PROGRESS TOWARDS THE TOTAL SYNTHESIS OF MITOMYCIN C

By

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Dissertation

Submitted to the Faculty of the

Graduate School of Vanderbilt University

in partial fulfillment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

in

Chemistry

August, 2012

Nashville, Tennessee

Approved:

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ACKNOWLEDGMENTS

I would like to express my gratitude to everyone who made my graduate career a success. Firstly, I would like to thank my advisor, Professor Jeffrey Johnston, for his dedication to his students. He has always held us to the highest standards and he does everything he can to ensure our success. During the challenges we faced in this project, he has exemplified the true spirit of research, and I am especially grateful to him for having faith in my abilities even when I did not.

I would like to acknowledge all the past and present members of the Johnston group for their intellectual discussion and their companionship. In particular, I would like to thank Aroop Chandra and Julie Pigza for their incredible support and guidance during my first few months in graduate school, Jayasree Srinivasan who worked on mitomycin C before me, and Anand Singh whose single comment "A bromine is as good as a carbon!" triggered the investigations detailed in section 2.6. I would also like to thank the other members of the group for their camaraderie, including Jessica Shackleford and Amanda Doody for their friendship, Hubert Muchalski for everything related to vacuum pumps and computers, Michael Danneman and Ken Schwieter for always making me laugh, and Matt Leighty and Ki Bum Hong for their useful feedback.

A simple thank you is not enough to acknowledge Dawn Makley and Mark Dobish, who have been my best friends and colleagues for the past five years. Dawn and I have been roommates as well – it is a testament to our friendship that after all that time together, we still haven't run out of things to talk about. I especially appreciate Mark and Julia Dobish for not only being great friends, but also for including me as family.

Of course, none of this would have happened if it had not been for my family. I am lucky to have a loving and fun family, and I would like to thank my parents, Dr. Mathew Mathew and Dr. Neena Mathew, for always being there for me. My father has always had great ambitions for both his daughters – I hope I am living up to them; my mother has always been more practical and grounded, and I have relied on her throughout for her advice and support. My sister, Jaya, still insists on calling me her baby sister and has always looked out for me, and I owe her thanks for her brisk encouragement when I was applying to graduate schools. And lastly, I would like to acknowledge my cat, Piper, and Dawn's cat, Tonks, for always being happy to see me.

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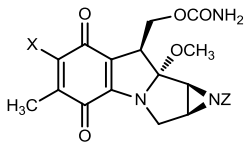
Mitomycin C

1.1. Mitomycin Family of Natural Products

The mitomycins were discovered in 1956 when mitomycins A (MMA, **1**) and B (MMB, **2**) were isolated from *Streptomyces caespitosus* (Figure 1).[1] In 1958, mitomycin C (MMC, **3**) was isolated by Wakaki and coworkers from the same strain. In 1960, porfiromycin (**4**) was isolated from *Streptomyces ardus* and in 1962, all four compounds were isolated from *Streptomyces verticillatus*.[2,3]

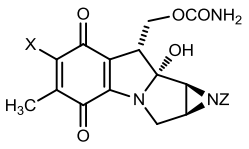
Figure 1. Classification of Mitomycin Family

Series A



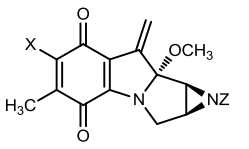
	X	Z
A (**1**)	OCH_3	H
C (**3**)	NH_2	H
F	OCH_3	CH_3
porfiromycin (**4**)	NH_2	CH_3

B



	X	Z
B (**2**)	OCH_3	CH_3
D	NH_2	CH_3

G



	X	Z
G	NH_2	CH_3
H	OCH_3	H
K (**5**)	OCH_3	CH_3

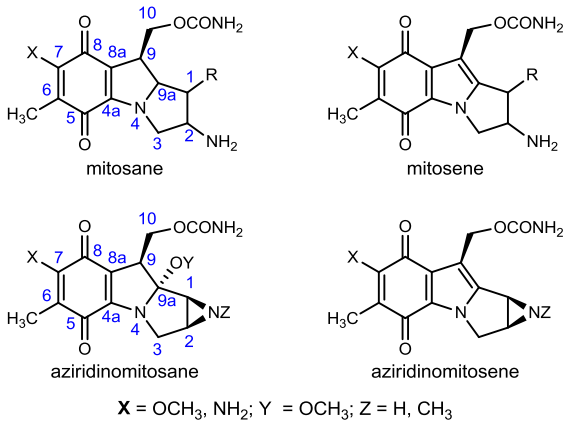
[1] Hata, T.; Sano, R.; Sugawara, A.; Matsume, K.; Shima, T.; Hoshi, T. *J. Antibiot.* **1956**, *9*, 141-146.
[2] Lefemine, D. V.; Dann, M.; Barbatschi, F.; Hausmann, W. K.; Zbinovsky, V.; Monnikendam, P.; Adam, J.; Bohonos, N. *J. Am. Chem. Soc.* **1962**, *84*, 3184-3185.
[3] Webb, J. S.; Cosulich, D. B.; Mowat, J. H.; Patrick, J. B.; Broschard, R. W.; Meyer, W. E.; Williams, R. P.; Wolf, C. F.; Fulmor, W.; Pidacks, C.; Lancaster, J. E. *J. Am. Chem. Soc.* **1962**, *84*, 3185-3187.

The mitomycin family of alkaloids is characterized by a tetracyclic aziridino-pyrrolo-indole skeleton and can be further classified into three groups, namely A, B and G, named after the first mitomycin isolated in that group. The most abundant mitomycins are represented in Figure 1. Mitomycins A and B both have a carbamoyloxymethyl side chain and are epimeric at the carbon bearing the side chain. The presence of the quinone, carbamoyl and aziridine functional groups, and their spatial relationships are important to their anti-tumor activity. The members of the mitomycin G class have a methylene side chain.[5]

Additional nomenclature identifying the skeletal oxidation state and the numbering system of the mitomycin family is shown in Figure 2.[4] Mitosenes and mitosanes consist of the *p*-quinone and are at the indole and indoline oxidation states respectively. A mitosane with an intact aziridine ring is called an aziridinomitosane. Mitomycins that are in the hydroquinone form are prefixed by the term *leuco* (Greek *leucos*: white, clear).[5]

[4] Remers, W. A.; Dorr, R. T. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley-Interscience: New York, 1988; Vol. 6, p 1.
[5] Andrez, J.-C. *Beilstein J. Org. Chem.* **2009**, *5*.

Figure 2. Nomenclature and Numbering of Mitomycin Skeleton



The mitomycins are highly colored and crystalline. The quinone chromophore gives distinct colors based on its substitution: mitomycin A (**1**) with one amino group and one methoxy group is reddish-violet, mitomycin C (**3**) with two amino groups is blue. Mitosane conversion to mitosenes is accompanied by a color change to purple and orange, respectively, because of the extended indoloquinone chromophore.[4]

After a series of revisions, the absolute configuration of mitomycin C was established to be (1*S*, 2*S*, 9*S*, 9a*R*) by anomalous dispersion X-ray crystallography. Biosynthetic studies were consistent with these results.[6,7,8,9]

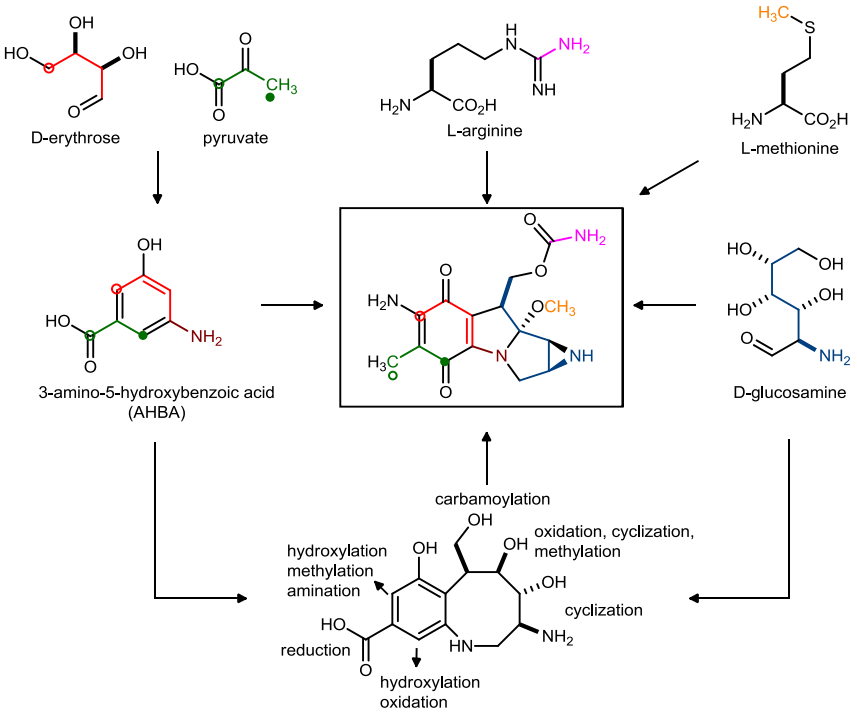
1.2. Biosynthesis

Biosynthetic studies of the mitomycins established that the *O*-methyl group came from L-methionine by feeding [methyl-^{14}C]-L-methionine to *Streptomyces verticillatus* (Figure 3). The origin of the carbamoyl group was determined to be L-arginine, which

[6] Tulinsky, A.; Van den Hende, J. H. *J. Am. Chem. Soc.* **1967**, *89*, 2905-2911.
[7] MMB: Yahashi, R.; Matsubara, I. *J. Antibiot.* **1976**, *29*, 104-106.
[8] Relationship between MMA, B and C: Hornemann, U.; Heins, M. J. *J. Org. Chem.* **1985**, *50*, 1301-1302.
[9] Revised MMC structure: Shirahata, K.; Hirayama, N. *J. Am. Chem. Soc.* **1983**, *105*, 7199-7200.

was first hydrolyzed to citrulline and then converted to carbamoyl phosphate before incorporation into the mitomycins. ^{14}C-labeling of the guanidine group of arginine and the ureido group of citrulline showed the incorporation of the labeled ureido group of citrulline into MMA and MMB.[10,11,12,13]

Figure 3. Biosynthetic Map for Mitomycin C



Labeling and degradative studies of D-glucosamine indicated incorporation into the aziridinopyrrolidine carbon skeleton with the amino group being converted to the aziridine ring (Figure 3).[14] This is in contrast to other natural products containing aziridines like azinomycins and azicemicins that utilize a glutamate or ornithine

[10] Lowden, P. A. S. In *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006, p 399-442.
[11] Hornemann, U.; Cloyd, J. C. *J. Chem. Soc. D* **1971**, 301-302.
[12] Hornemann, U.; Eggert, J. H. *J. Antibiot.* **1975**, *28*, 841-843.
[13] Bezanson, G. S.; Vining, L. C. *Can. J. Biochem.* **1971**, *49*, 911-918.
[14] Hornemann, U.; Kehrer, J. P.; Nunez, C. S.; Ranieri, R. L. *J. Am. Chem. Soc.* **1974**, *96*, 320-322.

derivative and aspartic acid respectively to generate the aziridine unit.[15] Aziridine formation is hypothesized to occur through an intramolecular S_N2 reaction.[10,16] The quinone ring of the mitomycins was derived from 3-amino-5-hydroxybenzoic acid (AHBA).[17] AHBA is primarily known as the universal precursor of ansamycin antibiotics and the biosynthetic pathway for its formation has been reviewed.[18] Analysis of the biosynthetic gene cluster in *Streptomyces lavendulae* revealed the presence of four coenzyme F420-dependent tetrahydromethanopterin reductase genes and one tetrahydromethanopterin-CoM methyltransferase gene.[19] Similar to methanogenic bacterial genes responsible for reduction of CO_2 to CH_4, these may be involved in the reduction of the carboxyl group of AHBA to the C6 methyl group. Three SAM-dependent methyltransferases that could be involved in addition of *O*- and *N*-methyl groups were identified. Two cytochrome P450 genes that could be responsible for hydroxylation at C5 and C7 were also found.

Since antibiotic resistance genes are often clustered with the biosynthetic genes, the genes conferring resistance to mitomycin upon the producing organism were also investigated. A MMC resistance gene (*mcrA*) responsible for producing a flavoprotein MCRA that covalently binds FAD cofactor was found which possibly confers resistance to MMC by oxidizing the reductively activated form of MMC. A MMC-specific drug export system is believed to be formed by the conjunction of a small soluble protein

[15] Ogasawara, Y.; Liu, H.-w. *J. Am. Chem. Soc.* **2009**, *131*, 18066-18068.
[16] Enzyme catalyzed S_N2 reactions review: O'Hagan, D.; Schmidberger, J. W. *Nat. Prod. Rep.* **2010**, *27*, 900-918.
[17] Anderson, M. G.; Kibby, J. J.; Rickards, R. W.; Rothschild, J. M. *J. Chem. Soc., Chem. Commun.* **1980**, 1277-1278.
[18] Floss, H. G.; Yu, T.-W.; Arakawa, K. *J. Antibiot.* **2011**, *64*, 35-44.
[19] Mao, Y.; Varoglu, M.; Sherman, D. H. *Chem. Biol.* **1999**, *6*, 251-263.

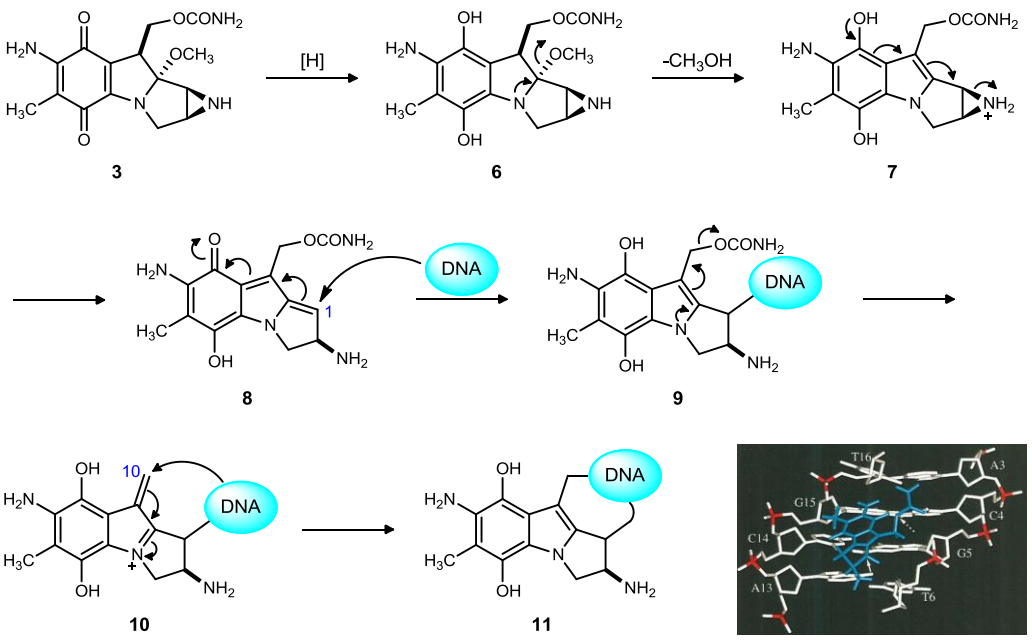
(Mrd)) that binds MMC noncovalently, thus preventing it from being activated, along with Mct, a membrane-bound MMC transport protein.[19,28]

1.3. Mechanism of Action

The mechanism of action of mitomycin C has been well studied and is summarized in Figure 4. Upon reductive activation in the cell, intermediate **6** spontaneously loses methanol to form the leucoaziridinomitosene **7**. Protonation of the aziridine results in aziridine ring opening and the formation of quinone methide **8** which is then alkylated by DNA at the C1 position. A retro-Michael elimination of the carbamate results in the formation of a second alkylating center at C10 (**10**) which is attacked by DNA to form the cross-linked adduct (**11**).[5,20,21,22] The initial reductive step can proceed via a one-electron or a two-electron reduction to the semiquinone or the hydroquinone, respectively. Recent work has indicated that the semiquinone species is more likely to form than the hydroquinone.[23,24,25,26,27]

[20] Tomasz, M. *Chem. Biol.* **1995**, *2*, 575-579.
[21] Moore, H. W. *Science* **1977**, *197*, 527-532.
[22] Szybalski, W.; Iyer, V. N. In *Antibiotics I, Mechanism of Action*; Gottlieb, D., Shaw, P. D., Eds.; Springer-Verlag: New York, 1967; Vol. 1, p 211-245.
[23] Egbertson, M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1987**, *109*, 2204-2205.
[24] Andrews, P. A.; Pan, S. S.; Bachur, N. R. *J. Am. Chem. Soc.* **1986**, *108*, 4158-4166.
[25] Danishefsky, S.; Ciufolini, M. *J. Am. Chem. Soc.* **1984**, *106*, 6424-6425.
[26] Suresh Kumar, G.; Lipman, R.; Cummings, J.; Tomasz, M. *Biochemistry* **1997**, *36*, 14128-14136.
[27] Kohn, H.; Zein, N.; Lin, X. Q.; Ding, J. Q.; Kadish, K. M. *J. Am. Chem. Soc.* **1987**, *109*, 1833-1840.

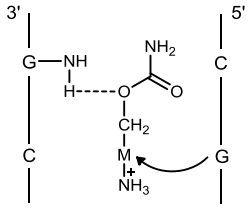
Figure 4. Mechanism of Action of Mitomycin C



The selectivity of MMC for tumor cells lies in its reductive bioactivation. MMC itself is inert to DNA and serves as a noncytotoxic prodrug.[28] The reduction of the quinone in MMC leads to a cascade of spontaneous transformations that culminate in the alkylation and crosslinking of DNA. The reducing environment required to activate MMC is mostly found in hypoxic solid tumor cells, which are otherwise resistant to most other chemotherapeutic treatments, and this makes MMC successful in certain cancer lines such as colon, breast and lung.[28,29] Once activated, MMC acts as a bifunctional alkylating agent and crosslinks DNA. Monoalkylation alone is not necessarily lethal in mammalian cells; it is this bifunctionality of MMC that allows it to readily crosslink DNA which results in cell death, thereby making it a potent antitumor drug.[20]

[28] Galm, U.; Hager, M. H.; Van Lanen, S. G.; Ju, J.; Thorson, J. S.; Shen, B. *Chem. Rev.* **2005**, *105*, 739-758.
[29] Sartorelli, A. C. *Biochem. Pharmacol.* **1986**, *35*, 67-69.

Figure 5. Schematic Illustration of Sequence-Selectivity



The isolation of monoalkylated and crosslinked MMC-DNA adducts showed MMC residing in the minor groove of DNA without greatly perturbing the structure of duplex DNA. MMC is selectively bound by the N2 group of guanine. Both alkylation and crosslinking are sequence-specific for the CpG sequence (5'-C-phosphate-G-3'). MMC requires two guanine residues on opposite strands to make a crosslink. The N2-amino group of the opposite strand guanine forms a specific H-bond with the C10 oxygen atom of activated MMC (Figure 5). This increases the rate of monoalkylation and the monoadduct is now poised to make the crosslink without significant structural reorganization of the DNA. [20,30]

1.4. Previous Syntheses of Mitomycin C

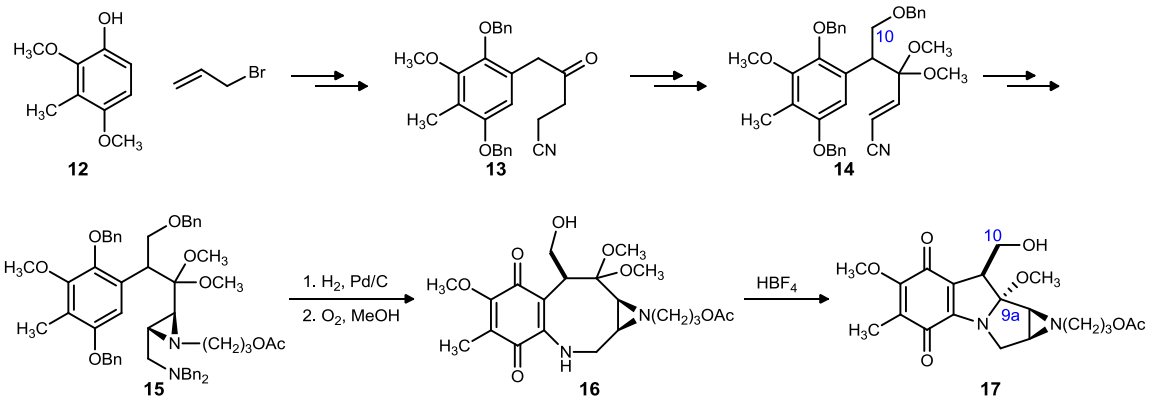
Mitomycin C has proven to be a challenging target for synthetic chemists. Despite numerous synthetic efforts towards MMC and syntheses of mitomycin K, only two total syntheses of MMC have been achieved so far.

Kishi completed the first total synthesis of racemic MMC in 1977. In designing his synthesis, Kishi noted that the least stable functionality of the mitomycins (the C9a *N*,*O*-ketal) was to be introduced at a late stage of the synthesis, after which the oxidation state of the intermediates needed to be maintained at the indole quinone to avoid elimination of this acid-sensitive moiety.[31] To meet these requirements, the key reaction was the installation of the C9a *N*,*O*-ketal in a transannular cyclization of eight-membered

[30] M Tomasz, R. L., D Chowdary, J Pawlak, GL Verdine, and K Nakanishi *Science* **1987**, *235*, 1204-1208.
[31] Kishi, Y. *J. Nat. Prod.* **1979**, *42*, 549-568.

ring **16**. The eight-membered ring **16** itself was to be prepared by a Michael addition of the amine into the quinone (Scheme 1).

Scheme 1. Kishi's Synthesis of (±)-Mitomycin C



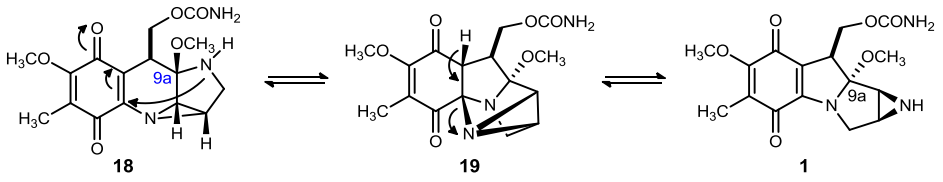
Compound **12**, obtained in three steps from commercially available 2,6-dimethoxytoluene, was allylated and then transformed to compound **13**. The methyloxy group (C10) was installed using a formaldehyde aldol (Scheme 1). A mild three step protocol was required to protect the ketone as the dimethyl ketal to prevent elimination of the protected C10 alcohol group.[32] The olefin in **14** was transformed to the aziridine in **15** by epoxide formation, followed by regioselective opening with lithium azide, Staudinger reduction and intramolecular substitution by the resulting amine.[33] Hydrogenolysis to remove the benzyl groups, air oxidation to the quinone with the concomitant Michael addition resulted in the formation of key intermediate **16**. Transannular cyclization was affected using tetrafluoroboric acid via the nucleophilic trapping of the oxonium intermediate, formed *in situ* from the ketal, by the pendant amine. Carbamoylation and

[32] Nakatsubo, F.; Cocuzza, A. J.; Keeley, D. E.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, *99*, 4835-4836.
[33] Nakatsubo, F.; Fukuyama, T.; Cocuzza, A. J.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, *99*, 8115-8116.

deprotection gave MMA, which upon ammonolysis gave MMC.[34] MMC was thus prepared in 44 steps from phenol **12** with an overall yield of 0.16% (47 steps from 2,6-dimethoxytoluene).[5] The high number of steps arises primarily from protecting group manipulations (for example: six steps to install and remove the aziridine protecting group) and certain functional group manipulations (for example: six steps to construct the aziridine). However, the synthetic strategy was a carefully designed assembly of the highly reactive components of MMC and led to the first successful synthesis.

The second and only other total synthesis of MMC was completed by Fukuyama in 1987. Kono reported the isolation of isomitomycin A (**18**) and albomitomycin A in 1987 (**19**); the equilibrium between these two compounds and MMA (**1**) was termed the mitomycin rearrangement (Scheme 2).[35] Fukuyama's approach to MMC utilized the fact that isomitomycin A contained the acid-sensitive C9a methoxy group attached to the less reactive bridgehead carbon therefore making it possible to install the C9a methoxy group at an earlier stage.

Scheme 2. The Mitomycin Rearrangement

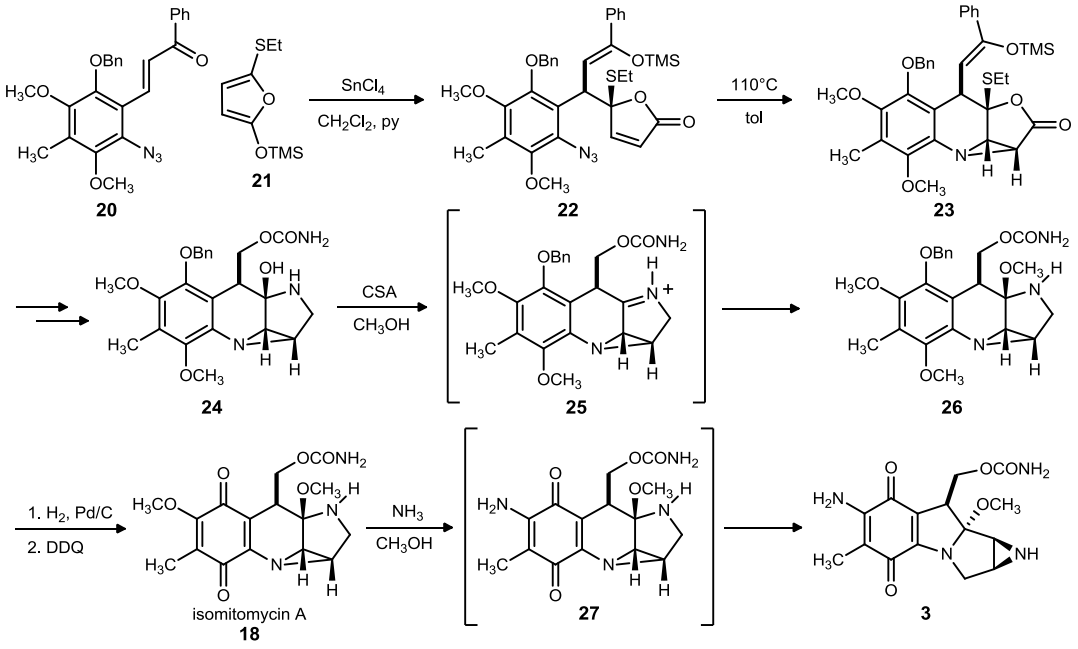


Fukuyama's synthesis (Scheme 3) started with chalcone **20** (obtained in 13 steps from 2,6-dimethoxytoluene, 45% overall yield).[36] Michael addition of furan **21** gave the

[34] Fukuyama, T.; Nakatsubo, F.; Cocuzza, A. J.; Kishi, Y. *Tetrahedron Lett.* **1977**, *18*, 4295-4298.
[35] Kono, M.; Saitoh, Y.; Shirahata, K.; Arai, Y.; Ishii, S. *J. Am. Chem. Soc.* **1987**, *109*, 7224-7225.
[36] Fukuyama, T.; Yang, L. *Tetrahedron Lett.* **1986**, *27*, 6299-6300.

silyl enol ether **22**. An intramolecular azide-olefin [3+2] addition followed by *in situ* N_2 evolution gave aziridine **23**. After conversion to **24**, careful treatment with 0.3 equivalents CSA in methanol installed the methoxy group via the highly strained iminium ion **25**. Hydrogenolysis and oxidation to the quinone gave isomitomycin A (**19**). Treatment with ammonia in methanol gave isomitomycin C (**27**) that rearranged to give MMC (**3**).[37,38] MMC was thus prepared in a total of 25 steps from 2,6-dimethoxyltoluene in an overall yield of 10%.[5]

Scheme 3. Fukuyama's Synthesis of Mitomycin C

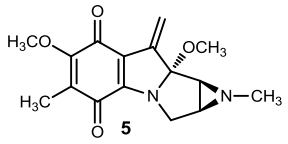


[37] Fukuyama, T.; Yang, L. *J. Am. Chem. Soc.* **1987**, *109*, 7881-7882.
[38] Fukuyama, T.; Yang, L. *J. Am. Chem. Soc.* **1989**, *111*, 8303-8304.

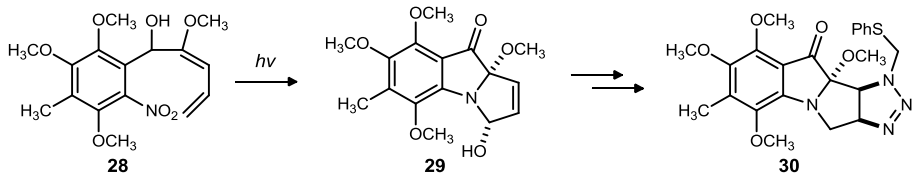
1.5. Syntheses of Mitomycin K

Mitomycin K (**5**, Figure 6) is another relatively simpler synthetic target from the mitomycin family, as it lacks the C9 stereochemistry seen in MMC. Danishefsky's synthesis of mitomycin K utilized an intramolecular cycloaddition of a dienyl nitroso substrate **28** (Scheme 4).[39] In essentially one step, the mitomycin skeleton was rapidly assembled including the *N*,*O*-ketal moiety and the olefin required for aziridine preparation. Azide-olefin addition gave triazoline **30**, that was then photolytically decomposed to give the requisite aziridine for mitomycin K.[40,41]

Figure 6. Mitomycin K



Scheme 4. Key Transformation in Danishefsky's Synthesis of Mitomycin K

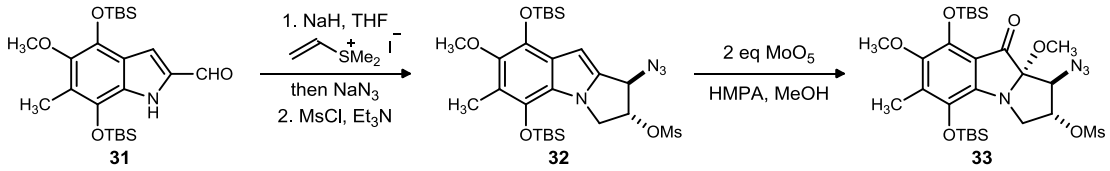


Jimenez's synthesis of mitomycin K built the mitomycin skeleton starting from highly substituted indole **31** (Scheme 5). The pyrrolidine was appended using indole addition into dimethylvinylsulfonium iodide to make the intermediate ylide which then attacks the aldehyde and eventually results in alkoxide displacement of dimethyl sulfide to form the mitomycin skeleton.[42,43] Compound **32** is then subjected to an unusual MoO_5 oxidation which installs the C9a methoxy group and also oxidizes C9 to the ketone.

[39] McClure, K. F.; Benbow, J. W.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1991**, *113*, 8185-8186.
[40] Benbow, J. W.; Schulte, G. K.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 915-917.
[41] Benbow, J. W.; McClure, K. F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 12305-12314.
[42] Wang, Z.; Jimenez, L. S. *J. Am. Chem. Soc.* **1994**, *116*, 4977-4978.
[43] Wang, Z.; Jimenez, L. S. *J. Org. Chem.* **1996**, *61*, 816-818.

Mitomycin K (**5**) can then be obtained by Petasis olefination and reduction of the azide to form the aziridine.[44]

Scheme 5. Key Transformations in Jimenez's Synthesis of Mitomycin K

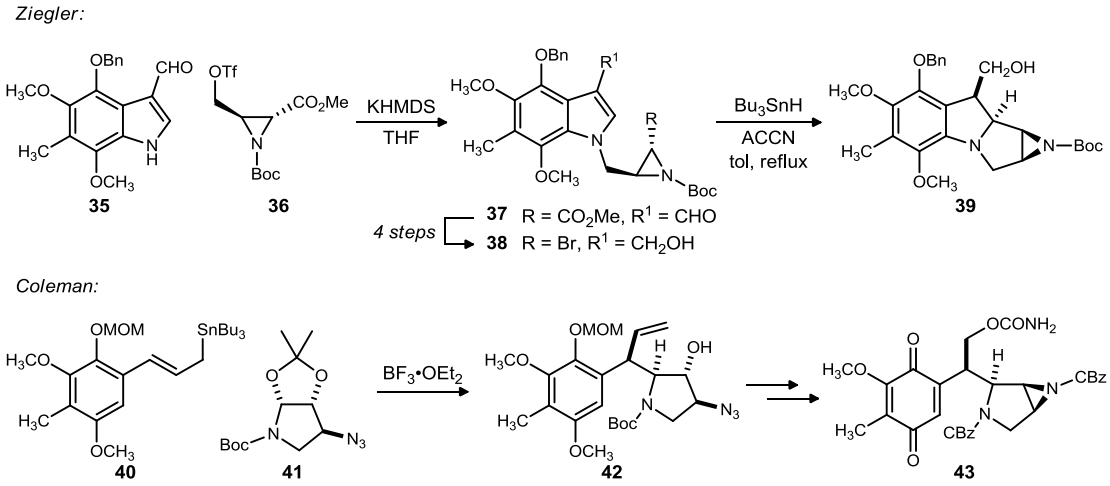


1.6. Other Synthetic Efforts towards Mitomycin C

There have been several other attempts to synthesize MMC (**3**).[5] Ziegler reported a 5-*exo*-trig cyclization of an aziridinyl radical in his synthesis of desmethoxy mitomycin A (**34**, Figure 7). Aziridinyl triflate **36** was installed using S_N2 displacement by indole **35** (Scheme 6). Treatment of bromide **38**, obtained from ester **37** in four steps, with tributyltin hydride led to the radical cyclization to form intermediate **39**. Subsequent functional group manipulations and oxidation of **39** gave **34**.[45]

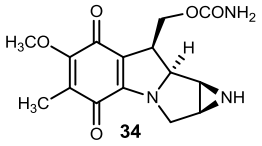
[44] Wang, Z.; Jimenez, L. S. *Tetrahedron Lett.* **1996**, *37*, 6049-6052.
[45] Ziegler, F. E.; Berlin, M. Y. *Tetrahedron Lett.* **1998**, *39*, 2455-2458.

Scheme 6. Overview of the Ziegler and Coleman Syntheses of Desmethoxymitomycin A



Coleman's synthesis (Scheme 6) of desmethoxy mitomycin A (**34**) utilized an allylation reaction to make the C9-C9a bond. Treatment of azide **41** with allyl stannane **40** gave intermediate **42**. Conversion to **43** followed by hydrogenolysis led to Michael addition of the pyrrolidine; subsequent oxidation gave desmethoxy mitomycin A (**34**).[46]

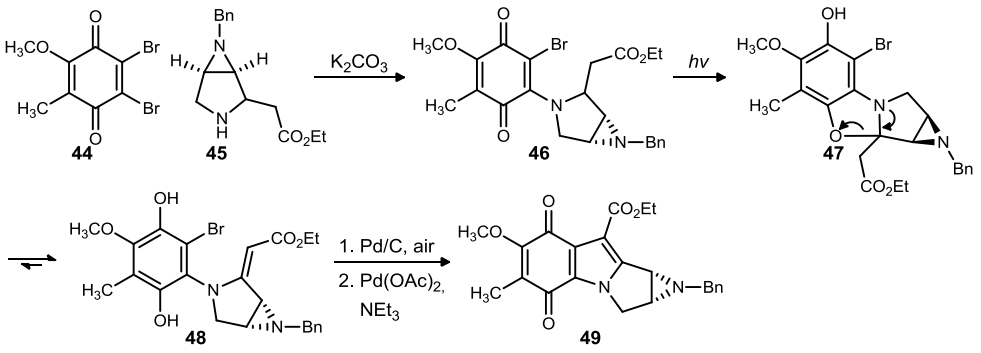
Figure 7. Desmethoxymitomycin A



Rapoport reported the synthesis of aziridinomitosene **49** using an intramolecular Heck coupling (Scheme 7). Addition of pyrrolidine **45** to dibromoquinone **44** was followed by photochemical isomerization[5] to compound **48**, which upon treatment with palladium underwent an intramolecular Heck coupling to yield aziridinomitosene **49**.[47]

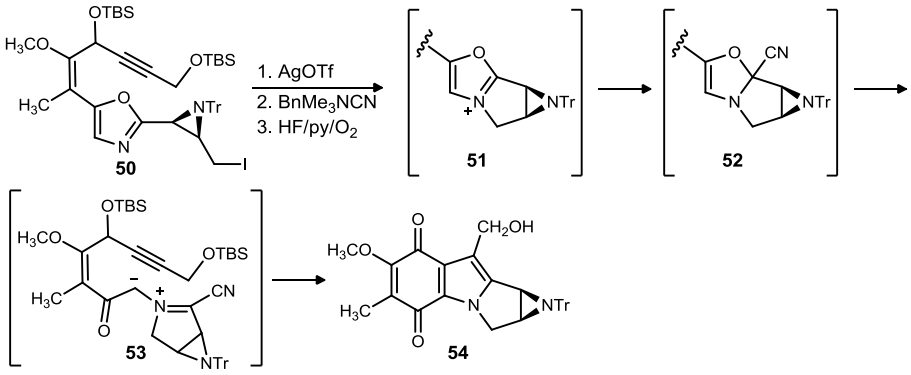
[46] Coleman, R. S.; Felpin, F.-X.; Chen, W. *J. Org. Chem.* **2004**, *69*, 7309-7316.
[47] Shaw, K. J.; Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 4515-4523.

Scheme 7. Rapoport's Approach to Mitomycin C



Vedejs constructed the quinone core using an intramolecular [3+2] cycloaddition between an azomethine ylide and an alkyne (Scheme 8). The azomethine ylide was prepared by silver triflate-mediated cyclization of oxazole **50** followed by cyanide addition and oxazole opening. [3+2] Cycloaddition of azomethine ylide **53** with the internal alkyne gave the tetracyclic core of MMC. [48,49]

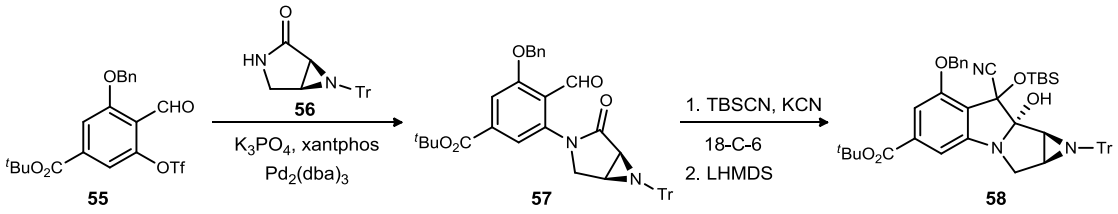
Scheme 8. Vedejs's Approach to Mitomycin C



[48] Vedejs, E.; Klapars, A.; Naidu, B. N.; Piotrowski, D. W.; Tucci, F. C. *J. Am. Chem. Soc.* **2000**, *122*, 5401-5402.
[49] Bobeck, D. R.; Warner, D. L.; Vedejs, E. *J. Org. Chem.* **2007**, *72*, 8506-8518.

More recently, Vedejs synthesized an aziridinomitosane using a lactam cyclization (Scheme 9). A palladium-catalyzed Buchwald coupling appended lactam **56** to the aryl ring (**55**). Treatment of **57** with TBSCN and catalytic KCN in the presence of 18-crown-6 gave a 1:1 diastereomeric mixture of the intermediate cyanohydrin, which upon deprotonation cyclizedn onto the lactam providing **58**, which was converted to an aziridinomitosane using TBAF to remove the cyanohydrin.[50]

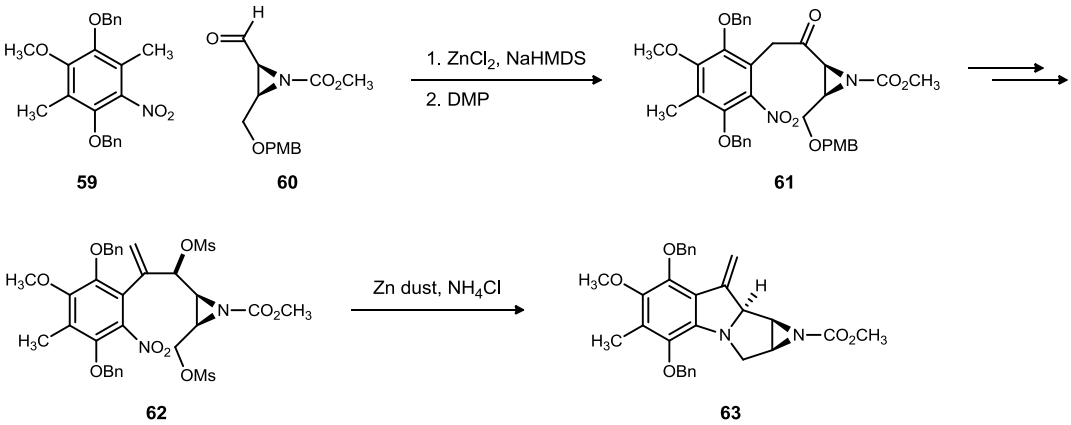
Scheme 9. Vedejs's Synthesis of an Aziridinomitosane



Williams reported the synthesis of a MMK analog lacking the C9a methoxy moiety. The synthesis of the tetracyclic core of MMK was accomplished in one step from an acyclic precursor using a reductive aminocyclization reaction. As shown in Scheme 10, the aziridine and the nitroarene were coupled to give intermediate **61**, after which the aminocyclization precursor **62** was prepared in 5 steps. Treatment of **62** with zinc dust resulted in the reductive aminocyclization to give tetracyclic **63** that was then subjected to hydrogenolysis to remove the benzyl groups and air oxidation to give a MMK analog.[51]

[50] Wiedner, S. D.; Vedejs, E. *Org. Lett.* **2010**, *12*, 4030-4033.
[51] Gubler, D. A.; Williams, R. M. *Tetrahedron Lett.* **2009**, *50*, 4265-4267.

Scheme 10. Key Transformations in Williams' Approach to a MMK analog



Chapter 2

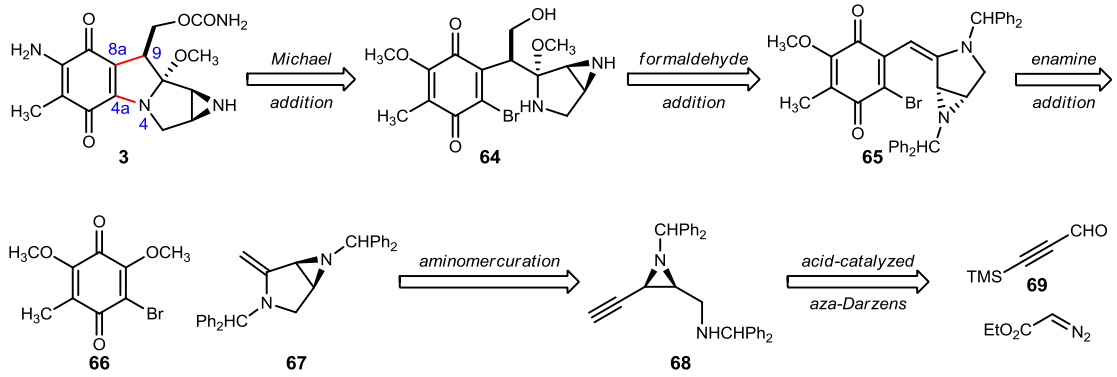
Studies Toward the Synthesis of Mitomycin C

2.1. Retrosynthetic Analysis

A highly convergent approach to mitomycin C (**3**) could be achieved by disconnection at the C4a-N4 and C8a-C9 junctions (Scheme 11). Intermediate **64** can be converted to MMC by Michael addition, ammonolysis and transformation of the alcohol to the carbamate. Formaldehyde addition across enamine **65** and iminium trapping with methanol gives **64**. Intermediate **65** can be obtained by aminomercuration of alkynyl amine **68** and quinone trapping of the resulting enamine (**67**). Our prior work has established that regioselectivity in coupling of the enamine with quinone **66** leads to substitution of the methoxy group.[52] The Brønsted acid-catalyzed aza-Darzens reaction will be used to quickly and efficiently install the *cis*-aziridine, thus allowing for a shorter and more convergent approach to the aminomercuration precursor. [53,54,55]

[52] Cox, A. L.; Johnston, J. N. *Org. Lett.* **2001**, *3*, 3695-3697.
[53] Antilla, J. C.; Wulff, W. D. *J. Am. Chem. Soc.* **1999**, *121*, 5099-5100.
[54] Antilla, J. C.; Wulff, W. D. *Angew. Chem. Int. Ed.* **2000**, *39*, 4518-4521.
[55] Williams, A. L.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 1612-1613.

Scheme 11. Proposed Retrosynthesis of Mitomycin C



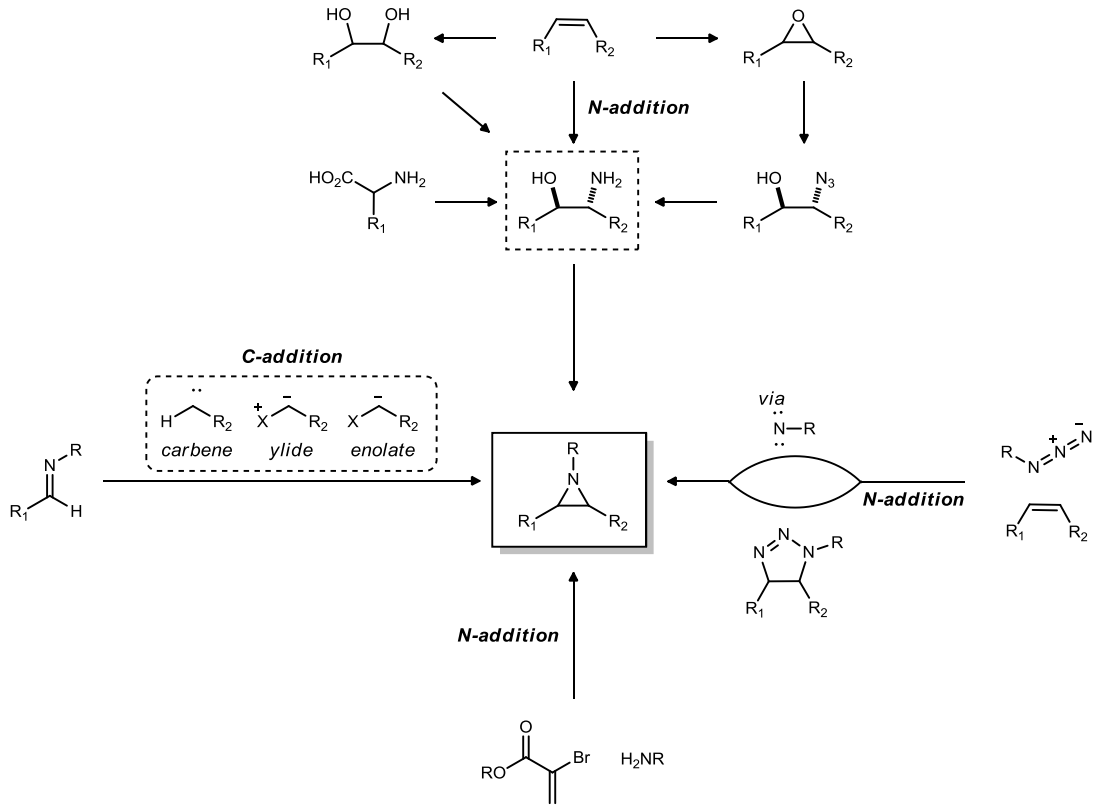
2.2. Construction of the Aziridine Subunit

2.2.1. Syntheses of Aziridines

Natural products containing aziridines generally exhibit DNA alkylation activity. The mitomycins, the azinomycins and the azicemicins are examples of aziridine-containing natural products with biological activity arising from the electrophilic nature of the aziridine moiety. The chemical synthesis of aziridines is an important tool for the syntheses of natural products and their analogs and in the design of novel bioactive agents. [56]

[56] Lowden, P. A. S. In *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006, p 399-442.

Scheme 12. Strategies for Aziridine Synthesis



The fundamental approach to aziridine synthesis involves an overall addition-substitution sequence to an olefin or an imine (Scheme 12). The earliest preparation of aziridines utilized the aminoalcohol as a precursor. Intramolecular substitution of the alcohol (after conversion to the mesylate or halide) by the amine results in the formation of the aziridine. Key developments in this approach include the improved syntheses of aminoalcohols using dihydroxylation, aminohydroxylation and epoxidation (Scheme 12). For example, Sharpless epoxidation has allowed the preparation of enantiomerically pure epoxides. Azide opening of the epoxide, reduction and phosphine-mediated ring closure

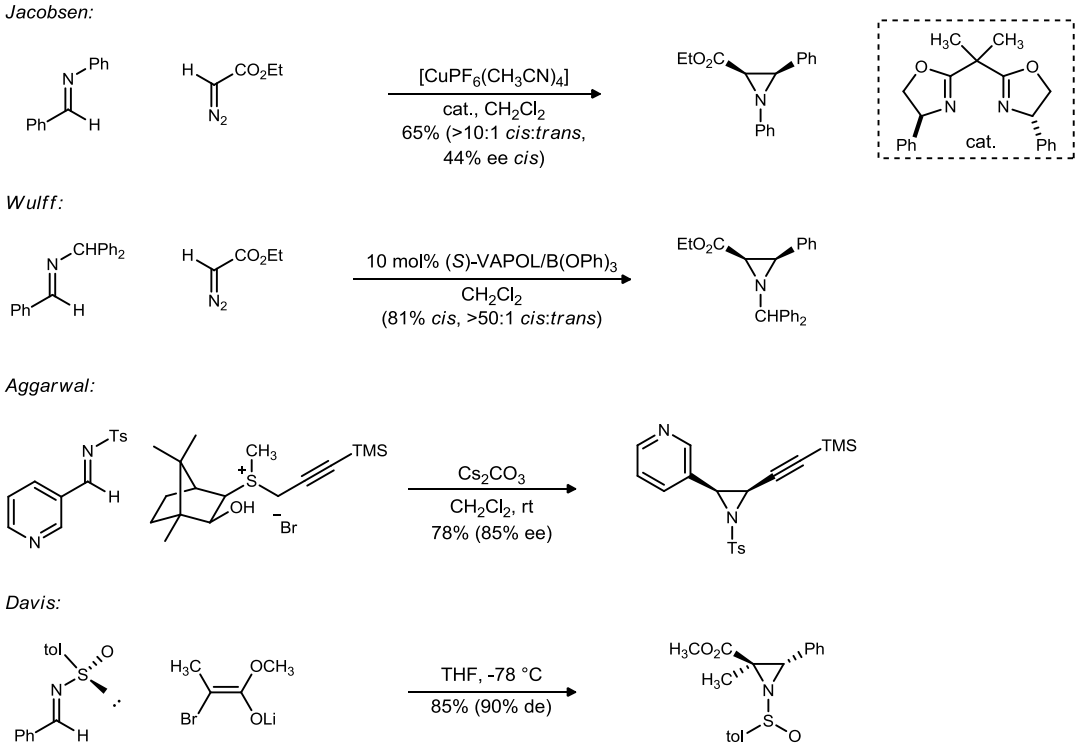
(Blum-Ittah aziridine synthesis) produces the enantiomerically pure aziridine (Scheme 13).[57,58]

Scheme 13. Phosphine-Mediated Ring Closure of Azidoalcohols

A more convergent aziridine synthesis is achieved by carbene, ylide and enolate addition to imines (Scheme 12). Addition of a carbene, generated from ethyl diazoacetate, to imines was reported as early as 1972.[59] The first catalytic asymmetric aziridine synthesis via a carbene was reported by Jacobsen (Scheme 14).[60] Wulff later reported the asymmetric synthesis of *cis*-aziridines from benzhydryl imines and ethyl diazoacetate with chiral boron Lewis acids.[53]

[57] Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247-258.
[58] Ittah, Y.; Sasson, Y.; Shahak, I.; Tsaroom, S.; Blum, J. *J. Org. Chem.* **1978**, *43*, 4271-4273.
[59] Baret, P.; Buffet, H.; Pierre, J. L. *Bull. Soc. Chim. Fr.* **1972**, 2493-2501.
[60] Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 676-678.

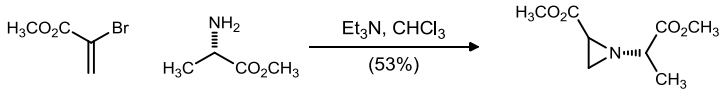
Scheme 14. Carbene, Ylide and Enolate Additions to Imines



Aggarwal reported the first catalytic asymmetric ylide aziridinations. The chiral sulfonium ylide was generated *in situ* from the corresponding sulfide and TMS-propargyl bromide, which then added to the *N*-tosylimine to yield the optically active aziridine (Scheme 14).[61] α-Bromoenolate addition to chiral sulfinimines is another effective method to prepare chiral aziridines (Scheme 14).[62] The Gabriel-Cromwell reaction involves a Michael addition of an amine to an α-bromoacrylate (Scheme 15). Intramolecular substitution of the bromide by the amine forms the aziridine.[63]

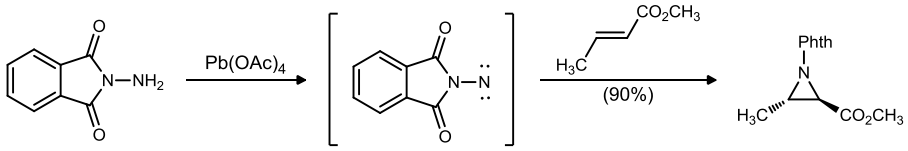
[61] Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341-2372.
[62] Davis, F. A.; Liu, H.; Zhou, P.; Fang, T.; Reddy, G. V.; Zhang, Y. *J. Org. Chem.* **1999**, *64*, 7559-7567.
[63] Filigheddu, S. N.; Taddei, M. *Tetrahedron Lett.* **1998**, *39*, 3857-3860.

Scheme 15. Gabriel-Cromwell Reaction



Azide addition to olefins is another convergent synthetic strategy to prepare aziridines, and was used in the Fukuyama and Danishefsky syntheses of the mitomycins.[37,40,41] The azide substituent dictates the reaction pathway; non-acyl azides generally proceed via the triazoline that then eliminates N_2 to form the aziridine, while acyl azides generate nitrenes that add to the olefin (Scheme 12). Nitrenes were traditionally generated using thermal and photochemical decomposition, but this resulted in a mixture of singlet and triplet nitrenes. Herein lay the drawback of nitrene addition to olefins: singlet nitrenes stereospecifically added to olefins while triplet nitrenes did not.[57] Rees performed the *in situ* generation of nitrenes by oxidation of hydrazine derivatives; these reactions showed improved stereoselectivity and implied the generation of singlet nitrenes under the reaction conditions (Scheme 16).[64]

Scheme 16. Nitrene Addition to Olefins



2.2.2. Brønsted Acid-Catalyzed Synthesis of Aziridines

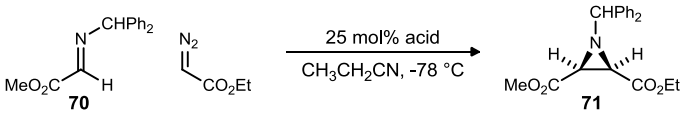
The Brønsted acid-catalyzed aza-Darzens reaction with ethyl diazoacetate as the latent enolate was developed as an extension of the Lewis acid-catalyzed version.[53] Ethyl

[64] Anderson, D. J.; Gilchrist, T. L.; Horwell, D. C.; Rees, C. W. *J. Chem. Soc. C* **1970**, 576-582.

diazoacetate was added to *N*-alkyl imines in the presence of catalytic Brønsted acid, despite the stoichiometric formation of basic *N*-alkyl amine.

A Brønsted acid screen with glyoxylate imine **70** and equimolar ethyl diazoacetate afforded *cis*-aziridine **71** in yields up to 74% (Scheme 17), indicating turnover of the Brønsted acid in spite of basic product formation. Trifluoroacetic acid, camphor sulfonic acid, hydrochloric acid and triflic acid were promising candidates, and decreasing pK_a of the acid was observed to increase reaction rate. As a result, triflic acid was used as the Brønsted acid of choice. The solvent did not affect the reaction yield but nonpolar solvents slowed the reaction (e.g. toluene, dichloromethane).[54]

Scheme 17. Brønsted Acid Screen of the Aza-Darzens Reaction of Ethyl Diazoacetate and an α-Imino ester[54]

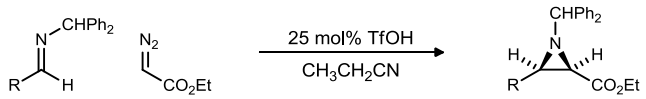


entry	acid	T (°C)	*t* (h)	yield (%)
1	none	25	24	<5
2	CH_3CO_2H	25	24	<5
3	CF_3CO_2H	25	18	63
4	CSA	25	18	74
5	HCl	0	2.5	58
6	TfOH	-78	6	67

The scope of the reaction is represented in Scheme 18. Electron-poor imines like the glyoxylate imines (entries 1 and 2) provided excellent *cis* selectivity and yields; alkyl imines (entries 4 and 7) gave good *cis* selectivity. Modest selectivity was observed for the *tert*-butyl (entry 5) and alkynyl groups (entry 8).[54, 65]

[65] Williams, A. L. Ph.D. Dissertation, Department of Chemistry, Indiana University, October 2004

Scheme 18. Variation of the Imine Substituent in the Brønsted Acid Catalyzed Aza-Darzens Reaction[65]



entry	R	T (°C)	*cis*:*trans*[a]	yield (%)
1	MeO_2C (**70**)	-78	>95:5	86
2	$^tBuO_2C$	-78	>95:5	89
3[b]	2-Py	-78	90:10	73
4	Cyclohexyl	25	80:20	42
5	^{t}Bu	25	60:40	45
6	Ph	0	82:18	42
7	cyclopropyl	25	82:18	40
8	C≡C−TMS(**72**)	-78	67:33	53

[a]Ratios were determined by crude ^{1}H NMR.[b]7 mol% TfOH

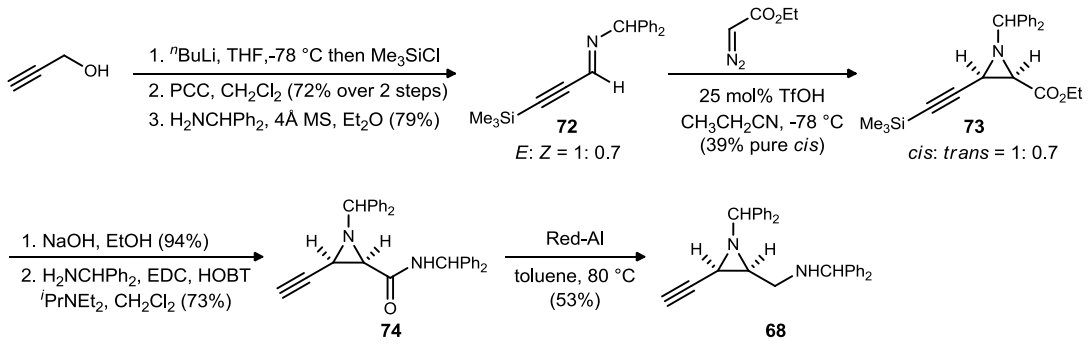
2.2.3. Synthesis of the Aziridine Subunit

The *cis*-aziridine required for mitomycin C is installed convergently using the Brønsted acid-catalyzed aza-Darzens reaction.[54] The imine substrate (**72**) for this reaction is prepared in three steps from commercially available propargyl alcohol. As outlined in Scheme 19, alkyne protection of propargyl alcohol,[66] oxidation[67] and condensation of the resulting aldehyde with diphenyl methylamine afforded imine **72** (*E*:*Z* ratio 1:0.7). The imine *E*:*Z* ratio is dependent on the alkyne protecting group and ranges from 1:0.7 (trimethylsilyl) to exclusively *E* geometry (triphenylsilyl).[68,69] The Brønsted acid-catalyzed aza-Darzens reaction of **72** with ethyl diazoacetate yielded *cis*-aziridine **73** in 39-53% yield (70% for triphenylsilyl *cis*-aziridine).[65,69] Saponification of the ethyl ester moiety of **73** and subsequent carbodiimide coupling with diphenyl methylamine gives

[66] Davison, E. C.; Forbes, I. T.; Holmes, A. B.; Warner, J. A. *Tetrahedron* **1996**, *52*, 11601-11624.
[67] Harris, N. J.; Gajewski, J. J. *J. Am. Chem. Soc.* **1994**, *116*, 6121-6129.
[68] Srinivasan, J. M. Ph.D. Dissertation, Department of Chemistry, Indiana University, December 2008
[69] Srinivasan, J. M.; Mathew, P. A.; Williams, A. L.; Huffman, J. C.; Johnston, J. N. *Chem. Commun.* **2011**, *47*, 3975-3977.

amide **74**. Reduction of the amide with Red-Al afforded the requisite coupling substrate **68**.[69]

Scheme 19. Preparation of Aziridine **68**



2.3. Construction of the Quinone Subunit

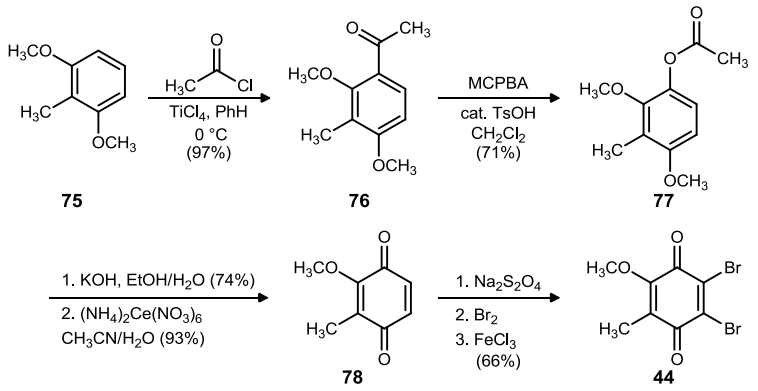
Nearly 200 of the naturally occurring quinones are potentially reductive alkylating agents because they are precursors to reactive quinone methides. Natural products containing these motifs are viable chemotherapeutic agents, as their bioreductive activation makes them significantly more toxic towards hypoxic tumor cells than normal cells or oxygen-rich tumor cells. [70] Mitomycin C is one such example, and as a result, has been the target of many synthetic chemists.

For the synthesis of MMC, the requisite quinone subunit **66** was prepared efficiently on large scale from commercially available 2,6-dimethoxytoluene (Scheme 20). Friedel-Crafts acylation followed by Baeyer-Villiger oxidation gave aryl acetate **77**. Saponification to the phenol and oxidation delivered quinone **78.**[71] Using Rapoport's procedure, dibromoquinone **44** was obtained by reduction to the hydroquinone, followed

[70] Moore, H. W.; Czerniak, R. *Med. Res. Rev.* **1981**, *1*, 249-280.
[71] Hans-Joachim Knölker, W. F., Kethiri R. Reddy *Synthesis* **2002**, 557-564.

by bromination and oxidation.[72] New methods to shorten the synthetic sequence by direct oxidation of 2,6-dimethoxytoluene to the quinone (**78**) using nitric acid and hydrogen peroxide in glacial acetic acid or hydrogen peroxide in formic acid were successful but lower yielding,[73,74] while the direct oxidation with CAN did not yield any of the desired quinone. Similarly, bromination of saponified **77** would shorten the synthesis of **44** by two steps, however, the reaction resulted in a mixture of mono- and dibromination products.[75] The synthetic route in Scheme 20 was chosen for its higher yields and convenience (no purification required).

Scheme 20. Preparation of Dibromoquinone **44**

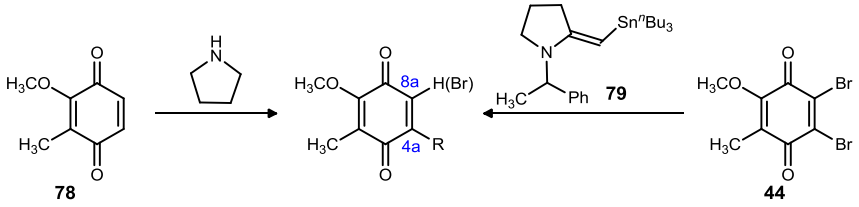


The regioselectivity of the prepared quinones was investigated in order to establish appropriate substitution for the MMC core. Rapoport performed pyrrolidine additions to unsubstituted quinone **78** and dibromoquinone **44** (Scheme 21). Both quinones favored addition at C4a.[72] Therefore addition of a nitrogen nucleophile would

[72] Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 2745-2752.
[73] González, R. R.; Gambarotti, C.; Liguori, L.; Bjørsvik, H.-R. *J. Org. Chem.* **2006**, *71*, 1703-1706.
[74] Herzon, S. B.; Calandra, N. A.; King, S. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 8863-8866.
[75] Fujisaki, S.; Eguchi, H.; Omura, A.; Okamoto, A.; Nishida, A. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1576-1579.

forge the desired C4a-N4 bond. However, since our proposed route to MMC utilized an enamine addition, C4a addition was undesirable. This was confirmed with stannyl enamine **79** addition to dibromoquinone **44**, that furnished the undesired regioisomer for MMC synthesis (Scheme 21).[52]

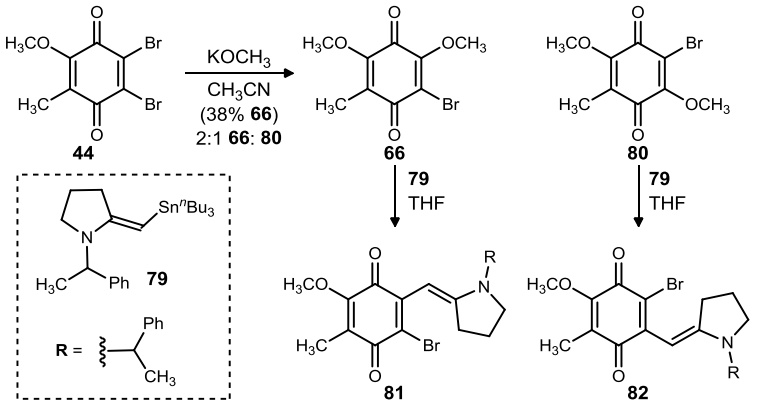
Scheme 21. Regioselectivity of Quinone Additions



In order to electronically differentiate C4a and C8a, the *vicinal* element effect was investigated. The *vicinal* element effect predicts that the substitution will occur through the pathway that best stabilizes the negative charge in the transition state.[76] However, methoxide substitution of the dibromoquinone showed a solvent-induced reversal of regioselectivity; desired **66** was favored in a 2:1 ratio with potassium methoxide in acetonitrile (Scheme 22) while undesired **80** was favored in a 2:1 ratio with magnesium methoxide in methanol.[52]

[76] Rappoport, Z. In *Adv. Phys. Org. Chem.*; Gold, V., Ed.; Academic Press: 1969; Vol. 7, p 1-114.

Scheme 22. Examination of the *Vicinal* Effect



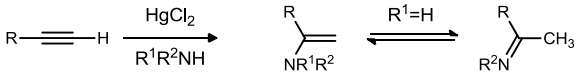
Stannyl enamine **79** addition to the bromomethoxyquinones **66** and **80** resulted in selective methoxide substitution, giving desired **81** and undesired **82** respectively (Scheme 22).[52] In these additions, the bromine is postulated to play a role in stabilizing the negative charge. This would indicate that the *vicinal* effect is operational in the regioselectivity of the enamine substitution.

2.4. Enamine-Quinone Coupling: Tandem Formation of N4-C9a, C9-C8a Bonds

The aminomercuration of terminal acetylenes with catalytic mercury(II) chloride to give imines or enamines was first reported by Barluenga in the 1980s (Scheme 23).[77,78,79] An intramolecular version of this reaction with alkynyl amine **68** (Scheme 25) should give the requisite enamine, which upon electrophilic trapping of quinone **66**, would provide an advanced intermediate towards MMC with a high level of convergency.

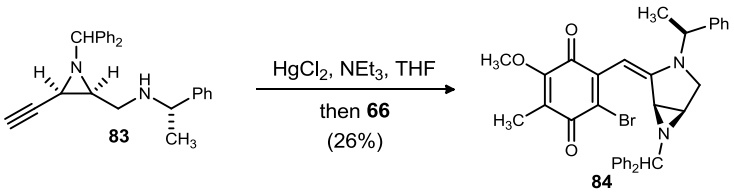
[77] Barluenga, J.; Aznar, F.; Liz, R.; Rodes, R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2732-2737.
[78] Barluenga, J. A., F.; Liz, R. *Synthesis* **1984**, 304-308.
[79] Barluenga, J.; Aznar, F.; Liz, R.; Cabal, M.-P. *Synthesis* **1986**, 960-962.

Scheme 23. Aminomercuration of Terminal Acetylenes



An initial investigation into the feasibility of an intramolecular aminomercuration used the α–methylbenzyl-protected amine **83** and quinone **66** (Scheme 24). Gratifyingly, treatment with $HgCl_2$ and *in situ* trapping of quinone **66** furnished intermediate **84**.[80] Consistent with earlier observations, the enamine added to C8a of the quinone and the resulting enamine was now ready for addition of the last carbon required for MMC before Michael addition into the quinone. The highly reactive nature of this intermediate complicated efforts to install C10;[81] in order to better control the reactivity of the coupled intermediate, the alkyl protecting group on the amine was changed to the diphenylmethyl group (DPM).

Scheme 24. Aminomercuration of Amine **83**

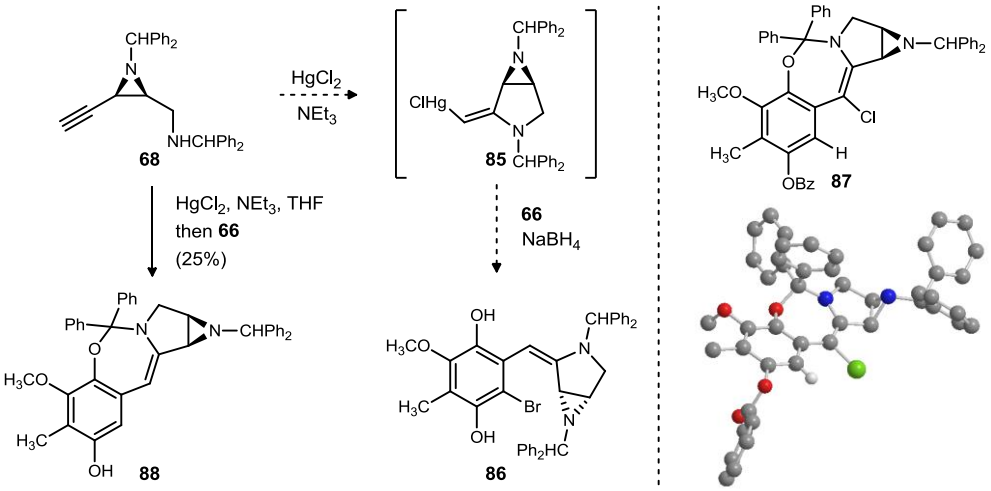


Treatment of diphenylmethyl-protected amine **68** with $HgCl_2$ followed by quinone **66** and $NaBH_4$ was expected to give hydroquinone **86** (Scheme 25). Spectroscopic data for the isolated product was unlike that of the α-methylbenzyl protected intermediate **84** but still corresponded to the expected hydroquinone product

[80] Williams, A. L.; Srinivasan, J. M.; Johnston, J. N. *Org. Lett.* **2006**, *8*, 6047-6049.
[81] Approximate half-life of coupled product **79** is 1.5 days at −15 °C. Rapid decomposition (on the order of minutes) was observed in chlorinated solvents.

86. In order to obtain additional data to elucidate the structure of compound **86**, it was treated with benzoyl chloride and triethylamine to esterify both phenolic hydroxyls. A single phenolic hydroxyl group was esterified despite varying reaction conditions. Deprotection of the pyrrolidine protecting group by oxidative cleavage was unsuccessful.[69]

Scheme 25. Aminomercuration of DPM-Amine **68**

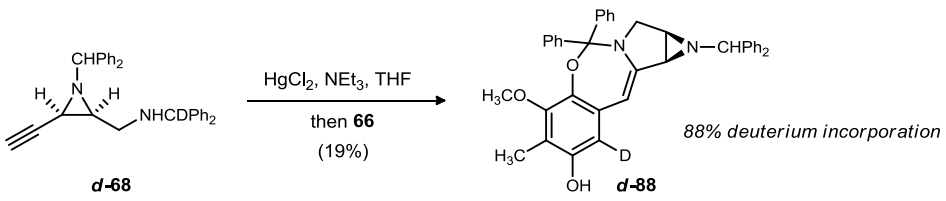


Since pyrrolidine deprotection proved to be difficult at this stage and the next step was to install C10, the enamine nucleophilicity was assessed using *N*-chlorosuccinimide. The chlorinated product was crystalline, and an X-ray structure was obtained (Scheme 25). This revealed that the bromine on the hydroquinone ring had been replaced by a hydrogen, and one phenolic hydroxyl group had formed a seven-membered ring with the pyrrolidine diphenylmethyl group. By retrospective analysis, the coupling reaction had resulted in an oxidative ketalization to form *N,O*-ketal **88**, thus explaining the previously observed reactivity (mono-benzoylation).[69]

This unusual transformation required two reducing equivalents during the reaction. The concomitant oxidation of the pyrrolidine diphenylmethyl group suggested an intramolecular source of one equivalent of hydride. This would also explain why the α-methylbenzyl protected pyrrolidine, which will not donate a hydride as readily, did not undergo ketalization (Scheme 24).[69]

The intramolecular hydride transfer hypothesis was investigated using a deuterium labeling experiment (Scheme 26). Deuterated alkynyl amine ***d*-68** was subjected to the standard reaction conditions. The coupled *N*,*O*-ketal showed an 88% deuterium incorporation; this verifies that one of the two reducing equivalents results from the intramolecular transfer of the diphenylmethyl methine. The second hydride is hypothesized to come from triethylamine or the solvent.[69]

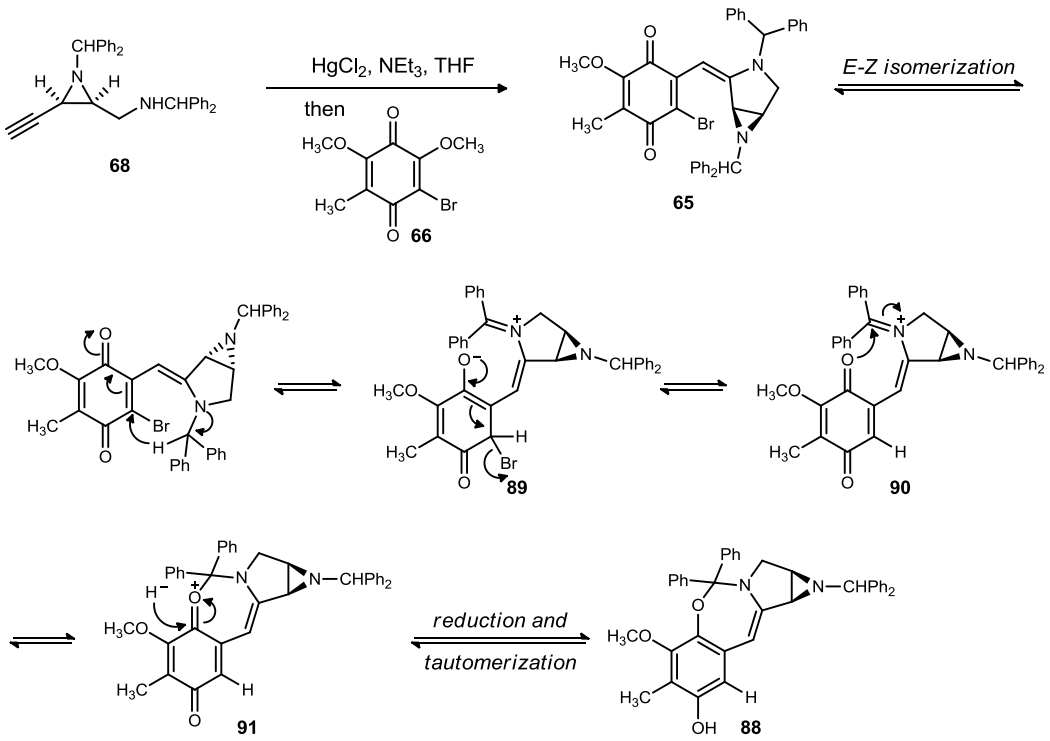
Scheme 26. Deuterium Labeling Experiment



Additionally, if the methine of the diphenylmethyl group were to be removed by using an α,α-diphenylethyl group, aminomercuration should give the nonketalized coupled product, analogous to the α–methylbenzyl case. Unfortunately, the standard reaction conditions produced the methyl ketone (arising from oxymercuration) with no quinone incorporation.[68]

With this data in hand, the mechanism of formation of *N*,*O*-ketal **88** can be proposed (Scheme 27). The initial aminomercuration of alkynyl amine **68** and subsequent enamine addition to quinone **66** would form coupled intermediate **65**. An *E*/*Z* isomerization would bring the pyrrolidine in close proximity for the 1,6-hydride shift of the diphenylmethyl methine, resulting in elimination of the bromide and subsequent cyclization of the quinone oxygen onto the iminium ion **90**. A second hydride addition and tautomerization would then give observed product **88**.[69]

Scheme 27. Proposed Mechanism for Oxidative Ketalization



The unexpected but powerful transformation from **68** and **66** to **88**, in essence a one-pot aminomercuration-quinone trapping-oxidative ketalization, delivers a useful advanced intermediate containing all but one of the required carbons for mitomycin C.

The oxidative ketalization provides differential protection for both phenolic hydroxyls and the pyrrolidine and aziridine nitrogens while maintaining the nucleophilicity of the enamine required to install C10, as evidenced by the chloroenamine formation.

At this point, the key accomplishments by Amie Williams and Jayasree Srinivasan were:

- preparation of an aziridinyl alkynyl amine using the Brønsted acid catalyzed aza-Darzens reaction
- investigation of quinone regioselectivity
- construction of an aziridine-containing pyrrolidine (N4-C9a bond) using aminomercuration and *in situ* regioselective coupling with the quinone (C9-C8a bond) to form an *N*,*O*-ketal lacking only C10 of the mitomycin skeleton
- mechanistic studies of the oxidative ketalization to form the *N*,*O*-ketal

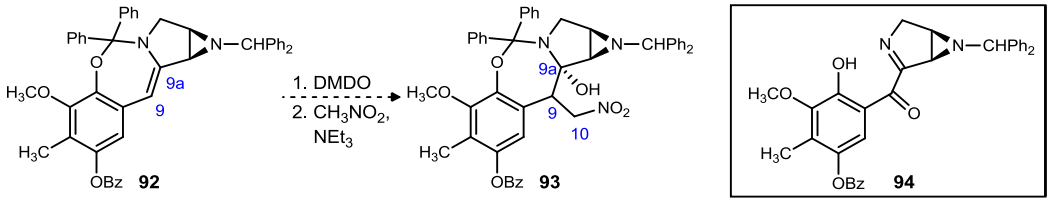
On the basis of these benchmarks, this dissertation highlights the following achievements:

- further investigations into *N*,*O*-ketal reactivity with carbon electrophiles
- successful installation of C10 using the *N*,*O*-ketal intermediate
- successful installation of C10 prior to the coupling of the alkynyl amine and the quinone using a methyl-substituted alkyne
- preparation of an aziridinyl pyrrolidine intermediate containing a functionalized C10
- construction of an aminoquinone (N4-C4a bond)

2.5. Installation of C10 on *N,O*-ketal Enamine

The coupling of quinone **66** and amine **68** resulted in the formation of advanced intermediate **88** that lacked only the carbamoyl carbon (C10) to complete the mitomycin skeleton. Initially, a simultaneous installation of C10 and the C9a methoxy group of MMC was envisioned by epoxidation and subsequent nucleophilic ring opening (Scheme 28). Unfortunately, this led to an inseparable mixture of two compounds that lacked the epoxide. The major product, tentatively assigned as ketone **94**, is postulated to arise from epoxide opening by the pyrrolidine nitrogen, followed by hydrolysis of the *N,O*-ketal and oxidation to the ketone. Other oxidation attempts resulted in the isolation of benzophenone but decomposition of the rest of the molecule.[68]

Scheme 28. Epoxidation Attempt on Enamine **92**

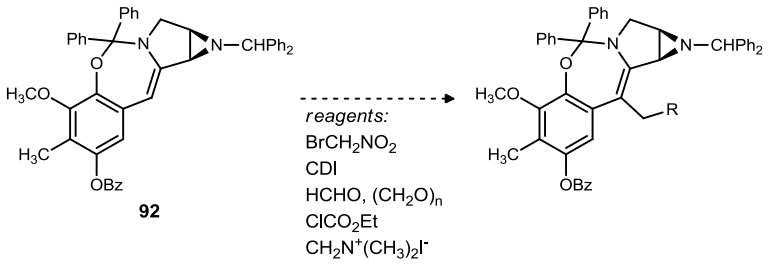


It seemed likely that the electron-rich hydroquinone ring and/or the aziridine nitrogen were interfering under the oxidative conditions. The oxidation of the hydroquinone and the concomitant *N,O*-ketal opening would give a product similar to highly reactive α-methylbenzyl-protected **84** (as discussed earlier) that rapidly decomposes. Therefore, an alternative strategy would harness intermediate **92**'s electron-rich nature by electrophilic enamine trapping, while retaining the *N,O*-ketal to stabilize these highly advanced intermediates.

Ideally, enamine **92** would be trapped with a one-carbon electrophile. Due to the limited availability of electrophilic one-carbon reagents, we also considered other suitable electrophiles, that could then be modified – either before installation (by designing a one-carbon analog) or after installation (by removing extra carbons via ozonolysis, decarboxylation etc.).

Accordingly, compound **92** was treated with a series of one-carbon electrophiles (Scheme 29). Bromonitromethane and carbonyldiimidazole (CDI) gave no reaction; treatment with Eschenmoser's salt,[68] formaldehyde (with and without Lewis-acids, e.g. $TiCl_4$, BF_3•OEt_2), paraformaldehyde and ethyl chloroformate led to no recognizable products.[82,83] In most cases, benzophenone was observed with decomposition of the rest of the compound as observed previously.

Scheme 29. One-Carbon Homologation Attempts



Formylation of **92** was also attempted. Riemer-Tiemann conditions with sodium hydroxide in chloroform at reflux gave no reaction.[84] Treatment with dichloromethyl

[82] $(CH_2O)_n$, $Mg(OMe)_2$: Wang, Y.; Wang, M.; Wang, L.; Wang, Y.; Wang, X.; Sun, L. *Appl. Organomet. Chem.* **2011**, *25*, 325-330.
[83] $Mg(OMe)_2$ preparation: (a) Wuttke, S.; Lehmann, A.; Scholz, G.; Feist, M.; Dimitrov, A.; Troyanov, S. I.; Kemnitz, E. *Dalton Trans.* **2009**, 4729-4734. (b) Brown, A. C.; Carpino, L. A. *J. Org. Chem.* **1985**, *50*, 1749-1750.
[84] Sharma, H.; Patil, S.; Sanchez, T. W.; Neamati, N.; Schinazi, R. F.; Buolamwini, J. K. *Bioorg. Med. Chem.* **2011**, *19*, 2030-2045.

methylether in the presence of titanium tetrachloride resulted in decomposition.[85] The Duff formylation reaction with hexamethylenetetramine in neat trifluoroacetic acid resulted in decomposition. Modification of the Duff reaction conditions using acetic acid, formic acid and aqueous hydrochloric acid did not improve the reaction outcome.[86,87] Performing the Duff reaction with TFA at lower temperatures revealed consumption of starting material to a compound that did not have aziridine protons, therefore it is likely that the aziridine opened with no other observable changes by ^{1}H NMR.

A variety of other electrophiles were also examined (Scheme 30). Phenyl isocyanate gave no reaction. An enamine-aldol reaction with ethyl glyoxylate led to decomposition (as did treatment with the methyl acetal of ethyl glyoxylate and diisopropylethylamine). Treatment of **92** with valeraldehyde resulted in decomposition due to acidic reaction conditions.[88] A one-electron oxidative allylation was investigated using allyltrimethylsilane and ceric ammonium nitrate which resulted in immediate decomposition; allylation with allyl bromide led to no conversion of starting material. A Diels-Alder reaction with nitrostyrene in refluxing toluene also gave no reaction.[89] Nitromethylation with tributyltin hydride gave no reaction, while manganese(III) acetate[90] resulted in decomposition. Cyclopropanation conditions also resulted in immediate decomposition of starting material.[91]

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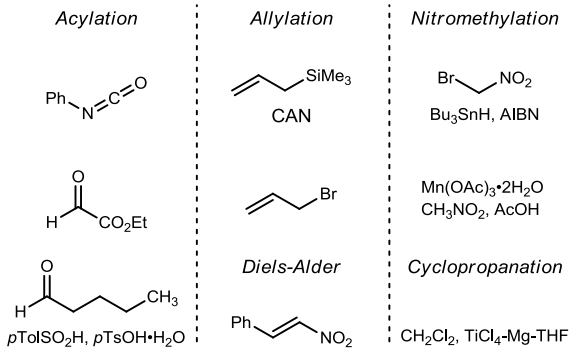
[85] Rieche, A.; Gross, H.; Höft, E. *Org. Synth.* **1973**, *Coll. Vol. 5*.
[86] Modified procedure from: Duff, J. C. *Journal of the Chemical Society (Resumed)* **1945**, 276-277.
[87] Modified procedure from: Duff, J. C.; Bills, E. J. *Journal of the Chemical Society (Resumed)* **1932**, 1987-1988.
[88] Palmieri, A.; Petrini, M. *J. Org. Chem.* **2007**, *72*, 1863-1866.
[89] Felluga, F.; Nitti, P.; Pitacco, G.; Valentin, E. *Tetrahedron* **1989**, *45*, 5667-5678.
[90] Kurz, M. E.; Chen, T.-y. R. *J. Org. Chem.* **1978**, *43*, 239-242.
[91] Tsai, C.-C.; Hsieh, I. L.; Cheng, T.-T.; Tsai, P.-K.; Lin, K.-W.; Yan, T.-H. *Org. Lett.* **2006**, *8*, 2261-2263.

Scheme 30. Enamine Reactivity Screen



It can be concluded that oxidation and direct carbon homologation of the enamine are difficult due to the competing reactive functionalities present in this advanced intermediate. Previous success of enamine halogenation using *N*-chlorosuccinimide (**87**) led to the next logical step, i.e. to introduce a carbon via the manipulation of C10 halides.

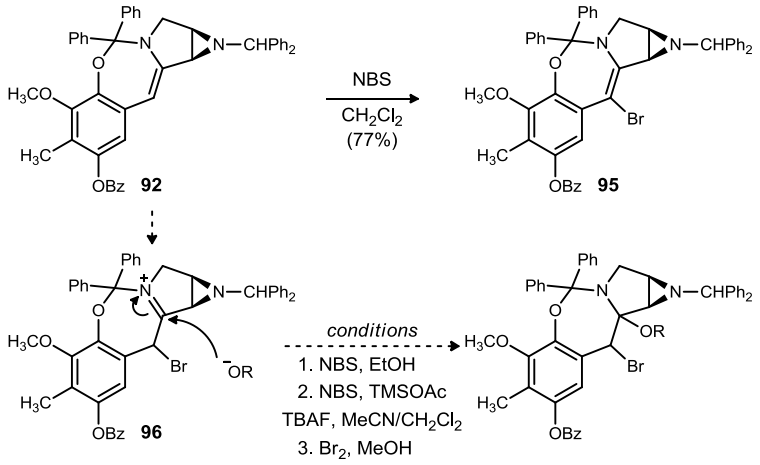
2.6. Installation of C10 on Bromoenamine

2.6.1. Preparation of the Bromoenamine

A C-X bond (X = halide) can be transformed into a C-C bond using a variety of conditions, such as lithium-halogen exchange, Grignard formation and cross-coupling reactions. We decided to use lithium-halogen exchange to install C10. In this regard, chlorination of enamine **92** using *N*-chlorosuccinimide had been achieved (**87**, Scheme 25) even though direct addition of carbon electrophiles to the enamine had been unsuccessful. Since bromides are more prevalent in metalation chemistry than chlorides, we sought to prepare bromoenamine **95**.

Treatment of enamine **92** with *N*-bromosuccinimide (NBS) resulted in clean conversion to desired bromoenamine **95** (Scheme 31).[68] Additionally, we considered trapping the intermediate iminium ion (**96**) with an oxygen nucleophile to install the C9a methoxy group. Various nucleophiles and brominating agents did not succeed in trapping the iminium ion, but formed bromoenamine **95** in varying yields with some decomposition (i.e. benzophenone formation). Additionally, sodium cyanide was added to a standard NBS reaction to see if an intermediate bromonium ion could be trapped; however, rapid decomposition was observed.

Scheme 31. Bromoenamine Formation and Iminium Trapping



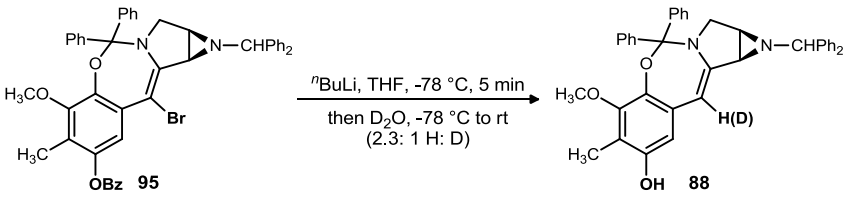
In conclusion, bromoenamine **95** was prepared for C10 homologation. Iminium ion **96** proved to be a fleeting intermediate and could not be captured to install the C9a methoxy group.

2.6.2. Lithium-Halogen Exchange on the Benzoyl-Protected Phenol

To investigate the formation of the C10-Li bond, bromoenamine **95** was subjected to lithium-halogen exchange followed by deuterium oxide addition. ^{1}H NMR revealed

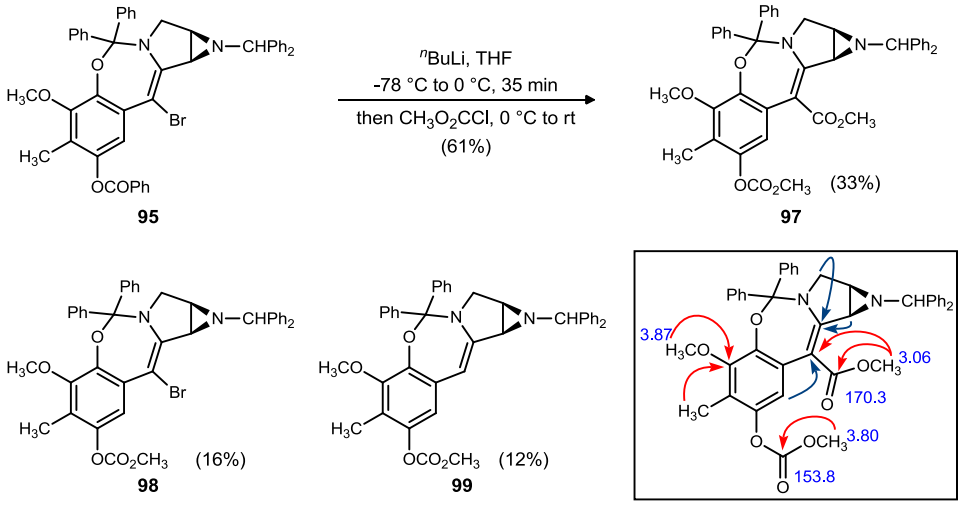
successful enamine deuteration accompanied by phenol deprotection (Scheme 32). The observed protonation of the enamine was presumably due to adventitious moisture present in the reaction mixture.

Scheme 32. Deuterium Addition to Bromoenamine **95**



The benzoyl group was clearly incompatible with butyllithium; it had been initially chosen to withstand oxidation. Since its deprotection was competitive with lithium-halogen exchange, an alternate protecting group was required. However, the extreme selectivity of enamine reactivity had already been realized with the success of halogenation, and the failure in alkylation and acylation. In order to ascertain the viability of adding a carbon electrophile, bromoenamine **95** was treated with 4.5 equivalents ^{n}BuLi and excess methyl chloroformate (Scheme 33).

Scheme 33. Methyl Chloroformate Addition to Bromoenamine



Desired vinylogous carbamate **97** with the carbonate-protected phenol was obtained in a 33% yield (Scheme 33). 2D NMR analysis confirmed the incorporation of the methyl ester at C9. In addition to methyl ester **97**, carbonate-protected bromoenamine **98** (16%) was formed. This suggested that the lithium-halogen exchange was slower than the benzoyl deprotection, perhaps due to steric congestion. Protonated carbonate **99** (12%), starting material **95** (5%) and protonated phenol **88** (trace by ^{1}H NMR) were also observed. Due to the competitive formation of side products, reproducibility of this reaction was low. In an attempt to increase reproducibility, different solvents were used to control the reactivity of butyllithium (toluene, THF-cyclohexane), but neither of these conditions produced any reaction.[92] The Turbo Grignard developed by Knochel (^{i}PrMgCl•LiCl) produced inconsistent results (no reaction or decomposition).[93,94] These

[92] Slocum, D. W.; Kusmic, D.; Raber, J. C.; Reinscheld, T. K.; Whitley, P. E. *Tetrahedron Lett.* **2010**, *51*, 4793-4796.
[93] Brückl, T.; Thoma, I.; Wagner, A. J.; Knochel, P.; Carell, T. *Eur. J. Org. Chem.* **2010**, *2010*, 6517-6519.
[94] Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333-3336.

experiments suggest that butyl lithium in THF provided the optimal reactivity for this system.

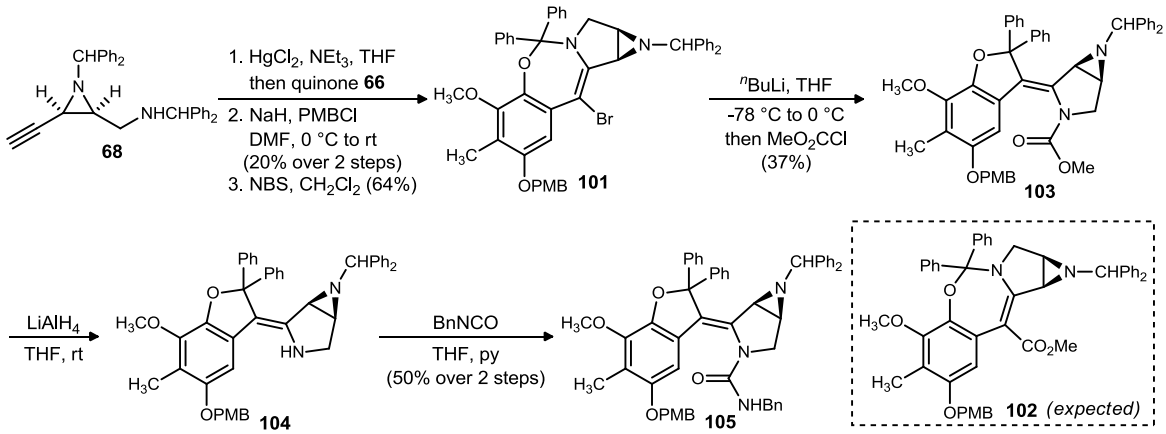
Installation of C10 was thus accomplished; vinylogous carbamate **97** contains all requisite carbons for MMC. Having confirmed the viability of the bromoenamine as an intermediate for C10 installation, there remains the need for a suitable phenol protecting group.

2.6.3. Lithium-Halogen Exchange on Other Protected Phenols

The criteria for an appropriate phenol protecting group were stability to strong bases, such as butyllithium, and to reducing agents (for future vinylogous carbamate reduction), and deprotection conditions compatible with the aziridine. The *p*-methoxybenzyl group (PMB) fulfilled these criteria with the attractive possibility of oxidative cleavage of the *N*,*O*-ketal with concomitant oxidation of the hydroquinone.

Amine **68** was coupled with quinone **66**, followed by phenol protection and bromination (Scheme 34). The PMB-enamine **100** and PMB-bromoenamine **101** were more reactive than their benzoyl counterparts; enamine **100** and bromoenamine **101** decomposed on gentle heating, and bromination of PMB-enamine **100** with NBS was significantly faster than on benzoyl-enamine **92** (3-5 min vs. 15-30 min).

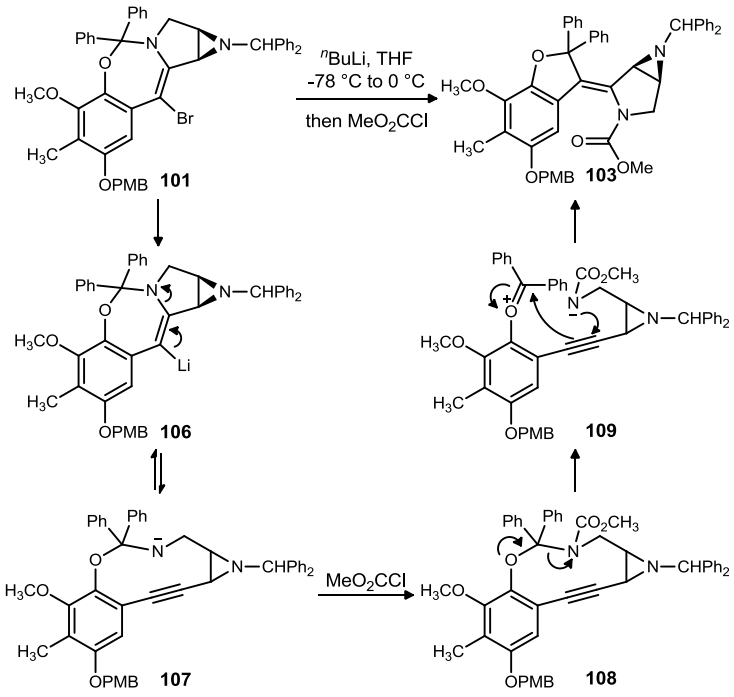
Scheme 34. Metalation of the PMB-Bromoenamine



Bromoenamine **101** was treated with butyllithium and methyl chloroformate (Scheme 34). Mass spectral data of the resulting product confirmed methyl ester incorporation but the expected vinylogous ester **102** had a carbonyl peak at 154.9 ppm by ^{13}C NMR (unlike benzoyl-protected vinylogous ester **97**: 170.3 ppm) and a C=O stretch at 1769 cm^{-1} by IR (unlike benzoyl-protected vinylogous ester **97**: 1701 cm^{-1}). 2D NMR experiments were not conclusive but indicated that the aziridine and the pyrrolidine were intact, as was the hydroquinone. Treatment with lithium aluminum hydride of the expected vinylogous carbamate **102** should form the C10-methylene alcohol. However, ^{1}H NMR and DEPT-135 lacked a CH_2 required for this structure. Mass spectrometry confirmed the complete removal of the methyl ester unit from the expected vinylogous carbamate **102** and IR indicated an NH/OH (broad absorption at 3509 cm^{-1}). This suggested *N*-acylation with methyl chloroformate. The lithium-halogen exchange product is tentatively assigned as **103**; the ^{13}C NMR and IR data correspond better with a carbamate, and the experimental data obtained from the reduction of carbamate **103** with lithium aluminum hydride correspond well with compound **104**.

To prevent *N*-acylation, the lithiated enamine was treated with Mander's reagent ($CNCO_2Me$) but only enamine protonation (**100**) was observed. This suggested that the reaction pathway took an unexpected turn *after* the lithium-halogen exchange. The proposed mechanism for this transformation is shown in Scheme 35. After lithiation, enamine **106** could be in equilibrium with alkyne **107**. Acylation of the nitrogen could then lead to *N,O*-ketal opening, and subsequent nitrogen attack on the alkyne and cyclization of the alkyne on the oxonium would then give carbamate **103**.

Scheme 35. Proposed Mechanism for **103** Formation

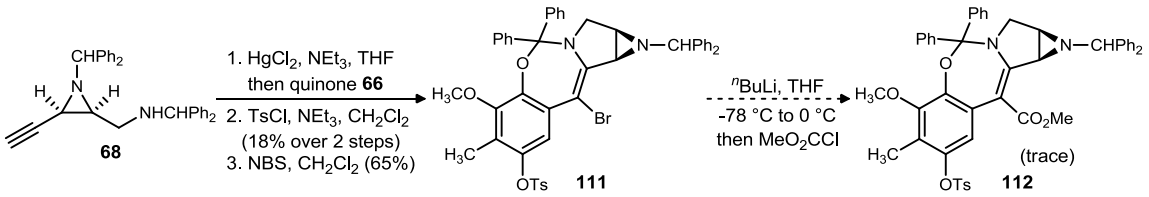


There clearly exists a striking relation between the phenol protecting group and lithiated enamine addition. This relationship is presumably electronic in nature due to the increased reactivity of the PMB-intermediates as compared to the benzoyl protected intermediates, as previously noted. If the electronic nature of the protecting group

determines the reaction pathway, then the desired metalation pathway can be achieved with an electron-withdrawing protecting group. Unfortunately, most electron-withdrawing groups are sensitive to butyllithium, however, the exception is a non-traditional protecting group for phenols i.e. the tosyl group.

Tosyl-bromoenamine **111** was prepared and subjected to standard lithium-halogen exchange conditions (Scheme 36). A complex reaction mixture was observed by ^{1}H NMR and showed some starting material, some protonated enamine and a trace amount of product.

Scheme 36. Metalation of Tosyl Bromoenamine **111**



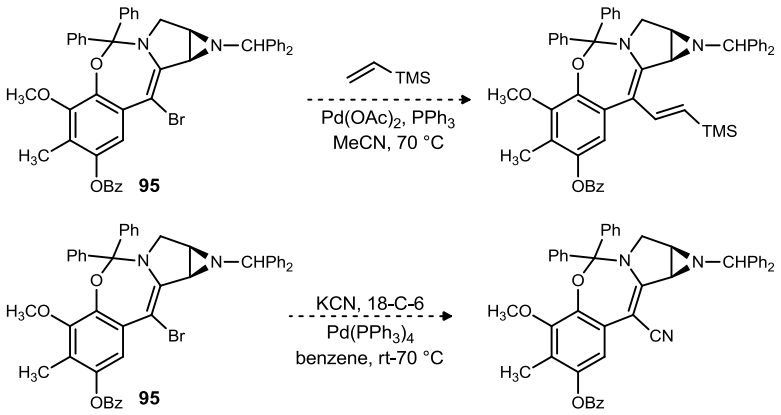
In conclusion, lithium-halogen exchange occurred readily on bromoenamines **95** and **101**; however, the subsequent pathway was highly dependent on the phenol protecting group. The benzoyl group gave desired *C*-acylation accompanied by undesired phenol deprotection, while the PMB group gave undesired *N*-acylation. Milder metalating conditions might be an alternative solution to C10 installation without phenol deprotection.

2.6.4. Other Metal-Mediated Attempts to Install C10

Palladium cross-couplings were explored in the hope of finding a mild non-nucleophilic metalating reagent (Scheme 37). Heck reaction of bromoenamine **95** gave a

complex mixture with no desired vinyl peaks by ^{1}H NMR. Cyanide substitution on bromoenamine **95** resulted in mostly starting material and no desired nitrile product.[95] Additionally, Grignard formation with magnesium in THF followed by methyl chloroformate addition, gave no conversion of bromoenamine **95**.

Scheme 37. Palladium Cross-Coupling Attempts



The bromide position of bromoenamine **95** was previously observed to react slower than the benzoyl group with butyllithium. Steric congestion at the bromoenamine could be the cause, and therefore, might explain the lower reactivity with larger metals (like palladium) endowed with bulky ligands.

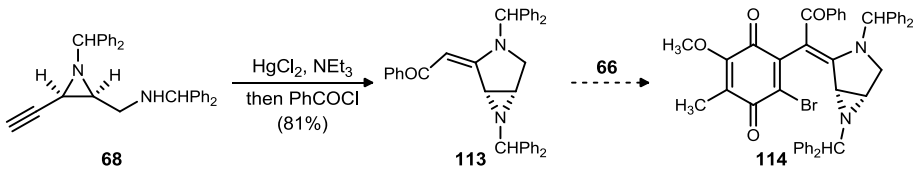
Our endeavor to introduce C10 on advanced intermediate **95** was successful under lithium-halogen exchange conditions, and afforded carbamate **97**, a promising intermediate towards the synthesis of MMC. While efforts to side-step phenol deprotection were not fruitful, the phenol carbonate (**97**) can be selectively manipulated, if necessary, to distinguish between the phenol and C10-alcohol.

[95] Yamamura, K.; Murahashi, S.-I. *Tetrahedron Lett.* **1977**, *18*, 4429-4430.

2.7. Installation of the C10-Methyl Prior to Coupling

Installation of C10 can be simplified by its introduction prior to the coupling, thereby reducing manipulations on the highly functionalized *N*,*O*-ketal **88**. Alkyne substituent effects on aminomercuration had not been previously investigated; hence the steric effects were unknown. Previous work with vinylogous amide **113**, prepared from terminal alkyne **68**, had established that an electron-withdrawing carbonyl group at the enamine position inhibited quinone addition.[65] In order to investigate the feasibility of introducing C10 via the alkyne prior to coupling, the methyl group was chosen, on account of its minimal steric and electronic effects. Additionally, allylic oxidation at the methyl position of methylated *N*,*O*-ketal **117** (Scheme 39) would provide the requisite alcohol for MMC.

Scheme 38. Vinylogous Amide Addition to Quinone **66**

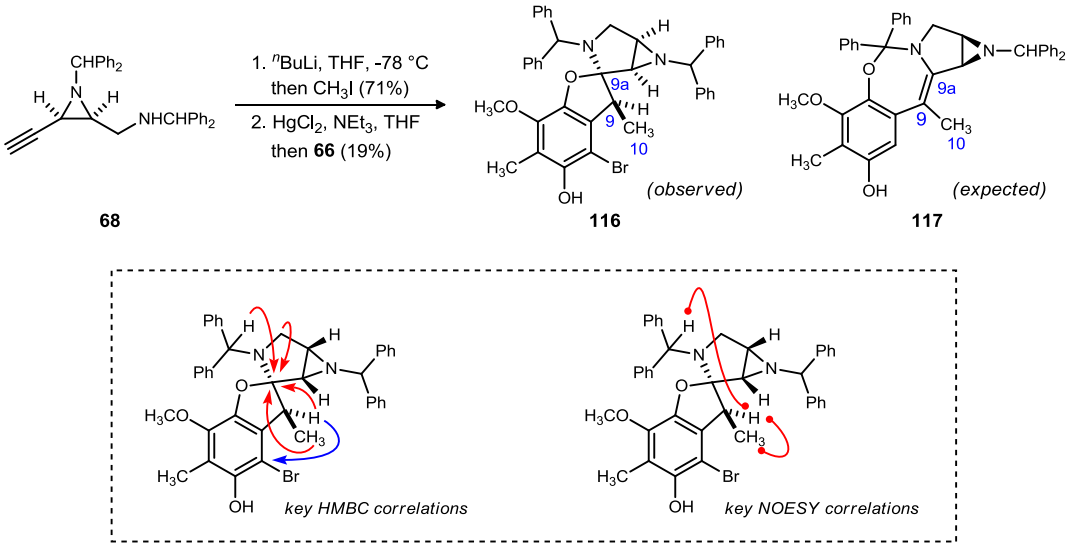


2.7.1. Preparation and Coupling of the Methyl-Substituted Alkyne

Methylation of terminal alkyne **68** was accomplished in 71% yield (Scheme 39). Standard coupling conditions with mercury(II) chloride, triethylamine and quinone **66** afforded a product that was spectroscopically different from expected *N*,*O*-ketal **117**. ^{1}H NMR revealed a methyl doublet instead of the expected singlet, and mass spectrometry indicated retention of bromine. The aziridine and the pyrrolidine were intact, as was the hydroquinone. 2D NMR analysis suggested (racemic) spiroketal **116** to

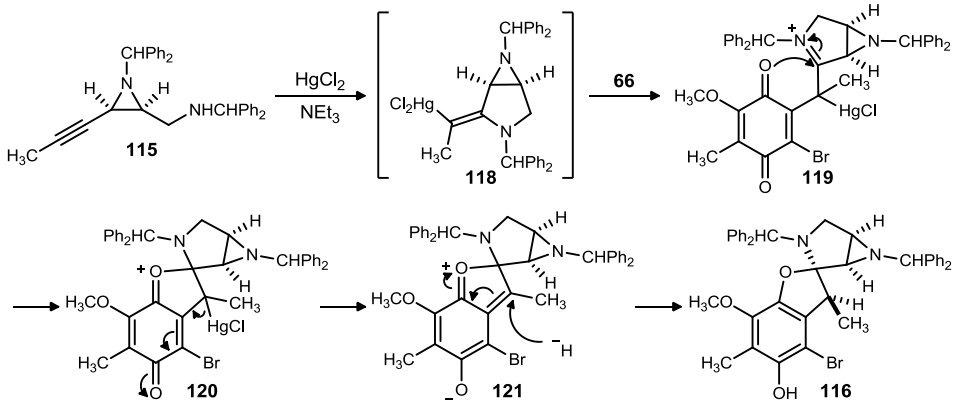
be the proposed product with the pyrrolidine nitrogen and the C10 methyl *anti* to each other.

Scheme 39. Coupling of Methyl-Substituted Alkyne with Quinone **66**



It was evident that methyl substitution of the alkyne had prevented the oxidative ketalization required to form the expected product **117**, presumably to accommodate the increased steric crowding at the alkyne terminus. Spiroketal **116** is hypothesized to form by quinone carbonyl addition to intermediate iminium ion **119**, following enamine addition into the quinone (Scheme 40). Demercuration and hydride addition to resulting quinone methide (hydride from triethylamine or the solvent) would give observed product **116**.

Scheme 40. Proposed Mechanism for Spiroketal **116** Formation



Spiroketal **116**, though unexpected, established the feasibility of introducing C10 prior to the coupling. It contains all carbons required for MMC at the correct oxidation state, with the exception of C10, which needs to be oxidized to the alcohol. Deprotection, *N*,*O*-ketal opening and subsequent Michael addition into the quinone would give MMC.

2.7.2. Deprotection of the Spiroketal

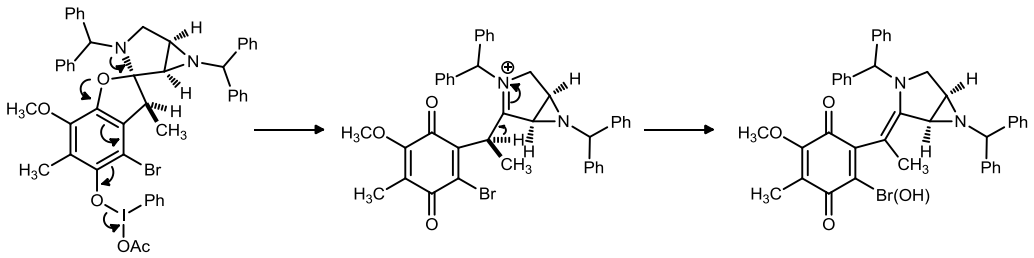
Deprotection of the pyrrolidine would ready spiroketal **116** for the subsequent transformations required to prepare MMC. If the aziridine deprotected faster or competitively, we would have access to the MMC core via Fukuyama's isomitomycin approach.[36,37] To this end, oxidative and reductive deprotection conditions were attempted for the pyrrolidine DPM group. Acylating deprotection conditions were attempted for the aziridine DPM group.

Table 1. DPM Deprotection Attempts

method	conditions	result
oxidation	1-2 eq DDQ	quinone oxidation
	2 eq CAN	bromine loss
	1.1 eq $PhI(OAc)_2$	
	10% Pd/C, EtOAc, air	
	1.5-2 eq DEAD	
	Ph_3CBF_4	no rxn
	O_2	
reduction	H_2, 20% $Pd(OH)_2/C$	decomposition
	10% Pd/C, cyclohexene	bromine loss
	Et_3SiH, TFA	
	$NaCNBH_3$, HCl, MeOH	mostly no rxn
acylation	NIS	decomposition
	NIS then $BnONH_2$	
	TCCA, 1M H_2SO_4	
	MeO_2CCl	no rxn

Standard oxidative deprotecting conditions with DDQ and CAN (Table 1) led to quinone oxidation but no deprotection. Additionally, a methyl singlet was observed by ^{1}H NMR suggesting formation of the enamine. Increasing the equivalents of DDQ to force deprotection led to rapid decomposition. Less common oxidizing agents gave similar results or no reaction. Further spectroscopic analysis was not undertaken, but preliminary data from mass spectrometry, indicating bromide loss, and ^{1}H NMR suggested that quinone oxidation was followed by enamine formation (Scheme 41) and Michael addition of water (or other nucleophiles, if present) into the quinone.

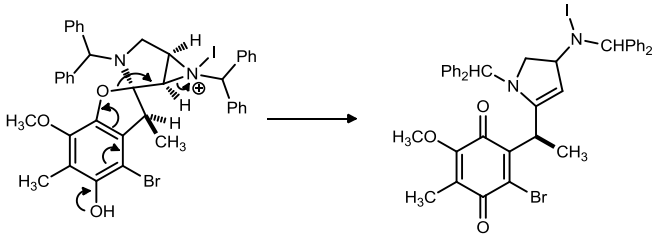
Scheme 41. Proposed Pathway under Oxidative Cleavage Conditions



Due to the lack of deprotection under oxidative conditions, attention was turned to reductive methods to remove the DPM group (Table 1). Hydrogenation, transfer hydrogenation and mild reducing agents resulted in complex reaction mixtures that mostly indicated decomposition of the aziridine. Purification of these complex mixtures performed on small scale was unsuccessful in these cases, but mass spectrometry of some impure products showed bromide loss but no removal of the DPM groups.

Deprotection by acylation of the aziridine and subsequent nucleophilic removal of the DPM group afforded reaction mixtures with no aziridine (Table 1). Using NIS, aziridine *N*-iodination is postulated to occur, followed by rapid ring opening by the phenol (Scheme 42). No reaction was observed with methyl chloroformate (Table 1).

Scheme 42. Proposed Pathway of Acylating Deprotection Conditions

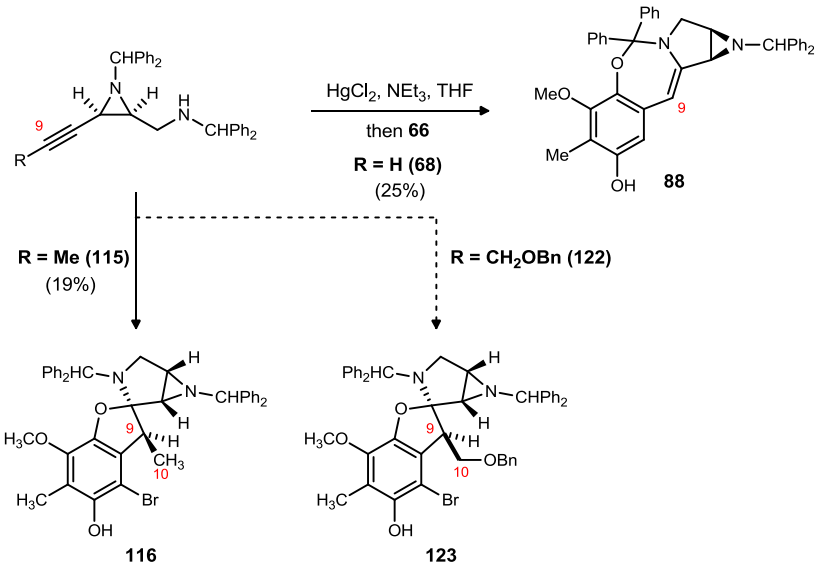


To summarize, the installation of C10 prior to the coupling reaction was accomplished, despite concerns of steric and electronic effects on aminomercuration and the subsequent quinone addition. Unexpected spiroketal **116** is a potential intermediate to MMC analog. Deprotection of spiroketal **116** has not been realized as yet due to competing reactive functionalities that result in complex mixtures; a possible solution to obtain selective deprotection are phenol protection or *N*,*O*-ketal opening before deprotection.

2.8. Installation of a Functionalized C10 Prior to Coupling

The success with the methyl(C10)-alkyne **115** validated C10 introduction prior to the coupling. MMC requires C10 at the alcohol oxidation state. However, the unforeseen reaction pathway with alkyne **115** implied that allylic oxidation to form the C10-alcohol was no longer possible (Scheme 43). To this end, a functionalized C10-alkynyl amine was sought. A cyclization product similar to the spiroketal (**116**) would be expected due to the steric similarity. The ideal choice would be a protected alcohol, and previous experience with vinylogous amide **113** (Scheme 38) negated the use of electron-withdrawing alcohol precursors, i.e. carbonyl, carboxyl and nitro groups. Therefore, a benzyl-protected alcohol was chosen because the electronics would not be unfavorable and deprotection using reductive methods should be compatible with more advanced intermediates.

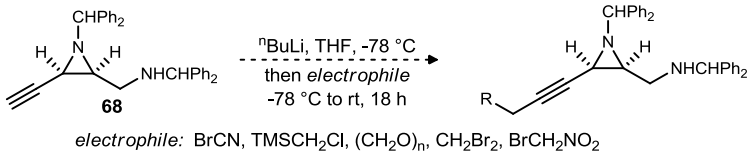
Scheme 43. Aminomercuration-Quinone Coupling Products Based on Alkyne Substitution



2.8.1. Preparation of the Functionalized C10 Aziridine

Introducing the methylene alcohol unit on alkyne **68** via deprotonation and addition to formaldehyde was unsuccessful (Scheme 44). Other electrophiles and bases (ethylmagnesium bromide) were unsuccessful as well. As a result, the methylene alcohol unit had to be installed earlier in the synthesis of the alkynyl amine.

Scheme 44. Alkyne Substitution

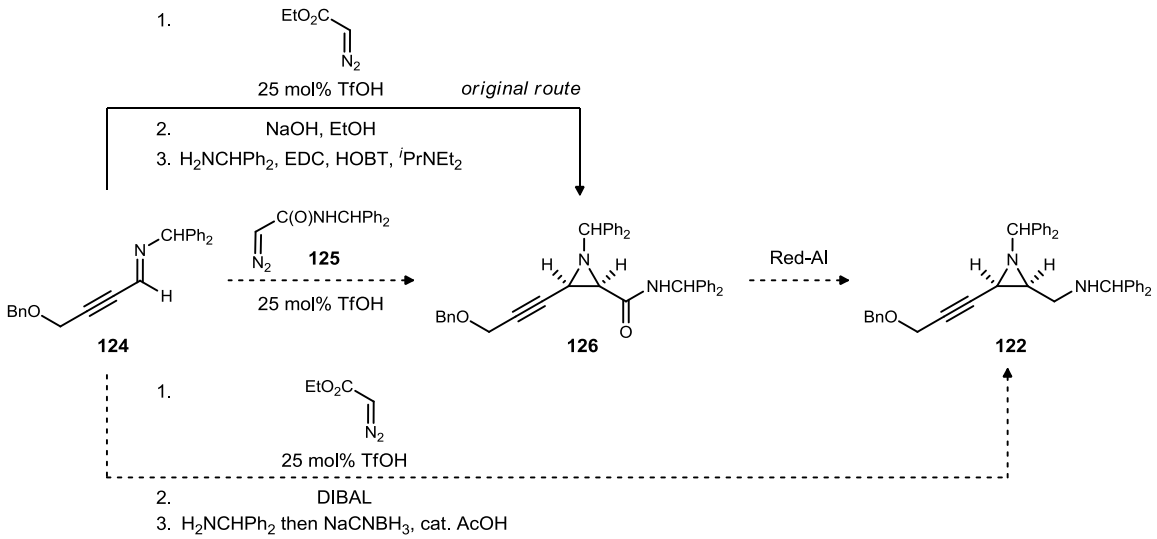


The modification of the synthesis of the alkynyl amine provided the opportunity to a) optimize the route further and b) investigate the protecting group choice for the aziridine and amine nitrogens, in the event that DPM-deprotection became problematic at later stages.

Our previous protocol for the preparation of the alkynyl amine had used ethyl diazoacetate in the aza-Darzens reaction (Scheme 45). The resulting *cis*-aziridinyl ester was converted to the corresponding amine via saponification, amide coupling and reduction. Two possible modifications of this sequence of reactions are outlined in Scheme 45, namely, substituting the diazoacetate with a diazoacetamide in the aza-Darzens reaction to directly provide the *cis*-aziridinyl amide, thereby shortening the synthesis by two steps. The second option utilizes the aza-Darzens reaction with the diazoacetate to provide the aziridinyl ester, which can then be reduced with DIBAL to the

aldehyde and transformed to the amine using reductive amination. This would shorten the synthesis by one step.

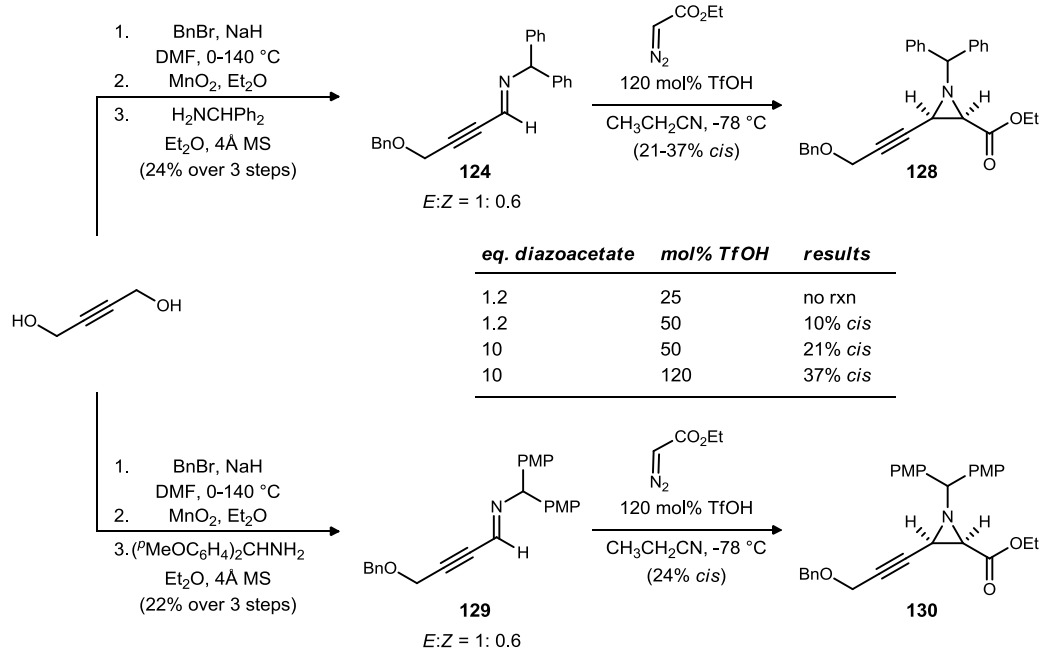
Scheme 45. Proposed Optimization of Alkynylamine Synthesis



The preparation of the imine (**124**) required for the aza-Darzens reaction, starts with commercially available 2-butyne-1,4-diol (Scheme 46). Monobenzylation of the diol is followed by oxidation to the aldehyde (**127**).[96] The aldehyde is then treated with diphenylmethyl amine to yield imine **124** (*E*:*Z* ratio = 1:0.6). At this stage, an alternate aziridine protecting group, i.e. the bis(*p*-methoxyphenyl)methyl (bis-PMP), was introduced in case DPM-deprotection was problematic at later stages.

[96] Nicolaou, K. C.; Bunnage, M. E.; McGarry, D. G.; Shi, S.; Somers, P. K.; Wallace, P. A.; Chu, X.-J.; Agrios, K. A.; Gunzner, J. L.; Yang, Z. *Chem.—Eur. J.* **1999**, *5*, 599-617.

Scheme 46. Preparation of the *cis*-Aziridinyl esters **127** and **129**



The imines were then subjected to the previously optimized conditions for the triflic acid catalyzed aza-Darzens reaction with ethyl diazoacetate (Scheme 46). The DPM-imine (**124**) initially yielded no reaction with 25 mol% triflic acid and equimolar ethyl diazoacetate. Increasing the equivalents of triflic acid and ethyl diazoacetate, however, improved the yield of the desired *cis*-aziridine **128**. The bis(PMP)-imine (**129**) yielded 8% *cis*-aziridine **130** under standard catalytic triflic acid conditions. In this case, an acid screen with both Brønsted and Lewis acids (CSA, $SnCl_4$, $TiCl_4$) produced no aziridine. Methanesulfonic acid treatment of bis(PMP)-imine **129** resulted in deprotection and hydrolysis to the aldehyde. Since imine deprotection was competing with the aza-Darzens reaction, and the desired addition was likely to be slower with the electron-rich bis(PMP) group, 10 equivalents ethyl diazoacetate and 120 mol% triflic acid were used.

The yield increased to 24% *cis*-**130** but the reproducibility of this reaction varies because of competitive imine decomposition.

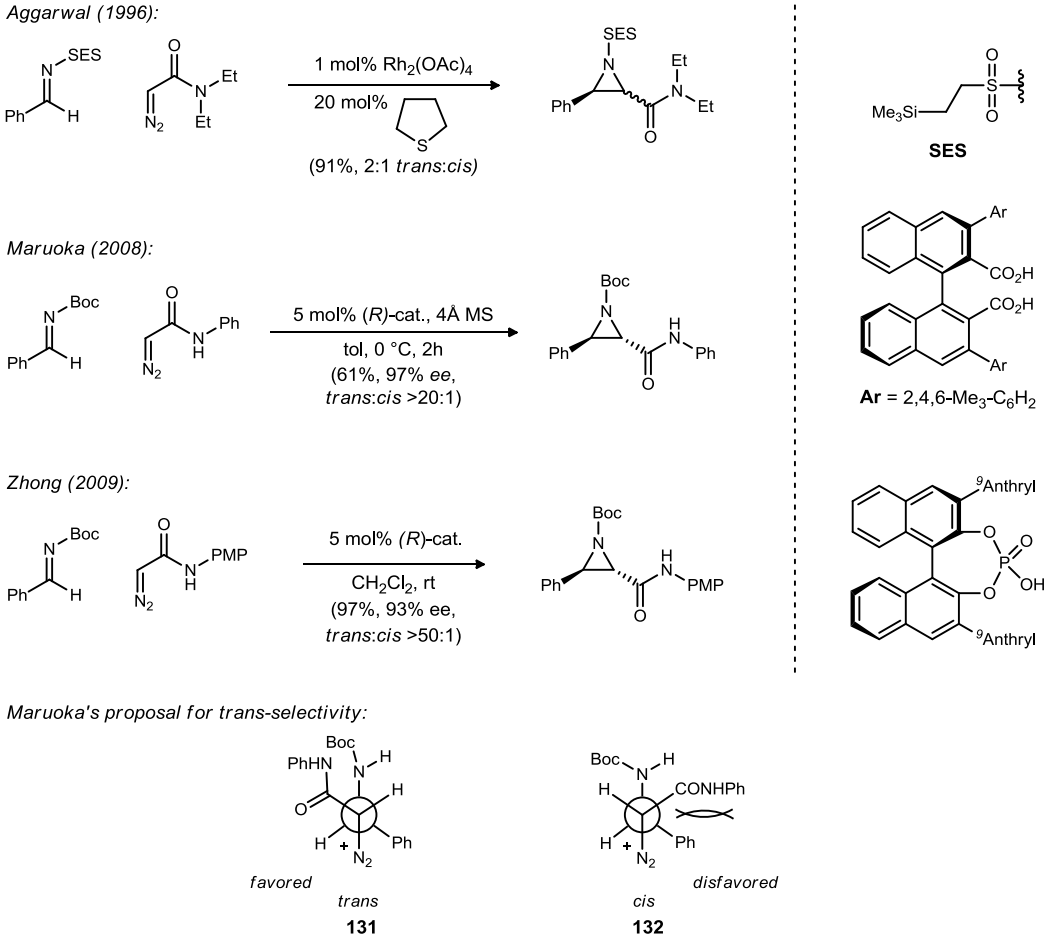
At this stage, the aza-Darzens reaction of imine **124** with diazoacetamide **125** was investigated. As mentioned previously, this would directly lead to amide **126**, eliminating the need to saponify ester **128** and then couple with diphenylmethyl amine.

The use of diazoacetamides instead of diazoacetates has been documented for both the Darzens and the aza-Darzens reactions.[97,98,99,100,101,102,103,104] The Darzens reaction with diazo-*N*,*N*-dimethylacetamide generated predominantly *cis*-epoxides for both aryl and aliphatic aldehydes.[97,98] The diastereoselection for the aza-Darzens reaction, however, had mixed results. In general, the literature indicates that aryl imines with electron-withdrawing groups on the nitrogen (Boc, SES) favored the *trans*-aziridine (Scheme 47).[99,100,101] The substitution on the diazoacetamide did not appear to affect the diastereoselection (mono- and di- substitution with aryl and alkyl groups). Maruoka postulated that the *trans* selectivity arises from the preference of the rotamer (**131**) with the antiperiplanar orientation of the aryl substituent of the imine and the amide group of the diazoacetamide. The formation of the *cis*-aziridine would require a synclinal orientation of these two groups, which would be destabilized by the steric repulsion (Scheme 47).[100]

---

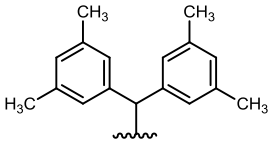
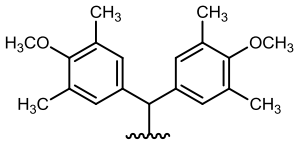
[97] Liu, W.-J.; Lv, B.-D.; Gong, L.-Z. *Angew. Chem. Int. Ed.* **2009**, *48*, 6503-6506.
[98] He, L.; Liu, W.-J.; Ren, L.; Lei, T.; Gong, L.-Z. *Adv. Synth. Catal.* **2010**, *352*, 1123-1127.
[99] Aggarwal, V. K.; Thompson, A.; Jones, R. V. H.; Standen, M. C. H. *J. Org. Chem.* **1996**, *61*, 8368-8369.
[100] Hashimoto, T.; Uchiyama, N.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 14380-14381.
[101] Zeng, X.; Zeng, X.; Xu, Z.; Lu, M.; Zhong, G. *Org. Lett.* **2009**, *11*, 3036-3039.
[102] Mukherjee, M.; Gupta, A. K.; Lu, Z.; Zhang, Y.; Wulff, W. D. *J. Org. Chem.* **2010**, *75*, 5643-5660..
[103] Desai, A. A.; Wulff, W. D. *J. Am. Chem. Soc.* **2010**, *132*, 13100-13103.
[104] Vetticatt, M. J.; Desai, A. A.; Wulff, W. D. *J. Am. Chem. Soc.* **2010**, *132*, 13104-13107.

Scheme 47. *trans*-Selective Aza-Darzens Reaction with Diazoacetamides



In 2010, Wulff and coworkers reported the generation of *cis*-aziridines from *N*-alkyl-protected benzaldimines with *N*-dialkyl diazoacetamides (Table 2).[102] They reported that *N*-DPM imines are productive, albeit in lower yield than the *N*-MEDAM-imines (Table 2, entry 3). Since our synthesis used DPM-imines, the aza-Darzens reaction should favor the *cis*-aziridine. The diazoacetamide of choice would be *N*-monosubstituted, preferably with a DPM or similar group.

Table 2. *cis*-Aziridination with Various Imines

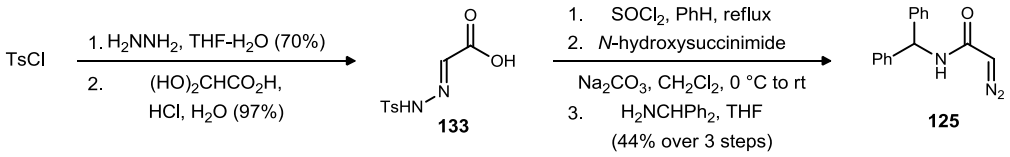
entry	R	yield
1[a]		18
2		66
3[b]		77

[a] 200 mol% $B(OPh)_3$ [b] 20 mol% cat., 80 mol% $B(OPh)_3$

The preparation of diazoacetamide **125** commenced with the synthesis of tosyl hydrazide from tosyl chloride, followed by condensation with glyoxylic acid to provide tosylhydrazone **133**. The carboxylic acid is then converted to the acid chloride and coupled with *N*-hydroxysuccinimide to give succinimidyl diazoacetate (**134**).[105,106,107] Treatment of **134** with diphenylmethyl amine affords the requisite diazoacetamide in 44% yield over three steps.[108] Attempts to directly couple tosylhydrazone **133** to *N*-hydroxysuccinimide with dicyclohexylcarbodiimide were unsuccessful,[109] as were attempts to couple **133** with diphenylmethyl amine.

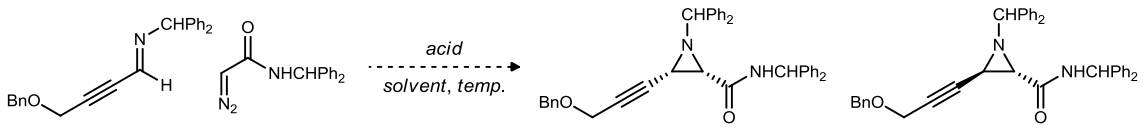
[105] Friedman, L. L., R. L.; Reichle, W. R. *Org. Synth.* **1973**, *Coll. Vol. 5*, 1055.
[106] Blankley, C. J. S., F. J.; House, H. O. *Org. Synth.* **1973**, *Coll. Vol. 5*, 258.
[107] Doyle, M. P.; Kalinin, A. V. *J. Org. Chem.* **1996**, *61*, 2179-2184.
[108] Saghatelian, A.; Buriak, J.; Lin, V. S. Y.; Reza Ghadiri, M. *Tetrahedron* **2001**, *57*, 5131-5136.
[109] Ouihia, A.; Rene, L.; Guilhem, J.; Pascard, C.; Badet, B. *J. Org. Chem.* **1993**, *58*, 1641-1642.

Scheme 48. Synthesis of Diazoacetamide **125**



Treatment of imine **124** with diazoacetamide **125** under standard Brønsted acid-catalyzed aza-Darzens reaction conditions gave no reaction despite using a stoichiometric amount of triflic acid. This was presumably due to the insolubility of the diazoacetamide in propionitrile. The diazoacetamide was soluble in THF and dichloromethane, but these reactions also returned starting material at −78 °C. At higher temperatures, the conversion was slightly improved but ^{1}H NMR analysis of the reaction mixture did not show *cis*-aziridine **135**. Using dichloromethane at −20 °C gave a side product that was possibly the *trans*-aziridine **136** (entry 6). A screen of Lewis acids revealed BF_3•OEt_2 to be the most effective in achieving conversion of starting material, and when repeated on a slightly larger scale, provided enough material for purification and characterization. Upon isolation, the predominant product was found to be the *trans*-aziridine (**136**, 8% yield).

Table 3. Optimization of aza-Darzens Reaction with Diazoacetamide **125**



124 **125** **135** **136**

entry	acid	solvent	temp.	result
1	TfOH	EtCN	-78 °C[b]	no rxn
2	TfOH	CH_2Cl_2	-78 °C	unreacted **125**
3	TfOH	THF	0 °C to rt	decomposition
4	TfOH	CH_2Cl_2	0 °C to rt	**136**[c]
5	TfOH	THF	-20 °C	trace **136**[c]
6	TfOH	CH_2Cl_2	-20 °C	13% **136**
7[d]	BF_3•OEt_2	CH_2Cl_2	-78 to -20 °C	8% **136**
8	$SnCl_4$	CH_2Cl_2	-78 to -20 °C	trace **136**[c]
9	$TiCl_4$[e]	CH_2Cl_2	-78 °C	decomposition
10	Et_2AlCl	CH_2Cl_2	-78 to -20 °C	trace **136**[c]

[a] 2 equiv. **125**, 120 mol% TfOH; 100 mol% acid for entries 7-10. [b] 1 eq. diazoacetamide **125** used. [c] *trans*-aziridine not isolated due to low conversion and/or reaction scale.

Looking back at the literature, soon after Wulff's initial report on *cis*-aziridination with *N*-alkyl-protected benzaldimines with *N*-dialkyl diazoacetamides, they reported the formation of *trans*-aziridines from *N*-alkyl-protected aryl and aliphatic imines with *N*-mono-alkyl- or *N*-mono-aryl-substituted diazoacetamides. Further studies using ONIOM calculations led to the hypothesis that the key interaction responsible for the switch in diastereoselection of the aza-Darzens reaction with diazoacetamides originated from a hydrogen bonding interaction between the amidic hydrogen and an oxygen atom in the chiral counterion (in this case, VANOL-polyborate).[103,104] The possibility of hydrogen bonding explains why our aza-Darzens reaction with a monosubstituted diazoacetamide favored the *trans*-aziridine.

Since diazoacetates favor *cis*-aziridines, the aza-Darzens reaction was attempted using succinimidyl diazoacetate, which is the activated ester precursor to diazoacetamide **125**. If this reaction produced the *cis*-aziridine, amide **126** could be easily obtained by

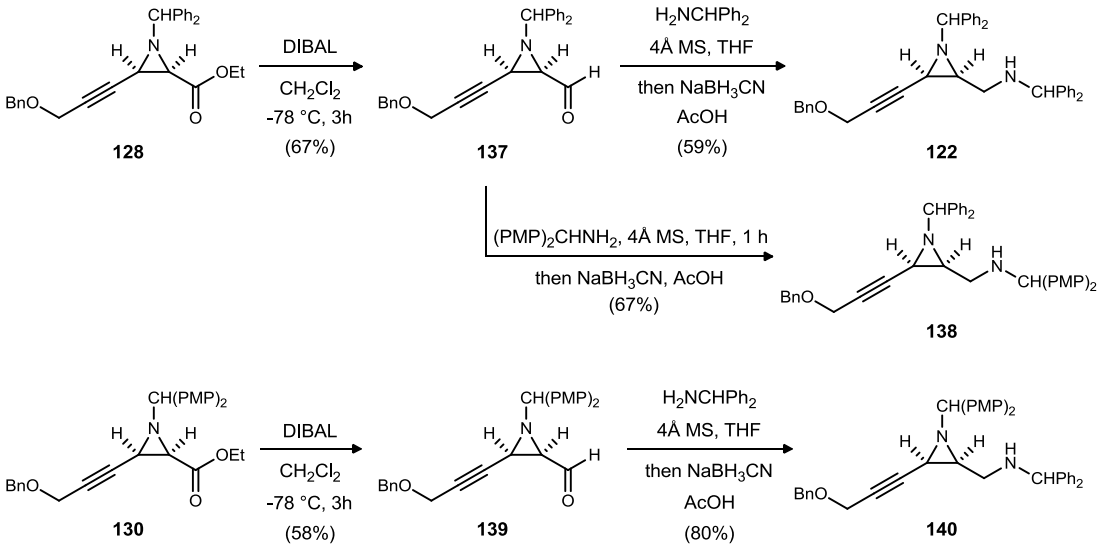
coupling the activated ester with diphenylmethyl amine. The reaction was performed in acetonitrile from −78 °C to 20 °C but yielded a complex mixture with no promising aziridine peaks.

Since MMC requires the *cis*-aziridine, and using the diazoacetamide in the aza-Darzens formed the *trans*-aziridine, this modification was no longer feasible. However, the aza-Darzens reaction with ethyl diazoacetate had successfully produced *cis*-aziridines **128** and **130**. Using the previously established route (Scheme 45), the ethyl ester of the aziridine (**128**) was subjected to saponification conditions (NaOH, EtOH/H_2O), which unfortunately resulted in aziridine ring opening. Trimethyltin hydroxide[110] and lithium hydroperoxide[111] gave the same result. Milder conditions such as potassium silanolate gave no reaction.[112] Direct ester to amide conversion using potassium *tert*-butoxide and diphenylmethyl amine was also unsuccessful.[113] This indicated the necessity to follow the second of the suggested modifications in Scheme 45.

To that end, aziridinyl ester **128** was treated with DIBAL and the resulting aldehyde was converted to amine **122** using reductive amination with diphenylmethyl amine followed by sodium cyanoborohydride with catalytic acetic acid (Scheme 49).[68114] Amines **138** and **140** were prepared in a similar fashion.

[110] Nicolaou, K. C.; Estrada, A. A.; Zak, M.; Lee, S. H.; Safina, B. S. *Angew. Chem. Int. Ed.* **2005**, *44*, 1378-1382.
[111] Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141-6144.
[112] Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *25*, 5831-5834.
[113] Zradni, F.-Z.; Hamelin, J.; Derdour, A. *Synth. Commun.* **2002**, *32*, 3525 - 3531.
[114] Modified from Assem, N.; Natarajan, A.; Yudin, A. K. *J. Am. Chem. Soc.* **2010**, *132*, 10986-10987. (cat. AcOH instead of $ZnCl_2$)

Scheme 49. Preparation of Differentially Protected Amines **122**, **138** and **140**



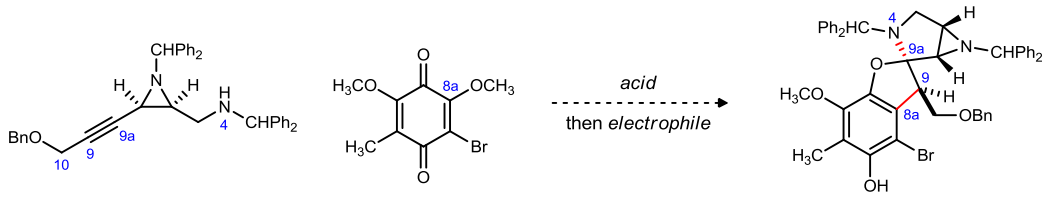
At this stage, the amine substrates for the aminomercuration-quinone coupling have been successfully synthesized with the desired C10-functionalization. The general route to the amine substrates has been shortened by using a DIBAL reduction and reductive amination to convert the aza-Darzens ester product to the requisite amines. Additionally, in an effort to further shorten the synthesis, a diazoacetamide was used in the aza-Darzens reaction instead of a diazoacetate; it is interesting to note that this fairly simple switch resulted in the formation of the undesired *trans*-aziridine as the major product.

2.8.2. Enamine-Quinone Coupling: Tandem Formation of N4-C9a, C9-C8a Bonds

The coupling of amine **122** and quinone **66** was examined (Table 4). Standard conditions using mercuric chloride and triethylamine in THF resulted in decomposition of the amine while the quinone remained unreacted. The key difference between amines **68** and **115** – which had successfully undergone aminomercuration and coupling – and

amine **122** lies in the greater steric bulk of the benzyloxymethylene substituent on the alkyne. It stands to reason that this inhibited either the initial aminomercuration step or the subsequent quinone addition.

Table 4. Enamine Formation and Coupling Attempts



entry	acid[a]	electrophile	result
1	$HgCl_2$	**66**	decomposition
2	$Hg(OTf)_2$	**66**	decomposition
3	HgI_2	**66**	decomposition
4	$Pd(acac)_2$	**66**	decomposition
5	$Zn(OAc)_2$	**66**	no rxn
6	$HgCl_2$[b]	**66**	decomposition
7	$HgCl_2$	CH_3COCl	decomposition
8	$HgCl_2$	NBS	decomposition

[a] Stoichiometric amount of Lewis acid used in all cases; bases and additives added where required [b] $NaBH_4$ added after quinone.

If the problem lay in the first step i.e. aminomercuration, the reaction should ideally yield unreacted amine, though it is possible that the amine decomposed upon exposure to mercuric chloride, prior to cyclization. In order to facilitate aminomercuration, the more reactive mercuric triflate was used.[115] However, in this case, the amine was unreactive at room temperature up to 45 °C. When the reaction was heated to 70 °C, TLC showed some consumption of the amine at which point the quinone was added. On continuing the reaction at 45 °C, the amine was completely consumed but the quinone remained untouched. Purification of the reaction mixture led to isolation of some

[115] $Hg(OTf)_2$ preparation: Nishizawa, M.; Morikuni, E.; Asoh, K.; Kan, Y.; Uenoyama, K.; Imagawa, H. *Synlett* **1995**, *1995*, 169,170.

benzyl alcohol; this indicates that while the amine is reacting, perhaps even cyclizing, $Hg(OTf)_2$ is promoting the elimination of the benzyloxy group. Similar results were observed with mercury(II) iodide catalyzed aminomercuration and palladium(II)-catalyzed aminopalladation; no reaction was observed with zinc acetate.[116,117] Control reactions for $Hg(OTf)_2$ and $Pd(acac)_2$ were run with the terminal alkyne (**68**) and produced expected *N*,*O*-ketal **88** without noticeable decomposition of the starting amine. Amine **122** was also treated with 10 mol% triflic acid to see if any cyclization occurred, however, only the triflic acid salt of the amine and unreacted amine were observed.

Due to the complex mixtures obtained during the reaction, the decomposition product of the amine could not be determined. This left the actual pathway of decomposition unknown: as mentioned previously, decomposition could occur prior to hydroamination-cyclization. It is also possible that the cyclization was occurring, but the subsequent quinone addition was slow or nonexistent – perhaps due to the sterics at the nucleophilic enamine position – which could result in decomposition of the highly reactive pyrrolidine enamine. In order to test this hypothesis, the reaction was quenched with acetyl chloride, which has a more accessible electrophilic site than the quinone. Acetyl chloride has been previously incorporated into the pyrrolidine enamine formed from the terminal alkyne **68**;[65] however, with amine **122**, complex mixtures were obtained. *N*-Bromosuccinimide was also used to quench the intermediate, but led to the same results as with acetyl chloride. This implied that the quinone was not the sole problem. It was also possible that while most of the quinone did not react, some coupled product could form but might be prone to decomposition. Previous work had shown that

[116] Prior, A. M.; Robinson, R. S. *Tetrahedron Lett.* **2008**, *49*, 411-414.
[117] Lei, A.; Lu, X. *Org. Lett.* **2000**, *2*, 2699-2702.

coupled quinone product **123** had been unstable and decomposed within a few hours; the coupled hydroquinone products however were more stable.[69] In the formation of spiroketal **116**, the hydride source for the reduction of the quinone to the hydroquinone was unknown. To this end, the reaction was performed with mercuric chloride and quinone **66** followed by addition of sodium borohydride to aid in the reduction to the hydroquinone, but the results were no different from the standard coupling reaction.

All these experiments led to the following conclusions: a) while the sterics at the alkyne position could inhibit either the cyclization or the subsequent quinone addition, the results did not conclusively determine the problematic step of this addition; however, since the amine did react, it seems likely that the intermediate enamine is forming, but decomposes before addition to the quinone; and b) using other more reactive and less hindered electrophiles did not encourage enamine addition, implying that the steric bulk at the nucleophilic position of the enamine could be inhibiting the addition. The logical solutions are to a) attempt to create a more stable enamine intermediate so that heat and/or acid conditions could be used to force the Michael addition, and b) to use a different substituent on the alkyne. Since MMC requires an alcohol oxidation state at the alkyne carbon, and the enamine requires an electron-neutral or electron-donating group for a successful addition, and as we have now learned, it requires a small group as well, this limits the choices, including a methyl-protected alcohol where the deprotection conditions would be incompatible with sensitive functionalities like the aziridine. As a result, the next step is to attempt to create a more stable enamine intermediate.

2.8.3. Cyclization of the Alkynyl Amine: A Brief Look at Haloamination Literature

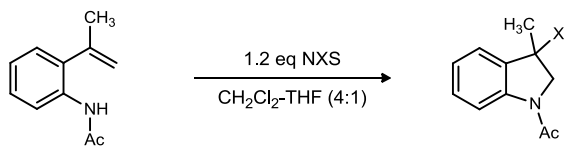
The ideal enamine intermediate envisioned was a haloenamine. With a haloenamine, it would be possible to perform the Michael addition and then dehalogenate to reform the enamine, or perform a metal-catalyzed coupling. Haloenamine formation had been briefly investigated previously, though unsuccessfully, when the aminomercuration reaction was quenched with NBS (Table 4). Here, it is investigated in more detail.

Previous literature reports have utilized halonium reagents in inter- and intramolecular haloamination reactions, though mostly with alkenes. *N*-Halosuccinimides are commonly used, either alone or in conjunction with metal catalysts (Scheme 50). Nishida reported the intramolecular haloamination reaction of *N*-halosuccinimide reagents with *o*-aminostyrene derivatives to form the corresponding 2,3-dihydroindoles.[118] For the more recalcitrant NCS, they used catalytic ytterbium triflate and trimethylsilyl chloride to promote the reaction, though still in low yield. Additionally, Sudalai reported bromoamination using *N*-bromosuccinimide and tosyl amine with styrene derivatives.[119] Notably, they were able to obtain both regioisomers selectively in high yields by changing their catalyst. More recently, Yeung reported a guanidine synthesis using a one-pot amine addition to dimethylcyanimide followed by bromoamination of the olefin.[120]

[118]Arisawa, M.; Ando, Y.; Yamanaka, M.; Nakagawa, M.; Nishida, A. *Synlett* **2002**, 1514-1516.
[119] Thakur, V. V.; Talluri, S. K.; Sudalai, A. *Org. Lett.* **2003**, *5*, 861-864.
[120] Zhou, L.; Chen, J.; Zhou, J.; Yeung, Y.-Y. *Org. Lett.* **2011**, *13*, 5804-5807.

Scheme 50. *N*-Halosuccinimide Promoted Haloaminations

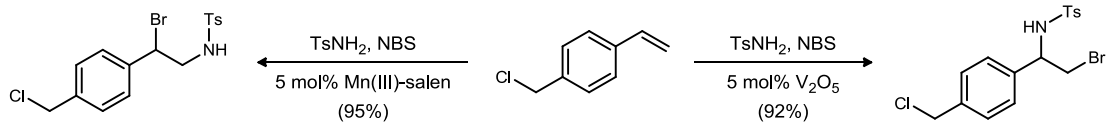
Nishida (2002):



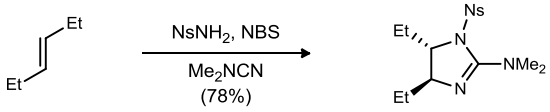
X	NXS (yield, %)	NXS[a] (yield, %)
I	89	45
Br	91	74
Cl	0	15

[a]additives: 5 mol% $Yb(OTf)_3$, 5 mol% TMSCl

Sudalai (2003):



Yeung (2011):

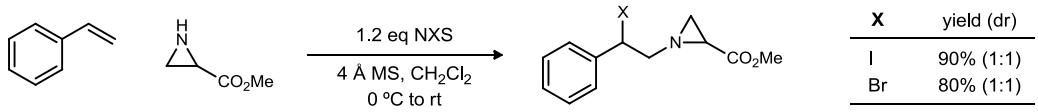


Yudin also utilized *N*-bromosuccinimide in a haloamination reaction of styrene derivatives with an aziridine (Scheme 51).[121] He proposed that the reaction proceeded via a nitrogen-centered aziridinyl radical. As outlined below, halogenation of the aziridine is followed by homolysis of the N-X bond. Addition to the alkene, followed by recombination of both the vinyl and halogen radicals provides the haloamination product.

[121]Yang, X.; Yudin, A. K. *Synlett* **2007**, 2912-2918.

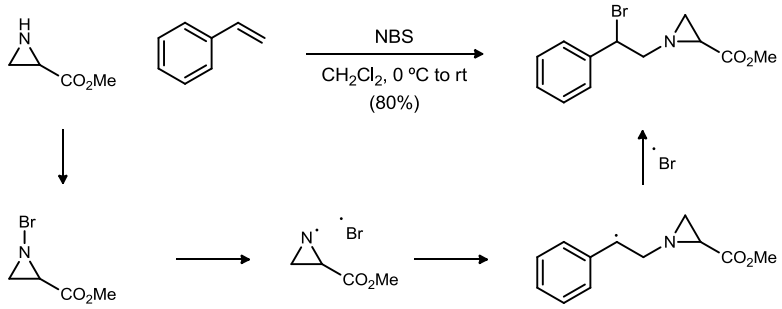
Scheme 51. Yudin's Haloamination Using a Nitrogen-Centered Aziridinyl Radical

Yudin (2007):



X	yield (dr)
I	90% (1:1)
Br	80% (1:1)

Yudin's proposed mechanism:

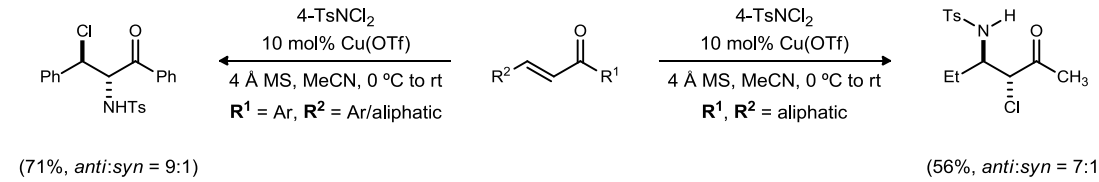


An alternative to *N*-halosuccinimides is *N*,*N*-dichloro-*p*-toluenesulfonamide ($TsNCl_2$) (Scheme 52). Li used $TsNCl_2$ as the nitrogen and halogen source in the haloamination of enones in the presence of catalytic CuOTf.[122] In this case, the regioselectivity of addition was found to be dependent on the ketone substituent. More recently, Feng reported an asymmetric chloroamination using $TsNCl_2$ in a scandium triflate catalyzed reaction with tosyl amine and enones; bromoamination and iodoamination under similar conditions were performed using NBS and NIS respectively.[123,124,125]

[122] Chen, D.; Timmons, C.; Chao, S.; Li, G. *Eur. J. Org. Chem.* **2004**, *2004*, 3097-3101.
[123] Cai, Y.; Liu, X.; Jiang, J.; Chen, W.; Lin, L.; Feng, X. *J. Am. Chem. Soc.* **2011**, *133*, 5636-5639.
[124] Cai, Y.; Liu, X.; Hui, Y.; Jiang, J.; Wang, W.; Chen, W.; Lin, L.; Feng, X. *Angew. Chem. Int. Ed.* **2010**, *49*, 6160-6164.
[125] Cai, Y.; Liu, X.; Li, J.; Chen, W.; Wang, W.; Lin, L.; Feng, X. *Chem.—Eur. J.* **2011**, *17*, 14916-14921.

Scheme 52. $TsNCl_2$ Promoted Haloaminations

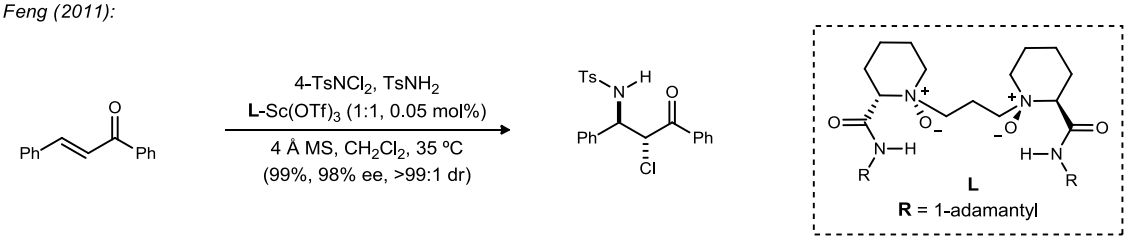
Li (2004):



(71%, *anti*:*syn* = 9:1)

(56%, *anti*:*syn* = 7:1)

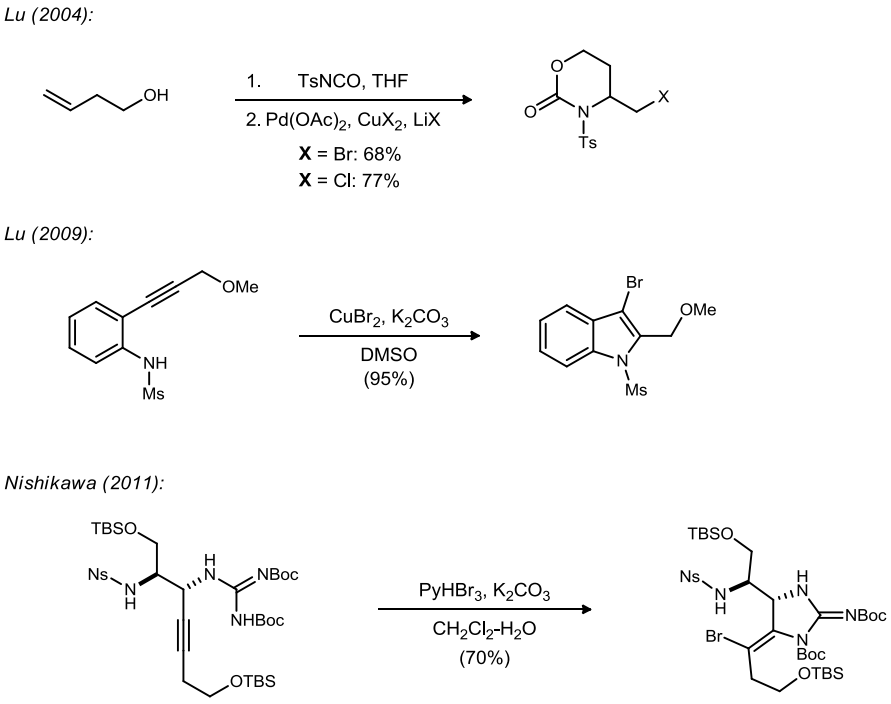
Feng (2011):



A few other selected examples of haloaminations are shown in Scheme 53. Lu reported a two-step protocol involving protection of an alcohol as its carbamate, which then underwent an intramolecular haloamination in the presence of palladium acetate, copper(II) halide and lithium halide.[126] In 2009, Lu used a similar procedure with alkynyl anilines in the presence of copper(II) bromide to form indoles. [127] Nishikawa reported that propargyl and homopropargyl guanidines, when treated with pyridinium tribromide in the presence of potassium carbonate, yielded five- and six-membered cyclic guanidines.[128] This methodology was then utilized towards his synthesis of the saxitoxin skeleton.[129]

[126] Lei, A.; Lu, X.; Liu, G. *Tetrahedron Lett.* **2004**, *45*, 1785-1788.
[127] Shen, Z.; Lu, X. *Adv. Synth. Catal.* **2009**, *351*, 3107-3112.
[128] Sawayama, Y.; Nishikawa, T. *Synlett* **2011**, 651-654.
[129] Sawayama, Y.; Nishikawa, T. *Angew. Chem. Int. Ed.* **2011**, *50*, 7176-7178.

Scheme 53. Miscellaneous Haloamination Procedures

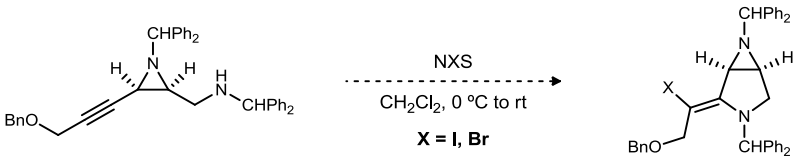


2.8.4. Cyclization of the Alkynyl Amine: Formation of the N4-C9a Bond

Treatment of amine **122** with *N*-iodosuccinimide in dichloromethane yielded a less polar spot by TLC (Scheme 54). No further conversion was obtained and the reaction was purified by column chromatography on silica gel. ^{1}H NMR analysis of the crude reaction mixture exhibited a mixture of two compounds and succinimide. However, no major product was observed following column chromatography. It is possible that the less polar spot observed was the *N*-iodoamine, which would be unstable to silica gel chromatography. In a separate experiment, the amine was treated with NBS. TLC monitoring showed immediate conversion to a less polar spot followed by rapid conversion to a more polar spot (within a few minutes at 0 °C). ^{1}H NMR analysis of the crude and purified reaction, however, showed no desired product or starting material.

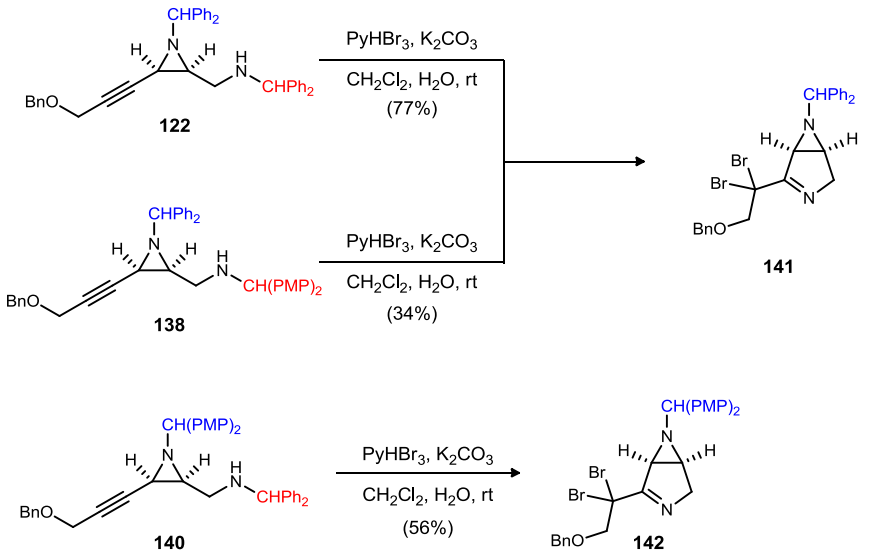
When amine **122** was treated with NCS and potassium carbonate to assist in deprotonation of the amine, there was no reaction.

Scheme 54. Attempted Haloamination with *N*-Halosuccinimides



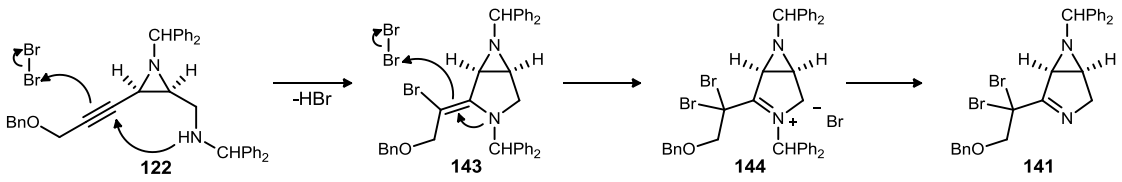
Treatment of amines **122** and **138** with pyridinium tribromide and potassium carbonate in dichloromethane-water overnight led to the formation of imine **141**. With amine **122**, deprotection of the diphenylmethyl group of the amine nitrogen was observed by the disappearance of the methine and aromatic protons by ^{1}H NMR. The deprotection of the amine, and not the aziridine, was confirmed by subjecting amine **140** to the reaction conditions. Deprotection of the diphenylmethyl group was observed but the bis(PMP) group was still in place. Amine **138** also showed deprotection of the amine bis(PMP) group but not the aziridine DPM group. The structure of imine **141** was assigned using ^{1}H NMR, ^{13}C NMR, DEPT and COSY experiments. ^{13}C NMR and DEPT of **141** revealed the presence of a quaternary carbon at 60 ppm (C-Br_2) and 172 ppm (C=N), consistent with the absence of the expected enamine. ^{1}H NMR and COSY showed no change in the coupling of the starting material, except for a W-coupling between one pyrrolidine proton and the aziridine proton. HRMS and IR provided confirmation of the assigned structure.

Scheme 55. Haloamination with Pyridinium Tribromide



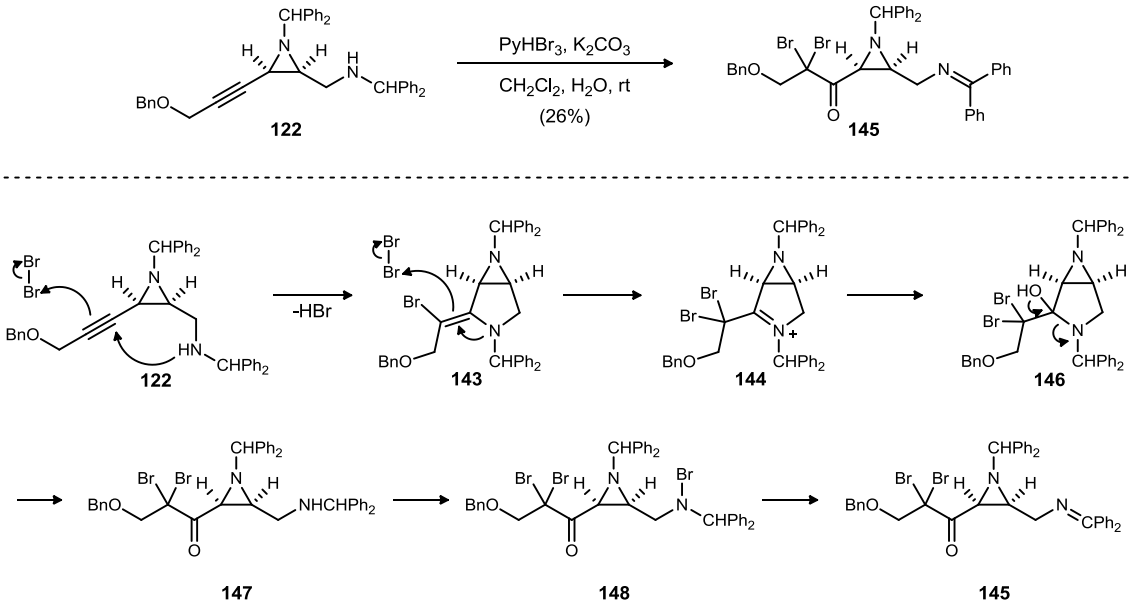
The mechanism of formation of imine **141** can occur via a radical pathway, similar to Yudin's proposed haloamination mechanism (Scheme 51), or via an ionic pathway (Scheme 56). Pyridinium tribromide exists in equilibrium with pyridinium hydrobromide and bromine. Addition of a bromonium ion to the alkyne followed by nucleophilic attack of the amine gives pyrrolidine enamine **143**. Enamine addition to a second equivalent of bromonium ion gives iminium **144**. Subsequent deprotection of the pyrrolidine nitrogen would lead to imine **141**.

Scheme 56. Proposed Mechanism of Formation of Dibromoimine **141**



Additionally, the reaction also produced ketone **145** (Scheme 57). This was evident from the ^{13}C NMR which showed a peak at 191.8 ppm. The remaining spectroscopic data was also consistent with the ketone structure. The ketone could result from hydrolytic opening of a common intermediate (**140**) in the pathway to the imine (**141**). Following opening to the ketone, oxidation of the diphenylmethyl group can occur by halogenation of the amine followed by elimination of HBr. The imine functionality of ketone **145** slowly hydrolyzed on standing in deuterated chloroform for 35 days to form benzophenone and the dibromoimine **141** (24% recovery).

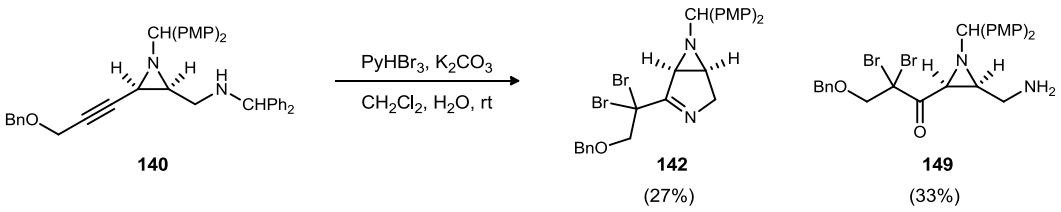
Scheme 57. Proposed Mechanism of Formation of the Ketone co-Product from Haloamination



Repeated experiments suggested that 2 equivalents of pyridinium tribromide produced the ketone in low yield while 4 equivalents produced the imine as the major product. With bis(PMP)-amine **140**, the corresponding dibromoimine **142** was produced in 27% yield and the corresponding deprotected ketone in 33% yield (Scheme 58).

Repeated experiments revealed an inconsistency in product yields; as a result, amine **122** was used in later experiments.

Scheme 58. Treatment of Amine **140** with Pyridinium Tribromide



In order to investigate the reactivity of the imine, hydrolysis of imine **141** to the corresponding ketone was attempted using 0.1M HCl in ether; this led to decomposition of starting material. Using silica gel in ethyl acetate-water returned only starting material. Additionally, stability of both the imine and the ketone to reaction conditions ($PyHBr_3$, CH_2Cl_2-H_2O) was assessed, imine **141** decomposed after a few hours, while ketone **145** remained mostly intact.

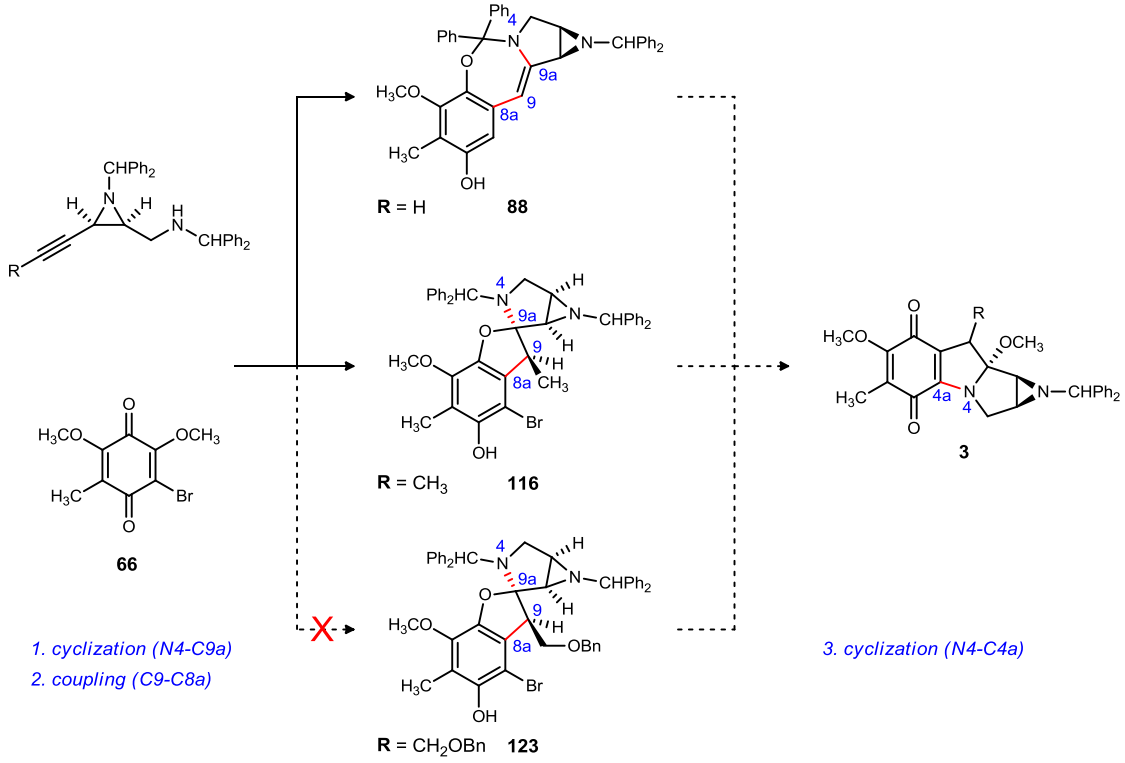
While both the imine and ketone could be investigated in additions to the quinone, the higher yielding imine was chosen for further experimentation.

2.8.5. Dibromoimine-Quinone Coupling: Formation of the N4-C4a Bond

The cyclization of the alkynyl amine set the stage for the Michael addition into the quinone. It was now important to assess the imine substrate for its ability as a Michael donor as it differed significantly from our previous enamine intermediates. Scheme 59 outlines the overall strategy for the formation of the key bonds between the quinone and the amines. Thus far, the first step has always been cyclization of the alkynyl amine to form the pyrrolidine enamine (N4-C9a bond). When using the unsubstituted alkyne **68**

and the methyl-substituted alkyne **115**, the following Michael addition to the quinone occurred in one pot to form ketals **88** and **116** respectively. These Michael additions occurred through the enamine, thereby forming the C9-C8a bond. Our final goal was to use the pyrrolidine amine nitrogen to add into the quinone at C4a. Quinone **66** was used because the regioselectivity of addition to the quinone had to occur first at C8a, then at C4a (Scheme 22).

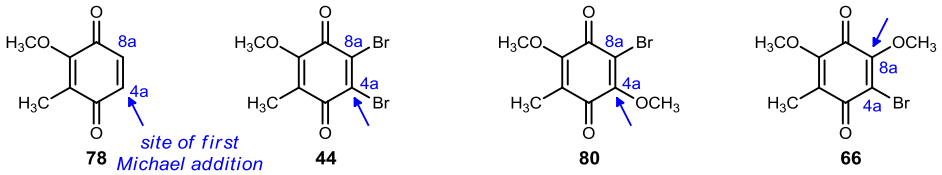
Scheme 59. Initial Strategy Towards Amine and Quinone Coupling



When using the benzyloxymethylene alkyne, we noticed that the one pot cyclization-coupling did not occur, presumably due to greater steric bulk at enamine carbon C9 (Scheme 59). Therefore, the best possible way to force addition of carbon C9 to the quinone at C8a was to perform an intramolecular addition, by first adding nitrogen

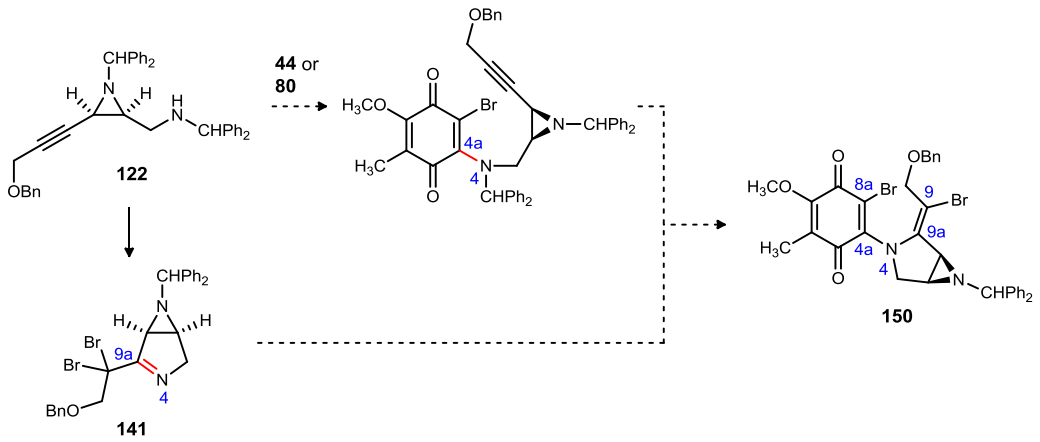
N4 to quinone carbon C4a. Revisiting quinone regioselectivity (Scheme 60, previously described in section 2.3), quinones **78**, **44** and **80** would all be viable candidates as the first addition would occur at C4a. In the case of quinones **44** and **80**, Michael addition would be followed by elimination. With quinone **78**, Michael addition would result in the formation of the hydroquinone, which required re-oxidation to the quinone before further manipulations.

Scheme 60. Quinone Regioselectivity of the First Michael Addition



Now that nitrogen N4 was chosen to perform the first Michael addition to the quinone, the following two options existed (Scheme 61): addition of amine **122** followed by cyclization, or addition of dibromoimine **141**. The end product of both pathways should only require intramolecular addition of enamine C9 to the quinone at C8a to give the MMC core.

Scheme 61. Possibilities with N4-C4a Addition

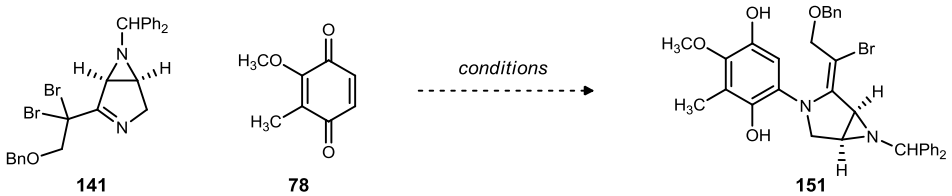


Our investigation began with dibromoimine **141**. We rationalized that since the imine center was fairly congested, unsubstituted quinone **78** would reduce steric crowding at least for one component of the reaction. Quinone **78** and dibromoimine **141** were unreactive in benzene, methanol and THF even at reflux. At reflux in methanol, decomposition of the dibromoimine was observed. The reluctance of any reaction except slow decomposition seemed to indicate that the nucleophilicity of the imine was significantly dampened when compared to our previous amine nucleophiles. The key factors influencing the nucleophilic attack are steric congestion (neopentyl and cyclic nitrogen nucleophile) and electronic effects (two adjacent bromines). The steric congestion could conceivably be eased by debromination prior to addition; the electronic factor can be rectified by increasing the electrophilicity of the quinone.

To increase the electrophilicity of the quinone, a Lewis acid screen was conducted. In most of these cases, imine decomposition was observed. Treatment with alkylating agents such as the Meerwein salt or trimethylsilyl triflate resulted in decomposition as well. Brønsted acids such as acetic acid resulted in no reaction. In some cases, partial reduction of the quinone to the phenol was observed. This could be

explained by a hydride transfer from the aziridine DPM group to the Lewis acid-activated quinone. However, this hypothesis was not experimentally confirmed because treatment of 1 equiv. quinone with 3 equiv. aziridine and 1 equiv. $SnCl_4$ resulted in decomposition of the aziridine and completely unreacted quinone (if the hydride transfer theory held, then the results would have been 2 equiv. unreacted aziridine and 1 equiv. phenol).

Table 5. Quinone Activation towards Dibromoimine Addition

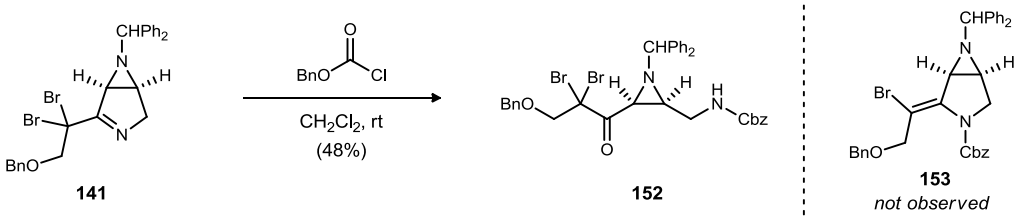


entry	reagents	solvent	results
Lewis acids:			
1	$Sc(OTf)_3$	MeOH	no rxn
2	$HgBr_2$	$CHCl_3$	no rxn
3	$FeCl_3$	THF	decomposition
4	$ZrCl_4$	tol	decomposition
5	$Hg(OTf)_2$	tol	decomposition
6	$Hg(OTf)_2$	MeCN	decomposition
7	$SnCl_4$	tol	decomposition
8	$TiCl_4$	tol	decomposition
Alkylating agents:			
9	TMSOTf	PhH	decomposition
10	Meerwein's salt	$CHCl_3$	decomposition
Protic acid:			
11	AcOH	MeOH	no rxn

Since the Michael addition seemed to be problematic, imine **141** was treated with electrophiles that were more reactive than the quinone. Michael acceptors such as dimethylethylidene malonate and *trans*-β-nitrostyrene were unreactive, even in refluxing solvent. In the latter case, addition of a mild base (PBAM•HOTf) to assist in imine debromination did not help. The potent Michael acceptor, methyl vinyl ketone, did not react with the imine in benzene at reflux; the addition of a Lewis acid (diethylaluminum

chloride) resulted in immediate decomposition. Moving on to highly reactive non-conjugated electrophiles like bromoacetyl bromide resulted in complex mixtures. Treatment with trimethyl aluminum in the hopes of a methyl transfer gave no reaction. The only electrophile that showed any reactivity without complete decomposition was benzyl chloroformate (Scheme 62). Initially, the goal had been to acylate the imine, followed by debromination to reform the enamine (**153**). To this end, the reaction was performed using base (triethylamine, benzyl amine) or zinc in different solvents. However, in each of these cases, the dominant product observed was ketone **152**. The reaction, when repeated without any additives, also proceeded in moderate yield to ketone **152**. This ketone was unsuccessfully treated with tin dichloride to do a Reformatsky-like reaction.[130] It was also treated with *n*-butyllithium and then quenched with water to see if lithium-halogen exchange was a feasible avenue; however, only decomposition was observed.[131]

Scheme 62. Imine Acylation with Benzyl Chloroformate

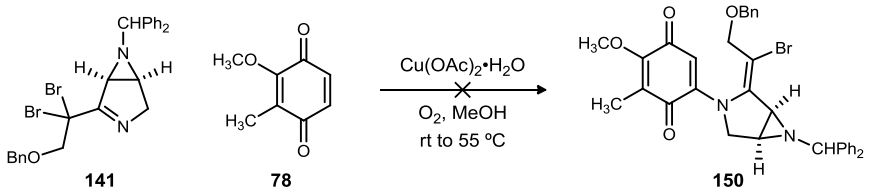


The addition was also attempted using Rapoport's conditions.[72] He had achieved addition of pyrrolidine to quinone **78** using cupric acetate monohydrate in the presence of

[130] Demir, A. S.; Tanyeli, C.; Mahasneh, A. S.; Aksoy, H. *Synthesis* **1994**, 155-157.
[131] Aoki, Y.; Oshima, K.; Utimoto, K. *Synlett* **1995**, 1071-1072.

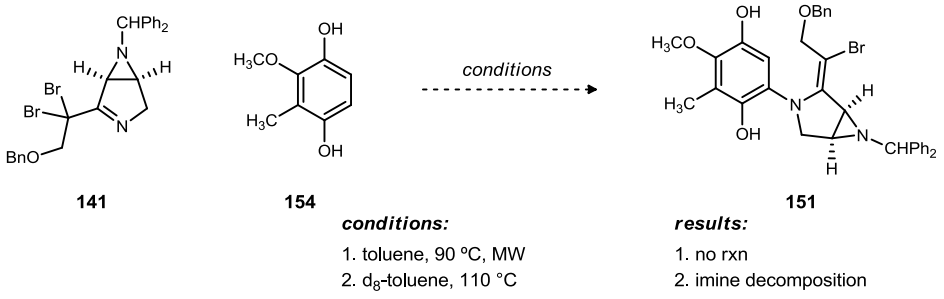
oxygen. In our case with dibromoimine **141**, there was no reaction at room temperature and the imine decomposed upon heating.

Scheme 63. Addition using Rapoport's Copper Acetate-Mediated Conditions



Final attempts to add the imine to the quinone used phenol **154** to effect a bromine transfer with the imine, which could then add in to give the desired product (Scheme 64). However, there was no reaction when the imine and phenol were heated at 90 °C. After reaching reflux, imine decomposition was observed. The dibromoimine was also treated with potassium methoxide in acetonitrile to force formation of the hemiaminal, thereby increasing the nucleophilicity of the nitrogen, but this resulted in decomposition as well.

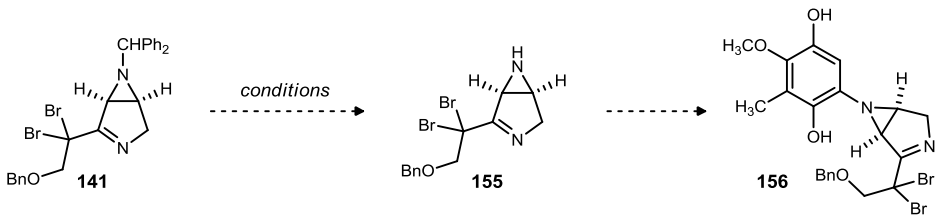
Scheme 64. Bromine Transfer Attempt Using Phenol **154**



Since the imine itself could not add into the quinone, a slightly different approach was considered using the aziridine nitrogen of the dibromoimine to add to quinone carbon C4a. This harks back to the mitomycin rearrangement to isomitomycin (Scheme 2). In Fukuyama's total synthesis of MMC, most of the chemistry was performed on the isomitomycin structure, and the mitomycin skeleton was unveiled at the very end of his synthesis using the isomitomycin-mitomycin rearrangement (Scheme 3). We experimented with aziridine deprotection to determine its feasibility. Due to the presence of the benzyl ether and the bromines, reductive methods were not considered viable. Previously, treatment with benzoyl chloroformate had resulted in acylation of the imine followed by hydrolysis to the ketone (Scheme 62); this eliminated the acylation followed by hydrolysis strategy to deprotect the aziridine. This left oxidative cleavage to deprotect the aziridine (Table 6). Ceric ammonium nitrate did not give any reaction. Trityl tetrafluoroborate did not give any reaction with one equivalent, however, the addition of the second equivalent resulted in decomposition.[132] This behavior was also observed with DDQ. Additionally, deprotection with TMSI-PPh_3 was performed on a similar DPM-protected aziridine (**68**) and resulted in decomposition of the aziridine.[133,134] The aziridine was also treated with trifluoroacetic acid, and triethylsilane and trifluoroacetic acid, and *N*-bromosuccinimide.[135,136] All of these conditions resulted in decomposition.

[132] Damico, R.; Broaddus, C. D. *J. Org. Chem.* **1966**, *31*, 1607-1612.
[133] Cha, K. H.; Kang, T. W.; Cho, D. O.; Lee, H.-W.; Shin, J.; Jin, K. Y.; Kim, K.-W.; Kim, J.-W.; Hong, C.-I. *Synth. Commun.* **1999**, *29*, 3533 - 3540.
[134] TMSI preparation *in situ*: Olah, G. A. N., S. C.; Gupta, B. G. B.; Malhotra, R. *Synthesis* **1979**, 61-62.
[135] Et_3SiH, TFA deprotection:Troyer, T. L. Dissertation, Department of Chemistry, Vanderbilt University, December 2008.
[136] NBS deprotection: Katoh, T.; Watanabe, T.; Nishitani, M.; Ozeki, M.; Kajimoto, T.; Node, M. *Tetrahedron Lett.* **2008**, *49*, 598-600.

Table 6. Deprotection Attempts on the Aziridine



entry	reagents	result
1	CAN	no rxn
2	DDQ then 0.1 N HCl[a]	no rxn then decompositon with 2 eq
3	Ph_3BF_4[a]	no rxn then decomposition with 2 eq
4	TFA	decomposition
5	Et_3SiH, TFA	decomposition
6	NBS then H_2NOMe•HCl	decomposition

[a]No reaction with 1 equiv. of reagent; decomposition on addition of second equiv.

In summary, the goal was to install a functionalized C10 onto the alkyne before cyclization and addition into the quinone. Installation of a functionalized C10 was achieved when the benzyloxyalkynyl amine **122** was successfully synthesized. Cyclization to forge the N4-C9a bond using standard aminomercuration conditions did not work; however, after investigating other metal-catalyzed and halonium-promoted cyclization, dibromoimine **141** was successfully prepared using pyridinium tribromide. Dibromoimine **141** – the key highly functionalized piece required to add into the quinone to form the N4-C4a bond – proved to be much too hindered to undergo a Michael addition. At this point, the next logical step is the addition of the amine nitrogen to the quinone first followed by cyclization (Scheme 61).

2.9. Coupling Prior to Cyclization: Formation of the N4-C4a Bond

This section outlines our attempts to couple nitrogen N4 of the aziridine partner to the quinone. The initial aziridine substrate was the benzyloxyalkynyl amine (**122**). The

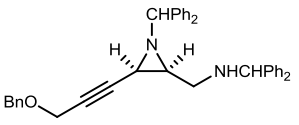
conclusion of these experiments (see section 2.9.1.) led us to prepare a modified aziridine with a free amine for the Michael addition.

2.9.1. Addition of the Benzyloxyalkynyl Amine to the Quinone

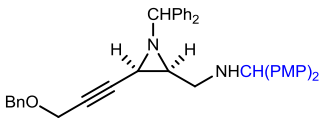
We attempted to perform the Michael addition with amine **122** and quinone **78** under our standard pyridinium tribromide cyclization conditions to see if any of the reactive intermediates in the dibromoimine formation would react with the quinone, but no coupling was detected (Table 7). Dibromoimine **141** was produced in 11% yield, and a trace amount of ketone **145** was observed while the quinone remained unchanged.

Amine **122** was treated with quinone **80** under basic conditions (triethylamine, potassium carbonate, DBU) at refluxing temperatures (THF, dichloromethane), but no reaction was observed (Table 7). Lewis acidic conditions ($Sc(OTf)_3$) also resulted in no reaction. Amine **138**, which should have a slightly more nucleophilic nitrogen because of the electron-donating bis(PMP) protecting group, was treated with sterically less hindered benzoquinone under basic conditions (pyridine, DBU) in benzene; this also resulted in no reaction. The Cbz-protected amine **152**, obtained by treating the dibromoimine with benzyl chloroformate, was also treated with unsubstituted quinone **78** in the presence of $Sc(OTf)_3$ at 0 °C, but this gave a complex reaction mixture.

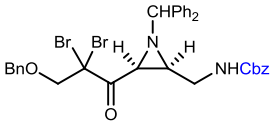
Table 7. Addition of Amine Nitrogen N4 to Quinone



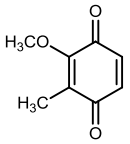
122



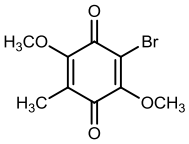
138



152



78



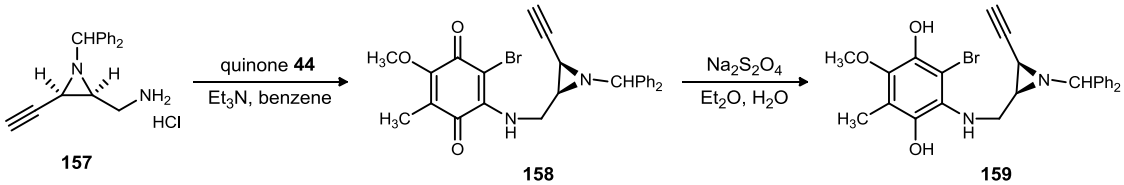
80

entry	amine	quinone	reagents	result
1	**122**	**78**	$PyHBr_3$, K_2CO_3, CH_2Cl_2	11% imine **141**
2	**122**	**80**	Et_3N, THF, reflux	no rxn
3	**122**	**80**	K_2CO_3, THF	no rxn
4	**122**	**80**	DBU, CH_2Cl_2, 60 °C, MW	no rxn
5	**122**	**78**	$Sc(OTf)_3$, benzene	no rxn
6	**138**	BQ	pyridine, benzene	no rxn
7	**138**	BQ	DBU, benzene	no rxn
8	**152**	**78**	$Sc(OTf)_3$, THF, 0 °C	decomposition

[a]BQ = benzoquinone

From these experiments, it is evident that the amine nitrogen is not sufficiently reactive when protected. We know from previous work that free amine **157** will add into the dibromoquinone (Scheme 65).[68] This indicates that the quinone substituents should not hinder the Michael addition, and the obvious course of action is to use a free amine.

Scheme 65. Addition of a Free Amine into the Dibromoquinone[68]

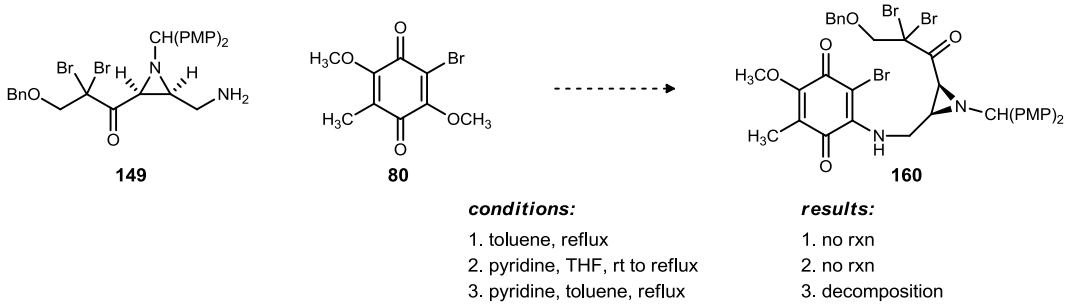


157 **158** **159**

The free amine **149**, obtained as a side product with pyridinium tribromide, was treated with quinone **80** in refluxing toluene (Scheme 66). Treating amine **149** and quinone **80** with pyridine in refluxing THF gave no reaction; however, taking the reaction

with pyridine in toluene to higher temperatures resulted in decomposition of the amine. It is not clear why this amine decomposed before the addition. It could be explained by the other reactive functionalities present. Intramolecular cyclization of the amine onto the ketone should form the dibromoimine, which has limited stability. While amine **149** did not cyclize to the dibromoimine when stirred in diethyl ether with 4Å molecular sieves, basic conditions under high temperatures could have resulted in cyclization. If this is the case, an alkynyl functionality similar to **122**, even if substituted, might not interfere with the addition to the quinone.

Scheme 66. Addition of Free Amine **149** into the Quinone

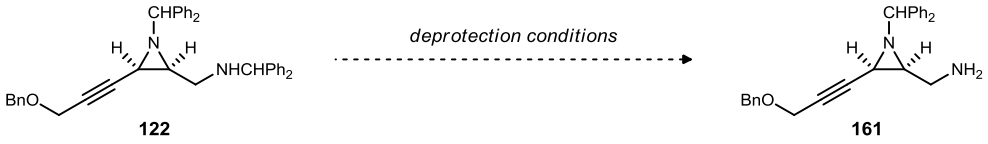


In order to obtain amine **161**, deprotection of the diphenylmethyl group was attempted (Table 8). Treatment of amine **122** with DDQ in dichloromethane and water gave only starting material. Heating the amine with DDQ in benzene with 4 Å molecular sieves formed the imine in 28% yield. Further treatment of the imine with 0.1 N aqueous HCl resulted in decomposition;[137] ^{1}H NMR analysis of the crude reaction mixture indicated aziridine ring opening. Hydrolysis under milder conditions (i.e. saturated aqueous NH_4Cl) gave the same result. Deprotection using trimethylsilyl iodide (generated

[137] Sampson, P. B.; Honek, J. F. *Org. Lett.* **1999**, *1*, 1395-1397.

in situ from sodium iodide and trimethylsilyl chloride) was attempted but also resulted in complete decomposition.[133,134] It is worthwhile to note that free amine **157** had been prepared by DPM deprotection using DDQ and 0.1 N aqueous HCl; in that case, a deprotection attempt using trifluoroacetic acid and triethylsilane resulted in decomposition.[68]

Table 8. Deprotection Conditions for Amine **122**



122 **161**

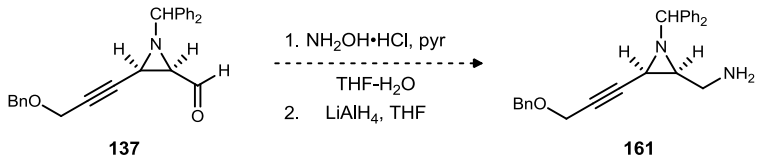
entry	conditions	results
1	DDQ, CH_2Cl_2-H_2O	no rxn
2	i. DDQ, 4Å MS, PhH, 65 °C[a] ii. 0.1 N HCl, Et_2O	decomposition
3	DDQ, 4Å MS, PhH, 65 °C then aq. NH_4Cl	decomposition
4	NaI, TMSCl, PPh_3[b]	decomposition

[a]28% Imine isolated after step i. [b]Performed on unsubstituted alkynyl amine **68**.

We also tried to prepare the free amine directly from the aldehyde (**137**) without having to resort to deprotection strategies. Aldehyde **137** was treated with hydroxylamine hydrochloride and pyridine to make the oxime, followed by reduction using lithium aluminum hydride.[138] The oxime was observed by ^{1}H NMR analysis of the reaction mixture after the first step; however, no product (**161**) or side products were discernible from ^{1}H NMR analysis of the reaction mixture after reduction.

[138] Thomas, P. J.; Axtell, A. T.; Klosin, J.; Peng, W.; Rand, C. L.; Clark, T. P.; Landis, C. R.; Abboud, K. A. *Org. Lett.* **2007**, *9*, 2665-2668.

Scheme 67. Attempt to Prepare Free Amine **161** from Aldehyde **137**

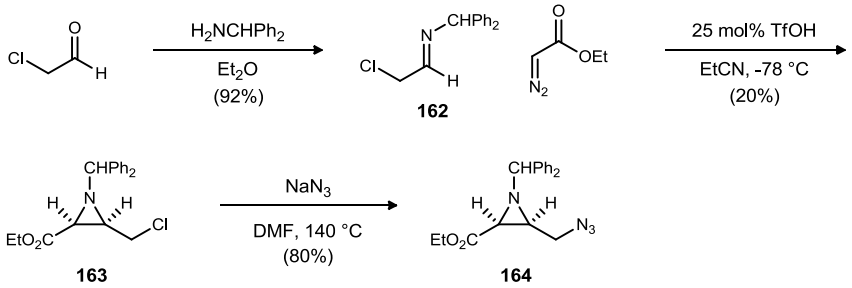


We considered alternate methods to prepare the free amine and thought that an azide would be a good precursor for a free amine. Azides are relatively easy to prepare, and an aziridinyl azide has been prepared before.[65,68] Additionally, azide reduction requires relatively mild conditions that would be compatible with the aziridine moiety.

2.9.2. Preparation of Free Amine 165

The preparation of the azide starts from commercially available chloroacetaldehyde (Scheme 68). Condensation with diphenylmethyl amine followed by the Brønsted acid catalyzed aza-Darzens reaction with ethyl diazoacetate furnished aziridine **163**. The chloride was then displaced with sodium azide to give the desired azide **164**.[65,68]

Scheme 68. Preparation of the Aziridinyl Azide

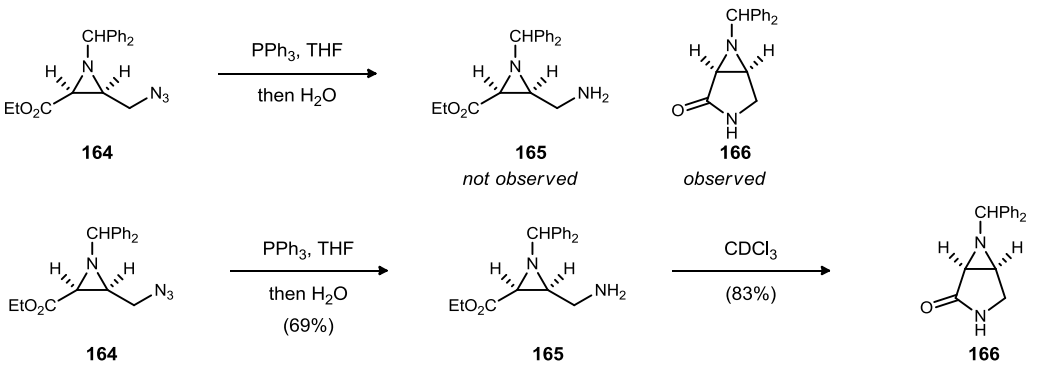


With the azide in hand, a quick experiment was run with the azide and the unsubstituted quinone (**78**) to see if a [3+2] cycloaddition would occur. The azide and the quinone were treated with triflic acid in acetonitrile at −20 °C and then quenched with water to hydrolyze any triazoline that formed, but only starting materials were observed. In a separate experiment, the azide and the quinone were heated in trifluorotoluene in the microwave at 80 °C. Slow consumption of the quinone was observed. The temperature was increased to 100 °C and ^{1}H NMR analysis of the reaction mixture showed that the azide remained unchanged but the quinone was reduced to the hydroquinone. This reduction was intriguing especially as there was no source of a reducing equivalent; had the aziridine diphenylmethine been the hydride source, decomposition of **164** should have been observed.

Staudinger reduction of the azide initially led to the formation of lactam **166**, formed from the cyclization of reduced **164** (Scheme 69).[139] Repeating the experiment with varying reaction times gave amine **165**. Upon standing, regardless of whether the amine is in solution or kept as a solid, lactam **166** starts to form. It is to be noted that the cyclization occurs faster in solution, and lactam **166** can be observed after 1 day in a 0.6:1 ratio with the amine.

[139] Vaultier, M.; Knouzi, N.; Carrié, R. *Tetrahedron Lett.* **1983**, *24*, 763-764.

Scheme 69. Staudinger Reduction of the Azide



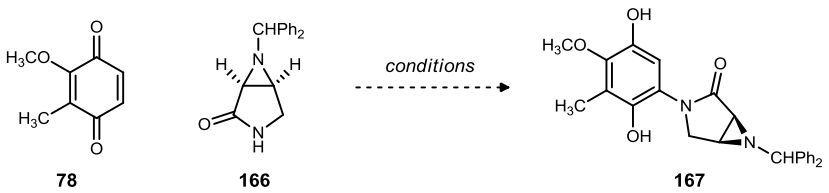
With amine **165** in hand, the coupling to the quinone can be attempted. Additionally, the inadvertent formation of lactam **166** provided an opportunity to test it in the coupling reaction as well.

2.9.3. Formation of the N4-C4a Bond

The two aziridine pieces used to test the coupling reaction were lactam **166** and amine **165**. Lactam addition to the quinone could be followed by installation of a two carbon unit on the quinone at C8a. If the two carbon unit contained a nucleophilic C9, then it could be used in an intramolecular addition to the lactam carbonyl, which would result in the formation of the C9-C9a bond as well as the hemiaminal required for MMC in one step.[50] In brief, the lactam **166** did not react under any of the reaction conditions (Table 9), including DBU, potassium carbonate and sodium hydride.[140] The cesium fluoride reaction conditions (entry 4) are known to promote addition of lactams to unsaturated esters but did not work in this case.[141]

[140] NaH deprotonation of amide: Perrin, C. L.; Lollo, C. P.; Hahn, C. S. *J. Org. Chem.* **1985**, *50*, 1405-1409.
[141] Han Ahn, K.; Jong Lee, S. *Tetrahedron Lett.* **1994**, *35*, 1875-1878.

Table 9. Lactam Addition to the Quinone

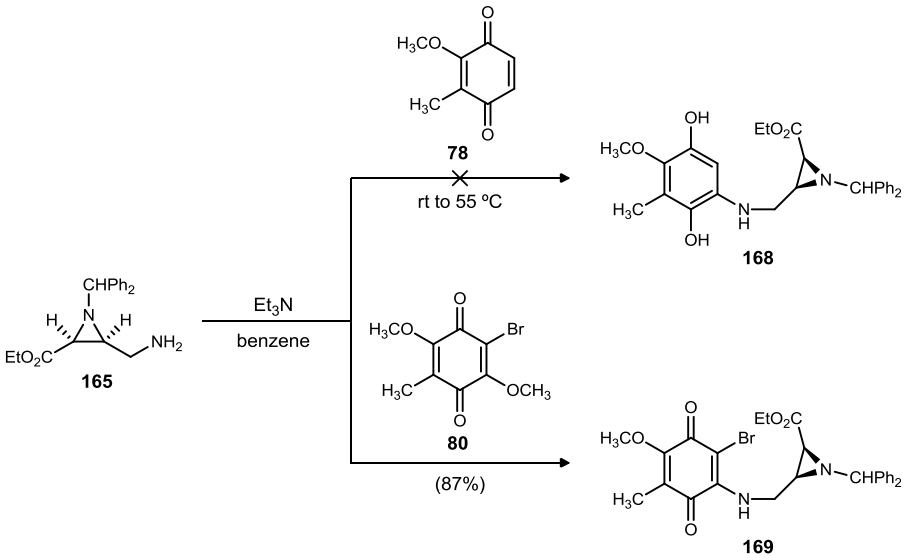


78 166 167

entry	reagents	results
1	DBU, 55-60 ºC	no rxn
2	K_2CO_3	no rxn
3	NaH then **78**	no rxn
4	CsF, $Si(OMe)_4$	no rxn

Meanwhile, we were also investigating the amine addition to the quinone (Scheme 70). Amine **165**, when treated with unsubstituted quinone **78** in triethylamine and benzene, merely cyclized to lactam **166** without quinone incorporation. When quinone **80** was used instead, amine **165** coupled readily to give the desired aminoquinone **169** in good yield.

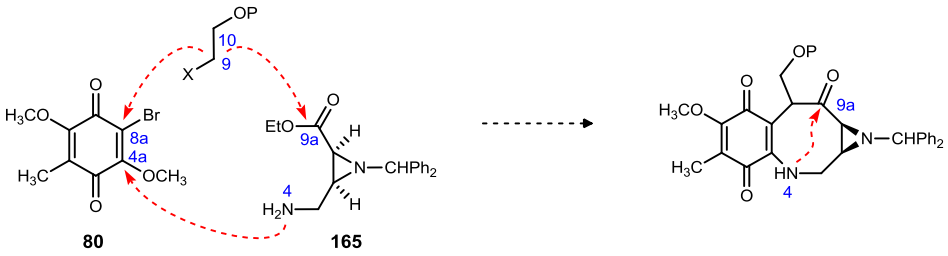
Scheme 70. Amine Addition to the Quinones



2.9.4. Functionalization of the Aminoquinone – Installing C9-10 Before Coupling

Now that the amine is successfully coupled to the quinone, the final carbons required for MMC (C9, C10) need to be installed. Before we proceeded, we addressed two key considerations: a) the site of initial addition of the C9-10 unit (should the addition occur on the quinone first (C9-C8a) or the aziridinyl ester first (C9a-C9)), and b) the timing of the C9-10 addition (should the addition be done prior to coupling or to the coupled product **169**). At the end of all these operations (formation of the C9-C8a, C9a-C9, N4-C4a bonds), we should be left with an eight-membered ring intermediate similar to that in Kishi's synthesis (Scheme 1), after which transannular cyclization of the amine (N4) to the ketone (C9a) will be the last step to construct the mitomycin core.

Scheme 71. Mapping the Bonds to be Formed

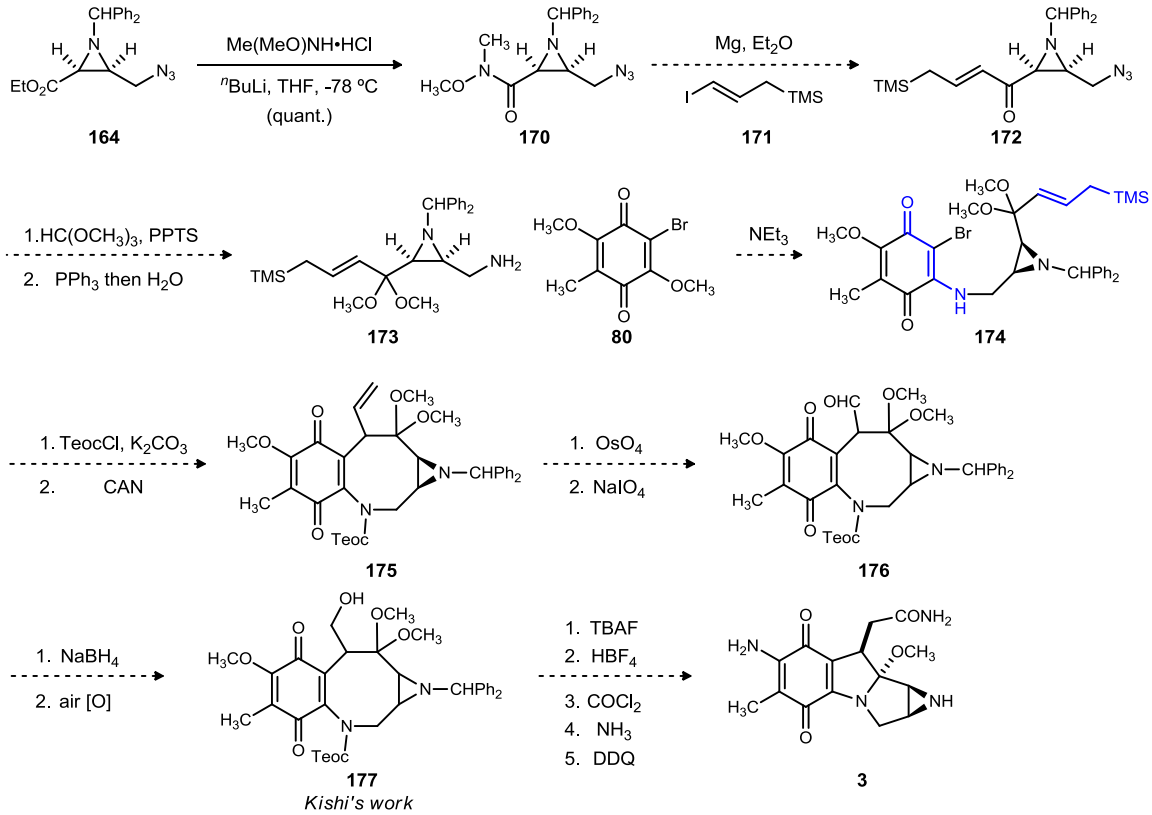


Scheme 71 outlines a map of the bonds that need to be formed between the three pieces. We have already established formation of N4-C4a, and in the section that follows, attempts to add the C9-10 unit to the aziridinyl ester (**165**) and to the quinone (**80**) prior to the coupling are discussed. Additionally, studies related to the addition of the C9-10 unit to the quinone moiety of the coupled aminoquinone **169** will be described.

I. Addition of the C9-10 unit to the Aziridinyl Ester Prior to the Coupling

Several functionalities were considered for the C9-10 unit. The key concern was the ability of the group to be transformed into the requisite carbamate of MMC using conditions compatible with the late stage intermediates. As shown in Scheme 72, the group chosen was an allyl silane, allowing us to close the eight-membered ring (transformation of **174** to **175**) with a CAN allylation between the allyl silane and the vinylogous amide (reacting partners shown in blue).[142] The allyl silane will be introduced using a Grignard addition of vinyl iodide **171** to Weinreb amide **170**.

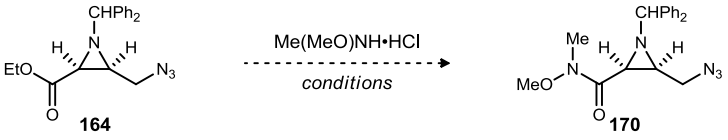
Scheme 72. Route to MMC with C9-10 Installation Prior to the Coupling



[142] Chandra, A.; Pigza, J. A.; Han, J.-S.; Mutnick, D.; Johnston, J. N. *J. Am. Chem. Soc.* **2009**, *131*, 3470-3471.

The preparation of the Weinreb amide was fairly straightforward (Table 10). The use of isopropyl magnesium chloride as the base resulted in the formation of only lactam **166**.[143] We hypothesize that the Grignard acted as a one electron reductant, ultimately converting the azide to the amine, which then cyclized under the strongly basic reaction conditions to the lactam. The more traditional method using trimethylaluminum gave no reaction, but using butyllithium resulted in clean and complete conversion of the ester to the desired Weinreb amide.[144,145]

Table 10. Preparation of the Weinreb Amide



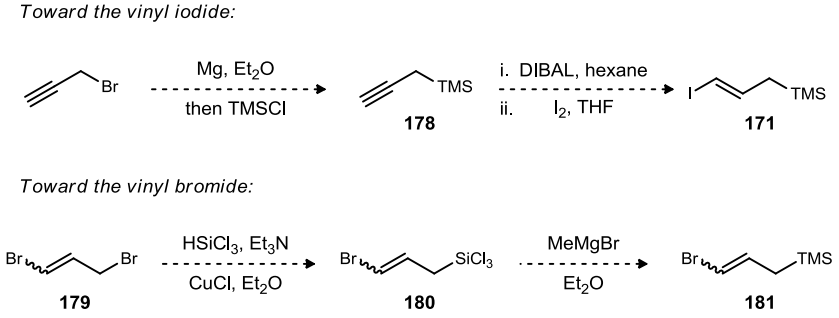
entry	reagents	conditions
1	^{i}PrMgCl, THF,-20 to -10 ºC	34% lactam **166**
2	Me_3Al, CH_2Cl_2,-10 ºC to rt	no rxn
3	^{n}BuLi, THF, -78 ºC	quant. **170**

Scheme 73 details the proposed syntheses of the allyl silanes (**171** and **181**). In order to make vinyl iodide **171**, the Grignard of propargyl bromide can attack trimethylsilyl chloride to yield the propargyl silane (**178**), which could then be reduced with DIBAL and quenched with iodine to provide vinyl iodide **171**.[146,147] The vinyl bromide (**181**) can be prepared starting from dibromopropene **179**. Substitution of the

[143] Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461-5464.
[144] Sha, C.-K.; Huang, S.-J.; Zhan, Z.-P. *J. Org. Chem.* **2002**, *67*, 831-836.
[145] Roche, C.; Labeeuw, O.; Haddad, M.; Ayad, T.; Genet, J.-P.; Ratovelomanana-Vidal, V.; Phansavath, P. *Eur. J. Org. Chem.* **2009**, 3977-3986.
[146] Beignet, J.; Jervis, P. J.; Cox, L. R. *J. Org. Chem.* **2008**, *73*, 5462-5475.
[147] Tietze, L. F.; Völkel, L.; Wulff, C.; Weigand, B.; Bittner, C.; McGrath, P.; Johnson, K.; Schäfer, M. *Chem.—Eur. J.* **2001**, *7*, 1304-1308.

bromide with a trichlorosilyl group, followed by conversion to a trimethylsilyl group would yield the desired vinyl bromide.[148,149,150] Both approaches failed in the first step despite varying the reaction conditions. In the case of the vinyl iodide, the propargyl silane was not formed despite varying the reaction conditions (Mg, MeMgBr, ^{n}BuLi). No propargyl bromide (or the allene with which it is in equilibrium) or product was seen by ^{1}H NMR in any of the crude reaction mixtures. ^{1}H NMR analysis of the reactions before and after the addition of TMSCl revealed a significant change in the peak shifts (possible decomposition on adding TMSCl), and comparison of the spectra between reactions showed no similarities. In the MeMgBr reaction, distillation from the reaction mixture did not give any distillate at the expected temperatures for the starting material or product. In the case of the vinyl bromide, the trichlorosilane was not successfully prepared.

Scheme 73. Synthetic Approach Towards the Allylsilanes



At this point, the addition into the quinone before coupling was also considered.

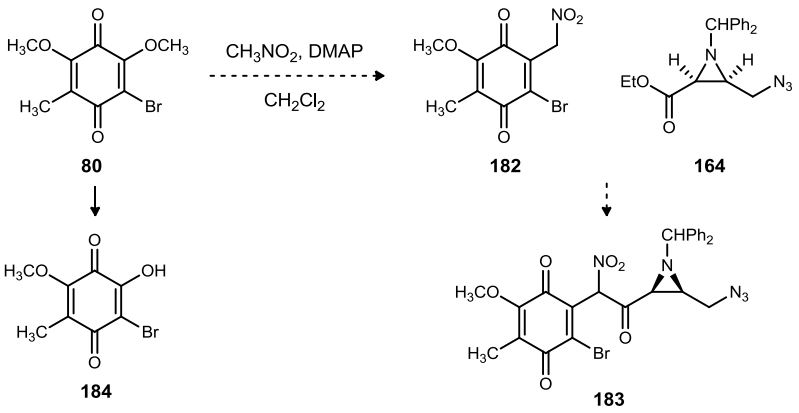
[148] Nishiyama, H.; Narimatsu, S.; Itoh, K. *Tetrahedron Lett.* **1981**, *22*, 5289-5292.
[149] Furuya, N.; Sukawa, T. *J. Organomet. Chem.* **1975**, *96*, C1-C3.
[150] Seyferth, D.; Mammarella, R. E. *J. Organomet. Chem.* **1978**, *156*, 299-305.

II. Addition of the C9-10 unit to the Quinone Prior to the Coupling

Prior to the investigation of the azide and aminoquinone, some work had been done on a slightly different route. The goal of this route was similar to the current goal in the addition of the C9-10 unit to the quinone before coupling. However, the difference was to create the C9-C9a bond before addition of the amine component to the quinone (N4 to C4a). Therefore the Michael addition of C9-10 into the quinone was followed by reduction and further testing of the C9-C9a coupling. The initial experiments in this route are relevant to the current work, and so will be discussed briefly first.

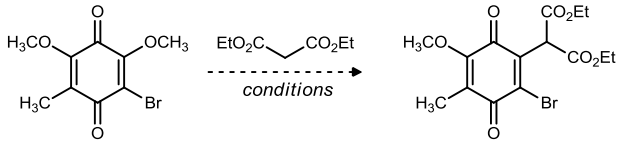
To begin, we experimented with addition to the quinone which would be followed by reduction to the hydroquinone. Nitromethane was chosen as a good nucleophile for the Michael addition (Scheme 74) as the resulting nitro group would make it easy to deprotonate the C9 carbon for addition into the ester group of **164**. Unfortunately, due to the ambident nucleophilicity of the nitro group, the addition occurred via the oxygen. The ^{1}H NMR spectra of the reaction after work up showed that one methoxide group had disappeared but the methylene expected from nitromethane addition through the nitrogen was not present. It was deduced that the methoxide was displaced by attack of the oxygen of the nitro group followed by hydrolysis during the work up to produce the hydroxyl.

Scheme 74. Nitromethane Addition to the Quinone



The next C9-10 unit chosen was methyl acetate since it could undergo Claisen condensation with the aziridinyl ester (**164**) and be transformed to the alcohol with relative ease. Deprotonation of methyl acetate using potassium methoxide in acetonitrile followed by addition to the quinone unfortunately gave a complex reaction mixture. Diethyl malonate, a much better Michael donor, was then used (Table 11). Preliminary reactions were not promising when a strong base (sodium ethoxide) gave complete consumption of starting material but no desired product, and milder bases (pyridine, diisopropylethyl amine) gave no reaction.

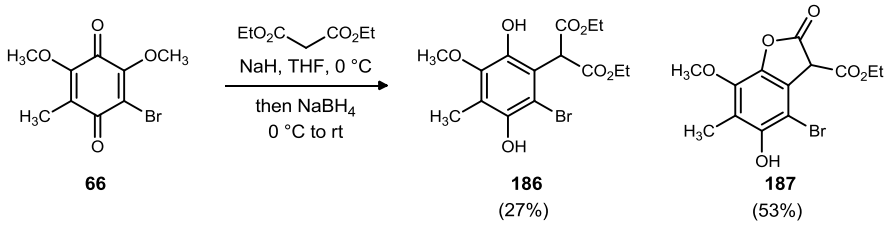
Table 11. Attempted Preparation of Quinone **185**



entry	reagents	conditions
1	NaOEt, EtOH	complex mixture
2	pyridine, THF	no rxn
3	$^{i}Pr_2NEt$, CH_2Cl_2	no rxn

Interestingly enough, when the base and quinone were combined, the color of the solution turned from the bright orange of the quinone to green; however, on removing the solvent or quenching the base, the reaction mixture turned orange again and showed unreacted starting material. If the color change back to orange indicated a retro-Michael, then the Michael adduct could be trapped with an *in situ* reduction to the hydroquinone. Therefore, the quinone was treated with diethyl malonate and diisopropylamine, followed by sodium borohydride. Though this produced the hydroquinone, no malonate was incorporated. When the base was switched to sodium hydride, hydroquinone **186** and lactone **187** were produced (Scheme 75). Hydroquinone **186** was treated with potassium carbonate in dichloromethane at reflux but did not convert to lactone **187**. The hydroquinone was also treated with triethylamine in THF but decomposed at reflux. *In situ* protection of the hydroquinone by addition of TBSCl after sodium borohydride did not give any protected hydroquinone, but produced lactone **187** in 44% yield while some silylated lactone was also isolated. As a result, lactone **187** was used in further experiments because it was consistently produced in the reaction and in better yield.

Scheme 75. Preparation of Hydroquinone **186** and Lactone **187**



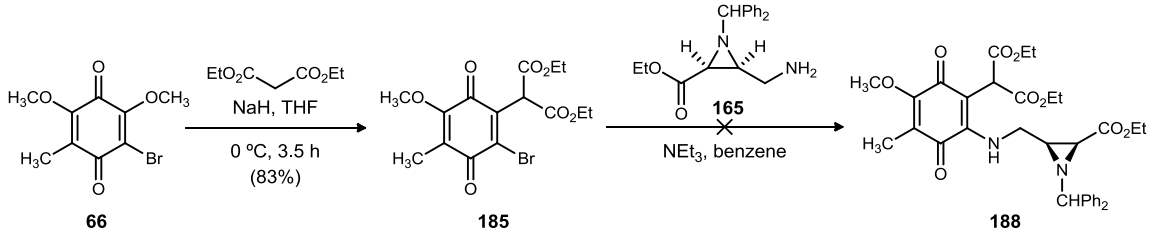
66 **186** (27%) **187** (53%)

The efforts to perform the Claisen condensation of lactone **187** with the aziridinyl ester (**164**) can be summarized as follows: a) basic conditions with sodium ethoxide in

ethanol (or ethanol:THF) at reflux gave no reaction, and b) sodium hydride in DMF at 130 °C for 5 min in the microwave gave unreacted ester **164** and decomposition of the lactone. It is interesting to note that the aziridine was not affected by basic conditions, as was previously observed with butyllithium (Scheme 33). Attempted decarboxylation of the lactone under Krapcho conditions resulted in decomposition as well. A one-pot attempt with the quinone (**66**), ethyl acetate, aziridinyl ester (**164**) and sodium ethoxide followed by sodium borohydride also gave no reaction.

Perhaps in view of the work just described, the desire to create the N4-C4a bond before the C9a-C9 bond is validated, as we have already successfully coupled amine **165** to quinone **80**. Towards our current goals, the malonate was added to quinone **66** using the same method as before with sodium hydride (Scheme 76). Addition of amine **164** to the quinone under standard conditions using triethylamine in benzene resulted in complete decomposition. The stability of the quinone was limited to a few days at room temperature in solution, but this seemed to be shortened significantly under mildly basic conditions.

Scheme 76. Preparation of Quinone **185** and Subsequent Coupling



Since neither the amine nor the quinone was recovered from the reaction mixture, quinone **185** was also treated with benzylamine in benzene to see if the problem was the

stability of **188**; however, this also resulted in decomposition. It is acknowledged that the malonate methine is highly acidic and could play a role in the reaction decomposition pathway. This could be addressed by reversing the order of couplings, adding the malonate after coupling the quinone and the amine.

2.9.5. Functionalization of the Aminoquinone – Installing C9-10 After Coupling

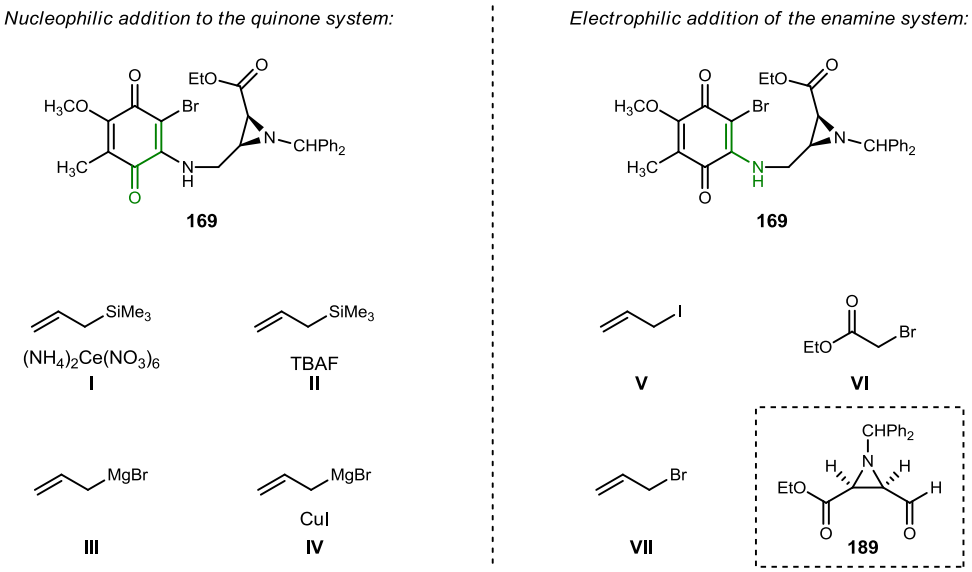
I. Addition of the C9-10 Unit to the Quinone Moiety of the Coupled Product

The addition of the C9-10 unit to the aminoquinone (**169**) was also investigated at the same time as the malonate addition to the quinone (**66**) from the preceding section. The results that are discussed below occurred before the successful addition of the malonate into the quinone. After outlining those results, the malonate addition to the aminoquinone will be discussed immediately after.

Scheme 77 shows an overview of the additions to aminoquinone **169**. These studies began with a CAN allylation using allyl trimethylsilane (**I**).[142] Using 2 equivalents of CAN in acetonitrile and warming from 0 °C to room temperature resulted in no reaction; the addition of 2 more equivalents of CAN gave complete conversion of the aminoquinone but the ^{1}H NMR spectrum of the reaction mixture was complex with some formation of aldehyde **189**. This indicated that aminoquinone **169** was reacting with CAN but not the allyl silane. The reaction was attempted again with an increased amount of allyl silane, but resulted in a complex mixture in which aldehyde **189** was not observed. Fluoride assisted addition of allyl trimethylsilane (**II**) using tetrabutylammonium fluoride in dichloromethane showed starting material by TLC while the ^{1}H NMR analysis of the crude reaction mixture showed consumption of starting material. The resulting side products decomposed during purification by silica gel column chromatography. The

addition of allyl magnesium bromide (**III**) to the quinone in THF at −78 °C showed some starting material and undetermined side products by ^{1}H NMR analysis of the crude reaction mixture. When the reaction was repeated and warmed from −78 °C to room temperature, complete decomposition was observed. Cuprate addition (**IV**) with allyl magnesium bromide and cuprous iodide in THF returned mostly starting material with a small amount of conversion to the same side product observed with the first Grignard reaction. The crude reaction mixtures were combined and purified by column chromatography but none of the fractions yielded any compounds with diagnostic allyl peaks. Control reactions for the cuprate addition were performed with dimethylethylidene malonate and quinone **66**. The former gave the expected product but the quinone returned starting material and some side products with no allyl peaks incorporated.

Scheme 77. Overview of Aminoquinone Additions



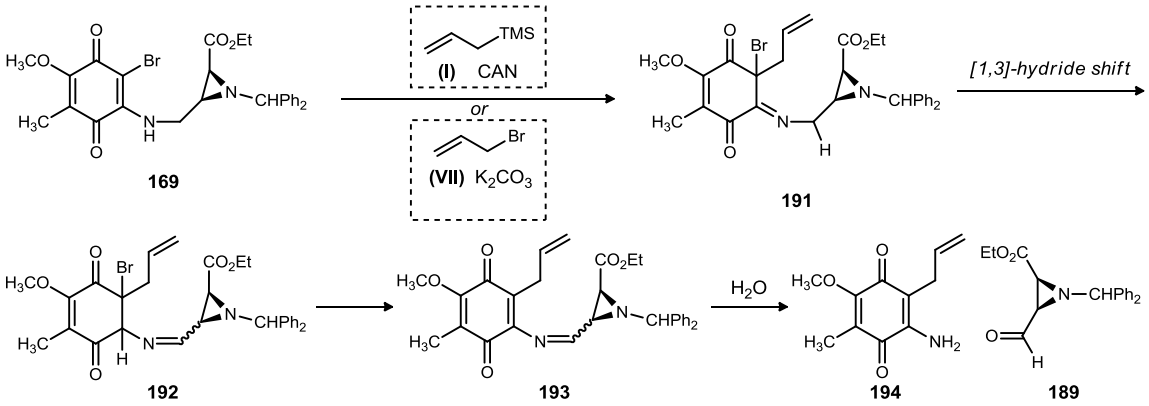
The ability of the enamine system to add to electrophiles was unclear because it has more of the characteristics of a vinylogous amide than an enamine. That said, the amine nitrogen should provide reactivity similar to an *N*-alkyl enamine. The additions to electrophiles began with allyl iodide (5 equivalents) in acetonitrile at reflux but no reaction was observed (**V**). Ethyl bromoacetate also gave no reaction at 85 °C for 5 min in the microwave in acetonitrile (**VI**).[151] This reaction was then heated at 100 °C for 30 min (monitored in 10 min intervals) and showed slow consumption of the starting material. Analysis of the reaction mixture by ^{1}H NMR revealed a complex mixture with no aziridine peaks, indicating that the aziridine nitrogen acylated faster than enamine addition. Treatment of the aminoquinone with allyl bromide and potassium carbonate in DMF (**VII**) suggested that *N*-allylation had occurred. The allylated product co-eluted with aldehyde **189** (seen previously in **I**) during column chromatography, and was consistently a 3:1 mixture of **190**:**189** by ^{1}H NMR analysis. Homonuclear decoupling experiments on the mixture assisted assignment of product peaks despite some peak overlap, and high resolution mass spectrometry confirmed the presence of the bromide.

The undesired aldehyde **189** has been observed twice so far: under oxidative conditions with CAN and allyl silane in acetonitrile (Scheme 77, **I**) and under non-oxidative basic conditions with allyl bromide and potassium carbonate in DMF (Scheme 77, **VII**). While the mechanism of its formation is uncertain, a possibility is outlined in Scheme 78. CAN allylation of aminoquinone **169** would proceed through the vinylogous amide system and result in the formation of intermediate **191**. This intermediate can also arise under allylation conditions with allyl bromide and potassium carbonate through addition via the enamine system of **169** (the major product *N*-allyl **190** arises from direct

[151] Huang, Z.-T.; Liu, Z.-R. *Chem. Ber.* **1989**, *122*, 95-100.

amine attack on allyl bromide). A [1,3]-hydride shift followed by elimination of a molecule of HBr will form imine **193**. This would then hydrolyze under aqueous work up procedures to form aldehyde **189**.

Scheme 78. Rationale for Aldehyde **189** Formation

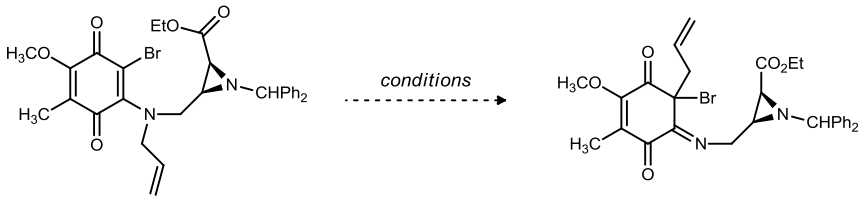


In the allyl bromide case, imine **191** can also be produced through a Claisen rearrangement of *N*-allylated aminoquinone **190**. The Claisen rearrangement was an interesting idea from our point of view because it would install the allyl group onto the quinone. The rearrangement intermediate **191** does not seem electronically favorable because it breaks the extended conjugation of the quinone. This might help explain why **191**, if it is formed during the reaction, tautomerizes to **192**. Thus far, the reactions had aqueous work up procedures (to remove CAN and DMF) but if **193** could be obtained, a reduction of the imine will give the desired adduct (in hydroquinone form).

To this end, the Claisen rearrangement was attempted by heating *N*-allylated aminoquinone **190** in toluene from 80 °C to 110 °C (Scheme 79). No reaction was observed, so the reaction was repeated in trifluorotoluene in the microwave. At 135 °C,

there was no reaction after 10 min but slow consumption of starting material was observed after another 20 min of heating. Unfortunately, when the reaction was heated for another 40 min, the starting material decomposed. Similar results were obtained when **190** was treated with triethylamine (to promote imine tautomerization/debromination) in trifluorotoluene: no conversion was observed from 80 °C to 100 °C but after heating at 135 °C, decomposition occurred.

Scheme 79. Claisen Rearrangement of *N*-Allylated Aminoquinone



190 **191**

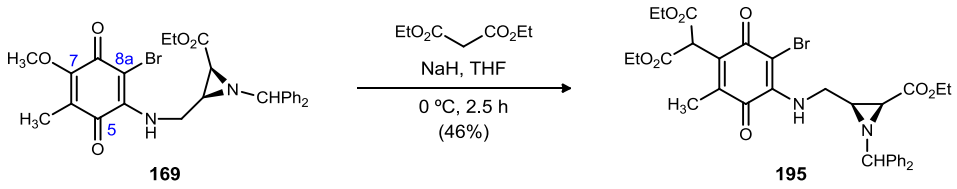
entry	condtions	T (ºC)[a]	time	result
1	d_8-toluene	110	7 h	no rxn
2	trifluortoluene	135	10 min	no rxn
		135	20 min	mostly sm
		135	40 min	decomposition
3	Et_3N, trifluorotoluene	80	10 min	no rxn
		100	30 min	no rxn
		135	20 min	decompostion

[a] All reactions heated in the microwave except entry 1. [b] Entry 1 monitored by ^1H NMR; entries 2-3 by TLC every 10 min.

At this time, the malonate addition to quinone **66** had just been achieved (Scheme 76), thereby making the C8a-C9 bond. Further attempts to couple the amine (**165**) to the quinone malonate (**185**) had resulted in decomposition. The goal now shifted to amine addition first followed by malonate addition. To that end, aminoquinone **169** was treated with diethylmalonate and sodium hydride in THF. While every other reaction on the

aminoquinone had resulted in complex mixtures, this reaction proceeded cleanly to give a single product. Unfortunately, the addition occurred at C7, not C8a.

Scheme 80. Malonate Addition to the Aminoquinone



This clearly indicated that aminoquinone **169** was not electronically suitable for the desired Michael addition. Prior expectation that the C5 carbonyl system would be the better Michael acceptor than the C8 system was correct, though the predicted site of addition was at C8a, not C7. We expected the electron donation from the amine to be counteracted by the bromine, while on the other side, the methoxide was a fairly good electron donating group and the methyl group would slightly increase the alkene electron density as well. In addition, the methoxide is not as good a leaving group as the bromide, and it was deduced that while the addition might be competitive, C8a should be favored. However, no desired regioisomer was evident in the ^{1}H NMR spectrum of the reaction.

Investigations thus far have revealed that a) the optimal order of addition is aziridinyl amine to quinone followed by C9-10 addition, b) diethyl malonate is a suitable C9-10 unit for the Michael addition to the aminoquinone, and c) while we have achieved coupling of the amine and quinone, as well as addition of C9-10, the regioselectivity of the addition needs to be reversed from C7 to C8a. In order to fix the regioselectivity, the two solutions proposed are: a) substitution (protection) of the amine nitrogen with an electron-withdrawing group, or b) the replacement of the bromide with the more

electronegative fluoride. Both of these options should make the C8a more electrophilic and are discussed below.

II. Modification of the Aminoquinone Regioselectivity: Amine Protection

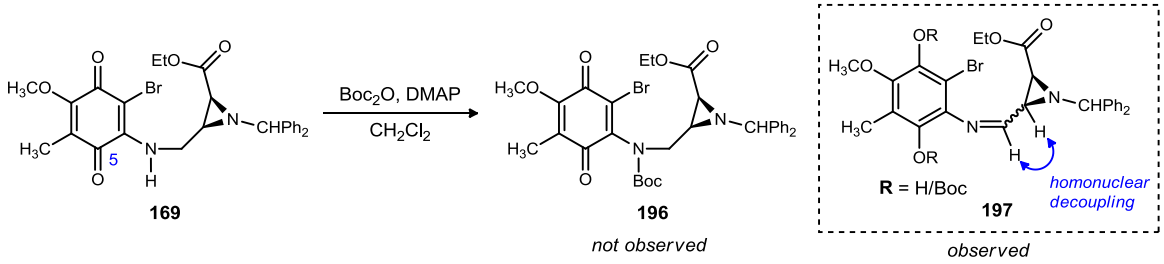
Carbamates, imides and sulfonamides are among common electron-withdrawing protecting group choices for amino groups. Treatment of aminoquinone **169** with tosyl chloride either gave no reaction with potassium carbonate in THF at reflux, or resulted in decomposition with potassium hydroxide in DME and sodium hydride in THF.[152] Previously, *N*-allylation had occurred with allyl bromide and potassium carbonate in DMF implying that the nitrogen was sufficiently nucleophilic to react with electrophiles. Acknowledging that the sterics of tosyl chloride may diminish its reactivity, we tried benzyl and phenyl isocyanate. Refluxing the aminoquinone with the isocyanate in chloroform or toluene, with and without pyridine, gave no reaction.[153] Deprotonation with sodium hydride in THF at 0 °C followed by addition of the isocyanate to the deprotonated amine **169** gave complex mixtures by ^{1}H NMR.[154]

The Boc group was then considered, since despite its sterically hindered nature, its otherwise high reactivity should assist in acylation. Addition of the aminoquinone to Boc-anhydride and DMAP in dichloromethane resulted in instant bubbling and a color change from pink to purple (aminoquinone **169** is bright pink; the color change to purple was observed before with NaH) (Scheme 81).[155] The purple color dissipated in 5 min and the light brown reaction mixture was quenched with aqueous ammonium chloride.

[152] *N*-Tosylation of indoles with KOH: Kikugawa, Y. *Synthesis* **1981**, 460-461.
[153] *N*-Acylation of pyrrolidine vinylogous carbamates with isocyanate and pyridine: Bahaji, E. H.; Bastide, P.; Bastide, J.; Rubat, C.; Tronche, P. *Eur. J. Med. Chem.* **1988**, *23*, 193-197.
[154] *N*-Acylation of pyrrolidine vinylogous carbamates with isocyanate and NaH: Davies, C. D.; Elliott, M. C.; Wood, J. L. *Tetrahedron* **2006**, *62*, 11158-11164.
[155] Muchalski, H. Dissertation, Department of Chemistry, Vanderbilt University, August 2012.

^{1}H NMR analysis of the reaction mixture after work up showed a single major product with Boc incorporation but in the hydroquinone form (Me and OMe peaks on the aromatic ring are usually ~1.9-2.0 ppm and ~4.0 ppm respectively for the quinones prepared so far, and >2.0 ppm and ~3.7 ppm for the hydroquinones). Column chromatography gave a mixture of two compounds, one of which was aldehyde **189** and the other was the putative product with Boc incorporation but a missing *N*-CH_2. Decoupling experiments showed coupling of the aziridine C-H to an imine C-H, and the product is proposed to be **197**. The upfield aliphatic region was not clean so it was unclear if there were one or two Boc groups, and if they were part of the product or not. The presence of an imine was confirmed by complete hydrolysis to the aldehyde (**189**) upon standing in $CDCl_3$, but the hydroquinone hydrolysis partner was not isolated due to its apparent instability.

Scheme 81. Aminoquinone Reaction with Boc-Anhydride and DMAP



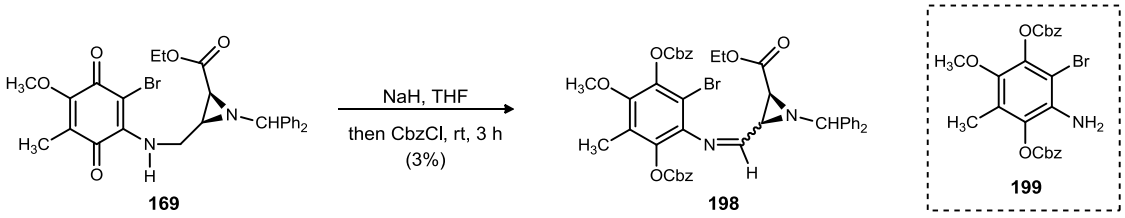
The Boc-acylation reaction was probed further discovering that the acylation did not occur without DMAP. The *in situ* reduction of putative imine **197** with sodium cyanoborohydride after Boc anhydride and DMAP addition resulted in a complex mixture with no aziridine peaks evident by ^{1}H NMR. If during the reaction only one of the quinone oxygens (on C5) was being acylated, then it could be through an initial *N*-

acylation followed by Boc transfer via a 5-membered ring intermediate. In this case, a nucleophile in the same pot might be able to capture the *N*-acylated intermediate. The reaction was performed with the simultaneous addition of Boc_2O, DMAP and diethylmalonate but gave no reaction in spite of adding excess reagents. Even if the malonate (5 equivalents) added to Boc_2O (10 equivalents plus 11 equivalents DMAP), there was still enough reagent to produce putative product **197**.

We believed the problem with the Boc-acylation was in the purification of the reaction – the putative product (**197**) was difficult to purify on small scale because it was always contaminated by some aldehyde (**189**), and repeated column chromatography resulted in complete conversion to the aldehyde. Definitive structural assignment of the product was hindered, precluding speculation about the mechanism for its formation. The experiment with diethyl malonate suggested that the Boc group was not transferred from the nitrogen, or that should the reaction undergo intramolecular Boc transfer, the malonate nucleophile was not reactive enough to perform a Michael addition into the *N*-Boc intermediate. In order to achieve our goal to reverse regioselectivity, it was important to know if both quinone oxygens were acylated as this implied that the nitrogen was not competitive toward acylation under these conditions to give the desired *N*-EWG aminoquinone. For this reason, another protecting group was sought which might be easier to separate from aldehyde **189** and if not, at least provide more information concerning the product by ^{1}H NMR analysis. The Cbz group was chosen because its benzyl peaks would not overlap with any of the starting material or aldehyde peaks (^{1}H NMR).

The aminoquinone (**169**) did not react with benzyl chloroformate in dichloromethane, nor did it react with benzyl chloroformate in the presence of DMAP and diisopropyl ethylamine in chloroform at reflux.[156] Sodium hydride deprotonation followed by benzyl chloroformate yielded a single major product by ^{1}H NMR, similar to **197**, which had an imine and two benzyl CH_2 peaks (Scheme 82).[157,158] Column chromatography afforded **198** in a very low yield (3%), which hydrolyzed to the aldehyde on standing within a few hours. LCMS of this sample showed a major peak at 516, which corresponds to the hydrolyzed hydroquinone partner with two Cbz groups (**199**), and a small peak corresponding to imine **198**. Another peak was observed at 472 (also with bromine isotope pattern) but was not identified.

Scheme 82. Aminoquinone Reaction with Benzyl Chloroformate



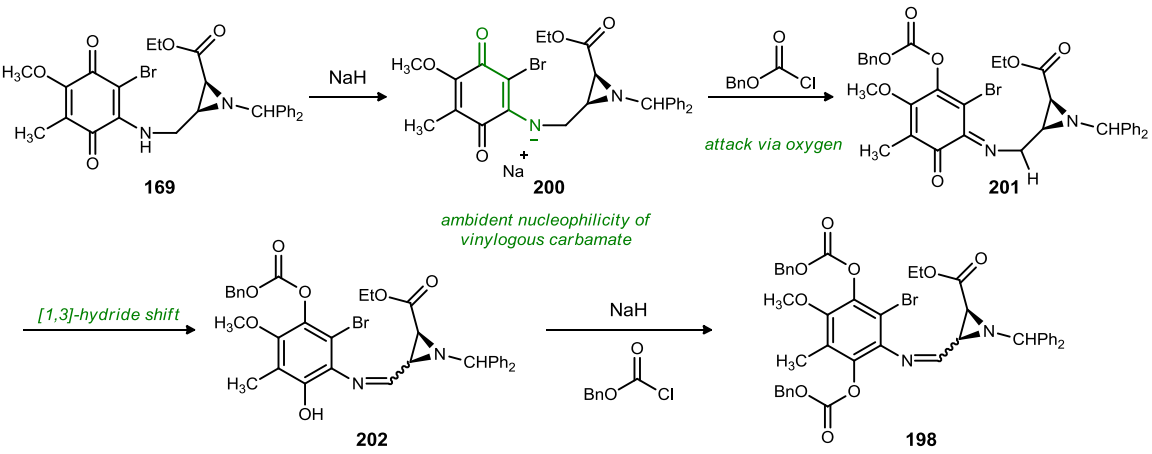
169 **198** **199**

The formation of imine **198** is proposed to occur as follows (Scheme 83). Sodium hydride deprotonates the amine, and the resulting anion **200** (similar to 4-pyridone anions that are well known for their ambident nucleophilicity)[159,154] adds to benzyl chloroformate via the oxygen to give intermediate **201**. [1,3]-Hydride transfer

[156] CbzCl, DMAP, DIPEA: Siddiqui A, Dai C, Mansoor U, Yang L, Vitharana L, Angeles A. Spirocondensed 1,3,4-thiadiazole derivatives for inhibiting KSP kinesin activity. WO 2009/052288.
[157] Shintani, R.; Yamagami, T.; Kimura, T.; Hayashi, T. *Org. Lett.* **2005**, *7*, 5317-5319.
[158] Rotzoll, S.; Reinke, H.; Fischer, C.; Langer, P. *Synthesis* **2009**, 69-78.
[159] Pyridone anion ambident reactivity: Breugst, M.; Mayr, H. *J. Am. Chem. Soc.* **2010**, *132*, 15380-15389.

(reminiscent of **192**, Scheme 78), followed by tautomerization to enol **202**, which will be deprotonated under basic conditions and can then add to benzyl chloroformate giving observed product **198**.

Scheme 83. Proposed Mechanism of Formation of Bis(Cbz)-**198**



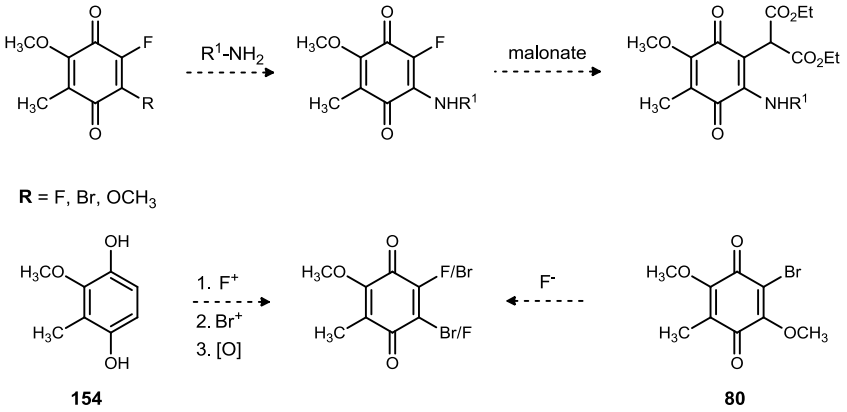
Now that it is clear that *O*-acylation of the aminoquinone (**169**) occurs before *N*-acylation, the regioselectivity switch from C7 to C8a of the aminoquinone (**169**) cannot be executed by decreasing the electron-donating power of the amine, but instead needs to be done by amplifying the electron-withdrawing power of the other substituent.

III. Modification of the Aminoquinone Regioselectivity: Fluoride Substitution

Fluoride replacement of the bromide should make the C8a addition site more electrophilic than the C7 site. The fluorine needs to be installed prior to the coupling of the quinone and the amine (Scheme 84). If the coupling proceeded as before, then the malonate addition should result at the desired fluorinated position. An unknown is the effect of fluorine on the regioselectivity of the first Michael addition. In the event that

amine addition at the undesired carbon predominates, a solution would be to make the difluorinated quinone, which should mimic the regioselectivity of the dibromoquinone (**44**, Scheme 21).

Scheme 84. Fluoride-Directed Addition Strategy



Both nucleophilic and electrophilic sources of fluorine were investigated. Nucleophilic fluoride addition to bromomethoxyquinone **80** were unsuccessful with potassium fluoride in DMSO,[160] potassium fluoride and 18-crown-6 in acetonitrile,[161] silver fluoride in dioxane,[162] and cesium fluoride in DMF. Fluoride addition to unsubstituted quinone **78** with potassium fluoride in DMSO was also unsuccessful.

Hydroquinone **154** was then treated with Selectfluor, but gave direct oxidation to the quinone without any fluorine addition.[163] *N*-Fluorobenzene succinimide (NFSI) is a milder reagent that has been shown to fluorinate phenols and *o*-hydroquinones with little or no oxidation. However, the electron rich nature of **154** may have promoted oxidation

[160] Pei, W.; Yang, W. *Synth. Commun.* **2010**, *40*, 535 - 539.
[161] Cameron, D.; Feutrill, G.; Griffiths, P.; Richards, K. *Aust. J. Chem.* **1982**, *35*, 1509-1512.
[162] Feiring, A. E.; Sheppard, W. A. *J. Org. Chem.* **1975**, *40*, 2543-2545.
[163] Nyland, R. L.; Luo, M.; Kelley, M. R.; Borch, R. F. *J. Med. Chem.* **2010**, *53*, 1200-1210.

over fluorination.[164] Since dibromoquinone **44** is prepared by bromination of the hydroquinone without concomitant oxidation (Scheme 20), hydroquinone **154** was treated with 1 equivalent NBS in dichloromethane with the expectation that mono-bromination would reduce the propensity to oxidize with fluoronium reagents in the next step. The monobromo hydroquinone was not stable to column chromatography so NFSI was added to the reaction after NBS but the quinone was still obtained.

Methylated hydroquinones have been fluorinated with Selectfluor in good yield, so hydroquinone **154** was methylated using dimethyl sulfate and potassium carbonate in acetone.[155,163] Treatment of the dimethylated hydroquinone with Selectfluor gave a mixture of several compounds, most of which looked to be quinone regioisomers. A possible fluorinated hydroquinone was isolated in 7% yield.[165] Treatment with NBS, however, resulted in complete decomposition.

It seemed that fluoro-(hydro)quinones were less stable than the bromo compounds previously prepared. As a result, bromination was performed first. Previously, fluorination of the hydroquinone (**154**) and monobromo hydroquinones had resulted in oxidation without fluorination. This time, the hydroquinone was methylated and brominated, so the propensity to oxidize should be further reduced. Bromination with NBS in $CDCl_3$-DMSO was observed by ^1H NMR after which NFSI was added. The reaction was heated at 60 °C but no fluorination occurred. The same results were obtained with NFSI in dioxane at reflux (101 °C); NFSI decomposes at 110 °C, so the reaction was not heated further. Apparently, methylation and bromination of the hydroquinone had significantly reduced its reactivity toward NFSI, so Selectfluor was

[164] Andreev, R.; Borodkin, G.; Shubin, V. *Russian Journal of Organic Chemistry* **2009**, *45*, 1468-1473.
[165] Fluorine peak observed at –130 ppm in ^{19}F NMR.

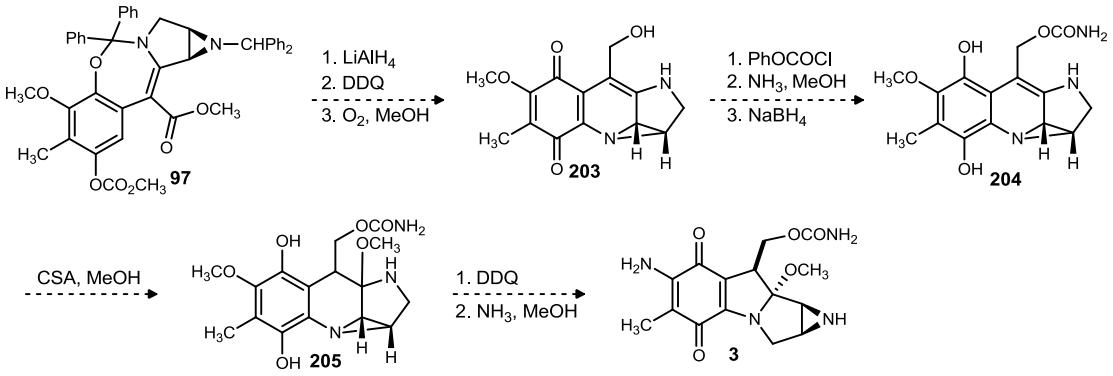
used instead. The reaction was performed in DMSO and heated but Selectfluor decomposed in DMSO at ~75 °C with no consumption of starting material. Propionitrile was used instead and gave mostly oxidation with some unreacted starting material.

Clearly, an alternate approach to synthesizing the fluoro-(hydro)quinones is needed. One such approach would install the fluorine using a diazonium salt obtained by reduction and diazotization of the nitro-hydroquinone, and shall be investigated in the future.

2.10. Conclusions and Future Directions

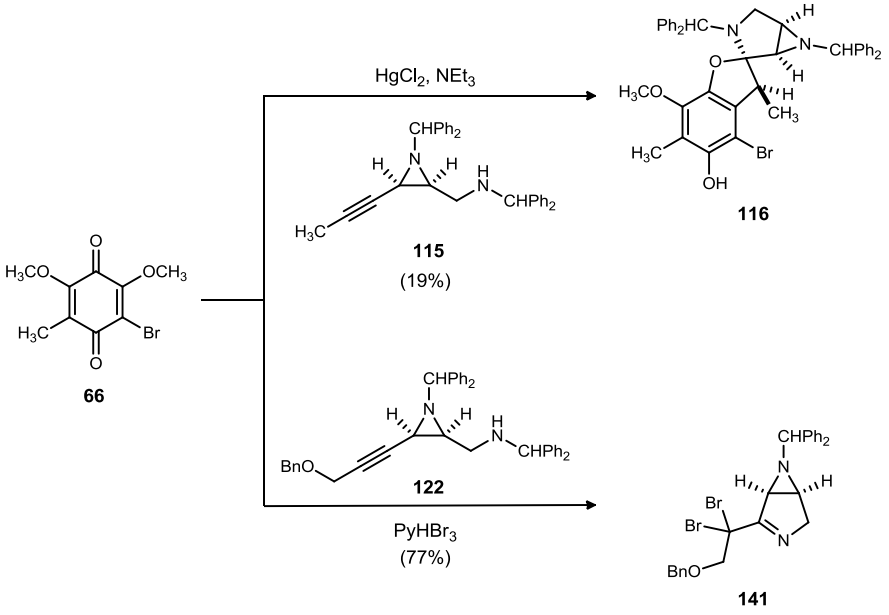
The installation of C10 on an advanced intermediate has been achieved using lithium-halogen exchange, thereby completing the carbon framework for MMC. Despite an undesired phenol reprotection, the vinylogous carbamate and the phenol carbonate of intermediate **97** can be reduced to the alcohol and phenol respectively (Scheme 85). Oxidative cleavage of the aziridine DPM group, and oxidation of the hydroquinone to the quinone with concomitant *N*,*O*-ketal opening should result in Michael addition of the free aziridine into the quinone, to form compound **203**. Conversion of the alcohol to the carbamate using Kishi's conditions,[34] followed by reduction to the hydroquinone should result in a reduced isomitomycin intermediate **204** analogous to that in Fukuyama's route.[37] Protonation and trapping of the iminium with methanol, and subsequent oxidation would give mitomycin A (**1**), which upon ammonolysis would afford MMC (**3**).

Scheme 85. Proposed Completion of Mitomycin C using Vinylogous Carbamate **97**



Installation of C10 prior to the coupling reaction was also accomplished (Scheme 86). The resulting spiroketal **116** contained an unfunctionalized methyl C10 and while it could be utilized to develop an analog of MMC, achieving the synthesis of MMC entailed functionalizing C10 prior to the coupling. Thus, the benzyloxyalkynyl amine **122** was synthesized but standard mercury-catalyzed coupling was not fruitful. Cyclization was achieved using pyridinium tribromide and produced dibromoimine **141**. Due to the relative instability of the dibromoimine and steric congestion at its reactive center, most coupling conditions resulted in decomposition and the coupling was not achieved. This necessitated the addition of the amine moiety of the aziridine fragment to the quinone prior to cyclization.

Scheme 86. Overview of C10 Installation Prior to Coupling

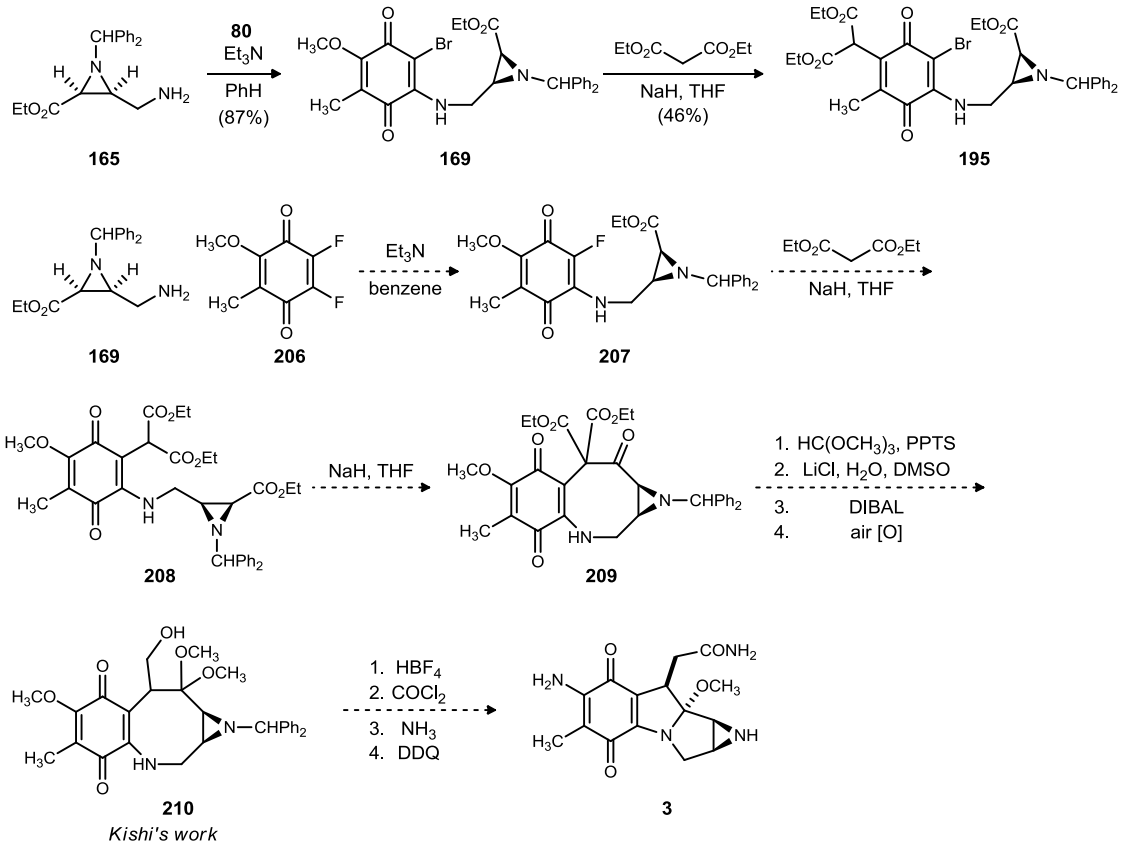


The requisite aminoquinone **169** was successfully synthesized from amine **165** and quinone **80** (Scheme 87). Since the Michael addition of the last two carbons of MMC (C9, C10) on **169** produced the undesired regioisomer, the corresponding fluoro-aminoquinone **207** will be prepared. The electronegativity of the fluorine should direct the substitution to give the desired regioselectivity. The Michael addition product **208** will then be subjected to an intramolecular cyclization to the eight-membered ring intermediate **209**.[166,167] Following protection of the ketone, the C10 alcohol will be obtained by decarboxylation and reduction of the ester to the alcohol. Since the reduction will also reduce the quinone, air oxidation will generate **210**, which is similar to an intermediate in Kishi's synthesis (**16**, Scheme 1).[34] Following Kishi's protocol,

[166] Malonate intramolecular cyclization onto ester: Dominguez, J. N.; Zapata, A. J.; Lobo, G. M.; Blanca, I. *Pharmazie* **1995**, *50*, 337-341.
[167] Malonate intramolecular cyclization onto ester: Sedelmeier, G.; Mickel, S. J.; Rueeger, H. (Novartis A. –G.; Novartis Pharma G.m.b.H). Process for alternative synthesis of aliskiren and intermediates. WO 2006024501, August 30, 2005.

unmasking the dimethyl ketal and cyclization with tetrafluoroboric acid, followed by carbamoylation, ammonolysis and deprotection of the aziridine will furnish MMC.

Scheme 87. Proposed Completion of MMC using Aminoquinone **207**



Chapter 3

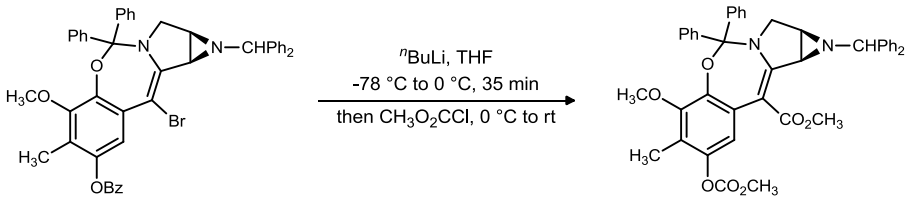
Experimental Section

All reagents and solvents were commercial grade and purified prior to use when necessary. Toluene, dichloromethane, acetonitrile and benzene were dried by passage through a column of activated alumina as described by Grubbs.[168] Thin layer chromatography (TLC) was performed using glass-backed silica gel (250 μm) plates and flash chromatography utilized 230–400 mesh silica gel from Sorbent Technologies. UV light, and/or the use of potassium iodoplatinate, ninhydrin, ceric ammonium molybdate and potassium permanganate solutions were used to visualize products. Anhydrous magnesium sulfate was used to dry organic solutions unless otherwise specified.

Nuclear magnetic resonance spectra (NMR) were acquired on a Bruker DRX-500 (500 MHz), Bruker AV-400 (400 MHz) or Bruker AV II-600 (600 MHz) instrument. Chemical shifts are measured relative to residual solvent peaks as an internal standard set to δ 7.26 and δ 77.16 ($CDCl_3$). IR spectra were recorded on a Thermo Nicolet IR100 spectrophotometer and are reported in wave numbers (cm^{-1}). Compounds were analyzed as neat films on a NaCl plate (transmission) or as a solution in chloroform. Mass spectra were recorded on a Thermo Electron Corporation MAT 95XP-Trap mass spectrometer by use of chemical ionization (CI), electron impact ionization (EI) or electrospray ionization (ESI) by the Indiana University Mass Spectrometry Facility, or on a Synapt hybrid quadrupole/oa-TOF mass spectrometer equipped with a dual chemical

[168] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520.

ionization/electrospray (ESCI) source by Vanderbilt University Mass Spectrometry Facility.



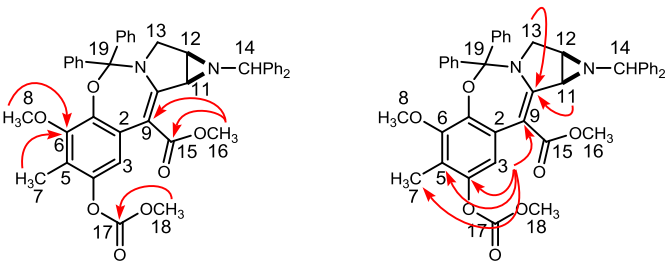
Compound 97. To a solution of the bromide (20.0 mg, 26.3 μmol) in THF (0.5 mL) at −78 °C was added ^{n}BuLi (47.0 μL, 117.5 μmol, 2.5M in hexanes). The reaction was stirred for 5 min, and then methyl chloroformate was added (50.0 μL, 64.7 μmol) at −78 °C. The reaction was allowed to warm to room temperature over 30 min and then concentrated. Column chromatography (neutral Al_2O_3, 0-20% ethyl acetate in hexanes) afforded the title compound (6.0 mg, 33%). R_f = 0.11 (20% EtOAc/hexanes); IR (film) 1763, 1701, 1255, 1130, 1040 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.3 Hz, 2 H), 7.55 (d, *J* = 6.7 Hz, 2 H), 7.39 (d, *J* = 7.2 Hz, 2 H), 7.35 (t, *J* = 7.6 Hz, 3 H), 7.23-7.29 (m, 9 H), 7.18 (t, *J* = 7.4 Hz, 2 H), 6.41 (s, 1 H), 3.87 (s, 3 H), 3.80 (s, 3 H), 3.75 (s, 1 H), 3.30 (d, *J* = 5.1 Hz, 1 H), 3.15 (dd, *J* = 11.0, 3.8 Hz, 1 H), 3.08 (d, *J* = 10.9 Hz, 1 H), 3.06 (s, 3 H), 2.54 (dd, *J* = 5.0, 3.8 Hz, 1 H), 1.97 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 170.3, 153.8, 150.8, 147.6, 145.9, 144.8, 143.3, 142.7, 142.3, 139.1, 128.6, 128.5(3C), 128.4, 128.4, 128.1, 127.8, 127.8, 127.2, 127.1(3C), 127.1(3C), 127.1, 126.4, 120.1, 114.6, 104.3, 97.9, 75.0, 61.0, 56.0, 55.2, 50.9, 50.0, 40.1, 9.2; HRMS (ESI): Exact mass calcd for $C_{43}H_{39}O_7N_2$ $[M+H]^+$ 695.2757, found 695.2759.

Structural Elucidation for Tetracyclic Vinylogous Carbamate 97

Key Features

The structure was assigned as the vinylogous carbamate using standard 1D and 2D NMR techniques. ^{1}H NMR indicated the presence of two new singlets integrating to 3H each, at 3.06 and 3.80 ppm, assigned as CH_3O- fragments. The absence of a deshielded (8.13 ppm) doublet associated with the benzoyl group in the vinyl bromide starting material indicated that the phenol had been deprotected. The absence of an alcohol proton (by ^{1}H and IR), and the presence of the second methyl group at 3.80 ppm suggested reprotection of the phenol as its methyl carbonate. ^{13}C NMR clearly indicated the presence of an ester at 170.3 ppm and a carbonate at 153.8 ppm. HMBC showed a strong $^{3}J_{HC}$ between H16 (3.06 ppm) and C15 (170.3 ppm) which confirmed assignment of the methyl ester (vinylogous carbamate). A strong $^{3}J_{HC}$ between H18 (3.80 ppm) and C17 (153.8 ppm) confirmed the assignment of the methyl carbonate. The methyl carbonate could be further distinguished from the aryl methyl ether (3.87 ppm) by the ether's strong $^{3}J_{HC}$ to C6 (150.8 ppm) combined with the strong $^{3}J_{HC}$ for H7 (1.97 ppm) to C6. Additional corroborating evidence included: 1) absence of H9 observed at 5.23 ppm in the starting material, 2) conservation of H3 at 6.41 ppm. The remaining structure assignment was straightforward, relying on chemical shifts and couplings by ^{1}H NMR, in combination with the HSQC experiment. IR confirmed the presence of a conjugated ester C=O at 1700 cm^{-1} and a carbonate C=O at 1763 cm^{-1}.

Figure 8. Key HMBC Correlations for **97**



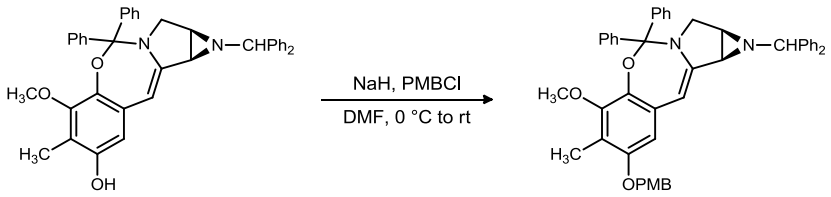
Additional Features

The proton at 6.41 ppm was assigned to aromatic proton H3 on the basis of strong HMBC correlations to C9, C4 (144.8 ppm), C5 (120.1 ppm) and weak correlations to C7 (9.2 ppm) were the key correlations used to assign 6.41 ppm as H3 and not H9.

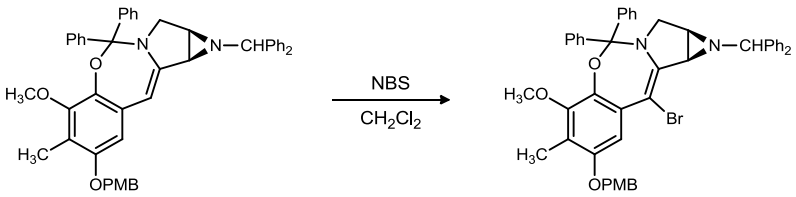
^{13}C assignments at quaternary carbons C2, C9 and C11 could be established by HMBC correlations from H13 (3.08 ppm) to C10 (147.6 ppm) and from H11 (3.30 ppm, weak) to C10. The ^{13}C shifts are as expected for an enamine and a conjugated ester,[169] and a vinylogous carbamate,[170] with C9 shifted substantially upfield from C10. The general trend for the ^{13}C shifts compared well to those of compound **95** and the benzoyl-protected unsubstituted enamine **92**.

The rest of the molecule is relatively unchanged by comparison to precursors. ^{1}H NMR showed, and HMBC confirmed, that the aziridine and amine were intact (with expected chemical shifts, splitting patterns and coupling constants). This indicates that it is highly unlikely that the amine or aziridine nitrogens were acylated. ^{1}H NMR indicated presence of all diphenyl methyl protons as well as methine H14 at 3.75 ppm. HMBC correlations from H14 to 142.7, 143.3 and protons between 127.05-127.11 ppm and a correlation from 7.39 ppm to C14 (75.9 ppm) confirmed that the aziridinyl diphenyl methyl group was still present. The key correlation that established the presence of the *N,O*-ketal diphenyl groups was an HMBC correlation from aromatic protons at 7.55 ppm to C19 (97.9 ppm).

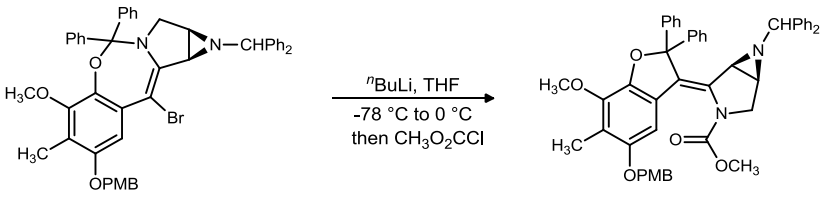
[169] Pretsch, E.; Bühlmann, P.; Affolter, C. *Structure Determination of Organic Compounds*; 3 ed.; Springer: New York, 2000.
[170] Ramtohul, Y. K.; Chartrand, A. *Org. Lett.* **2007**, *9*, 1029-1032. ^{13}C NMR taken in acetone-d_6.



Compound 100. To a solution of the phenol (18.0 mg, 31.1 μmol) in anhydrous DMF (100 μL) at 0 °C was added NaH (4.1 mg, 160 μmol), followed by PMBCl (6.0 μL, 44 μmol). The reaction mixture was stirred for 30 min at 0 °C. The solution was allowed to warm to room temperature and stirred for an additional 15 min. The reaction was quenched with water and then stirred vigorously. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water, brine and then dried, filtered and concentrated. The crude product was purified via column chromatography (neutral alumina, 0-20% ethyl acetate in hexanes) to afford the title compound (7.3 mg, 35%). R_f = 0.39 (20% EtOAc/hexanes); IR (film) 1652, 1602, 1515, 1492, 1468, 1451, 1432, 1249, 1109, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (b, 2H), 7.65 (d, *J* = 7.3 Hz, 2 H), 7.49 (d, *J* = 7.2 Hz, 2 H), 7.42 (t, *J* = 7.4 Hz, 3 H), 7.24-7.36 (m, 13 H), 6.92 (d, *J* = 8.7 Hz, 2 H), 6.18 (s, 1 H), 5.36 (s, 1 H), 4.81 (dd, *J* = 15.0, 11.1 Hz, 2 H), 3.95 (s, 3 H), 3.84 (s, 3 H), 3.79 (s, 1 H), 3.22 (dd, *J* = 10.6, 3.4 Hz, 1 H), 3.15 (d, *J* = 10.6 Hz, 1 H), 3.00 (d, *J* = 5.1 Hz, 1 H), 2.64 (dd, *J* = 5.0, 3.4 Hz, 1 H), 2.13 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 159.1, 152.3, 150.7, 143.9, 143.8, 143.4, 143.3, 141.7, 139.8, 129.8, 128.9, 128.5, 128.1, 128.0, 127.9, 127.7, 127.7, 127.4, 127.2, 127.1, 127.0, 116.1, 113.7, 106.3, 98.3, 96.5, 74.7, 70.0, 60.9, 55.5, 50.3, 41.4, 9.2; HRMS (ESI): Exact mass calcd for $C_{47}H_{43}O_4N_2$ $[M+H]^+$ 699.3196, found 699.3220.



Compound 101. To a solution of the enamine (150.0 mg, 226.1 mmol) in CH_2Cl_2 (4.6 mL) at rt was added NBS (48.0 mg, 269.7 mmol). The reaction mixture was stirred for 20 min and then concentrated. Column chromatography (neutral alumina, 0-20% ethyl acetate in hexanes) afforded the desired bromoenamine (112.1 mg, 64%). R_f = 0.40 (20% EtOAc/hexanes); IR (film) 1594, 1514, 1449, 1406, 1248, 1124, 702 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.5 Hz, 2 H), 7.45 (d, *J* = 7.4 Hz, 2 H), 7.37 (t, *J* = 7.6 Hz, 3 H), 7.26-7.31 (m, 10 H), 7.17-7.23 (m, 5 H), 6.87 (d, *J* = 5.9 Hz, 2 H), 6.86 (s, 1 H), 4.82 (s, 2 H), 3.87 (s, 3 H), 3.85 (s, 1 H), 3.81 (s, 3 H), 3.70 (d, *J* = 5.1 Hz, 1 H), 3.25 (d, *J* = 10.7 Hz, 1 H), 3.19 (dd, *J* = 10.7, 3.6 Hz, 1 H), 2.56 (dd, *J* = 4.7, 4.0 Hz, 1 H), 2.04 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 159.1, 152.1, 150.5, 144.0, 143.3, 143.2, 142.8, 140.9, 138.9, 129.6, 129.1, 128.8, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.7, 127.7, 127.5, 127.4, 127.3, 127.2, 127.0, 117.5, 113.7, 108.9, 97.4, 93.7, 74.7, 70.0, 60.9, 56.5, 55.2, 53.7, 40.6, 9.0; HRMS (ESI): Exact mass calcd for $C_{47}H_{42}O_4BrN_2$ $[M+H]^+$ 777.2301, found 777.2325.



(*E*)-Methyl 6-benzhydryl-2-(7-methoxy-5-((4-methoxybenzyl)oxy)-6-methyl-2,2-diphenylbenzofuran-3(2H)-ylidene)-3,6-diazabicyclo[3.1.0]hexane-3-carboxylate (103). To a solution of the bromide (48.0 mg, 61.7 μmol) in THF (4.2 mL) at −78 °C was added ^{n}BuLi (60.0 μL, 149 μmol, 2.49 M in hexanes). The reaction was stirred for 5 min, and then allowed to warm to 0 °C and stirred for an additional 1.5 h at 0 °C. The reaction was cooled to −78 °C, and ^{n}BuLi (62.0 μL, 154 μmol, 2.49 M in hexanes) was added. The reaction was allowed to warm to 0 °C and stirred for an additional 1.5 h. Methyl chloroformate (30.0 μL, 388 μmol) was added, and the reaction was stirred at rt for an additional 1 h and concentrated. Column chromatography (neutral alumina, 0-20% ethyl acetate in hexanes) afforded the title compound as a pale yellow foam (17.5 mg, 37%). R_f = 0.19 (20% EtOAc/hexanes); IR (film) 1769, 1614, 1515, 1454, 1265, 1220, 1119 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (d, *J* = 3.1 Hz, 2 H), 7.31 (d, *J* = 7.8 Hz, 2 H), 7.11-7.30 (m, 16 H), 7.10 (d, *J* = 4.1 Hz, 2 H), 6.94 (d, *J* = 8.6 Hz, 2 H), 6.62 (s, 1 H), 4.86 (s, 2 H), 3.83 (s, 3 H), 3.80 (s, 1 H), 3.76 (s, 3 H), 3.74 (s, 3 H), 3.61 (dd, *J* = 6.4, 5.9 Hz, 2 H), 2.50 (dd, *J* = 6.1, 5.9 Hz, 1 H), 2.46 (d, *J* = 6.1 Hz, 1 H), 2.17 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 159.4, 154.9, 153.6, 150.7, 142.7, 142.4, 139.7, 132.4, 130.0, 128.8, 128.3, 128.2, 127.9, 127.9, 127.8, 127.3, 127.2, 122.8, 114.8, 114.0, 110.6, 91.2, 77.9, 70.3, 61.0, 55.6, 55.3, 54.0, 47.0, 33.8, 9.5; HRMS (ESI): Exact mass calcd for $C_{49}H_{45}O_6N_2$ $[M+H]^+$ 757.3278, found 757.3279.

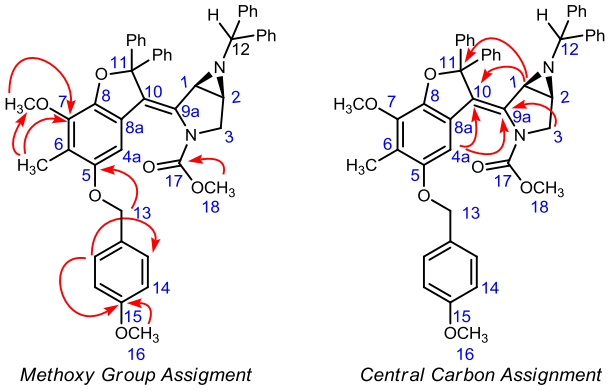
Structural Elucidation for Carbamate 103

Key Features

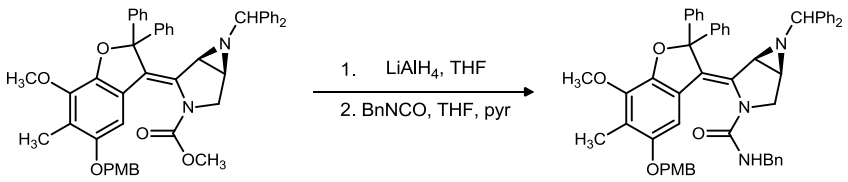
The structure was assigned using standard 1D and 2D NMR techniques. The presence of the C17 carbamate was evident from ^{13}C NMR (153.6 ppm) and IR (carbonyl at 1769 cm^{-1}). A singlet, integrating to 3H, at 3.80 ppm, was assigned as the carbamate (H18) due to a strong HMBC $^{3}J_{CH}$ correlation to C17 (153.6 ppm). The methyl carbamate was distinguished from the aryl methyl ether (3H at 3.76 ppm) by a strong HMBC correlation to C7 (150.7 ppm); this assignment was confirmed by an HMBC correlation between the methyl at C6 (3H at 2.17 ppm) and C7 (150.7 ppm). It was further distinguished from the PMB methyl ether (H16, 3.74 ppm) which showed an HMBC correlation to C15 (159.4 ppm), and was assigned based on HMBC correlations between H14 (6.94 ppm) and C15 (159.4 ppm). Enamine carbon C9a (139.7 ppm) was tentatively assigned using HMBC correlations from H3 (3.61 ppm), and H4a (6.62 ppm); enamine carbon C10 using HMBC correlations from H1 (2.46 ppm) and H4a (6.62 ppm); diphenylcarbon C11 using H1 (2.46 ppm).

Additional Features

Figure 9. Key Correlations for Carbamate **103**

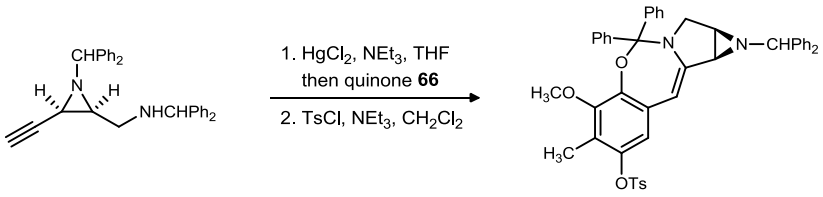


The aromatic carbons were assigned based on ^{13}C NMR and HMBC correlations with the C6 methyl and H4a, and these were in agreement with precursor compounds; the aziridine and pyrrolidine moieties were assigned based on ^{13}C NMR, coupling from ^{1}H NMR, and HMBC correlations.



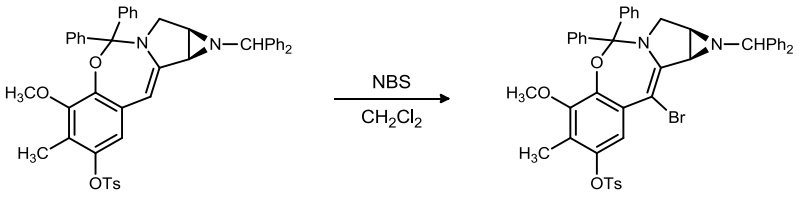
(*E*)-6-Benzhydryl-N-benzyl-2-(7-methoxy-5-((4-methoxybenzyl)oxy)-6-methyl-2,2-diphenylbenzofuran-3(2H)-ylidene)-3,6-diazabicyclo[3.1.0]hexane-3-carboxamide (105). To a solution of the carbamate (8.5 mg, 11 μmol) in THF (0.4 mL) at rt, lithium aluminum hydride (0.7 mg, 18 μmol) was added. The reaction was stirred for 1 h and then lithium aluminum hydride (2.0 mg, 53 μmol) was added. After TLC showed complete consumption of starting material, the reaction was quenched with aq. KF. The aqueous layer was extracted with ethyl acetate. The organic layers were dried, filtered and concentrated to afford the crude amine (7.2 mg). To a solution of the crude amine in THF at rt was added benzyl isocyanate (4.5 μL, 36 μmol) and pyridine (3.0 μL, 37 μmol). The reaction mixture was stirred for 2 d and then concentrated. Column chromatography (neutral alumina, 20-50% ethyl acetate in hexanes) afforded the title compound (5.3 mg, 50% over two steps). R_f = 0.10 (20% EtOAc/hexanes); IR (film) 3414, 2925, 1746, 1515, 1454, 1249, 1117 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.6 Hz, 2H), 7.38-7.31 (m, 10H), 7.28-7.18 (m, 8H), 7.06 (b, 2H), 6.94 (d, *J* = 8.6 Hz, 2H), 6.64 (s, 1H), 5.25 (b dd, *J* = 5.9, 5.8 Hz, 1H), 4.89 (s, 2H), 4.34 (dd, *J* = 14.9, 6.4 Hz, 1H), 4.22 (dd, *J* = 15.6, 5.8 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 1H), 3.75 (s, 3H), 3.61 (b, 2H), 2.45 (b, 1H), 2.31 (d, *J* = 5.3 Hz, 1H), 2.18 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 159.6, 154.8, 154.4, 151.7, 142.8, 142.6, 141.3, 139.9, 138.6, 130.0, 129.1, 129.1, 128.7, 128.7, 128.6, 128.5,

128.3, 128.2, 128.0, 127.9, 127.7, 127.6, 127.6, 127.4, 127.2, 122.9, 115.6, 114.1, 110.7, 90.9, 78.0, 70.6, 61.0, 55.5, 54.2, 47.0, 45.4, 34.1, 9.7; HRMS (ESI): Exact mass calcd for $C_{55}H_{50}O_5N_3$ $[M+H]^+$ 832.3745, found 832.3644.



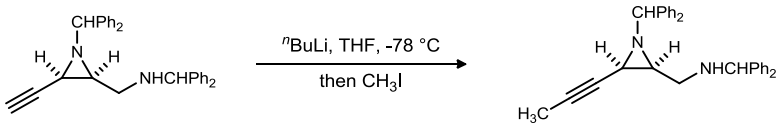
Compound 110. To a solution of the alkynyl amine (152.0 mg, 354.7 μmol) in THF (1.5 mL) at rt was added $HgCl_2$ (48.1 mg, 177 μmol) and triethylamine (300 μL, 2 mmol). The reaction mixture was stirred for 4 h and then the quinone (92.8 mg, 355 μmol) was added. The reaction mixture was stirred overnight, and then filtered through a pad of celite and concentrated to provide the crude phenol as a brown oil. To a solution of the crude phenol in CH_2Cl_2 (3.0 mL) at 0 °C was added triethylamine (100 μL, 700 μmol) and tosyl chloride (93.2 mg, 489 μmol). The reaction mixture was allowed to warm to rt and stirred for an additional 1 h at rt. Triethylamine (300 μL, 2 mmol) was added, and then the reaction mixture was stirred for an additional 4 h and concentrated. Column chromatography (neutral alumina, 5-40% ethyl acetate in hexanes) afforded the tosylated phenol as a white foam (42.3 mg, 18% over 2 steps). R_f = 0.15 (20% EtOAc/hexanes); IR (film) 3061, 2930, 1650, 1451, 1371, 1191, 1067 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.5 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 7.4 Hz, 2H), 7.40 (dd, *J* = 7.7, 7.6 Hz, 3H), 7.31-7.25 (m, 10H), 7.23 (d, *J* = 7.5 Hz, 2H), 7.21 (d, *J* = 8.2 Hz, 3H), 6.30 (s, 1H), 5.12 (s, 1H), 3.83 (s, 3H), 3.76 (s, 1H), 3.18

(dd, *J* = 10.6, 3.5 Hz, 1H), 3.07 (d, *J* = 10.6 Hz, 1H), 2.95 (d, *J* = 5.0 Hz, 1H), 2.62 (dd, *J* = 4.6, 3.9 Hz, 1H), 2.43 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 150.7, 146.3, 145.0, 144.8, 143.3, 143.3, 143.2, 139.5, 132.8, 129.6, 129.1, 128.1, 128.7, 128.7, 128.6, 128.6, 128.4, 128.2, 128.1, 127.9, 127.5, 127.4, 127.3, 127.1, 120.4, 116.4, 97.7, 97.3, 74.8, 61.0, 55.7, 50.2, 41.4, 21.5, 9.8; HRMS (CI): Exact mass calcd for $C_{46}H_{41}O_5N_2S$ $[M+H]^+$ 733.2731, found 733.2704.

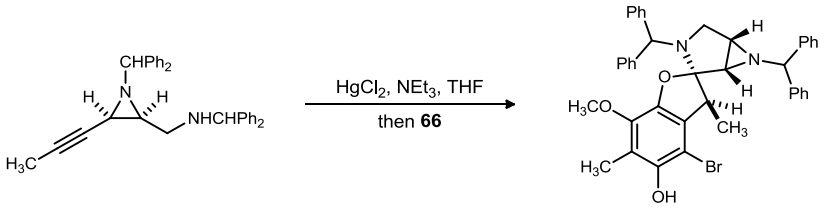


Compound 111. To a solution of the enamine (37.1 mg, 50.6 μmol) in CH_2Cl_2 (1.0 mL) at rt was added *N*-bromosuccinimide (9.7 mg, 54.5 μmol). The reaction mixture was stirred for 10 min and then concentrated. Column chromatography (neutral alumina, 0-20% ethyl acetate in hexanes) afforded the title compound as a white foam (26.5 mg, 65%). R_f = 0.30 (20% EtOAc/hexanes); IR (film) 2926, 1595, 1449, 1404, 1372, 1190, 1178 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.3 Hz, 2H), 7.46-7.43 (m, 5H), 7.37 (dd, *J* = 7.8, 7.6 Hz, 3H), 7.31-7.27 (m, 7H), 7.23-7.18 (m, 7H), 6.56 (s, 1H), 3.86 (s, 3H), 3.84 (s, 1H), 3.62 (d, *J* = 5.1 Hz, 1H), 3.21 (d, *J* = 1.7 Hz, 2H), 2.56 (ddd, *J* = 5.1, 2.0, 2.0 Hz, 1H), 2.40 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 150.8, 145.6, 145.1, 145.1, 143.4, 143.2, 142.9, 142.8, 138.8, 132.6, 129.7, 128.9, 128.8, 128.7, 128.7, 128.5, 128.4, 128.1, 128.1, 127.8, 127.6, 127.4, 127.3, 122.5, 118.9, 98.0, 92.3,

74.8, 61.3, 56.6, 53.6, 40.6, 21.9, 10.1; HRMS (CI): Exact mass calcd for $C_{46}H_{40}O_5BrN_2S$ $[M+H]^+$ 811.1836, found 811.1842.



***N*-((1-Benzhydryl-3-(prop-1-yn-1-yl)aziridin-2-yl)methyl)-1,1-diphenylmethanamine (115).** To a solution of the terminal alkyne (204.8 mg, 477.9 μmol) in THF (1.0 mL) at −78 °C was added ^{n}butyllithium (192.0 μL, 480.0 μmol). The reaction mixture was stirred for 30 min at −78 °C and then methyl iodide (130 μL, 2 mmol) was added. The reaction mixture was allowed to warm to rt and then stirred for an additional 40 min, and then concentrated. Column chromatography (silica gel, 0-40% ethyl acetate in hexanes) afforded the title compound as a pale yellow foam (32.3 mg, 71%). R_f = 0.33 (20% EtOAc/hexanes); IR (film) 3303, 3026, 1599, 1493, 1452, 737, 701 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.6 Hz, 2H), 7.34 (d, *J* = 7.2 Hz, 2H), 7.31 (dd, *J* = 7.8, 7.5 Hz, 2H), 7.25-7.15 (m, 14H), 4.68 (s, 1H), 3.63 (s, 1H), 2.77 (dd, *J* = 12.2, 5.3 Hz, 1H), 2.69 (dd, *J* = 12.2., 7.0 Hz, 1H), 2.18 (dd, *J* = 6.4, 1.7 Hz, 1H), 2.08-2.04 (m, 1H), 1.77 (d, *J* = 0.86 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 144.2, 144.0, 143.0, 142.5, 128.7, 128.6, 128.5, 128.4, 128.4, 128.4, 128.0, 127.9, 127.4, 127.3, 127.2, 78.1, 78.0, 75.7, 67.2, 48.2, 44,9, 33.7, 4.0; HRMS (CI): Exact mass calcd for $C_{32}H_{31}N_2$ $[M+H]^+$ 443.2482, found 443.2491.



3',6'-Dibenzhydryl-4-bromo-7-methoxy-3,6-dimethyl-3H-3',6'-diazaspiro[benzofuran-2,2'-bicyclo[3.1.0]hexan]-5-ol (116). To a solution of the alkynylamine (24.6 mg, 55.6 μmol) in THF (300 μL) at rt was added $HgCl_2$ (7.4 mg, 27 μmol) and triethylamine (47.5 μL, 341 mmol). The reaction mixture was stirred for 4 h and then the quinone (14.7 mg, 56.3 μmol) was added. The reaction mixture was stirred overnight, and then filtered through a pad of celite and concentrated. Column chromatography (neutral alumina, 0-40% ethyl acetate in hexanes) provided the title compound (9.0 mg, 24%). R_f = 0.42 (20% EtOAc/hexanes); IR (film) 3060, 2924, 1493, 1452, 1424, 1102, 700 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.4 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 7.1 Hz, 2H), 7.42-7.38 (m, 4H), 7.36-7.30 (m, 4H), 7.28-7.23 (2H), 7.16-7.14 (m, 2H), 6.66 (dd, *J* = 8.0, 1.7 Hz, 2H), 5.24 (s, 1H), 3.75 (s, 1H), 3.52 (s, 3H), 3.31 (d, *J* = 9.8 Hz, 1H), 3.13 (q, *J* = 7.0 Hz, 1H), 2.82 (dd, *J* = 9.9, 2.8 Hz, 1H), 2.82 (d, *J* = 5.1 Hz, 1H), 2.40 (dd, *J* = 5.2, 2.6 Hz, 1H), 2.19 (s, 3H), 0.67 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 144.0, 143.5, 143.2(2C), 142.4, 141.8, 140.8, 130.3, 130.0, 128.7, 128.6, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.8, 127.1, 127.0, 117.1, 112.0, 99.1, 74.9, 60.6, 59.4, 47.4, 41.2, 40.3, 15.6, 10.1; HRMS (ESI): Exact mass calcd for $C_{40}H_{38}O_3BrN_2$ $[M+H]^+$ 673.2066, found 673.2042.

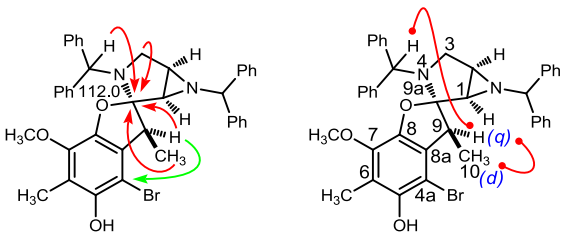
Structural Elucidation for Spiroketal 116

Key Features

The structure was assigned as the spiroketal using standard 1D and 2D NMR techniques. ^{1}H NMR indicated the presence of a new quartet, integrating to 1H, at 3.13 ppm ($^{3}J_{HH}$ = 7.0 Hz). HSQC assigned this methine to a carbon at 41.2 ppm. A doublet integrating to 3H at 0.67 ppm ($^{3}J_{HH}$ = 7.0 Hz) was also observed. This was assigned to the C10 methyl group, and established the H9-C9-C10 connectivity. Additionally, HMBC showed a $^{2}J_{HC}$ between H10 (0.67 ppm) and C9 (41.2 ppm), and between H9 (3.13 ppm) and C10 (15.6 ppm); NOESY showed a correlation between H9 (3.13 ppm) and H10 (0.67 ppm).

The spiroketal connectivity was established as follows: a) The presence of the C8a-C9 bond was indicated by HMBC correlations ($^{3}J_{HC}$) between H9 and C4a (99.1 ppm), H9 and C8 (143.2 ppm), H10 and C8a (130.3 ppm), and a weak $^{4}J_{HC}$ between H6 and C4a (99.1 ppm). b) The location of C9a (112.0 ppm) was deduced from its HMBC correlations ($^{3}J_{HC}$) with H10, N4-DPM methine (5.24 ppm) and both H3 protons (3.31 ppm, 2.82 ppm). An additional correlation was observed between C9a and H9. Furthermore, the ^{13}C shift at 112.0 ppm was within the expected *N*,*O*-ketal carbon range (as observed in previous compounds). The key NOESY correlations shown in Figure 10 indicate the *anti* orientation of the pyrrolidine nitrogen and the C10 methyl group.

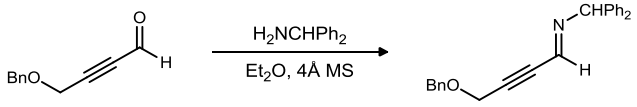
Figure 10. Key Correlations for Spiroketal **116**



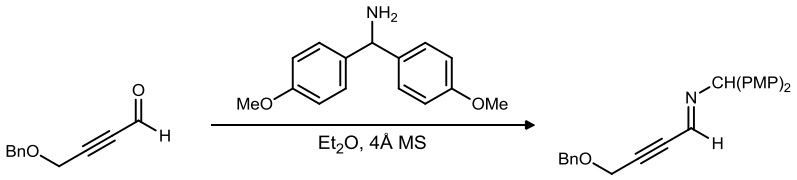
Additional Features

The remaining structure assignment was relatively straightforward, relying on chemical shifts, coupling by ^{1}H NMR and HSQC data. These assignments were confirmed by HMBC and NOESY correlations. All other carbon and proton shifts were

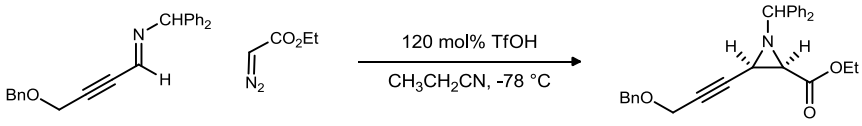
similar to the precursor compounds. The aromatic carbons were assigned based on HMBC correlations to C6-methyl (2.19 ppm) and C7-methoxy (3.52 ppm). The aziridine and pyrrolidine moieties are relatively unchanged, as evidenced by HMBC and NOESY correlations, and ^{1}H and ^{13}C shifts. The presence of the DPM methines are deduced from observed HMBC correlations to the aromatic DPM groups and to the aziridine and pyrrolidine protons, in addition to the expected chemical shifts by ^{1}H and ^{13}C NMR.



***N*-(4-(Benzyloxy)but-2-yn-1-ylidene)-1,1-diphenylmethanamine (124).** To a solution of the aldehyde (526.8 mg, 3.024 mmol) and 4Å molecular sieves in diethyl ether (3.0 mL) at rt was added aminodiphenylmethane (0.51 mL, 2.9 mmol). The reaction mixture was stirred for 40 min, and then filtered and concentrated to afford the desired imine (1.008 g, 98%) as a mixture of the *E*:*Z* isomers in a 1:0.6 ratio. R_f = 0.47 (20% EtOAc/ hexanes); IR (film) 3028, 2858, 1609, 1583, 1493, 1453, 1073, 1028 739, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 1.2 Hz, 0.6H), 7.74 (br s, 1H), 7.39-7.31 (m, 19.2H), 7.29-7.23 (m, 4.8H), 6.22 (s, 0.6H), 5.52 (s, 1H), 4.64 (s, 3.2H), 4.40 (d, *J* = 1.1 Hz, 1.2H), 4.36 (d, *J* = 0.96 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 144.8, 143.1, 142.6, 142.0, 137.1, 136.9, 128.6, 128.5, 128.5, 128.1, 127.7, 127.3, 127.2, 94.7, 89.0, 83.8, 79.7, 78.7, 72.8, 72.0, 72.0, 57.6, 57.3.

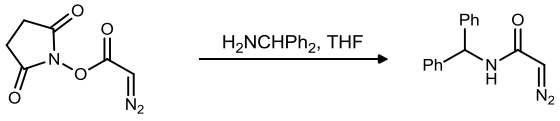


***N*-(4-(Benzyloxy)but-2-yn-1-ylidene)-1,1-bis(4-methoxyphenyl)methanamine (129).** To a solution of the aldehyde (510.1 mg, 2.928 mmol) and 4 Å molecular sieves in diethyl ether (3.0 mL) at rt was added bis(4-methoxyphenyl)methanamine (693.2 mg, 2.849 mmol). The reaction mixture was stirred for 10 min, and then filtered and concentrated to afford the desired imine (1.033 g, 88%) as a mixture of the *E*:*Z* isomers in a 1:0.6 ratio. R_f = 0.15 (20% EtOAc/ hexanes); IR (film) 2836, 1608, 1510, 1249, 1175, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (br s, 0.6H), 7.68 (s, 1H), 7.38-7.19 (m, 14.4H), 6.87-6.84 (m, 6.4H), 6.11 (s, 0.6H), 5.43 (s, 1H), 4.63 (s, 1.2H), 4.62 (s, 2H), 4.39 (d, *J* = 1.0 Hz, 1.2H), 4.34 (d, *J* = 0.8 Hz, 2H), 3.79 (s, 3H), 3.78 (s, 1.8H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 144.8, 135.5, 134.9, 128.6 (2C), 128.6, 128.3, 128.0, 126.7, 88.7, 79.6, 78.0, 72.4, 58.0, 55.7; HRMS (CI): Exact mass calcd for $C_{26}H_{25}O_3N$ $[M]^+$ 399.1829, found 399.1835.



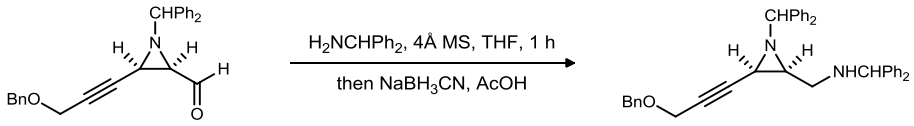
Ethyl 1-benzhydryl-3-(3-(benzyloxy)prop-1-yn-1-yl)aziridine-2-carboxylate (126). To a solution of the imine (21.3 mg, 62.7 μmol) in propionitrile (0.4 mL) at –78 °C was

added triflic acid (7.00 μL, 87.5 μmol), followed by drop-wise addition of ethyl diazoacetate (78.0 μL, 752 μmol). The reaction mixture was stirred for 6 h and then quenched with satd. aq. $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried, filtered and concentrated. Column chromatography (silica gel, 10% ethyl acetate in hexanes) afforded the desired *cis*-aziridine (9.9 mg, 37%). R_f = 0.29 (20% EtOAc/hexanes); IR (film) 3029, 2921, 2850, 1748, 1726, 1494, 1454, 1193, 1070 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 7.1, 7.0 Hz, 4H), 7.34-7.32 (m, 5H), 7.30 (dd, *J* = 7.6, 6.3 Hz, 4H), 7.25-7.22 (m, 2H), 4.56 (d, *J* = 11.6 Hz, 1H), 4.54 (d, *J* = 11.6 Hz, 1H), 4.22 (dq, *J* = 10.9, 7.1 Hz, 1H), 4.19 (dq, *J* = 10.9, 7.1 Hz, 1H), 4.18 (dd, *J* = 16.3, 1.5 Hz, 1H), 4.15 (dd, *J* = 15.9, 1.3 Hz, 1H), 3.78 (s, 1H), 2.62 (d, *J* = 6.5 Hz, 1H), 2.56 (d, *J* = 6.5 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 167.4, 141.7, 137.6, 128.7, 128.7, 128.5, 128.3, 128.0, 127.6 (2C), 127.5, 81.4, 78.7, 77.4, 71.5, 61.4, 57.6, 44.8, 34.3, 14.4; HRMS (ESI): Exact mass calcd for $C_{28}H_{28}O_3N$ $[M+H]^+$ 426.2069, found 426.2077.



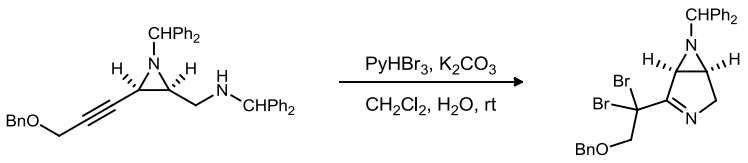
***N*-Benzhydryl-2-diazoacetamide (125).** Glyoxylic acid *p*-tosylhydrazone, the acid chloride and succinimidyl diazoacetate were prepared according to previously reported procedure and used without purification.[105,106,107] Benzhydryl diazoacetamide was prepared using literature procedure[108] and purified using a base wash (satd. aq. $NaHCO_3$) and trituration with diethyl ether to afford a yellow solid (44% over 3 steps). R_f = 0.12

(20% EtOAc/ hexanes); IR (film) 3250, 3089, 2100, 1604, 1541, 1371 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 7.6, 7.3 Hz, 4H), 7.28 (t, *J* = 7.3 Hz, 3H), 7.23 (d, *J* = 7.3 Hz, 4H), 6.27 (br s, 1H), 5.57 (br d, *J* = 6.7 Hz, 1H), 4.76 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 141.6, 128.9, 127.7, 127.5, 57.5, 47.6; HRMS: decomp.



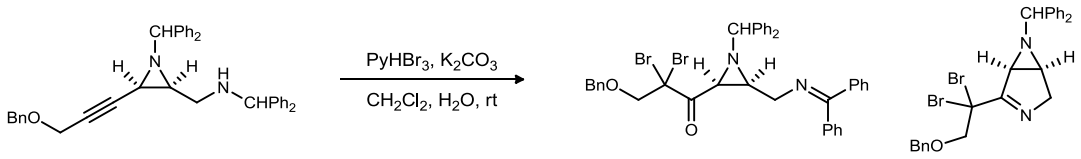
***N*-((1-Benzhydryl-3-(3-(benzyloxy)prop-1-yn-1-yl)aziridin-2-yl)methyl)-1,1-diphenylmethanamine (122).** To a solution of the aldehyde (171.8 mg, 450.4 μmol) in THF (9.0 mL) and 4 Å molecular sieves at rt was added benzhydryl amine (70 μL, 400 μmol). After 1 h, sodium cyanoborohydride (66.3 mg, 1.05 mmol) and acetic acid (27.8 μL, 485 μmol) were added. The reaction was stirred overnight at rt and then quenched with satd aq $NaHCO_3$. After stirring for 1 h, the reaction mixture was filtered and the layers were separated. The aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried, filtered and concentrated. Column chromatography (SiO_2, 5-40% ethyl acetate in hexanes) afforded the amine as a yellow foam (146.7 mg, 59%). R_f = 0.43 (20% EtOAc/ hexanes); IR (film) 3061, 3027, 2850, 1599, 1493, 1452, 1350, 1070, 1028, 742, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.3 Hz, 2H), 7.40-7.32 (m, 10H), 7.26-7.18 (m, 13H), 4.70 (s, 1H), 4.57 (s, 2H), 4.17 (d, *J* = 1.6 Hz, 2H), 3.71 (s, 1H), 2.84 (dd, *J* = 12.3 Hz, 5.1 Hz, 1H), 2.72 (dd, *J* = 12.2, 7.2 Hz, 1H), 2.29 (dt, *J* = 6.2, 1.5 Hz, 1H), 2.19 (ddd, *J* = 7.0, 6.4, 5.0 Hz, 1H) [N*H* not observed]; ^{13}C NMR (100 MHz, $CDCl_3$) ppm 144.1, 143.9, 142.9, 142.4, 137.6, 128.7, 128.5, 128.5,

128.4 (2C), 128.3, 128.0 (2C), 127.7, 127.4, 127.3, 127.2 (2C), 126.9, 126.9, 83.6, 78.0, 77.8, 71.4, 67.2. 57.6, 48.2, 45.2, 33.2; HRMS (ESI): Exact mass calcd for $C_{39}H_{37}ON_2$ $[M+H]^+$ 549.2906, found 549.2927.



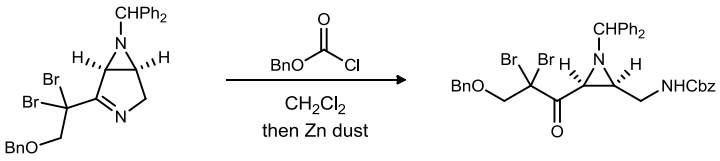
6-Benzhydryl-2-(2-(benzyloxy)-1,1-dibromoethyl)-3,6-diazabicyclo[3.1.0]hex-2-ene (141). To a solution of the amine (30.2 mg, 55.0 μmol) and potassium carbonate (28.1 mg, 203 μmol) in dichloromethane (1.0 mL) and water (1.0 mL) was added pyridinium tribromide (30.9 mg, 96.6 μmol). After 1 h at rt, a second portion of pyridinium tribromide (35.1 mg, 109 μmol) was added. The reaction was stirred overnight and then quenched with satd aq sodium sulfite. After 30 min, the layers were separated and the aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried and concentrated. Column chromatography (silica gel, 10-40% ethyl acetate in hexanes) afforded the imine (23.1 mg, 77%). R_f = 0.28 (20% EtOAc/ hexanes); IR (film) 3030, 2921, 2857, 1660, 1602, 1493, 1451, 1317, 1272, 1112, 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.20 (m, 15H), 4.71 (d, *J* = 12.6 Hz, 1H), 4.67 (d, *J* = 12.4 Hz, 1H), 4.17 (d, *J* = 18.0 Hz, 1H), 4.11 (d, *J* = 11.4 Hz, 1H), 4.05 (d, *J* = 11.5 Hz, 1H), 3.87 (dd, *J* = 18.0, 4.1 Hz, 1H), 3.63 (s, 1H), 3.48 (d, *J* = 2.9 Hz, 1H), 2.95 (dd, *J* = 4.5, 4.0 Hz, 1H) ^{13}C NMR (150 MHz, $CDCl_3$) ppm 172.8, 142.6, 142.2, 137.6, 128.6(2C), 128.5(2C), 128.4(2C), 128.3(2C), 127.9, 127.9(2C), 127.6, 127.3, 127.1(2C),

77.7, 75.4, 73.8, 62.5, 60.1, 50.7, 47.6; HRMS (ESI): Exact mass calcd for $C_{26}H_{24}OBr_2N_2Na$ $[M+Na]^+$ 561.0153, found 561.0138.



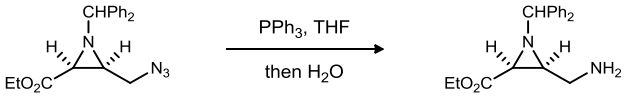
1-(1-Benzhydryl-3-(((diphenylmethylene)amino)methyl)aziridin-2-yl)-3-(benzyloxy)-2,2-dibromopropan-1-one (145). To a solution of the amine (174.7 mg, 318.4 μmol) and potassium carbonate (218.6 mg, 1.582 mmol) in dichloromethane (3.0 mL) and water (3.0 mL) was added pyridinium tribromide (202.9 mg, 634.4 μmol). After 3 h at rt, a second portion of pyridinium tribromide (208.9 mg, 653.1 μmol) was added. The reaction was stirred overnight and then quenched with satd aq sodium sulfite. After 30 min, the layers were separated and the aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried and concentrated. Column chromatography (silica gel, 10-40% ethyl acetate in hexanes) afforded the title compound as a yellow oil (34.7 mg, 15%) and the dibromoimine (89.1 mg, 52%). R_f = 0.33 (20% EtOAc/hexanes); IR (film) 3061, 3029, 2920, 1658, 1599, 1450, 1278 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.15 (m, 23H), 7.05-7.02 (m, 2H), 4.59 (d, *J* = 12.4 Hz, 1H), 4.55 (d, *J* = 12.4 Hz, 1H), 4.03 (d, *J* = 11.4 Hz, 1H), 3.96 (s, 1H), 3.95 (d, *J* = 11.6 Hz, 1H), 3.64 (dd, *J* = 15.1. 5.4 Hz, 1H), 3.46 (dd, *J* = 15.1, 6.8 Hz, 1H), 3.41 (d, *J* = 6.6 Hz, 1H), 2.96 (ddd, *J* = 6.4, 6.4, 5.9 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 191.8, 142.5, 142.1, 137.5, 128.7, 128.6, 128.5, 128.5, 128.5, 128.0, 128.0, 127.9, 127.8, 127.8, 127.5, 127.4, 127.3, 78.1, 76.0, 73.8,

64.9, 52.6, 51.2, 45.0; HRMS (ESI): Exact mass calcd for $C_{39}H_{35}O_2Br_2N_2$ $[M+H]^+$ 721.1065, found 721.1088.

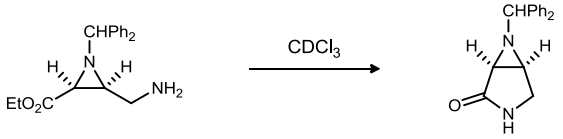


Benzyl ((1-benzhydryl-3-(3-(benzyloxy)-2,2-dibromopropanoyl)aziridin-2-yl)methyl)carbamate (152). To a solution of the imine (4.1 mg, 7.6 μmol) in dichloromethane (450 μL) was added benzyl chloroformate (2.0 μL, 14 μmol). After 2.5 h stirring, Zn dust (2.6 mg, 39 μmol)[171] was added and the reaction mixture was stirred overnight. Filtration and removal of the solvent afforded the ketone as a brown oil (2.4 mg, 47%). R_f = 0.16 (20% EtOAc/ hexanes); IR (film) 3420, 3030, 2924, 1718, 1509, 1452, 1258, 1115 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.39-7.27 (m, 20H), 5.00 (d, *J* = 12.0 Hz, 1H), 4.93 (d, *J* = 12.6 Hz, 1H), 4.67 (bdd, *J* = 6.0, 6.0 Hz, 1H), 4.64 (s, 2H), 4.16 (d, *J* = 11.4 Hz, 1H), 4.00 (d, *J* = 11.4 Hz, 1H), 3.87 (s, 1H), 3.34 (d, *J* = 6.6 Hz, 1H), 3.28 (ddd, *J* = 6.6, 6.0, 2.4 Hz, 1H), 2.71 (dd, *J* = 6.6, 6.0 Hz, 1H), N*H* not observed ^{13}C NMR (150 MHz, $CDCl_3$) ppm 192.0, 156.4, 142.4, 141.6, 137.0, 136.7, 128.8 (2C), 128.65 (2C), 128.60 (2C), 128.56 (2C), 128.2, 128.15, 128.08 (2C), 128.0 (2C), 127.9, 127.7 (2C), 127.4, 127.2 (2C), 77.6, 76.0, 74.1, 66.7, 64.0, 49.6, 45.2, 38.7; HRMS (ESI): Exact mass calcd for $C_{34}H_{33}O_4Br_2N_2$ $[M+H]^+$ 691.0807, found 691.0800.

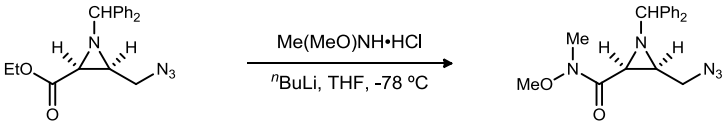
[171] Zn dust was found to be unnecessary for the reaction.



Ethyl 3-(aminomethyl)-1-benzhydrylaziridine-2-carboxylate (165). The azide (31.7 mg, 94.2 μmol) and triphenylphosphine (30.2 mg, 115 μmol) were stirred in THF (1.9 mL) at rt overnight. Water (15 μL) was added and the reaction was stirred for a further 7 h. The reaction mixture was diluted with CH_2Cl_2, dried, filtered and concentrated to give a pale yellow solid. Column chromatography (silica gel, 0-10% methanol in dichloromethane) afforded the amine as a white solid (20.3 mg, 69%). MP R_f = 0.17 (10% MeOH/ dichloromethane); IR (film) 3369, 3027, 2977, 2926, 1735, 1450, 1384, 1296, 1191, 1033, 750, 702 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.4 Hz, 2H), 7.40 (d, *J* = 7.3 Hz, 2H), 7.30 (dd, *J* = 7.7, 7.6 Hz, 4H), 7.25-7.21 (m, 2H), 4.20 (dq, *J* = 11.0, 7.3 Hz, 1H), 4.18 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.74 (s, 1H), 2.84 (bdd, *J* = 13.3, 4.7 Hz, 1H), 2.79 (bdd, *J* = 13.1, 6.5 Hz, 1H), 2.39 (d, *J* = 6.7 Hz, 1H), 2.20 (ddd, *J* = 6.8, 6.8, 5.5 Hz, 1H), 2.00 (br s, 2H), 1.26 (dd, *J* = 7.2, 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 169.4, 142.9, 142.1, 128.8 (2C), 128.6 (2C), 127.9 (2C), 127.8, 127.3, 127.2 (2C), 77.7, 61.2, 47.9, 43.3, 40.4, 14.3; HRMS (CI): Exact mass calcd for $C_{19}H_{23}O_2N_2$ $[M+H]^+$ 311.1765, found 311.1764.



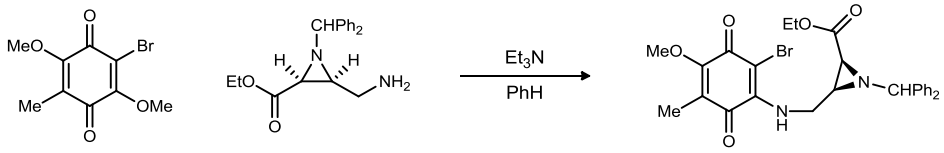
6-Benzhydryl-3,6-diazabicyclo[3.1.0]hexan-2-one (166). The amine (16.4 mg, 52.8 μmol) was heated gently in deuterated chloroform in a J-Young tube until complete conversion achieved as determined by ^{1}H NMR spectroscopy. The solvent was removed and the residue chromatographed (silica gel, 75% ethyl acetate in hexanes then 5-10% methanol in dichloromethane) to afford the lactam (11.6 mg, 83%). R_f = 0.25 (EtOAc); IR (film) 3227, 2921, 2852, 1699, 1449, 1063, 743, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.40 (m, 4H), 7.34-7.28 (m, 4H), 7.27-7.20 (m, 2H), 5.52 (br s, 1H), 3.70 (s, 1H), 3.47 (bd, *J* = 10.8 Hz, 1H), 3.36 (dd, *J* = 10.8, 3.9 Hz, 1H), 2.79 (ddd, *J* = 4.5, 4.0, 1.8 Hz, 1H), 2.57 (d, *J* = 4.6 Hz, 1H) ^{13}C NMR (125 MHz, $CDCl_3$) ppm 174.1, 142.6, 142.0, 128.7 (4C), 127.6, 127.5 (3C), 127.2 (2C), 75.0, 44.7, 43.0, 40.9; HRMS (CI): Exact mass calcd for $C_{17}H_{17}ON_2$ $[M+H]^+$ 265.1346, found 265.1338.



3-(Azidomethyl)-1-benzhydryl-N-methoxy-N-methylaziridine-2-carboxamide (170). Prepared according to literature procedure:[172] 53.6 mg (159 μmol) azidoester produced 56.3 mg (quant.) Weinreb amide with no purification required. R_f = 0.15 (20% EtOAc/ hexanes); IR (film) 3029, 2928, 2855, 2097, 1667, 1451, 1333, 1182, 1109, 1011, 747, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.4 Hz, 2H), 7.44 (d, *J* = 7.3 Hz,

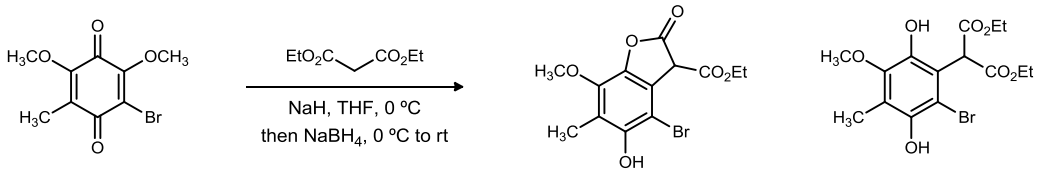
[172] Roche, C.; Labeeuw, O.; Haddad, M.; Ayad, T.; Genet, J. –P.; Vidal, V. R-; Phansavath, P. *Eur. J. Org. Chem.* **2009**, 3977-3986.

2H), 7.33-7.28 (m, 4H), 7.24-7.18 (m, 2H), 3.83 (s, 1H), 3.53 (d, *J* = 6.3 Hz, 2H), 3.50 (br s, 3H), 3.18 (s, 3H), 2.91 (br d, *J* = 5.4 Hz, 1H), 2.33 (dt, *J* = 6.4, 6.4 Hz, 1H) ^{13}C NMR (125 MHz, $CDCl_3$) ppm 168.3, 142.5, 142.3, 128.7 (2C), 128.6 (2C), 127.6 (2C), 127.3 (2C), 127.3 (2C), 77.9, 61.5, 49.3, 44.8, 40.4, 32.6; HRMS (ESI): Exact mass calcd for $C_{19}H_{21}O_2N_5Na[M+Na]^+$ 374.1593, found 374.1577.



Ethyl 1-benzhydryl-3-(((2-bromo-4-methoxy-5-methyl-3,6-dioxocyclohexa-1,4-dien-1-yl)amino)methyl)aziridine-2-carboxylate (169). To amine (3.2 mg, 10.3 μmol) and quinone (5.6 mg, 21.4 μmol) in benzene (200.0 μL) at rt was added triethylamine (5.0 μL, 35.9 μmol). After 2 days, the red residue was purified by column chromatography (silica gel, 20% ethyl acetate/hexanes) to afford the title compound as a bright pink oil (5.3 mg, 95%). R_f = 0.21 (20% EtOAc/ hexanes); IR (film) 3321, 2923, 2853, 1735, 1657, 1587, 1513, 1451, 1381, 1318, 1198, 1106, 1033, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 7.45 (d, *J* = 7.4 Hz, 2H), 7.32-7.29 (m, 4H), 7.23 (d, *J* = 7.3 Hz, 1H), 7.19 (dd, *J* = 7.6, 7.2 Hz, 2H), 7.12 (dd, *J* = 7.2, 7.2, 1H), 6.16 (br s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.18 (ddd, *J* = 14.5, 7.3, 5.0 Hz, 1H), 4.11 (s, 3H), 3.71 (s, 1H), 3.66 (ddd, *J* = 14.3, 7.0, 7.0 Hz, 1H), 2.57, (ddd, *J* = 7.0, 6.9, 5.1 Hz, 1H), 2.45 (d, *J* = 6.5 Hz, 1H), 1.84 (s, 3H), 1.27 (t, *J* = 7.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 181.9, 175.0, 169.1, 157.4, 143.9, 142.3, 141.9, 128.8 (2C), 128.6 (2C), 128.0 (2C), 127.7, 127.4, 127.1 (3C), 122.6, 77.9, 61.8,

61.5 (2C), 45.2, 43.3, 14.3, 8.7; HRMS (ESI): Exact mass calcd for $C_{27}H_{27}O_5BrN_2Na$ $[M+Na]^+$ 561.1001, found 561.0983.

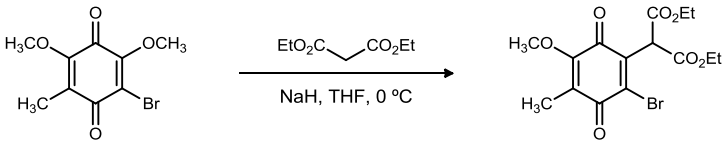


Ethyl 4-bromo-5-hydroxy-7-methoxy-6-methyl-2-oxo-2,3-dihydrobenzofuran-3-carboxylate (187) and diethyl 2-(2-bromo-3,6-dihydroxy-5-methoxy-4-methylphenyl)malonate (186). To the quinone (50.1 mg, 190 µmol) and diethyl malonate (29.1 µL, 190 µmol) in THF (2.0 mL) at 0 °C was added sodium hydride (9.4 mg, 390 µmol). The resulting dark blue reaction mixture was stirred at 0 °C for 30 min and then sodium borohydride (14.5 mg, 380 µmol) was added. The reaction mixture was allowed to warm to rt. After TLC showed complete conversion of starting material, the reaction was quenched with 3M HCl at 0 °C. After stirring at rt for 30 min, diethyl ether was added and the layers were separated. The aqueous later was extracted with Et_2O. The organic layers were dried, filtered and concentrated. The crude residue was passed through a silica plug (eluted with dichloromethane, then with 5% methanol in dichloromethane) to afford the lactone (35.1 mg, 53%) and the diester (20.1 mg, 27%).

Ethyl 4-bromo-5-hydroxy-7-methoxy-6-methyl-2-oxo-2,3-dihydrobenzofuran-3-carboxylate (187). R_f = 0.48 (50% EtOAc/ hexanes); IR (film) 3474, 2924, 1811, 1741, 1480, 1424, 1305, 1132, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.40 (s, 1H), 4.60 (s, 1H), 4.30 (q, J = 7.1 Hz, 2H), 3.99 (s, 3H), 2.22 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) ppm 168.2, 163.9, 148.0, 142.4, 138.5, 121.2, 119.5, 99.1, 63.2, 60.6, 52.6, 14.1, 10.2; HRMS (ESI): Exact mass calcd for $C_{13}H_{13}O_6BrNa$ $[M+Na]^+$ 366.9793, found 366.9807.

Diethyl 2-(2-bromo-3,6-dihydroxy-5-methoxy-4-methylphenyl)malonate (186). R_f = 0.50 (5% MeOH/dichloromethane); IR (film) 3443, 2937, 1736, 1461, 1420, 1303, 1178, 1086 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (br s, 1H), 5.32 (br s, 1H), 5.18 (s, 1H), 4.26 (q, *J* = 7.1 Hz, 4H), 3.80 (s, 3H), 2.23 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 168.5, 147.4, 145.0, 142.6, 119.7, 118.6, 107.9, 62.4, 61.0, 55.1, 14.1, 10.4; HRMS (ESI): Exact mass calcd for $C_{15}H_{19}O_7BrNa$ $[M+Na]^+$ 413.0212, found 413.0230.



Diethyl 2-(2-bromo-5-methoxy-4-methyl-3,6-dioxocyclohexa-1,4-dien-1-yl)malonate (185). To a solution of the quinone (25.0 mg, 95.7 µmol) and malonate (15.0 µL, 98.8 µmol) in THF (1.0 mL) at 0 °C was added sodium hydride (20.3 mg, 846 µmol). After 3 h, the reaction mixture was quenched with satd aq NH_4Cl. The aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried, filtered and concentrated. Column chromatography (SiO_2, 20% ethyl acetate in hexanes) afforded the title compound as an orange oil (30.8 mg, 83%). R_f = 0.15 (10% EtOAc/ hexanes); IR (film) 2982, 2932, 1745, 1666, 1303, 1251, 1164, 1032 cm^{-1}; ^{1}H NMR (600 MHz,

$CDCl_3$) δ 4.95 (s, 1H), 4.26 (q, J = 7.1 Hz, 4H), 4.04 (s, 3H), 2.02 (s, 3H), 1.29 (t, J = 7.1 Hz, 6H) ^{13}C NMR (150 MHz, $CDCl_3$) ppm 179.8, 178.6, 165.6 (2C), 155.8, 140.2, 139.3, 128.4, 62.5 (2C), 61.3, 54.6, 14.1 (2C), 9.9; HRMS (ESI): Exact mass calcd for $C_{15}H_{17}O_7BrNa$ $[M+Na]^+$ 411.0055, found 411.0062.