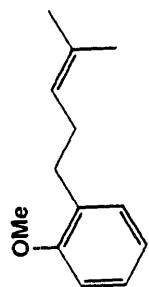
1-(1'-Methoxyphenyl)-4-methylpent-3-ene (65). A 25-mL, two-necked, round-bottomed flask ("A") equipped with a rubber septum, argon inlet adapter, and magnetic stir bar was charged with freshly cut lithium wire (0.072 g, 10.4 mmol), naphthalene (1.36 g, 10.6 mmol), and 5 mL of THF. The resulting mixture was stirred at 25 °C for 3 h (after 30 sec, the solution changed from colorless to dark green). A solution of anhydrous ZnCl₂-dioxane (1.22 g, 5.44 mmol) in 5 mL of THF was then added dropwise to flask A via cannula over 10 min, and the resulting solution was stirred at 25 °C for 20 min. A solution of 5-bromo-2-methyl-2-pentene⁵⁰ (67) (0.385 g, 2.36 mmol) in 1 mL of THF was added over 1 min via cannula, the resulting solution was stirred at 25 °C for 4.5 h, and then the unreacted zinc was allowed to settle over 2 h. A 50-mL, two-necked flask ("B") equipped with a rubber septum and a condenser fitted with an argon inlet adapter was charged with 2-bromoanisole (0.221 g, 1.18 mmol), PdCl₂(dppf)^{56b,57} (0.087 g, 0.12 mmol), and 5 mL of THF. The brown alkylzinc bromide solution in flask A was transferred into flask B via cannula over 1 min. The residual unreacted zinc was washed with an additional 3 mL of THF. The reaction mixture was heated at reflux for 15 h, and then cooled to room temperature, diluted with 20 mL of 10% HCl solution, stirred for 15 min, and then poured into 40 mL of ether and 20 mL of 10% HCl solution. The aqueous phase was separated and extracted with two 20-mL portions of ether, and the combined organic layers were washed with 35 mL of water and 40 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to afford 1.421 g of an orange solid. Column chromatography on silica gel (gradient elution with 0-20% benzene in hexane) afforded 0.208 g (93%) of **65** as a clear, colorless liquid.

IR (thin film): 2960, 2920, 2860, 1600, 1590, 1490, 1460, 1440, 1375, 1290, 1240, 1175, 1110, 1050, 1035, and 750 cm^{-1}

^1H NMR (300 MHz, CDCl_3): 7.14 (m, 2 H), 6.85 (m, 2 H), 5.20 (t, $J = 7$ Hz, 1 H), 3.79 (s, 3 H), 2.60-2.65 (m, 2 H), 2.24-2.29 (m, 2 H), 1.68 (s, 3 H), and 1.57 (s, 3 H)

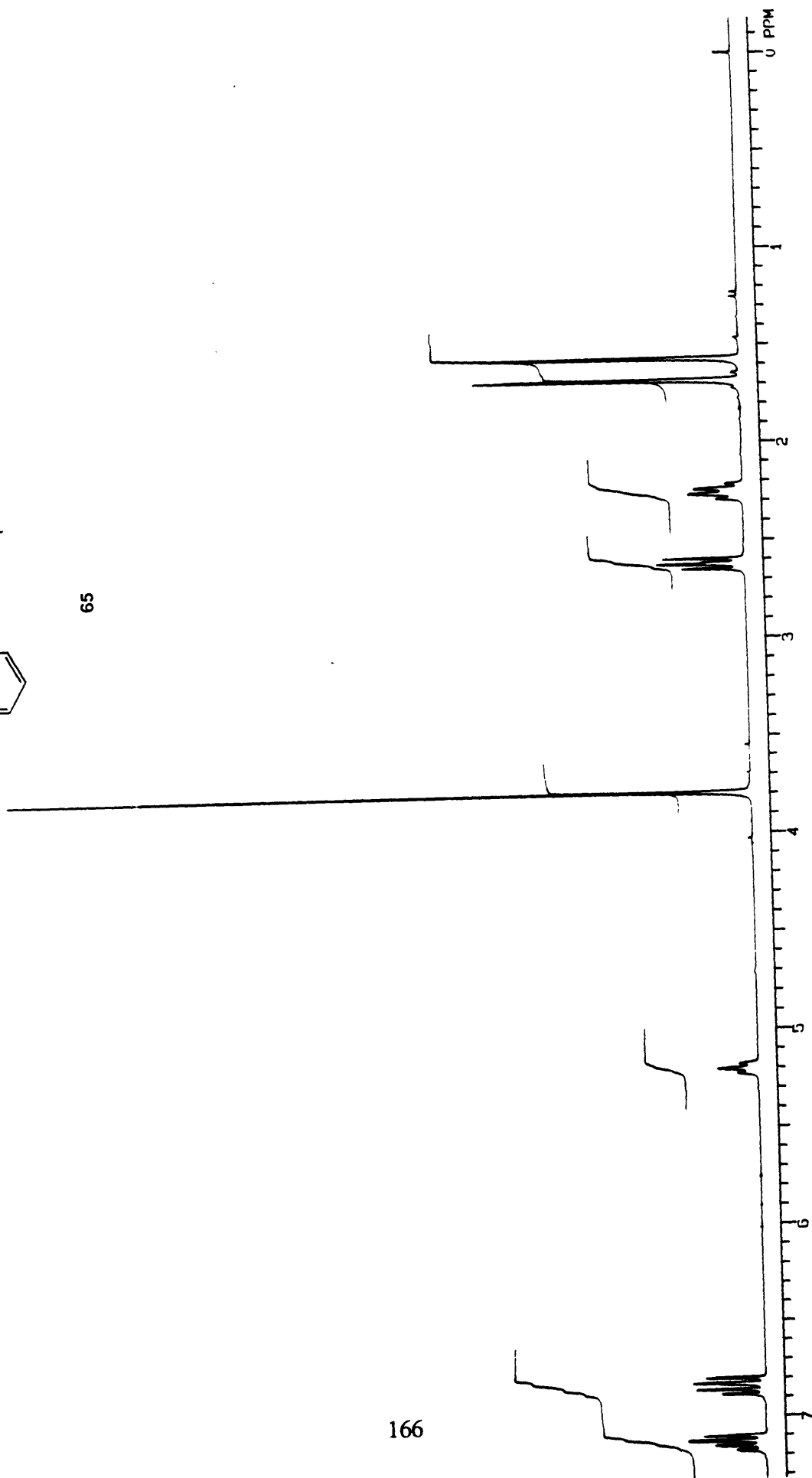
^{13}C NMR (75 MHz, CDCl_3): 157.5, 131.7, 130.8, 129.8, 126.9, 124.3, 120.3, 110.1, 55.2, 30.5, 28.3, 25.6, and 17.5

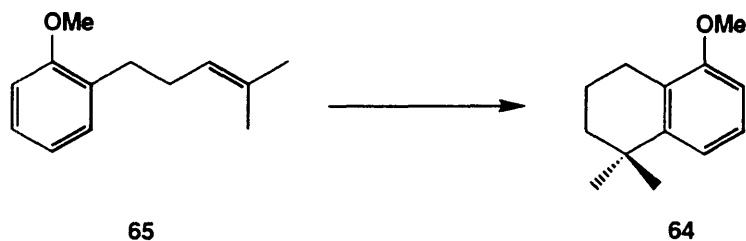
Elemental Analysis: Calcd for $\text{C}_{13}\text{H}_{18}\text{O}$: C, 82.06; H, 9.53
Found: C, 81.73; H, 9.79



65

166





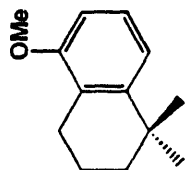
1,1-Dimethyl-5-methoxytetralin (64). A 500-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, glass stopper, and a rubber septum was charged with a solution of 1-(1'-methoxyphenyl)-4-methylpent-3-ene (**65**) (8.30 g, 43.7 mmol) in 230 mL of CH₂Cl₂ and cooled at 0 °C while AlCl₃ (5.81 g, 43.7 mmol) was added in one portion. The resulting orange solution was stirred at 0 °C for 20 min and then poured into 300 mL of ice-water. The aqueous phase was separated and extracted with two 100-mL portions of ether, and the combined organic phases were washed with two 100-mL portions of water, 150 mL of saturated NaHCO₃ solution, and 150 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to afford 7.72 g of a pale yellow oil. Column chromatography on 40 g of silica gel (elution with petroleum ether) furnished 7.14 g (86%)³¹⁷ of **64** as a clear, colorless oil, with spectral data consistent with that previously reported for this compound.⁴⁸

IR (thin film): 3080, 2940, 2870, 1580, 1460, 1440, 1385, 1360, 1345, 1315, 1250, 1150, 1065, 780, and 720 cm⁻¹

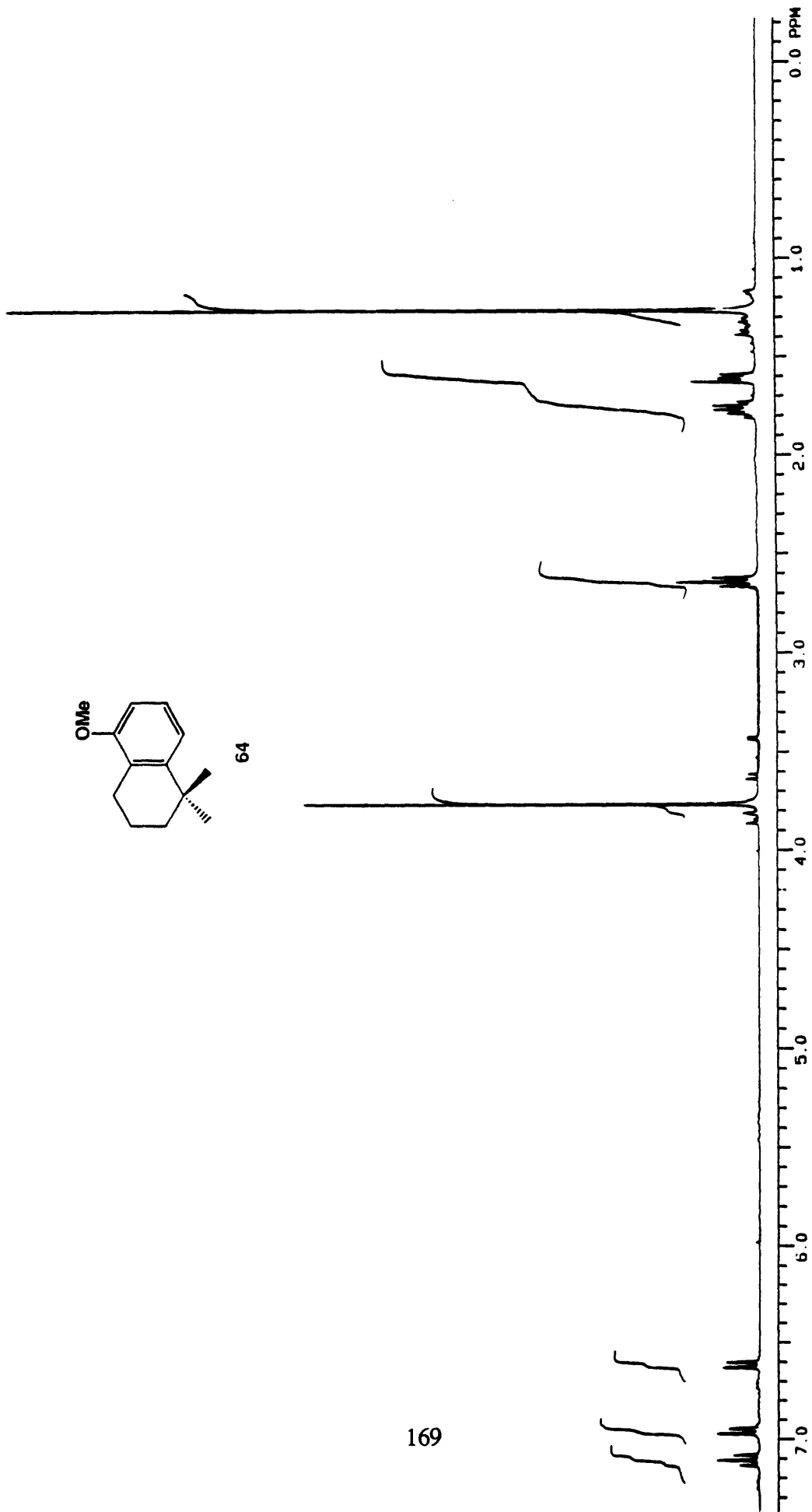
¹H NMR (300 MHz, CDCl₃): 7.11 (app t, J = 8 Hz, 1 H), 6.95 (dd, J = 1.5, 8 Hz, 1 H), 6.62 (dd, J = 1.5, 8 Hz, 1 H), 3.77 (s, 3 H), 2.65 (t, J = 6.4 Hz, 2 H), 1.74-1.82 (m, 2 H), 1.59-1.63 (m, 2 H), and 1.28 (s, 6 H)

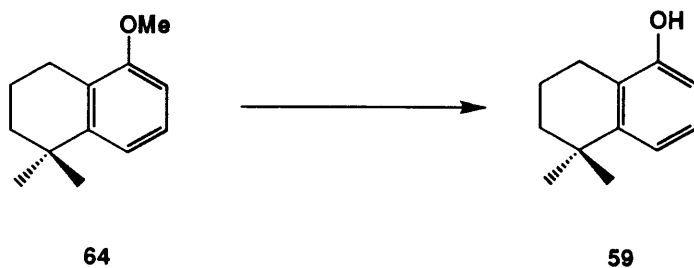
³¹⁷. In other runs the yield for this reaction ranged from 86-87%.

^{13}C NMR (75 MHz, CDCl_3): 156.8, 147.1, 125.8, 125.2, 118.7, 106.4, 55.2, 38.7, 33.8, 31.7, 23.9, and 18.9



64



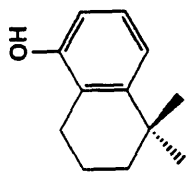


1,1-Dimethyl-5-tetralol (59) . A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, a glass stopper, and a pressure-equalizing dropping funnel was charged with a solution of 1,1-dimethyl-5-methoxytetralin (**64**) (6.75 g, 35.5 mmol) in 100 mL of CH₂Cl₂. The solution was cooled at -78 °C, and a solution of boron tribromide (1.0 M in CH₂Cl₂, 35.5 mL, 35.5 mmol) was added via the dropping funnel over ca. 40 min. The reaction mixture was allowed to warm to 25 °C over the course of 4 h. The resulting brown-red solution was then poured into 150 mL of water and 500 mL of ether. The aqueous layer was separated and extracted with two 50-mL portions of ether, and the combined organic phases were washed with 350 mL of saturated NaHCO₃ solution and 400 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to afford 5.65 g of a brown oil. Recrystallization from 75 mL of hexane provided 4.88 g of 1,1-dimethyl-5-tetralol **59** as white crystals. Concentration of the mother liquor and subsequent recrystallization afforded a total yield of 5.12 g (82%) of **59**: mp 111-112 °C (lit. 112.5-113.5)⁴⁴; spectral data was consistent with that previously reported for this compound.

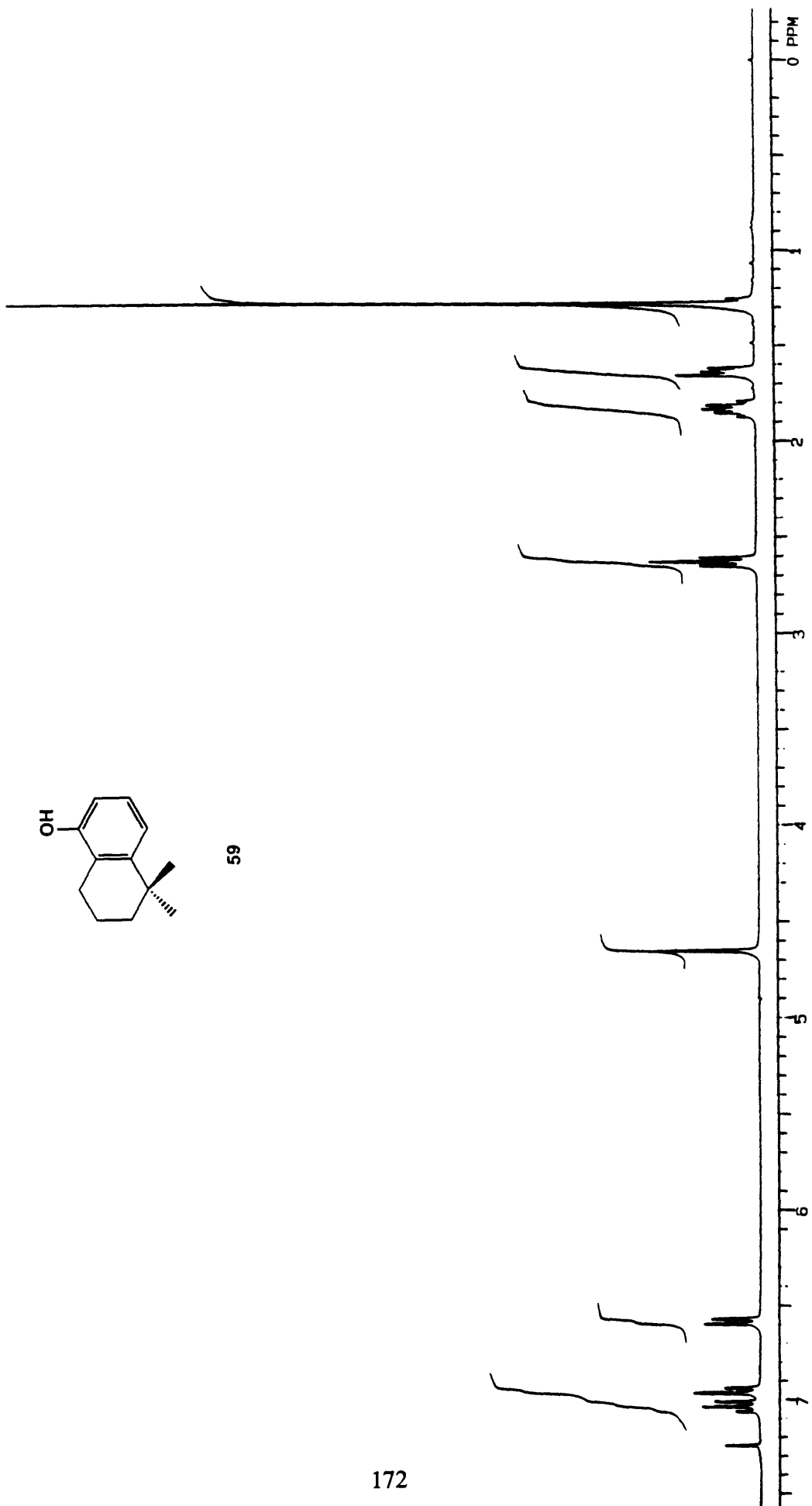
IR (CCl₄): 3400, 2980, 2975, 2860, 1575, 1450, 1360, 1250, 1200, and 1060 cm⁻¹

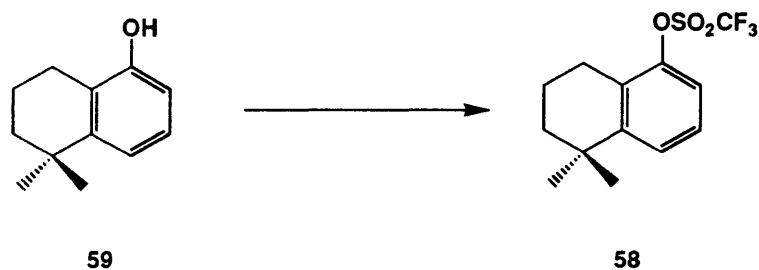
¹H NMR (300 MHz, CDCl₃): 7.03 (t, J = 8 Hz, 1 H), 6.95 (d, J = 8 Hz, 1 H), 6.59 (dd, J = 1, 8 Hz, 1 H), 4.65 (br s, 1 H), 2.63 (t, J = 6.4 Hz, 2 H), 1.81-1.85 (m, 2 H), 1.62-1.66 (m, 2 H), and 1.28 (s, 6 H)

^{13}C NMR (75 MHz, CDCl_3): 152.9, 147.6, 126.1, 122.5, 118.9, 111.4, 38.6,
33.8, 31.6, 23.5, and 18.7



59





1,1-Dimethyl-5-tetralyl trifluoromethanesulfonate (58). A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, a rubber septum, and a pressure-equalizing addition funnel was charged with a solution of 1,1-dimethyl-5-tetralol (**59**) (4.70 g, 26.7 mmol) and DMAP (3.26 g, 26.7 mmol) in 100 mL of pyridine and then cooled at 0 °C. After 20 min, trifluoromethanesulfonic anhydride (11.29 g, 6.73 mL, 40.0 mmol) was added dropwise via the addition funnel over 5 min. The reaction mixture was allowed to warm to 25 °C over 1 h and then stirred at 25 °C for 48 h. The resulting mixture was partitioned between 150 mL of 5% HCl solution and 150 mL of ether, and the aqueous phase was separated and extracted with three 75-mL portions of ether. The combined organic layers were washed with 150 mL of water, six 150-mL portions of half-saturated aqueous CuSO₄ solution, and 200 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to afford 7.18 g (87%)³¹⁸ of the triflate **58** as a yellow oil, which was used in the next step without further purification.

IR (thin film): 2960, 2930, 1610, 1570, 1470, 1450, 1420, 1360, 1340, 1250, 1210, 1140, 1110, 1070, 970, 960, 910, 820, 790, 780, 750, and 710 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 7.36 (d, J = 8 Hz, 1 H), 7.19 (t, J = 8 Hz, 1 H), 7.03 (d, J = 8 Hz, 1 H), 2.78 (t, J = 6 Hz, 2 H), 1.78-1.84 (m, 2 H), 1.65-1.68 (m, 2 H), 1.30 (s, 6 H)

³¹⁸. In other runs the yield for this reaction ranged from 86-87%.

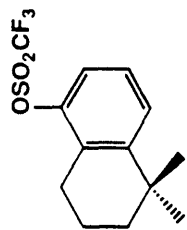
^{13}C NMR (75 MHz, CDCl_3)

149.4, 148.0, 129.5, 126.7, 120.7, 117.8, 116.5,
38.2, 34.1, 31.7, 24.5, and 18.5

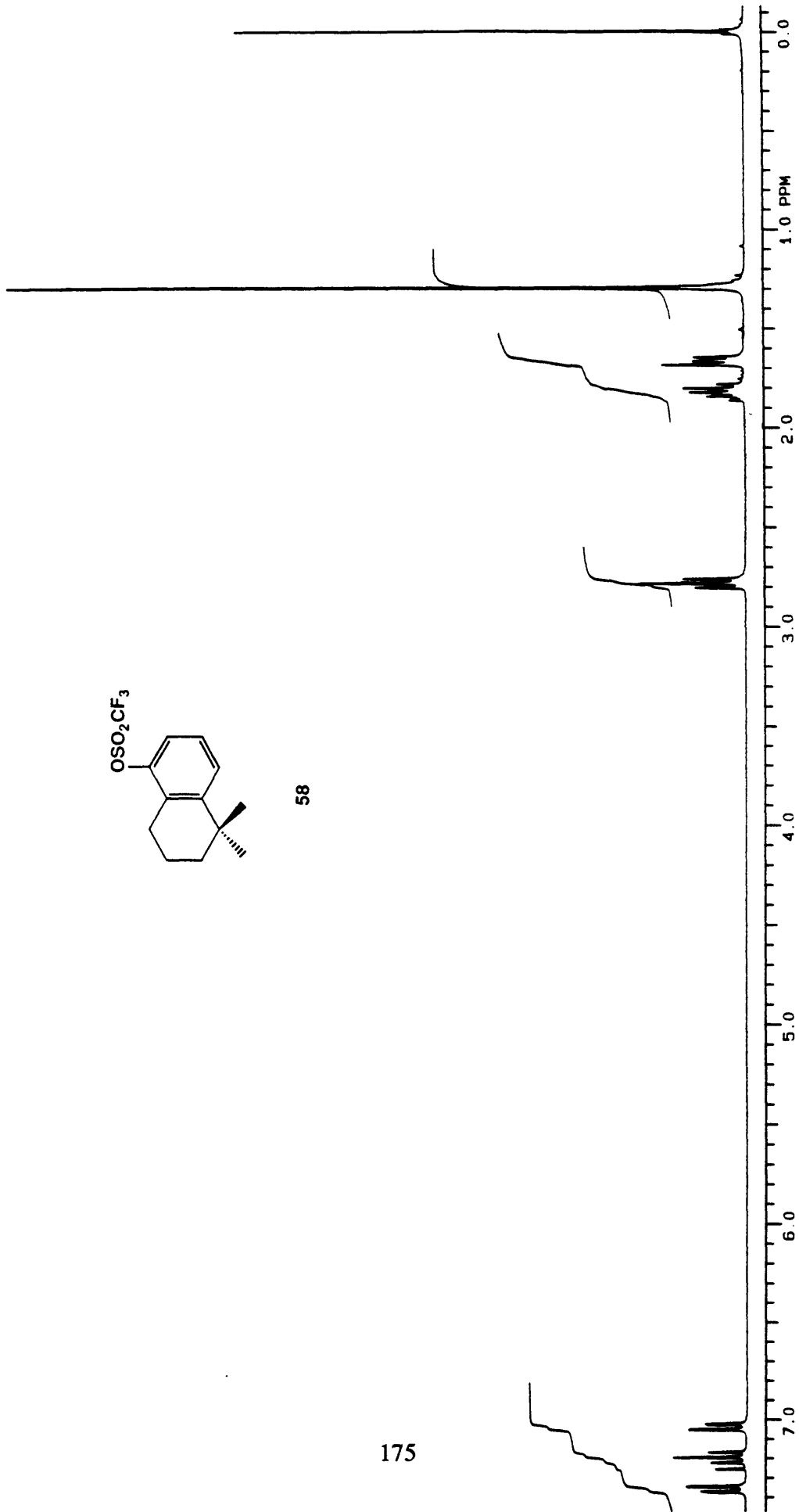
HRMS:

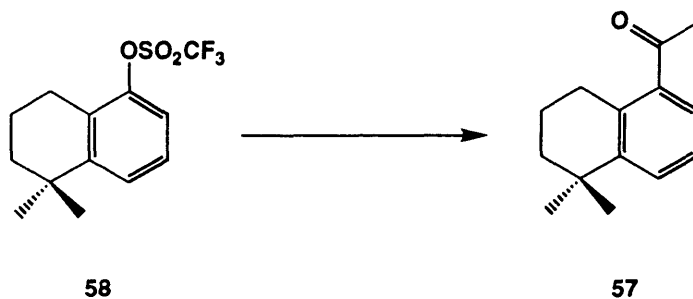
Calcd for $\text{C}_{13}\text{H}_{15}\text{F}_3\text{O}_3\text{S}$: 308.0694

Found: 308.0692



58





1-(5,5-Dimethyl-5,6,7,8-tetrahydro-1-naphthoyl)-1-ethanone (57). A 50-mL Fisher-Porter tube was charged with LiCl (0.800 g, 18.8 mmol) and 4 Å molecular sieves (0.400 g) and flame dried under vacuum. The tube was then charged via cannula with a solution of the triflate **58** (1.870 g, 6.07 mmol), tetramethyltin (1.25 g, 0.97 mL, 6.98 mmol), and 2,6-di-*tert*-butylhydroxytoluene (ca. 10 mg) in 8 mL of DMF. A solution of 1,1'-bis(diphenylphosphino)ferrocenylpalladium(II) chloride (0.262 g, 0.30 mmol) in 20 mL of DMF was then added, and the tube was sealed and pressurized to 50 psi with carbon monoxide. The reaction mixture was vented, repressurized with CO, and heated at 90 °C for 29 h. After cooling to room temperature, the tube was vented, opened, and the reaction mixture was diluted with 75 mL of ether and 100 mL of water. The aqueous phase was separated and extracted with two 75-mL portions of ether, and the combined organic layers were washed with 100 mL of half-saturated aqueous KF solution, two 100-mL portions of water, 125 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to afford 1.39 g of a red-brown oil. Column chromatography on silica gel (gradient elution with 0-5% ethyl acetate-petroleum ether) furnished 0.823 g (67%)³¹⁹ of the ketone **57** as cream-colored crystals: mp 30-31 °C.

IR (CCl₄): 3060, 2960, 2920, 2860, 1685, 1575, 1440, 1380, 1350, 1285, 1270, 1250, 1205, 1180, 1170, 1150, 1100, 1080, 1010, 980, 960, 945, 800, and 730 cm⁻¹

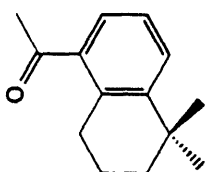
³¹⁹. In other runs the yield for this reaction ranged from 59-67%.

^1H NMR (300 MHz, CDCl_3): 7.46 (dd, $J = 1.2, 8$ Hz, 1 H), 7.37 (dd, $J = 1.2, 8$ Hz, 1 H), 7.21 (t, $J = 8$ Hz, 1 H), 2.90 (t, $J = 6$ Hz, 2 H), 2.55 (s, 3 H), 1.73-1.78 (m, 2 H), 1.64-1.68 (m, 2 H), and 1.30 (s, 6 H)

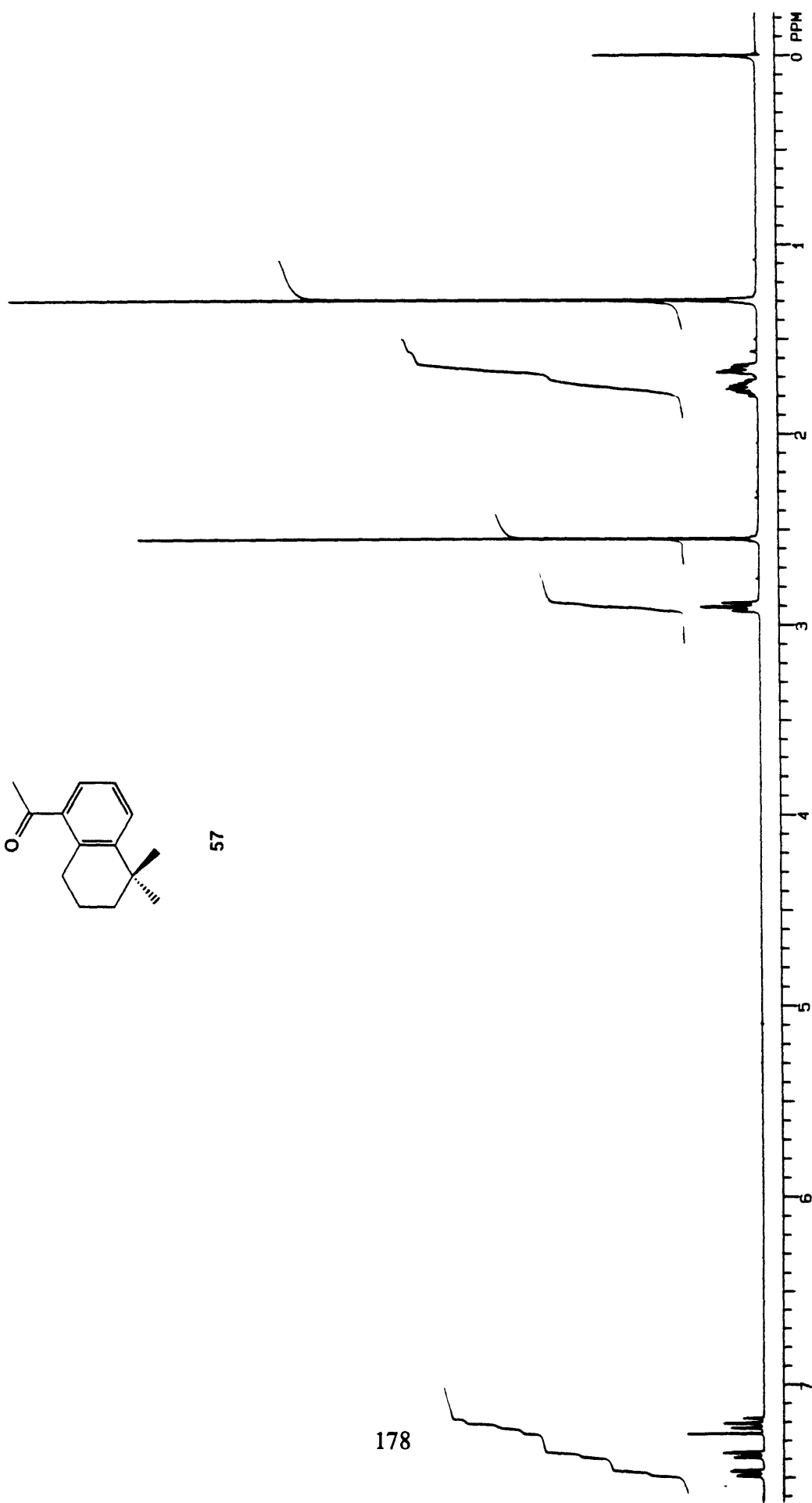
^{13}C NMR (75 MHz, CDCl_3): 203.4, 147.1, 138.9, 135.3, 129.9, 125.6, 125.2, 38.4, 34.1, 32.0, 30.2, 28.8, and 19.4

UV λ_{max} (CCl_4): 259 ($\epsilon = 1,300$) and 289 (890)

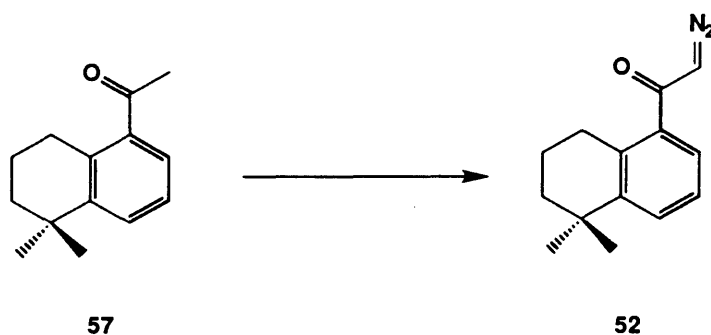
Elemental Analysis: Calcd for $\text{C}_{14}\text{H}_{18}\text{O}$: C, 83.12; H, 8.97
Found: C, 82.82; H, 8.58



57



178



2-Diazo-1-(5,5-dimethyl-5,6,7,8-tetrahydro-1-naphthyl)-1-ethanone (52). A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, a rubber septum, and a glass stopper was charged with a solution of 1,1,1,3,3,3-hexamethyldisilazane (1.132 g, 1.48 mL, 7.01 mmol) in 20 mL of tetrahydrofuran and cooled at 0 °C while *n*-butyllithium solution (2.50 M in hexane, 2.58 mL, 6.45 mmol) was added dropwise over ca. 2 min. The resultant solution of LiHMDS was stirred at 0 °C for 15 min and then cooled at -78 °C while a solution of ketone **57** (1.18 g, 5.83 mmol) in 9 mL of THF was added dropwise over 15 min. The solution of the resulting enolate was stirred at -78 °C for 35 min, after which time 2,2,2-trifluoroethyl trifluoroacetate (1.376 g, 0.94 mL, 7.02 mmol) was added in one portion. The reaction mixture was stirred at -78 °C for 45 min, and then poured into 50 mL of 1N HCl solution and 60 mL of ether. The aqueous phase was separated and extracted with 50 mL of ether, and the combined organic layers were washed with 40 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to afford a pale green oil, which was dissolved in 13 mL of acetonitrile and transferred to a 25-mL, one-neck flask equipped with a magnetic stir bar and a rubber septum. Water (0.11 g, 0.11 mL, 6.11 mmol), triethylamine (0.947 g, 1.22 mL, 8.75 mmol), and methanesulfonyl azide (1.407 g, 1.0 mL, 11.62 mmol) were added, and the resultant yellow solution was stirred at 25 °C for 6 h. The reaction mixture was concentrated and the residual oil was partitioned between 60 mL of Et₂O and 40 mL of 2N NaOH solution. The organic phase was washed with three

40-mL portions of 2N NaOH solution, three 30-mL portions of water, and 30 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to afford 1.63 g of a green oil. Column chromatography on silica gel (gradient elution with 2-4% ethyl acetate-hexane) provided 1.094g (82%) of the α -diazo ketone **52** as a yellow solid: mp 65-66 °C.

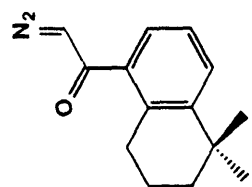
IR (CCl₄): 3080, 2960, 2940, 2870., 2100, 1620, 1585, 1450, 1350, 1270, 1240, 1210, 1180, and 1150 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 7.45 (dd, J = 2, 8 Hz, 1 H), 7.15 (m, 2 H), 5.52 (br s, 1 H), 2.92 (t, J = 6 Hz, 2 H), 1.75-1.80 (m, 2 H), 1.65-1.69 (m, 1 H), and 1.30 (s, 6 H)

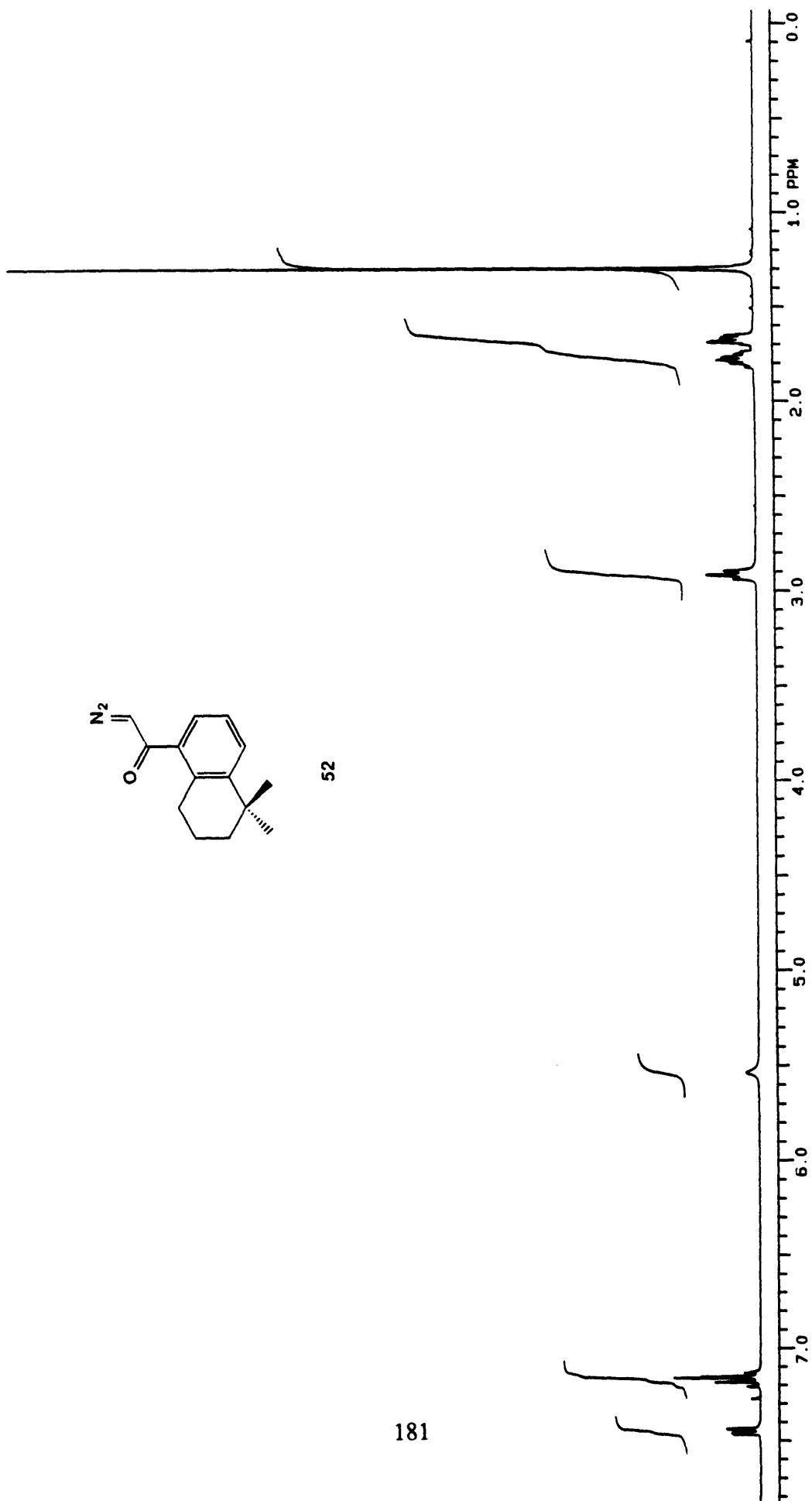
¹³C NMR (75 MHz, CDCl₃): 191.2, 147.1, 138.1, 134.3, 129.4, 125.4, 124.0, 56.5, 38.6, 34.2, 32.0, 28.2, 19.3

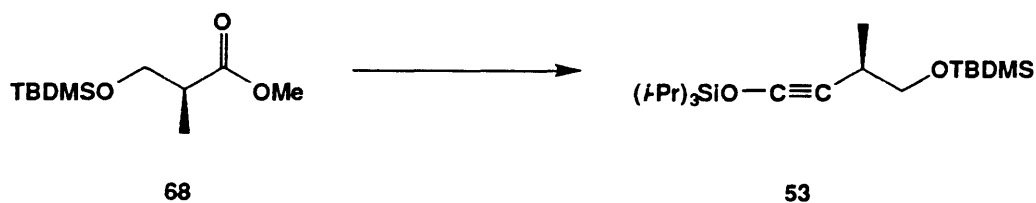
UV λ_{\max} (CCl₄): 258 (ϵ = 1,300) and 262 (12,300)

Elemental Analysis: Calcd for C₁₄H₁₅ON₂: C, 73.66; H, 7.06;
N, 12.27
Found: C, 73.90; H, 6.91;
N, 11.99



52





2-(*S*)-1-*tert*-Butyldimethylsilyloxy-2-propyl)-1-triisopropylsilyloxyacetylene

(53). A 500-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, and glass stopper was charged with a solution of dibromomethane (4.35 g, 1.75 mL, 25.0 mmol) in 35 mL of THF and cooled at $-78\text{ }^{\circ}\text{C}$. A 100-mL, three-necked flask equipped with an argon inlet adapter, a glass stopper, and a rubber septum was charged with a solution of 2,2,6,6-tetramethylpiperidine (4.08 g, 4.87 mL, 28.9 mmol) in 35 mL of THF and cooled at $0\text{ }^{\circ}\text{C}$ while *n*-butyllithium (2.46 M in hexane, 11.05 mL, 27.2 mmol) was added dropwise over ca. 5 min. The lithium tetramethylpiperidide solution was stirred at $0\text{ }^{\circ}\text{C}$ for 15 min, cooled at $-78\text{ }^{\circ}\text{C}$, and transferred via cannula into the dibromomethane solution over 10 min. The resulting bright yellow solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 15 min. A precooled ($-78\text{ }^{\circ}\text{C}$) solution of the ester **68** (2.71 g, 11.6 mmol) in 35 mL of THF was added dropwise via cannula over 10 min, and the resulting orange solution was stirred for 10 min at $-78\text{ }^{\circ}\text{C}$. *n*-Butyllithium (2.46 M in hexane, 22.7 mL, 55.8 mmol) was added over 10 min, and the reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 10 min, and then at $25\text{ }^{\circ}\text{C}$ for 45 min. The orange-brown solution was cooled at $-78\text{ }^{\circ}\text{C}$ while a precooled ($-78\text{ }^{\circ}\text{C}$) solution of triisopropylsilyl chloride (11.2 g, 12.5 mL, 58.3 mmol) in 35 mL of THF was added via cannula over 10 min. The reaction mixture was allowed to warm to $0\text{ }^{\circ}\text{C}$ and then stirred at $0\text{ }^{\circ}\text{C}$ for 5 h. The reaction mixture was diluted with 100 mL of hexane and 100 mL of saturated NaHCO_3 solution, and the aqueous phase was separated and extracted with two 100-mL portions of hexane. The combined organic phases were washed with 200 mL of saturated NaHCO_3 solution, 200 mL of water, and 200 mL of saturated NaCl solution,

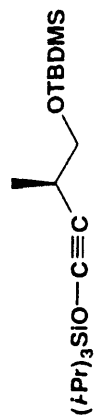
dried over Na₂SO₄, filtered, and concentrated initially at 20 mmHg and then at <0.005 mmHg for 12 h. Excess triisopropylsilyl chloride was then removed under vacuum (0.2 mmHg, 44-46 °C) and the resulting solution was placed under vacuum (<0.005 mmHg) for 48 h. Column chromatography on silica gel (elution with hexanes) afforded 1.35 g (31%) of the known silyloxyacetylene **53**¹⁹⁻²⁰ as a colorless oil: [α]_D²⁵ -2.64° (CHCl₃, *c* 0.65).

IR (thin film): 2950, 2900, 2860, 2280, 1465, 1380, 1360, 1330, 1305, 1260, 1130, 1110, 1090, 1040, 1010, 880, 840 and 770 cm⁻¹

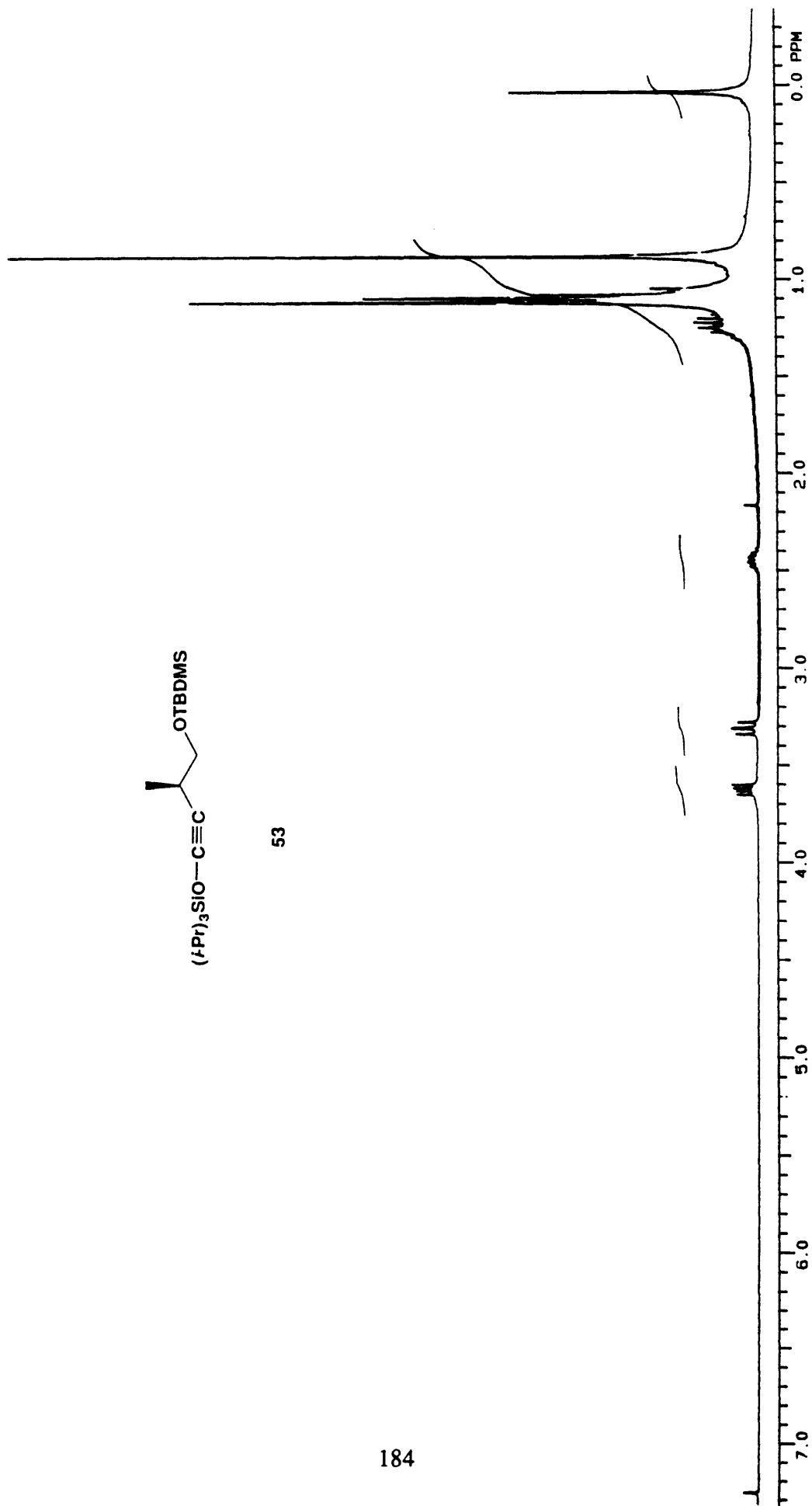
¹H NMR (300 MHz, CDCl₃): 3.63 (dd, *J* = 5, 10 Hz, 1 H), 3.31 (app t, *J* = 10 Hz, 1 H), 2.45 (m, 1 H), 1.26 (m, 3 H), 1.11 (d, *J* = 6 Hz, 18 H), 0.89 (s, 9 H), and 0.04 (s, 6 H)

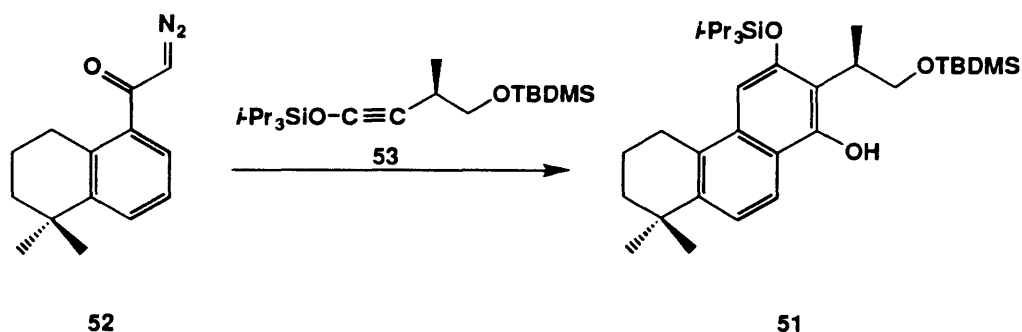
¹³C NMR (75 MHz, CDCl₃): 88.0, 68.4, 32.5, 27.7, 25.7, 18.5, 18.1, 17.1, 11.6, and -5.7.

HRMS: Calcd for C₁₆H₃₃O₂Si₂ (M⁺ -C₄H₉): 313.2017
Found: 313.2019



53





3-((*S*)-1-*tert*-butyldimethylsilyloxy-2-propyl)-7,7-dimethyl-4-hydroxy-2-triisopropylsilyl-oxy-7,8,9,10-tetrahydrophenanthrene (51). A solution of the α -diazo ketone **52** (0.817 g, 3.58 mmol), siloxyacetylene **53** (2.00 g, 5.87 mmol), and 50 mL of benzene was distributed equally between four 20-cm Vycor tubes (15 mm I.D.) fitted with rubber septa. The reaction mixtures were degassed (three freeze-pump-thaw cycles at $-196\text{ }^{\circ}\text{C}$, ca. 0.1 mmHg) and then irradiated with 253.7 nm light for 24 h in a Rayonet photoreactor. The contents of the tubes were then combined in a 100-mL pear-shaped flask and concentrated to afford 3.34 g of an orange oil. Column chromatography on silica gel (gradient elution with 0-5% methylene chloride-hexane) furnished 1.31 g (64%)³²⁰ of **51** as off-white crystals: mp $145\text{-}147\text{ }^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{25} -10.2$ (CHCl_3 , c 1.34).

IR (CCl_4): 3600-3300, 3300-3150, 2925, 2850, 1620, 1590, 1560, 1500, 1460, 1400, 1360, 1320, 1300, 1260, 1230, 1200, 1120, 1080, 1000, 940, 920, 880, 840, and 780 cm^{-1}

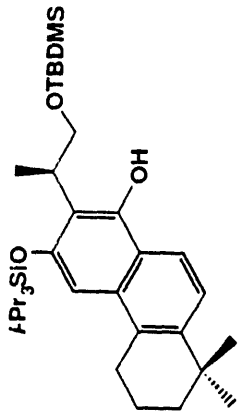
^1H NMR (300 MHz, CDCl_3): 9.72 (s, 1 H), 8.05 (d, $J = 9\text{ Hz}$, 1 H), 7.29 (d, $J = 9\text{ Hz}$, 1 H), 6.83 (s, 1 H), 4.00 (br s, 2 H), 3.94 (m, 1 H), 2.90 (app t, $J = 6\text{ Hz}$, 2 H), 1.91-1.95 (m, 2 H), 1.68-1.72 (m, 2 H), 1.38 (d, $J = 7\text{ Hz}$, 3 H), 1.33, (s, 6 H), 1.14 (d, $J = 7\text{ Hz}$, 18 H), 0.98 (s, 9 H), 0.18 (s, 3 H), and 0.13 (s, 3 H)

³²⁰. In other runs the yield for this reaction ranged from 55-65%.

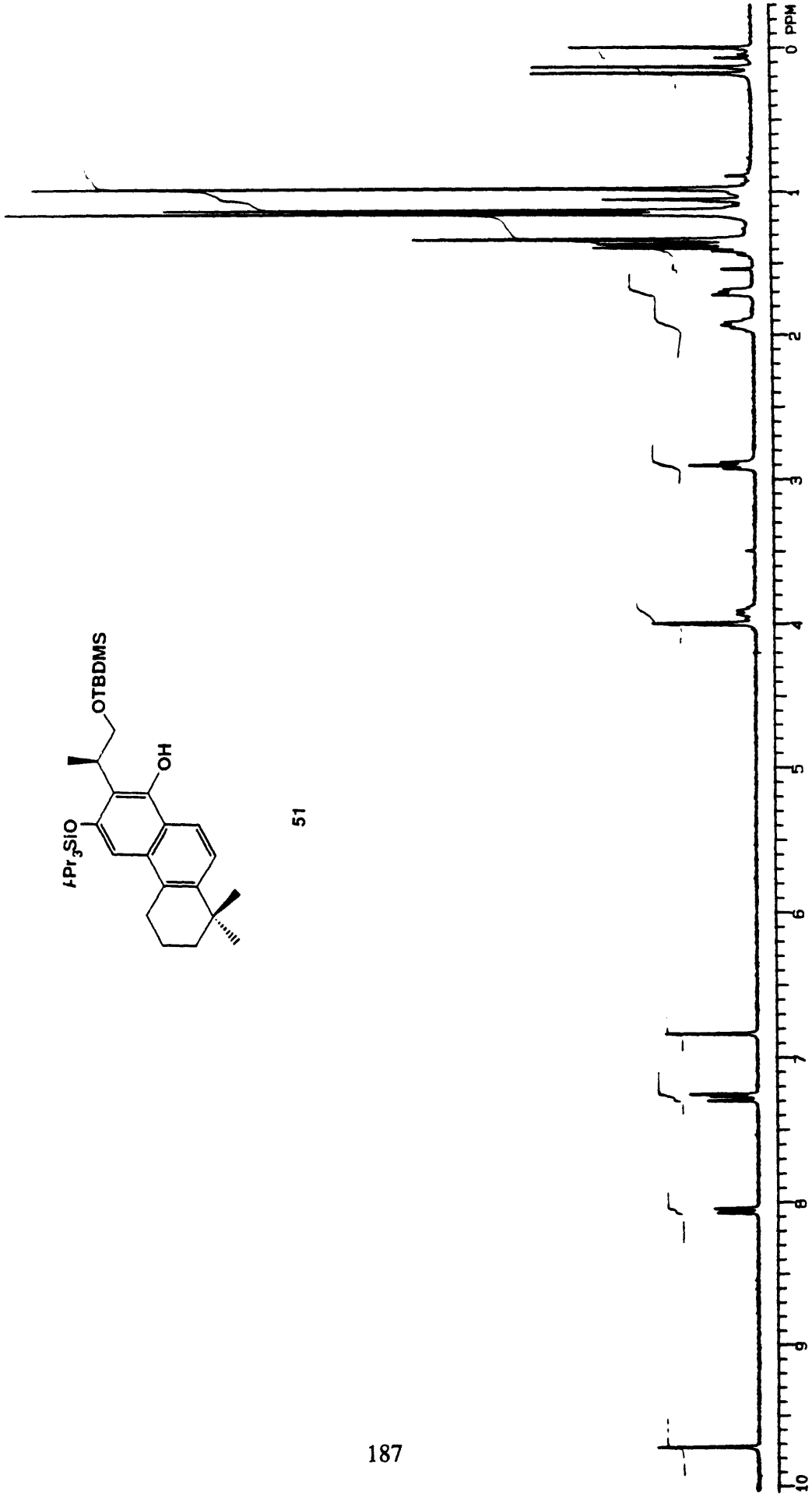
^{13}C NMR (75 MHz, CDCl_3): 153.3, 152.7, 143.1, 132.5, 128.3, 121.7, 120.7, 120.0, 117.3, 101.7, 69.3, 38.8, 33.9, 31.4, 31.2, 26.8, 25.7, 19.4, 18.2, 18.0, 14.8, 12.9, and -5.9.

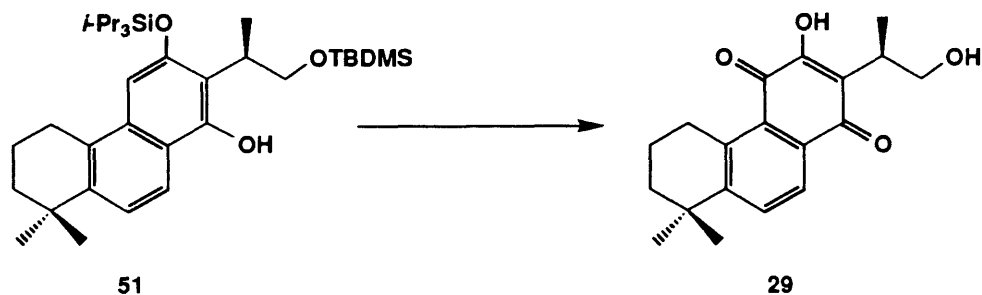
UV λ_{max} (CCl_4): 257 ($\epsilon = 10,000$), 260 (8,300), and 285 (4,200)

HRMS: Calcd for $\text{C}_{34}\text{H}_{58}\text{O}_3\text{Si}_2$: 570.3925
Found: 570.3923



51





7,7-Dimethyl-2-hydroxy-3-((*S*)-1-hydroxy-2-propyl)-7,8,9,10-tetrahydro-1,4-phenanthrenquinone (29, (+)-neocryptotanshinone). A 25-mL, pear-shaped flask fitted with a rubber septum was charged with a solution of the phenol **51** (0.585 g, 1.03 mmol) in 15 mL of THF and cooled at -78 °C. Tetra-*n*-butylammonium fluoride solution (1.0 M in THF, 2.25 mL, 2.25 mmol) was then added dropwise over 5 min, and oxygen was bubbled into the reaction mixture via a syringe needle. The cooling bath was removed and the reaction mixture was allowed to warm to 25 °C. The resulting dark red solution was stirred at 25 °C for 40 h, while oxygen was continued to be bubbled into the solution, and then poured into 100 mL of 10% aqueous HCl solution and 100 mL of CH₂Cl₂. The aqueous phase was separated and extracted with two 50-mL portions of CH₂Cl₂, and the combined organic layers were washed with 100 mL of 10% HCl solution, 100 mL of water, and 100 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to afford 0.656 g of a red oil. Column chromatography on silica gel (gradient elution with 1-20% ethyl acetate-methylene chloride) provided 0.270 g (84%)³²¹ of (+)-neocryptotanshinone (**29**) as a bright yellow solid: mp 163-165 °C (lit. 165-167 °C);²⁹ [α]_D²⁵ +29.2° (CHCl₃, *c* 0.73) (lit. [α]_D²⁵ +29.8° (CHCl₃, *c* 0.84)).²⁹

IR (CCl₄): 3330, 2970, 2940, 2870, 1770, 1660, 1570, 1465, 1420, 1385, 1330, 1295, 1265, 1205, 1030, and 955 cm⁻¹

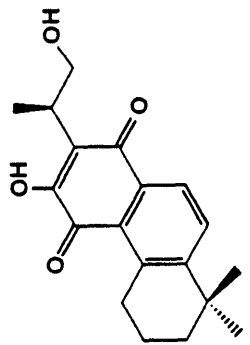
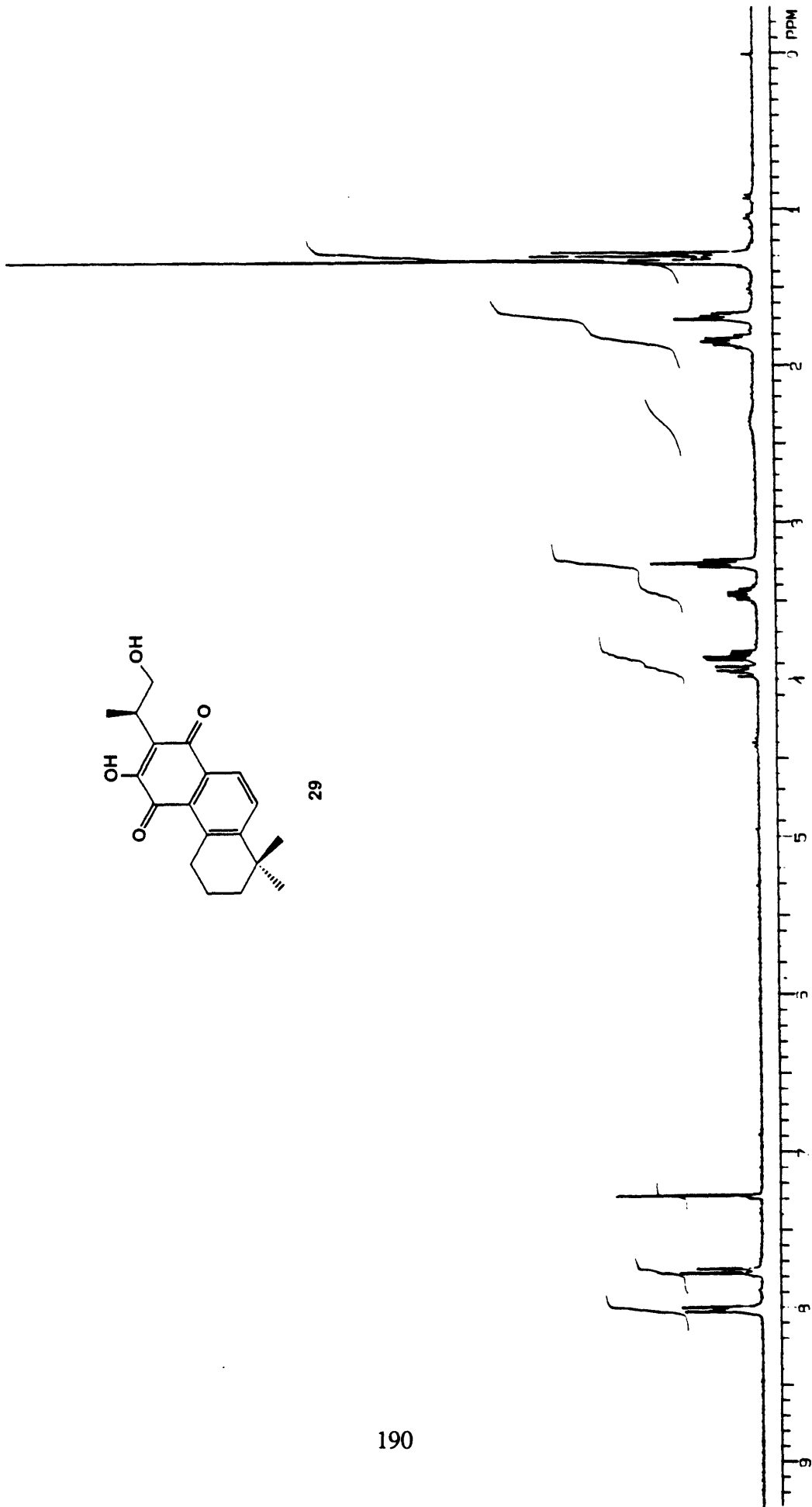
³²¹. In other runs the yield for this reaction ranged from 82-84%.

^1H NMR (300 MHz, CDCl_3): 8.00 (d, $J = 8$ Hz, 1 H), 7.75 (d, $J = 8$ Hz, 1 H), 7.27 (br s, 1H), 3.94 (dd, $J = 8, 11$ Hz, 2 H), 3.84 (dd, $J = 5, 11$ Hz, 1 H), 3.45 (ddq, $J = 5, 7, 8$ Hz, 1 H), 3.25 (t, $J = 6$ Hz, 2 H), 1.80-1.86 (m, 2 H), 1.66-1.70 (m, 2 H), 1.32 (s, 6 H), and 1.28 (d, $J = 7$ Hz, 3 H)

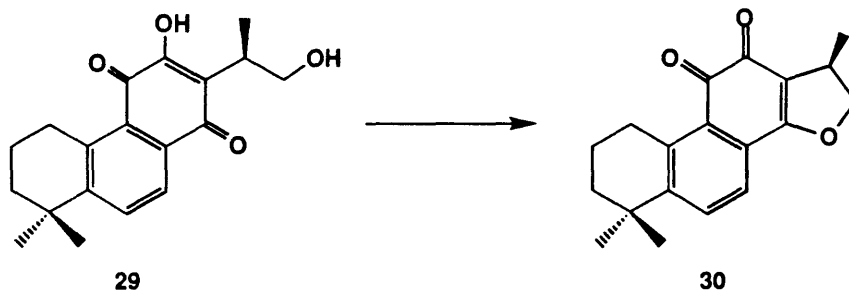
^{13}C NMR (75 MHz, CDCl_3): 185.4, 182.8, 154.0, 152.9, 140.9, 133.5, 132.5, 126.3, 125.1, 122.9, 65.5, 37.8, 34.8, 33.0, 31.7, 29.9, 19.0, and 14.5

UV λ_{max} (CCl_4): 256 ($\epsilon = 14,100$), 274 (20,400), and 345 (3,000)

Elemental Analysis: Calcd for $\text{C}_{19}\text{H}_{22}\text{O}_4$: C, 72.59; H, 7.05
Found: C, 72.81; H, 7.24



29



8,8-Dimethyl-3-(S)-methyl-3,4,8,9,10,11-octahydro-[3,2-c]-furophenanthra-1,2-dione (30, (-)-cryptotanshinone). A 25-mL, pear-shaped flask was charged with a solution of (+)-neocryptotanshinone (**29**) (0.126 g, 0.401 mmol) in 5 mL of ethanol. Concentrated H₂SO₄ (3 mL) was then added dropwise over 10 min (caution: exothermic reaction), and the resulting dark red solution was stirred for 45 min at 25 °C. The reaction mixture was then poured into 50 mL of water and 50 mL of ether. The aqueous phase was separated and extracted with two 50-mL portions of ether, and the combined organic layers were washed with two 80-mL portions of 5% HCl solution, 80 mL of saturated NaHCO₃ solution, and 80 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to afford 0.214 g of an orange solid. Column chromatography on 8 g of silica gel (gradient elution with 0-20% ethyl acetate-methylene chloride) provided 0.118 g (100%) of (-)-cryptotanshinone (**30**) as orange-red crystals: mp 188-190 °C (lit 191-192 °C);³⁰ [α]_D²⁵ -84.5° (CHCl₃, *c* 1.82) (lit. [α]_D²⁵ -79.9° (CHCl₃, *c* 0.18)).³⁰

IR (CCl₄): 2870, 2840, 2780, 1660, 1625, 1560, 1470, 1410, 1370, 1340, 1305, 1260, 1205, 1175, 1160, and 950 cm⁻¹

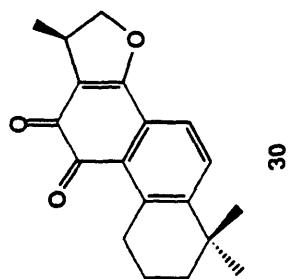
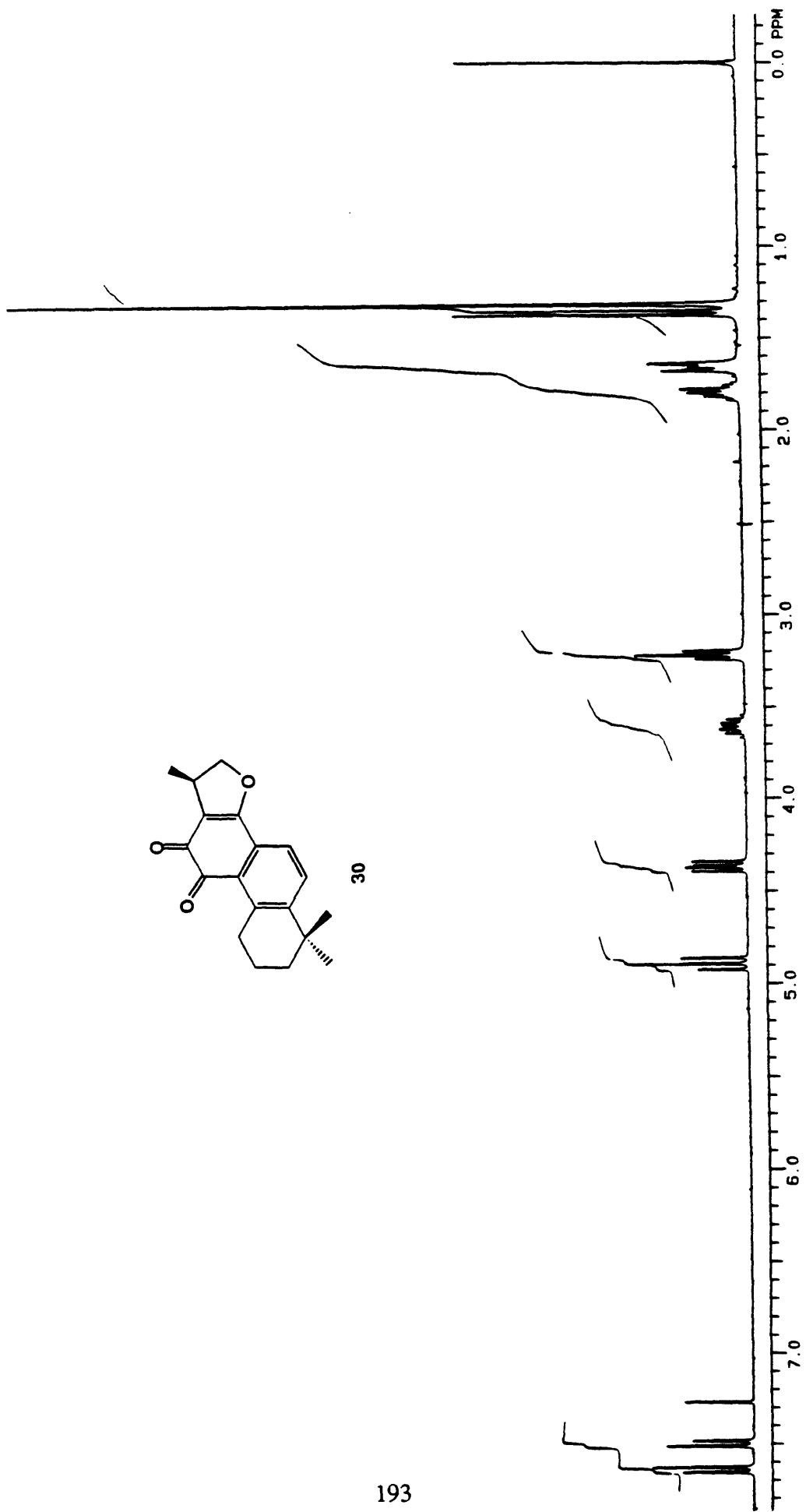
¹H NMR (300 MHz, CDCl₃): 7.64 (d, *J* = 8 Hz, 1 H), 7.51 (d, *J* = 8 Hz, 1 H), 4.89 (app t, *J* = 9 Hz, 1 H), 4.38 (dd, *J* = 6, 9 Hz, 1 H), 3.60 (ddq, *J* = 6, 7, 9 Hz, 1 H), 3.22 (t, *J* =

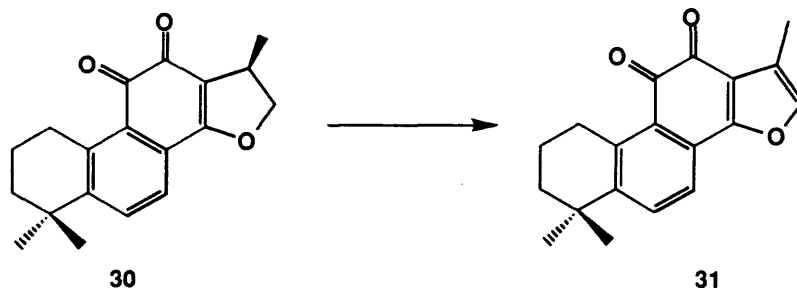
7 Hz, 2 H), 1.76-1.84 (m, 2 H), 1.64-1.69 (m, 2 H), 1.36 (d, $J = 7$ Hz, 3 H), and 1.31 (s, 6 H)

^{13}C NMR (75 MHz, CDCl_3): 184.2, 175.6, 170.8, 152.3, 143.7, 132.5, 128.3, 126.2, 122.5, 118.3, 81.4, 37.8, 34.8, 34.6, 31.9, 29.6, 19.0, and 18.8

UV λ_{max} (CCl_4): 218 ($\epsilon = 19,500$), 262 (28,800), 270 (22,900), 290 (7100), and 353 (2,800)

Elemental Analysis: Calcd for $\text{C}_{19}\text{H}_{20}\text{O}_3$: C, 77.00; H, 6.80
Found: C, 77.21; H, 6.78





8,9,10,11-Tetrahydro-3,8,8-trimethyl-[3,2-c]-furophenanthra-1,2-dione (31, tanshinone IIA). A 25-mL, two-necked, pear-shaped flask equipped with an argon inlet adapter and a rubber septum was charged with DDQ (0.220 g, 0.971 mmol), (-)-cryptotanshinone (0.115 g, 0.389 mmol), and 10 mL of benzene. The reaction mixture was stirred at 25 °C for 42 h, and then filtered and concentrated to afford 0.416 g of a dark brown-red solid. Column chromatography on silica gel (gradient elution with 0-75% chloroform-benzene) furnished 0.104 g (91%) of tanshinone IIA (**31**) as red crystals: mp 199-200 °C (lit. 196-198 °C).³⁰

IR (CCl₄): 3140, 2960, 2840, 2780, 1690, 1670, 1640, 1585, 1540, 1465, 1430, 1410, 1390, 1370, 1290, 1200, 1170, 1150, 1080, 1030, 1000, 970, 925, and 840 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 7.63 (d, J = 8 Hz, 1 H), 7.55 (d, J = 8 Hz, 1 H), 7.22 (q, J = 1.3 Hz, 1 H), 3.18 (t, J = 6 Hz, 2 H), 2.26 (d, J = 1.3 Hz, 3 H), 1.78-1.82 (m, 2 H), 1.64-1.68 (m, 2 H), and 1.31 (s, 6 H)

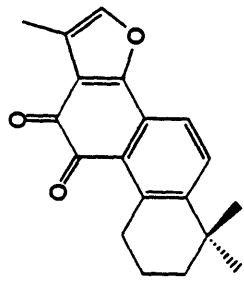
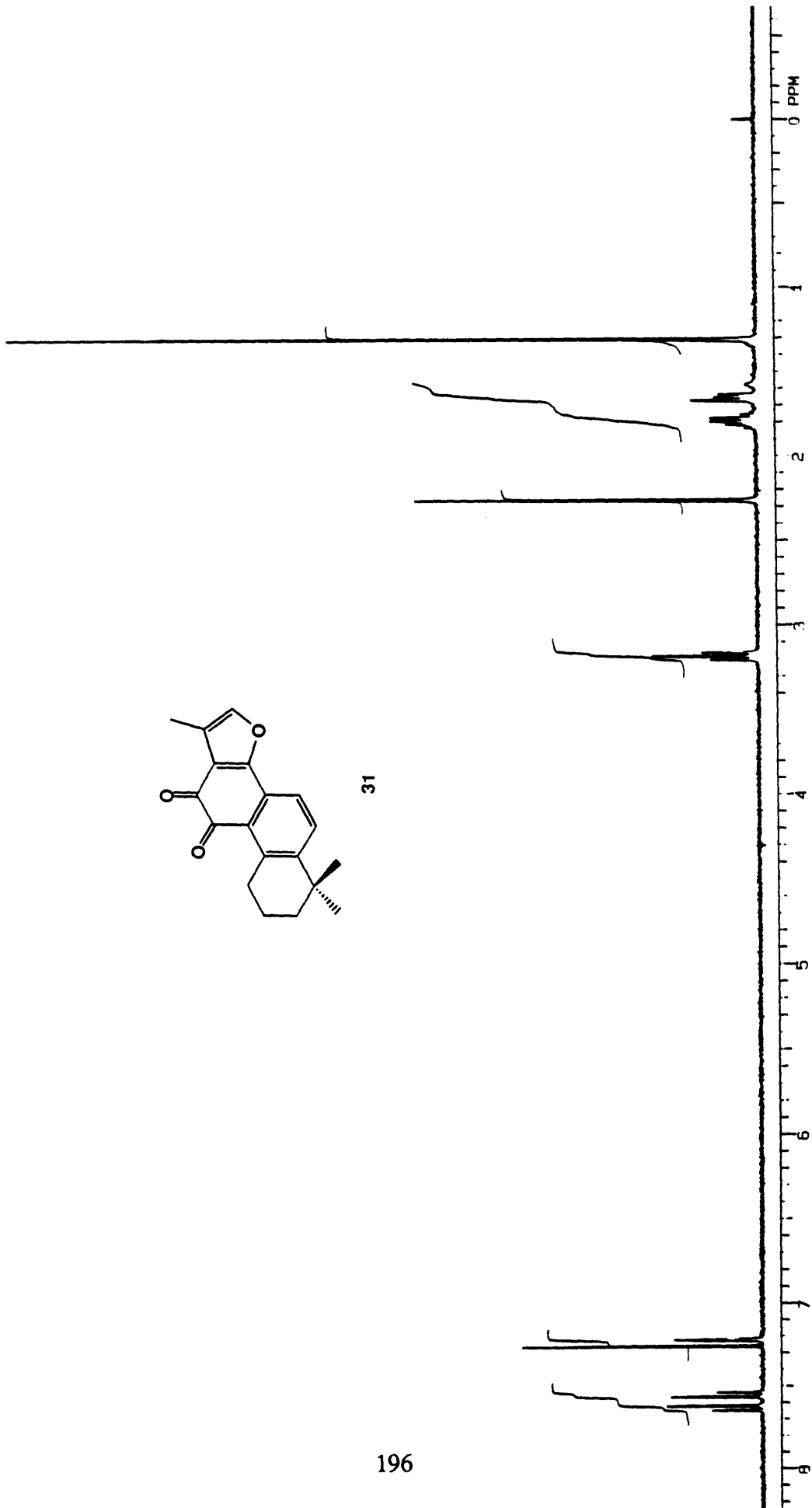
¹³C NMR (75 MHz, CDCl₃): 183.6, 175.8, 161.7, 150.1, 144.5, 141.3, 133.5, 127.5, 126.5, 121.1, 120.3, 119.9, 37.8, 34.7, 31.8, 29.9, 19.1 and 8.8

UV λ_{max} (CCl₄): 220 (ε = 28,800), 250 (25,100), and 269 (27,500)

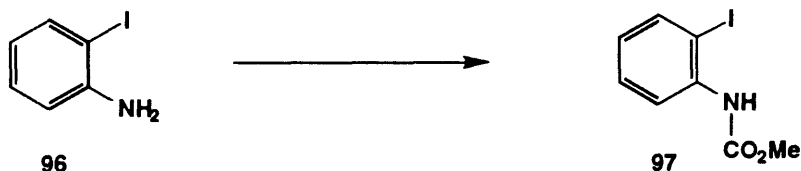
Elemental Analysis:

Calcd for $C_{19}H_{18}O_3$: C, 77.53 ; H, 6.16.

Found: C, 77.40 ; H, 6.19



31



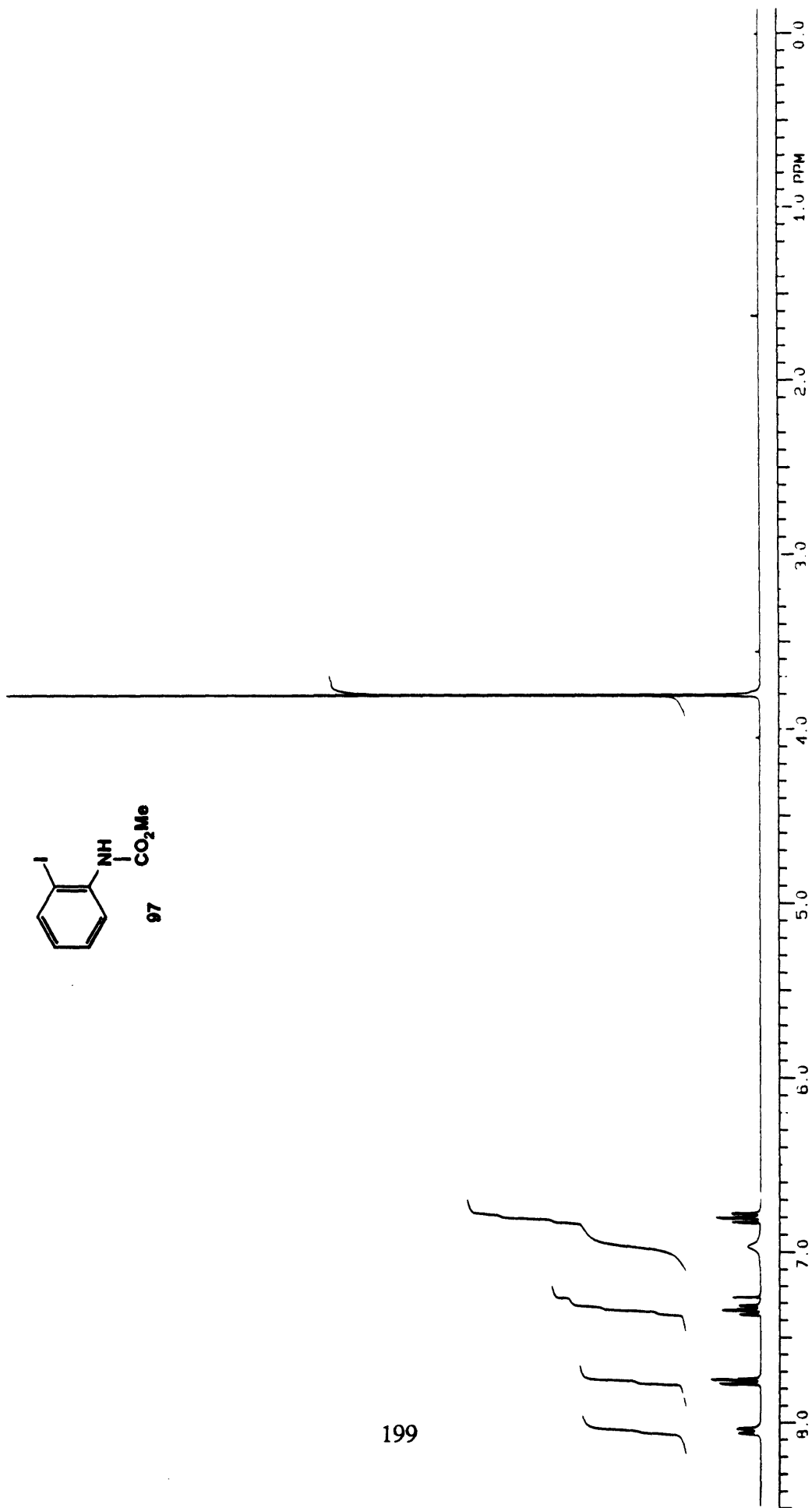
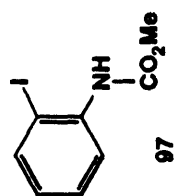
N-(Methoxycarbonyl)-2-iodoaniline (97). A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, a glass stopper, and an argon inlet was charged with 2-iodoaniline (1.50 g, 6.85 mmol), pyridine (0.67 mL, 0.65 g, 8.22 mmol), and 18 mL of CH₂Cl₂. The solution was cooled at 0 °C, and methyl chloroformate (0.79 mL, 0.97 g, 10.3 mmol) was added dropwise over 3 min. The reaction mixture was stirred at 0 °C for 15 min, allowed to warm to room temperature over 20 min, and quenched with 20 mL of 1 M HCl. The reaction mixture was then transferred to a separatory funnel with the aid of 100 mL of CH₂Cl₂ and 80 mL of water. The aqueous layer was separated and extracted with two 30-mL portions of CH₂Cl₂, and the combined organic phases were washed with 50 mL of water, 50 mL of saturated NaHCO₃ solution, and 50 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to give 2.0 g of a brown solid. Column chromatography on 15 g of silica gel (elution with 5% ethyl acetate-hexane) produced 1.77 g (94%)³²² of **97** as a white solid, mp 57-58 °C, with spectral data consistent with that previously reported for this compound.¹²⁶

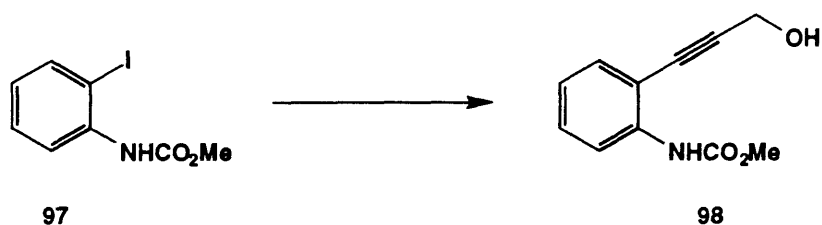
IR (CCl₄): 3390, 2950, 1745, 1585, 1570, 1510, 1440, 1420, 1300, 1280, 1240, 1210, 1120, 1070, 1030, 1010, and 950 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 8.05 (br d, J = 8 Hz, 1 H), 7.75 (dd, J = 1.5, 7.6 Hz, 1 H), 7.34 (td, J = 1.5, 7 Hz, 1 H), 6.95 (br s, 1 H), 6.80 (td, J = 1.5, 7.6 Hz, 1 H), and 3.81 (s, 3H)

³²² In other runs the yield for this reaction ranged from 88-94%.

^{13}C NMR (75 MHz, CDCl_3): 153.8, 138.8, 138.3, 129.2, 125.0, 120.3, 88.8,
and 52.5





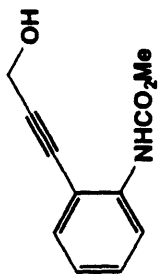
N-(Methoxycarbonyl)-2-(3-hydroxy-1-propynyl)aniline (#). A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, a glass stopper, and an argon inlet was charged with N-(methoxycarbonyl)-2-iodoaniline (**97**) (0.290 g, 1.05 mmol), propargyl alcohol (0.07 mL, 0.07 g, 1.26 mmol), and 10 mL of Et₂NH. PdCl₂(PPh₃)₂ (0.015 g, 0.021 mmol) and CuI (0.002 g, 0.011 mmol) were added, and the reaction mixture was stirred at room temperature for 20 h. The solvent was then removed by rotary evaporation, and the residue was partitioned between 50 mL of water and 50 mL of ether. The aqueous layer was separated and extracted with two 30-mL portions of ether, and the combined organic phases were washed with 30 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to give 0.288 g of a brown oil. Column chromatography on 6 g of silica gel (elution with 30% ethyl acetate-hexane) produced 0.214 g (100%)³²³ of the propargylic alcohol **98** as a brown solid, mp 59-60 °C, with spectral data consistent with that previously reported for this compound.¹²⁶

IR (CHCl₃): 3600, 3410, 3050, 2960, 2870, 2220, 1730, 1585, 1520, 1455, 1350, 1310, 1220, 1120, 1070, 1020, 950, and 840 cm⁻¹

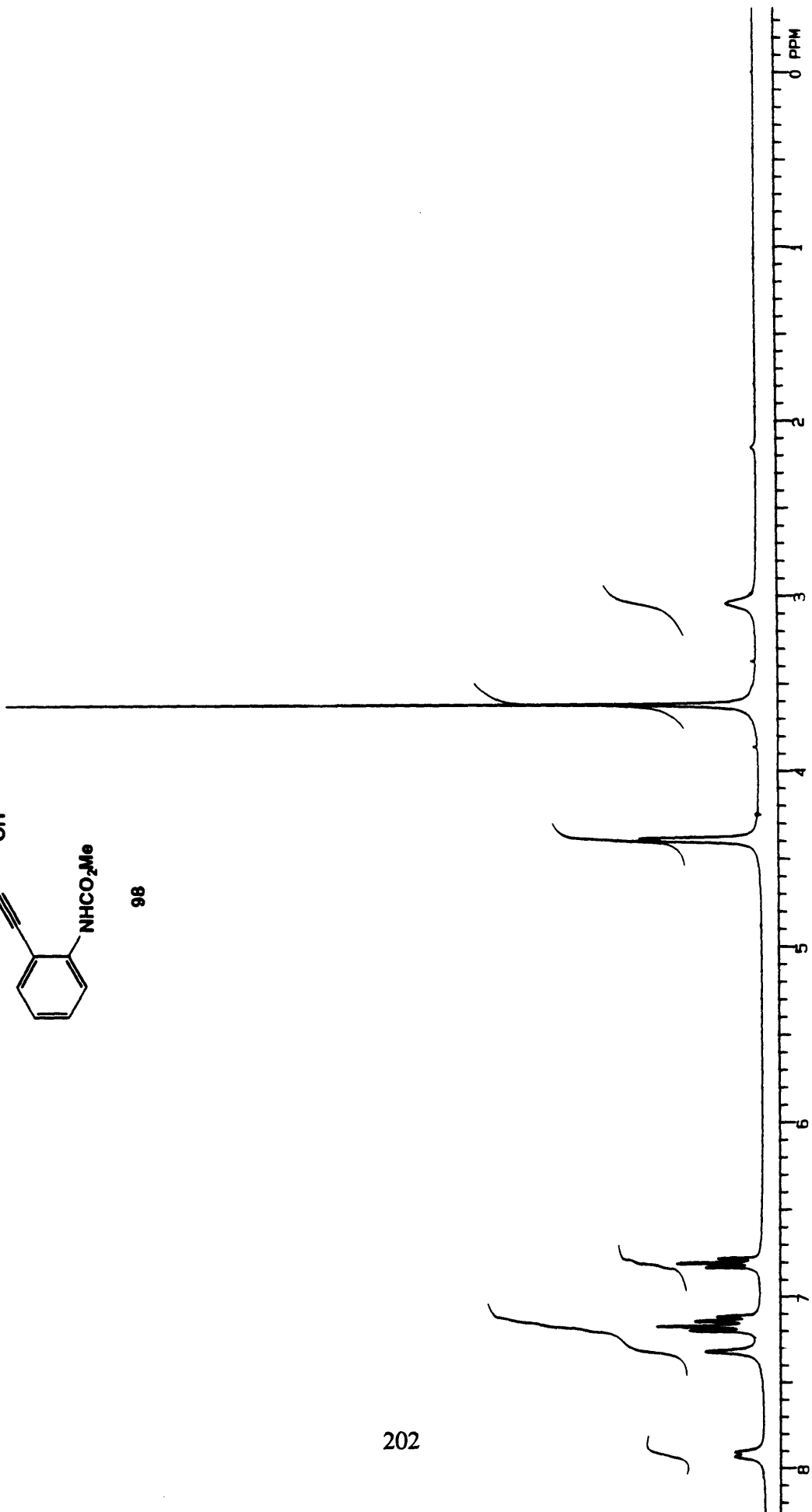
¹H NMR (300 MHz, CDCl₃): 7.92 (br d, J = 8 Hz, 1 H), 7.32 (br s, 1 H), 7.17 (ddd, J = 1.5, 7.5, 7.5 Hz, 1 H), 7.13 (dd, J = 1.5, 7 Hz, 1 H), 6.80 (td, J = 1.1, 7.6 Hz, 1 H), 4.39 (d, J = 3.8 Hz, 2 H), 3.62 (s, 3 H), and 3.04 (br s, 1H)

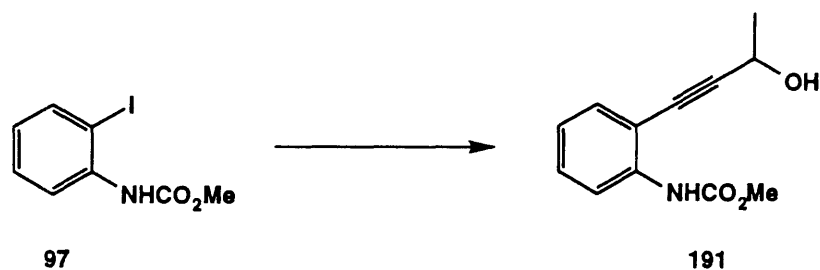
³²³. In other runs the yield for this reaction ranged from 95-100%.

^{13}C NMR (75 MHz, CDCl_3): 154.0, 139.0, 132.0, 129.8, 122.7, 118.0, 111.0,
94.4, 80.6, 52.5, and 51.3



98





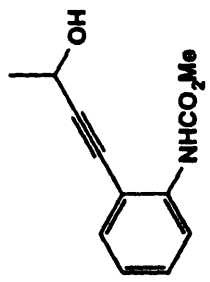
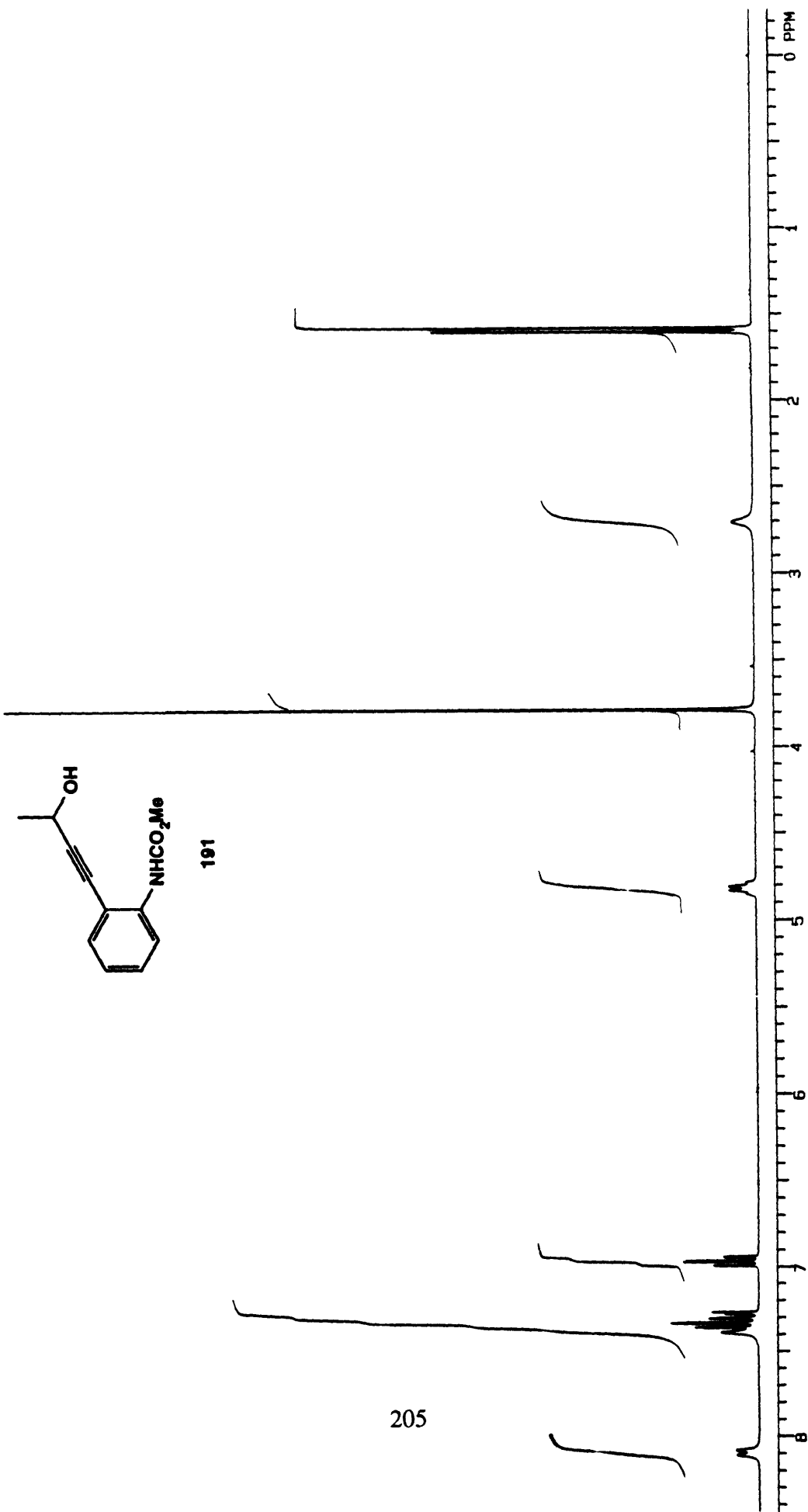
N-(Methoxycarbonyl)-2-(3-hydroxy-1-butynyl)aniline (191). A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, a glass stopper, and an argon inlet was charged with N-(methoxycarbonyl)-2-iodoaniline (**97**) (1.31 g, 4.73 mmol), 3-butyn-2-ol (0.44 mL, 0.397 g, 5.67 mmol), and 40 mL of Et₂NH. PdCl₂(PPh₃)₂ (0.100 g, 0.14 mmol) and CuI (0.018 g, 0.090 mmol) were added, and the reaction mixture was stirred at room temperature for 24 h. The solvent was then removed by rotary evaporation, and the residue was partitioned between 150 mL of water and 150 mL of CH₂Cl₂. The aqueous layer was separated and extracted with two 50-mL portions of CH₂Cl₂, and the combined organic phases were washed with 150 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to give 1.33 g of a brown oil. Column chromatography on 25 g of silica gel (gradient elution with 5-30% ethyl acetate-hexane) produced 1.04 g (100%)³²⁴ of the propargylic alcohol **191** as a brown solid, mp 56-58 °C, with spectral data consistent with that previously reported for this compound.¹²⁶

IR (CHCl₃): 3500-3260, 2980, 1730, 1580, 1525, 1450, 1305, 1235, 1210, 1120, 1100, 1060, 1030, 930, 860, 840, and 750 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 8.10 (br d, J = 8 Hz, 1 H), 7.39 (br s, 1 H), 7.31 (m, 2 H), 6.97 (td, J = 1, 8 Hz, 1 H), 4.82 (q, J = 6.6 Hz, 1 H), 3.79 (s, 3 H), 2.71 (br s, 1 H), and 1.59 (d, J = 6.6 Hz, 3 H)

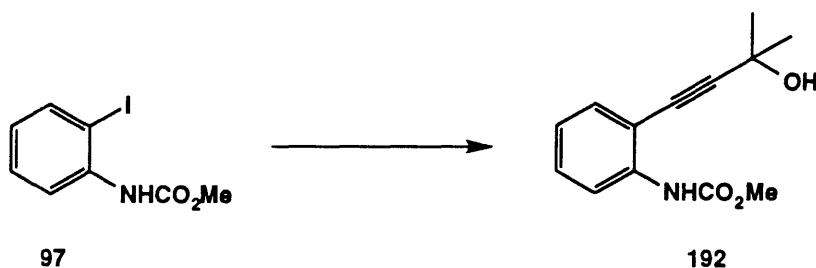
³²⁴. In other runs the yield for this reaction ranged from 92-100%.

^{13}C NMR (75 MHz, CDCl_3): 153.7, 139.0, 131.8, 129.8, 122.5, 117.8, 110.8, 98.2, 79.1, 58.8, 52.4, and 24.4



191

205

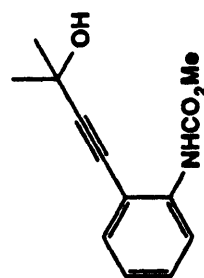


N-(Methoxycarbonyl)-2-(3-hydroxy-3-methyl-1-butynyl)aniline (192). A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, a glass stopper, and an argon inlet was charged with N-(methoxycarbonyl)-2-iodoaniline (**97**) (0.300 g, 1.08 mmol), 2-methyl-3-butyn-2-ol (0.13 mL, 0.109 g, 1.30 mmol), and 10 mL of Et₂NH. PdCl₂(PPh₃)₂ (0.023 g, 0.032 mmol) and CuI (0.004 g, 0.022 mmol) were added, and the reaction mixture was stirred at room temperature for 72 h. The solvent was then removed by rotary evaporation, and the residue was partitioned between 50 mL of water and 50 mL of ether. The aqueous layer was separated and extracted with two 35-mL portions of ether, and the combined organic phases were washed with 50 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to give 0.477 g of a brown oil. Column chromatography on silica gel (elution with 30% ethyl acetate-hexane) produced 0.232 g (96%) of the propargylic alcohol **192** as a light brown solid, mp 74-74.5 °C, with spectral data consistent with that previously reported for this compound.¹²⁶

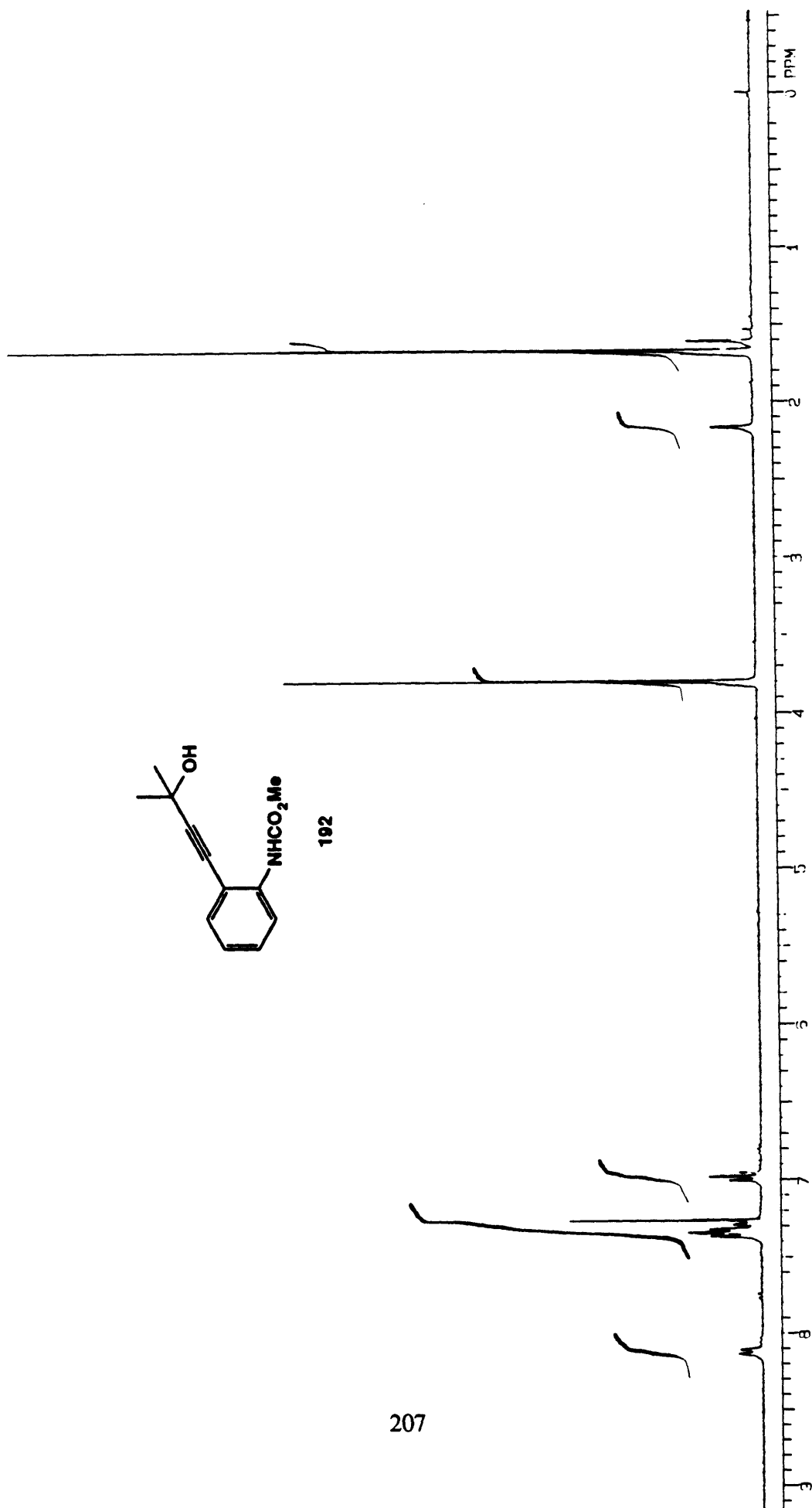
IR (CCl₄): 3500-3300, 2980, 1720, 1580, 1520, 1450, 1360, 1300, 1235, 1210, 1060, 950, 900, and 750 cm⁻¹

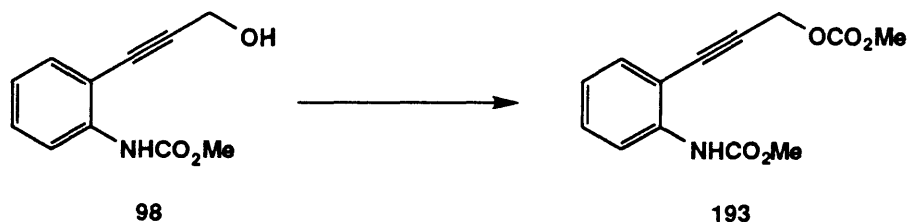
¹H NMR (300 MHz, CDCl₃): 8.12 (br d, J = 8 Hz, 1 H), 7.33 (m, 3 H), 6.98 (td, J = 1, 8 Hz, 1 H), 3.80 (s, 3 H), 2.19 (br s, 1 H), and 1.69 (s, 6 H)

¹³C NMR (75 MHz, CDCl₃): 153.8, 138.8, 131.5, 129.5, 122.4, 117.8, 111.0, 101.2, 83.9, 65.4, 52.4, and 31.4



192





N-(Methoxycarbonyl)-2-(3-methoxycarbonyloxy-1-propynyl)aniline (193). A 25-mL, three-necked, round-bottomed flask equipped with a rubber septum, a glass stopper, and an argon inlet was charged with the propargylic alcohol **98** (0.214 g, 1.05 mmol), DMAP (0.256 g, 2.09 mmol), and 10 mL of CH₂Cl₂, and the solution was cooled at 0 °C. Methyl chloroformate (0.12 mL, 0.148 g, 1.57 mmol) was added dropwise over 2 min, and the reaction mixture was stirred at 0 °C for 5 min, and at room temperature for 24 h. The reaction mixture was then partitioned between 50 mL of CH₂Cl₂ and 50 mL of water. The aqueous layer was separated and extracted with two 30-mL portions of CH₂Cl₂, and the combined organic phases were washed with 30 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to give 0.247 g of a yellow oil. Column chromatography on 10 g of silica gel (gradient elution with 30-50% ethyl acetate-hexane) produced 0.247 g (90%)³²⁵ of the propargylic carbonate **193** as a pale yellow oil.

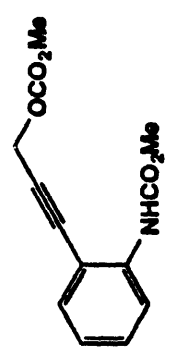
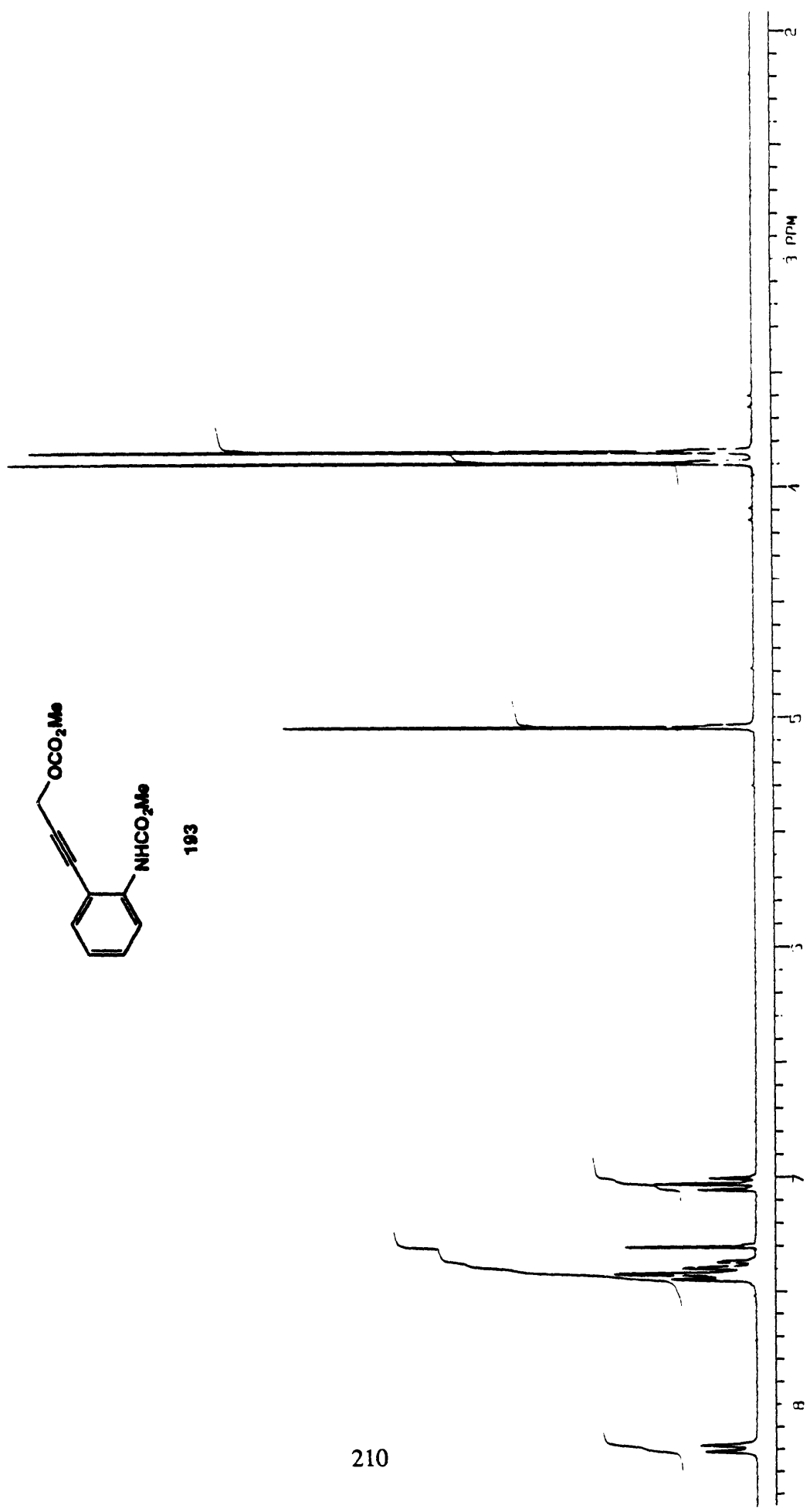
IR (thin film): 3400, 3360, 2995, 2230, 1755, 1580, 1520, 1450, 1370, 1300, 1280-1200, 1110, 1060, 1040, 990, 940, 900, 840, 790, and 755 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 8.19 (br d, J = 8 Hz, 1 H), 7.40 (m, 3 H), 7.03 (t, J = 7.6 Hz, 1 H), 5.04 (s, 2 H), 3.89 (s, 3 H), and 3.84 (s, 3 H)

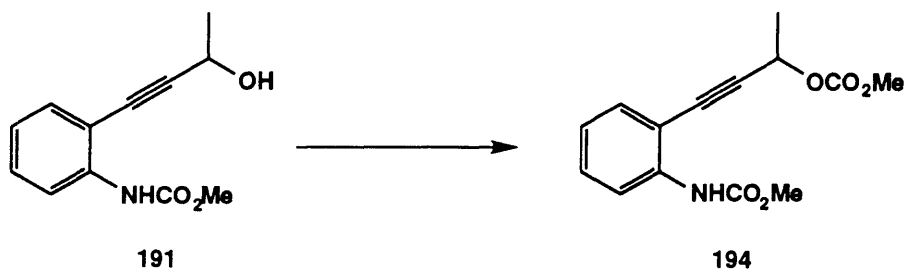
³²⁵. In other runs the yield for this reaction ranged from 89-90%.

^{13}C NMR (75 MHz, CDCl_3): 155.2, 153.7, 139.7, 132.1, 130.4, 122.5, 117.8, 110.0, 89.4, 82.6, 56.0, 55.1, and 52.4

HRMS: Calcd for $\text{C}_{13}\text{H}_{13}\text{NO}_5$: 263.0794
Found: 263.0791



193



N-(Methoxycarbonyl)-2-(3-methoxycarbonyloxy-1-butynyl)aniline (194). A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, a glass stopper, and an argon inlet was charged with the propargylic alcohol **191** (0.464 g, 2.12 mmol), DMAP (0.517 g, 4.23 mmol), and 20 mL of CH₂Cl₂, and the solution was cooled at 0 °C. Methyl chloroformate (0.25 mL, 0.300 g, 3.17 mmol) was added dropwise over 2 min, and the reaction mixture was stirred at 0 °C for 30 min, allowed to warm to room temperature over 1 h, and then quenched with 100 mL of 5% HCl solution. The reaction mixture was then transferred into a separatory funnel with the aid of 80 mL of CH₂Cl₂. The aqueous layer was separated and extracted with 50 mL of CH₂Cl₂, and the combined organic phases were washed with 100 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to give 0.583 g of a yellow oil. Column chromatography on 15 g of silica gel (elution with 30% ethyl acetate-hexane) produced 0.538 g (92%)³²⁶ of the propargylic carbonate **194** as a yellow oil.

IR (thin film): 3400, 3340, 2995, 2950, 2220, 1735, 1580, 1520, 1450, 1375, 1345, 1300, 1260, 1230, 1210, 1160, 1110, 1080, 1060, 1040, 1020, 940, 915, 860, 790, and 755 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 8.15 (br d, J = 8 Hz, 1 H), 7.43 (br s, 1 H), 7.36 (m, 2 H), 6.97 (td, J = 1.5, 8 Hz, 1 H), 5.52 (q, J

³²⁶. In other runs the yield for this reaction ranged from 90-92%.

= 7 Hz, 1 H), 3.83 (s, 3 H), 3.80 (s, 3 H), and
1.67 (d, J = 7 Hz, 3 H)

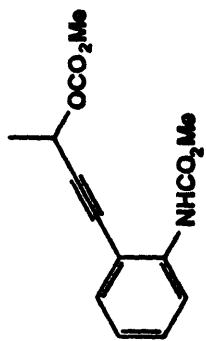
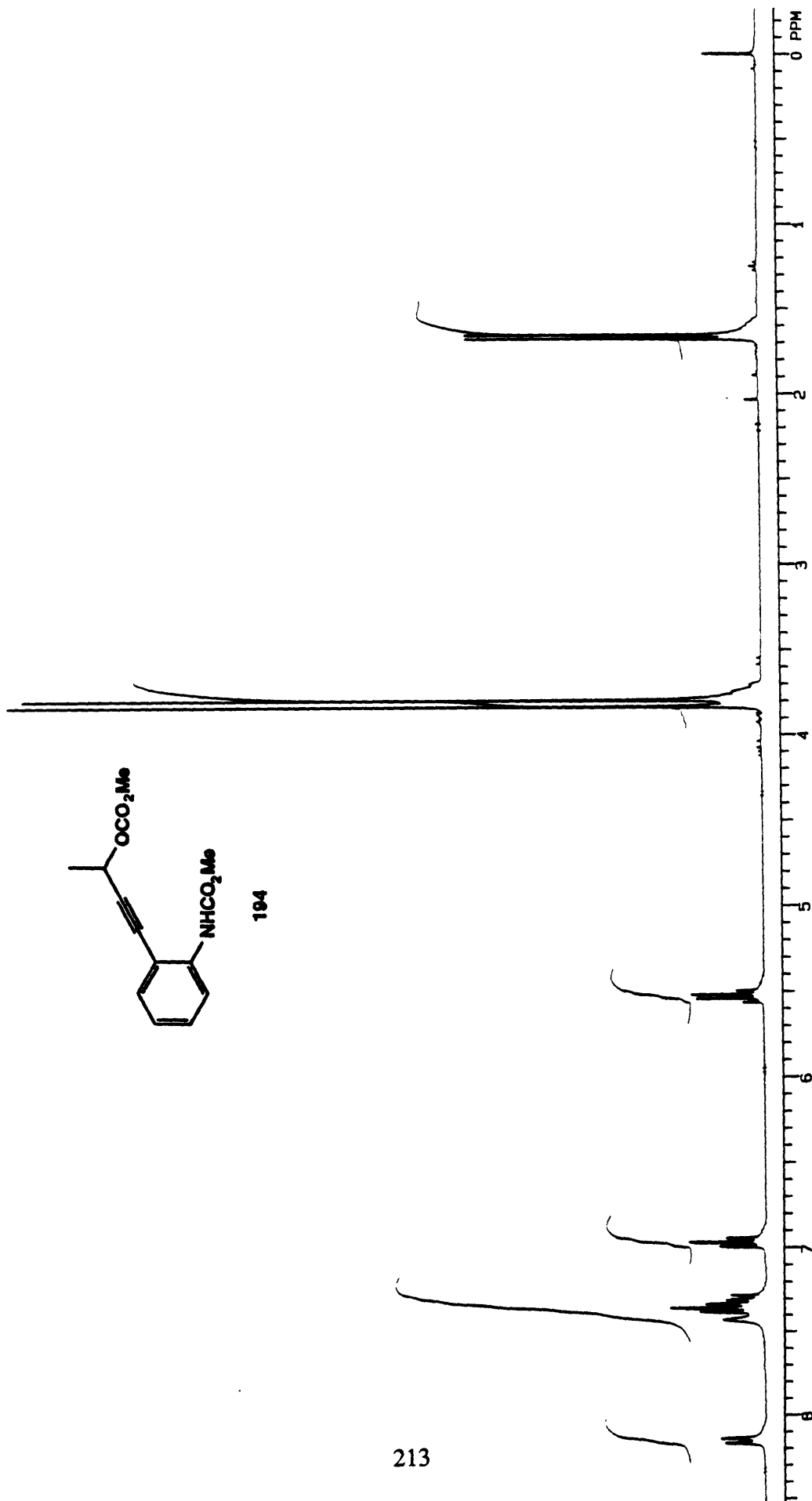
^{13}C NMR (75 MHz, CDCl_3):

154.7, 153.5, 139.5, 131.7, 130.0, 122.2, 117.6,
109.9, 93.6, 80.8, 64.7, 54.9, 52.3, and 21.1

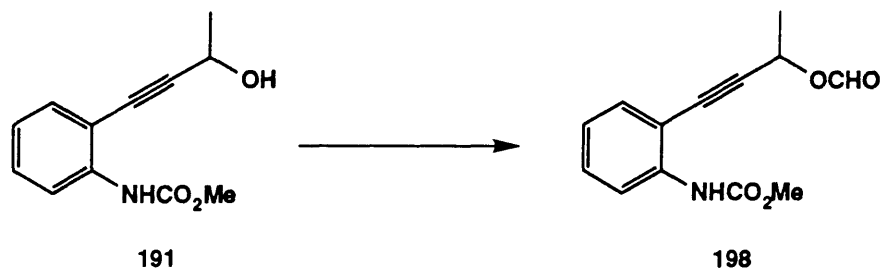
HRMS:

Calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_5$: 277.0950

Found: 277.0950



194

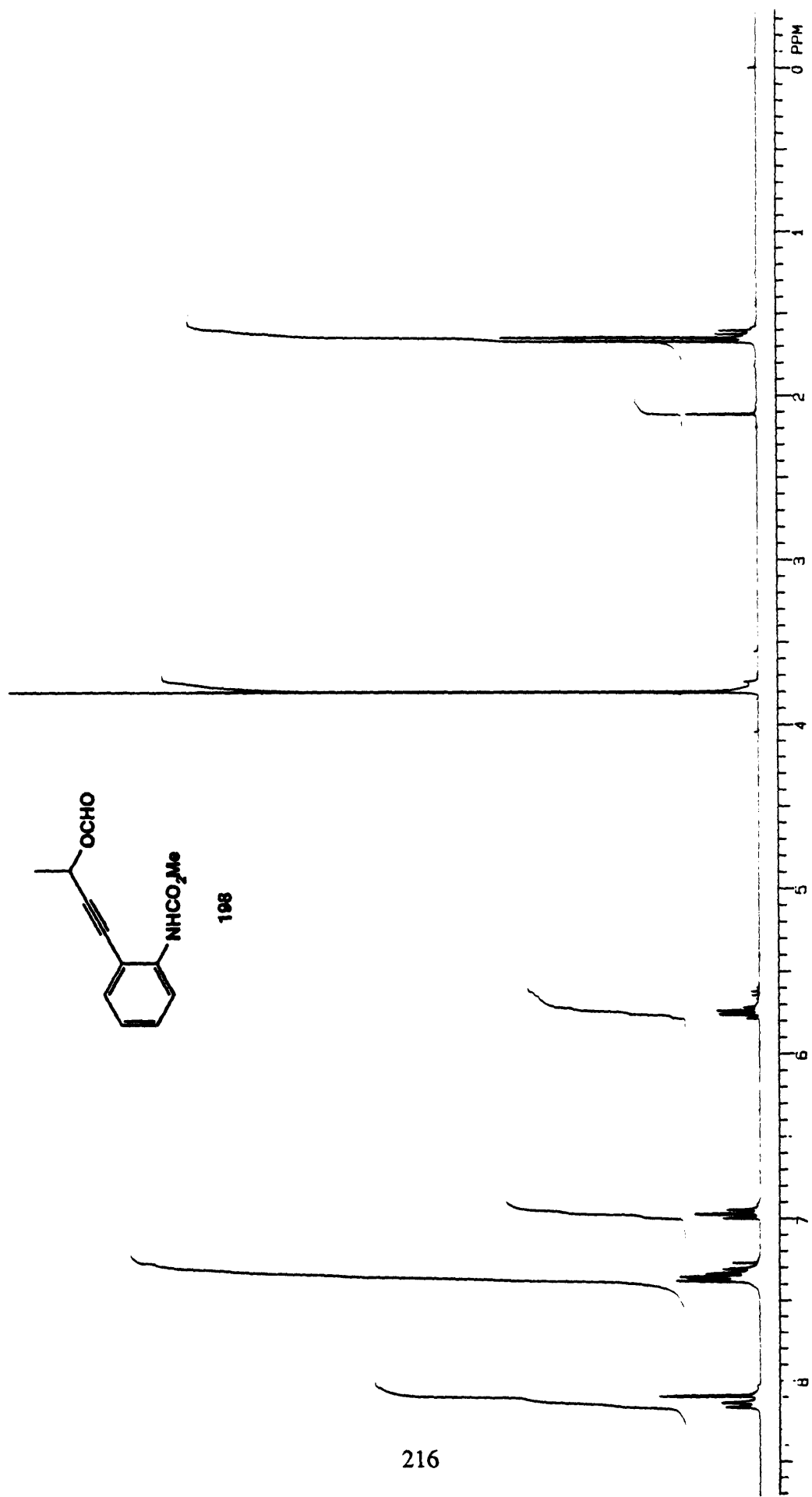


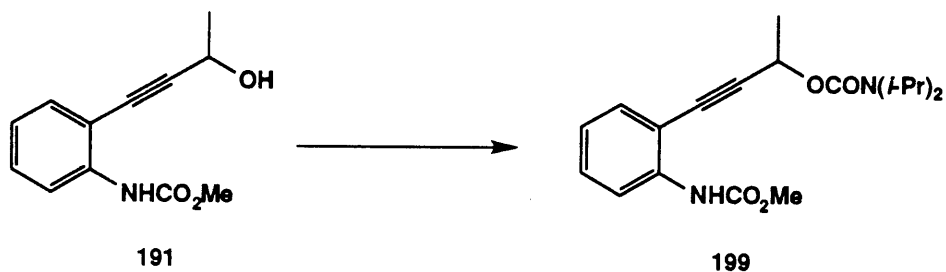
N-(Methoxycarbonyl)-2-(3-formyloxy-1-butynyl)aniline (198). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum, a glass stopper, and an argon inlet was charged with the propargylic alcohol **191** (0.130 g, 0.593 mmol), DMAP (0.145 g, 1.19 mmol), and 6 mL of CH₂Cl₂, and the solution was cooled at 0 °C. Acetic formic anhydride (0.09 mL, 0.078 g, 0.889 mmol) was added dropwise over 1 min, and the reaction mixture was stirred at 0 °C for 2 h, allowed to warm to room temperature over 10 h, and then quenched with 30 mL of 3% HCl solution. The reaction mixture was then transferred into a separatory funnel with the aid of 30 mL of CH₂Cl₂. The aqueous layer was separated and extracted with 20 mL of CH₂Cl₂, and the combined organic phases were washed with 30 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to give 0.206 g of a yellow oil. Column chromatography on 5 g of silica gel (elution with 30% ethyl acetate-hexane) produced 0.130 g (89%) of the propargylic formate **196** as a pale yellow oil.

IR (thin film): 3400, 3360, 2990, 2940, 2220, 1740, 1720, 1580, 1520, 1450, 1370, 1335, 1305, 1280, 1230, 1210, 1160, 1120, 1080, 1060, 1040, 1020, 950, 915, 8350, and 760 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 8.15 (br d, J = 8 Hz, 1 H), 8.09 (s, 1 H), 7.33 (m, 3 H), 6.97 (dt, J = 1.5, 7.6 Hz, 1 H), 5.74 (dq, J = 1, 6.7 Hz, 1 H), 3.80 (s, 3 H), and 1.66 (d, J = 6.7 Hz, 3 H)

^{13}C NMR (75 MHz, CDCl_3): 159.7, 153.5, 139.5, 131.8, 130.1, 122.3, 117.7,
109.9, 93.6, 80.8, 60.6, 52.5, and 21.2





N-(Methoxycarbonyl)-2-(3-*N,N*-diisopropylcarbamoyloxy-1-butynyl)aniline (199).

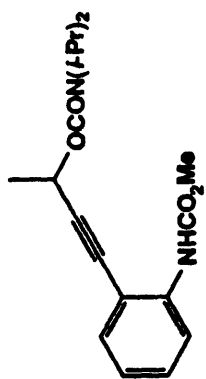
A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and an argon inlet was charged with the propargylic alcohol **191** (0.240 g, 1.09 mmol), DMAP (0.067 g, 0.547 mmol), pyridine (0.44 mL, 0.433 g, 5.47 mmol), *N,N*-diisopropylcarbamoyl chloride and 5 mL of CH₃CN, and the solution was heated at reflux for 16 h, allowed to cool to room temperature, and quenched with 30 mL of 3% HCl solution. The reaction mixture was then transferred into a separatory funnel with the aid of 30 mL of CH₂Cl₂. The aqueous layer was separated and extracted with 25 mL of CH₂Cl₂, and the combined organic phases were washed with 30 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to give 0.385 g of a yellow oil. Column chromatography on 8 g of silica gel (gradient elution with 10-20% ethyl acetate-hexane) produced 0.280 g (74%) of the propargylic carbamate **199** as a clear, colorless oil.

IR (thin film): 3380, 3290, 2960, 2220, 1730, 1680, 1580, 1520, 1445, 1300, 1280, 1210, 1120, 1080, 1060, 1040, and 750 cm⁻¹

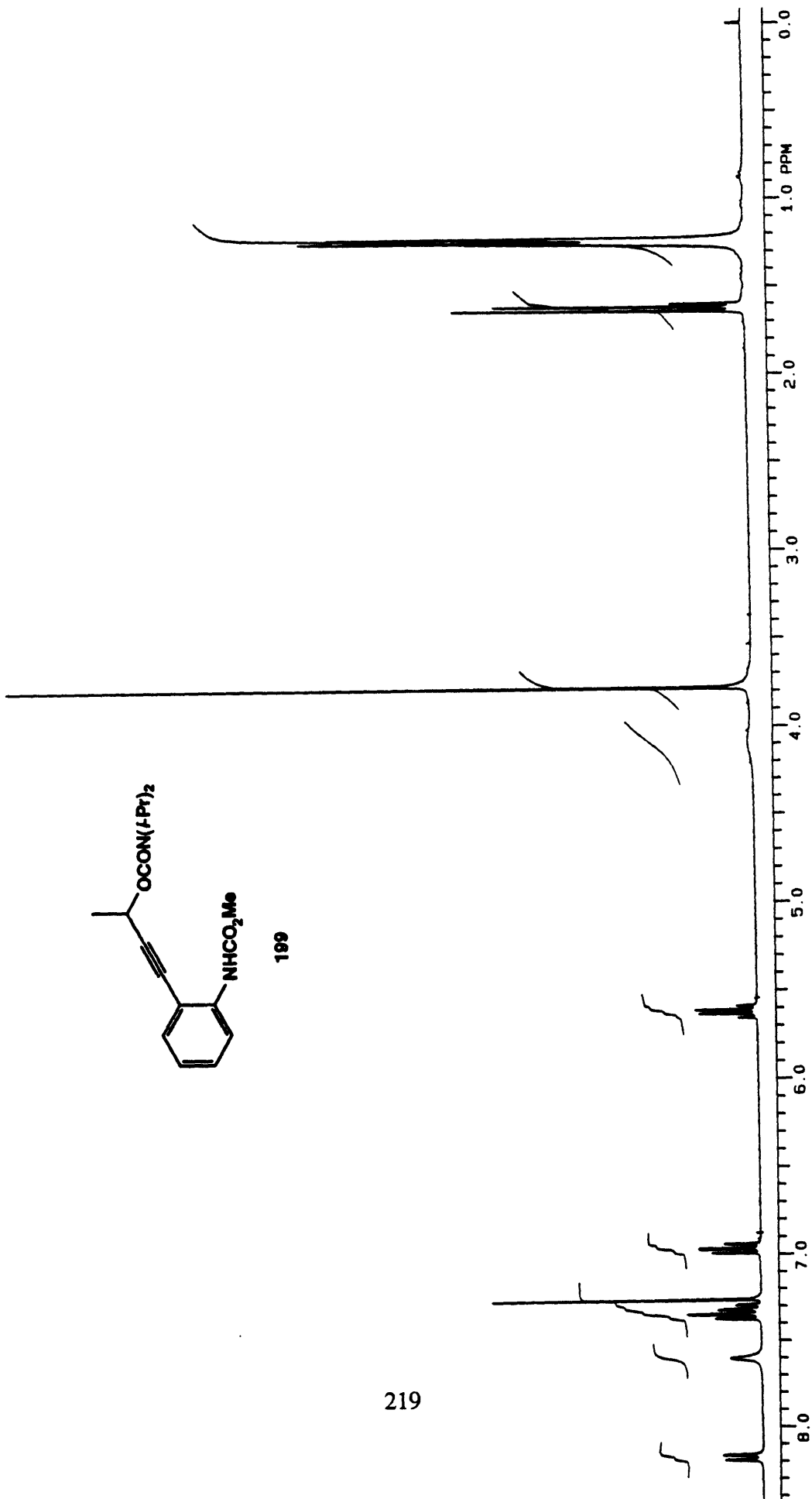
¹H NMR (300 MHz, CDCl₃): 8.18 (d, *J* = 8 Hz, 1 H), 7.60 (br s, 1 H), 7.33 (m, 2 H), 6.97 (td, *J* = 1.5, 8 Hz, 1 H), 5.62 (q, *J* = 7 Hz, 1 H), 4.1 (br m, 1 H), 3.79 (s, 3 H), 1.63 (d, *J* = 7 Hz, 3 H), 1.25 (d, *J* = 7 Hz, 6 H), and 1.23 (d, *J* = 7 Hz, 12 H)

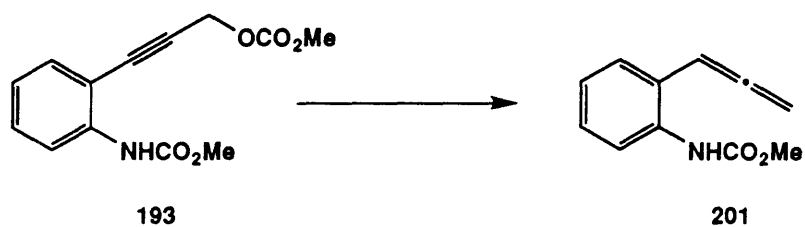
^{13}C NMR (75 MHz, CDCl_3): 154.4, 153.7, 139.9, 131.5, 129.9, 122.0, 117.4, 110.4, 95.7, 79.3, 60.9, 52.1, and 21.2

HRMS: Calcd for $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}_4$: 346.1893
Found: 346.1895



199



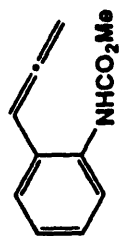


N-(Methoxycarbonyl)-2-(allenyl)aniline (201). A 10-mL, two-necked, round-bottomed flask equipped with a rubber septum and an argon inlet was charged with the propargylic carbonte **193** (0.109 g, 0.414 mmol), ammonium formate (0.052 g, 0.828 mmol), and 5 mL of THF. Pd₂(dba)₃ (0.019 g, 0.021 mmol) and tributylphosphine (0.02 mL, 0.017 g, 0.083 mmol) were added, and the reaction mixture was stirred at room temperature for 24 h, filtered through florisil, and concentrated to afford 0.366 g of an orange solid. Column chromatography on 20 g of silica gel (gradient elution with 0-10% ethyl acetate-hexane) produced 0.066 g (81%) of allene **201** as a yellow solid, mp 52-53 °C, with spectral data in excellent agreement with that previously reported for this compound.

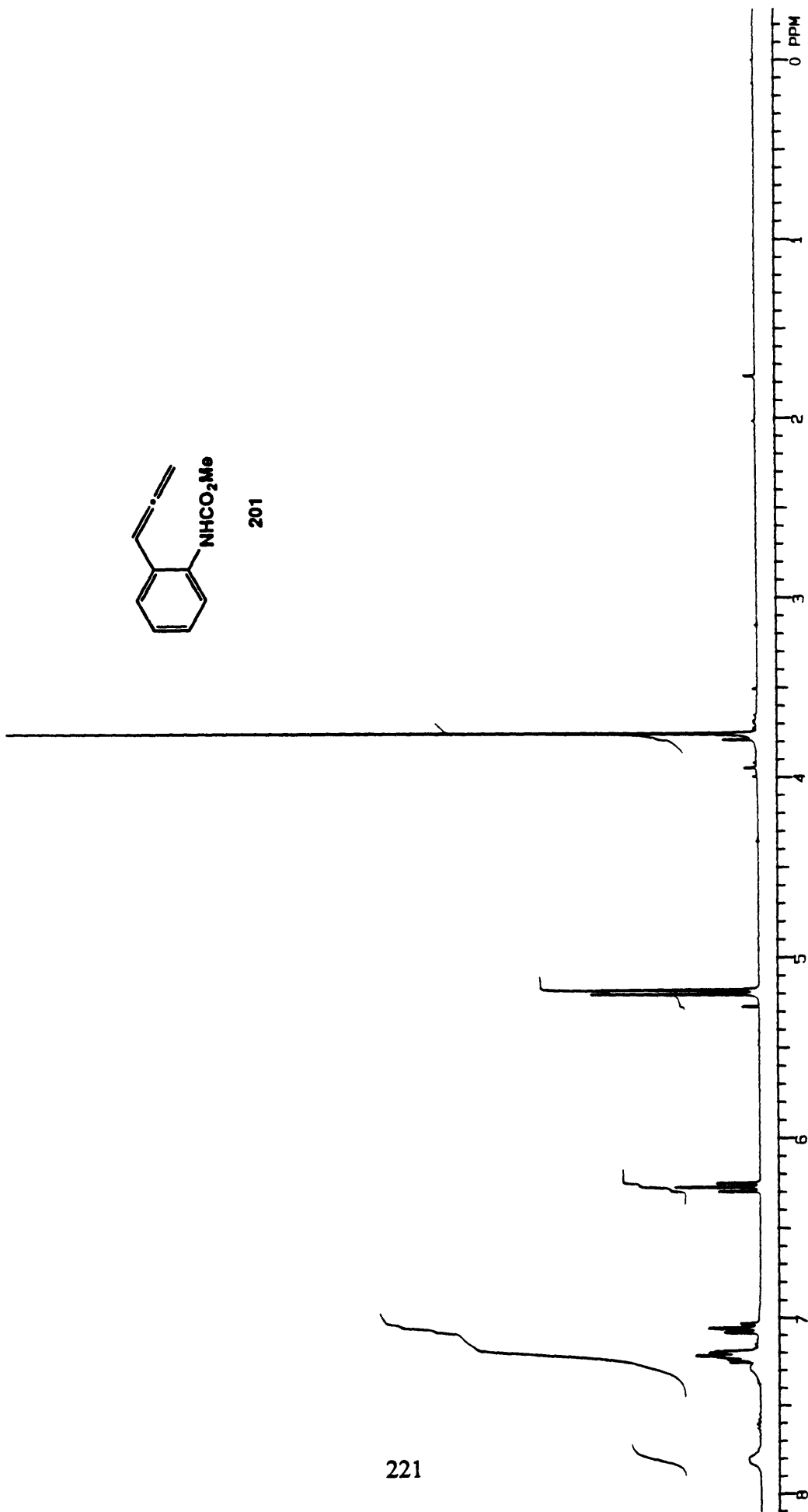
IR (thin film): 3400, 2960, 1945, 1750, 1590, 1530, 1460, 1305, and 1220 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 7.80 (br d, J = 6 Hz, 1 H), 7.28 (br s, 1 H), 7.22 (m, 2 H), 7.06 (app t, J = 8 Hz, 1 H), 6.27 (t, J = 7 Hz, 1 H), 5.19 (d, J = 7 Hz, 2 H), and 3.76 (s, 3 H)

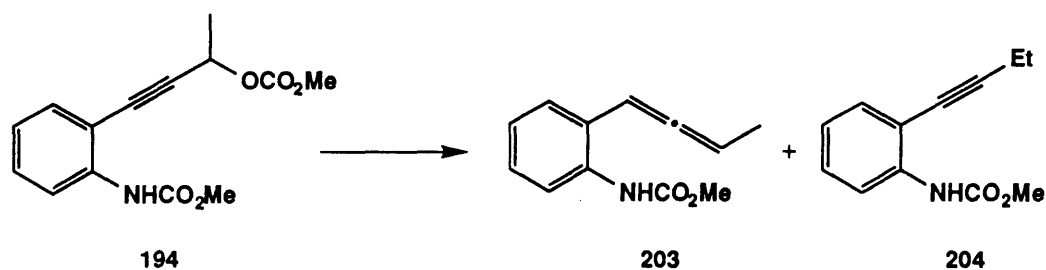
¹³C NMR (75 MHz, CDCl₃): 209.9, 154.4, 136.0, 135.2, 128.8, 127.9, 124.2, 121.9, 90.5, 78.7, and 52.3



201



221



N-(Methoxycarbonyl)-2-(1-butadienyl)aniline (203) and N-(Methoxycarbonyl)-2-(1-butynyl)aniline (204). A 10-mL, two-necked flask equipped with a rubber septum and an argon inlet was charged with the propargylic carbonate **194** (0.096 g, 0.346 mmol), ammonium formate (0.044 g, 0.692 mmol), and 4 mL of THF. Pd₂(dba)₃ (0.016 g, 0.017 mmol) and tributylphosphine (0.017 mL, 0.014 g, 0.069 mmol) were added and the reaction mixture was stirred at room temperature for 48 h, filtered through florisil, and concentrated to afford 0.182 g of a brown oil. Column chromatography on 20 g of silica gel (gradient elution with 0-5% ethyl acetate-hexane) produced 0.022 g (ca. 31%) of allene **203** (contaminated with an aromatic compound) as a yellow oil,³²⁷ and 0.023 g (33%) of the acetylene **204** as a yellow oil.

Spectral data for allene **203**:

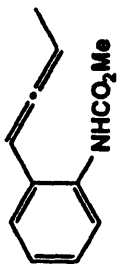
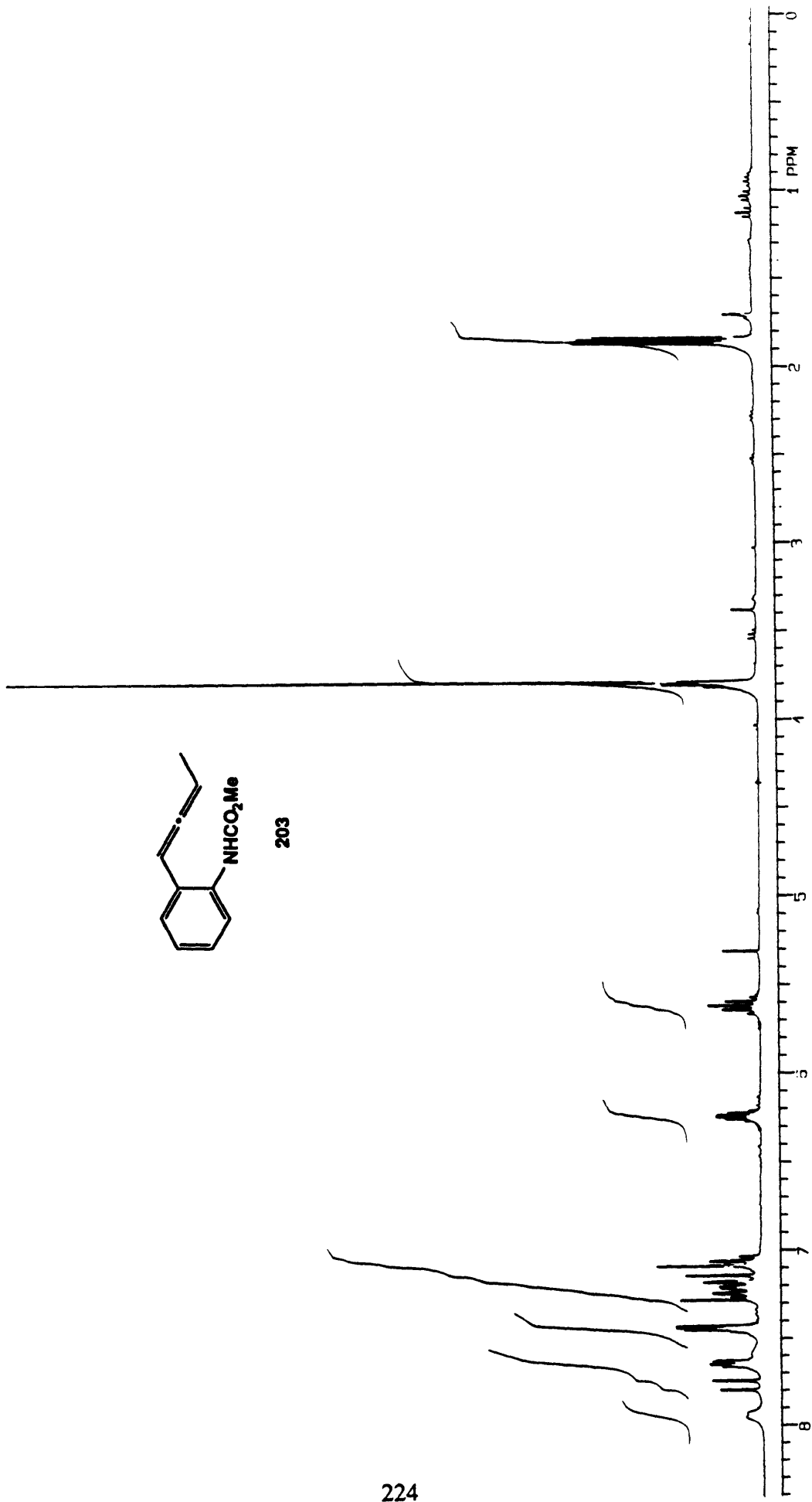
IR (thin film): 3360, 2940, 1945, 1720, 1585, 1520, 1450, 1340, 1300, 1220, 1190, 1095, 1060, 980, 870, and 750 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 7.93 (br d, J = 7 Hz, 1 H), 7.60 (br s, 1 H), 7.43 (m, 2 H), 7.06 (m, 1 H), 6.24 (dq, J = 3.3, 6.7 Hz, 1 H), 5.61 (qd, J = 7, 7 Hz, 1 H), 3.79 (s, 3 H), and 1.85 (dd, J = 3.3, 7 Hz, 3 H)

³²⁷. A second chromatographic purification failed to produce the allene in any higher purity.

^{13}C NMR (75 MHz, CDCl_3): 203.6, 154.0, 135.0, 127.6, 127.1, 126.8, 123.1, 120.0, 96.4, 86.8, 52.1, and 14.3

HRMS: Calcd for $\text{C}_{12}\text{H}_{13}\text{NO}_2$: 203.0946
Found: 203.0947



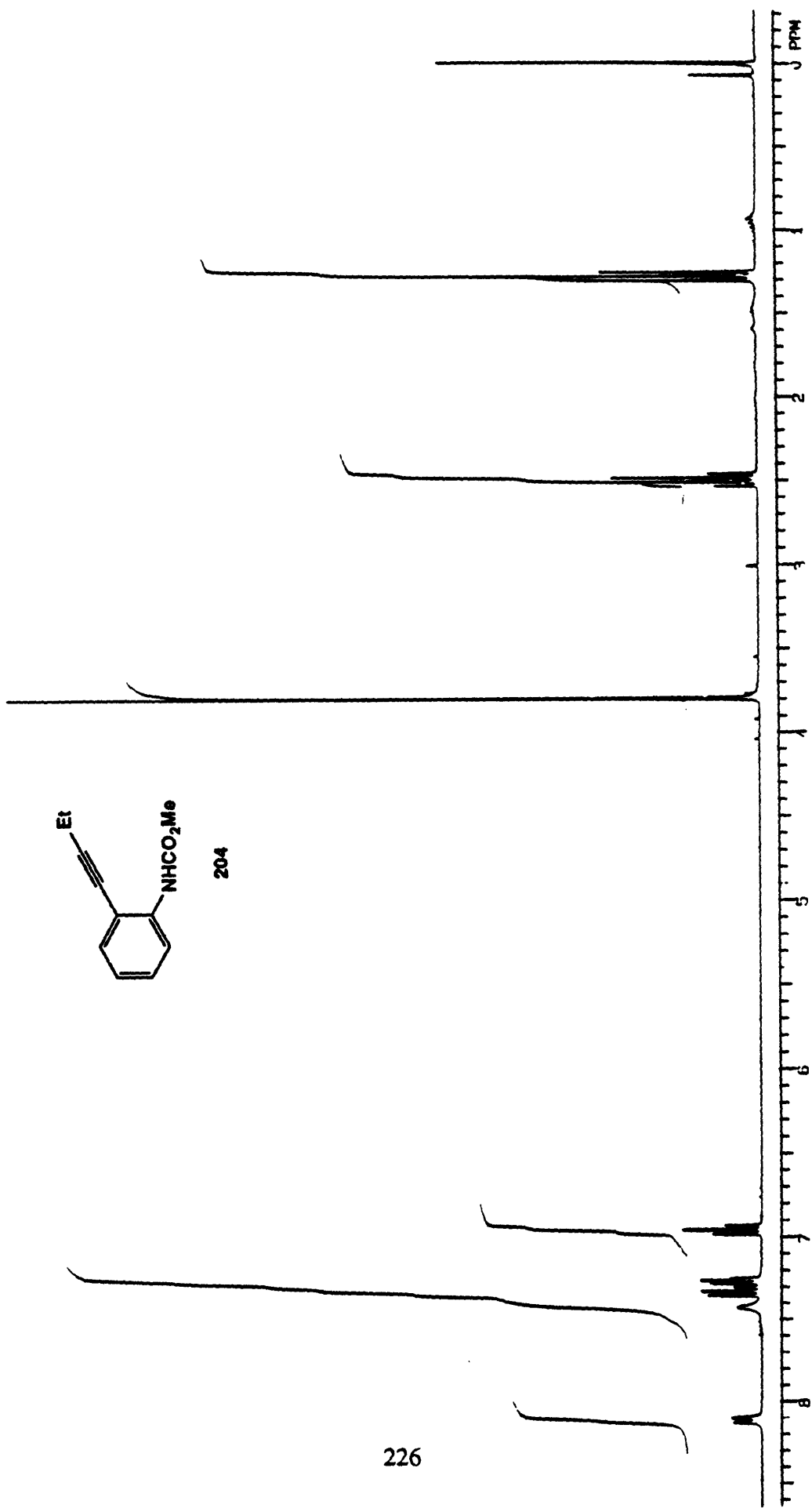
203

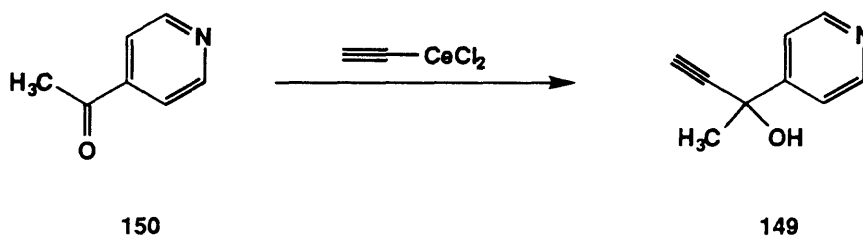
Spectral data for acetylene **204**:¹²⁶

IR (thin film): 3380, 2940, 2220, 1730, 1580, 1510, 1445, 1300, 1230, 1210, 1060, and 750 cm^{-1}

^1H NMR (300 MHz, CDCl_3): 8.11 (br d, $J = 8$ Hz, 1 H), 7.43 (br s, 1 H), 7.30 (m, 2 H), 6.96 (td, $J = 1, 7.6$ Hz, 1 H), 3.80 (s, 1 H), 2.49 (q, $J = 7.5$ Hz, 2 H), and 1.28 (t, $J = 7.5$ Hz, 3 H)

^{13}C NMR (75 MHz, CDCl_3): 153.7, 138.9, 131.6, 128.9, 122.3, 117.3, 112.1, 98.9, 75.1, 52.3, 13.9, and 13.3





2-(4-Pyridyl)-3-butyn-2-ol (149). A 250-mL, three-necked, round-bottomed flask equipped with a glass stopper, a rubber septum, and an argon inlet was charged with 40 mL of THF and then cooled at $-78\text{ }^{\circ}\text{C}$. Acetylene was bubbled into the THF for 20 min. *n*-BuLi (2.60 M solution in hexane, 7.50 mL, 19.5 mmol) was added dropwise over 10 min, and the reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ under an acetylene atmosphere for 20 min. A pre-cooled ($-78\text{ }^{\circ}\text{C}$) slurry of CeCl_3 (5.00 g, 20.3 mmol) in 37 mL of THF was then added via cannula over 5 min, and the resulting orange suspension was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h. A pre-cooled ($-78\text{ }^{\circ}\text{C}$) solution of 4-acetylpyridine (0.86 mL, 0.945 g, 7.80 mmol) in 45 mL of THF was then added via cannula over 5 min, and the reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 5 h, allowed to warm to room temperature over 30 min, and then quenched with 100 mL of water. The reaction mixture was then transferred into a separatory funnel with the aid of 100 mL of ethyl acetate. The aqueous layer was separated and extracted with three 50-mL portions of ethyl acetate, and the combined organic phases were washed with 150 mL of saturated NaCl solution, dried over MgSO_4 , filtered, and concentrated to give 1.09 g of an orange-brown solid. Column chromatography on 15 g of silica gel (gradient elution with 20-80% ethyl acetate-hexane) afforded 1.08 g (94%)³²⁸ of the propargylic alcohol **149** as tan crystals, mp $148.5\text{-}149\text{ }^{\circ}\text{C}$.

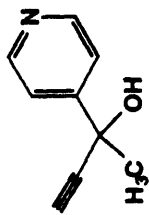
IR (CCl_4): 3550-3400, 3300, 3075, 3040, 2120, 1715, 1600, 1490, 1450, 1170, 1050, 1030, 985, 880, 850, 760, and 700 cm^{-1}

³²⁸ In other runs the yield for this reaction ranged from 85-94%.

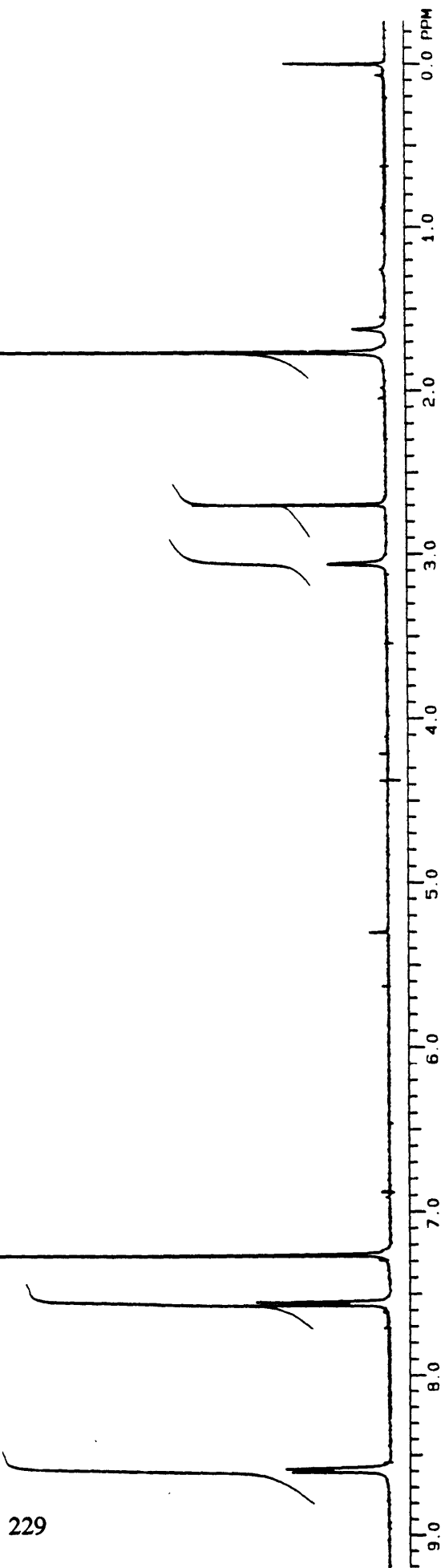
^1H NMR (300 MHz, CDCl_3): 8.57 (dd, $J = 1.7, 4.5$ Hz, 2 H), 7.56 (dd, $J = 1.6, 4.5$ Hz, 2 H), 3.48 (br s, 1 H), 2.70 (s, 1 H), and 1.77 (s, 3 H)

^{13}C NMR (75 MHz, d_6 -DMSO): 155.1, 149.7, 120.1, 87.6, 74.9, 67.3, and 32.9

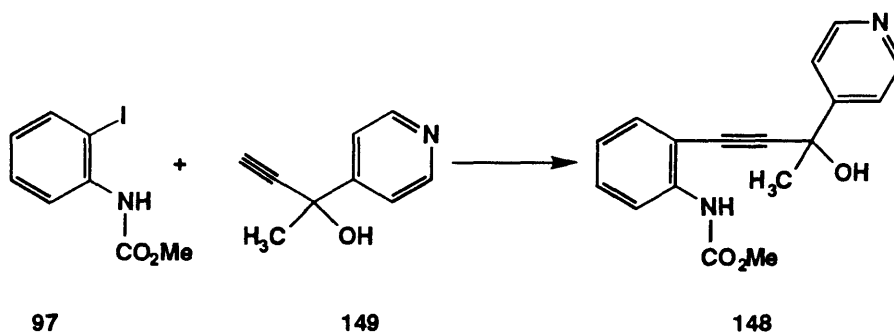
Elemental Analysis: Calcd for $\text{C}_9\text{H}_9\text{NO}$: C, 73.45; H, 6.16; N, 9.52
Found C, 73.30; H, 6.18; N, 9.37



149



229



N-(Methoxycarbonyl)-2-(3-hydroxy-3-(4-pyridyl)-1-butynyl)aniline (148). A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, a glass stopper, and an argon inlet was charged with N-(methoxycarbonyl)-2-iodoaniline (**97**) (0.660 g, 2.38 mmol), the propargylic alcohol **149** (0.292 g, 1.98 mmol), and 12 mL of Et₂NH. PdCl₂(PPh₃)₂ (0.070 g, 0.099 mmol) and CuI (0.011 g, 0.060 mmol) were added, and the reaction mixture was stirred at room temperature for 44 h. The solvent was then removed by rotary evaporation, and the residue was partitioned between 100 mL of CH₂Cl₂ and 100 mL of water. The aqueous layer was separated and extracted with two 50-mL portions of CH₂Cl₂, and the combined organic phases were washed with 100 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to give 0.919 g of an orange-brown solid. Column chromatography on 40 g of silica gel (gradient elution with 50-90% ethyl acetate-hexane) produced 0.567 g (96%)³²⁹ of the propargylic alcohol **148** as an off-white solid, mp 152.5-153.5 °C.

IR (nujol): 3400, 1750, 1580, 1520, 1450, 1375, 1310, 1240, 1210, 1145, 1065, 750, and 720 cm⁻¹

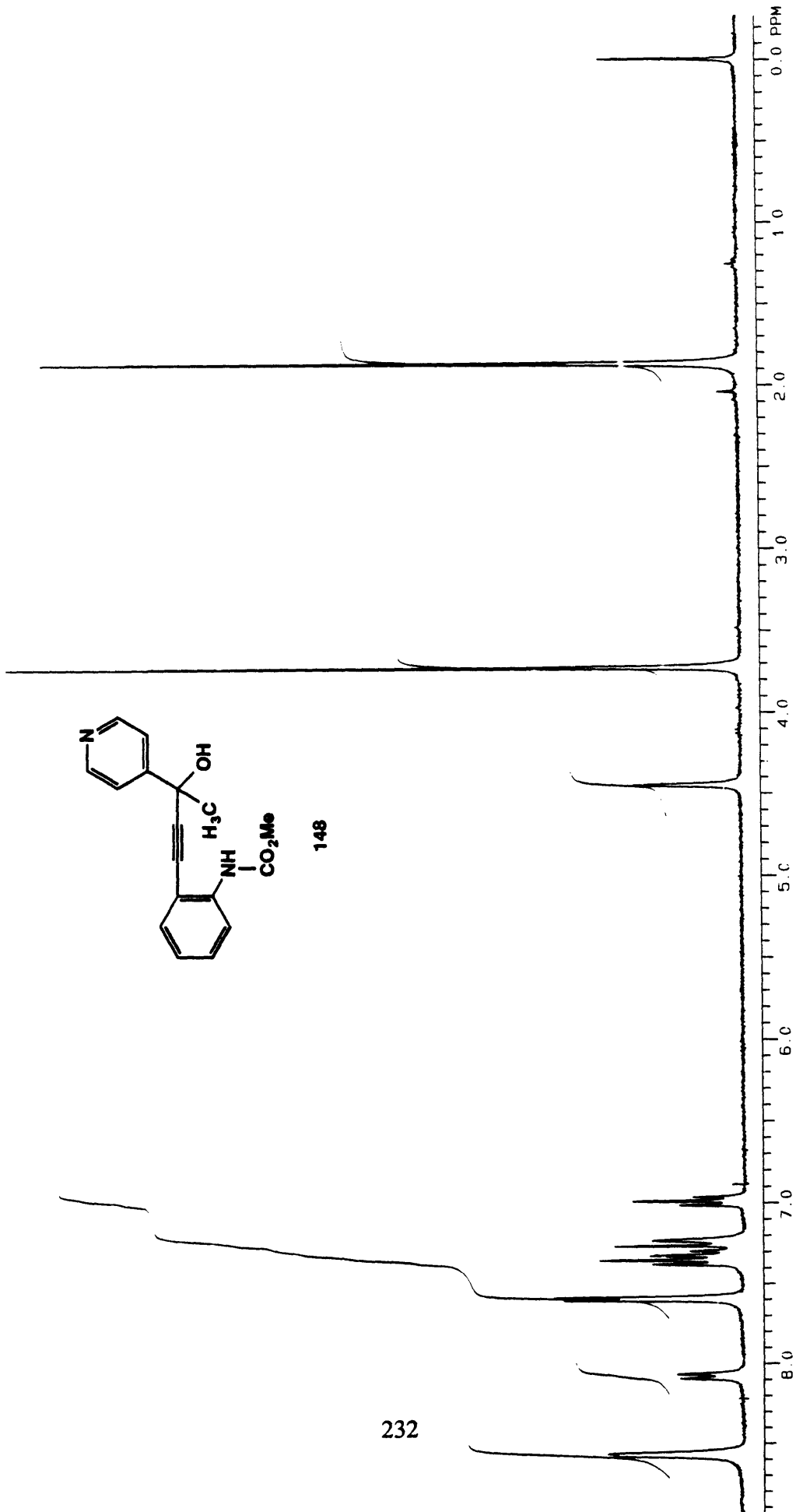
¹H NMR (300 MHz, CDCl₃): 8.57 (br d, J = 6 Hz, 2 H), 8.08 (br d, J = 8 Hz, 1 H), 7.59 (d, J = 6 Hz, 2 H), 7.23-7.38 (m, 3 H), 6.99 (t, J = 7 Hz, 1 H), 4.45 (br s, 1 H), 3.73 (s, 3 H), and 1.87 (s, 3 H)

³²⁹. In other runs the yield for this reaction ranged from 83-96%.

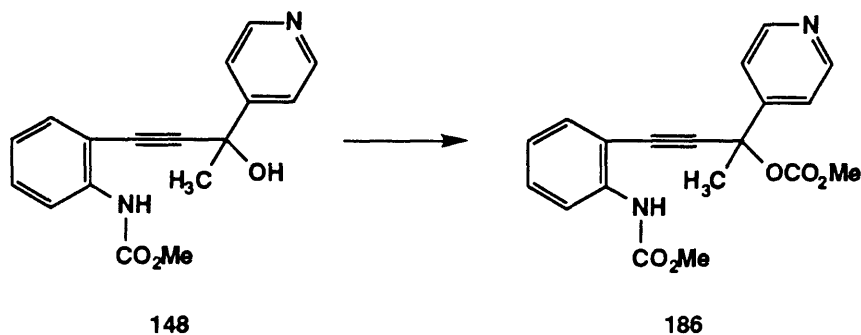
^{13}C NMR (75 MHz, CDCl_3): 154.6, 153.6, 150.0, 139.3, 131.8, 130.3, 122.7, 120.0, 118.0, 110.3, 98.5, 80.6, 69.4, 52.5, and 33.0

HRMS: Calcd for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_3$: 296.1161
Found: 296.1159

Elemental Analysis: Calcd for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_3$: C, 68.90; H, 5.53;
N, 9.27
Found C, 68.97; H, 5.44;
N, 9.46



232



N-(Methoxycarbonyl)-2-(3-methoxycarbonyloxy-3-(4-pyridyl)-1-butynyl)aniline

(186). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and an argon inlet was charged with the propargylic alcohol **148** (0.348 g, 1.18 mmol), DMAP (0.287 g, 2.35 mmol), and 10 mL of CH₂Cl₂, and the solution was cooled at 0 °C. Methyl chloroformate (0.14 mL, 0.167 g, 1.76 mmol) was added dropwise over 1 min, and the reaction mixture was stirred at 0 °C for 15 min, and then at room temperature for 16 h. The reaction mixture was then partitioned between 50 mL of CH₂Cl₂ and 50 mL of water. The aqueous layer was separated and extracted with two 25-mL portions of CH₂Cl₂, and the combined organic phases were washed with 50 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to give 0.334 g of a yellow oil. Column chromatography on 10 g of silica gel (gradient elution with 50-85% ethyl acetate-hexane) produced 0.300 g (72%)³³⁰ of the propargylic carbonate **185** as a pale yellow oil.

IR (thin film): 3400, 3360, 2995, 2230, 1755, 1580, 1520, 1450, 1370, 1300, 1280-1200, 1110, 1060, 1040, 990, 940, 900, 840, 790, and 755 cm⁻¹

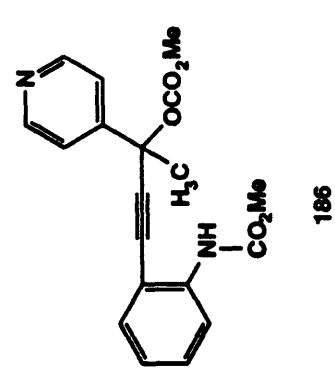
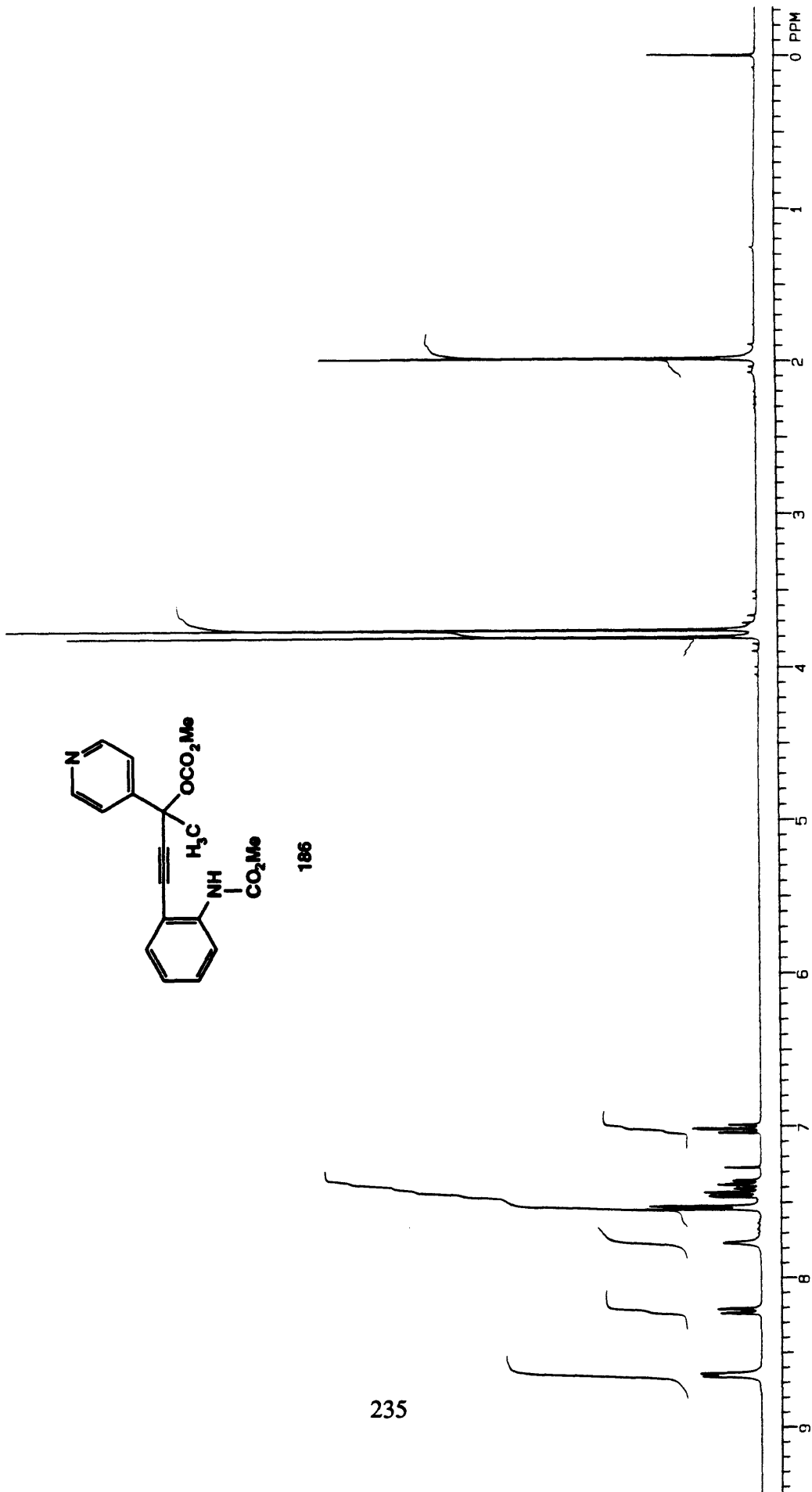
¹H NMR (300 MHz, CDCl₃): 8.65 (br d, J = 5.6 Hz, 2 H), 8.23 (d, J = 8.5 Hz, 1 H), 7.77 (br s, 1 H), 7.53 (dd, J = 1.6, 4.5 Hz, 2 H), 7.45 (dd, J = 1.6, 7.6 Hz, 1 H), 7.38 (td, J

³³⁰. In other runs the yield for this reaction ranged from 73-77%.

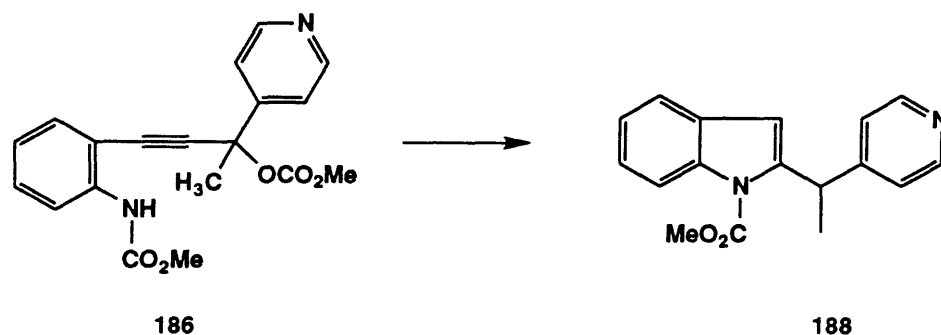
= 1.6, 8.5 Hz, 1 H), 7.02 (td, J = 1, 7.6 Hz, 1 H),
3.81 (s, 3 H), 3.76, (s, 3 H), and 1.99 (s, 3 H)

^{13}C NMR (75 MHz, CDCl_3): 154.0, 153.6, 150.5, 150.3, 140.6, 131.7, 130.6,
122.3, 119.7, 118.1, 109.6, 93.0, 83.9, 77.0,
54.9, 52.3, and 31.2

HRMS: Calcd for $\text{C}_{13}\text{H}_{13}\text{NO}_5$: 354.1216
Found: 354.1213



235



N-(Methoxycarbonyl)-2-(1-(4-pyridil)-ethyl)indole (188). A 10-mL, two-necked flask equipped with a rubber septum and an argon inlet was charged with the propargylic carbonate **186** (0.166 g, 0.468 mmol), ammonium formate (0.059 g, 0.936 mmol), and 4 mL of THF. Pd₂(dba)₃.CHCl₃ (0.024 g, 0.023 mmol) and tributylphosphine (0.023 mL, 0.019 g, 0.094 mmol) were added and the reaction mixture was stirred at room temperature for 72 h, and then filtered through florisil and concentrated to afford 0.136 g of an orange solid. Column chromatography on 10 g of silica gel (elution with 50% ethyl acetate-hexane) produced 0.105 g (80%)³³¹ of indole **188** as a light brown solid, mp 99-101 °C.

IR (CCl₄): 2940, 2920, 1720, 1580, 1540, 1435, 1420, 1380, 1350, 1310, 1220, 1185, 1100, 1075, 1035, 800, and 730 cm⁻¹

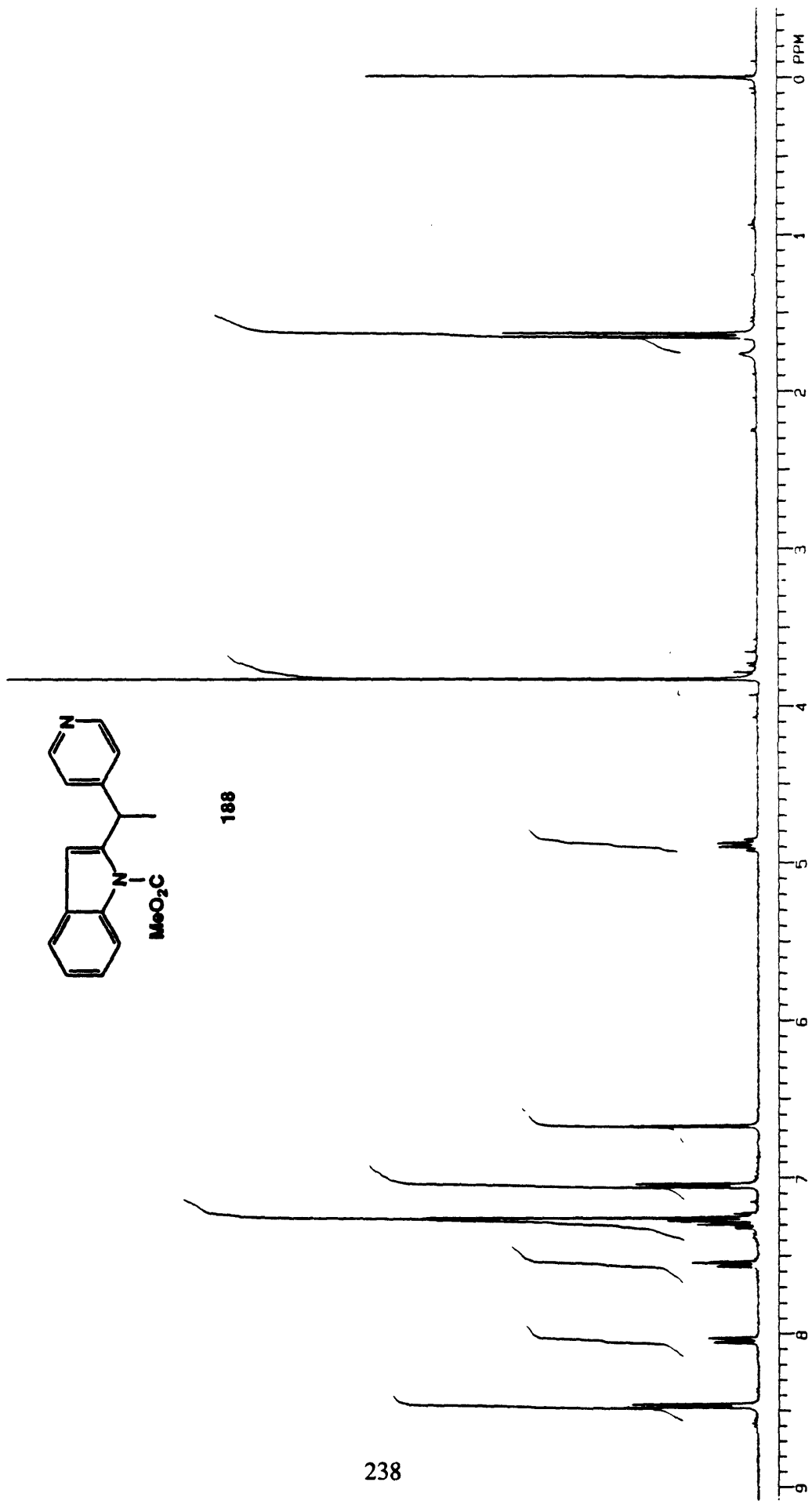
¹H NMR (300 MHz, CDCl₃): 8.47 (dd, J = 1.5, 4.5 Hz, 2 H), 8.05 (d, J = 7.6 Hz, 1 H), 7.55 (m, 1 H), 7.23-7.33 (m, 2 H), 7.05 (dd, J = 1.5, 4.5 Hz, 2 H), 6.67 (s, 1 H), 4.89 (q, J = 7 Hz, 1 H), 3.80 (s, 3H), and 1.64 (d, J = 7 Hz, 3 H)

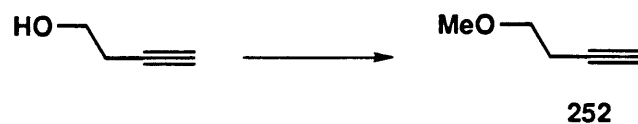
³³¹. In other runs the yield for this reaction ranged from 71-78%.

^{13}C NMR (75 MHz, CDCl_3): 154.7, 151.9, 149.9, 142.8, 136.8, 128.9, 124.4, 123.2, 122.4, 120.4, 115.8, 108.9, 53.3, 39.0, and 22.4

HRMS: Calcd for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2$: 280.1212
Found: 280.1216

Elemental Analysis: Calcd for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2$: C, 72.84; H, 5.75;
N, 9.99
Found: C, 72.46; H, 5.79;
N, 9.60





4-Methoxy-1-butyne (252). A 100-ml, three-necked, round-bottomed flask equipped with a mechanical stirrer, a gas inlet adapter and a pressure-equalizing addition funnel was charged with 3-butyn-1-ol (5.68 mL, 5.25 g, 75 mmol), tetra-*n*-butylammonium iodide (0.300 g), and 50% NaOH solution (30 g, 375 mmol). The slurry was cooled at 0 °C and stirred for 10 min. Dimethylsulfate (21.0 mL, 28.5 g, 225 mmol) was then added over 45 min, and the reaction mixture was stirred at 0 °C for 1 h, and at 25 °C for 8 h. The reaction mixture was cooled at 0 °C, 25 mL of conc. NH₄OH solution was added, and the reaction mixture was stirred at 0 °C for 30 min. The resulting solution was then poured into 30 mL of saturated NaCl solution. The organic layer was separated and washed with 15 mL of saturated NaCl solution. Careful extraction provided 5.05 g (80%)³³² of ether **252** as a yellow oil, with spectral data in excellent agreement with that previously reported for this compound.^{333ref}

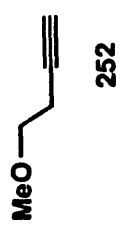
IR (thin film): 3280, 2920, 2870, 2820, 2730, 2110, 1460, 1380, 1330, 1260, 1230, 1190, 1110, 1060, 995, 980 (sh), 925, and 815 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 3.52 (t, J = 6.6 Hz, 2 H) , 3.39 (s, 3 H), 2.47 (td , J = 6.6, 2.8 Hz, 2 H), and 2.00 (t, J = 2.8 Hz, 1 H)

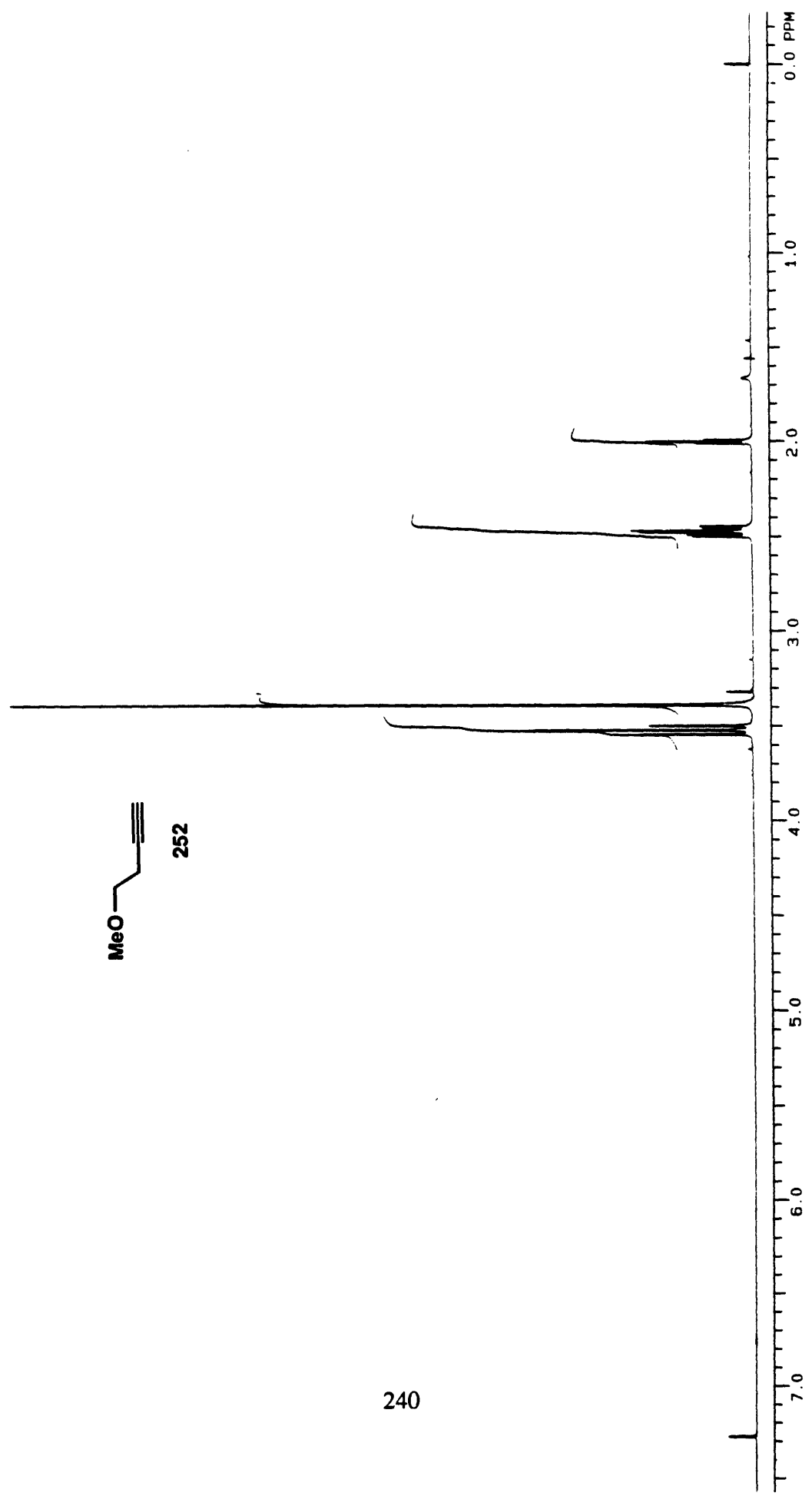
¹³C NMR (75 MHz, CDCl₃): 81.3, 70.6, 69.2, 58.7, and 19.7

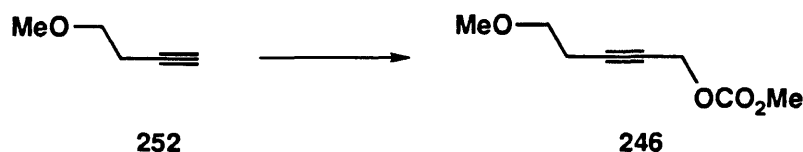
332. In other runs the yield for this reaction ranged from 73-80%.

333. McCusker, P. A.; Kroeger, J. W. *J. Am. Chem. Soc.* **1937**, *59*, 213.



240





5-Methoxy-1-Methoxycarbonyloxy-pent-2-yne (246). A 100-ml, three-necked, round-bottomed flask equipped with a rubber septum, a gas inlet adapter, and a glass stopper was charged with the acetylene **252** (0.99 mL, 0.841 g, 10 mmol) and 30 mL of THF and the solution was cooled at -78 °C. *n*-BuLi (2.44 M solution in hexane, 4.1 mL, 10 mmol) was added over 2 min and the resulting solution was stirred at -78 °C for 15 min. A suspension of paraformaldehyde (0.390 g, 13 mmol) in 10 mL of THF was then added via cannula, and the reaction mixture was heated at reflux for 2 h, and then cooled to 0 °C. Methyl chloroformate (0.97 mL, 1.18 g, 12.5 mmol) was then added over 1 min, and the reaction mixture was stirred at 0 °C for 30 min and at rt for 1 h. The reaction mixture was then partitioned between 50 mL of water and 50 mL of ether. The aqueous layer was separated and extracted with 30 mL of ether, and the combined organic phases were washed with 50 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated. Column chromatography on silica gel (elution with 15% ethyl acetate-hexane) provided 1.279 g (74%) of the carbonate **246** as a clear, colorless oil.

IR (thin film): 3000-2800, 2220, 1750, 1445, 1375, 1260, 1110, 945, and 785 cm⁻¹

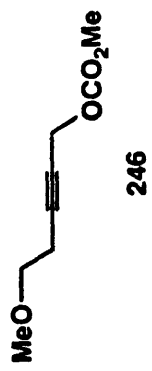
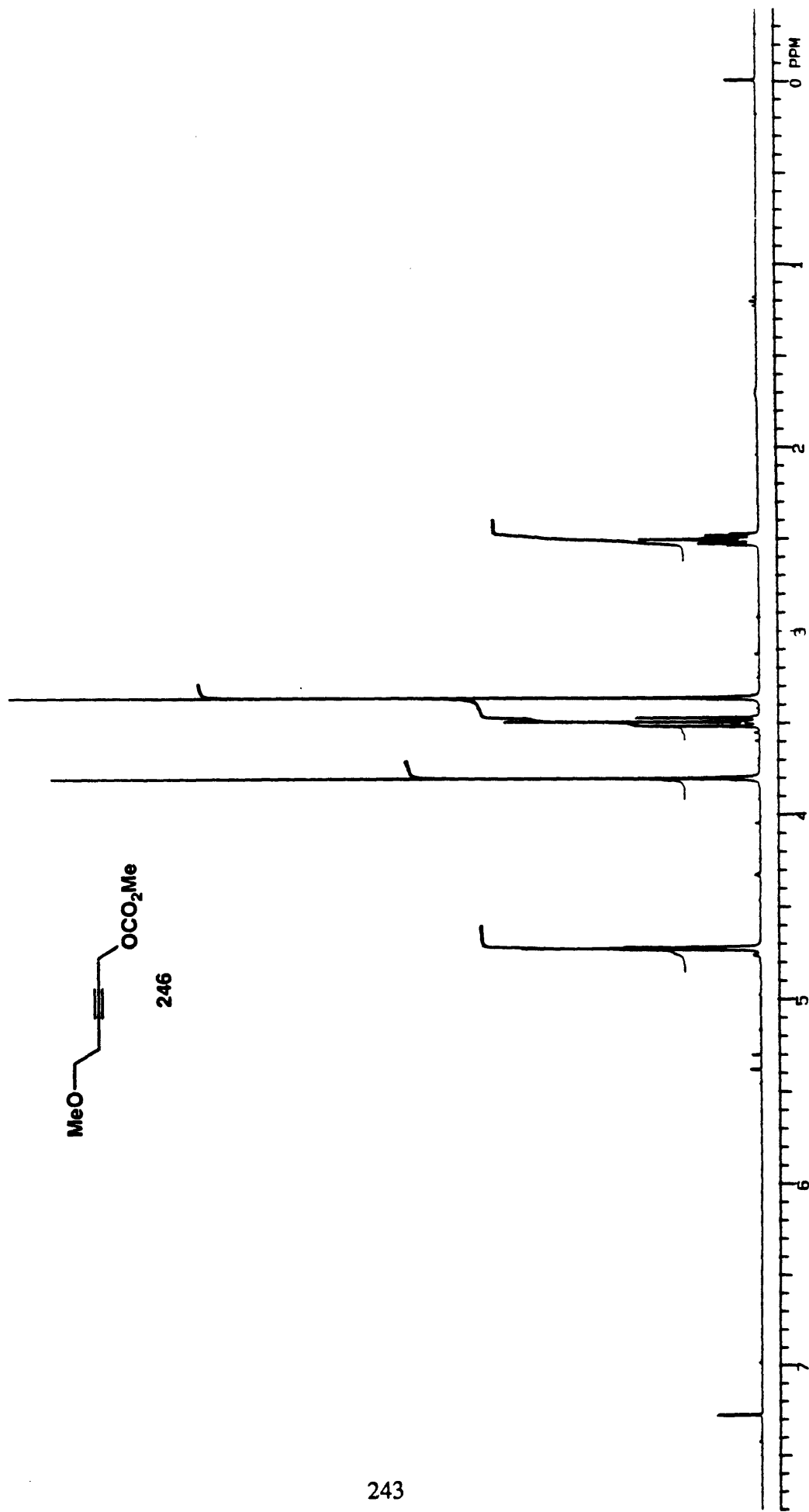
¹H NMR (300 MHz, CDCl₃): 4.72 (t, J = 2 Hz, 2 H), 3.91 (d, J = 2 Hz, 3 H), 3.49 (t, J = 6.8 Hz, 2 H), 3.36 (s, 3 H), and 2.50 (tt, J = 6.8, 2 Hz, 2 H)

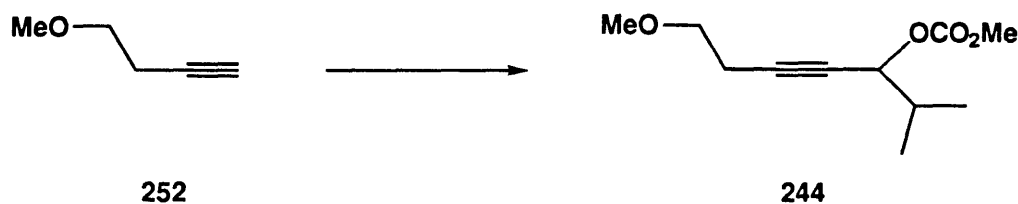
¹³C NMR (75 MHz, CDCl₃): 155.3, 85.0, 74.4, 70.4, 58.7, 56.1, 55.0, and 20.0

HRMS:

Calcd for $C_8H_{12}O_4$: 172.0736

Found: 172.0734





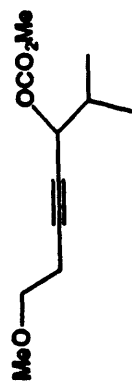
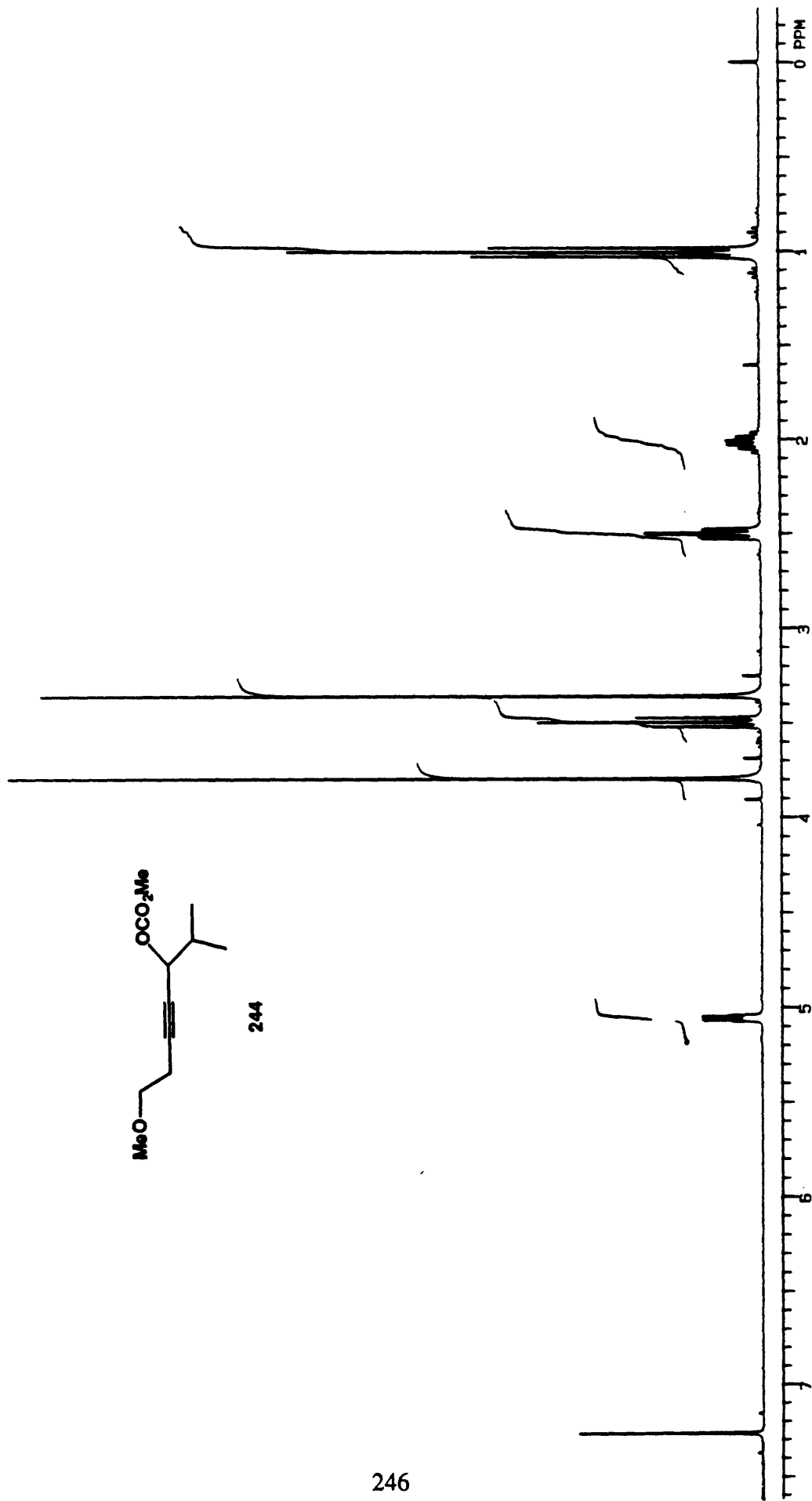
5-Methoxycarbonyloxy-6-methyl-1-methoxy-hept-3-yne (244)). A 100-ml, three-necked, round-bottomed flask equipped with a rubber septum, a gas inlet adapter, and a glass stopper was charged with the acetylene **252** (1.19 mL, 1.01 g, 12.0 mmol) and 30 mL of THF and the solution was cooled at -78 °C. *n*-BuLi (2.47 M solution in hexane, 4.86 mL, 12.0 mmol) was added over 5 min and the resulting solution was stirred at -78 °C for 15 min. A solution of isobutyraldehyde (0.91 mL, 0.721 g, 10 mmol) in 20 mL of THF was then added via cannula, and the reaction mixture was stirred at -78 °C for 3 h, and then allowed to warm to 0 °C. Methyl chloroformate (0.97 mL, 1.18 g, 12.5 mmol) was then added over 1 min, and the reaction mixture was stirred at 0 °C for 30 min and at rt for 15 min. The reaction mixture was then partitioned between 100 mL of water and 50 mL of ether. The aqueous layer was separated and extracted with 50 mL of ether, and the combined organic phases were washed with 100 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to afford 2.15 g of a yellow oil. Column chromatography on 30 g of silica gel (elution with 10% ethyl acetate-hexane) provided 1.832 g (86%)³³⁴ of the propargylic carbonate **244** as a clear, colorless oil.

IR (thin film): 2960, 2920, 2860, 2220, 1750, 1440, 1385, 1370, 1335, 1260, 1185, 1150, 1115, 970, and 785 cm⁻¹

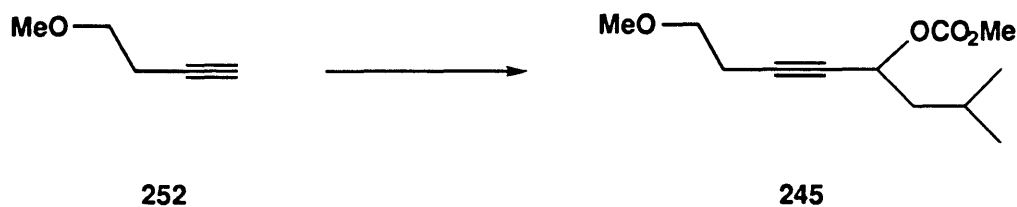
334. In other runs the yield for this reaction ranged from 83-86%.

Hz, 2 H) , 2.01 (m, 1 H), 1.02 (d, J = 7 Hz, 3 H),
and 1.00 (d, J = 7 Hz, 6 H)

^{13}C NMR (75 MHz, CDCl_3): 155.2, 84.2, 77.2, 73.5, 70.7, 58.6, 54.8, 32.6,
19.9, 18.1, and 17.4



244



1-Methoxy-5-methoxycarbonyloxy-7-methyl-oct-3-yne (245). A 50-ml, three-necked, round-bottomed flask equipped with a rubber septum, a gas inlet adapter, and a glass stopper was charged with the acetylene **252** (0.50 mL, 0.425 g, 5.06 mmol) and 20 mL of THF and the solution was cooled at -78 °C. *n*-BuLi (2.59 M solution in hexane, 1.95 mL, 5.06 mmol) was added over 2 min and the resulting solution was stirred at -78 °C for 15 min. A solution of isovaleraldehyde (0.45 mL, 0.363 g, 4.21 mmol) in 5 mL of THF was then added via cannula, and the reaction mixture was stirred at -78 °C for 3 h, and then allowed to warm to 0 °C. Methyl chloroformate (0.41 mL, 0.497 g, 5.26 mmol) was then added over 1 min, and the reaction mixture was stirred at 0 °C for 15 min and at rt for 30 min. The reaction mixture was then partitioned between 50 mL of water and 50 mL of ether. The aqueous layer was separated and extracted with 25 mL of ether, and the combined organic phases were washed with 75 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to afford 0.912 g of a yellow oil. Column chromatography on 20 g of silica gel (elution with 10% ethyl acetate-hexane) provided 0.807 g (84%) of the propargylic carbonate **245** as a clear, colorless oil.

IR (thin film): 2960, 2880, 2240, 1750, 1440, 1370, 1340, 1320, 1265, 1190, 1160, 1115, 1035, 935, and 790 cm⁻¹

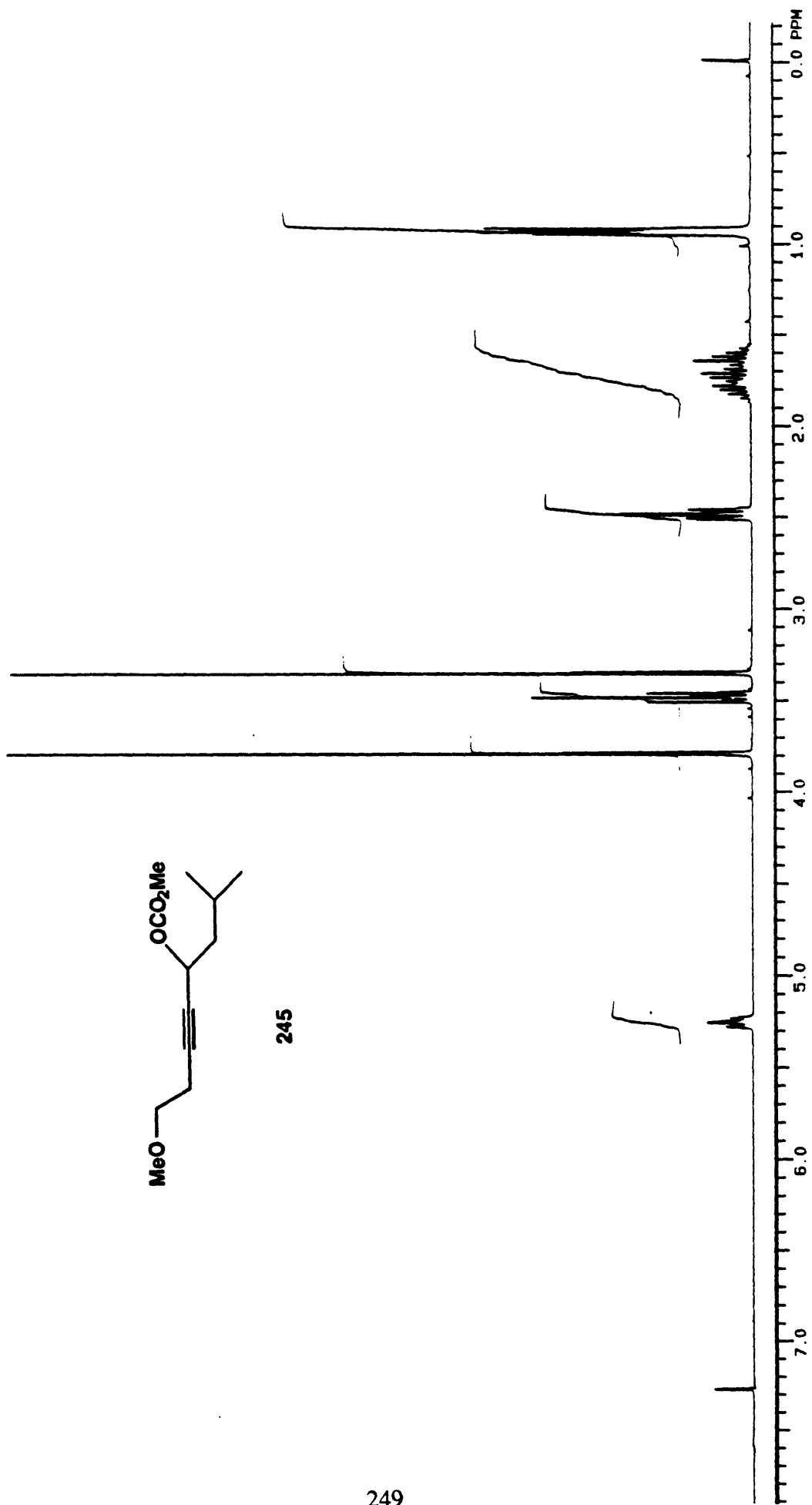
¹H NMR (300 MHz, CDCl₃): 5.26 (tt, *J* = 2.2, 6 Hz, 1 H), 3.79 (d, *J* = 2.6 Hz, 3 H), 3.48 (td, *J* = 2.2, 7 Hz, 2 H), 3.36 (d, *J* = 2.6 Hz, 3 H), 2.49 (td, *J* = 2.2, 7 Hz, 2 H), 1.60-1.88 (m, 3 H), 0.94 (d, *J* = 6 Hz, 3 H), and 0.93 (d, *J* = 6 Hz, 3 H)

^{13}C NMR (75 MHz, CDCl_3): 154.9, 83.5, 78.2, 70.6, 67.4, 58.7, 54.8, 43.9, 24.7, 22.4, and 20.0

HRMS: Calcd for $\text{C}_{12}\text{H}_{20}\text{O}_4$: 228.1362
Found: 228.1362



245





7-Methoxy-3-methoxycarbonyloxy-3-methyl-1-phenyl-hept-4-yne (241). A 50-ml, three-necked, round-bottomed flask equipped with a rubber septum, a gas inlet adapter, and a glass stopper was charged with the acetylene **252** (0.20 mL, 0.170 g, 2.02 mmol) and 8 mL of THF and the solution was cooled at -78 °C. *n*-BuLi (2.44 M solution in hexane, 0.83 mL, 2.02 mmol) was added over 2 min and the resulting solution was stirred at -78 °C for 20 min. A solution of benzyl acetone (0.24 mL, 0.240 g, 1.62 mmol) in 2 mL of THF was then added via cannula, and the reaction mixture was stirred at -78 °C for 2 h, and then allowed to warm to 0 °C. Methyl chloroformate (0.19 mL, 0.230 g, 2.43 mmol) was then added over 2 min, and the reaction mixture was stirred at 0 °C for 30 min and at rt for 30 min. The reaction mixture was then partitioned between 50 mL of water and 50 mL of ether. The aqueous layer was separated and extracted with 25 mL of ether, and the combined organic phases were washed with 75 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to afford 0.421 g of a yellow oil. Column chromatography on 10 g of silica gel (gradient elution with 10%-15% ethyl acetate-hexane) provided 0.344 g (73%) of the propargylic carbonate **241** as a pale yellow oil.

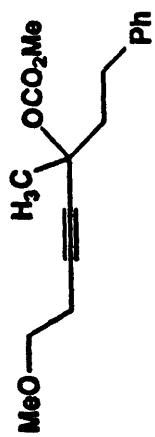
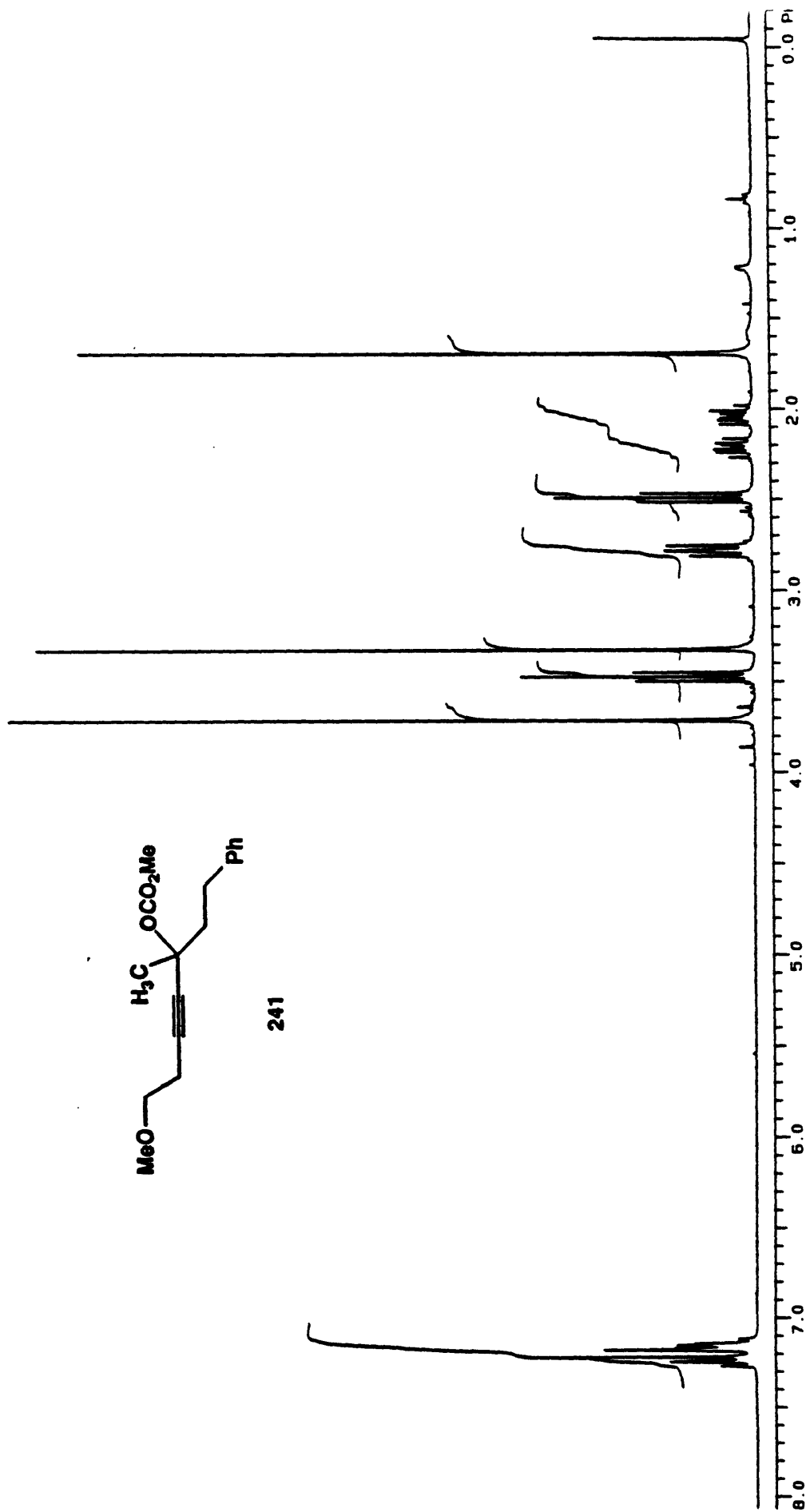
IR (thin film): 3160, 3120, 3080, 3030, 2860, 2240, 1750, 1600, 1495, 1440, 1370, 1330, 1260, 1165, 1110, 1080, 1055, 995, 940, 850, 785, 745, and 695 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 7.22- 7.27(m , 2 H) , 7.14- 7.18 (m , 3 H), 3.72 (s , 3 H) , 3.47 (t , J = 7 Hz, 2 H), 3.33 (s , 3 H) , 2.78 (app t , J = 8.5 Hz, 2 H), 2.49 (t , 7 Hz, 2

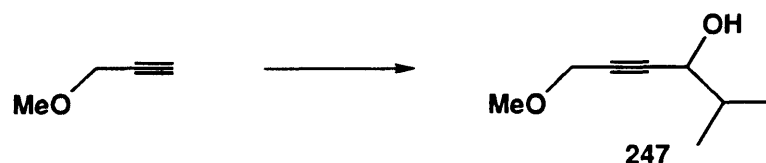
H), 2.19- 2.24 (m , 1 H), 2.01 -2.08 (m , 1 H) ,
and 1.69 (s , 3 H)

^{13}C NMR (75 MHz, CDCl_3): 153.5, 141.5, 128.4, 125.9, 83.4, 80.5, 77.2,
70.8, 58.7, 54.3, 43.6, 30.7, 26.6, and 20.0

HRMS: Calcd for $\text{C}_{17}\text{H}_{22}\text{O}_4$: 290.1518
Found: 290.1518



241



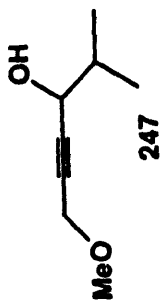
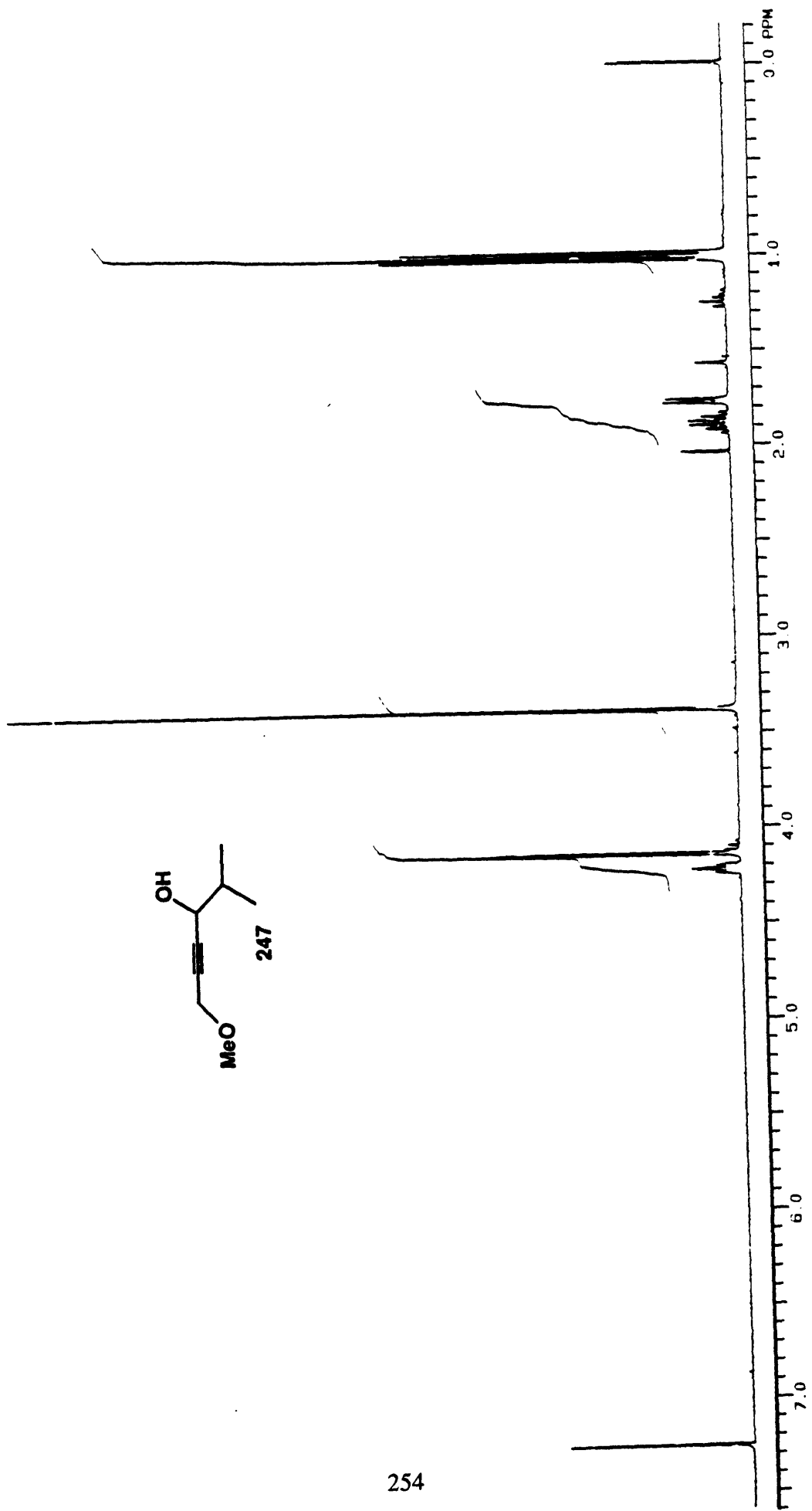
4-Hydroxy-1-methoxy-5-methyl-hex-2-yne (247). A 50-ml, three-necked, round-bottomed flask equipped with a rubber septum, a gas inlet adapter, and a glass stopper was charged with methyl propargyl ether (0.75 mL, 0.623 g, 8.88 mmol) and 24 mL of THF and the solution was cooled at 0 °C. *n*-BuLi (2.45 M solution in hexane, 3.63 mL, 8.88 mmol) was added over 3 min and the resulting solution was stirred at 0 °C for 30 min. A solution of isobutyraldehyde (0.54 mL, 0.427 g, 5.92 mmol) in 5 mL of THF was then added via cannula, and the reaction mixture was stirred at 0 °C for 1 h, and then at rt for 1 h. The reaction mixture was then partitioned between 50 mL of saturated NH₄Cl solution and 50 mL of ether. The aqueous layer was separated and extracted with 50 mL of ether, and the combined organic phases were washed with 50 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to afford 1.487 g of a yellow oil. Column chromatography on 30 g of silica gel (gradient elution with 10-30% ethyl acetate-hexane) provided 0.815 g (97%)³³⁵ of the propargylic alcohol **247** as a clear, colorless oil.

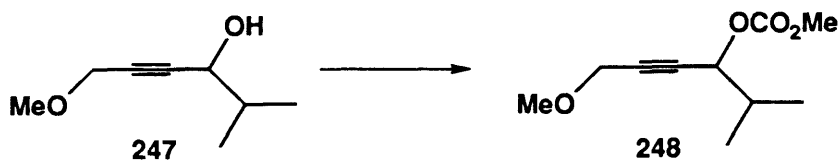
IR (thin film): 3500-3200, 2960, 2920, 2860, 1455, 1365, 1185, 1140, 1095, 1025, and 895 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 4.23 (br m, 1 H), 4.15 (d, *J* = 1.6 Hz, 2 H), 3.39 (s, 3 H), 1.88 (m, 1H), 1.77 (dd, *J* = 5.5, 1.6 Hz, 1 H), 1.02 (d, *J* = 6 Hz, 3 H), and 1.01 (d, *J* = 6 Hz, 3 H)

¹³C NMR (75 MHz, CDCl₃): 86.2, 81.3, 68.0, 59.9, 57.6, 34.5, 18.1, and 17.6

³³⁵. In other runs the yield for this reaction ranged from 87-97%.





4-Methoxycarbonyloxy-1-methoxy-5-methyl-hex-3-yne (248). A 50-ml, three-necked, round-bottomed flask equipped with a rubber septum, a gas inlet adapter, and a glass stopper was charged with the propargylic alcohol **247** (0.720 g, 5.06 mmol) and 35 mL of CH₂Cl₂ and the solution was cooled at 0 °C. DMAP (1.08 g, 8.86 mmol) was then added and the reaction was stirred at 0 °C for 5 min. Methyl chloroformate (0.59 mL, 0.718 g, 7.60 mmol) was then added dropwise over 1 min, and the reaction mixture was stirred at 0 °C for 30 min, and at rt for 15 min. The reaction mixture was then partitioned between 100 mL of 5% HCl solution and 100 mL of CH₂Cl₂. The aqueous layer was separated and extracted with 50 mL of CH₂Cl₂, and the combined organic phases were washed with 100 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to afford 1.91 g of an orange oil. Column chromatography on 40 g of silica gel (gradient elution with 5-10% ethyl acetate-hexane) provided 0.856 g (85%)³³⁶ of the propargylic carbonate **248** as a clear, colorless oil.

IR (thin film): 2960, 2930, 2870, 2820, 2230, 2190, 1750, 1440, 1355, 1335, 1265, 1185, 1150, 1135, 1095, 965, 940, 900, and 780 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 5.12 (br d, J = 5.5 Hz, 1 H), 4.15 (s, 2 H), 3.81 (s, 3 H), 3.38 (s, 3 H), 2.01-2.11 (m, 1 H), 1.05 (d, J = 7 Hz, 3 H), and 1.03 (d, J = 7 Hz, 3 H)

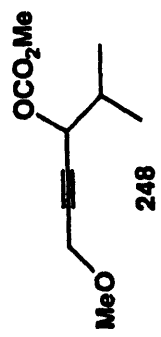
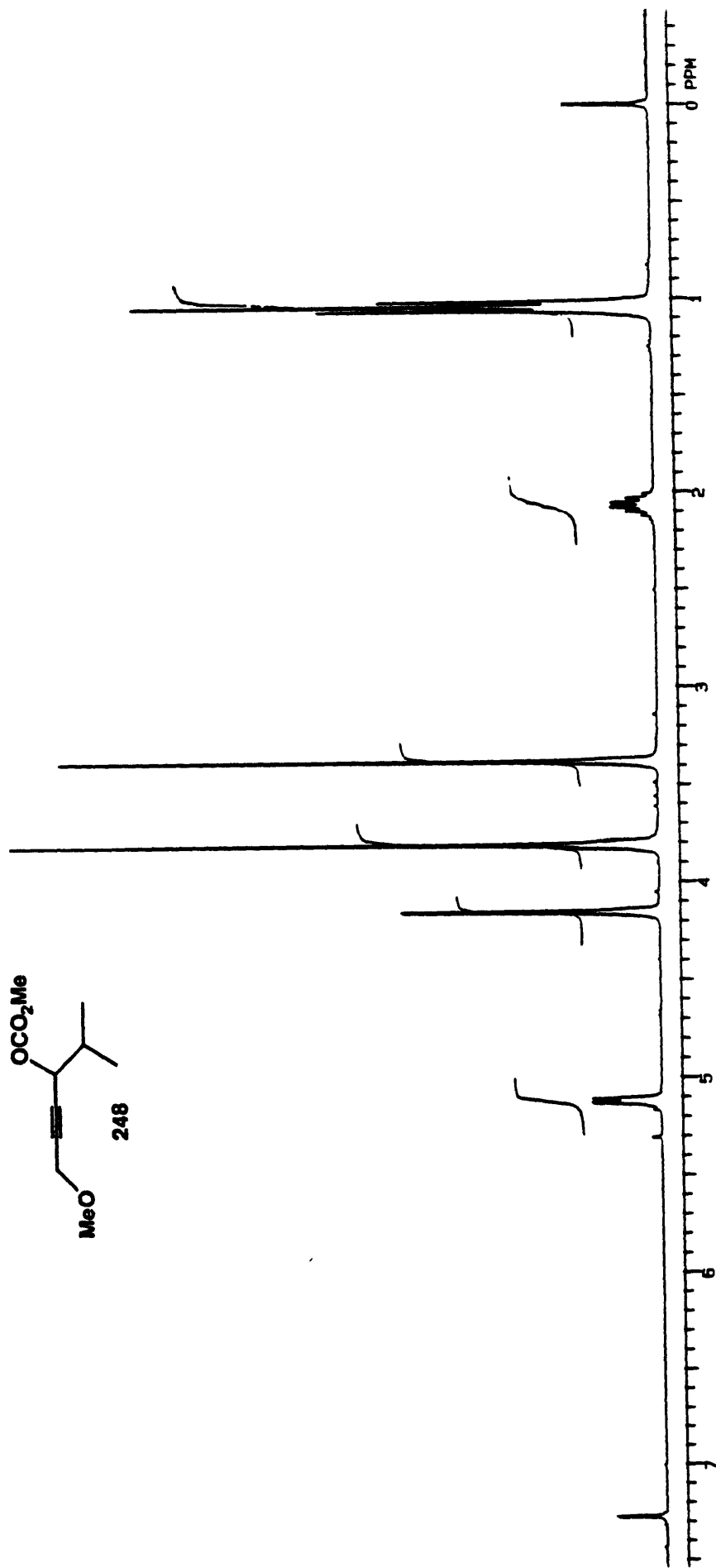
¹³C NMR (75 MHz, CDCl₃): 155.1, 82.7, 82.0, 73.1, 59.7, 57.5, 54.9, 32.4, 18.0, and 17.5

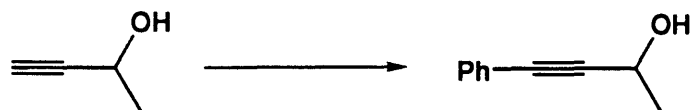
³³⁶. In other runs the yield for this reaction ranged from 77-85%.

HRMS:

Calcd for $C_{10}H_{16}O_4$: 200.1049

Found: 200.1049





249

1-Phenyl-2-butyn-3-ol (249). A 50-ml, three-necked, round-bottomed flask equipped with a rubber septum, a gas inlet adapter, and a glass stopper was charged with iodobenzene (0.60 mL, 1.093 g, 5.36 mmol) and 20 mL of Et₂NH. 3-Butyn-2-ol (0.50 mL, 0.451 g, 6.43 mmol), CuI (0.012 g, 0.107 mmol), and PdCl₂(Ph₃P)₂ (0.113 g, 0.161 mmol) were then added and the reaction mixture was stirred at rt for 18 h. Et₂NH was then removed using the aspirator and the residue was partitioned between 100 mL of water and 100 mL of CH₂Cl₂. The aqueous layer was separated and extracted with 50 mL of CH₂Cl₂ and the combined organic phases were washed with 100 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to afford 1.103 g of a red-brown oil. Column chromatography on 22 g of silica gel (gradient elution with 5-30% ethyl acetate-hexane) provided 0.783 g (100%)³³⁷ of the alcohol **249** as a light brown oil.

IR (thin film): 3500-3100, 2980, 2920, 2860, 2220, 1595, 1490, 1440, 1370, 1320, 1100, 1070, 1020, 930, 850, and 750 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 7.43 (m, 2 H) , 7.30 (m, 3 H), 4.76 (m, 1 H), 1.88 (d , J = 5 Hz, 1 H), and 1.56 (d, J = 6 Hz, 3 H)

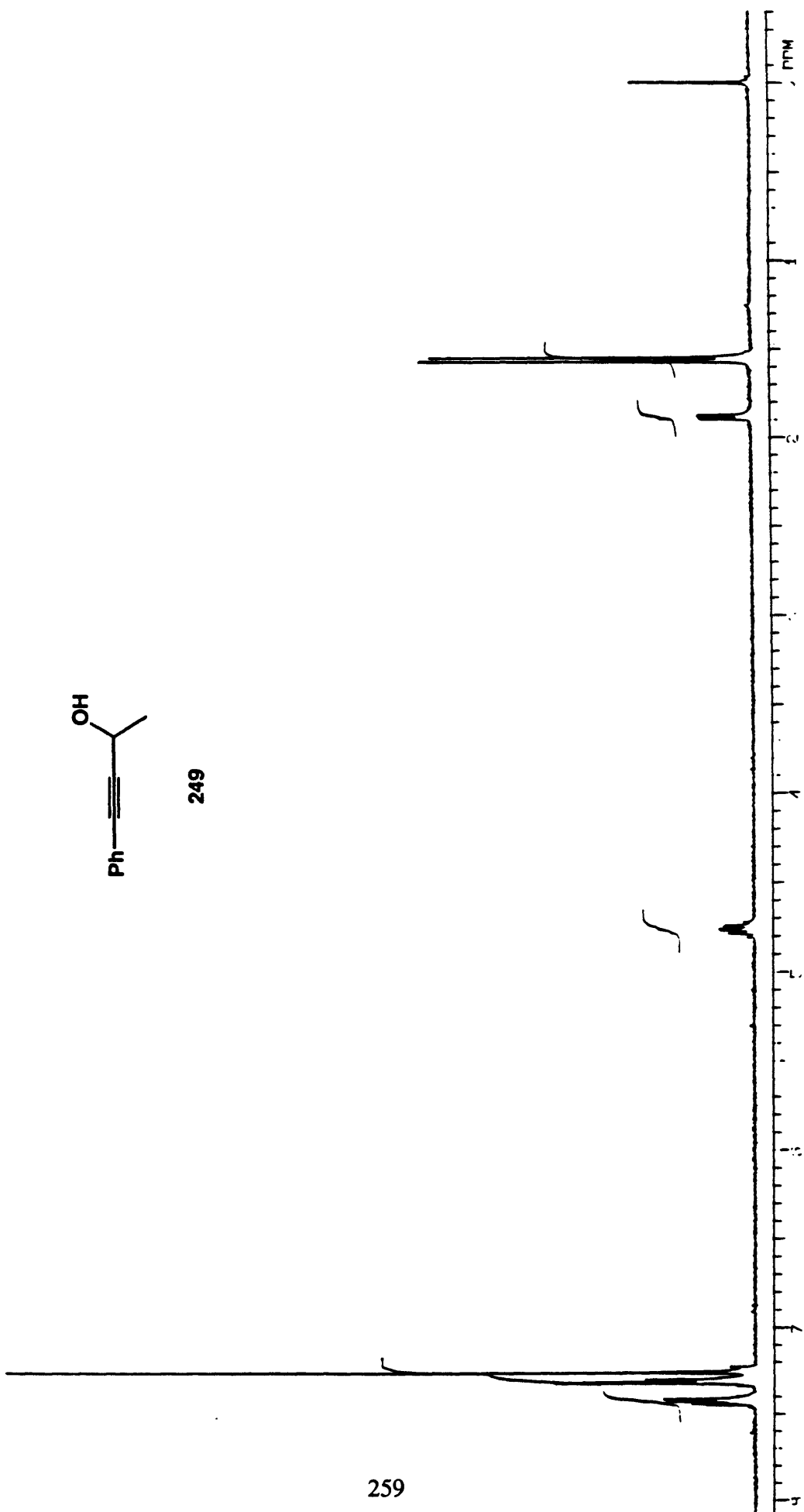
¹³C NMR (75 MHz, CDCl₃): 131.6, 128.3, 128.2, 122.5, 90.9, 84.0, 58.9, and 24.5

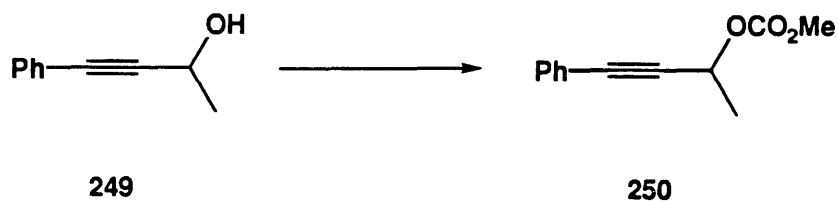
HRMs: Calcd for C₁₀H₁₀O: 146.0732
 Found: 146.0729

337. In other runs the yield for this reaction ranged from 95-100%.



249





3-Methoxycarbonyloxy-1-phenylbutyne (250). A 50-ml, three-necked, round-bottomed flask equipped with a rubber septum, a gas inlet adapter, and a glass stopper was charged with the propargylic alcohol **249** (0.763 g, 5.22 mmol) and 35 mL of CH₂Cl₂ and the solution was cooled at 0 °C. DMAP (1.275 g, 10.4 mmol) was then added and the reaction mixture was stirred at 0 °C for 10 min. Methyl chloroformate (0.60 mL, 0.740 g, 7.83 mmol) was then added dropwise over 1 min, and the reaction mixture was stirred at 0 °C for 30 min, and at rt for 1 h. The reaction mixture was then poured into 100 mL of 5% HCl solution and 50 mL of CH₂Cl₂. The aqueous layer was separated and extracted with 50 mL of CH₂Cl₂, and the combined organic phases were washed with 80 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to afford 1.09 g of an orange oil. Column chromatography on 20 g of silica gel (gradient elution with 5-10% ethyl acetate-hexane) provided 0.942 g (88%)³³⁸ of the carbonate **250** as a pale yellow oil.

IR (thin film): 3000, 2940, 2240, 1755, 1490, 1445, 1350, 1320, 1270, 1110, 1080, 1020, 940, 920, 860, 790, 760, and 690 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 7.44 (m, 2 H) , 7.30 (m, 3 H), 5.56 (q, J = 6.7 Hz, 1 H), 3.82 (s, 3 H), and 1.64 (d, J = 6.7 Hz, 3 H)

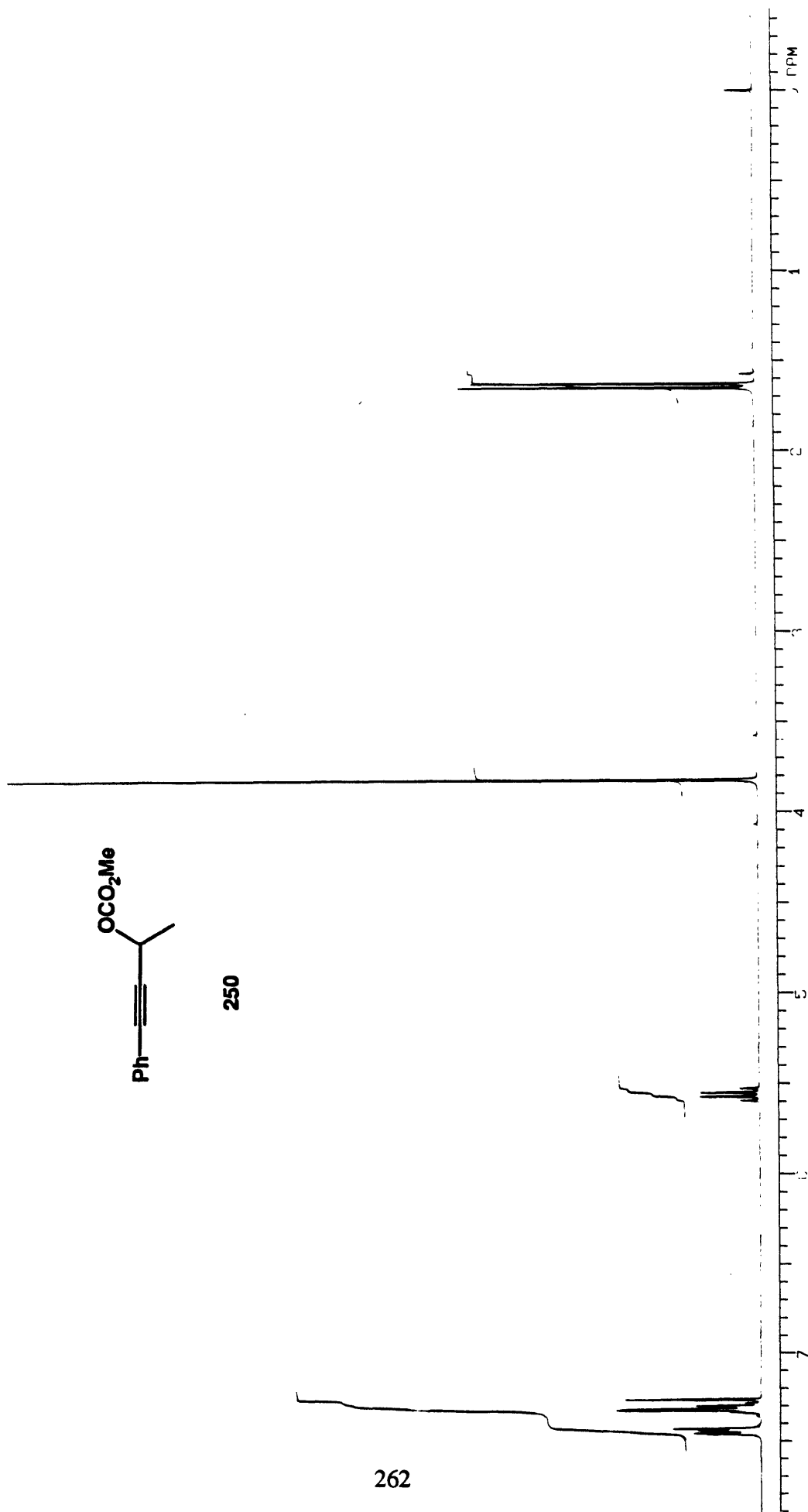
¹³C NMR (75 MHz, CDCl₃): 154.0, 131.8, 128.6, 128.1, 122.0, 86.6, 85.4, 64.9, 54.9, and 21.6

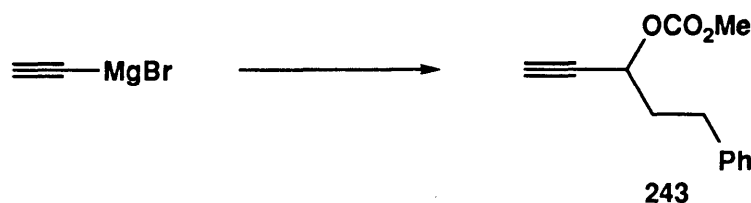
³³⁸. In other runs the yield for this reaction ranged from 77-88%.

HRMS:

Calcd for $C_{12}H_{12}O_3$: 204.0786

Found: 204.0787





3-Methoxycarbonyloxy-5-Phenylpentyne (243). A 50-ml, three-necked, round-bottomed flask equipped with a rubber septum, a gas inlet adapter, and a glass stopper was charged with ethynylmagnesium bromide (0.5 M solution in ether, 12.5 mL, 6.25 mmol) and 10 mL of THF and the solution was cooled at 0 °C. A solution of hydrocinnamaldehyde (0.66 mL, 0.671 g, 5.0 mmol) in 10 mL of THF was then added via cannula over 5 min, and the reaction mixture was stirred at 0 °C for 30 min. Methyl chloroformate (0.58 mL, 0.709 g, 7.5 mmol) was then added over 1 min, and the reaction mixture was stirred at 0 °C for 30 min and at rt for 1 h. The reaction mixture was then partitioned between 50 mL of saturated NH₄Cl solution and 50 mL of ether. The aqueous layer was separated and extracted with 30 mL of ether, and the combined organic phases were washed with 75 mL of saturated NaCl solution, dried over MgSO₄, filtered and concentrated to afford 1.02 g of a yellow oil. Column chromatography on 20 g of silica gel (elution with 10% ethyl acetate-hexane) provided 0.808 g (74%)³³⁹ of the propargylic carbonate **243** as a colorless oil.

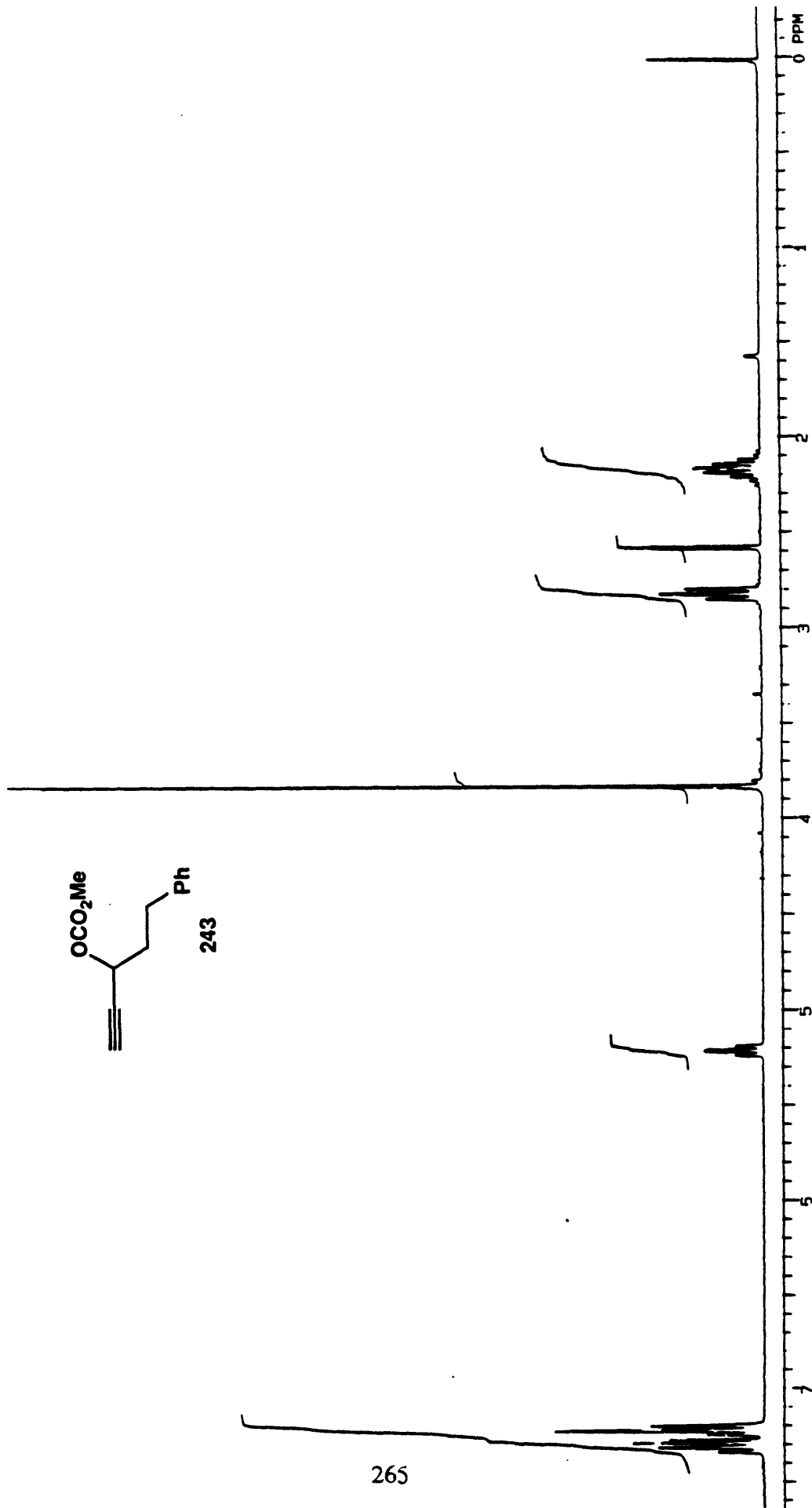
IR (thin film): 3280, 3020, 2950, 2850, 2110, 1745, 1600, 1490, 1440, 1345, 1260, 1175, 1100, 1010, 950, 785, and 740 cm⁻¹

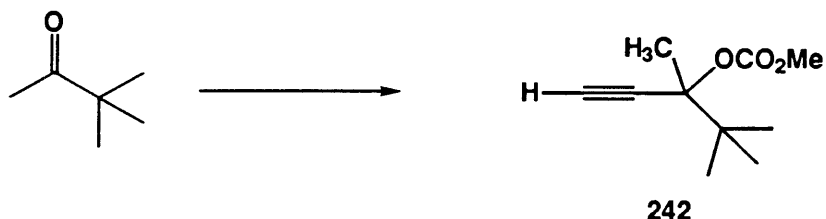
¹H NMR (300 MHz, CDCl₃): 7.20-7.34 (m, 5 H), 5.21 (tt, J = 6.6, 1 Hz, 1 H), 3.84 (d, J = 1 Hz, 3 H), 2.82 (app t, J = 8 Hz, 2 H), 2.58 (t, J = 1 Hz, 1 H), and 2.14-2.22 (m, 2 H)

³³⁹. In other runs the yield for this reaction ranged from 64-74%.

^{13}C NMR (75 MHz, CDCl_3): 154.9, 140.4, 128.5, 128.4, 126.2, 80.2, 74.8, 67.2, 55.0, 36.1, and 31.0

HRMS: Calcd for $\text{C}_{13}\text{H}_{14}\text{O}_3$: 218.0943
Found: 218.0942





3-Methoxycarbonyloxy-3,4,4-trimethylpentyne (242). A 100-ml, three-necked, round-bottomed flask equipped with a rubber septum, a gas inlet adapter, and a glass stopper was charged with ethynylmagnesium bromide (0.5 M solution in Et₂O, 30 mL, 15 mmol) and cooled at 0 °C. A solution of pinacolone (1.32 mL, 1.05 g, 10 mmol) in 20 mL of THF was then added via cannula over 2 min, and the reaction mixture was stirred at 0 °C for 2 h, and then at rt for 1 h. The reaction mixture was cooled at 0°C, methyl chloroformate (1.16 mL, 1.42 g, 15 mmol) was added over 1 min, and the reaction mixture was stirred at 0 °C for 30 min, and at rt for 16 h. The reaction mixture was then partitioned between 100 mL of saturated NH₄Cl solution and 50 mL of ether. The aqueous layer was separated and extracted with two 50-mL portions of ether, and the combined organic phases were washed with 50 mL of water, 50 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to afford 1.997 g of a brown oil. Column chromatography on 30 g of silica gel (elution with 10% ethyl acetate-hexane) provided 1.48 g (80%) of the propargylic carbonate **242** as a pale yellow oil.

IR (thin film): 3280, 2960, 2905, 2880, 2110, 1750, 1440, 1390, 1365, 1260, 1155, 1125, 1060, 1000, 940, 910, 865, and 785 cm⁻¹

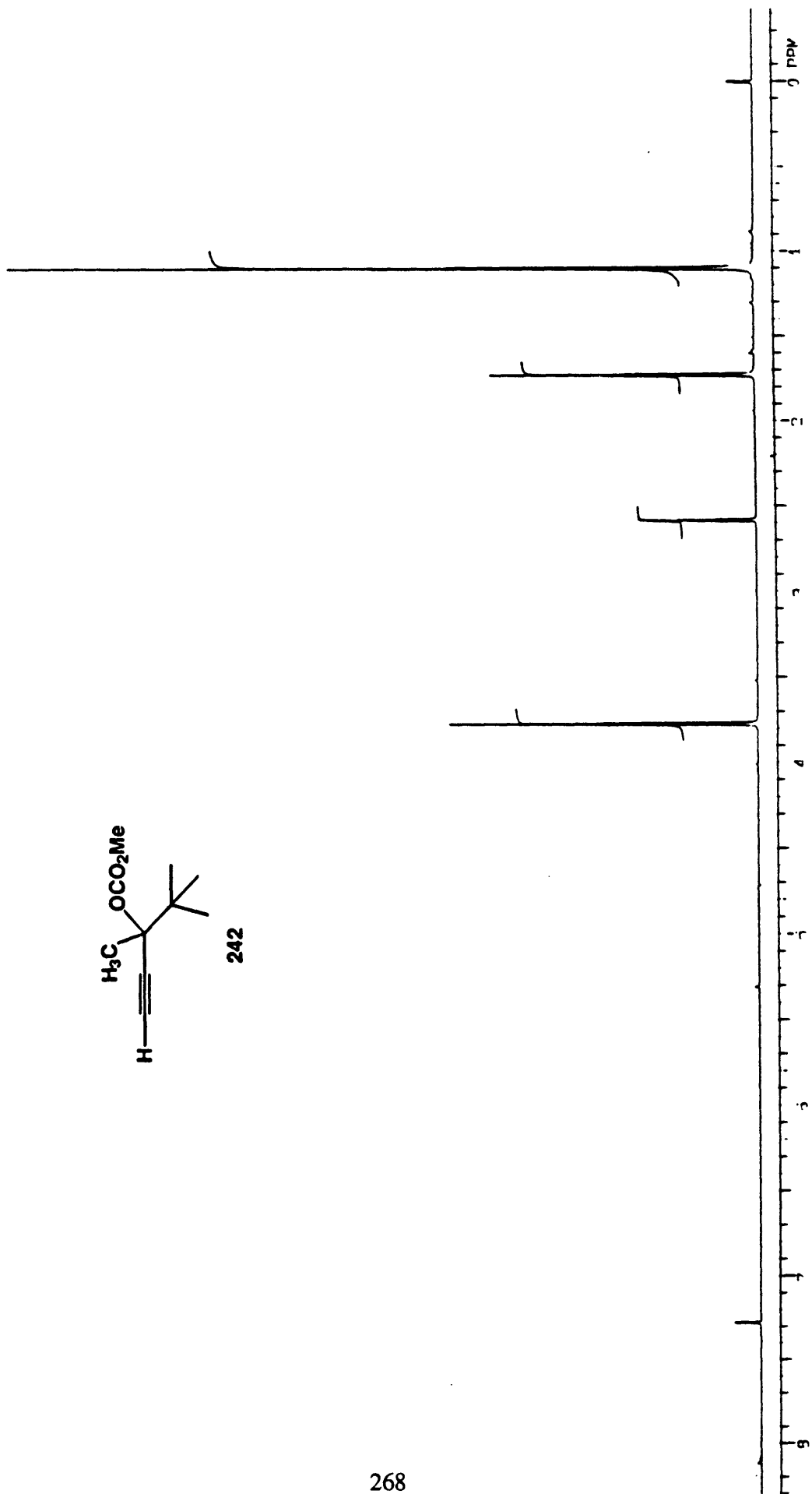
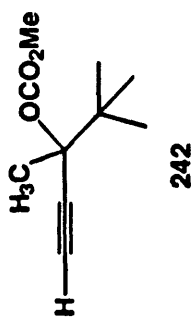
¹H NMR (300 MHz, CDCl₃): 3.77 (s , 3 H) , 2.58 (s , 1 H), 1.73 (s, 3 H), and 1.10 (s, 9 H)

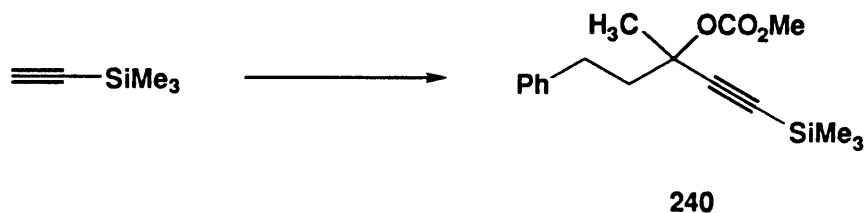
¹³C NMR (75 MHz, CDCl₃): 153.8, 82.6, 82.4, 74.5, 54.3, 38.9, 24.9, and 20.5

HRMS:

Calcd for $C_{10}H_{16}O_3$: 184.1100

Found: 184.1103





3-Methoxycarbonyloxy-3-methyl-5-phenyl-1-trimethylsilylpentyne (240). A 100-ml, three-necked, round-bottomed flask equipped with a rubber septum, a gas inlet adapter, and a glass stopper was charged with trimethylsilylacetylene (0.83 mL, 0.589 g, 6.0 mmol) and 30 mL of THF and the solution was cooled at -78 °C. *n*-BuLi (2.73 M solution in hexane, 2.2 mL, 6 mmol) was added over 3 min and the resulting solution was stirred at -78 °C for 20 min. A solution of benzyl acetone (0.75 mL, 0.741 g, 5.0 mmol) in 10 mL of THF was then added via cannula, and the reaction mixture was stirred at -78 °C for 3 h, and allowed to warm to 0 °C. Methyl chloroformate (0.48 mL, 0.591 g, 6.25 mmol) was then added over 1 min, and the reaction mixture was stirred at 0 °C for 15 min, and at rt for 30 min. The reaction mixture was then partitioned between 100 mL of water and 100 mL of ether. The aqueous layer was separated and extracted with 50 mL of ether, and the combined organic phases were washed with 100 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to afford 1.755 g of a yellow oil. Column chromatography on 20 g of silica gel (elution with 20% ethyl acetate-hexane) provided 1.358 g (89%)³⁴⁰ of the propargylic carbonate **240** as a clear, colorless oil.

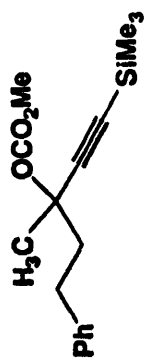
IR (thin film): 3070, 3030, 2960, 2840, 2170, 1750, 1715, 1600, 1495, 1440, 1370, 1290-1230, 1165, 1085, 1060, 940, 895, 840, 790, 755, and 700 cm⁻¹

³⁴⁰. In other runs the yield for this reaction ranged from 75-89%.

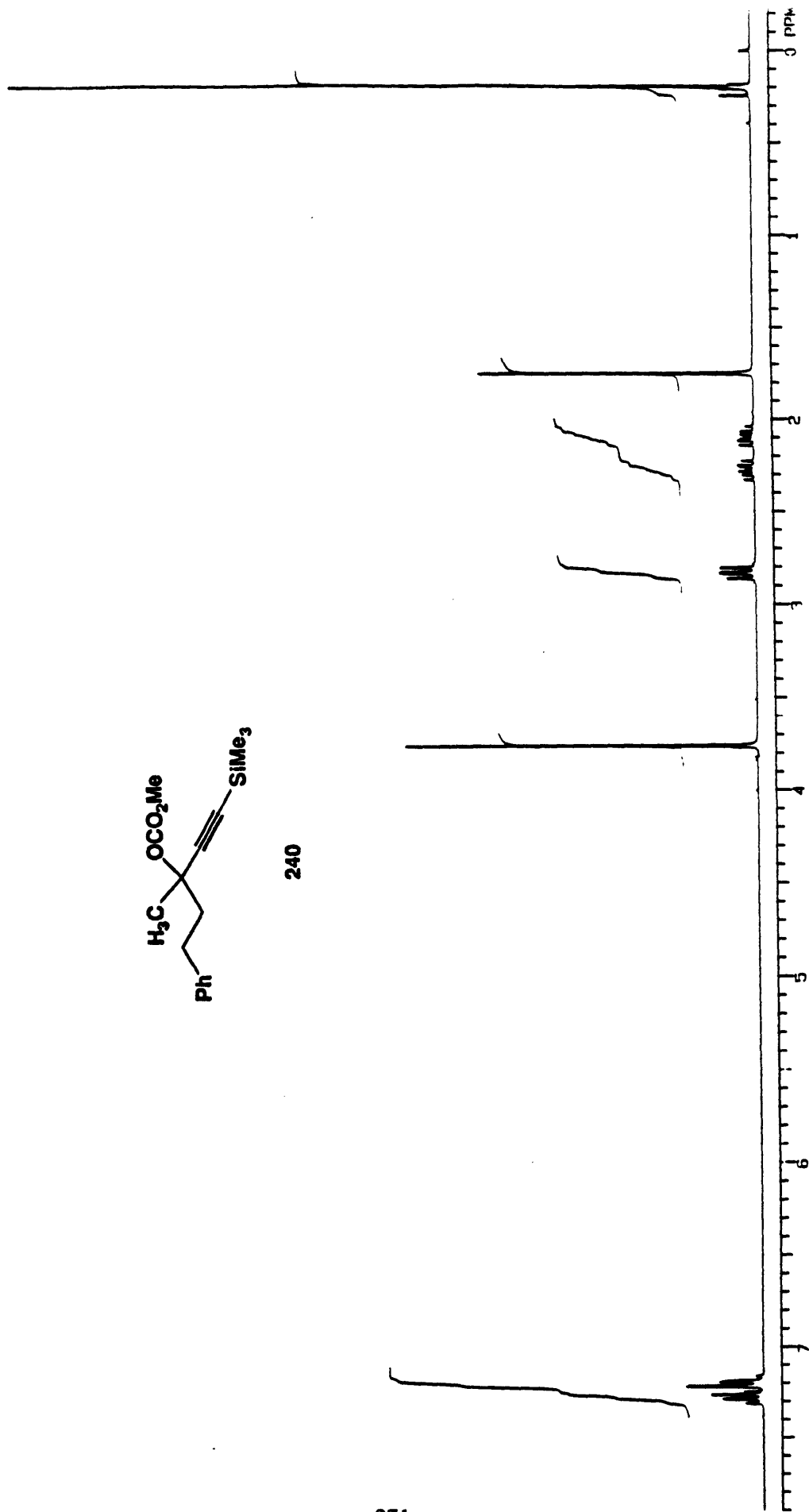
^1H NMR (300 MHz, CDCl_3): 7.19- 7.29 (m , 5 H) , 3.79 (s , 3 H), 2.83 (app t ,
J = 8 Hz, 2 H), 2.23- 2.33 (ddd, J = 7, 8 , 9.5 Hz
, 1 H), 2.04- 2.14 (ddd, J = 7, 8 , 9.5 Hz , 1 H),
1.75 (s , 3 H) , and 0.20 (s , 9 H)

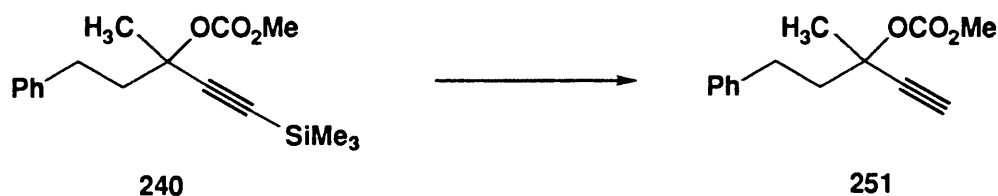
^{13}C NMR (75 MHz, CDCl_3): 153.3, 141.4, 128.4, 125.9, 104.3, 90.7, 77.3,
54.3, 43.4, 30.7, 26.4, and -0.20

HRMS: Calcd for $\text{C}_{17}\text{H}_{24}\text{O}_3\text{Si}$: 304.1495
Found: 304.1495



240





3-Methoxycarbonyl-3-methyl-1-phenyl-pent-4-yne (251). A 25-ml, three-necked, round-bottomed flask equipped with a rubber septum, a gas inlet adapter, and a pressure-equalizing addition funnel was charged with acetylene **240** (0.600 g, 1.97 mmol) and 4 mL of EtOH. A solution of AgNO₃ (0.446 g, 2.62 mmol) in 2 mL of H₂O and 6 mL of EtOH was then added dropwise via the addition funnel over 10 min. A white precipitate formed. The reaction mixture was stirred for an additional 15 min. A solution of KCN (0.822 g, 12.6 mmol) in 4 mL of H₂O was then added over 5 min, and the reaction mixture was stirred for 45 min. The precipitate dissolved. The reaction mixture was then partitioned between 20 mL of water and 20 mL of ether. The aqueous layer was separated and extracted with 15 mL of ether, and the combined organic phases were washed with 35 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated. Column chromatography on 10 g of silica gel (gradient elution with 10% ethyl acetate-hexane) provided 0.434 g (95%)³⁴¹ of the propargylic carbonate **251** as a clear, colorless oil.

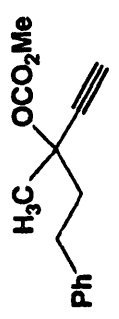
IR (thin film): 3260, 3040, 3010, 2940, 2850, 2100, 1750, 1600, 1490, 1435, 1370, 1290, 1165, 1060, 1025, 935, 880, and 785 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 7.17- 7.32 (m, 5 H) , 3.79 (s, 3 H), 2.85 (td , J = 4, 8 Hz, 2 H), 2.66 (s, 1 H), 2.23- 2.34 (m, 1 H), 2.07- 2.17 (m, 1 H), and 1.75 (s, 3 H)

³⁴¹. In other runs the yield for this reaction ranged from 94-95%.

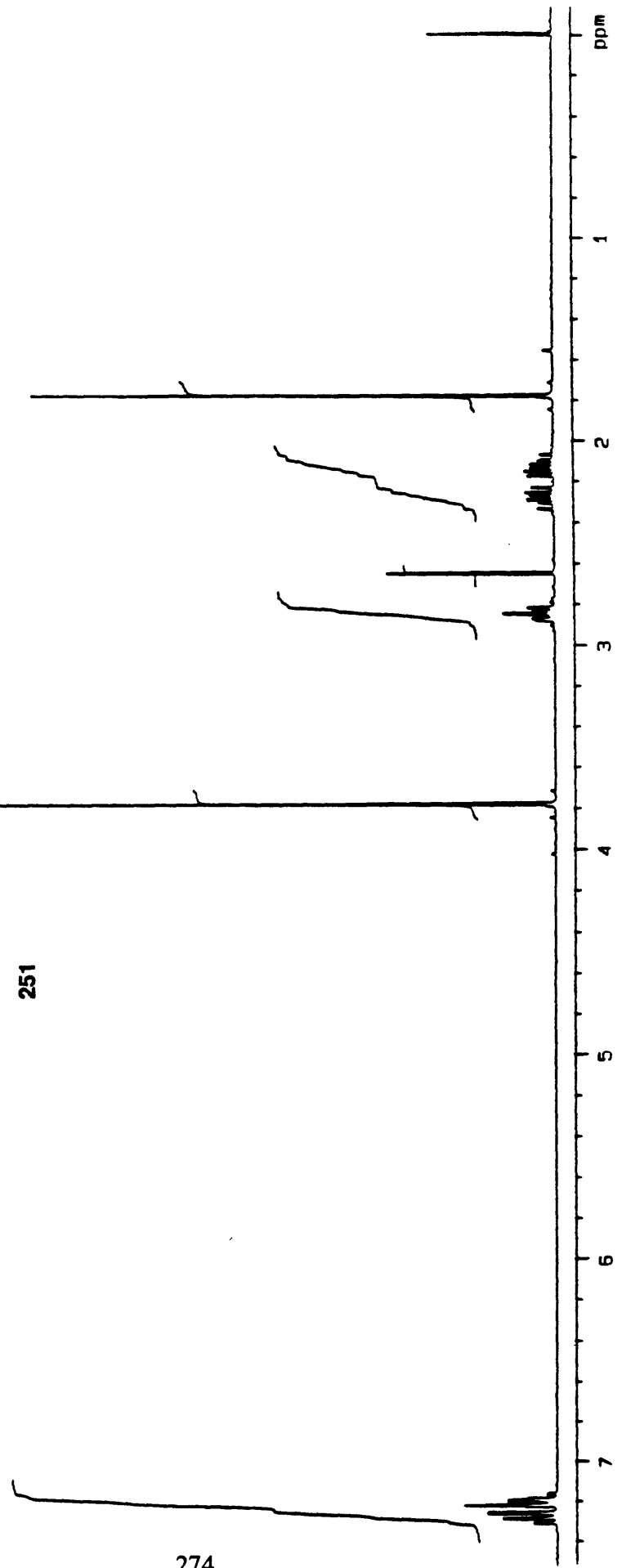
^{13}C NMR (75 MHz, CDCl_3): 153.3, 141.1, 128.45, 128.42, 126.0, 91.6, 82.9, 74.2, 54.4, 43.3, 30.5, and 26.4

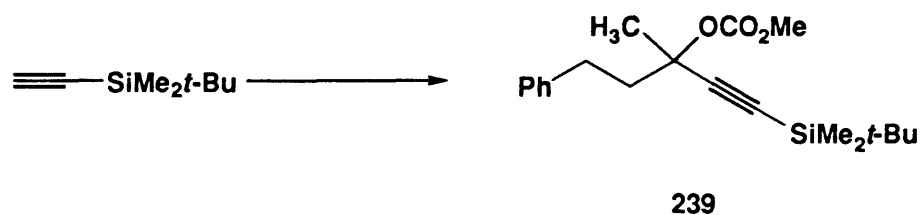
HRMS: Calcd for $\text{C}_{14}\text{H}_{16}\text{O}_3$: 232.1010
Found: 232.1014



251

274





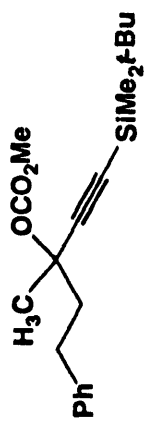
3-Methoxycarbonyloxy-3-methyl-5-phenyl-1-*t*-butyltrimethylsilylpentyne (239). A 50-ml, three-necked, round-bottomed flask equipped with a rubber septum, a gas inlet adapter, and a glass stopper was charged with *t*-butyltrimethylsilylacetylene (0.372 g, 2.65 mmol) and 10 mL of THF and the solution was cooled at -78 °C. *n*-BuLi (2.41 M solution in hexane, 1.10 mL, 2.65 mmol) was added over 3 min and the resulting solution was stirred at -78 °C for 15 min. A solution of benzyl acetone (0.32 mL, 0.314 g, 2.12 mmol) in 6 mL of THF was then added via cannula, and the reaction mixture was stirred at -78 °C for 3 h, and allowed to warm to 0 °C. Methyl chloroformate (0.20 mL, 0.250 g, 2.65 mmol) was then added over 1 min, and the reaction mixture was stirred at 0 °C for 30 min, and at rt for 2 h. The reaction mixture was then partitioned between 30 mL of water and 30 mL of ether. The aqueous layer was separated and extracted with 20 mL of ether, and the combined organic phases were washed with 50 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to afford 0.526 g of a yellow oil. Column chromatography on 20 g of silica gel (elution with 15% ethyl acetate-hexane) provided 0.495 g (67%) of the propargylic carbonate **239** as a clear, colorless oil.

IR (thin film): 2940, 2920, 2850, 2160, 1750, 1490, 1440, 1370, 1360, 1260, 1160, 1060, 940, 880, 820, 770, 690, and 670 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 7.20- 7.32 (m , 5 H) , 3.76 (s , 3 H), 2.85 (app t , J = 8.5 Hz, 2 H), 2.22- 2.32 (m, 1 H), 2.02- 2.12 (m, 1 H), 1.77 (s , 3 H) , 0.97 (s, 9 H), and 0.14 (s , 6 H)

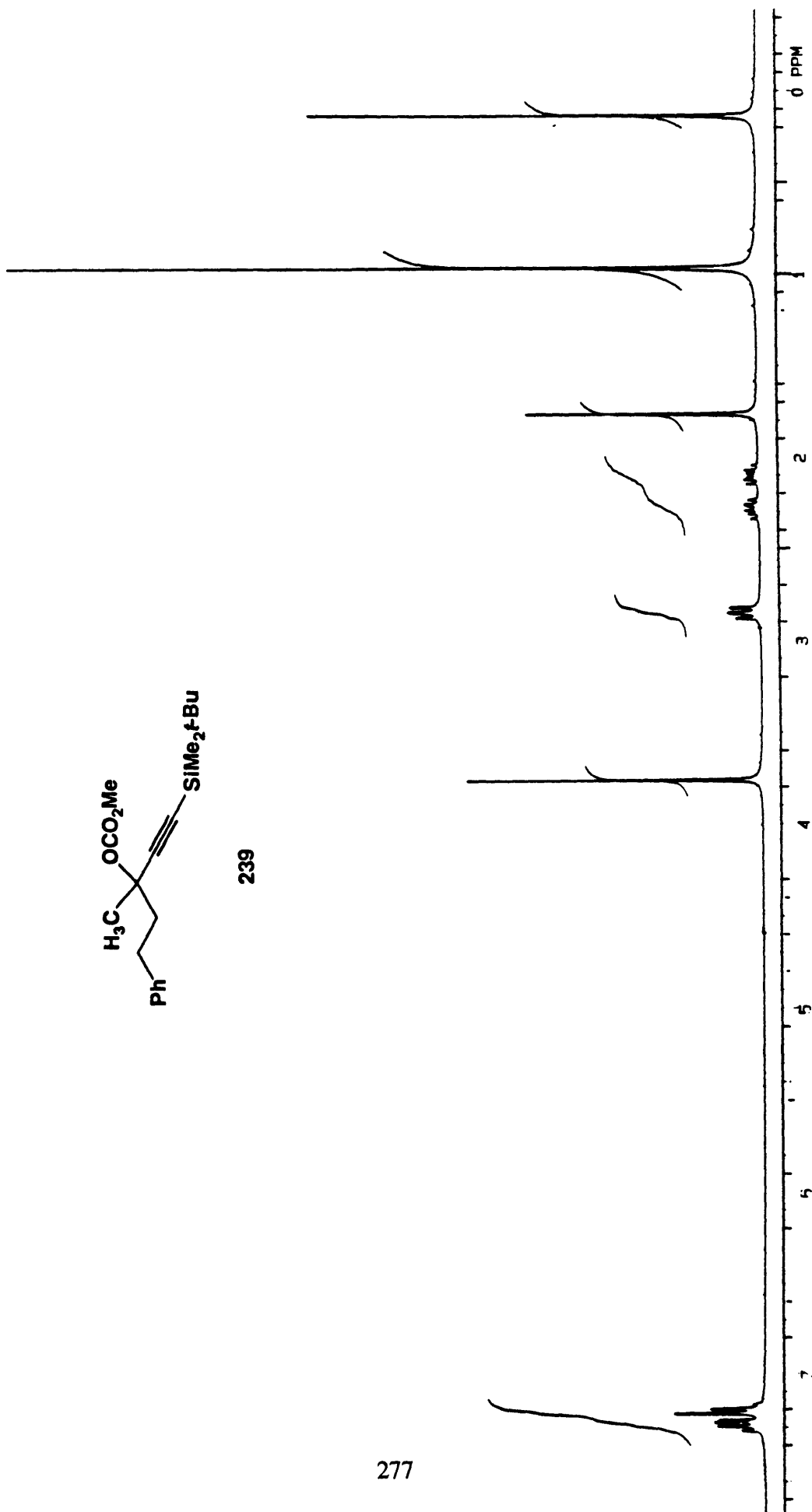
^{13}C NMR (75 MHz, CDCl_3): 153.3, 141.4, 128.4, 125.9, 104.9, 89.1, 77.3, 54.3, 43.5, 30.8, 26.5, 26.0, 16.5, and -4.8

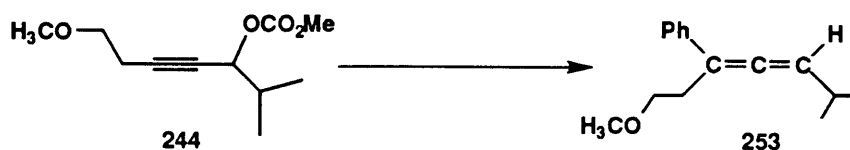
HRMS: Calcd for $\text{C}_{20}\text{H}_{30}\text{SiO}_3$: 346.1964
Found: 346.1964



239

277





General Procedure for the Coupling of Phenylboronic Acid and (*E*)-1-Octenylboronic Acid with Propargylic Carbonates. Synthesis of 1-Methoxy-6-methyl-3-phenyl-3,4-heptadiene (253**).** A 10-mL, two-necked, round-bottomed flask equipped with a rubber septum and a reflux condenser fitted with an argon inlet was charged with the propargylic carbonate **244** (0.250 g, 1.17 mmol), phenylboronic acid (0.171 g, 1.40 mmol), PdCl₂(dppf) (0.043 g, 0.0583 mmol), K₂CO₃ (0.323 g, 2.33 mmol), and 5 mL of DME. The solution was heated at reflux for 8 h, allowed to cool to room temperature, and then transferred to a separatory funnel with the aid of 25 mL of ether and 25 mL of water. The aqueous layer was separated and extracted with 30 mL of ether, and the combined organic phases were washed with 50 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to give 0.233 g of a brown oil. Column chromatography on 10 g of silica gel (elution with 1% ethyl acetate-hexane) provided 0.170 g (67%)³⁴² of the allene **253** as a clear, colorless oil.

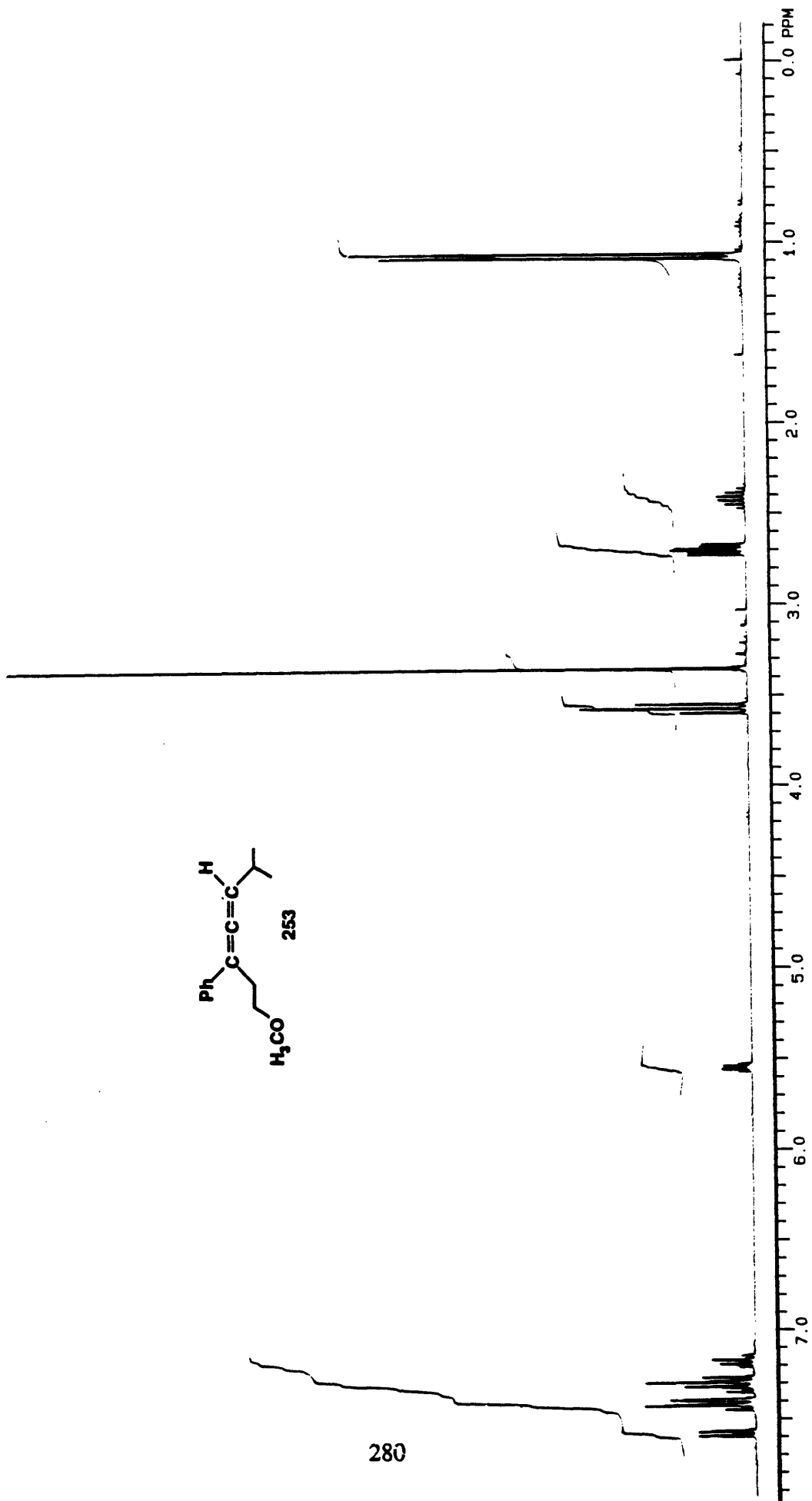
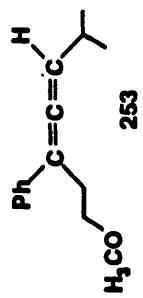
IR (thin film): 3080, 3050, 3020, 2950, 2920, 2860, 2820, 1940, 1590, 1490, 1455, 1375, 1290, 1180, and 1110 cm⁻¹

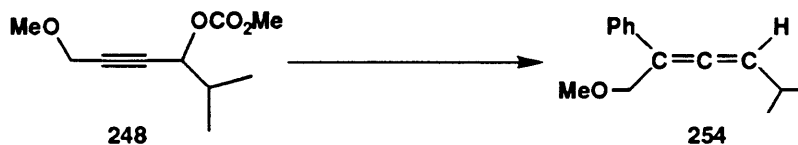
¹H NMR (300 MHz, CDCl₃): 7.40 (dt, *J* = 2, 7.5 Hz, 2 H), 7.30 (td, *J* = 2, 7.5 Hz, 2 H), 7.20 (tt, *J* = 2, 7.4 Hz, 1 H), 5.52-5.59 (dt, *J* = 3, 7 Hz, 1 H), 3.85 (t, *J* = 7.4 Hz, 2 H), 3.37 (s, 3 H), 2.70 (td, *J* = 3, 7.4 Hz, 2 H), 2.42 (app sep, *J* = 7, 1 H), and 1.08 (app d, *J* = 7 Hz, 6 H)

³⁴². In other runs the yield for this reaction ranged from 65-67%.

^{13}C NMR (75 MHz, CDCl_3): 201.9, 137.0, 128.3, 126.4, 125.5, 103.2, 102.3,
71.4, 58.6, 29.8, 28.6, and 22.6

HRMS: Calcd for $\text{C}_{15}\text{H}_{20}\text{O}$: 216.1514
Found: 216.1515





1-Methoxy-5-methyl-2-phenyl-2,3-hexadiene (254). The reaction of the propargylic carbonate **248** (0.189 g, 0.944 mmol), phenylboronic acid (0.127 g, 1.04 mmol), PdCl₂(dppf) (0.021 g, 0.028 mmol), K₂CO₃ (0.261 g, 1.888 mmol), in 5 mL of DMF for 5 h at reflux according to the general procedure produced 0.420 g of a brown oil. Column chromatography on 15 g of silica gel (gradient elution with 1-5% ethyl acetate-hexane) provided 0.115 g (60%)³⁴³ of the allene **254** as a pale yellow oil.

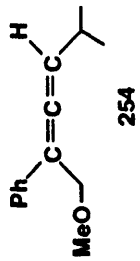
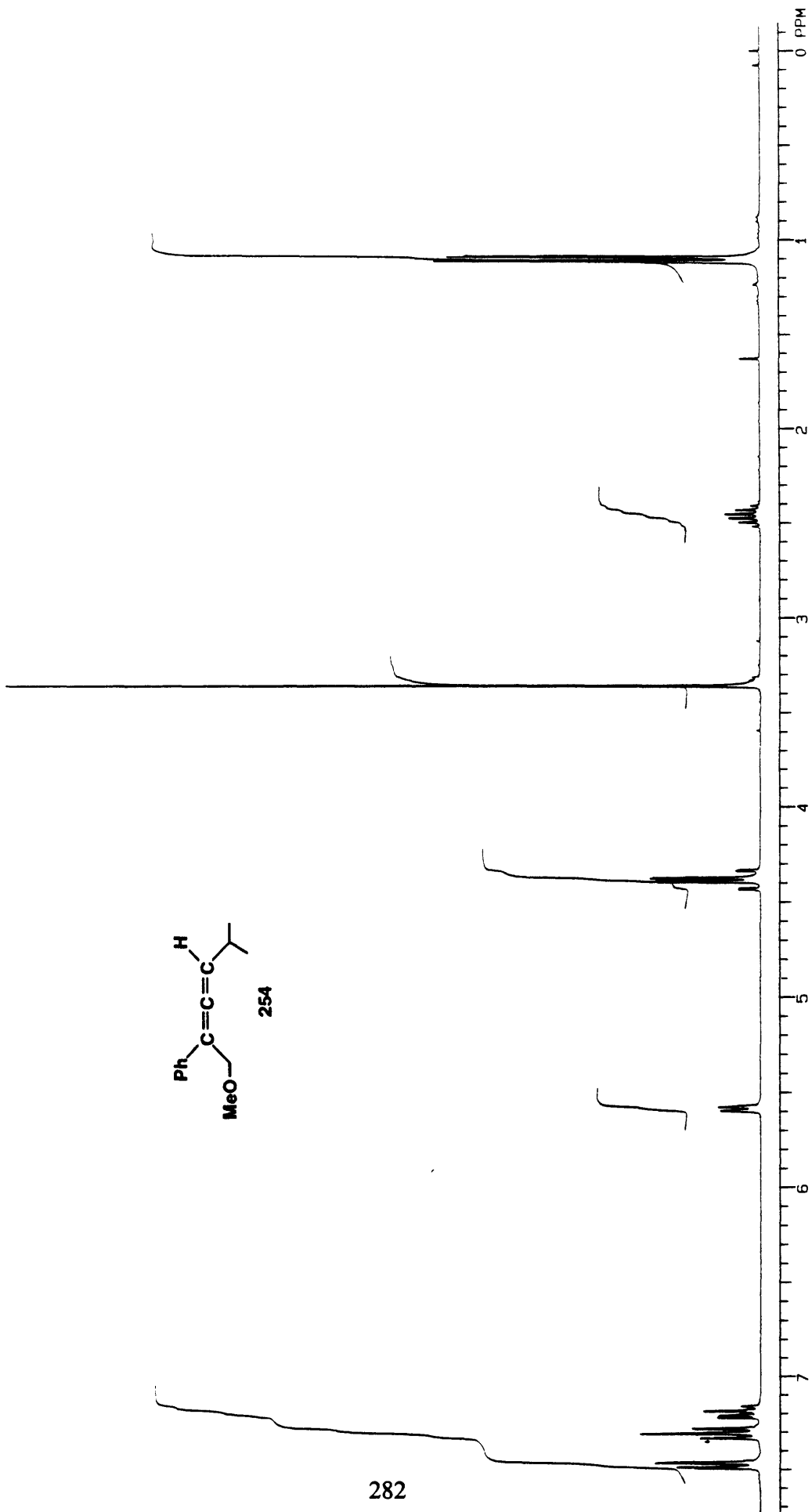
IR (thin film): 3050, 3020, 2960, 2920, 2860, 2800, 1940, 1590, 1490, 1450, 1400, 1375, 1360, 1315, 1280, 1180, 1090, 1040, 1020, 950, 910, 760, and 690 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 7.48 (dt, J = 1.2, 8.5 Hz, 2 H), 7.31 (td, J = 2, 7.5 Hz, 2 H), 7.20 (app t, J = 7 Hz, 1 H), 5.59 (app d, J = 6 Hz, 1 H), 4.33-4.43 (m, 2 H), 3.39 (s, 3 H), 2.41-2.51 (m, 1 H), 1.11 (d, J = 6.8 Hz, 3 H), and 1.10 (d, J = 6.8 Hz, 3 H)

¹³C NMR (75 MHz, CDCl₃): 203.8, 135.4, 128.4, 126.7, 126.1, 103.5, 101.5, 72.6, 57.4, 28.6, 22.7, and 22.6

HRMS: Calcd for C₁₄H₁₈O: 202.1358
 Found: 202.1355

343. In other runs the yield for this reaction ranged from 65-67%.



282



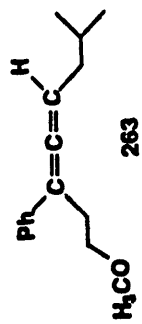
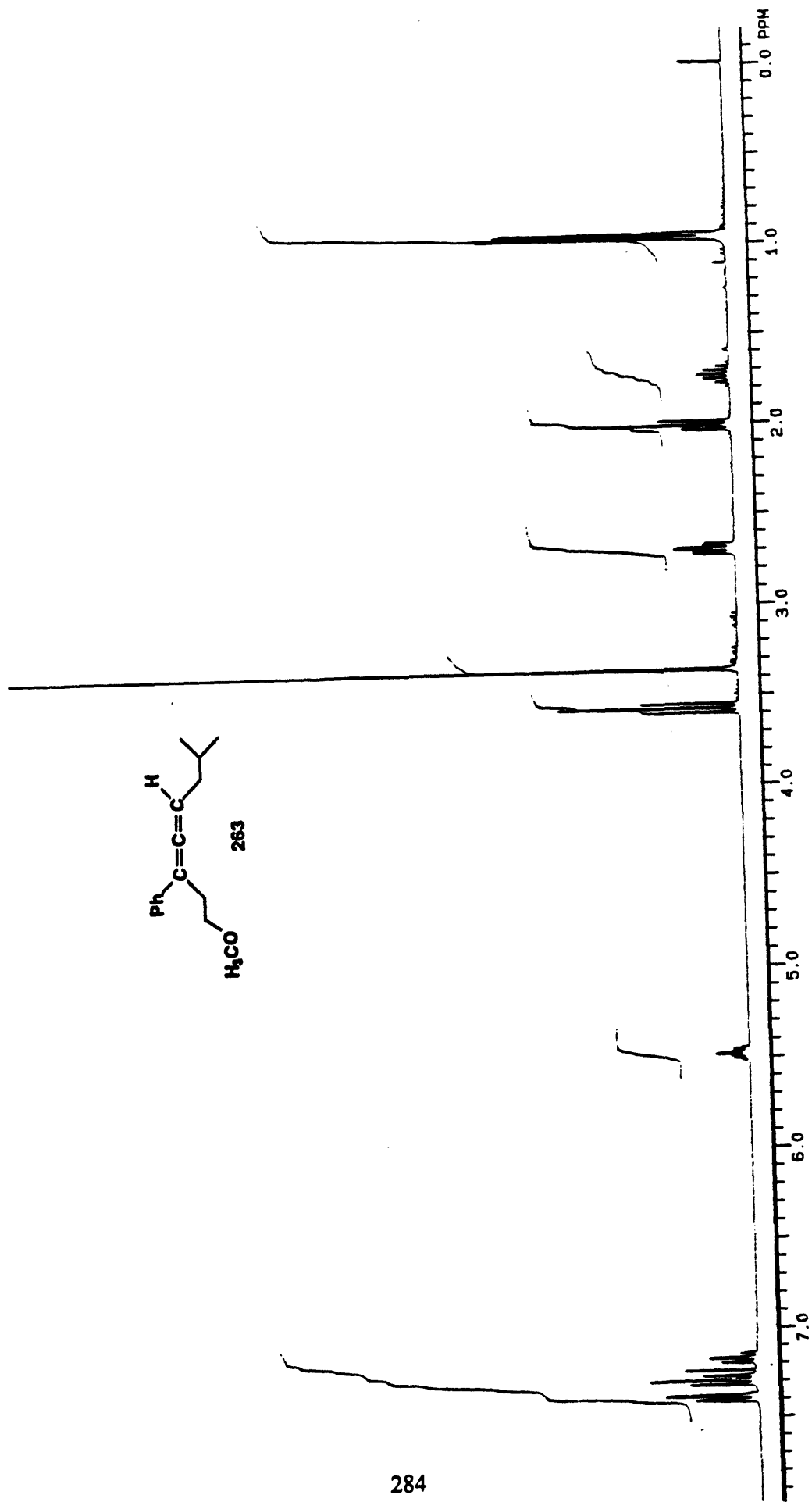
1-Methoxy-7-methyl-3-phenyl-3,4-octadiene (263). The reaction of the propargylic carbonate **245** (0.262 g, 1.15 mmol), phenylboronic acid (.210 g, 1.72 mmol), PdCl₂(dppf) (0.042 g, 0.057 mmol), K₂CO₃ (0.317 g, 2.30 mmol), in 10 mL of DME for 18 h at reflux according to the general procedure produced 0.369 g of a brown oil. Column chromatography on 20 g of silica gel (elution with 2% ethyl acetate-hexane) provided 0.172 g (65%) of the allene **263** as a clear, colorless oil.

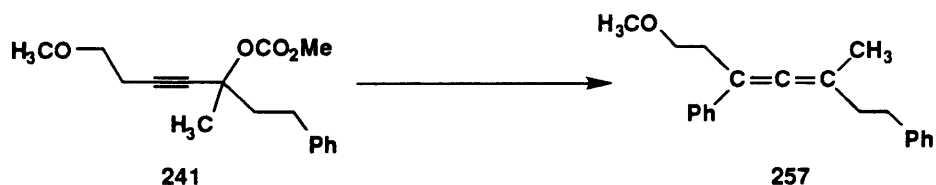
IR (thin film): 3050, 3020, 2950, 2920, 2860, 1940, 1590, 1490, 1445, 1375, 1360, 1325, 1265, 1180, 1110, 1065, 960, 830, 745, and 690 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 7.40 (dd, J = 1.5, 7.3 Hz, 2 H), 7.31 (br t, J = 7.5 Hz, 2 H), 7.18 (app br t, J = 7 Hz, 1 H), 5.44-5.52 (m, 1 H), 3.58 (t, J = 7.3 Hz, 2 H), 3.37 (s, 3 H), 2.70 (td, J = 3, 7.3 Hz, 2 H), 2.02 (t, J = 7.3 Hz, 2 H), 1.68-1.78 (app sep, J = 6.5 Hz, 1 H), 0.97 (d, J = 6.5 Hz, 3 H), and 0.96 (d, J = 6.5 Hz, 3 H)

¹³C NMR (75 MHz, CDCl₃): 204.0, 136.9, 128.2, 126.3, 125.7, 101.4, 93.4, 71.5, 58.7, 38.6, 30.1, 28.8, and 22.6

Elemental Analysis: Calcd for C₁₆H₂₂O: C, 83.43; H, 9.63
 Found: C, 83.43; H, 9.45





1-Methoxy-5-methyl-3,7-diphenyl-3,4-heptadiene (257). The reaction of the propargylic carbonate **251** (0.145 g, 0.500 mmol), phenylboronic acid (0.094 g, 0.075 mmol), PdCl₂(dppf) (0.018 g, 0.025 mmol), K₂CO₃ (0.138 g, 1.00 mmol), in 5 mL of DME for 44 h at room temperature according to the general procedure produced 0.189 g of an orange oil. Column chromatography on 10 g of silica gel (gradient elution with 0-5% ethyl acetate-hexane) provided 0.114 g (78%)³⁴⁴ of the allene **257** as a clear, colorless oil.

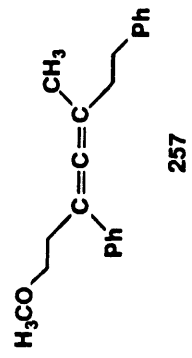
IR (thin film): 3060, 3020, 2980, 2920, 1945, 1595, 1490, 1445, 1370, 1180, 1110, 960, 740, and 690 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 7.23-7.29 (m, 6 H), 7.17-7.19 (br d, J = 7 Hz, 4 H), 3.44 (m, 2 H), 3.33 (s, 3 H), 2.78 (t, J = 8 Hz, 2 H), 2.63 (td, J = 2, 7 Hz, 2 H), 2.41 (t, J = 8 Hz, 2 H), and 1.82 (s, 3 H)

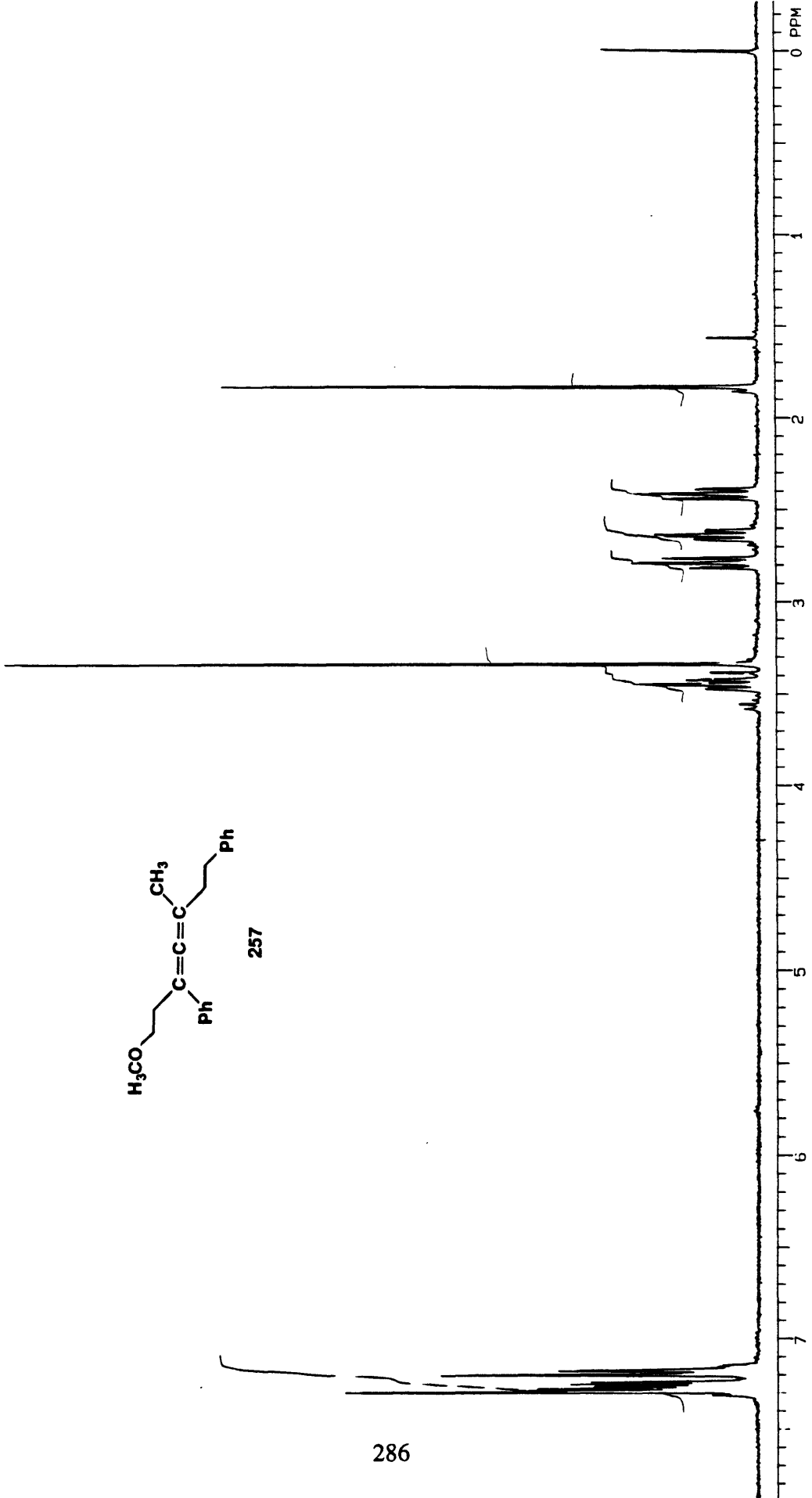
¹³C NMR (75 MHz, CDCl₃): 201.2, 141.8, 137.6, 128.2, 126.2, 125.7, 102.7, 101.9, 71.5, 58.6, 35.9, 33.9, 30.4, and 19.1

Elemental Analysis: Calcd for C₂₁H₂₄O: C, 86.25; H, 8.27
 Found: C, 86.51; H, 8.02

³⁴⁴. In other runs the yield for this reaction ranged from 74-78%.



257



286



3,4,4-Trimethyl-1-phenyl-1,2-pentadiene (259). The reaction of the propargylic carbonate **242** (0.184 g, 1.00 mmol), phenylboronic acid (0.127 g, 1.25 mmol), PdCl₂(dppf) (0.037 g, 0.050 mmol), K₂CO₃ (0.207 g, 1.50 mmol), in 5 mL of DME for 15 h at reflux according to the general procedure produced 0.208 g of a brown oil. Column chromatography on 10 g of silica gel (elution with hexane) provided 0.112 g (60%) of the allene **259** as a pale yellow oil.

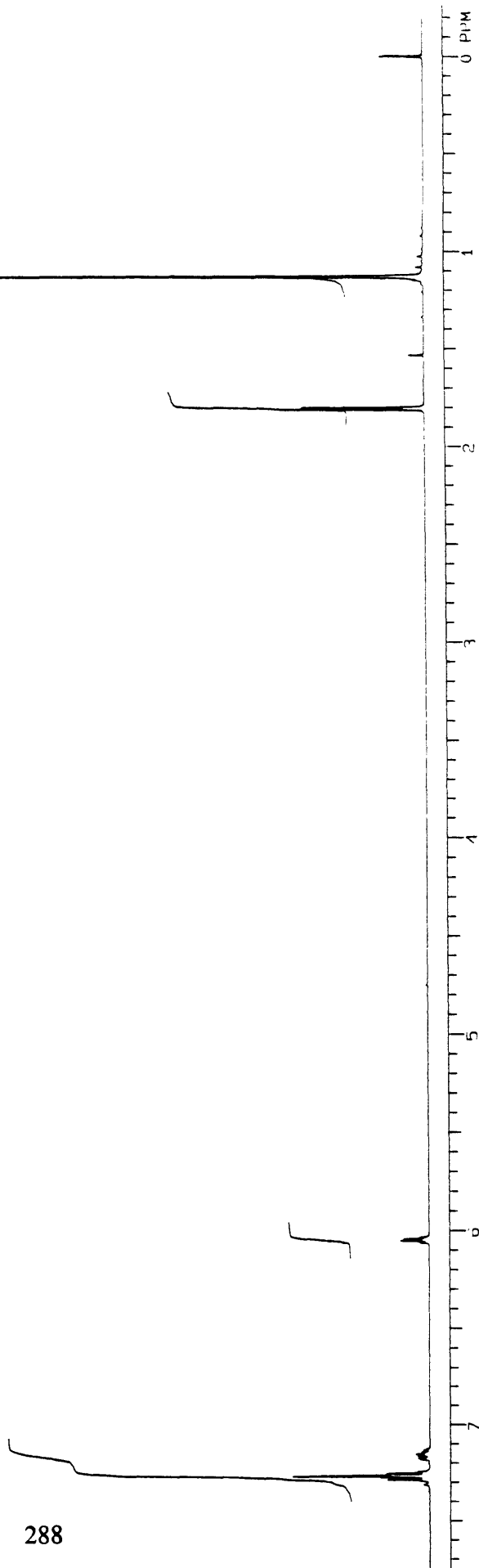
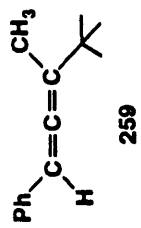
IR (thin film): 3060, 3020, 2960, 2900, 2860, 1945, 1595, 1490, 1470, 1460, 1360, 1245, 1195, 1170, 1110, 900, 810, 735, and 685 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 7.25-7.29 (m, 4 H), 7.12-7.18 (m, 6 H), 6.05 (q, J = 3 Hz, 1 H), 1.81 (d, J = 3 Hz, 3 H), and 1.13 (s, 9 H)

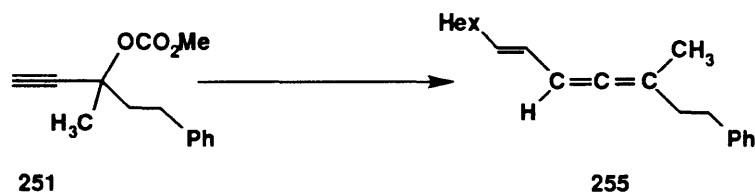
¹³C NMR (75 MHz, CDCl₃): 201.8, 136.3, 128.5, 126.3, 126.2, 112.6, 94.1, 34.2, 29.1, and 14.7

HRMS: Calcd for C₁₄H₁₈: 186.1409
 Found: 186.1409

Elemental Analysis: Calcd for C₁₄H₁₈: C, 90.26; H, 9.74
 Found: C, 89.91; H, 9.76



288



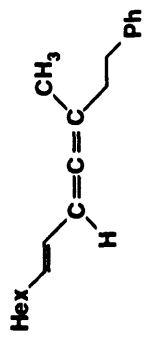
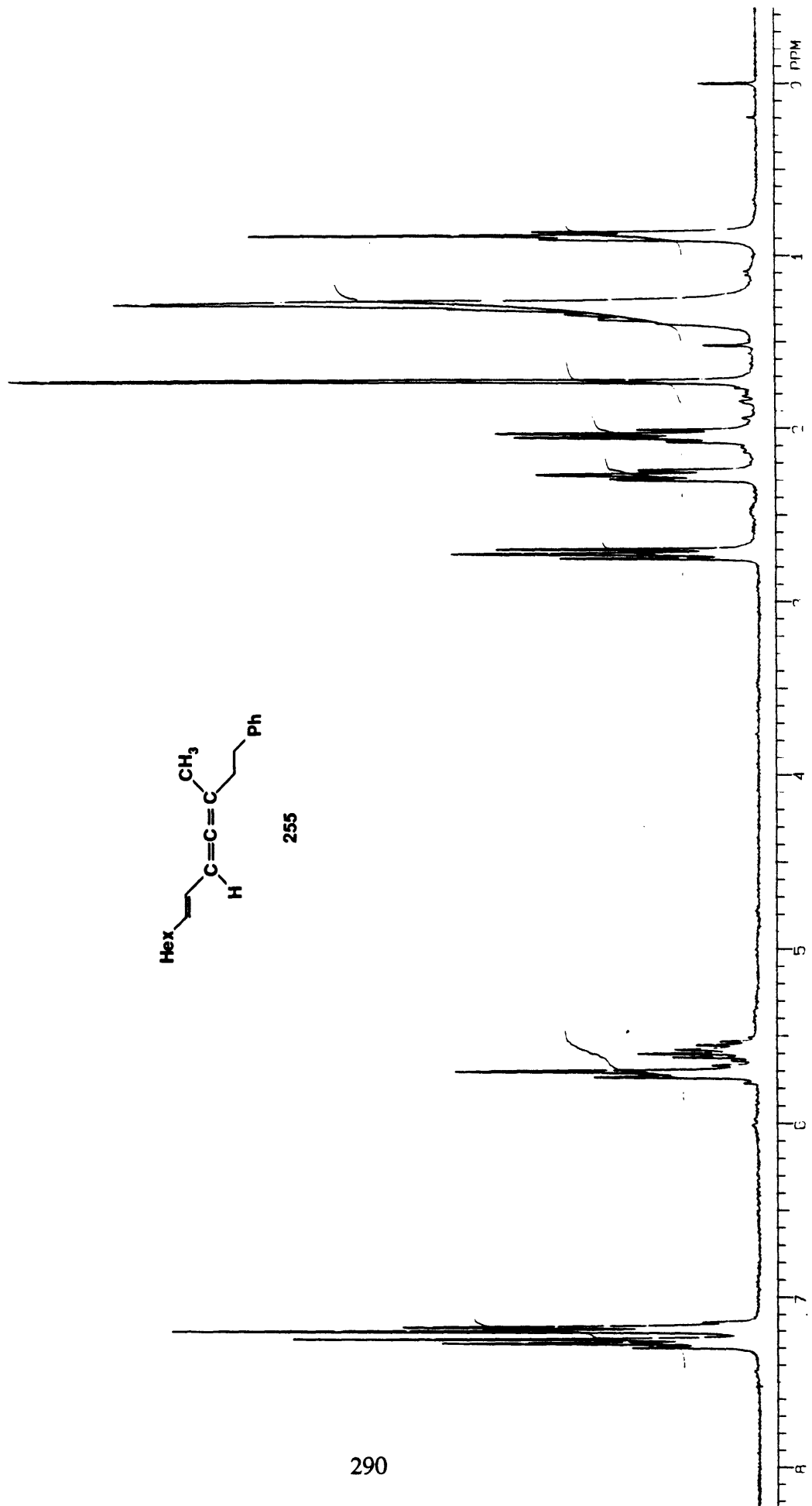
3-Methyl-1-phenyl-3,4,6(*E*)-tridecatriene (255). The reaction of the propargylic carbonate **241** (0.190 g, 0.818 mmol), (*E*)-1-octenylboronic acid (0.255 g, 1.64 mmol), PdCl₂(dppf) (0.030 g, 0.041 mmol), K₂CO₃ (0.283 g, 2.05 mmol), in 4.5 mL of DME for 16 h at reflux according to the general procedure produced 0.185 g of a brown oil. Column chromatography on 20 g of silica gel (gradient elution with 0-1% ethyl acetate-hexane) provided 0.112 g (51%) of the allene **255** as a clear, colorless oil.

IR (thin film): 3020, 2920, 2860, 1950, 1665, 1600, 1490, 1450, 1370, 960, and 695 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 7.24-7.30 (m, 2 H), 7.15-7.20 (m, 3 H), 5.67-5.74 (m, 2 H), 5.55-5.62 (m, 1 H), 2.73 (t, J = 7 Hz, 2 H), 2.27 (m, 2 H), 2.04 (app q, J = 7 Hz, 2 H), 1.73 (s, 3 H), 1.28-1.39 (m, 8 H), and 0.89 (br t, J = 6.5 Hz, 3 H)

¹³C NMR (75 MHz, CDCl₃): 203.8, 142.1, 132.1, 128.4, 128.2, 126.5, 125.7, 100.0, 94.0, 35.8, 33.9, 32.7, 31.8, 29.4, 28.9, 22.6, 18.3, and 14.1

HRMS: Calcd for C₂₀H₂₈: 268.2191
 Found: 268.2189



255



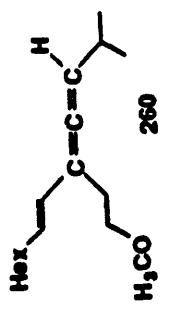
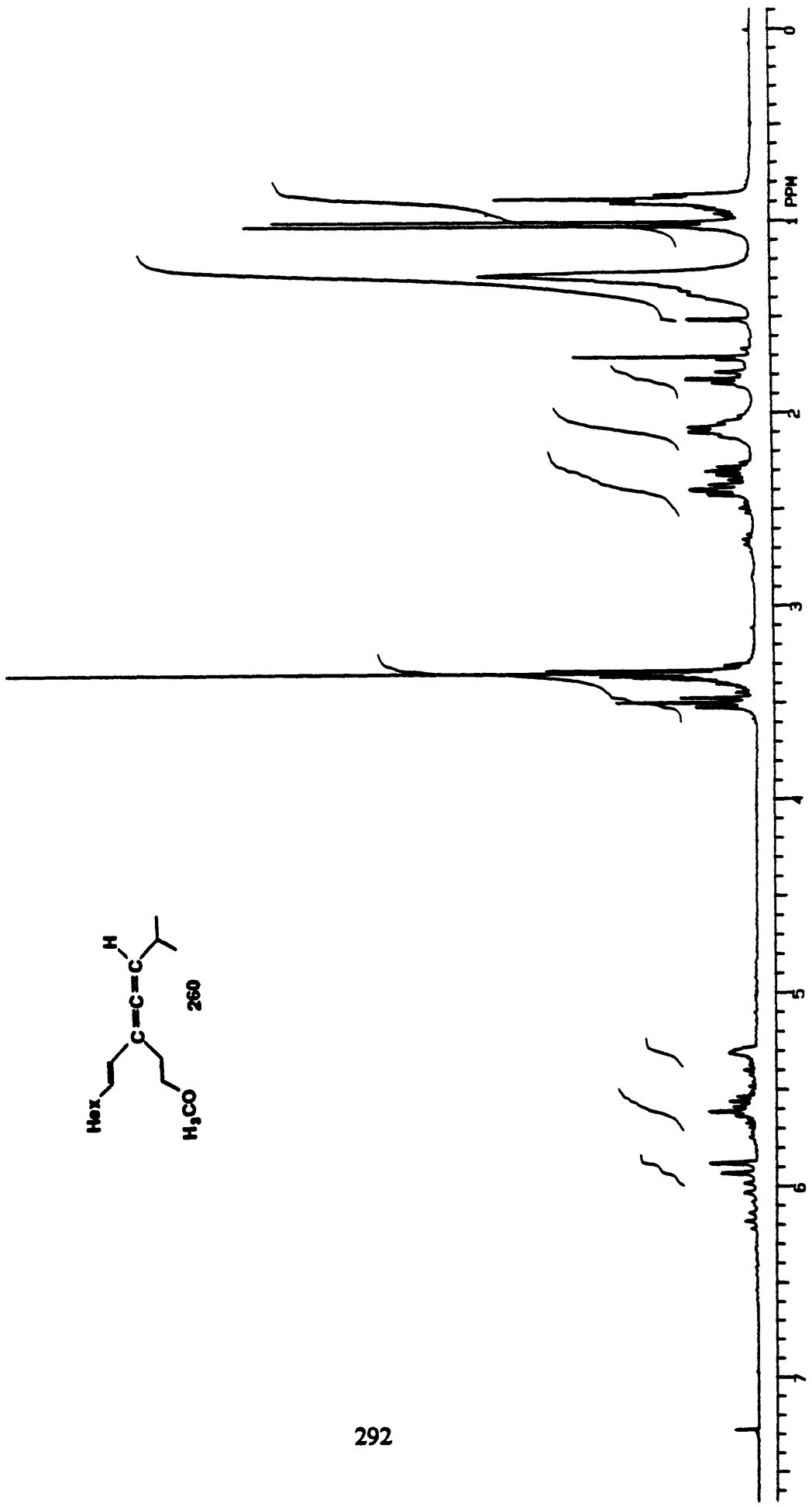
3-Methyl-1-phenyl-3,4,6(*E*)-tridecatriene (260). The reaction of the propargylic carbonate **244** (0.187 g, 0.874 mmol), (*E*)-1-octenylboronic acid (0.273 g, 1.75 mmol), PdCl₂(dppf) (0.032 g, 0.044 mmol), K₂CO₃ (0.302 g, 2.19 mmol), in 5 mL of DME for 14 h at reflux according to the general procedure produced 0.193 g of a brown oil. Column chromatography on 10 g of silica gel (gradient elution with 0-1% ethyl acetate-hexane) provided 0.116 g (ca. 53%) of the allene **260** (containing an impurity that could not be separated after a second chromatography) as a very unstable pale yellow oil.

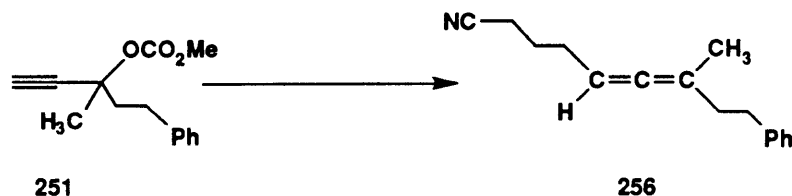
IR (thin film): 2920, 2850, 1950, 1730, 1580, 1520, 1450, 1370, 1270, 1110, and 960 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 5.91 (d, *J* = 16 Hz, 1 H), 5.58 (dt, *J* = 8, 16 Hz, 1 H), 5.31 (m, 1 H), 5.55-5.62 (m, 1 H), 3.51 (t, *J* = 8 Hz, 2 H), 3.36 (s, 3 H), 2.38-2.44 (m, 2 H), 2.29-2.36 (m, 2 H), 1.80-1.86 (m, 2 H), 1.25-1.39 (br m, 8 H), 1.02 (d, *J* = 7 Hz, 6 H), and 0.89 (br t, *J* = 8 Hz, 3 H)

¹³C NMR (75 MHz, CDCl₃): 203.7, 128.9, 128.0, 102.6, 99.7, 71.3, 58.5, 33.0, 31.7, 29.5, 29.0, 28.9, 28.5, 22.6, 22.5, and 14.1

HRMS: Calcd for C₁₇H₃₀O: 250.2297
 Found: 250.2295





General Procedure for the Coupling of 9-BBN derivatives with Propargylic Carbonates. Synthesis of 8-cyano-3-methyl-1-phenyl-3,4-octadiene (256). A 10-mL, two-necked, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet and a rubber septum was charged with allyl cyanide (0.19 mL, 0.156 g, 2.32 mmol) and 2 mL of DME and cooled at 0 °C. 9-BBN (0.5 M solution in THF, 4.64 mL, 2.32 mmol) was added dropwise over 2 min and the solution was stirred at 0 °C for 1 h and then at room temperature for 2 h. A solution of the propargylic carbonate **251** (0.180 g, 0.775 mmol) in 3 mL of DME was added via cannula over 30 sec, PdCl₂(dppf) (0.028 g, 0.039 mmol) and K₃PO₄ (0.494 g, 2.32 mmol) were each added in one portion, and the resulting solution was heated at reflux for 3 h, allowed to cool to room temperature, and then transferred to a separatory funnel with the aid of 25 mL of ether and 25 mL of water. The aqueous layer was separated and extracted with 30 mL of ether, and the combined organic phases were washed with 50 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to give 0.186 g of a brown oil. Column chromatography on 10 g of silica gel (gradient elution with 0-5% ethyl acetate-hexane) provided 0.120 g (69%) of the allene **256** as a pale yellow oil.

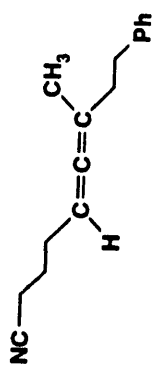
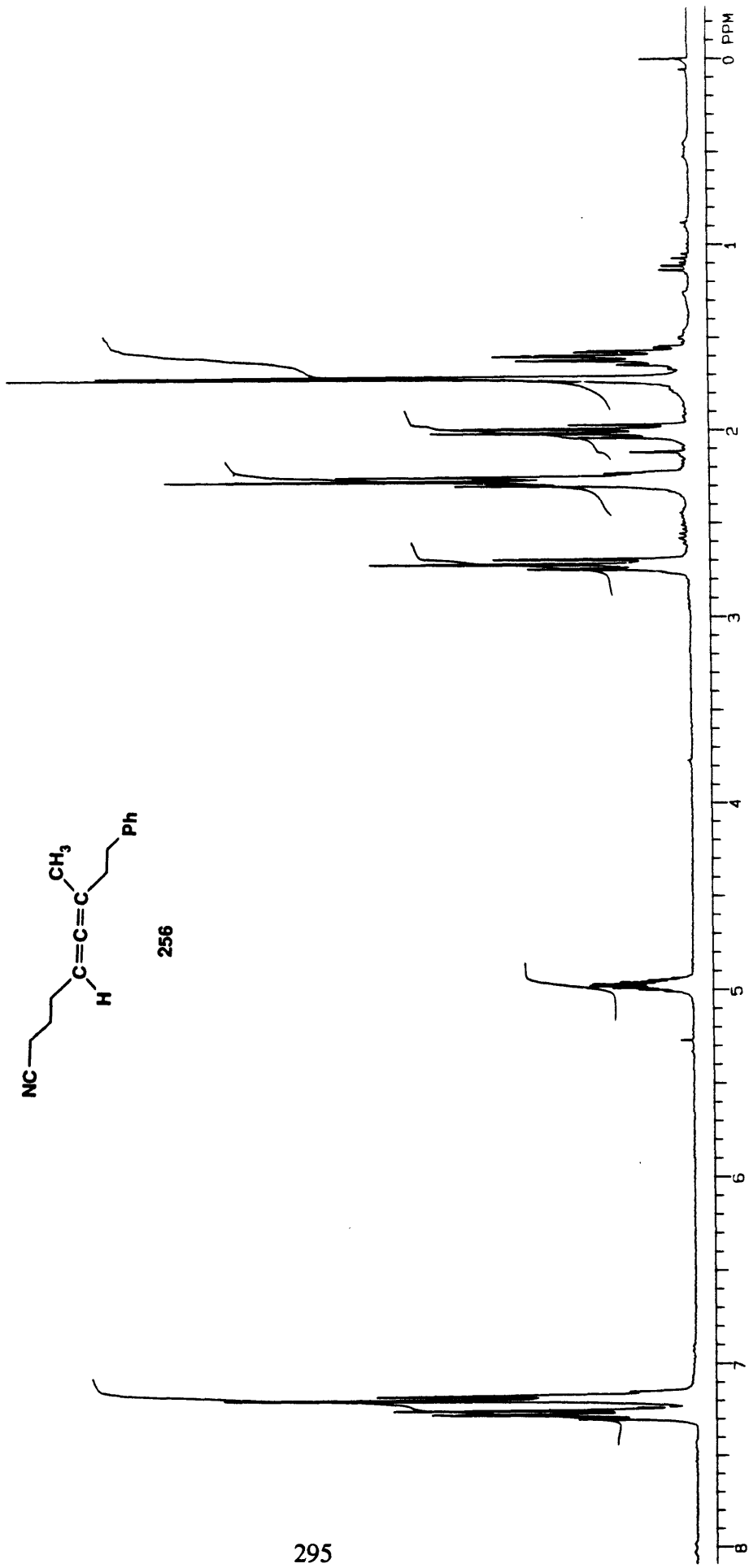
IR (thin film): 3060, 3020, 2920, 2850, 2240, 1960, 1600, 1495, 1445, 1370, 1070, 1025, 735, and 690 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 7.17-7.30 (m, 5 H), 4.94-5.00 (m, 1 H), 2.72 (t, J = 7.7 Hz, 2 H), 2.23-2.30 (m, 4 H), 1.97-2.04 (m, 2 H), 1.71 (s, 3 H), and 1.57-1.65 (m, 2H)

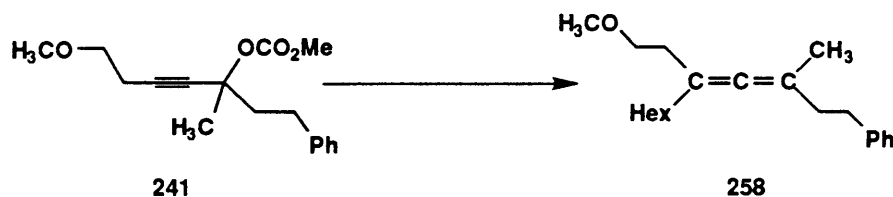
^{13}C NMR (75 MHz, CDCl_3): 201.8, 141.9, 128.3, 128.2, 125.7, 119.6, 99.9, 88.5, 35.5, 33.7, 27.8, 24.5, 19.1, and 16.2

HRMS: Calcd for $\text{C}_{16}\text{H}_{19}\text{N}$: 225.1518
Found: 225.1514

Elemental Analysis: Calcd for $\text{C}_{16}\text{H}_{19}\text{N}$: C, 85.28; H, 8.50; N, 6.22
Found: C, 84.97; H, 8.68; N, 5.87



256



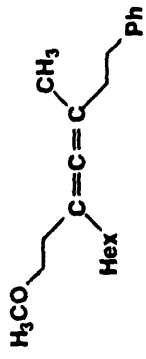
5-Methoxyethyl-3-methyl-3,4-undecadiene (258). The reaction of 1-hexene (0.23 mL, 0.157 g, 1.86 mmol), 9-BBN (0.5 M solution in THF, 3.72 mL, 1.86 mmol), the propargylic carbonate **241** (0.180 g, 0.620 mmol), PdCl₂(dppf) (0.023 g, 0.031 mmol), and K₂CO₃ (0.257 g, 1.86 mmol) in 5 mL of DME for 20 h at room temperature according to the General Procedure produced 0.175 g of a brown oil. Column chromatography on 10 g of silica gel (elution with 2% ethyl acetate-hexane) provided 0.064 g (34%) of the allene **258** as a clear, colorless oil.

IR (thin film): 3060, 3020, 2920, 2860, 1600, 1490, 1450, 1370, 1330, 1250, 1180, 1110, 720, and 690 cm⁻¹

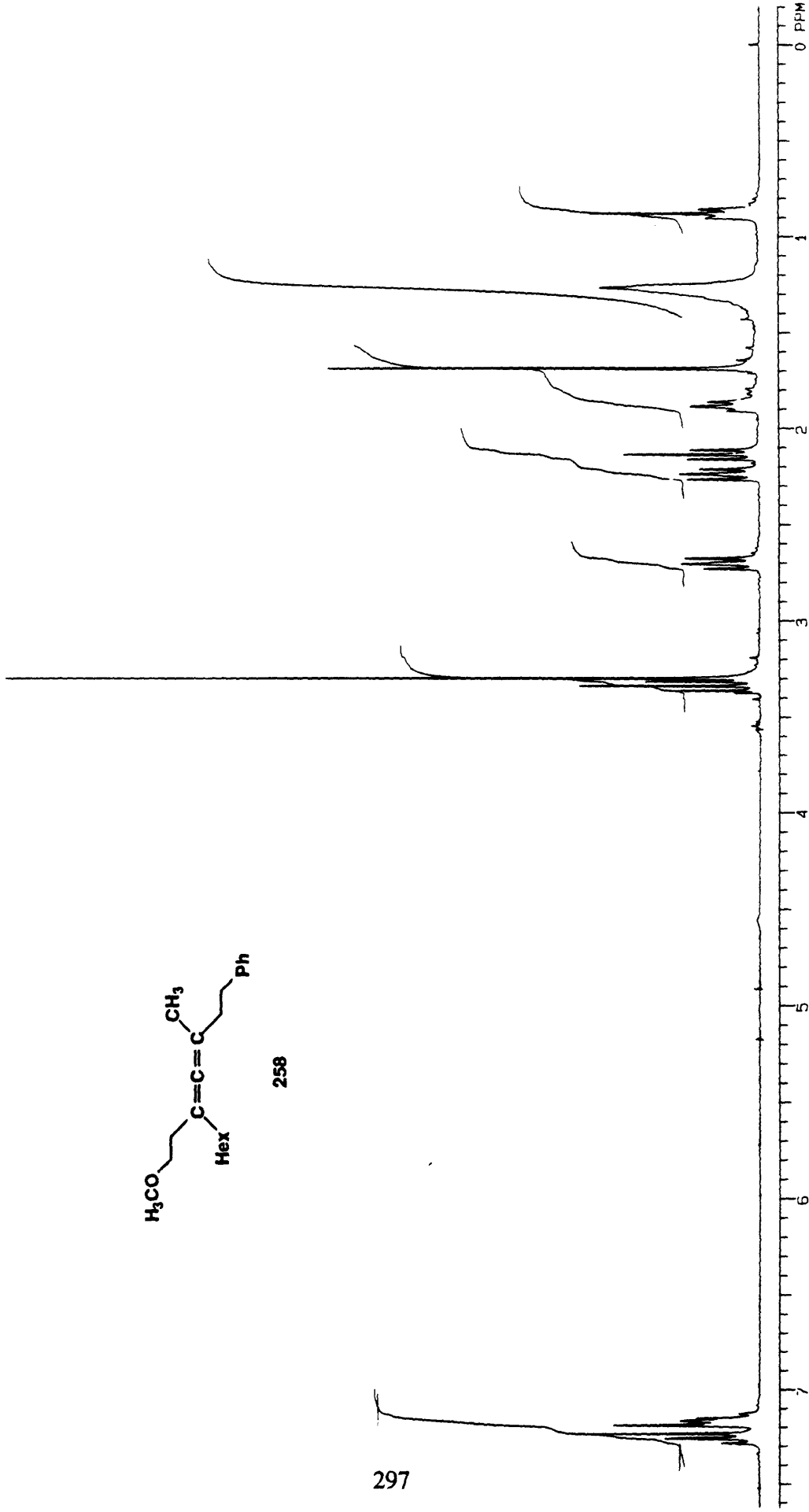
¹H NMR (300 MHz, CDCl₃): 7.24-7.30 (m, 2 H), 7.15-7.19 (m, 3 H), 3.34 (t, J = 7 Hz, 2 H), 3.30 (s, 3 H), 2.71 (app t, J = 8 Hz, 2 H), 2.24 (app t, J = 8 Hz, 4 H), 2.14 (t, J = 7 Hz, 2 H), 1.86 (br t, J = 7 Hz, 2 H), 1.69 (s, 3H), 1.24-1.32 (br m, 8 H), and 0.88 (br t, J = 7 Hz, 3 H)

¹³C NMR (75 MHz, CDCl₃): 198.2, 142.4, 128.3, 125.6, 100.6, 99.8, 71.4, 58.5, 36.0, 34.1, 33.4, 32.9, 31.8, 29.0, 27.7, 22.7, 19.6, and 14.1

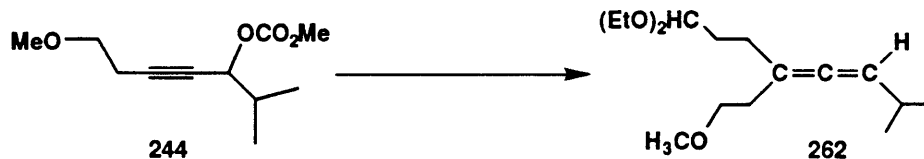
HRMS: Calcd for C₁₆H₁₉N: 300.2453
 Found: 300.2449



258



297



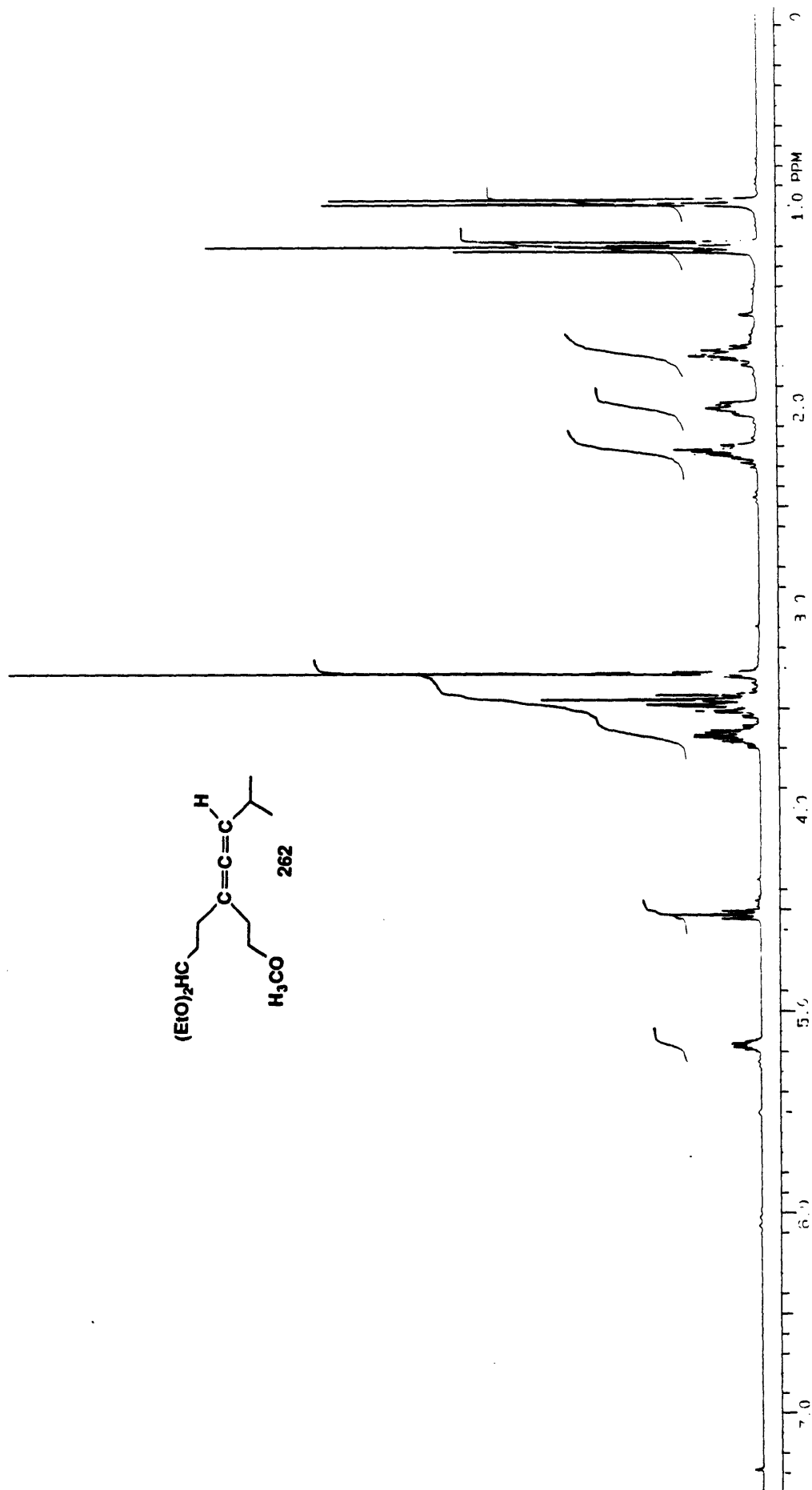
4-Methoxyethyl-7-methyl-4,5-octadienal diethyl acetal (262). The reaction of acrolein diethyl acetal (0.47 mL, 0.400 g, 3.07 mmol), 9-BBN (0.5 M solution in THF, 6.14 mL, 3.07 mmol), the propargylic carbonate **244** (0.219 g, 1.02 mmol), PdCl₂(dppf) (0.037 g, 0.051 mmol), K₂CO₃ (0.566 g, 3.07 mmol), and K₃PO₄ (0.652 g, 3.07 mmol) in 3 mL of DME for 3 h at reflux according to the General Procedure produced 0.247 g of a brown oil. Column chromatography on 13 g of silica gel (gradient elution with 1-5% ethyl acetate-hexane) provided 0.196 g (71%) of the allene **262** as a clear, colorless oil.

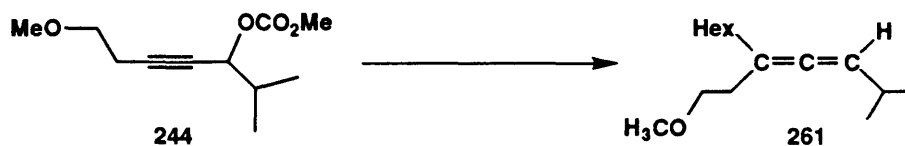
IR (thin film): 2960, 2920, 2870, 1960, 1730, 1450, 1410, 1375, 1300, 1255, 1190, 1120, 1060, 965, 870, 805, and 600 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 5.14-5.19 (m, 1 H), 4.53 (t, J = 6 Hz, 1 H), 3.61-3.67 (m, 2 H), 3.35-3.52 (m, 4 H), 3.33 (s, 3 H), 2.20-2.26 (m, 3 H), 1.98-2.02 (m, 2 H), 1.70-1.77 (m, 2 H), 1.21 (t, J = 7.4 Hz, 6 H), and 0.98 (app d, J = 7 Hz, 6 H)

¹³C NMR (75 MHz, CDCl₃): 198.7, 102.5, 101.8, 100.6, 71.2, 61.0, 58.5, 33.0, 31.7, 28.3, 28.0, 22.6, 22.57, and 15.4

HRMS: Calcd for C₁₆H₃₀O₃: 270.2195
 Found: 270.2195





5-Methoxyethyl-2-methyl-3,4-undecadiene (261). The reaction of 1-hexene (0.30 mL, 0.202 g, 2.40 mmol), 9-BBN (0.5 M solution in THF, 4.80 mL, 2.40 mmol), the propargylic carbonate **244** (0.171 g, 0.80 mmol), PdCl₂(dppf) (0.029 g, 0.040 mmol), and K₂CO₃ (0.389 g, 2.80 mmol) in 7 mL of DME for 16 h at reflux according to the General Procedure produced 0.312 g of a brown oil. Column chromatography on 20 g of silica gel (elution with 2% ethyl acetate-hexane) provided 0.113 g (63%) of the allene **261** as a pale yellow oil.

IR (thin film): 3020, 2960, 1960, 1450, 1380, 1360, and 1110 cm⁻¹

¹H NMR (300 MHz, CDCl₃): 5.11-5.15 (m, 1 H), 3.46 (t, J = 7 Hz, 2 H), 3.34 (s, 3 H), 2.18-2.26 (m, 3 H), 1.92-1.97 (m, 2 H), 1.35-1.44 (m, 2 H), 1.24-1.33 (br m, 6 H), 0.99 (d, J = 7 Hz, 6 H), and 0.88 (br t, J = 7 Hz, 3 H)

¹³C NMR (75 MHz, CDCl₃): 199.0, 102.2, 99.8, 71.4, 58.6, 33.2, 32.7, 31.8, 29.1, 28.4, 27.7, 22.7, and 14.1

HRMS: Calcd for C₁₅H₂₈O: 224.2140
 Found: 224.2137

