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A UNIFIED APPROACH TO MITOMYCINOIDS:
APPLICATION OF A NOVEL ENE-LIKE REACTION

by

Dennis Paul Lovett

A THESIS SUBMITTED IN
PARTIAL FULFILLMENT OF THE
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DOCTOR OF PHILOSOPHY

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Houston, Texas
May, 1999
ABSTRACT

A UNIFIED APPROACH TO MITOMYCINOIDS: APPLICATION OF A NOVEL ENE-LIKE REACTION

by

Dennis Paul Lovett

Previously published syntheses of two mitomycins, mitomycin C (1) and FR900482 (2), display suitably functionalized eight-membered heterocycles as critical intermediates (3 and 4). A general approach to all mitomycinos may thus evolve from a benzazocenone of the type 5, which would require appropriate substituents on the aromatic ring as dictated by the various target molecules. The key to a unified strategy for the synthesis of mitomycinos is thus a concise, efficient route to structures of type 5. Unfortunately, the preparation of medium ring heterocycles of this type is generally troublesome. The research described herein has been directed toward the development of a practical solution to this problem.

\[ \text{PMP = } \rho\text{-methoxyphenyl} \]

We describe the application of our novel ene-like reaction for the construction of benzazocinone intermediates of type 8 as well as research towards various methods to
transform them into suitable intermediates of type 5 for the total synthesis of mitomycinoids.

\[ \text{MIP} = 2\text{-methoxyisopropyl} \]

We also developed an efficient method for construction of properly functionalized aldehydes (9 and 10) for our ene-like reaction, as well as the synthesis of an achiral diol which can be desymmetrized for use in an enantiocontrolled synthesis (11→12). The information accumulated from these experiments will, undoubtedly, be helpful in completion of the total synthesis of FR900482 and other mitomycinoids, which continues in our laboratories.

\[ \text{PMP} = \rho\text{-methoxyphenyl} \]
ACKNOWLEDGEMENTS

My graduate career, spanning 2 advisors and 3 continents, is undoubtedly the most unusual experience ever by a graduate student. I therefore have a great number of persons to thank. First, I would like to thank Prof. Tohru Fukuyama for his guidance during the first 3 years of my Ph.D studies. His drive and love of organic synthesis were an inspiration to me. Second, I cannot thank Prof. Marco Ciufolini enough for adopting me into the Ciufolini “family” after Prof. Fukuyama accepted a professorship at the University of Tokyo, for his optimism during times of frustrating chemical results and for providing the opportunity to live in France for 14 months.

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To my parents and relatives, for their support during my exceptionally long education, thank you for your patience.
Dedicated to my father
# TABLE OF CONTENTS

I. Glossary of Abbreviations
II. Introduction
III. Synthetic Background
IV. Discussion
   A. Exploratory work under supervision of T. Fukuyama
   B. Application of an ene-like reaction for the synthesis of mitomycinoids
   1. Model studies towards the formation of the critical benzazocinone
   2. Synthesis of complex aldehydes for the ene-like reaction
   3. Benzazocinone formation from complex aldehydes
   4. The chemistry of benzazocinones 214, 247, 250, and 254
V. Experimental Technical Notes
VI. Experimental Index
VII. Experimental Procedures
   A. Model compounds
   B. Synthesis of branched aldehyde for FR900482
   C. Progression toward the total synthesis of FR900482
VIII. Appendices
IX. References
GLOSSARY OF ABBREVIATIONS

Ac            acetyl
AcAc          acetylacetonate
Alloc         alloxy carbonyl
Bio-Nu        bionucleophile
Bn            benzyl
BOM           benzyl oxymethyl
Bz            benzyoyl
CAN           cemic ammonium nitrate
Cbz           benzyloxycarbonyl
CSA           camphorsulfonic acid
DBU           1,8-diazabicyclo[5.4.0]undec-7-ene
DCC           1,3-dicyclohexylcarbodiimide
DDQ           2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIAD          diisopropyl azodicarboxylate
DIBAL-H       diisobutylaluminum hydride
DMAP          4-(dimethylamino)pyridine
DMF           \[N,N\text{-dimethylformamide}\\)
DMS           dimethyl sulfide
DMSO          dimethyl sulfoxide
DMTS          dimethylthexylsilyl
DNA           deoxyribonucleic acid
DPPA          diphenyl phosphoryl azide
ee            enantiomeric excess
fod           6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato
HMBC          heteronuclear multiple bond correlation
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>HMBC</td>
<td>heteronuclear multiple bond correlation</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>LAH</td>
<td>lithium aluminum hydride</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>lithium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>3-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>MIP</td>
<td>2-methoxyisopropyl</td>
</tr>
<tr>
<td>MMTS</td>
<td>methyl methythiomethyl sulfoxide</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethyl</td>
</tr>
<tr>
<td>MoO$_2$•HMPA</td>
<td>(hexamethylphosphoramido)oxodiperoxomolybdenum</td>
</tr>
<tr>
<td>2-MP</td>
<td>2-methoxypropene</td>
</tr>
<tr>
<td>Ms</td>
<td>methanesulfonyl</td>
</tr>
<tr>
<td>NaNaph</td>
<td>sodium naphthalenide</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NMO</td>
<td>N-methylmorpholine-N-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>Nu</td>
<td>nucleophile</td>
</tr>
<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
</tr>
<tr>
<td>PDC</td>
<td>pyridinium dichromate</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>Piv</td>
<td>pivoy</td>
</tr>
<tr>
<td>PMP</td>
<td>4-methoxyphenyl</td>
</tr>
<tr>
<td>PPA</td>
<td>polyphosphoric acid</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium 4-toluenesulfonate</td>
</tr>
<tr>
<td>py</td>
<td>pyridine</td>
</tr>
<tr>
<td>SAM</td>
<td>S-adenosyl methionine</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Name</td>
</tr>
<tr>
<td>-------------</td>
<td>------------------------------------------------</td>
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<tr>
<td>TBDPS</td>
<td><em>tert</em>-butyldiphenylsilyl</td>
</tr>
<tr>
<td>TEA</td>
<td>triethylamine</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethylsulfonyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TIPS</td>
<td>triisopropylsilyl</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TPAP</td>
<td>tetrapropylammonium perruthenate</td>
</tr>
<tr>
<td>Trisyl</td>
<td>2,4,6-trisopropylbenzene sulfonyl</td>
</tr>
<tr>
<td>Troc</td>
<td>2,2,2-trichloroethoxycarbonyl</td>
</tr>
<tr>
<td>Ts</td>
<td>4-toluenesulfonyl</td>
</tr>
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INTRODUCTION

Mitomycins are a group of pharmacologically active natural products that can be divided into two families: their namesake, the mitomycins 1-13, 17, and FR900482 - type compounds, 14-16 (Figure 1). The first mitomycin to be reported, mitomycins A (1) and B (6), were isolated from chloroform extracts of the broth filtrate of the actinomycete *Streptomyces caespitosus* by Hata and co-workers at Kitasato Institute in 1956.\(^1\) Two years later Wakaki and co-workers at Kyowa Hakko reported the isolation of mitomycin C from the same fermentation broth but at a slightly higher pH,\(^2\) and in 1960 DeBoer, at the Upjohn Co., described the isolation of porfiromycin (4, N-methylmitomycin C) from a culture of *Streptomyces arbus.*\(^3\) There are over one dozen different mitomycins presently known and all show biological activity with the exception of mitiromycin (17), isolated by Lederle Laboratories in 1962.\(^4\)

<table>
<thead>
<tr>
<th>A-type mitomycin</th>
<th>B-type mitomycin</th>
<th>G-type mitomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>Y</td>
<td>X</td>
</tr>
<tr>
<td>2. C</td>
<td>NH₂</td>
<td>7. D</td>
</tr>
<tr>
<td>5. M</td>
<td>MeNH</td>
<td>10. L</td>
</tr>
</tbody>
</table>

14. FR900482 Z = CHO  
15. FR66979 Z = CH₂OH  
16. FK973  
17. mitiromycin

Figure 1
In 1987, scientists at Kyowa Hakko isolated and characterized two novel isomers of mitomycin A, isomitomycin A (18) and albolotomycin A (19), from \textit{S. caesipitosus} cultures used for the commercial production of mitomycins (Figure 2). Mitomycin A, isomitomycin A, and albolotomycin A exist in an equilibrium and interchange via Michael and retro-Michael reactions through a process appropriately termed the "Mitomycin Rearrangement". This rearrangement was the basis for a creative total synthesis of mitomycin C by Fukuyama and Yang.

![Figure 2](image)

Also in 1987, Imanaka and co-workers at Fujisawa Pharmaceutical Company isolated FR900482 (14) from a culture of \textit{Streptomyces sandaensis} No. 6897. The new substance existed as a mixture of 2 isomers, 14a and 14b, in a ratio of 2:1 (Figure 3), as ascertained by $^1$H and $^{13}$C NMR, as well as TLC behavior. The interconversion of 14a to 14b occurs rapidly and it is believed to proceed through an intermediate ketone 20. The ketone intermediate has never been isolated nor observed; however structures similar to 20 are popular synthetic targets for several approaches towards mitomycinoids.

![Figure 3](image)

Conversion of 14 to the triacetate, FK973 (16, 16a:16b = 1:8), allowed an X-ray diffractometric study that defined structure and absolute stereochemistry of the new antibiotic. Fujisawa scientists also discovered that \textit{S. sandaensis} No. 6897 produces a
reduced form of 14, FR66979 (15), which may also be derived synthetically from FR900482 by catalytic hydrogenation (Figure 4).  

![Chemical Structures]

Figure 4

The structural similarities between FR900482 / 66979 (14, 15) and the mitomycins, e.g., mitomycin C (2), are obvious, as are the major differences between them. Common features of the mitomycinoids include the aziridine and carbamoyloxymethyl side chain. In addition to the difference in the relative stereochemistry of the carbamoyl-oxymethyl side chain, the presence of a fully substituted benzoquinone in the mitomycins and the novel hydroxylamine hemiketal of FR900482 / 66979 constitute the sum of the structural differences between the two families.

Both the Fujisawa compounds and the mitomycins are believed to express their antitumor activity via a bioreductive mechanism that activates the molecules for cross-linking alkylation of double-stranded DNA. In the case of mitomycins, bioreductive activation seemingly produces a semiquinone intermediate, 21, which undergoes facile

![Chemical Reactions]

Figure 5
elimination of the angular methoxy function to give the indolic radical 22. Further reduction of this reactive intermediate yields hydroquinone 23, termed a mitosene (Figure 5).⁹

Mitosenes are fragile species and represent the putative active forms of mitomycins. Their cytotoxicity is believed to result from their ability to cross-link DNA. Expulsion of the carbamate side chain, facilitated by the electron rich indole nucleus, generates a powerful alkylation agent 24, which resembles a Mannich-Michael-type acceptor. A generic bionucleophile, such as DNA, can react as shown below and become alkylated to form the monoadduct 25. Mitomycins also contain a highly reactive aziridine functionality, which is further activated for nucleophilic ring opening by the electron rich indole unit. A second bionucleophile, e.g., another group located on the same DNA chain that participated in the initial alkylation event, may interact with the aziridine to give the dialkylated species 26 or 27 (Figure 6). This event could result in cross-linking of DNA, thus interrupting DNA replication.¹⁰

Figure 6

FR900482 and FK973 lack the quinone unit of the mitomycins; therefore, their metabolic activation must follow a different mechanistic pathway. Several theories¹¹ were proposed for this activation, including the surmise that FR66979 was the reductive activation product. However, a hypothesis originally formulated by Fukuyama has now
gained widespread acceptance. The Fukuyama mechanism envisions a two electron bioreductive cleavage of the N-O bond in the hydroxylamine hemiketal to form amino ketone 28. Transannular closure to the aminal 29, elimination of water and tautomerization would then give mitosene 30 (Figure 7).\textsuperscript{12} Extensive studies using L1210 cells have shown that, indeed, a mitosene-like intermediate appears to be involved in the activation of both FR900482 and FK973, thus enabling them to form DNA-DNA and DNA-protein cross-links.\textsuperscript{13} This was demonstrated through the isolation of bis-alkylation products of FR900482 and FK973 with DNA by Hopkins.\textsuperscript{14}

![Chemical Structures]

**Figure 7**

Mitomycin C has found use in the treatment of gastrointestinal cancers (prescribed under the tradename Mutamycin\textsuperscript{®} in the United States) but its high toxicity precludes its use as an antibiotic. FR900482 has been shown to be more potent (FK973 is three times as potent) as an antitumor agent but less toxic than mitomycin C.\textsuperscript{15} The reduced toxicity of 14 - 16 relative to mitomycins is most likely due to the absence of the quinoid nucleus. It is well established that quinones can disrupt oxidative phosphorylation, thus causing severe depletion of cellular ATP.\textsuperscript{16} Moreover, \textit{in vivo} reoxidation of hydroquinone metabolites of mitomycins by molecular oxygen generates peroxidic species (superoxide, hydroperoxide, etc.) that are sources of oxygen radicals. These can cause oxidative scission of single-strand DNA. The occurrence of such events inside a cell could lead to cell death. While this would be a desirable effect as far as tumor cells are concerned, peroxidic agents also
appear to be responsible for several of the undesired toxic side effects so common among cancer drugs. It is worth noting that FR900482 has been shown to be active against P388 cells that are mitomycin C and vincristine resistant.\textsuperscript{15}

Not surprisingly, both mitomycins and FR900482 / FR66979 appear to share a common biosynthetic origin. Experiments on the biosynthesis of mitomycin C\textsuperscript{17} and FR900482\textsuperscript{18} have identified 3-amino-5-hydroxybenzoic acid and D-glucosamine as precursors. Further studies to determine the primary precursors to 3-amino-5-hydroxybenzoic acid revealed that [4-\textsuperscript{13}C]-D-erythrose and [3-\textsuperscript{13}C]-pyruvic acid are incorporated into mitomycin C.\textsuperscript{19} Intact D-glucosamine has been shown to be incorporated as the right half of the molecule in both mitomycin C and FR900482.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure8.png}
\caption{Figure 8}
\end{figure}

The known stereochemistry of D-glucosamine also assisted in establishing the absolute stereochemistry of mitomycin C.\textsuperscript{20} The carbamate functionality is transferred from L-citrulline\textsuperscript{21} and the methyl group present in the angular methoxy functionality is provided by L-methionine (probably as SAM, Figure 8).\textsuperscript{22}
SYNTHETIC BACKGROUND

The potent antitumor activity and unique molecular structure of the mitomycinoids have resulted in a great deal of synthetic interest since the structural elucidation of mitomycin A in 1962. To date, there have been only three published total syntheses of mitomycin C, two of mitomycin K and three of FR900482. This section will outline briefly these syntheses as well as other significant developments towards mitomycinoids reported by other research groups. This overview underscores the inherent difficulties presented by the synthesis of these compounds and the persistent need for efficient new methods for their resolution.

MITOMYCIN C

As mentioned previously, mitomycin C is a very potent chemotherapeutic agent but is also very toxic. Hundreds of analogues have been prepared in an effort to increase activity and minimize toxicity; however no substantial success has yet been achieved. An efficient total synthesis would open avenues to analogues not available through manipulation of the natural products. This has enticed chemists to research diverse synthetic routes to mitomycins. It was soon discovered that such an objective was far more challenging than anticipated. The introduction of the angular methoxy function and its propensity to be eliminated, thus resulting in aromatization of the molecular core to an indole or an indoloquinone system, represented especially serious problems. Such difficulties were finally overcome by Kishi, who described the first synthesis of mitomycins A and C in 1977. This was followed ten years later by the Fukuyama synthesis of mitomycins A and C via isomitomycin A. More recently, Danishefsky reported the first synthesis of a mitomycin in the G series (mitomycin K), while the work of Jimenez has unveiled a conceptually novel avenue to these molecules. These landmark efforts are highlighted below.
**Kishi's total synthesis**

The overall strategy for this synthesis was to form the critical eight-membered ring (32) through the Michael addition of an amine into a benzoquinone and then transannular cyclization to form the 5,5 fused ring system of the mitomycins (Figure 9). The presence of an expressed quinone served to retard loss of the sensitive angular oxygen functionality in late intermediates. Recall that the quinoid form of mitomycins is considerably more stable than its reduced forms.

![Chemical structures](image)

**Figure 9**

Construction of the eight-membered ring is outlined in Scheme 1. Commercial dimethoxytoluene 33 was advanced to 35 in a conventional fashion. A five-step chain elongation afforded keto nitrile 36 through the opening of an epoxide with lithioacetanitrile, followed by Jones oxidation, hydroxymethylation with basic formaldehyde and acetate formation. It was not possible to form ketal 37 directly due to the loss of acetic acid from the side chain, therefore a five-step sequence via the thioketal was utilized for this transformation. Standard selenium chemistry provided the unsaturated nitrile 38. Sequential reduction of the nitrile with DIBAL-H and sodium borohydride yielded the alcohol, which was acetylated to give allylic acetate 39. Dihydroxylation with osmium tetroxide afforded a 1:1 mixture of chromatographically separable diastereomeric diols 40. Selective mesylation and base treatment gave epoxide 41. Manipulation of the epoxide into aziridine 43 was quite lengthy (seven steps) and necessitated a three-step protection and a two-step deblocking later in the synthesis. The epoxide was opened with lithium azide to form an azidodiol, which was dimesylated. Compound 42 was obtained upon selective displacement of the primary mesylate with dibenzylamine. Staudiger-type
reduction of the azide, base treatment and reduction afforded an aziridine, which required \( N \)-protection to prevent its Michael-type addition to the quinone resulting upon the subsequent oxidation of the aromatic unit. The sensitivity of the aziridine unit to many \( N \)-deprotection conditions rendered various nitrogen blocking groups entirely unsuitable, and required the development of an unusual protocol. Thus, Michael addition of the aziridine to acrolein, carbonyl reduction with borane and \( O \)-acetylation gave the 3-acetoxypropylaziridine derivative 44.

Scheme 1

Catalytic hydrogenation removed all five benzyl groups and upon air oxidation of the resulting hydroquinone to the benzoquinone, the Michael addition of the primary amine formed the eight-membered ring 45. The desired transannular cyclization occurred upon treatment with fluoroboric acid. The total synthesis of 1 was completed by formation of the carbamate, conversion of the methoxyquinone to an aminooquinone and protecting group
removal (Scheme 2). While this was truly a landmark synthesis, the overall yield of 0.2\% over 46 steps left room for improvement.

![Scheme 2](image)

**Fukuyama's first total synthesis**\(^{62}\)

The second total synthesis of mitomycin C was inspired by the discovery of two novel isomers of mitomycin A, isomitomycin A (18) and albotomitomycin A (19), by scientists at the Kyowa Hakko Pharmaceutical Company. Because mitomycin A, isomitomycin A, and albotomitomycin A exist in an equilibrium and interconvert via Michael additions through the "Mitomycin Rearrangement" (Scheme 2), construction of isomitomycin or albotomitomycin would ultimately allow the synthesis of mitomycin A and therefore mitomycin C. This method proved to be a vast improvement over Kishi's total synthesis in both yield (6\% vs. 0.2\%) and number of steps required (30 vs 46).

The Fukuyama synthesis of mitomycin C relies on 2 critical reactions. The first is a conjugate addition of a furan into a properly substituted chalcone and the second is an intramolecular azide-olefin cyclization to form the tetracyclic core of isomitomycin (Figure 10).

![Figure 10](image)
The synthesis of chalcone 47 (Scheme 3) was carried out by standard synthetic methods in 12 steps and 64 % overall yield from 2,6-dimethoxy toluene. Formylation of 33, followed by Dakin oxidation and basic methanolysis provided phenol 34. This procedure afforded a slightly improved yield (98 % vs. 95 %) compared to Kishi's synthesis. A three-step sequence consisting of acetylation, nitration with fuming nitric acid and hydrolysis of the acetate gave nitro phenol 51. Catalytic hydrogenation of the nitro group to an amine was followed by conversion to azido phenol 52 via the diazonium ion. Lederer-Manasse hydroxymethylation with formaldehyde and aqueous potassium hydroxide was followed by selective benzylation of the phenol and PCC oxidation to afford benzaldehyde 53. Aldol reaction with acetophenone provided chalcone 47 as a highly crystalline material.

Scheme 3

Construction of the ethylthiosiloxoy furan was accomplished in three steps from furfural (54) (Scheme 4). Reaction of furfural with singlet oxygen (rose bengal, hν) afforded γ-hydroxy-α, β-unsaturated lactone 55. Treatment with ethanethiol and catalytic HCl gave ethylthio derivative 56. Silylation with trimethylsilyl chloride and triethylamine afforded 48 in 77 % yield after vacuum distillation.

Scheme 4
Condensation of the chalcone with the furan proceeded stereoselectively to give azido butenolide 49, which underwent facile thermal azide-olefin cyclization. Tetracyclic aziridine 50 thus emerged. Aminolysis of the lactone with 3-(3,4-dimethoxybenzyloxy)propylamine and methyl ether formation of the resulting tertiary alcohol provided methoxy lactam 57 (Scheme 5).

![Chemical structure images]

**Scheme 5**

Sodium borohydride reduction of the ketone, conversion of the resulting alcohol into the chloride then heating in the presence of lithium bromide and DBU resulted in formation of styrene 58. Ozonolysis and borohydride reduction expressed the hydroxymethyl side chain, which was derivatized to the required carbamate 59 by sequential treatment with phenyl chloroformate and ammonia. The veratryl ether protecting group was then removed under mild conditions by DDQ oxidation. A two step, one pot reduction of the lactam with DIBAL-H to form pentacyclic aminal 60 was followed by sodium cyanoborohydride reduction of the tetrahydroxazine to give N-(3-hydroxypropyl)-pyrrolidine 61. This reduction is likely to proceed through an iminium intermediate produced through nitrogen assisted loss of one of the neighboring oxygen functionalities. The regioselectivity of this reaction is probably due to the fact that loss of the angular methoxy group is strongly disfavored, since it occupies a bridgehead position and its departure would result in an anti-Bredt structure. Hydrogenolytic debenzylation and DDQ oxidation furnished the expected p-quinone. The total synthesis of isomitomycin A was
achieved by removal of the last protecting group using a two step protocol. A Swern oxidation of the alcohol gave aldehyde 62 which when treated with a 2:1 mixture of acetic acid and pyrrolidine underwent a retro-Michael reaction of the intermediate enamine to give isomitomycin A (18, Scheme 6).

Scheme 6

Isomitomycin A was converted to mitomycin A (1) via the “Mitomycin Rearrangement” by treatment of 18 with 1 eq. of aluminum triisopropoxide in methanol. Stirring in methanolic ammonia completed the total synthesis of mitomycin C (2) (Scheme 7).

Scheme 7

Fukuyama’s second total synthesis

While the first Fukuyama synthesis represented a significant improvement over Kishi’s synthesis, an even better synthesis still utilizing the “Mitomycin Rearrangement” was unveiled less than two years later. Various modifications to the previous strategy as well as the discovery that isomitomycin A can be directly transformed into mitomycin C reduced the number of linear steps to 26 and improved the yield to 10% overall.
The first change in strategy was the preservation of the silyl enol ether formed in the conjugate addition. Recall that in the previous approach, this intermediate had been hydrolyzed to a ketone. Thus, reaction of 47 and 48 as before, but without an acidic workup, gave 62, which again was converted to tetracyclic lactone 63 by refluxing in toluene (Scheme 8).

![Scheme 8](image)

Reduction of the lactone with DIBAL-H and acetylation of the hemiacetal afforded 64. Treatment with catalytic ruthenium dioxide hydrate and sodium periodate cleaved the silyl enol ether to give the aldehyde and oxidized the sulfide to a sulfone. Reduction of the aldehyde by NaBH₄ afforded alcohol 65. A three-step procedure was used to accomplish two goals, formation of the carbamate and pyrrolidine ring. Thus, treatment of the 65 with trichloroacetyl isocyanate was followed by exposure to methanolic ammonia, resulting in formation of the carbamate. Excess ammonia also deacetylated the acetoxy acetal and caused the subsequent elimination of ethanesulfonate to form a keto-aldehyde. The latter reacted further with ammonia to give a cyclic aminal, which upon reduction with NaBH₄ gave hydroxypyrrolidine 66. Acidic methanol catalyzed the exchange of the hydroxyl group for a methoxy unit (67) most likely via a bridgehead iminium or imine intermediate. Hydrogenolytic removal of the benzyl ether and oxidation to the benzoquinone with DDQ furnished isomitomycin A (18). Due to the favorable equilibrium between mitomycin C and isomitomycin C, simple treatment of 18 with methanolic ammonia completed the total synthesis of mitomycin C (2) without the need for a prior isomerization step (Scheme 9).
MITOMYCIN K

In addition to the three previous syntheses of mitomycins A and C, two syntheses of a type G mitomycin, mitomycin K (12) have been published. The G-type mitomycins differ from the A type compounds by the presence of an exocyclic methylene group in lieu of a carbamoyloxy methyl chain. The electrophilicity of the resultant vinyl quinone moiety, even in the absence of bioreduction, and its ability to act as a Michael acceptor impart a great deal of reactivity, and therefore of instability, to these molecules. A total synthesis remains nevertheless an important goal because of the potential of G-type antibiotics in bioactivation and mechanistic studies.

A total synthesis of mitomycin K in 11 steps from diene 68 and 0.3 % overall yield was reported by Danishefsky in 1992. The key step was a hetero-Diels-Alder reaction of an oxygenated diene with a nitroso dienophile, obtained in turn by photochemical reduction of an aromatic nitro group. Four years later, Jimenez reported an improved synthesis of mitomycin K requiring only thirteen steps from commercially available 2,5-dimethylanisole and proceeding in an overall 1.4 % yield. The synthesis hinged on the oxidation of the C9-
9α double bond of an indolic intermediate to give substance 71, which bears great similarity the Danishefsky compound 69 (Figure 11).

Danishefsky’s total synthesis

The synthesis begins with the addition of butadienyl anion 73 to benzaldehyde 72, which was synthesized by using methodology. Irradiation of 68 induced a well-known intramolecular redox process that oxidized the benzylic carbinol to a ketone and reduced the nitro group to nitroso. This event precipitated a hetero-Diels-Alder reaction and rearrangement to yield 69. Oxidation of the aminal to the amide and 1,3 dipolar

Scheme 10
cycloaddition of the olefin with azidomethyl phenyl sulfide gave tetracyclic compound 74. Conversion of the amide to amine 75 was accomplished via a three step procedure consisting of reduction to the aminal, derivatization as a thiocarbonyl ester and removal thereof with tributyltin hydride. Photolysis of the triazoline and Raney nickel desulfurization provided N-methyl aziridine 76. Addition of trimethylsilylmethyl lithium to the ketone and oxidation with silver (II) picolinate furnished benzoquinone 77. Peterson elimination affected by PPTS completed the total synthesis (Scheme 10).

Jimenez' total synthesis\textsuperscript{26}

Construction of starting material 70 from 2,5-dimethylanisole required only eight steps and gave an 11 % overall yield.\textsuperscript{27} The introduction of the C9a methoxy group by treatment of pyrroloindole 70 with (MoO\textsubscript{3}·HMPA) resulted in an approximately 2:1 ratio of 71a to 71b. After separation, 71a was subjected to a Staudiger reduction to form the aziridine, which was N-methylated to give 78. Addition of trimethylsilylmethyl lithium to the ketone as earlier described by Danishefsky provided compound 79. Treatment with pyridinium chlorochromate (PCC) oxidatively cleaved the silyl groups and promoted the Peterson olefination to yield mitomycin K, 12 (Scheme 11).

![Scheme 11](image-url)
FR900482

The vast amount of research conducted towards the synthesis of mitomycins allowed Fukuyama to report the total synthesis of (±)-FR900482 in 1992, less than five years after its discovery. Three years later, Danishefsky published a more concise total synthesis that utilized a hetero-Diels-Alder reaction and an intramolecular Heck reaction as key steps. The sole enantioselective route to this antibiotic to date is credited to Terashima, who in 1996 reported a total synthesis of (+)-FR900482 relying on the coupling of an aromatic amine and a homochiral fragment derived from L-diethyltartrate.

Fukuyama’s total synthesis of (±)-FR900482.

In 1992, Fukuyama and co-workers reported the first total synthesis of (±)-FR900482. The synthesis required 43 steps and gave a 1% overall yield. As with the Fukuyama mitomycin C synthesis, the use of an aldol addition of an α-silyloxyfurans into chalcones is the foundation of this approach (Figure 12).

![Figure 12]

Catalytic hydrogenation of known aniline 83, azide formation and protection of the phenol as a MOM ether afforded 84. Benzyl bromination with NBS and benzoyl peroxide followed by displacement of the benzyl bromide with p-methoxyphenol provided protected benzyl alcohol 85. After ether exchange, reduction of the ester with DIBAL-H and oxidation of the alcohol with PCC gave benzoaldehyde 80 required for the aldol addition. Treatment of 80 and α-silyloxyfuran 81 with catalytic tin tetrachloride yielded 82 (Scheme 12).
The olefinic unit in the reactive butenolide 82 was protected through Michael addition of thiophenol. A three-step sequence involving acetylation of the benzylc alcohol, reductive removal of acetate and azide reduction with zinc and acetic acid provided aniline 86. The creation of the desired eight-membered ring (87) was realized starting with reduction of the lactone with DIBAL-H to the lactol. This intermediate isomerized easily by ring-chain tautomerism and the resulting free aldehyde condensed with the aromatic amine to furnish an imine. This imine was further reduced with NaCNBH₄ to obtain heterocycle 87. Treatment with acetic anhydride resulted in protection of the aniline and the alcohol. Oxidation of the thiophenyl moiety with m-CPBA followed by heating afforded olefin 88. Basic hydrolysis of the acetate, epoxidation of the olefin with m-CPBA and then Swern oxidation of the alcohol provided compound 89. Addition of the hydroxymethyl functionality, reduction of the ketone, selective protection of the primary alcohol as a tert-butyldimethylsilyl ether and deprotection of the acetamide with DIBAL-H produced 90. N-oxidation with m-CPBA followed by treatment with acetic anhydride and a Swern oxidation delivered intermediate 91, which was ready for transformation into the hydroxylamine hemiketal. Deacetylation with hydrazine resulted in transannular cyclization to the [3.3.1] bicyclic system of FR900482. Removal of the silyl protecting group with TBAF, protection of the diol as an acetonide, and opening of the epoxide with NaN₃, gave azide 92 (Scheme 13).
Scheme 13

The resulting alcohol was protected as a mesylate and the acetonide protecting group was changed to a carbonate. CAN oxidation removed the p-methoxyphenol protecting group to give benzyl alcohol 93. Oxidation and protection of the alcohol as the dimethylacetal followed. Staudiger reduction of the azide resulted in the formation of aziridine 94. Removal of the benzyl ether via catalytic hydrogenation and perchloric acid hydrolysis of the acetal set the stage for the final reaction, ammonolysis of the carbonate into the carbamate, which completed the total synthesis of FR900482 (14, Scheme 14).

Scheme 14

Danishefsky’s total synthesis of (±)-FR900482

Danishefsky and Schkeryantz reported the second total synthesis of (±)-FR900482 in 1995. The key steps of this synthesis are a hetero-Diels-Alder reaction of an arylnitroso dienophile and an intramolecular Heck reaction to form the bicyclic core of FR900482.
This synthesis, while an improvement of Fukuyama's, was still lengthy (34 steps) and provided only a 4% yield overall.

Standard synthetic manipulations produced iodobenzene 93 in 7 steps from methyl vanillin. Reduction of the nitro group to an amine and reoxidation with Oxone® (potassium peroxymonosulfate) afforded the dienophilic nitroso benzene 94. Cycloaddition of 94 with diene 95, obtained from 1-methoxymethylbutadiene and paraformaldehyde, proceeded regioselectively, and acetylation of the resulting alcohol gave acetate 96. Dihydroxylation and treatment with triflic anhydride furnished monotriflate alcohol 97. Nucleophilic displacement of the triflate with tetrabutylammonium azide followed by triflation of the remaining alcohol gave 98. Formation of the required aziridine occurred upon reaction of 98 with triphenyl phosphine. Protection delivered carbamoyl aziridine 99 (Scheme 15, R = CO₂Me).

![Scheme 15](image)

In preparation for a Heck reaction, intermediate 99 was processed through hydrolysis of the acetate, Swern oxidation and Wittig olefination. The emerging olefin 100 cyclized smoothly under standard Heck coupling conditions, thus providing the [3.3.1] bicyclic core of FR900482 101 (Scheme 16, R = CO₂Me).
Elaboration of 101 continued with the formation of spiroepoxide 102 via Mitsunobu cyclization of a diol. Reductive cleavage of the epoxide with Sml₂ and hydrogenolytic debenzylation produced a phenolic alcohol that was protected as the bis-triisopropylsilyl ether. Treatment with DIBAL-H effected reduction of the methyl ester and the removal of the carbamoyl protecting group of the aziridine to afford 103. Selective reprotection of the aziridine with $N$-((methoxycarbonyl)oxy)succinimide and oxidation of the benzyl alcohol provided benzaldehyde 104. After removal of the silyl protecting groups with TBAF, formation of a dicarbonate, and deprotection of the methoxymethyl ether, compound 105 was poised for the final steps of the synthesis. These steps consisted of ammonolysis of the carbonates to give the free phenol and carbamate side chain and finally the removal of the methyl carbamate from the aziridine to give FR900482, 14 (Scheme 17, R = CO₂Me).
Terashima's total synthesis of (+)-FR900482\textsuperscript{31}

Even though the total synthesis of FR900482 by Terashima and co-workers is eight steps longer than Danishefsky's and gave an overall yield of 1.6 \%, it is the only enantioselective synthesis published to date. The general strategy was to combine aromatic amine 107 (15 steps from diacid 106) and homochiral fragment 109 (15 steps from diethyl tartrate 108) to give 110 (Scheme 18). Further manipulation of this intermediate into a dialdehyde allows the use of an aldol reaction to form the critical eight-membered ring intermediate.

Scheme 18

The steps leading to the aldehyde are as follows. Zinc and acetic acid treatment of 110 released both the trichloroethyl carbamate and acetonide protecting groups. The amino alcohol was chemoselectively \textit{N}-tosylated and then \textit{O}-mesylated in preparation for \textit{N}-tosylaziridine formation by treatment with sodium hydride to provide \textit{N}-tosyl aziridine 111. Removal of the silyl protecting groups and oxidation afforded the requisite dialdehyde (112). The aldol reaction was effected by treatment with LiHMDS and the resulting \textit{\beta}-hydroxy aldehyde was reduced to the diol \textit{in situ} with \textit{NaBH}_4 to avoid elimination of water. Chemoselective silylation of the primary alcohol and Dess-Martin oxidation furnished ketone 113. Removal of the silyl protecting group and treatment with DBU isomerized the side chain to the desired stereochemistry prior to reduction of the
ketone to alcohol 114 (Scheme 19). This isomerization is noteworthy because it illustrates that the relative stereochemistry of aziridine and side chain units corresponds to the thermodynamic configuration, and that once a stereocenter (in this case the aziridine) is fixed in this benzazocinone ring system, the correct relative stereochemistry of the other stereocenters may be controlled.

Scheme 19

A seven-step sequence was used to install the hydroxylamine hemiketal moiety. The primary alcohol was silylated, while the aniline nitrogen was deblocked, oxidized to the hydroxylamine with m-CPBA and protected as the O-acetyl hydroxylamine (115). Dess-Martin oxidation, silyl protecting group removal and treatment with potassium carbonate in methanol furnished the tetracyclic core of FR900482, 116 (Scheme 20).

Scheme 20

Formation of the carbamate side chain was carried out using a two step procedure consisting of sequential treatment with trichloromethyl chloroformate and ammonia. Acetylation of the resultant hemiketal provided 117. Removal of tosyl and benzyloxy-
methyl protecting groups gave the O-acetyl derivative of FR66979, 118. Swern oxidation and removal of the acetate completed the synthesis of FR900482, 14 (Scheme 21).

Other significant approaches

Since its structural elucidation was first reported, FR900482 has prompted many approaches to the synthesis of its complex framework. Possible routes, which have yet to result in a total synthesis to date, have been disclosed by Williams, Rapoport, Dmitrienko, Martin and Sulikowski. Of particular interest are the Martin and Sulikowski approaches and therefore they deserve brief reviews.

The key synthetic maneuver in the Martin approach is a ring closing metathesis reaction based on the pioneering work of Grubbs. When diene 119 was treated with a molybdenum carbene catalyst, azocene 120 was obtained in a 77% yield (Scheme 22). The use of a more fully functionalized olefin could form Fukuyama intermediate 88, thereby resulting in a formal total synthesis.

Sulikowski's approach is based on enantioselective carbene insertion into a C-H bond. Modest levels of absolute stereocontrol were achieved by the use of a Pfaltz-Evans-type catalyst (121→122, ca. 15% ee). Also of special note is the use of a Dmitrienko oxidative rearrangement of aminal 123 with dimethyl dioxirane, thus eliminating the use of
protection / deprotection schemes found in the Fukuyama and Terashima syntheses (Scheme 23).

Scheme 23
DISCUSSION

A. Exploratory work under supervision of T. Fukuyama

Critical synthetic intermediates in Kishi’s synthesis of mitomycin C (45) and in Fukuyama’s (91) and Terashima’s (113) syntheses of FR900482 display a suitably functionalized benzazocinone unit. A general approach to all mitomycins may thus evolve from a benzazocenone of the type 125, which would require appropriate substituents on the aromatic ring as dictated by the various target molecules. A regioslective aldol condensation with formaldehyde could install a hydroxymethyl unit at the benzylic position, thus permitting the ultimate creation of the carbamoyloxymethyl side chain. Suitable manipulations of the olefin would permit introduction of the aziridine (Figure 13). The key to a unified strategy for the synthesis of mitomycins is thus a concise, efficient route to structures 125. Unfortunately, the preparation of medium ring heterocycles of this type is generally troublesome. The research described herein has been directed toward the development of a practical solution to this problem.

Figure 13

Overall, ten major (and several minor) strategies for benzazocinone formation were explored during my tenure in the Fukuyama group. The use of simple model compounds for these studies held the potential to give misleading information about the applicability of the various reactions with complex substrates that would be used in the context of a total
synthesis. Accordingly, all exploratory work was carried out with intermediates carrying a full complement of substituents on the aromatic ring and a significant concentration of functionality on the aliphatic portions. This research focused on mitomycins and it thus involved studies on penta- or hexasubstituted aromatic compounds. In each case, the construction of these substrates required considerable effort.

Figure 14 illustrates the range of synthetic strategies explored. Two of these routes relied on a Michael addition of an enolate to a benzoquinone (a) or amine to a benzoquinone monoketal (c). Route b involved intramolecular cyclopropanation of a derivative of the benzoquinone used in route a. Four routes, d, e, f, and g, envisioned various modes of epoxide opening reactions for ring closure. Finally, approaches resting on intramolecular Evans aldol reaction (h), a combination Evans / Heck strategy (i), and a Mitsunobu / Claisen protocol (j), were investigated.
Route a was based on a double Michael addition an \(\omega\)-amino-\(\beta\)-keto-ester to a benzoquinone. The synthesis of amine acetal 132 (Scheme 24) was fairly straightforward but lengthy. Addition of vinyl magnesium bromide to freshly distilled benzaldehyde gave alcohol 126. Mercuric acetate-promoted ether exchange and thermal Claisen rearrangement afforded styrene aldehyde 127. Reduction with sodium borohydride and activation of the alcohol as a mesylate gave 128. Displacement of the mesylate with benzylamine and then protection as the benzylcarbamate provided 129, which was ozonolyzed to the aldehyde and subsequently protected as the dimethylacetal 131. Removal of the Cbz protecting group by catalytic hydrogenation furnished benzylamine 132.

![Scheme 24](image)

Phenol 34 was oxidized to benzoquinone 133 with CAN. Michael addition of amine 132 to the benzoquinone by the method of Rapoport\(^\text{38}\), in which the reaction is run under an oxygen atmosphere to reoxidize the initial aromatic addition product, furnished benzoquinone 134. Acidic hydrolysis of the acetal did not yield the desired aldehyde, but it gave instead vinyl ether 135 (Scheme 25). This product may have formed through addition of the OH group of the enol form of the aldehyde to the quinone, followed by air oxidation of the aromatic intermediate. Alternatively, a hemiacetal form of the aldehyde

![Scheme 25](image)
might have added to the quinone, and the resulting acetal could have suffered acid-promoted elimination to a vinyl ether.

A slight modification was needed to suppress this unfortunate reactivity. Reduction of benzoquinone 134 to the hydroquinone and in situ protection as the diacetate produced a mixture of two products, the benzylamine 136 and the acetamide 137 (Scheme 26).

![Scheme 26](image)

Loss of the N-benzyl group was not of great concern to us at the time. The two compounds were easily separable and both were carried forward under identical reaction conditions. Nonetheless, a more direct avenue to benzyl-type substrates was devised as follows. Aldehyde 130 was condensed with the enolate of ethyl acetate. Deprotection of the Cbz group afforded the β-hydroxy-ester (139, Scheme 27).

![Scheme 27](image)

Conjugate addition of 139 to 133 under Rapoport conditions followed by oxidation with PCC afforded 140. This substance proved to be resistant to all attempts at cyclization with a variety of reagents (Scheme 28).

![Scheme 28](image)
This result was not completely unexpected because the benzylamino group in 140 strongly diminishes the electrophilic reactivity of the π bond destined to accept the enolate of the β-keto-ester. It seemed plausible that replacement of the N-benzyl unit with an electron-withdrawing group, such as a carbonyl, would favor the final cyclization step. Indeed, hydrolysis of acetal 137 followed by ethyl diazoacetate addition provided β-keto-ester 142. Exposure to sodium methoxide under an oxygen atmosphere induced removal of the phenolic acetates and oxidation of the hydroquinone to the benzoquinone. Quite unlike 140, acetamide substrate 142 cyclized rapidly to the desired eight-membered ring 144 (Scheme 29).

Scheme 29

Regrettably, the synthesis of 142 was inefficient and could not be improved. These difficulties induced us to explore the use of a diazo derivative of β-keto-ester 140 in route b. Treatment of the β-keto-ester with tosyl azide resulted in diazo transfer to yield compound 145. Several attempts at copper catalyzed cyclopropanation produced none of the desired 146 (Scheme 30).

Scheme 30

Route c was reminiscent of the Kishi total synthesis. The general idea behind this approach was the addition of protected propargyl alcohol 148 to ary lacetaldehyde 147. Ring closure would be effected by an intramolecular Michael addition of a primary amine
into a benzoquinone monoketal. The desired benzazocene 152 would be formed upon aromatization via elimination of methanol (Figure 15).

![Reaction pathway diagram](image)

**Figure 15**

Allyl benzene 153 was synthesized from phenol 43 by allyl ether formation and Claisen rearrangement. Mesylation and ozonolysis provided aldehyde 147, which was coupled with lithiated propargyl tetrahydropyranyl ether to furnish alcohol 149. Protection of the newly formed alcohol as the TBS ether, removal of the THP ether and partial reduction of the alkyne under Lindlar conditions yielded allylic alcohol 152. A Mitsunobu reaction utilizing DPPA substituted the alcohol with an azide, which was reduced to the amine (150) with zinc and acetic acid (Scheme 31).

![Scheme 31](image)

**Scheme 31**

Preparation of the benzoquinone monoketal proceeded by basic hydrolysis of the mesylate and oxidation with [bis(trifluoroacetoxy)iodo]benzene and methanol to afford 151. Unfortunately, it was not possible to affect cyclization of 151 to 152 by either heating or treatment with TEA (Scheme 32).
The oxygen functionality (alcohol or ketone) present in the critical benzazocene could be introduced directly during eight-membered ring formation through the agency of an intramolecular epoxide opening reaction. Study of routes d, e, f, and g served to address this hypothesis. The new approach offered the additional benefit that utilization of an asymmetric epoxidation protocol for the preparation of the substrates would result in an enantiocontrolled synthesis.

Work by Ugura on use of methyl methylthiomethyl sulfoxide (MMTS) as a formyl dianion equivalent prompted us to explore its use for closure of the eight-membered ring (Route d, Scheme 33). Sulfonamide 156 was synthesized in three steps (silyl protection, hydrogenation and treatment with phenylsulfonyl chloride) from commercial 2-nitrobenzyl alcohol. Mitsunobu reaction with allyl alcohol was followed by TBAF removal of the silyl group to afford olefin alcohol 157. Transformation of the benzyl alcohol into a bromide and epoxidation provided the substrate for the Ugura reaction (159). Disappointingly, this step afforded complex mixtures of products, causing us to abandon this strategy.

Route e and f were based on epoxide opening reactions, wherein the aromatic ring acts as the nucleophile. Both routes began with the same starting material, nitro phenol 51.
Preparation of the substrate for route e involved protection of the phenol as the base resistant methoxymethyl ether (161). The substrate for route f was simply protected as the dimethylthexylsilyl ether (163). Nitro groups on both compounds were reduced by catalytic hydrogenation and then 162 was prepared by alkylation with 1-mesylxy-4-pentene, while the aniline derived from 163 was N-mesyalted (164, Scheme 34).

![Scheme 34](image)

We now needed to advance 162 to bromoepoxide 166. Halogen-metal exchange, e.g., with t-BuLi, would produce an organometallic intermediate that was expected to cyclize via nucleophilic epoxide opening. This step was expected to favor attack at the less hindered primary position of the oxirane ring, in accord with well documented principles of epoxide reactivity. The amine was thus protected as the methyl carbamate and the olefin was epoxidized. Aromatic ring bromination to 166 failed to produce any of the desired 166 under a variety of conditions, including treatment with bromine or with pyridinium bromide perbromide (Scheme 35).

![Scheme 35](image)

A different approach to ring closure involved a Lewis acid catalyzed epoxide opening as shown in Scheme 35. It was anticipated that significant activation had to be provided to the epoxide unit to promote interception by the feeably nucleophilic aromatic
ring. This could be achieved by the use of strongly oxophilic Lewis acids. In contrast to ordinary nucleophilic processes (vide supra), activation of an epoxide with a strong Lewis acid tends to favor attack at the more substituted carbon atom of an oxirane ring. This is probably due to accumulation of the positive charge created by the Lewis acid on the carbon atom better able to sustain positive character. Consequently, the reaction was set up in such a way that the primary carbon of the epoxide and the departing oxygen atom would emerge as the hydroxymethyl side chain.

A Mitsunobu reaction between 5-hexen-1-ol and N-(methylsulfonyl)-aniline 164 and epoxidation of the resulting olefin provided 168. TBAF treatment deprotected the silyl ether and gave phenol 169. Attempts at cyclization, e.g., by treatment with trimethyl aluminum in toluene resulted in destruction of the starting material (Scheme 36).

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Scheme 36
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The final epoxide opening strategy (Route g) was inspired by earlier work carried out in the Fukuyama group by Martin Linsell. Acetylation, nitration, reduction and N-acetylation of phenol 34 gave compound 171. Benzylation of the acetamide and hydrolysis of the acetate furnished phenol 172. Allylation and thermal Claisen rearrangement gave 164. This was followed by benzyl ether formation and epoxidation with m-CPBA to provide 174. Deprotonation of the amide with LDA gave benzazocinone 175 (Scheme 37). Conversion of this compound into more advanced intermediates was hindered by the inability to remove the benzyl protecting group from the amine. Many other protecting groups besides benzyl (carbamates, methoxymethyl and 3-acetoxy propyl) also fared poorly. Work on this route was thus suspended. The reasons for the resistance of 175 to deprotection remain unclear at this time.
Scheme 37

At this stage of our research, we turned our attention to the application of a different class of asymmetric reactions for the synthesis of mitomycins. An enantioselective intramolecular aldol reaction seemed to hold promise for eight-membered ring closure (Route h). Enantiocontrol could be secured if substituent $X_c$ on 176-177 were a chiral auxiliary such as an Evans oxazolidinone or an Oppolzer camphor-derived sulfonamide (Figure 16).

Figure 16

An even more interesting alternative envisioned a sequence commencing with enantioselective alkylation of Evans or Oppolzer enolates (178), followed by formation of acid chloride 179 and culminating with an intramolecular Heck carbonylation (Route i) as a means to create the key benzazocenone 180 (Figure 17).

Figure 17
Against our better judgment, but for expedience, a simple model study was devised to test these ideas. Arylacetic acids displaying variable substitution on the aromatic ring formed the Evans derivative without incident. However, it was found that the behavior of Evans complexes under aldolization conditions was strongly influenced by the nature of the substituents present on the benzene nucleus. Derivatives of aryl acetic acid lacking ortho substituents or containing only one ortho alkyl ether or sulfonyle ester reacted with different aldehydes under a variety of conditions commonly used in Evans aldol reactions to form aldol products in only 23-30 % yield. The majority of the starting material failed to react and was recovered untouched. Extensive D$_2$O quenching experiments revealed that the problem was caused by the failure of Evans derivatives of substituted arylacetic acids to enolize efficiently, seemingly due to severe nonbonding interactions exerted within the enolate by the aryl ortho substituents. By contrast, no evidence was found of unfavorable steric effects during the aldol step proper. Indeed, when Y was a nitro group, and X was hydrogen (Figure 18) the reaction yield increased to 40-50 %, most likely due to the enhanced acidity of the benzylic proton. However, if the substrate had two ortho substituents, as would be required for the synthesis of all mitomycins, the steric congestion present in the molecule completely suppressed enolization and, consequently, the aldol reaction.

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>Yield</th>
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<tr>
<td>H</td>
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<td>23 %</td>
</tr>
<tr>
<td>OMs</td>
<td>H</td>
<td>30%</td>
</tr>
<tr>
<td>H</td>
<td>NO$_2$</td>
<td>40-50 %</td>
</tr>
<tr>
<td>OBn</td>
<td>NO$_2$</td>
<td>no enolate formed</td>
</tr>
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</table>

Figure 18
We decided not to explore the use of Oppolzer auxiliaries in this process, because our conclusion that the limitation of the reaction lies in the inability of the arylacetic substrates to enolize efficiently, but not in the nature of the auxiliary, rendered our chances for success rather slim.

The foregoing complications also ruled out the enantiocontrolled alkylation of the enolate of 178 in preparation for an intramolecular Heck carbonylation reaction. Nonetheless, this approach held considerable appeal. We decided to explore a variant of this reaction that would furnish an achiral azocenone, later to be further elaborated in a stereocontrolled manner, perhaps by the use of the Terashima isomerization procedure. The synthesis of acid chloride 183 required ten steps from the known phenol 153. Benzylolation of the phenol, ozonolytic cleavage of the olefin, oxidation of the aldehyde to the acid and methyl ester formation with diazomethane gave 181. Nitration, reduction to the amine and treatment with mesyl chloride afforded N-mesylaniline 182. Mitsunobu coupling with allyl alcohol and conversion of the methyl ester into the acid chloride (183) in two steps gave the substrate for the Heck reaction. Under traditional Heck reaction conditions the desired benzazocenone was not formed, but instead, lactone 185 was obtained (Scheme 38).

The final route explored during this cycle of my research was a Mitsunobu / Claisen approach (Route 4). The basis of this strategy was to utilize a Mitsunobu reaction to
alkylate the known N-sulfonyl aniline 164. After protecting group manipulation, the substrate would be subjected to a second Mitsunobu reaction to form a meta-cyclophane (188). Claisen rearrangement would then furnish the desired eight-membered ring (189, Figure 19).

![Chemical structures](image)

**Figure 19**

Construction of the allylic acetate (186) began by the acid catalyzed hydration of dihydropyran (190) to give lactol 191. A Wittig reaction and protection with dihydropyran furnished THP protected unsaturated ester 192. A chemoselective reduction of the ester with DIBAL-H was followed by acetylation of the newly formed alcohol and removal of the THP ether to provided 186 (Scheme 39).

![Chemical reactions](image)

**Scheme 39**

N-mesylaniline 164 condensed normally with alcohol 186 under standard Mitsunobu conditions to give alkylated product 193. Removal of both the silyl and acetate protecting groups furnished phenol alcohol 187. This material was successfully cyclized to the metacyclophane (188) under Mitsunobu conditions in a dilute solution (0.046M), but unfortunately in only 30% yield. Even though Mitsunobu coupling of allylic alcohols may form materials arising from S_N2' reactivity, we observed no evidence of any product arising from this reaction mode. This is most likely due to a preference to form the larger, less strained 12-membered ring, rather than the smaller, considerably more strained 10-membered cyclophane. Claisen rearrangement of 188 occurred with difficulty, and only at
temperatures above 200 °C. However at these high temperatures decomposition became a problem. The desired transformation to 189 was therefore accomplished in only a 30% yield upon refluxing a solution of 188 in diethylaniline (230 °C) for 24 h (Scheme 40).

Even a substrate that was lacking all the sensitive functionalities that would be present in actual synthetic intermediates was thus affording alarmingly low yields. These setbacks induced us to search for entirely different solutions.
B. Application of an ene-like reaction for the synthesis of mitomycinoids

The successful avenue to benzazocinones established in the course of my research rests on the use of a carbonyl ene-like reaction that was developed in the laboratory of M. A. Ciufolini in the mid-1990’s. This new ene-like methodology allows practically any aldehyde to combine with vinyl ethers in which the oxygen is located on the central carbon of an allylic system; for example, 2-methoxypropene (2-MP). The reaction occurs under the catalytic influence of a one to one molar complex of Yb(fod)$_2$ and AcOH at a catalyst load of typically 0.5 mol%, and it is run at room temperature (Figure 20). The usage of the term “ene-like” is not intended to imply any specific mechanism, but merely to express the outcome of the overall transformation. The primary product of this process is a homoallylic alcohol, 196, which may be isolated. The reaction typically employs an excess of vinyl ether, since 2-MP and other such compounds are inexpensive commodity chemicals and therefore under the slightly acidic conditions of the reaction, the alcohol adduct reacts further with excess vinyl ether to afford mixed ketal 197. This chemistry has been thoroughly reviewed for a *Tetrahedron* Symposium-in-Print devoted to modern synthetic techniques.

![Figure 20](image)

The ene adduct of 2-MP may be transformed to a wide range of synthetically useful building blocks (Figure 21). For instance, ozonolysis or simple acidic hydrolysis yield, respectively, β-hydroxy esters or β-hydroxy methyl ketones, which are formally aldol condensation products. Our ene reaction is thus a fully catalytic equivalent of an aldol condensation. However, the mild conditions required for the transformation bypass the requirement for bases (LDA, LiHMDS, etc.) low temperatures and inert atmospheres. Furthermore, 2-MP is an acetone equivalent and therefore it permits the preparation of
formal acetone aldol products. These intermediates are difficult to prepare by typical aldol protocols, because the enolate of acetone, like that of other small ketones, is not well-behaved.

The electron-rich enol ether present in ene products reacts with various electrophiles such as peracids, NBS, arylsulfur and arylselenium halides, to give a range of derivatives, which may be further manipulated to yield synthetically useful educts. Indeed, our ene reaction has already provided access to the total syntheses of a prostanoid, (±)-chlorovulone II, and a terpenoid, (±)-phyllanthocin.

![Diagram of chemical structures and reactions]

Figure 21

1. **Model Studies Towards the Formation of the Critical Benzazocinone**

It was envisioned that the ene-like reaction of an appropriately substituted phenylacetaldehyde 198 with 2-MP could ultimately lead to benzazocinone 199 if the generic functionality "N" were an electrophilic form of nitrogen capable of reacting with the nucleophilic carbon of the vinyl ether (Figure 22).

![Diagram of model studies reaction]

Figure 22
In order to realize the goal of constructing the critical heterocycle, we needed to address two fundamental questions. First, what kind of substituent "N" was best suited to accomplish the desired ring closing step and second, would a highly oxygenated / functionalized aldehyde behave properly in our ene-like reaction? To address the first question a simple model study was devised.

We opted to use an azide as the nitrogenous group because of its ability to react very effectively in 1,3-dipolar cycloadditions. A triazoline 201 thus obtained appeared to be likely to undergo deazoniation, either under thermal or photochemical conditions, to produce a 1,3-diradical intermediate, 202. This species would probably cyclize to alkoxyaziridine 203. Substance 203 is in fact a strained mixed aminal that should undergo rapid hydrolysis to benzazocinone 200 upon exposure to water (Figure 23).

![Chemical structures](https://example.com/structures.png)

**Figure 23**

The model aldehyde substrate was synthesized from commercially available 2-aminophenethyl alcohol (204) starting with diazotization / azidation to azido alcohol 205. Oxidation to aldehyde 206 was carried out in an unusual manner by using a Sharpless RuCl$_3$/NaIO$_4$ system (Scheme 41). This treatment normally converts a primary alcohol to an acid; however, careful monitoring of the reaction allowed us to stop the oxidation at the stage of aldehyde. Several other oxidation procedures (Swern, PCC, PDC, TPAP / NMO) were explored, but these were found to be inferior to the Sharpless method, due to the production of considerable amounts of byproducts that complicated the chromatographic purification of the aldehyde. Some of these byproducts arose through
oxidative degradation of the side chain, a well known problem during oxidation of homobenzylic alcohols. The azido aldehyde reacted under standard ene conditions to afford adduct 207 in 95-98 % yield. Refluxing in toluene promoted intramolecular 1,3-dipolar cycloaddition to yield triazoline (208a,b) in 48-55 % chromatographed yield.

Scheme 41

This transformation is noteworthy, in that it produces a 7-membered ring. Moreover, the cycloaddition proceeds stereoselectively to give a 7:1 ratio of anti to syn isomers. The assignment of relative regiochemistry rests on the observation of large couplings (11 and 8 Hz) between the proton residing on the carbon bearing the OMIP group and the two neighboring protons in the NMR spectrum of the major isomer. Figure 24 shows an MM+ optimized structure of the anti and syn isomers of an analogue of 208, wherein the MIP unit is approximated as a methyl group and extraneous atoms deleted for clarity. Only the anti isomer displays sufficiently large dihedral angles between proton a and the neighboring hydrogens b and e to present 8-11 Hz couplings.

Figure 24

Furthermore, the approximate transition states (TS) for the 1,3-dipolar cycloaddition leading to the isomeric triazolines were estimated by fixing the distance
between the terminal nitrogen atoms of the azides and the olefinic carbon atoms of the vinyl ether to 2.4 Å. Analysis of the approximate TS leading to the syn isomer revealed the TS is affected by a severe nonbonding interaction between the oxygen atoms on the vinyl ether and the methoxy / OMIP unit. This steric inhibition is absent in the TS leading to the anti isomer thereby resulting in its preferential formation.

Triazolines such as 201 proved to be fairly stable; however, a few basic precautions were necessary to avoid undesirable side reactions. It was discovered that excessive thermal activation causes loss of diazomethane through a retro 1,3 cycloaddition and formation of an isolable imidate (209). A similar cycloreversion of diazomethane finds precedent in the work of Huisgen.\(^\text{46}\) Furthermore, we observed that the ease of this reaction, as measured by the temperature necessary to induce cycloreversion, depends on the nature of substituent Z (Figure 25). When Z = H, temperatures above 120 °C were necessary to promote the transformation. By contrast, when Z is a protected hydroxymethylene group (\textit{vide infra}), cycloreversion commenced at temperatures of about 100 °C. Thus, cyclization of ene adducts wherein Z = H may be effected in refluxing toluene (T = 110 °C), whereas for Z = alkyl, cyclization must be conducted in refluxing benzene (T = 80 °C).

![Reactions](image)

**Figure 25**

A second undesired, but also preventable, reactivity of the triazoline was the loss of methanol under mild acidic conditions to form the aromatic triazole (211). Even adventitious acidity was sufficient to induce this conversion. The problem may be avoided simply by adding solid K₂CO₃ to all reactions involving the triazoline. It is also advisable to use deuterated benzene, instead of deuterochloroform, as a solvent for NMR studies of
triazolines, since DCI, a common contaminant in CDCl$_3$, is an effective catalyst for aromatization (Figure 26). Acid sensitivity does not prevent purification of triazolines by silica gel chromatography; however, partial degradation does occur under these conditions. Purification, on the other hand, is required to remove colored impurities and other highly absorptive byproducts that interfere with the subsequent photochemical step (vide infra). It was discovered that removal of undesirable byproducts could be achieved simply by filtering the crude toluene solution of triazoline 201 through a short plug of basic alumina prior to photolysis.

![Figure 26](image)

Irradiation of a THF solution of the triazoline in a Pyrex flask by using an ordinary Sylvania 275W sunlamp resulted in formation of benzazocinone 214 in 78% yield (Scheme 42). As indicated earlier, it is likely that photochemical activation caused extrusion of dinitrogen from 208 and consequent formation of a diradical (212), which recombined to form methoxyaziridine 213. This reactive, strained intermediate probably is rapidly hydrolyzed upon aqueous workup. It should be noted that aziridine 213 has been isolated from the reaction mixture and characterized by NMR.

![Scheme 42](image)

It should also be noted that triazoles of type 211 are not useful for our purposes. The work of Wender$^{47}$ suggests that a photochemical conversion of the triazole to the desired 200 may be possible through the mechanism of Scheme 43. However, our triazole resisted photolytic extrusion of dinitrogen under the foregoing conditions, while irradiation
with a high pressure mercury lamp as a light source and use of quartz flasks, as described by Wender, yielded a complex mixture of products.

Scheme 43

2. Synthesis of Complex Aldehydes for the Ene-like Reaction

Now that the first question was answered and our synthetic approach had been validated, the second question demanded attention. In all, six different aldehydes were synthesized for further study of the ene-like reaction. Aldehyde 218 clearly possesses the substitution required for the synthesis of the mitomycins, while the other five aldehydes, 219 - 223, bear the substitution pattern of FR900482 and related compounds. The FR900482 aldehydes can be further subdivided into non-branchied, 219 and 220, and branched derivatives, 221 - 223 (Figure 27). The syntheses of the non-branchied versions of the aldehydes featured the use of a nitrile as an aldehyde equivalent. DIBAL-H reduction of the cyano group provided an intermediate imine (not isolated), which was ultimately hydrolyzed to afford the aryl acetaldehyde cleanly and in high yield. This modification of the scheme utilized earlier for the synthesis of model aldehyde 206 avoided the low yielding oxidation of a homobenzylic alcohol.

Figure 27
Synthesis of the aldehyde for mitomycins commenced with Lederer-Manasse hydroxymethylation of compound 52 with formaldehyde and NaOH was followed by selective protection of the phenol as a methyl ether to yield benzylalcohol 224. Formation of the benzyl chloride with thionyl chloride and nucleophilic displacement with NaI. LiCN in DMF gave the benzyl cyanide (226). Optimization of this seemingly trivial reaction required significant experimentation. In the absence of NaI the yield of this reaction was 20-25 %, however by first adding 2 eq. of NaI 10 min. prior to LiCN addition, the yields increased to 88-90 %. We presume that an initial Finkelstein reaction of 225 with iodide ion furnished a highly reactive benzyl iodide, which participated in S$_2$N$_2$-type reaction with cyanide ion much more efficiently than the chloride substrate. DIBAL-H reduction of 226 and hydrolysis gave the desired aldehyde (218) in 84 % yield (Scheme 44).

![Scheme 44](image)

Compound 227 (the methyl ether analog of 84) served as a common precursor for the preparation of non- branched FR900482 aldehydes, 219 and 220. DIBAL-H reduction of the ester group furnished benzyl alcohol 226. The synthesis of 220 included 2 additional steps, radical bromination and displacement with $p$-methoxyphenol, prior to ester reduction with DIBAL-H. Both benzylic alcohols were subjected to the same optimized three-step reaction sequence (identical to the previous mitomycin scheme) to yield aryl acetaldehydes 219 and 220 (Scheme 45).
Scheme 45

An interesting side note to this strategy is that DIBAL-H reduction of model arylacetonitriles lacking ortho substituents proceeded in only 21 % yield. By analogy with our previous attempts at inducing an enantiocntrolled aldol reaction, we surmised that arylacetonitriles lacking ortho groups may readily access a conformation of the type A (Figure 28). Favorable stereoelectronic alignment of the marked C–H bond with the aromatic π* orbitals may increase the acidity of the proton to such an extent that the basicity of DIBAL-H, or of derived species, is now sufficient to deprotonate the substrate. The resulting enolate anion presumably resists cyano group reduction and may react further to form undesired byproducts. By contrast, ortho substitution probably forces the molecule into a conformation of the type B, wherein only the cyano group can provide activation to the benzylic protons. The kinetic acidity of the C-H bonds may now be sufficiently low that cyano group reduction occurs normally.

Figure 28

Our attention now turned to the search for a concise avenue to the branched aldehyde substrates, 222 and 223.\textsuperscript{48} The synthesis of aldehyde 223 commenced with commercially available 5-nitro vanillin (230). This material may be used either as the
methyl ether or converted to benzyl analog 231 by treatment with HBr in AcOH,\textsuperscript{49} followed by selective protection of the non-conjugated phenol with benzyl bromide and NaH. Treatment with triflic anhydride and pyridine formed the aryl triflate (232),\textsuperscript{50} which underwent nucleophilic aromatic substitution (probably via a Meisenheimer complex, 233) upon reaction with the sodium salt of dimethyl malonate. Desired aryl malonate 234 emerged without any detectable formation of the product of a Knoevenagel reaction (Scheme 46).

![Scheme 46](image)

Interestingly, the use of Meldrum's acid instead of dimethyl malonate resulted in considerable formation of Knoevenagel products. To illustrate, treatment of triflate 232 with the sodium salt of Meldrum's acid, a mixture of products resulting from nucleophilic aromatic substitution (235), Knoevenagel reaction and triflate hydrolysis (236), or both modes of reactivity (237) was obtained (Scheme 47). The reasons for this are not clear, but probably the significant acidity of Meldrum's acid adducts facilitate dehydration of a reversibly formed aldol intermediate through a "push-pull" type activation (Figure 29).

![Scheme 47](image)
Benzaldehyde 234 was reduced with sodium borohydride and transformed to the benzyl chloride with thionyl chloride. Reaction with sodium 4-methoxyphenoxime provided the protected benzyl alcohol 238. Original attempts to reduce both esters and the nitro group simultaneously with LAH yielded complex mixtures of products arising from side-reactions involving the various intermediates formed. An improved protocol involved initial reduction of the ester units with borane-dimethyl sulfide complex\textsuperscript{31} followed by hydrogenation of the nitro group over Raney nickel thus afforded aniline 239 in 77\% yield. This material was then transformed into azide 240 under standard conditions. Diol azide 237 was an intermediate goal of this synthetic strategy because of its potential usage in a route towards an enantiocontrolled synthesis of FR900482. However, for the purpose of further exploration, the racemic aldehyde was utilized. Monobenzyl ether formation followed by PCC oxidation afforded desired aldehyde 223 (Scheme 48).

We note that the choice of diol azide 240 as an intermediate was motivated by important strategic considerations. Notice that this molecule is symmetric but prochiral. Diols of similar structure may be easily desymmetrized by chemoenzymatic methods; e.g.,
by enantioselective transesterification or enantioselective acetate hydrolysis. As shown in Scheme 49, desymmetrization would furnish aldehyde 241, in which the absolute stereochemistry of the sidechain is controlled and thence benzazocinone 243, in scalemic form. This would permit an enantiocontrolled synthesis of FR900482. However, for the purpose of further exploration, racemic materials were employed in the present study.

Scheme 49

The chemical behavior of these substituted aldehydes in the three-step benzazocinone forming sequence is discussed in the following section.

3. Benzazocinone Formation from Complex Aldehydes

The more complex, highly oxygenated aldehydes reacted under the conditions of our ene-like reaction in essentially the same manner as the simpler substrates. Only a slight increase in catalyst loads (1-3 % instead of 0.5 %) and longer reaction times (1-14 days instead of 17 hours) were necessary for completion of the reaction. It is worthy of note that conventional methodology for carbonyl ene reactions would surely fail with highly oxygenated, sensitive aldehydes 219 - 223. These sensitive substrates would not be compatible with the suprastostiochiometric quantities of powerful Lewis acids (e.g., Et₂AlCl) normally used to induce such transformations.

The aldehyde bearing the mitomycin substitution pattern reacted under standard conditions in our ene-like reaction under the catalytic influence of 2 % Yb(fod), for 21
hours to give ene adduct 245. Thermal cyclization of this compound provided triazoline 246 (Scheme 50).

\[
\begin{align*}
\text{Me} & \text{O} \\
\text{Me} & \text{N}_3 \\
\text{Me} & \text{O} \\
\text{Me} & \text{CHO} \\
\text{Me} & \text{O} \\
\text{218} & \\
\text{2-MP} & \text{Yb(fod)}_3 \\
\text{AcOH, SiO}_2 & 95\% \\
\text{Me} & \text{O} \\
\text{Me} & \text{N}_3 \\
\text{Me} & \text{O} \\
\text{Me} & \text{OMe} \\
\text{Me} & \text{O} \\
\text{245} & \\
\text{benzene reflux} & 41\% \\
\text{Me} & \text{O} \\
\text{Me} & \text{N}_3 \\
\text{Me} & \text{O} \\
\text{Me} & \text{OMe} \\
\text{Me} & \text{O} \\
\text{246} & \\
\end{align*}
\]

Scheme 50

Photolysis of triazoline 246 usually proceeded smoothly to give the desired benzazocinone 247 in average yields of 40-45\%, however in one instance a significant amount of triazole 248 byproduct was obtained. The exact origin of this byproduct is still unclear, but as already mentioned trace amounts of acid can catalyze the elimination of methanol and aromatization of the triazoline (Scheme 51). The p-bromobenzoate derivative of the triazole was a highly crystalline material and prompted us to obtain an X-ray crystal structure (Appendix A).

\[
\begin{align*}
\text{Me} & \text{O} \\
\text{Me} & \text{O} \\
\text{N} & \text{N} \\
\text{Me} & \text{O} \\
\text{Me} & \text{OMe} \\
\text{Me} & \text{N}_3 \\
\text{246} & \\
& \text{hv} \\
\text{K}_2\text{CO}_3 \\
\text{wet THF} & \\
\text{Me} & \text{O} \\
\text{Me} & \text{O} \\
\text{N} & \text{N} \\
\text{Me} & \text{O} \\
\text{Me} & \text{OMe} \\
\text{Me} & \text{N}_3 \\
\text{247} & \\
\text{Me} & \text{O} \\
\text{Me} & \text{OMe} \\
\text{N} & \text{N} \\
\text{Me} & \text{O} \\
\text{Me} & \text{OMe} \\
\text{Me} & \text{N}_3 \\
\text{248} & \\
\end{align*}
\]

Scheme 51

Treating the FR900482 substituted aldehyde 219 under standard ene-like reaction conditions utilizing 1\% Yb(fod)$_3$ for 79 hours gave ene adduct 249 in 88\% yield. Thermal 1,3-dipolar cycloaddition in refluxing benzene and photolysis delivered benzazocinone 250. After purification, pure benzazocinone 250 was obtained as a beige

\[
\begin{align*}
\text{Me} & \text{O} \\
\text{Me} & \text{N}_3 \\
\text{219} & \\
\text{2-MP} & \text{Yb(fod)}_3 \\
\text{AcOH, SiO}_2 & 98\% \\
\text{Me} & \text{O} \\
\text{Me} & \text{N}_3 \\
\text{Me} & \text{O} \\
\text{Me} & \text{OMe} \\
\text{Me} & \text{O} \\
\text{249} & \\
\text{1. } \Delta \\
\text{2. } \text{hv} & 15\% \\
\text{Me} & \text{O} \\
\text{Me} & \text{OMe} \\
\text{N} & \text{O} \\
\text{Me} & \text{O} \\
\text{250} & \\
\end{align*}
\]

Scheme 52
solid which was stable at ambient temperature for several months without any trace of decomposition (Scheme 52).

The branched aldehydes, 221 and 223, both reacted under the conditions of our ene-like reaction in essentially the same manner as the non-branched substrates. Only a slight increase in catalyst loads to 3-5 % and longer reaction times, ranging from 6 days (221) to 2 weeks (223) were necessary for completion of the reaction (Scheme 53). There is a delicate balance that must be maintained with respect to catalyst load. The higher the percentage of catalyst, the faster the reaction occurs, but also the extent of 2-MP polymerization will be greater. If an insufficient amount of catalyst is used then the reaction time becomes excessive and polymer formation increases with the potential for inclusion of the desired product into the growing polymer chain.

![Chemical structure](image)

**Scheme 53**

Thermal cyclization of 251 and 252 followed by photolysis delivered benzazocinones 253 and 254 (Scheme 53). These reactions were only run once and have not been fully optimized (*vide infra*). Studies directed toward the advancement of benzazocinones 214, 247, 250, and 254 to more complex synthetic intermediates are detailed in the next section.

4. The Chemistry of Benzazocinones 214, 247, 250, and 254

The conversion of 255 to the critical benzazocenone common to both families of mitomycinoids (256) may be accomplished in a number of possible ways, as shown in Figure 30. In this formulation, group “O” present on several intermediates could be either
a ketone or an alcohol. Substance 200 could be subjected to a 1,3 transposition of ketone and alcohol, followed by elimination of the OH unit to afford 257. Alternatively, deprotection of the alcohol, activation and elimination to give isomeric enone 258 would set the stage for a Wharton reaction leading to the target. Formation of enol derivatives of 200, shown below as structures 259 and 260, could also provide access to the synthetic goal by various routes. Finally, a Shapiro reaction would permit conversion of 200 into 255 in only two steps.

![Diagram showing chemical structures](image)

**Figure 30**

The 1,3 transposition of the ketone began with reduction of the carbonyl, acetylation of both alcohol and aniline units, and acidic workup to remove the MIP protecting group. Alcohol 262 thus obtained was oxidized to the ketone by using catalytic TPAP and NMO. Treatment with DBU of the resulting β-acetoxy ketone 263 promoted elimination of the acetate. However, the product obtained from this step was not the desired enone 264, but rather the deconjugated isomer 265 (Scheme 54). We presume that product 265 arose through E1cb-type elimination, followed by formation of an extended enolate of intermediate 264 and reprotonation at the α-position. Unfortunately, this presumption is not supported by experimental evidence. Indeed, when the elimination
step was carried out in an NMR tube (0.2 eq aliquots of DBU in C6D6) with continuous monitoring of the reaction, we were unable to detect signals of an intermediate attributable to structure 264. Conversely, it seems improbable that DBU may be able to induce E2-type reaction of an acetate ester.

![Scheme 54](image)

The structure of 265 was confirmed by extensive NMR experiments, chemical evidence and X-ray crystallography (Appendix B). The 1H NMR spectrum of 265 exhibited an olefinic proton as a broad doublet at δ = 7.20 ppm coupled to a second olefinic H that appeared as doublet of triplets at δ = 5.03 ppm. These chemical shifts were inconsistent with structure 264. Here, enone resonance would cause the chemical shift of H_B (the more highly split signal due to proximity to the methylene group) to be downfield relative to that of H_A, which should appear as a broad doublet (due to allylic coupling) at about 6 ppm (Figure 31). By contrast, the electron donating effect of enamide 265 would reverse the position of proton resonances, as observed experimentally. Moreover, two-dimensional long-range 1H-13C heteronuclear correlation NMR (2D HMBC) revealed that

![Figure 31](image)
the carbonyl carbon was indeed coupled (³J) to the allylic protons; acoupling not possible for structure 264.

We also observed that treatment of the elimination product, that is, enamide 265, with mild acid resulted in isomerization to indole aldehyde 268. This conversion occurred even when the compound stood for several hours in solution in deuterated chloroform, which is often contaminated with traces of acid (DCl, see above). Only enamide 265 could possibly undergo such a transformation (Scheme 55).

![Scheme 55](image)

It seemed plausible that an analogous elimination reaction of a substrate in which the ketone is not expressed would produce the desired regiochemistry, because the absence of a free carbonyl group would deny the possibility of double bond isomerization after elimination. Protection of the aniline as the benzamide and acidic workup thus gave the free alcohol, which was protected as silyl ether 269. Ketone reduction and activation of the resultant alcohol as the mesylate provided compound 270. This material proved to be unusually resistant to elimination. For instance, exposure of 270 to DBU in refluxing

![Scheme 56](image)
THF, standard conditions for E2 processes, resulted in no reaction at all. Elimination did occur at temperatures above 100 °C in neat DBU, but disappointingly, only the undesired regioisomer 271 of the olefin was obtained (Scheme 56). Mild acid treatment also caused ring fragmentation of 271 as witnessed before for 272.

Our attention then shifted to the potential use of a Wharton reaction as an avenue to allylic alcohol of type 255. Mild acid treatment of 250 resulted in cleavage of the MIP group. The emerging aminoalcohol 273 was N,O-diacetylated and the resulting 274 was subjected to DBU elimination. Once again, it was found that the product of this reaction was the deconjugated enone 276 (Scheme 57). The propensity of either isomer of the desired enone to undergo deconjugation induced us to explore the thermodynamic properties of our systems by computational methods. Both molecular mechanics (MM+) and MNDO (restricted Hartree-Fock) calculations revealed a substantial preference for the deconjugated isomer of either enone system. To illustrate, isomerization of 275 is calculated to be exothermic by 3.1 kcal/mol.

![Chemical structures depicting the reaction pathways and products](image)

Scheme 57

It was surmised that the elimination step could be facilitated by enhancing the nucleofugic properties of the leaving group. If sufficient activation were provided to the departing oxygen, then hopefully elimination could occur under sufficiently gentle conditions that the enone would not isomerize. Substance 250 was N-acetylated prior to
removal of the MIP group. Subsequent treatment with mesyl chloride and TEA provided mesylate 278. This material proved not to be a viable synthetic intermediate. First of all. DBU treatment proceeded with deconjugation, as in the case of acetate 274. Secondly, the compound was readily inclined to undergo an unexpected transannular cyclization to 279 (Scheme 58). It is remarkable that the acetamidc functions as a nitrogen nucleophile in this reaction, the ease of which is a testimony to the close proximity of the nitrogen atom to the backside of the mesylate-bearing the carbon center. The structure of 279 was confirmed by X-ray crystallography (Appendix C).

![Scheme 58](image)

In an attempt to recover from the setbacks described above, we examined the possibility of using olefin 276 as a starting point for the preparation of 255. In that connection, we attempted epoxidation of 276 with m-CPBA. A very rapid reaction ensued, but remarkably, only the Baeyer-Villiger product 281 (Scheme 59) was obtained. This observation testifies to the exceptional degree of strain present in N-acyl benzazocenones of the type 276.

![Scheme 59](image)
Parallel studies with the benzazocinone displaying a mitomycin-type substitution uncovered an interesting property. Due presumably to the steric hindrance provided by the ortho methoxy group, it is extremely difficult to acylate the aromatic amine in 247. This is in contrast to the FR-type substrate 250, which may be N-acylated quite easily as discussed above. Compound 284 was thus prepared as shown in Scheme 60. Treatment of β-acetoxy ketone 283 with exactly one equivalent of DBU (25°C, THF) yielded some of the desired regioisomer of enone 284. This material was still prone to isomerize to the deconjugated enone, but the problem could be alleviated by avoiding the use of excess DBU.

![Scheme 60](image)

Whereas conditions for the production of 284 were not optimized at this stage, one could surmise that the conjugated isomer of the enone could be obtained if the aromatic amine were not acetylated. This hypothesis was supported by calculations. The isomerization of FR900482-type system 285 to 286 was calculated to be endothermic (MNDO-RHF; Scheme 61). With these important data in hand, we proceeded to study an analogous process with substrate 285.

![Scheme 61](image)
N-protection of heterocycle 250 as a trichloroethylcarbamate and subsequent O-acetylation proceeded smoothly to give 288. Removal of the Troc protecting group under neutral conditions by the use of Cd/Pb couple, a methodology developed in our laboratories, and DBU elimination provided the long sought enone 285 with the desired regiochemistry and in fair yields (Scheme 62). It was surprising to observe that a seemingly innocuous N-protection had such a great impact on the chemical properties of the system and therefore on the regiochemistry of the elimination.

This favorable turn of events provided little cause for celebration. It was soon discovered that enone 285 is quite sensitive to acidic agents, which promote an unusually facile anti-Baldwin 5-endo trig transannular conjugate addition. The severe ring strain and the proximity of the amine to the β-olefinic carbon on the opposite side of the ring were seemingly sufficient to overcome the usual difficulties associated with this mode of cyclization. Isomerization to 279 was catalyzed by silica gel and even by the slight traces of acid present in deuterochloroform. This necessitated the use of deuterated benzene as the solvent for all NMR work.

![Scheme 62](image)

A stable, synthetically useful olefin was finally produced in the form of enol ether 290 through treatment of N-Troc bezazocinone 289 with TMS triflate and TEA. This result suggests that a panoply of similar techniques could be used to convert the photochemical products of type 200 to the key allylic alcohols of type 255. For instance.
silyl enol ether 290 could be subjected to a sequence of bromination, stereoselective syn-facial reduction of the ketone and epoxide formation (Scheme 63). Compound 291 is structurally similar to an intermediate in the Fukuyama synthesis of FR900482.

Yet another possibility lies in the formation of enol triflate 293. Deoxygenation with tributyltin hydride under zerovalent palladium catalysis should result in a concise avenue to protected allylic alcohol 294 (Scheme 64).

Lastly, a Shapiro reaction of the 2,4,6-trisopropylbenzenesulfonyle hydrazone of 254 should proceed with analogous regiochemistry, since a similar deprotonation process would be involved (Scheme 65).

In conclusion, we applied our novel ene-type reaction for the construction of benzazocinones and researched various methods to transform them into suitable intermediates for the total synthesis of mitomycins. We also developed an efficient method of constructing properly functionalized aldehydes for our ene reaction, as well as the synthesis of an achiral diol which can be desymmetrized for use in an enantiocontrolled
synthesis. The information accumulated from these experiments will undoubtedly be helpful in completion of the total synthesis of FR900482 and other mitomycinoids, which continues in our laboratories.
EXPERIMENTAL

TECHNICAL NOTES

Melting points (m.p.), determined on a Büchi Dr. Tottoli apparatus, are reported uncorrected. $^1$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) spectra were measured in CDCl$_3$ or C$_6$D$_6$ and were recorded on a Bruker AC300 instrument and processed using MacFID 5.4 software by Tecmag Inc. 2D-HMBC spectra were obtained with the assistance of Dr. William Wilson using a Bruker AMX500 MHz instrument. High temperature NMR spectra were obtained on a Bruker AC-300 by Mme. Odile Miani. Chemical shifts are reported in parts per million (ppm) on the $\delta$ scale downfield from tetramethylsilane ($\delta = 0$); coupling constants in Hertz (Hz). Spin multiplicities are described as: s (singlet); d, dd, ddd (doublet, doublet of doublets, etc.); t (triplet); q (quartet); m (multiplet) and further qualified as b (broad); c (complex); app (apparent). Infrared (IR) spectra were recorded on a Perkin Elmer 1720-X FT-IR spectrometer from films deposited on NaCl and are reported in wavenumbers (cm$^{-1}$). Mass spectra (MS) and high resolution mass spectra (HRMS) were obtained on a Finnegan MAT95 instrument at 70-100 eV, using direct probe insertion at temperatures of 100-250 °C. Analytical thin layer chromatography (TLC) and preparative TLC (PTLC) were performed on fluorescent Whatman precoated analytical plates, 0.25mm thick. Column chromatography was performed on 60-200 mesh grade 62 silica gel. Reagents and solvents were used as supplied with the following exceptions: methylene chloride, distilled over calcium hydride; tetrahydrofuran, distilled from sodium benzophenone ketal; 2-methoxypropene, distilled under argon. All moisture or oxygen sensitive reactions were conducted under argon atmosphere. High pressure hydrogenations were carried out in a stainless steel Parr general purpose bomb.
### EXPERIMENTAL INDEX

<table>
<thead>
<tr>
<th>Unsubstituted model compounds</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azide alcohol 205</td>
<td>68</td>
</tr>
<tr>
<td>Azide aldehyde 206</td>
<td>71</td>
</tr>
<tr>
<td>Ene adduct of 2-azido phenacetaldehyde 207</td>
<td>74</td>
</tr>
<tr>
<td>Triazoline 208</td>
<td>77</td>
</tr>
<tr>
<td>Benzazocinone 214</td>
<td>80</td>
</tr>
<tr>
<td>Triazole 248</td>
<td>83</td>
</tr>
<tr>
<td>Benzazocinone alcohol 297</td>
<td>87</td>
</tr>
<tr>
<td>N-Acetyl O-acetyl alcohol 262</td>
<td>90</td>
</tr>
<tr>
<td>β-Acetoxyketone 263</td>
<td>93</td>
</tr>
<tr>
<td>Enamide 265</td>
<td>96</td>
</tr>
<tr>
<td>Indole aldehyde 268</td>
<td>101</td>
</tr>
<tr>
<td>N-Benzoyl benzazocinone 298</td>
<td>103</td>
</tr>
<tr>
<td>N-BenzoylO-pivoyl ketone 299</td>
<td>106</td>
</tr>
<tr>
<td>N-BenzoylO-pivoyl benzazocinol 300</td>
<td>109</td>
</tr>
<tr>
<td>N-Benzoyl-O-pivoyl benzazocinol O-mesylate 301</td>
<td>113</td>
</tr>
<tr>
<td>N-Benzoyl enamide 302</td>
<td>117</td>
</tr>
<tr>
<td>N-Benzoyl aldehyde 303</td>
<td>120</td>
</tr>
<tr>
<td>Benzazocinone alcohol 304</td>
<td>123</td>
</tr>
<tr>
<td>N-Benzoyl-O-benzoyl benzazocinone 305</td>
<td>126</td>
</tr>
<tr>
<td>Deconjugated N-benzoyl benzazocenone 306</td>
<td>129</td>
</tr>
<tr>
<td>Baeyer-Villiger product 307</td>
<td>132</td>
</tr>
<tr>
<td>N-Benzoyl tert -butyldimethylsilyl ether ketone 269</td>
<td>134</td>
</tr>
<tr>
<td>N-Benzoyl tert -butyldimethylsilyl ether alcohol 308</td>
<td>137</td>
</tr>
</tbody>
</table>
### Unsubstituted model compounds cont.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-Benzoyl tert -butyldimethylsilyl ether mesylate 270</td>
<td>140</td>
</tr>
<tr>
<td>N-Pivoyl tert -butyldimethylsilyl ether ketone 310</td>
<td>143</td>
</tr>
<tr>
<td>N-Pivoyl tert -butyldimethylsilyl ether alcohol 311</td>
<td>146</td>
</tr>
<tr>
<td>N-Pivoyl tert -butyldimethylsilyl ether mesylate 312</td>
<td>149</td>
</tr>
<tr>
<td>Trichloroethylcarbamate benzazocinone alcohol 313</td>
<td>152</td>
</tr>
<tr>
<td>Trichloroethylcarbamate benzazocinone acetate 314</td>
<td>155</td>
</tr>
<tr>
<td>O-Acetyl benzazocinone 315</td>
<td>159</td>
</tr>
<tr>
<td>Conjugated enone 316 and deconjugated enone 317</td>
<td>163</td>
</tr>
<tr>
<td>Transannular ketone 318</td>
<td>166</td>
</tr>
</tbody>
</table>

### Synthesis of branched aldehyde for FR900482

<table>
<thead>
<tr>
<th>Compound</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catechol 319</td>
<td>169</td>
</tr>
<tr>
<td>Benzyl ether 231</td>
<td>172</td>
</tr>
<tr>
<td>Triflate 232</td>
<td>176</td>
</tr>
<tr>
<td>Aryl dimethylmalonate 234</td>
<td>179</td>
</tr>
<tr>
<td>Benzyl alcohol 320</td>
<td>183</td>
</tr>
<tr>
<td>p-Methoxyphenyl protected benzyl alcohol 238</td>
<td>186</td>
</tr>
<tr>
<td>Malonate addition to benzylic position, compound 321</td>
<td>190</td>
</tr>
<tr>
<td>Diol 322</td>
<td>193</td>
</tr>
<tr>
<td>Diol amine 239</td>
<td>197</td>
</tr>
<tr>
<td>Diol azide 240</td>
<td>200</td>
</tr>
<tr>
<td>Monobenzyl ether azide alcohol 323</td>
<td>204</td>
</tr>
<tr>
<td>Mono tert -butyldimethylsilyl ether azide alcohol 324</td>
<td>208</td>
</tr>
<tr>
<td>Diacetate azide 325</td>
<td>211</td>
</tr>
<tr>
<td>Monobenzyl ether azide aldehyde 223</td>
<td>214</td>
</tr>
<tr>
<td>Mono tert -butyldimethylsilyl ether azide aldehyde 326</td>
<td>217</td>
</tr>
<tr>
<td>Progress towards the total synthesis</td>
<td>Page</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Benzyl ether ene adduct 252</td>
<td>220</td>
</tr>
<tr>
<td>Benzyl ether triazoline 327</td>
<td>224</td>
</tr>
<tr>
<td>tert-Butyldimethyilsilyl ether triazoline 329</td>
<td>229</td>
</tr>
<tr>
<td>Imidate 330 and amide 331</td>
<td>232</td>
</tr>
<tr>
<td>Benzyl ether benzazocinone 254</td>
<td>236</td>
</tr>
<tr>
<td>2,4,6-Triisopropylbenzenesulfonyl hydrazone 295</td>
<td>240</td>
</tr>
</tbody>
</table>
2-Azidophenethyl alcohol 205

A solution of NaNO₂ (5.17 g, 75.0 mmol) in H₂O (25 ml) was added dropwise to a rapidly stirring salt-ice bath cooled solution of alcohol 204 (6.86 g, 50.0 mmol) in 4N H₂SO₄ (52 ml) maintained between 0 °C and -5 °C by efficient cooling. After completion of the addition, the mixture was stirred for 30 minutes. A solution of NaN₃ (5.17 g, 79.5 mmol) in H₂O (25 ml) was added as rapidly as possible while avoiding excess foaming. The mixture was stirred at 0 °C or below for an additional 30 minutes before it was allowed to warm to room temperature by removal of the cooling bath and was then stirred at room temperature for 1 hour. The mixture was extracted with Et₂O (3 x 50 ml) and the combined extracts were collected and washed with sat. NaHCO₃ (3 x 20 ml), H₂O (1 x 20 ml), sat. NaCl (1 x 20 ml). The ethereal extracts were collected and dried over anhydrous MgSO₄ and the solvent was removed under vacuum to give 6.02 g of a reddish oil (74%). Silica gel chromatographic purification of the crude material yielded 5.69 g of 205 as a reddish purple oil (70 %). Rᵣ = .07 (40% Et₂O / hexane).

¹H NMR (CDCl₃): 7.20 (4H, m), 3.84 (2H, t, J = 6.6 Hz), 2.87 (2H, t, J = 6.6 Hz), 1.53 (1H, bs)

¹³C NMR (CDCl₃): 138.1, 131.1, 129.9, 127.7, 124.6, 117.9, 62.1, 34.5

IR: 3350, 2934, 2881, 2121, 1582, 1489, 1451, 1284, 1046

MS (EI+): 164 (M+1), 163 (M+, 32), 118, 106 (100), 89, 77

HRMS (EI+): Calculated for C₈H₈N₃O: 163.0745
Found: 163.0746
2-Azidophenethyl alcohol 205
2-Azidophenethyl alcohol 205
2-Azido phenacetaldehyde 206

\[
\begin{align*}
\text{205} & \quad \text{RuCl}_3, \text{KIO}_4 \\
& \quad \text{CCl}_4, \text{MeCN, H}_2\text{O} \\
\rightarrow & \quad \text{206}
\end{align*}
\]

To alcohol 205 (5.17 g, 31.7 mmol) and RuCl₃ (0.42 g, 1.58 mmol) in an 11:7:7 mixture of H₂O:CCl₄:MeCN (62.3 ml : 62.3 ml : 97.9 ml) was added KIO₄ (21.87 g, 95.1 mmol) portionwise. Rapid magnetic stirring for efficient mixing was neccesary. The reaction was monitored by TLC until no alcohol was observed. The suspension was filtered through a plug of Celite® to remove the inorganic salts and then the plug was rinsed with 100 ml of Et₂O. All solutions were collected and put into a separatory funnel. The aqueous layer was separated and washed with Et₂O (1 x 50 ml). The organic layers were collected and washed with H₂O (2 x 100 ml) and then dried over anhydrous MgSO₄. After removal of the solvent in vacuo, the solid product was purified by flash chromatography to give 2.43 g of aldehyde 206 as a yellow oil (48%). Rᵣ = .35 (40% Et₂O / hexane).

¹H NMR (CDCl₃): 9.71 (1H, t, J = 3.6 Hz), 7.26 (4H, m), 3.68 (2H, d, J = 3.6 Hz)

¹³C NMR (CDCl₃): 199.4, 139.4, 132.4, 129.7, 125.7, 124.5, 118.9, 46.7

IR: 3028, 2961, 2824, 2726, 2126, 172, 1584, 1490, 1287, 1160

MS (Cl⁺): 162 (M+1, 8), 146, 135, 134 (100), 106
2-Azido phenacetaldehyde 206
2-Azido phenacetaldehyde 206
Ene adduct of 2-azido phenacetaldehyde 207

\[
\begin{array}{c}
\text{CHO} \\
\text{N}_3
\end{array}
\xrightarrow{\text{Yb(fod)$_3$: AcOH}}
\begin{array}{c}
\text{OMe} \\
\text{N}_3 \\
\text{MIP} \\
\text{OMe}
\end{array}
\]

A slurry of aldehyde 206 (2.43 g, 15.1 mmol), 2-methoxypropene (28.9 ml), Yb(fod)$_3$ (79.9 mg, 75.5 μmol), 0.1M solution of acetic acid in CH$_2$Cl$_2$ (0.75 ml, 75.5 μmol) and silica gel (79.9 mg) in CH$_2$Cl$_2$ (28.9 ml) was stirred at room temperature for 17 hours and the reaction end point was determined by NMR using C$_6$D$_6$ as solvent. The reaction was quenched with sat. NaHCO$_3$ and extracted with CH$_2$Cl$_2$ (2 x 20 ml). The organic layers were collected, dried over anhydrous Na$_2$SO$_4$ and concentrated. Taking up the yellow oil in MeOH with catalytic K$_2$CO$_3$ and stirring for 30 minutes prior to filtering off the precipitated polymer gave 4.44 g (96%) of 207 as a pale yellow oil which was used in the next step without further purification.

$^1$H NMR (C$_6$D$_6$): 6.92-6.76 (4H, m), 4.55 (1H, m), 4.08 (1H, d, J = 1.7 Hz), 3.92 (1H, d, J = 1.7 Hz), 3.23 (3H, s), 3.09 (3H, s), 2.72 (1H, B of AB, dd, J$_1$ = 13.7 Hz, J$_2$ = 7.3 Hz), 2.39 (1H, A of AB, dd, J$_1$ = 13.7 Hz, J$_2$ = 5.5 Hz), 1.35 (3H, s), 1.19 (3H, s)

$^{13}$C NMR (C$_6$D$_6$): 161.5, 138.5, 132.3, 131.3, 124.2, 117.8, 108.7, 100.6, 82.5, 69.4, 54.0, 48.6, 42.0, 37.4, 25.1, 24.8

IR: 2991, 2941, 2828, 2122, 1656, 1582, 1490, 1451, 1380, 1288, 1205, 1075, 1019

MS (Cl+): 306 (M+1, 9), 274, 246, 188, 174, 154, 134, 106, 85 (100)

HRMS (Cl+): Calculated for C$_{16}$H$_{24}$N$_2$O$_3$: 306.1818
Found: 306.1819
Ene adduct of 2-azido phenacetaldehyde 207
Ene adduct of 2-azido phenacetaldehyde 207
A solution of ene adduct 207 (1.35 g, 4.42 mmol) and catalytic K₂CO₃ in 10 ml of toluene was put into a sealed tube and degassed for 15 minutes with argon prior to heating to 110 °C for 4 hours. The reaction was monitored by NMR in C₆D₆. The toluene solution was stirred with Darco® decolorizing charcoal for 15 minutes and then passed through a short plug of Celite®. The solvent was removed in vacuo yielding an 1.32 g of an orange oil which was purified by flash chromatography (50% Et₂O / hexanes) to afford 0.652 g 208 (48%). R₉ = .36 (80% Et₂O / hexane).

mp (EtOAc / hexane): 88 - 90 °C

¹H NMR (C₆D₆): 7.82 (1H, dd, J₁ = 7.8 Hz, J₂ = 0.8 Hz), 7.08-6.74 (3H, m). 4.31 (1H, m), 4.14 (1H, B of AB, d, J = 18.4 Hz), 3.48 (1H, A of AB, d, J = 18.4 Hz), 3.10 (3H, s), 2.96 (1H, B of AB, dd, J₁ = 5.4 Hz, J₂ = 3.5 Hz), 2.57 (1H, A of AB, dd, J₁ = 13.3 Hz, J₂ = 2.2 Hz). 2.46 (3H, s), 1.60 (1H, B of AB, dd, J₁ = 13.3 Hz, J₂ = 11.0 Hz). 1.89 (1H, A of AB, dd J₁ = 11.0 Hz, J₂ = 3.3 Hz), 1.28 (3H, s). 1.27 (3H, s)

¹³C NMR (C₆D₆): 140.5, 131.6, 130.6, 128.1, 126.1, 122.2, 101.5, 91.3, 75.3, 75.3, 64.8, 51.2, 49.3, 47.1, 45.3, 25.8, 25.7

IR: 2990, 2940, 2123, 1486, 1074, 1028, 757

MS (Cl⁺): 306 (M+1, 20), 274, 246, 206, 188 (100), 174, 148, 134

HRMS (Cl⁺): Calculated for C₁₆H₂₄N₅O₅: 306.1818
Found: 306.1826
Triazoline 208
Triazoline 208
Benzazocinone 214

A round-bottomed flask was charged with 208 (624.7 mg, 2.04 mmol), catalytic K₂CO₃, and wet THF (20 ml) and purged with argon for 15 minutes prior to irradiation with a Sylvania 275W sunlamp for 17 hours. The reaction was followed by NMR (C₆D₆) and TLC. The solution was diluted with 20 ml Et₂O and washed with 50% sat. NaHCO₃ (10 ml). The ethereal solution was dried with anhydrous MgSO₄ and removed in vacuo to give 558.7 mg of 214 as a yellow oil. Purification by flash chromatography (50% Et₂O / hexane) yielded 322.9 mg (60 %). Rᵣ = .27 (60% Et₂O / hexane).

¹H NMR (C₆D₆):  6.99 (1H, t, J = 7.3 Hz), 6.94 (1H, d, J = 7.9 Hz), 6.73 (1H, t, J = 7.3 Hz), 4.13 (1H, m), 3.43 (1H, B of AB, d, J = 18.0 Hz), 3.23 (1H, A of AB, d, J = 18.0 Hz), 3.12 (3H, s), 3.01 (1H, B of AB, dd, J₁ = 14.5 Hz, J₂ = 9.0 Hz), 2.82 (1H, A of AB, dd, J₁ = 14.5 Hz, J₂ = 4.2 Hz), 2.80 (2H, d, J = 5.6 Hz), 1.23 (6H, s)

¹³C NMR (C₆D₆):  211.1, 146.7, 134.6, 128.5, 124.0, 120.5, 120.2, 101.4, 69.4, 58.3, 49.6, 46.3, 41.3, 25.7, 25.6

IR:  3408, 2990, 2943, 2123, 1709, 1605, 1494, 1207, 1026, 751

MS (Cl+):  264 (M⁺1, 100), 232, 192, 174, 146

HRMS (Cl+): Calculated for C₁₃H₁₂NO₃: 264.1600
Found: 264.1605
Benzazocinone 214
Benzazocinone 214
Triazole 248

Accidental exposure of the mitomycin substituted triazoline 246 to mild acidic conditions resulted in elimination of methanol and formation of triazole 248 as beige needles.

m.p. 134-135 °C (EtOAc / hexane)

$^1$H NMR (C$_6$D$_6$): (+70 °C) 7.59 (1H, s), 4.35 (1H, app. quintet, J = 6.5 Hz), 3.82 (3H, s), 3.80 (3H, s), 3.73 (3H, s), 3.15 (3H, s), 2.76 (2H, bs). 2.55 (2H, bs), 2.34 (3H, s), 1.34 (3H, s), 1.28 (3H, s)

$^{13}$C NMR (C$_6$D$_6$): 153.2, 150.4, 135.4, 131.4, (peak under C$_6$D$_6$), 126.8, 126.7, 125.3, 101.3, 72.3, 62.8, 61.4, 60.4, 49.4, 31.6, 29.2, 25.8, 25.6

IR: 3436, 2989, 2942, 1640, 1460, 1400, 1264, 1208, 1184, 1148, 1094, 1035, 978, 858

MS (EI+): 377 (M+, 88), 345, 318, 305, 288, 276, 262, 246, 230, 217, 202, 73 (100)

HRMS (EI+): Calculated for C$_{19}$H$_{27}$N$_3$O$_5$: 377.1950
Found: 377.1950
Triazole 248

+70 deg.
Triazole 248
Triazole 248
Benzazocinone alcohol 297

\[
\begin{align*}
\text{Benzazocinone } 214 & \rightarrow \text{NaBH}_4, \text{MeOH} \\
& \rightarrow 297
\end{align*}
\]

Benzazocinone 214 (322.9 mg, 1.23 mmol) in 10 ml of EtOH was stirred at 0 °C and NaBH₄ (55.8 mg, 1.47 mmol) was added portionwise over 5 minutes. The mixture was stirred for 10 minutes, then concentrated and partitioned between Et₂O and H₂O. The ethereal layer was washed with sat. NaHCO₃ (5 ml), H₂O (5 ml) and then brine (5 ml). Drying over MgSO₄ and concentration yielded 297 (326.3 mg, 100%) as a pale yellow oil, which was used in the next reaction without further purification. Rᵣ = .12 (60% Et₂O / hexane).

^1H NMR (C₆D₆): 7.00 (1H, m), 6.91 (1H, m), 6.68 (1H, app.t, J = 7.4Hz), 6.35 (1H, app.d, J = 7.4 Hz), 4.22 (1H, m), 4.13 (1H, m), 3.74 (1H, m), 3.46 (1H, m), 3.33 (1H, m), 3.12 and 3.05 (3H, 2 singlets), 2.94-2.82 (2H, m), 1.96-1.71 (2H, m), 1.28 (3H, s), 1.27 (3H, s)

^13C NMR (C₆D₆): 148.3, 134.1, 128.2, 123.1, 119.0, 118.5, 101.8, 101.4, 70.6, 69.7, 52.0, 49.9, 40.7, 38.9, 26.0

IR: 3412, 3396, 2991, 2944, 1609, 1494, 1380, 1020

MS (EI+): 265 (M+1, 59), 192 (100), 174, 158, 146, 130, 120, 106, 91, 73

HRMS (EI+): Calculated for C₁₅H₂₃NO₃: 265.1678
Found: 265.1681

HRMS (Cl+): Calculated for C₁₅H₂₄NO₃: 266.1756
Found: 266.1751
Benzazocinone alocol 297
Benzazocinone alcohol 297
**N-Acetyl O-acetyl alcohol 262**

![Chemical structure](image)

To a stirring solution of **297** (247.4 mg, 0.939 mmol) in pyridine (4 ml) was added acetic anhydride (213 µl, 2.25 mmol). The mixture was stirred at room temperature for 1 hour and then the solvents were removed *in vacuo*. The residue was dissolved in CH₂Cl₂ and washed sequentially with 2N HCl, sat. NaHCO₃, and brine. The organic layer was dried over anhydrous Na₂SO₄ and the solvent was removed. Flash chromatography of the crude alcohol yielded 175.4 mg of **262** (67%). R<sub>f</sub> = 0.14 (Et₂O)

**¹H NMR (CDCl₃):**

7.35-7.15 (4H, m), 4.94 (2H, m), 4.30 (1H, m), 3.95 (1H, m).
3.02 (1H, A of AB, dd, J₁ = 10.8 Hz, J₂ = 4.2 Hz), 2.90 (2H, m).
2.71 (1H, B of AB, dd, J₁ = 10.8 Hz, J₂ = 10.4 Hz), 2.41 (1H, bs), 2.02 (3H, s), 1.74 (3H, s) (mixture of diastereomers)

**¹³C NMR (CDCl₃):**

171.3, 170.6, 141.1, 136.0, 133.6, 130.6, 129.2, 128.1, 69.6, 67.3, 52.8, 40.7, 37.7, 22.0, 21.1 (one diastereomer)

**IR:**

3409, 2932, 1734, 1641, 1493, 1404, 1371, 1239, 1121, 1077, 1033

**MS (Cl⁺):**

278 (M⁺+1, 13), 277 (M⁺), 218, 217, 175, 174, 160, 156, 149, 146, 130, 118 (100)

**HRMS (Cl⁺):**

Calculated for C₁₅H₂₀NO₄: 278.1392
Found: 278.1401
N-Acetyl O-acetyl alcohol 262
N-Acetyl O-acetyl alcohol 262
β-Acetoxyketone 263

A slurry of alcohol 262 (36.3 mg, 0.131 mmol), NMO (30.7 mg, 0.262 mmol), 5 Å molecular sieves (30 mg) and TPAP (4.6 mg, 12 μmol) was stirred at room temperature until the absence of starting material was observed by TLC. Dilution with \( \text{Et}_2\text{O} \), filtration through Celite®, rinsing the filter cake with \( \text{Et}_2\text{O} \) and removal of solvent \textit{in vacuo} afforded crude 263 as a colorless oil. Purification by flash chromatography yielded 21.0 mg (58 %) of 263. \( R_f = 0.25 \) (\( \text{Et}_2\text{O} \)).

\(^1\text{H} \text{NMR (CDCl}₃\)): 7.42-7.17 (4H, m), 5.43 (0.5H, m), 5.14 (0.5H, m), 5.06 (0.5H, B of AB, dd, \( J_1 = 14.0 \text{ Hz}, J_2 = 5.9 \text{ Hz} \)), 4.79 (0.5H, A of AB, dd \( J_1 = 13.2 \text{ Hz}, J_2 = 5.9 \text{ Hz} \)), 3.88 (0.5H, B of AB, d, \( J = 15.4 \text{ Hz} \)), 3.75 (0.5H, A of AB, dd, \( J_1 = 15.4 \text{ Hz}, J_2 = 8.8 \text{ Hz} \)), 3.01 (0.5H, B of AB, dd, \( J_1 = 14.0 \text{ Hz}, J_2 = 2.9 \text{ Hz} \)), 2.90 (0.5H, A of AB, dd, \( J_1 = 13.2 \text{ Hz}, J_2 = 8.8 \text{ Hz} \)), 2.77 (0.5H, B of AB, d, \( J = 9.6 \text{ Hz} \)), 2.70 (0.5H, A of AB, dd, \( J_1 = 9.6 \text{ Hz}, J_2 = 2.9 \text{ Hz} \)), 2.06 and 1.93 (3H, 2 singlets), 1.73 and 1.71 (3H, 2 singlets) (mixture of conformers)

\(^{13}\text{C} \text{NMR (CDCl}₃\)): 203.2, 170.7, 170.1, 142.8, 134.8, 131.0, 129.7, 129.4, 128.4, 70.3, 50.5, 48.9, 44.1, 21.8, 20.8 (major conformer)

**IR:**
3481, 2936, 1738, 1702, 1667, 1494, 1376, 1295, 1235, 1037

**MS (EI+):**
275 (M+, 2), 215, 187, 173 (100), 145, 118, 91

**HRMS (Cl+):**
Calculated for \( \text{C}_{15}\text{H}_{18}\text{NO}_4 \): 276.1236
Found: 276.1239
β-Acetoxyketone 263
β-Acetoxyketone 263
Enamide 265

![Chemical Structure](image)

DBU (12 µl, 72.3 µmol) was slowly added to a stirring solution of 263 (19.9 mg, 72.3 µmol) in CH₂Cl₂. The mixture was stirred for 1 hour before quenching with 2N HCl. The organic layer was separated and washed with sat. NaHCO₃ and brine. The solution was dried over anhydrous Na₂SO₄ and removed in vacuo. Flash chromatography yielded 8.2 mg of 265 (53%) as colorless crystals. Rᵢ = .53 (Et₂O).

m.p.: 103-4 °C

^1H NMR (CDCl₃): 7.48-7.29 (4H, m), 7.20 (1H, m), 5.03 (1H, ddd, J₁ = 9.9 Hz, J₂ = 4.0 Hz, J₃ = 3.5 Hz), 3.81 (1H, A of AB, d, J = 16.8 Hz). 3.58 (1H, B of AB, d, J = 16.8 Hz), 2.82 (1H, A of AB, ddd, J₁ = 13.9 Hz, J₂ = 4.0 Hz, J₃ = 3.0 Hz), 2.55 (1H, B of AB, dd, J₁ = 13.9 Hz, J₂ = 9.9 Hz), 1.80 (3H, s)

^13C NMR (CDCl₃): 204.8, 169.9, 138.1, 135.7, 130.6, 129.8, 129.7, 128.9, 121.4, 107.1, 46.8, 39.0, 22.3

IR: 3420, 2922, 1712, 1678, 1580, 1493, 1455, 1427, 1375, 1307, 1111, 1038, 1235, 781, 721

MS (Cl+): 216 (M+1, 24), 215 (M+), 187, 172, 130, 117, 91, 65 (100)

HRMS (Cl+): Calculated for C₁₃H₁₄NO₂: 216.1025

Found: 216.1024
Enamide 265

[Graph of two chemical spectra showing peaks at various ppm values.

The first graph shows peaks primarily in the 3 to 9 ppm range.

The second graph shows peaks primarily between 100 and 220 ppm.]
Enamide 265

500 MHz

HMBC 3-bond correlation
HMBC 3-bond correlation, upfield

HMBC 3-bond correlation, downfield
Enamide 265
Indole aldehyde 268

Upon standing in CDCl₃ enamide 265 underwent a ring fragmentation and recombination to provide indole aldehyde 268.

¹H NMR (CDCl₃): 9.85 (1H, t, J = 1.2 Hz), 7.70 (1H, app.dd, J₁ = 7.7 Hz, J₂ = 1.2 Hz), 7.50 (1H, app.dd, J₁ = 6.8 Hz, J₂ = 2.1 Hz), 7.26 (2H, m), 6.43 (1H, s), 3.39 (2H, t, J = 7.1 Hz), 2.89 (2H, dt, J₁ = 7.1 Hz, J₂ = 1.2 Hz), 2.82 (3H, s)

MS (EI+): 215 (M+, 48), 187, 173, 144, 130 (100), 117
Indole aldehyde 268
**N-Benzoyl benzazocinone 298**

\[
\begin{align*}
&\text{OMIP} \quad \text{BzCl, TEA} \\
&\text{CH}_2\text{Cl}_2; \text{H}^+ \quad \text{298 Bz}
\end{align*}
\]

Benzazocinone **214** (334.6 mg, 1.27 mmol) and TEA (213 µl, 1.53 mmol) in 2.0 ml of \(\text{CH}_2\text{Cl}_2\) was treated with benzoyl chloride (177 µl, 1.53 mmol) and stirred for 30 minutes. The solution was poured into 2N HCl and then extracted with \(\text{CH}_2\text{Cl}_2\). The combined organic extracts were washed with sat NaHCO\(_3\) and brine before drying over \(\text{Na}_2\text{SO}_4\). Removal of the solvent gave 313.4 mg (84%) of crude **298** as a beige solid.

\(R_f = 0.15\) (80% Et\(_2\)O / hexane)

\(^1\text{H NMR (CDCl}_3\text{):}\) 7.50-7.20 (5H, m), 7.16 (3H, m), 7.04 (1H, app.t, \(J = 7.7\) Hz), 5.66 (2H, AB, d, \(J = 14.7\) Hz), 4.36 (1H, m), 3.62 (1H, m), 3.23 (1H, m), 2.88 (1H, m), 2.65 (1H, m) (mixture of conformers)

\(^{13}\text{C NMR (CDCl}_3\text{):}\) 205.4, 169.6, 141.0, 135.1, 134.2, 132.4, 130.5, 130.4, 129.3, 129.0, 128.6, 127.7, 70.3, 61.3, 51.3, 43.1 (major conformer)

**IR:**

3444, 2927, 2358, 1712, 1623, 1495, 1386, 1292, 1212, 1188, 1072, 1035

**MS (El\(^+\):**

295 (M\(^+\), 100), 267, 224, 171, 162, 144, 118, 106, 91, 77

**HRMS (El\(^+\):**

Calculated for \(\text{C}_{18}\text{H}_{17}\text{NO}_3\): 295.1208

Found: 295.1208
N-Benzoyl benzazocinone 298
N-Benzoyl benzazocinone 298
**N-Benzoyl-O-pivoyl benzazocinone 299**

Benzamide alcohol 298 (111.5 mg, 0.377 mmol) and catalytic DMAP in TEA (63 µl, 0.45 mmol) and 2.0 ml of CH₂Cl₂ was treated with pivoyl chloride (55 µl, 0.45 mmol) and stirred for 30 minutes. The solution was poured into 2.0 ml of 2N HCl and then extracted with CH₂Cl₂ (2 x 2 ml). The combined organic extracts were washed with 2 ml of sat. NaHCO₃ and 2 ml of brine before drying over Na₂SO₄. Removal of the solvent and silica gel purification gave 127.1 mg (89%) of 299 as a beige solid. Rₜ = 0.62 (80% Et₂O / hexane)

**¹H NMR (CDCl₃):** 7.51-7.11 (8.5H, m), 6.92 (0.5H, app.d, J = 7.4 Hz), 5.71 (0.5H, B of AB, d, J = 14.7 Hz), 5.57 (0.5H, B of AB, d, J = 16.2 Hz), 5.25 (0.5H, m), 4.66 (0.5H, app.t, J = 11.4 Hz), 3.72 (0.5H, A of AB, d, J = 16.2 Hz), 3.66 (0.5H, A of AB, d, J = 14.7 Hz), 3.34 (0.5H, app.t, J = 10.6 Hz), 3.20 (0.5H, B of AB, d, J = 12.1 Hz), 2.93 (1H, app.td, J = 4.0 Hz), 2.87 (1H, A of AB, dd, J₁ = 12.1 Hz, J₂ = 7.4 Hz), 2.65 (1H, app.td, J₁ = 12.9, J₂ = 2.6 Hz), 1.20 (4.5H, s), 0.96 (4.5H, s) (mixture of conformers)

**¹³C NMR (CDCl₃):** 205.2, 177.2, 169.4, 141.8, 134.4, 134.0, 130.5, 129.6, 129.4, 129.0, 128.8, 128.7, 127.8 (major conformer)

**IR:** 2973, 1724, 1651, 1601, 1579, 1494, 1448, 1379, 1283, 1156, 1042

**MS (El+):** 379 (M+, 16), 277, 249, 172, 144, 105 (100), 91, 77

**HRMS (El+):** Calculated for C₂₃H₂₅NO₄: 379.1784
Found: 379.1782
N-Benzoyl-O-pivoyl benzazocinone 299
N-Benzoyl-O-pivoyl benzazocinone 299
N-Benzyol-O-pivoyl benzazocinol 300

To a stirring solution of benzamide pivoylate 299 (67.8 mg, 0.163 mmol) in 0.5 ml MeOH at 0 °C was added NaBH₄ (1.8 mg, 49 μmol). After stirring for 5 minutes the reaction was quenched with 0.5 ml sat. NaHCO₃ and the MeOH was removed in vacuo. The aqueous solution was extracted with Et₂O (3 x 2 ml) and the combined extracts were washed with 2 ml of brine and dried over MgSO₄. The solvent was removed to afford 46.5 mg (68%) of crude 300. Silica gel chromatography provided 44.5 mg (65%) of pure 300. Rᵣ = .38 (80% Et₂O / hexane)

¹H NMR (CDCl₃): 7.36-7.06 (8.5H, m), 6.99 (0.5H, app.d, J = 7.4 Hz), 5.41 (0.5H, m), 5.06 (1H, AB, dd, J₁ = 9.6 Hz, J₂ = 5.2 Hz), 4.45 (0.5H, app.t, J = 8.8 Hz), 4.11 (0.5H, bs), 3.65 (0.5H, bs), 3.22 (0.5H. B of AB, dd, J₁ = 14.0 Hz, J₂ = 2.2 Hz), 3.12 (0.5H, A of AB, dd, J₁ = 14.0 Hz, J₂ = 2.9 Hz), 2.93-2.70 (1H, m), 2.26 (0.5H, m), 1.98 (0.5H, app.d, J = 15.4 Hz), 1.58 (0.5H, B of AB, ddd, J₁ = 12.5 Hz, J₂ = 8.8 Hz, J₃ = 2.9 Hz), 1.47 (0.5H, A of AB, dd, J₁ = 14.7 Hz, J₂ = 8.8 Hz), 1.25 and 1.12 (9H, 2 singlets) (mixture of diastereomers)

¹³C NMR (CDCl₃): 177.3, 172.1, 142.5, 135.8, 134.8, 132.2, 129.9, 129.5, 129.2, 128.5, 128.2, 127.6 (major diastereomer)

IR: 3439, 2972, 2363, 1724, 1634, 1494, 1448, 1397, 1285, 1160, 1049, 1042, 914, 732

MS (EI+): 381 (M+, 9), 296, 278, 174, 105 (100), 77, 57
\textit{N-Benzoyl-O-pivoyl benzazocinol 300}

\text{HRMS (EI+):} \quad \text{Calculated for } C_{23}H_{27}NO_4: \quad 381.1940
\text{Found:} \quad 381.1941
N-Benzoyl-O-pivoyl benzazocinol 300
$N$-Benzoyl-$O$-pivoyl benzazocinol 300
N-Benzoyl-O-pivoyl benzazocinol O-mesylate 301

![Chemical structure](image)

Alcohol 300 (44.5 mg, 0.111 mmol), TEA (23 μl, 0.17 mmol) and catalytic DMAP in 0.5 ml CH₂Cl₂ was treated with MsCl (13 μl, 0.17 mmol). After stirring for 30 minutes the reaction was poured into 2 ml sat. NaHCO₃ and extracted with CH₂Cl₂ (2 x 2 ml). The combined organic extracts were washed with 2 ml of brine and the solvent removed in vacuo. Silica gel chromatography yielded 43.3 mg (79%) of mesylate 301.

Rₜ = 0.45 (80% Et₂O / hexane)

¹H NMR (CDCl₃): 7.36-7.08 (8.5H, m), 6.95 (0.5H, app.t, J = 7.4 Hz), 5.30-5.06 (2H, m), 4.98 (0.5H, m), 4.81 (0.5H, m), 3.50 (0.5H, m), 3.17 (2H, s), 3.16 (0.5H, m), 3.02 (1H, s), 2.92-2.65 (2H, m), 2.54-2.17 (1.5H, m), 1.77 (0.5H, m), 1.26 (6H, s), 1.11 (3H, s), 0.94 and 0.85 (9H, 2 singlets), 0.13, 0.12 and 0.07 (6H, 3 singlets) (mixture of diastereomers)

¹³C NMR (CDCl₃): 177.9, 170.7, 142.2, 135.2, 132.9, 130.7, 130.1, 129.3, 129.0, 128.2, 128.0, 127.7, 73.7, 70.1, 55.8, 52.8, 38.8, 38.0, 34.4, 27.0 (major diastereomer)

IR: 2971, 2359, 1724, 1651, 1494, 1448, 1396, 1362, 1337, 1283, 1158, 1100, 939, 915, 731

MS (EI⁺): 459 (M⁺, 6), 364, 261, 252, 156, 105 (100), 77, 57
**N-Benzoyl-O-pivoyl benzazocinol O-mesylate 301**

![Chemical Structure](image)

HRMS (EI+):  
Calculated for C$_{24}$H$_{29}$NSO$_6$: 459.1716  
Found: 459.1715
$N$-Benzoyl-$O$-pivoyl benzazocinol $O$-mesylate 301
$N$-Benzoyl-$O$-pivoyl benzazocinol $O$- mesylate 301
Mesylate 301 (28.9 mg, 58 µmol) was put into a screwtop vial and was dissolved in 174 µl DBU. The tube was placed into an oil bath preheated to 140 °C and stirred for 1 hour. The tube was cooled and partitioned between water and Et₂O. The ethereal extracts were washed with brine and dried over MgSO₄. After solvent removal the crude oil was purified by PTLC to give 7.7 mg (33%) of enamide 302. Rf = 0.65 (60% Et₂O / hexane)

¹H NMR (C₆D₆): (+70 °C) 7.74 (1H, d, J = 10.6 Hz), 7.22 (1H, m), 6.85 (6H, m). 6.56 (1H, m), 5.06 (1H, m), 4.60 (1H, app.q, J = 10.4 Hz), 3.17 (1H, B of AB, dd, J₁ = 13.4 Hz, J₂ = 5.4 Hz), 2.96 (1H, m). 1.77 (2H, m), 1.60 (2H, s), 1.36 (1H, s), 1.16 (7H, s)

IR: 3436, 2966, 2364, 1724, 1667, 1601, 1580, 1493, 1448, 1317, 1279, 1157, 1145, 1031

MS (EI+): 363 (M+, 3), 261, 156, 105 (100), 77, 57

HRMS (EI+): Calculated for C₂₃H₂₅NO₅: 363.1834

Found: 363.1831
N-Benzyol enamide 302

+70 deg.
$N$-Benzyol enamide 302
N-Benzoyl aldehyde 303

Upon standing in CDCl₃, enamide 302 underwent a ring fragmentation reaction to give aldehyde 303.

¹H NMR (CDCl₃): 9.74 (1H, app.s), 8.64 (1H, bs), 8.01 (2.5H, m), 7.57-7.45 (3H, m), 7.33 (1H, td, J₁ = 8.1 Hz, J₂ = 2.2 Hz), 7.17 (2.5H, m) 4.85 (1H, m), 3.03 (1H, B of AB, dd, J₁ = 14.0 Hz, J₂ = 5.2 Hz), 2.78 (1H, A of AB, dd, J₁ = 14.0 Hz, J₂ = 8.1 Hz), 2.49 (1H, m), 2.02 (1H, m), 1.10 (9H, s)

¹³C NMR (CDCl₃): 200.9, 179.0, 166.6, 136.4, 134.6, 131.2, 128.5, 128.4, 127.9, 127.7, 127.6, 125.4, 125.1, 73.2, 40.1, 38.8, 37.3, 26.9, 25.7

IR: 3335, 2927, 2862, 2358, 1724, 1662, 1583, 1520, 1480, 1452, 1396, 1365, 1288, 1158, 1073, 1030, 755

MS (EI+): 381 (M+, 3), 280, 279, 174, 105 (100), 77

HRMS (EI+): Calculated for C₂₃H₂₇NO₄: 381.1940
Found: 381.1946
N-Benzoyl aldehyde 303
$N$-Benzoyl aldehyde 303
Benzazocinone alcohol 304

\[
\begin{array}{c}
\text{OMIP} \\
\text{214} \quad \text{H} \quad \text{MeOH} \\
\xrightarrow{\text{SOCl}_2} \\
\text{304} \quad \text{H} \\
\end{array}
\]

To a stirring solution of benzazocinone 214 (570.1 mg, 2.16 mmol) in 10 ml of MeOH was added 10 μl of SOCl₂. The reaction turned red and was observed to be complete by TLC. The solution was titrated with TEA until the solution was yellow (10 drops) and the solvents were removed in vacuo. The crude alcohol was purified by silica gel chromatography using an increasing solvent gradient (40% to 80% Et₂O / hexane). 196.6 mg (48%) of alcohol 304 was obtained as a light yellow solid. Rₜ = .18 (80% Et₂O / hexane)

\(^1\)H NMR (CDCl₃): 7.22-7.01 (3H, m), 6.84 (0.5H, app.t, J = 8.1 Hz), 6.76 (0.5H, app.d, J = 8.1 Hz), 5.09 (0.5H, app.t, J = 6.6 Hz), 4.60 (0.5H, m), 4.01 (0.5H, B of Ab, d, J = 16.9 Hz), 3.84 (1H, s), 3.74-3.60 (1.5H, m), 3.21-2.80 (1.5H, m, contains unknown impurity), 2.41 (0.5H, A of AB, d, J = 16.9 Hz), 1.84 (0.5H, m), 1.68 (0.5H, m) (mixture of conformers)

\(^13\)C NMR (CDCl₃): 212.1, 148.4, 134.0, 131.2, 128.0, 126.6, 125.3, 120.4, 69.1, 62.3, 47.7, 37.4 (major conformer)

IR: 3407, 2927, 2246, 1704, 1604, 1493, 1326, 1260, 1066, 971, 913, 737

MS (EI+) 191 (M+, 71), 164, 142, 120 (100), 106, 62

HRMS (EI+) Calculated for C₁₁H₁₅NO₂: 191.0946

Found: 191.0948
Benzazocinone alcohol 304
N-Benzoyl-O-benzoyl benzazocinone 305

Benzazocinone 304 (36.8 mg, 111 µmol), TEA (18 µl, 133 µmol) and catalytic DMAP in 1.0 ml of CH₂Cl₂ was treated with benzoyl chloride (15 µl, 133 µmol) and stirred for 30 minutes. The solution was poured into 1 ml 2N HCl and then extracted with CH₂Cl₂ (2 x 2 ml). The combined organic extracts were washed with sat NaHCO₃ and brine before drying over Na₂SO₄. Removal of the solvent and silica gel chromatography gave 37.0 mg (76 %) of pure 305 as a white foam. Rₚ = .57 (80% Et₂O / hexane)

¹H NMR (CDCl₃): 8.05 (1H, app.d, J = 7.4 Hz), 7.70 (1H, app.d, J = 7.4 Hz), 7.62-7.27 (7.5H, m), 7.25-7.09 (4H, m), 6.94 (0.5H, app.d, J = 7.4 Hz), 5.76 (0.5H, B of AB, d, J = 16.2 Hz), 5.69 (0.5H, B of AB, d, J = 14.7 Hz), 5.57 (0.5H, bs), 4.97 (0.5H, app.t, J = 11 Hz), 3.80 (0.5H, A of AB, d, J = 14.7 Hz), 3.49 (0.5H, app.t, J = 11 Hz), 3.32 (0.5H, app.t, J = 11 Hz), 3.10-2.80 (3H, m)

¹³C NMR (CDCl₃): 204.1, 169.4, 165.3, 141.7, 134.3, 134.0, 133.2, 132.8, 130.6, 129.6, 129.5, 129.1, 128.7, 128.4, 127.8, 71.9, 62.3, 47.7, 39.8

IR: 3060, 2929, 2359, 1718, 1651, 1601, 1578, 1494, 1450, 1379, 1271, 1178, 1112, 1071, 1039, 714

MS (EI⁺) 399 (M⁺, 43), 354, 277, 249, 144, 105, 77 (100)

HRMS (EI⁺) Calculated for C₂₅H₂₁NO₄: 399.1470
Found: 399.1469
N-Benzoyl-O-benzoyl benzazocinone 305
N-Benzoyl-O-benzoyl benzazocinone 305
Deconjugated N-Benzoyl benzazocenone 306

To a stirring flask containing ketone 305 (37.0 mg, 93 μmol) in 0.5 ml THF was added DBU (14 μl, 93 μmol) dropwise. After stirring for 10 minutes, TLC revealed the reaction was approximately 50% complete so an additional 14 μl (93 μmol) of DBU was added. When the reaction was complete by TLC, the reaction mixture was diluted with 1 ml Et2O and passed through a short silica gel plug. Purification by PTLC afforded 8.5 mg (33%) of deconjugated enone 306. Rf = .35 (40% Et2O / hexane x 4)

^1H NMR (CDCl₃): 7.40-7.04 (9h, m), 6.21 (1H, d, J = 11.8 Hz), 5.94 (1H, dt, J₁ = 11.8 Hz, J₂ = 6.6 Hz), 5.29 (1H, B of AB, d, J = 16.2 Hz), 3.80 (1H, A of AB, d, J = 16.2 Hz), 3.60 (1H, m), 3.10 (1H, m)

^13C NMR (CDCl₃): 204.3, 171.1, 141.2, 134.8, 134.3, 131.3, 130.1, 129.2, 128.9, 128.4, 128.3, 127.6, 126.6, 126.3, 59.2, 44.0

IR: 3449, 2925, 2363, 1719, 1652, 1494, 1448, 1371, 1311, 1126, 1113, 796, 698

MS (EI+): 277 (M+, 6), 239, 188, 172, 144, 117, 105 (100), 91, 77

HRMS (EI+): Calculated for C₁₈H₁₅NO₂: 277.1103
Found: 277.1100
Deconjugated N-Benzoyl benzazocenone 306
Baeyer-Villiger product 307

\[
\begin{align*}
\text{306} & \xrightarrow{m\text{-CPBA}} \text{CH}_2\text{Cl}_2 \\
\text{307}
\end{align*}
\]

To a stirring flask containing enone 306 (8.5 mg, 31 μmol) in 0.5 ml CH\textsubscript{2}Cl\textsubscript{2} was added \textit{m}-CPBA (5.8 mg, 34 μmol) in one portion. After stirring for 1 hour the reaction was complete by TLC, and the reaction mixture was diluted with 2 ml of CH\textsubscript{2}Cl\textsubscript{2} and washed with 1 ml 2N HCl, sat. NaHCO\textsubscript{3} (2 x 2 ml), and 1 ml of brine. The organic solution was dried over Na\textsubscript{2}SO\textsubscript{4} and then the solvent was removed. Purification by PTLC afforded 5.8 mg (64%) of heterocycle 307. \(R_f = .42\) (60% Et\textsubscript{2}O / hexane x 2).

\(^1\text{H NMR (CDCl}_3\)): \(7.61-7.07\) (9H, m), \(6.90\) (0.5H, bs), \(6.66\) (0.5H, m), \(6.26\) (0.5H, bs), \(5.93\) (0.75H, bs), \(5.63\) (0.75H, m), \(5.30-5.11\) (0.5H, m). \(3.16\) (1H, B of AB, dd, \(J_1 = 16.2\) Hz, \(J_2 = 8.1\) Hz), \(2.87\) (1H, A of AB, d, \(J = 16.2\) Hz)

\(\text{IR:}\) 3649, 3064, 2931, 1747, 1670, 1489, 1448, 1363, 1298, 1139, 1033, 973, 730, 699
Baeyer-Villiger product 307
N-Benzoyl-O-tert-butyldimethylsilyl ether benzazocinone 269

A stirring solution of benzamide alcohol 298 (79.0 mg, 0.238 mmol), imidazole (32.4 mg, 0.476 mmol) and a catalytic amount of DMAP in 1.0 ml of CH₂Cl₂ was treated with tert-butyldimethylsilyl chloride (71.8 g, 0.476 mmol) portionwise. After stirring for 30 minutes the solution was quenched with 1 ml 2N HCl and separated. The organic layer was washed with sat. NaHCO₃ and then brine to afford 87.0 g (89 %) of 269 as a yellow oil after silica gel purification (50 % Et₂O / hexane).

¹H NMR (CDCl₃): 7.50-7.40 (2H, m), 7.31-6.94 (7H, m), 5.68 (0.75H, B of AB. d, J = 14.7 Hz), 5.44 (0.25H, B of AB, d, J = 16.2 Hz), 4.40 (0.25H, app.t, J = 7.4), 3.67 (1H, m), 3.59 (0.75H, A of AB, d, J = 14.7 Hz), 3.29 (0.75H, app.t, J = 10.3 Hz), 3.13-2.97 (1H, m), 2.94 (0.25H, A of AB, dd, J₁ = 16.2 Hz, J₂ = 5.5 Hz), 2.75-2.52 (2H, m), 0.9 (9H, m), 0.13-0.06 (6H, 3 singlets) (mixture of conformers)

¹³C NMR (CDCl₃): 205.5, 169.5, 147.1, 135.3, 135.2, 134.0, 132.3, 130.3, 129.4, 129.1, 129.0, 127.7, 71.3, 61.3, 52.1, 44.3, 25.7, 18.0. -4.9 (major conformer)

IR: 3468, 3061, 3029, 2930, 2857, 2360, 1715, 1651, 1646, 1601, 1578, 1494, 1448, 1377, 1287, 1258, 1147, 1087, 971, 909, 837, 777

MS (EI+): 409 (M+, 6), 352, 334, 304, 230, 179 (100), 106, 77

HRMS (EI+): Calculated for C₂₄H₃₁NSiO₃: 409.2073
            Found: 409.2072
$N$-Benzoyl-$O$-tert-butylidimethylsilyl ether benzazocinone 269
N-Benzoyl-O-tert-butyldimethylsilyl ether benzazocinone 269
N-Benzyloxyl-O-tert-butyldimethylsilyl ether alcohol 308

To a stirring solution of benzamide silyl ether 269 (87.0 mg, 0.212 mmol) in 1.0 ml MeOH at 0 °C was added NaBH₄ (2.2 mg, 0.049 mmol). After stirring for 5 minutes the reaction was quenched with 0.5 ml sat. NaHCO₃ and the MeOH was removed in vacuo. The aqueous solution was extracted with Et₂O (3 x 2 ml) and the combined extracts were washed with 2 ml of brine and dried over MgSO₄. The solvent was removed to afford 67.4 mg (77%) of pure 308 after silica gel chromatography (80% Et₂O / hexane).

¹H NMR (CDCl₃): 7.38-7.00 (9H, m), 5.03 (0.75H, m), 4.46 (1H, m), 4.01 (1H, m), 3.56 (0.5H, bs), 3.13 (1H, m), 2.82 (1H, m), 2.59 (1H, m), 2.16 (0.75H, m), 1.84 (0.5H, m), 1.46 (0.5H, m), 1.30 (1H, m), 0.94 and 0.85 (9H, 2 singlets), 0.11 and 0.05 (6H, 2 singlets) (mixture of diastereomers)

¹³C NMR (CDCl₃): 172.2, 142.3, 136.5, 135.0, 132.8, 129.8, 129.2, 128.2, 128.0, 127.7, 127.5, 70.3, 67.5, 63.7, 57.4, 40.4, 39.2, 25.7, -4.8 (major diastereomer)

IR: 3419, 3063, 2928, 2856, 2359, 1634, 1600, 1577, 1494, 1447, 1397, 1295, 1255, 1100, 1048, 919, 837, 776, 731, 616

MS (EI+): 411 (M+, 2), 393, 355, 336, 262, 174, 158, 130, 106, 77, 75 (100)

HRMS (EI+): Calculated for C₂₄H₃₃NSiO₃: 411.2230
Found: 411.2237
N-Benzoyl-\textit{O-}tert\textit{-\textit{butyldimethylsilyl}} ether alcohol 308
$N$-Benzoyl-$O$-tert-butyldimethylsilyl ether alcohol 308
Alcohol 308 (67.4 mg, 0.164 mmol), TEA (25 μl, 0.18 mmol) and catalytic DMAP in 0.5 ml of CH₂Cl₂ was treated with mesyl chloride (14 μl, 0.18 mmol) and stirred for 30 minutes. The solution was poured into 2N HCl and then extracted with CH₂Cl₂ (2 x 1 ml). The combined organic extracts were washed with sat. NaHCO₃ (2 x 1 ml) and brine (2 x 1 ml) before drying over Na₂SO₄. Removal of the solvent and silica gel purification gave 66.7 mg (83 %) of pure 270.

¹H NMR (CDCl₃): 7.32-7.00 (9H, m), 5.22 (1.5H, m), 4.83 (0.5H, m), 4.35 (0.5H, m), 3.95 (0.5H, m), 3.43 (0.5H, m), 3.13 and 3.02 (3H, 2 singlets), 2.96 (0.75H, m), 2.78-2.56 (1.75H, m), 2.38 (0.75H, m), 2.12 (0.75H, m), 1.87 (0.75H, m), 1.67 (0.75H, m) (mixture of diastereomers)

¹³C NMR (CDCl₃): 170.6, 142.2, 136.6, 135.5, 133.4, 130.2, 129.8, 128.9, 128.5, 128.0, 127.6, 74.2, 69.6, 55.5, 42.1, 38.9, 37.7, 18.2, -4.9 (major diastereomer)

IR: 2953, 2932, 2857, 2359, 1651, 1601, 1578, 1493, 1447, 1391, 1362, 1302, 1256, 1179, 1103, 1051, 939, 921, 838, 777, 730, 702, 609

MS (EI+): 432 (M+, 100), 336, 262, 232, 158, 105, 77
\textit{N-Benoyl-\textit{O-}tert-\textit{butyldimethylsilyl} ether mesylate 270}
Alcohol 309 (185.8 mg, 0.674 mmol), tert-butylidemethylsilyl chloride (202.8 mg, 1.35 mmol), imidazole (91.9 mg, 1.35 mmol), catalytic DMAP in 2.0 ml of CH₂Cl₂ was stirred for 30 minutes. The solution was poured into 2N HCl and then extracted with CH₂Cl₂. The combined organic extracts were washed with sat NaHCO₃ and brine before drying over Na₂SO₄. Removal of the solvent and silica gel purification (60% Et₂O / hexane) gave 201.4 mg (77 %) of 310 as a white solid. Rᵣ = .68 (80% Et₂O / hexane)

¹H NMR (CDCl₃): 7.32-7.10 (4H, m), 5.55 and 5.21 (1H, 2 doublets, J₁ = 14.7 Hz, J₂ = 15.4 Hz), 4.45 (0.25H, app.t, J = 8.1 Hz), 3.74 (0.75H, m), 3.44-3.08 (2.5H, m), 2.94 (0.5H, m), 2.82 (1H, m), 2.54 (1H, m), 1.11 and 0.93 (18H, 2 singlets), 0.16, 0.13, 0.10, and 0.06 (6H, 4 singlets) (mixture of conformers)

¹³C NMR (CDCl₃): 205.8, 177.6, 141.9, 136.1, 132.2, 129.2, 128.7, 128.1, 71.4, 63.6, 51.9, 44.8, 41.4, 29.0, 25.6, 18.0, -5.0 (major conformer)

IR: 2957, 2931, 2885, 1714, 1645, 1494, 1363, 1259, 1201, 1088, 986, 910, 837, 777, 667

MS (El⁺): 389 (M⁺, 2), 332, 314, 287, 258, 248, 230, 159, 144, 118, 85, 75, 73, 57 (100)

HRMS (El⁺): Calculated for C₂₂H₃₃NSiO₃: 389.2386
Found: 389.2387
$N$-Pivoyl-$O$-tert-butylidimethylsilyl ether benzazocinone 310
$N$-Pivoyl-$O$-tert-butyldimethylsilyl ether benzazocinone 310
N-Pivoyl-O-tert-butyldimethylsilyl ether alcohol 311

\[
\begin{array}{c}
\text{OTBS} \\
\text{Piv}
\end{array}
\xrightarrow{\text{NaBH}_4, \text{MeOH}}
\begin{array}{c}
\text{OTBS} \\
\text{Piv}
\end{array}
\]

To a stirring solution of pivoylamide silyl ether 310 (201.4 mg, 0.517 mmol) in 1.0 ml MeOH at 0 °C was added NaBH₄ (5.8 mg, 0.16 mmol). After stirring for 5 minutes the reaction was quenched with 0.5 ml sat. NaHCO₃ and the MeOH was removed in vacuo. The aqueous solution was extracted with Et₂O (3 x 2 ml) and the combined extracts were washed with 2 ml of brine and dried over MgSO₄. The solvent was removed to afford 152.8 mg (76 %) of pure 311 after silica gel chromatography (60% Et₂O / hexane). Rₜ = .59 (60% Et₂O / hexane).

\(^1\)H NMR (CDCl₃): 7.29-7.15 (9H, m), 4.84 (1H, m), 4.40 (0.5H, m), 4.28 (0.5H, m), 4.03 (0.5H, m), 3.92 (0.25H, m), 3.14 (0.75H, B of AB, dd, J₁ = 14.0 Hz, J₂ = 3.7 Hz), 2.82 (0.75H, A of AB, d, J = 14.0 Hz), 2.75-2.50 (1.75H, m), 2.06 (0.75H, m), 1.79 (0.25H, m), 1.32 (0.25H, m), 1.08 (0.75H, m), 0.99, 0.97, 0.91, and 0.86 (18H, 4 singlets), 0.11, 0.09, 0.08, 0.07, and 0.03 (6H, 5 singlets) (mixture of conformers)

\(^{13}\)C NMR (CDCl₃): 180.2, 143.0, 137.8, 132.5, 128.6, 128.0, 127.5, 70.4, 68.8, 63.7, 60.3, 43.7, 39.3, 28.8, 25.8, 18.0, -4.8 (major conformer)

IR: 3436, 2957, 2931, 2857, 1622, 1493, 1401, 1365, 1256, 1200, 1101, 1049, 900, 836, 776, 734, 636

MS (EI+): 334 (M-57,100), 316, 288, 232, 174, 158, 130, 118, 75, 73, 57

HRMS (EI+): Calculated for C₁₈H₂₈NSiO₃: 334.1835
Found: 334.1837
N-Pivaloyl-O-tert-butylidimethylsilyl ether alcohol 311
$N$-Pivoyl-$O$-tert-butyldimethylsilyl ether alcohol 311
**N-Pivoyl-O-tert-butyldimethylsilyl ether mesylate 312**

![Chemical structure of 311 and 312](image)

Alcohol **311** (131.9 mg, 0.337 mmol), TEA (56 µl, 0.40 mmol) and catalytic DMAP in 2.0 ml CH₂Cl₂ was treated with MsCl (31 µl, 0.40 mmol). After stirring for 30 minutes the reaction was poured into 2 ml sat. NaHCO₃ and extracted with CH₂Cl₂ (2 x 2 ml). The combined organic extracts were washed with 2 ml of brine and the solvent removed in vacuo. Silica gel chromatography (40% Et₂O / hexane) yielded 155.9 mg (98%) of pure mesylate **312**. R<sub>t</sub> = .53 (2% MeOH / CH₂Cl₂).

**¹H NMR (CDCl₃):**

7.33-7.14 (4H, m), 5.05 (1H, m), 4.90 (0.75H, m), 4.66 (0.25H, m), 4.29 (0.5H, m), 3.94 (0.75H, m), 3.10 and 2.97 (3H, 2 singlets), 2.84-2.61 (2.5H, m), 2.18 (0.25H, m), 2.04 (0.75H, m), 1.67 (0.25H, m 1.52 (1H, m), 0.97, 0.90 and 0.85 (18H, 3 singlets), 0.11, 0.09, 0.08 and 0.04 (6h, 4 singlets) (mixture of conformers)

**¹³C NMR (CDCl₃):**

177.6, 142.5, 137.6, 129.8, 129.4, 129.0, 128.2, 74.4, 69.6, 58.3, 42.5, 39.0, 37.6, 37.3, 29.0, 28.7, 25.7, -4.9, -5.1 (major conformer)

**IR:**

2957, 2932, 2857, 2361, 1728, 1635, 1600, 1493, 1362, 1256, 1176, 1113, 1044, 924, 837, 777

**MS (EI+):**

412 (M-57, 96), 328, 316, 288, 242, 232, 158 (100), 153, 130, 85, 73, 57
N-Pivoyl-O-tert-butyldimethylsilyl ether mesylate 312
$N$-Pivoyl-$O$-tert-butyldimethylsilyl ether mesylate 312
Trichloroethylcarbamate benzazocinone 313

To a stirring solution of aniline alcohol 214 (49.8 mg, 0.26 mmol) and K₂CO₃ (82.7 mg, 0.56 mmol) in 2 ml of THF was added trichloroethyl chloroformate (72 µl, 0.78 mmol). After TLC revealed no starting material remained, the reaction was quenched with 1 ml of 50% saturated NaHCO₃. The 2 phases were separated and the aqueous phase was extracted with Et₂O (2 x 1 ml). The combined organic layers were washed with 1 ml of brine and then dried over MgSO₄. After solvent removal and silica gel chromatography (60% E/H) 64.2 mg (84 %) of Troc protected alcohol 313 as a cream colored foam was obtained. \( R_f = 0.36 \) (80% Et₂O / hexane)

\(^1\)H NMR (CDCl₃): 7.32-7.08 (4H, m), 5.06 (1H, d, J = 15.4 Hz), 4.83 (1H, B of AB, dd, J₁ = 14.0 Hz, J₂ = 11.8 Hz), 4.65 (1H, A of AB, dd, J₁ = 14.0 Hz, J₂ = 11.8 Hz), 4.41 (1H, bs), 3.73 (0.5H, app.t, J = 10.3 Hz), 3.60 (1H, m), 3.27-2.95 (3H, m), 2.88 (0.5H, app.d, J = 14.0 Hz), 2.64 (1H, app.t, J = 11.8 Hz) (mixture of conformers)

\(^13\)C NMR (CDCl₃): 205.1, 153.6, 138.7, 135.4, 132.0, 129.3, 128.9, 127.7, 94.8, 75.2, 70.5, 61.8, 51.4, 43.0 (major conformer)

IR: 3467, 2925, 2253, 1724, 1584, 1495, 1402, 1356, 1402, 1356, 1326, 1286, 1153, 1036, 913, 870, 718

MS (El⁺): 367 (M⁺, 46), 365, 323, 321, 296, 294 (100), 281, 265, 218, 188, 174, 146, 144, 119, 91, 65
Trichloroethylcarbamate benzazocinone 313
Trichloroethylcarbamate benzazocinone 313
Trichloroethylcarbamate O-acetyl benzazocinone 314

![Chemical Structure](image)

To a stirring solution of alcohol 313 (218.7 mg, 0.596 mmol), TEA (125 μl, 0.895 mmol), and catalytic DMAP in 5 ml CH₂Cl₂ was added Ac₂O (85 ul, 0.89 mmol) dropwise. After stirring for 30 minutes and the absence of starting material was revealed by TLC the solution was washed with 2N HCl (2 x 2ml) and then separated. The aqueous layers were extracted with 1 ml of CH₂Cl₂. The organic layers were combined and then washed with sat. NaHCO₃ (2 x 2ml), H₂O (2 x 2ml), brine (1 x 2 ml) and then dried over Na₂SO₄. Removal of the solvent yielded 224.7 (92 %) of acetate 314. Rₐ = .65 (80% Et₂O / hexane)

\(^1\)H NMR (CDCl₃): 7.38-7.10 (4H, m), 5.37 (0.5H, app.t, J = 7.4 Hz), 5.10 (1H, B of AB, t, J = 15.4 Hz), 4.88 (1H, B of AB, dd, J₁ = 12.5 Hz, J₂ = 5.9 Hz), 4.66 (1H, A of AB, dd, J₁ = 12.5 Hz, J₂ = 9.6 Hz), 4.83-4.75 (0.5H, m), 3.67 (1H, A of AB, t, J = 15.4 Hz), 3.33-3.13 (2H, m), 3.08 (0.5H, app.d, J = 11.8 Hz), 2.97-2.84 (1H, m), 2.69 (0.5H, app.d, J = 9.6 Hz), 2.09 and 1.90 (3H, 2 singlets) (mixture of conformers)

\(^13\)C NMR (CDCl₃): 203.7, 169.6, 153.7, 138.9, 134.8, 132.4, 129.4, 129.0, 127.8, 95.0, 75.4, 69.0, 62.0, 47.9, 37.4, 21.2

IR: 3421, 2931, 1724, 1496, 1402, 1288, 1239, 1220, 1191, 1151, 1044, 1026, 913, 826, 718

MS (EI+): 409 (M+, 26), 407, 351 (100), 349, 323, 306, 291, 188, 174, 161, 133, 130, 103, 90, 89, 63
Trichloroethylcarbamate \textit{O}-acetyl benzazocinone 314

\begin{center}
\includegraphics[width=0.3\textwidth]{figure.png}
\end{center}

\begin{itemize}
\item HRMS (EI+): Calculated for $\text{C}_{16}\text{H}_{16}\text{NO}_{5}\text{Cl}_3$: 407.0094
\item Found: 407.0092
\end{itemize}
Trichloroethylcarbamate \textit{O}-acetyl benzazocinone 314
Trichloroethylcarbamate O-acetyl benzazocinone 314
**O-Acetyl Benzazocinone 315**

To a stirring solution of Troc carbamate 314 (224.7 mg, 0.550 mmol) and 10% Pb/Cd couple (308.0 mg, 2.74 mmol) prepared according to reference X in 2 ml of THF was added 2 ml of a 1M solution of NH$_4$OAc. The biphasic solution was stirred rapidly until TLC revealed the absence of starting material (approx. 1 hr). The solution was diluted with 2 ml Et$_2$O and filtered through a short plug of Celite® and then the 2 layers were separated. The aqueous layer was extracted with 2 ml of Et$_2$O and then the organic layers were collected. The combined organic layers were washed with 2 ml of NaHCO$_3$ and 2 ml of brine. The ethereal layers were dried over MgSO$_4$ and then the solvent was removed in vacuo to afford 93.6 mg (74 %) of crude aniline 315. Purification using silica gel chromatography (80% Et$_2$O / Hexane) yielded 73.2 mg (57%) of pure aniline 315.

R$_r$ = .34 (80% Et$_2$O/Hexane)

$^1$H NMR (CDCl$_3$): 7.12 (1H, app.t, J = 7.4), 7.05 (1H, app.d, J = 7.4), 6.83 (1H, app.t, J = 7.4), 6.75 (1H, app.d, J = 7.4), 5.14 (1H, m), 4.08 (0.5H, bs), 3.92 (1H, B of AB, d, J = 17.6 Hz), 3.78 (1H, A of AB, d, J = 17.6 Hz), 3.21 (1H, B of AB, dd, J$_1$ = 9.6 Hz, J$_2$ = 3.7 Hz), 3.16 (1H, B of AB, dd, J$_1$ = 11.0 Hz, J$_2$ = 6.6 Hz), 3.03 (1H, A of AB, dd, J$_1$ = 14.7 Hz, J$_2$ = 3.7 Hz), 2.89 (1H, A of AB, dd, J$_1$ = 11.8 Hz, J$_2$ = 6.6 Hz), 2.04 (3H, s)

$^{13}$C NMR (CDCl$_3$): 211.1, 170.0, 145.8, 133.7, 128.5, 122.9, 120.9, 120.3, 70.9, 58.3, 43.3, 37.6, 21.1

IR: 3410, 2929, 1734, 1713, 1605, 1495, 1428, 1376, 1326, 1313, 1241, 1139, 1091, 1026, 752
O-Acetyl benzazocinone 315

MS (EI+): 233 (M+, 81), 205, 173, 146 (100), 131, 119, 115, 103, 91, 77, 65, 51

HRMS (EI+): Calculated for C$_{13}$H$_{15}$NO$_3$: 233.1052
Found: 233.1052
O-Acetyl benzazocinone 315
O-Acetyl benzazocinone 315
Conjugated enone 316 and deconjugated enone 317

To acetate 315 (63.0 mg, 0.272 mmol) in 1 ml of THF was added DBU (49 \mu l, 0.33 mmol). After 30 minutes TLC revealed the reaction was not complete so excess DBU (32 \mu l, 0.22) was added. Upon completion of the reaction the reaction mixture was quenched with 1 ml of sat. NaHCO₃. The layers were separated and the organic layer was washed with 1 ml brine and then dried over MgSO₄. The solvent was removed to give 26.9 mg (58%) of a crude mixture of enones. Preparative TLC purification afforded 3.8 mg (8%) of desired enone 316 and 6.5 mg (14%) of deconjugated enone 317.

Deconjugated enone 317

\(^1\)H NMR (CDCl₃): 7.16-7.04 (2H, m), 6.79 (1H, app. t, J = 8.1 Hz), 6.65 (1H, app. d, J = 8.1 Hz), 6.56 (1H, d, J = 11.8 Hz), 5.53 (1H, dt, J₁ = 11.8 Hz, J₂ = 8.1 Hz), 3.99 (2H, s), 3.50 (2H, d, J = 8.1 Hz)

\(^13\)C NMR (CDCl₃): 206.8, 145.7, 134.4, 133.6, 129.2, 121.6, 121.3, 118.8, (1 sp2 carbon missing) 51.5, 41.2

IR: 3403, 2922, 1716, 1603, 1504, 1490, 1420, 1326, 1273, 1112, 749

MS (EI+): 173 (M+, 70), 144, 130 (100), 117

HRMS (EI+): Calculated for C₁₁H₁₁NO: 173.0841
Found: 173.0841
Deconjugated enone 317
Pyrroloindoline 318

Attempted silica gel purification of the crude mixture of enones 316 and 317 or exposure of enone 316 to mild acid catalyzed an anti-Baldwin Michael addition to give pyrroloindoline 318.

$^1$H NMR (CDCl$_3$): 7.17 (2H, m), 6.86 (1H, app.t, $J = 7.4$ Hz), 6.64 (1H, app.d, $J = 7.4$ Hz), 4.41 (1H, m), 3.76 (1H, B of AB, d, $J = 18.4$ Hz), 3.64 (1H, A of AB, d, $J = 18.4$ Hz), 3.37 (1H, B of AB, dd, $J_1 = 16.2$ Hz, $J_2 = 8.8$ Hz), 3.08 (1H, A of AB, d, $J = 16.2$ Hz), 2.44 (1H, B of AB, dd, $J_1 = 17.6$ Hz, $J_2 = 6.6$ Hz), 2.21 (1H, A of AB, dd, $J_1 = 17.6$ Hz, $J_2 = 10.3$ Hz)

$^{13}$C NMR (CDCl$_3$): 215.6, 128.7, 128.1, 127.8, 125.6, 120.6, 110.7, 62.7, 58.8, 42.4, 34.4

IR: 3359, 3304, 2923, 2852, 1748, 1605, 1480, 1461, 1362, 1263, 1152, 1118, 1073, 751

MS (EI+): 173 (M+, 54), 146, 144, 130, 117 (100), 91, 77, 65

HRMS (EI+): Calculated for C$_{11}$H$_{11}$NO$_1$ 173.0841
Found: 173.0841
Pyrroloindoline 318
Catechol 319

A round bottomed flask charged with 12.0 g (60.9 mmol) of 5-nitro vanillin, 230, 120 ml of 48% HBr and 120 ml acetic acid was heated at 120 °C for 22 hours. The acidic solvents were removed in vacuo and then 100 ml toluene was added to the flask and then evaporated to assist in the removal of water. The brownish yellow solids were collected and placed into a glass fiber Soxhlet extraction thimble. Using toluene as the extraction solvent the thimble was continually extracted until the filtrate was colorless. The toluene was removed in vacuo to yield 9.27 g (83 %) of catechol 319 as a dull yellow solid.

Rf = .21 (2% MeOH / CH₂Cl₂)

mp (toluene): 134-135 °C

¹H NMR (d₆-DMSO): 10.04 (exchangable, s), 9.81 (1H, s), 7.98 (1H, d, J = 1.8 Hz), 7.93 (exchangable, s), 7.47 (1H, d, 1.8 Hz)

¹³C NMR (d₆-DMSO): 190.8, 148.5, 147.4, 137.5, 127.2, 119.8, 116.0

IR: 3228, 2928, 1692, 1620, 1548, 1458, 1355, 1298, 1251, 1100, 1016, 939, 871, 764

MS (El+): 184 (M+1, 10), 183 (M+, 94), 165, 135, 107, 57 (100)

HRMS (El+): Calculated for C₇H₅NO₃: 183.0168
                         Found: 183.0168
Benzyl ether 231

To a stirring flask containing 18.31 g catechol 319 (100 mmol) in 250 ml of DMF was added 5.30 g of 95% NaH (210 mmol) and stirred for 10 minutes. Addition of 13.08 ml of BnBr (110 mmol) was carried out over 30 minutes. Upon completion of the reaction as evidenced by TLC, the solution was carefully poured into a well stirred beaker containing 250 ml 4N HCl and 250 ml brine. The magnetic stirred was removed and the beaker was covered and stored at -20 °C for 2 hours. The solid precipitate was filtered off and washed with H₂O (2 x 100 ml). The filtrate was extracted with Et₂O (3 x 100 ml) and the combined organic layers were washed with H₂O (3 x 100 ml) then brine (1 x 100 ml) before drying over anhydrous Na₂SO₄. Removal of the solvent in vacuo afforded a crude yellow solid which was recrystallized from EtOAc / hexanes to give 16.59 g (61 %) of benzyl ether 231 as bright yellow crystals. Rₜ = .42 (2% MeOH / CH₂Cl₂)

mp (EtOAc / hexane): 141 °C

¹H NMR (CDCl₃): 11.23 (1H, s), 9.85 (1H, s), 8.22 (1H, s), 7.70 (1H, s), 7.51-7.30 (5H, m), 5.25 (2H, s)

¹³C NMR (CDCl₃): 188.7, 151.6, 149.9, 135.0, 133.6, 128.8, 128.6, 127.74, 127.5, 121.4, 115.6, 71.7

IR: 3197, 2364, 1694, 1615, 1573, 1551, 1456, 1336, 1271, 1234, 1098, 1036, 747, 694

MS (EI+): 274 (M+1, 2), 273 (M+, 9), 92, 91 (100), 65
Benzyl ether 231

HRMS (EI+): Calculated for C_{14}H_{11}NO_2: 273.0637
            Found: 273.0636
Benzyl ether 231
Triflate 232

\[
\begin{align*}
\text{BnO} & \quad \text{H} \\
\text{CH}_2\text{Cl}_2 & \quad \text{Tf}_2\text{O}, \text{py} \\
\text{NO}_2 & \quad \text{CH}_2\text{Cl}_2
\end{align*}
\]

To a stirred solution of 14.23 g (52.1 mmol) of benzyl ether 231 in 250 ml of dry CH\(_2\)Cl\(_2\) and 6.32 ml (78.1 mmol) pyridine in a flame dried flask was added 9.64 ml (57.3 mmol) triflic anhydride dropwise at 0 °C. The bronze yellow solution was stirred at 0 °C for 30 minutes prior to quenching the reaction by careful addition of 100 ml of 2.5N HCl. The solution was separated and the aqueous phase was extracted with CH\(_2\)Cl\(_2\) (2 x 25 ml). The combined extracts were washed with sat. NaHCO\(_3\) (2 x 50 ml), H\(_2\)O (1 x 50 ml) and brine (1 x 50 ml) and then dried over anhydrous Na\(_2\)SO\(_4\). Filtration through a 50 g plug of silica gel and rinsing with CH\(_2\)Cl\(_2\), gave, upon concentration 21.0 g (99 %) of triflate 232 as yellow needles. The product was used in the next reaction without further purification. 

\[R_f = .85 \,(2\% \text{ MeOH} / \text{CH}_2\text{Cl}_2)\]

mp (EtOAc / hexane): 103 °C

\(^1\text{H NMR (CDCl}_3\):\quad 9.98 (1H, s), 8.11 (1H, d, J = 1.8 Hz), 7.87 (1H, d, J = 1.8 Hz), 7.43 (5H, m), 5.32 (2H, s)

\(^13\text{C NMR (CDCl}_3\):\quad 188.0, 152.8, 143.2, 135.3, 133.6, 129.0, 128.9, 127.8, 120.4, 119.1, 116.8, 116.2, 72.7

IR: \quad 3406, 3097, 2857, 1710, 1607, 1548, 1429, 1352, 1292, 1214, 1132, 1050, 932, 867, 739

MS (Cl\(+\):\quad 406 (M+1, 15), 274, 131, 91 (100)

HRMS (Cl\(+\)): \quad Calculated for C\(_{15}\)H\(_{11}\)NSO\(_3\)F\(_3\): 406.0208
\quad Found: 406.0204
Aryl dimethylmalonate 234

\[
\begin{align*}
\text{BnO} & \quad \text{OTf} & \quad \text{CH}_2(\text{CO}_2\text{Me})_2 & \quad \text{NaH, DMF} & \quad \text{BnO} & \quad \text{CO}_2\text{Me} \\
\text{NO}_2 & \quad \text{OHC} & \quad & & \quad \text{NO}_2 & \quad \text{OHC}
\end{align*}
\]

To a stirring slurry of 4.89 g (36.83 mmol) of 95% NaH and 70 ml DMF in a flame dried flask under argon atmosphere was added dropwise 4.20 ml (36.83 mmol) dimethylmalonate. The mixture was stirred until clear and then 7.11 g (17.54 mmol) of triflate 232 in 15 ml DMF was added dropwise. The red solution was stirred for 15 minutes and then quenched with slow dropwise addition of 100 ml of 2N HCl until the solution changed from red to orange and then the remainder was added. After stirring until the flask cooled to room temperature, the flask was stored at -20 °C for 2 hours. The light yellow crystals were filtered and washed with H2O and then ice cold MeOH. The crystals were dried in vacuo and afforded 6.02 g (89 %) of 234, which was sufficiently pure to use without further purification. Recrystallization can be carried out from hot EtOAc / hexanes. R<sub>f</sub> = .19 (40% Et<sub>2</sub>O / hexane, run twice)

mp (EtOAc / hexane): 139-140 °C

<sup>1</sup>H NMR (CDCl₃): 9.97 (1H, s), 8.08 (1H, d, J = 1.8 Hz), 7.75 (1H, d, J = 1.8 Hz), 7.37 (5H, m), 5.43 (1H, s), 3.64 (6H, s)

<sup>13</sup>C NMR (CDCl₃): 189.18, 166.28, 158.06, 150.36, 136.83, 134.54, 128.64, 128.57, 127.58, 124.09, 119.15, 114.92, 72.03, 52.80, 49.08

IR: 2954, 2361, 1748, 1708, 1612, 1579, 1539, 1435, 1356, 1282, 1200, 1157, 1052, 1019, 740, 700

MS (EI+): 387 (M+), 370, 310, 296, 222, 121, 92, 91 (100), 59
Aryl dimethylmalonate 234

\[
\begin{align*}
\text{BnO} & \quad \text{CO}_2\text{Me} \\
\text{OH} & \quad \text{CO}_2\text{Me} \\
\text{NO}_2 & 
\end{align*}
\]

HRMS (EI+): Calculated for C_{15}H_{17}NO_3: 387.0954
Found: 387.0953
Aryl dimethylmalonate 234
Benzyl alcohol 320

To a stirring solution of 22.87 g (59.0 mmol) of benzaldehyde 234 in 150 ml MeOH and 150 ml CH₂Cl₂ was added portionwise 0.67 g (17.7 mmol) of NaBH₄ at room temperature. The mixture was stirred for 30 minutes before concentrating the solvent to a small volume and redisolving in 300 ml Et₂O and washing with H₂O (2 x 50 ml). The organic layers were dried over MgSO₄ and the solvent removed to yield 22.97 g (100 %) of benzyl alcohol 320. Recrystallization from hot EtOAc / hexanes affords fine colorless needles. Rₜ = .11 (60% Et₂O / hexane, run twice).

mp (EtOAc / hexane): 113-114 ºC

¹H NMR (CDCl₃): 7.58 (1H, d, J = 1.8 Hz), 7.38 (5H, m). 7.30 (1H, d, J = 1.8 Hz), 5.34 (1H, s), 5.14 (2H, s), 4.70 (2H, s), 3.63 (6H, s)

¹³C NMR (CDCl₃): 167.3, 157.6, 150.0, 143.6, 135.3, 128.6, 127.5, 117.0, 115.2, 114.9, 71.8, 63.6, 52.7, 48.9

IR: 3445, 2953, 1747, 1537, 1434, 1356, 1287, 1200, 1158, 1031, 911, 850, 746, 700

MS (EI+): 389 (M+, 372, 312, 298, 121, 92 , 91 (100), 65

HRMS (EI+): Calculated for C₁₉H₁₉NO₅: 389.1110
Found: 389.1108
Benzyl alcohol 320
Benzyl alcohol 320

[Graph showing spectral analysis with various peaks and wavenumbers indicated.]
$p$-Methoxyphenyl protected benzyl alcohol 238

To a well stirred, flame dried round bottomed flask containing 10.37 g (26.6 mmol) benzyl alcohol 320 and 0.2 ml DMF dissolved in 100 ml CH$_2$Cl$_2$ was added 2.91 ml (39.9 mmol) SOCl$_2$. After stirring for 30 minutes, the solvent was removed *in vacuo* to give a light beige solid, which was suitably pure for the next reaction.

To a slurry of 1.41 g (55.86 mmol) of 95 % NaH in DMF was added 3.63 g (29.2 mmol) of 4-methoxyphenol and stirred for 10 minutes prior to cooling the solution to 0 °C. The crude benzyl chloride was dissolved in 50 ml DMF and added slowly to the well stirred sodium 4-methoxyphenoxide solution maintaining the solution temperature ≤ 0 °C. CAUTION: Failure to maintain temperatures ≤ 0 °C results in the formation of products derived from malonate addition to the benzylic position (321). Following the complete addition of the benzyl chloride, the solution was stirred for 15 minutes at 0 °C and then quenched by slow addition of 200 ml 4N HCl. The solution was allowed to warm to room and then it was extracted with Et$_2$O (2 x 100 ml, 1 x 50 ml). The combined ethereal layers were washed with H$_2$O (3 x 50 ml) and brine (1 x 100). After drying the solution over MgSO$_4$ and solvent evaporation, the crude solid was purified by silica gel chromatography to yield 9.53 g (72 %) of protected benzyl alcohol 238 as a yellow solid which can be further purified by recrystallization from EtOAc / hexanes to give light yellow needles.

R$_f$ = 0.66 (80% Et$_2$O / hexane).
p-Methoxyphenyl protected benzyl alcohol 238

\[
\begin{array}{c}
\text{BnO} \\
\text{CO}_2\text{Me} \\
\text{CO}_2\text{Me} \\
\text{OPMP} \\
\text{NO}_2
\end{array}
\]

mp (EtOAc / hexane): 82-83 °C

\[^1\text{H NMR (CDCl}_3\text{):} \quad 7.68 \text{ (1H, d, } J = 1.8 \text{ Hz),} \\
7.38 \text{ (5H, m),} \\
7.36 \text{ (1H, d, } J = 1.8 \text{ Hz),} \\
6.86 \text{ (4H, dd, } J = 8.1, 2.9), \\
5.37 \text{ (1H, s),} \\
5.15 \text{ (2H, s),} \\
5.04 \text{ (2H, s),} \\
3.78 \text{ (3H, s),} \\
3.66 \text{ (6H, s)}
\]

\[^{13}\text{C NMR (CDCl}_3\text{):} \quad 167.2, \\
157.6, \\
154.4, \\
152.2, \\
150.1, \\
140.0, \\
135.2, \\
128.7, \\
128.4, \\
127.5, \\
117.6, \\
115.8, \\
115.7, \\
115.5, \\
114.8, \\
71.9, \\
69.2, \\
55.7, \\
52.7, \\
48.9
\]

IR: 2951, 1747, 1622, 1538, 1509, 1434, 1357, 1289, 1232, 1160, 1038, 827, 745, 699

MS (EI+): 495 (M+, 100), 419, 372, 206, 123, 91

HRMS (EI+): Calculated for C\textsubscript{26}H\textsubscript{22}NO\textsubscript{9}: 495.1529

Found: 495.1532
$p$-Methoxyphenyl protected benzyl alcohol 238

![NMR Spectra](image-url)
$p$-Methoxyphenyl protected benzyl alcohol 238
Malonate addition to benzylic position, compound 321

\[
\begin{align*}
\text{R}_t &= .52 \ (80\% \text{ Et}_2\text{O / hexane}) \\
^1\text{H NMR (CDCl}_3\r): &\quad 7.60 \ (1\text{H, s}), \ 7.36 \ (1\text{H, s}), \ 7.30 \ (10\text{H, m}), \ 7.14 \ (1\text{H, s}), \ 6.97 \ (1\text{H, s}), \ 6.78 \ (4\text{H, dd, J = 8.1, 2.9}), \ 5.24 \ (1\text{H, s}), \ 4.93 \ (2\text{H, s}), \\
&\quad 4.80 \ (2\text{H, s}), \ 4.43 \ (2\text{H, s}), \ 4.01 \ (2\text{H, s}), \ 3.77 \ (3\text{H, s}), \ 3.61 \ (6\text{H, s}), \ 3.58 \ (6\text{H, s}) \\
^{13}\text{C NMR (CDCl}_3\r): &\quad 168.3, \ 167.3, \ 157.3, \ 156.4, \ 154.4, \ 152.1, \ 151.2, \ 149.0, \ 140.4, \\
&\quad 139.9, \ 135.4, \ 135.1, \ 128.6, \ 128.6, \ 128.3, \ 128.2, \ 127.5, \ 126.8, \\
&\quad 120.4, \ 119.5, \ 119.1, \ 116.3, \ 116.0, \ 115.7, \ 115.1, \ 114.7, \ 77.4, \\
&\quad 71.6, \ 71.5, \ 68.7, \ 61.5, \ 55.7, \ 53.16, \ 52.7, \ 48.9, \ 39.4 \\
\text{IR:} &\quad 3472, \ 2951, \ 1741, \ 1619, \ 1538, \ 1508, \ 1433, \ 1359, \ 1286, \ 1232, \\
&\quad 1174, \ 1041, \ 912, \ 829, \ 736, \ 699 \\
\text{MS (El+):} &\quad 866 \ (M+, \ 2), \ 790, \ 495, \ 419, \ 91 \ (100)
\end{align*}
\]
Product of malonate addition to benzylic position 321
Product of malonate addition to benzylic position 231
A stirring flask fitted with a short-path distillation head under argon was charged with 11.51 g (23.2 mmol) of malonate 238 and dissolved in 200 ml dry THF. Via syringe, 30.3 ml (60.5 mmol) of a 2M solution of borane dimethyl sulfoxide complex (BH$_3$·SMe$_2$) in THF was then added to the solution and then heated until the slow co-distillation of THF and DMS commenced (1 drop per 10 sec). As the level of the solvent fell, more dry THF was added. The solution was continuously refluxed until TLC indicated the absence of starting material and the mono-reduction product. The solution was cooled to room temperature and then excess borane was quenched by VERY slow addition of 50% sat. NaHCO$_3$. The organic layer was separated and the aqueous layer was extracted with Et$_2$O (2 x 50 ml). The combined organic layers were washed with H$_2$O (2 x 50 ml) and brine (1 x 50 ml) before drying over MgSO$_4$. Removal of the solvent in vacuo resulted in 10.74 g (100 %) of crude 322 as a viscous oil. Silica gel flash chromatography using 50% EtOAc / hexane as eluent afforded 8.44 g (83 %) of pure 322 as a yellow viscous oil. R$_f$ = .17 (80% Et$_2$O / hexane).

$^1$H NMR (CDCl$_3$): 7.40 (5H, m), 7.27 (1H, s), 7.21 (1H, s), 6.86 (4H, m), 5.10 (2H, s), 4.98 (2H, s), 4.15 (2H, A of AB, dd, J$_1$ = 11.0, J$_2$ = 7.7 Hz), 3.94 (2H, B of AB, dd, J$_1$ = 10.3, J$_2$ = 5.9 Hz), 3.78 (3H, s), 3.40 (1H, quintet, J = 6.6 Hz)

$^{13}$C NMR (CDCl$_3$): 158.1, 154.3, 153.1, 152.2 138.9, 135.1, 128.9, 128.7, 127.8, 121.0, 115.8, 114.8, 114.4, 113.8, 71.4, 69.2, 63.6, 55.7, 45.3
Diol 322

\[
\begin{align*}
\text{IR:} & \quad 3401, 2954, 1730, 1617, 1531, 1506, 1455, 1434, 1361, 1278, \\
& \quad 1228, 1142, 1040, 911, 825, 784, 735, 699
\end{align*}
\]

\[
\begin{align*}
\text{MS (EI+):} & \quad 439 (M^+, 14), 268, 123, 91 (100)
\end{align*}
\]

\[
\begin{align*}
\text{HRMS (EI+):} & \quad \text{Calculated for } C_{24}H_{25}NO_7: \quad 439.1631 \\
& \quad \text{Found:} \quad 439.1631
\end{align*}
\]
Diol 322
A round bottom flask was charged with 8.44 g (19.2 mmol) of nitro diol 322, 100 ml MeOH and 2.0 g of moist Raney nickel, which was rinsed 3 times with MeOH before addition to the reaction mixture. The flask fitted with a hydrogen balloon and purged of oxygen with the assistance of a water aspirator. The mixture was stirred for 14 hours and as the hydrogen was consumed the balloon was refilled. The mixture was filtered through Celite® and the cake washed with 50 ml MeOH. The solvent was removed in vacuo to afford 7.35 g (94 %) of crude amino diol 239 as a light tan foam, Rf = .06 (Et2O). The crude product was of sufficient purity to use in the next reaction, however flash chromatography could be carried out using 2% MeOH / CH2Cl2.

mp (CDCl3):  80 °C (DCl salt)

1H NMR (CDCl3):  7.36 (5H, m), 6.85 (4H, m), 6.50 (1H, s), 6.41 (1H, s), 4.06 (2H, A of AB, m), 3.92 (2H, A of AB, m), 3.76 (3H, s), 3.44 (1H, bm)

13C NMR (CDCl3):  158.2, 153.9, 152.9, 146.4, 137.4, 136.6, 128.7, 128.1, 127.7, 115.7, 114.6, 113.5, 109.8, 102.4, 70.5 (x2), 63.8, 55.7, 42.4

IR:  3366, 2927, 1739, 1611, 1582, 1508, 1440, 1378, 1230, 1132, 1035, 826, 737, 700

MS (EI+):  409 (M+, 82), 391, 286, 268, 238 (100), 146, 105, 91

HRMS (EI+):  Calculated for C24H27NO5:  409.1889
               Found:  409.1885
Diol aniline 239
Diol azide 240

In a large beaker with efficient magnetic stirring was dissolved 8.38 (20.5 mmol) of amino diol 239 in 200 ml of 10% H₂SO₄ and 100 ml of 1,4-dioxane. The stirred solution was cooled to -5 °C with an NaCl / ice bath. Small volumes of 1,4-dioxane were added in the event of precipitation of the amino diol. A solution of 2.12 g (30.7 mmol) of NaNO₂ in 30 ml H₂O was added dropwise over 15 minutes carefully maintaining the reaction temperature ≤ 0 °C. After addition was complete, the solution was stirred for 30 minutes at -5 °C. A solution of 2.12 g (32.6 mmol) of NaN₃ in 30 ml H₂O was added as quickly as possible while avoiding excessive foaming. The mixture was stirred for 30 minutes at -5 °C and then warmed slowly to room temperature and then stirred for an additional 1 hour at room temperature. The solution was extracted with Et₂O (3 x 50 ml) and then organic layers were collected and washed with sat. NaHCO₃ (2 x 50 ml), H₂O (1 x 50 ml), and brine (1 x 50 ml). The ethereal solutions were dried over MgSO₄ before removal of solvent in vacuo. The crude azido diol 240 was purified on silica gel using 80% Et₂O / hexanes as eluent to afford 7.80 g (82 % for 2 steps), Rₖ = .32 (Et₂O).

¹H NMR (CDCl₃): 7.39 (5H, m), 6.92-6.84 (6H, m), 5.06 (2H, s), 4.96 (2H, s), 4.14 (2H, B of AB, dd, J₁ = 10.3 Hz, J₂ = 7.4 Hz), 3.85 (2H, A of AB, dd, J₁ = 10.3 Hz, J₂ = 5.2 Hz), 3.78 (3H, s), 3.9-3.7 (1H, b, hidden under other peaks)

¹³C NMR (CDCl₃): 158.4, 154.2, 152.6, 140.0, 138.4, 135.9, 128.8, 128.4, 127.6, 119.2, 115.8, 114.7, 110.0, 107.7, 70.9, 70.1, 64.2, 55.7, 42.7
Diol azide 240

IR: 3367, 2950, 2113, 1608, 1580, 1509, 1434, 1377, 1230, 1035, 910, 826, 735, 699

MS (EI+): 435 (M+, 62), 312, 284, 264, 236, 123, 91 (100)

HRMS (EI+): Calculated for C_{24}H_{20}N_{2}O_{5}: 435.1794
Found: 435.1795
Diol azide 240
Mono-benzyl ether alcohol 323

\[
\begin{align*}
\text{OPMP} \ 240 & \xrightarrow{\text{BnBr, NaH, DMAP, THF}} \text{OPMP} \ 323
\end{align*}
\]

To a stirring solution of 1.64 g (3.77 mmol) of azido diol 240, 0.238 g (9.43 mmol) of 95% NaH and 138.2 mg (1.131 mmol) of DMAP in 40 ml of THF was added 0.49 ml (4.14 mmol) of BnBr dropwise. The reaction was monitored by TLC and when the reaction was complete the reaction was quenched with 10 ml of 0.5N HCl and diluted with 20 ml of Et₂O. The layers were separated and the aqueous layer was extracted with Et₂O (1 x 20 ml). The combined organic layers were washed with sat. NaHCO₃ (2 x 20 ml) and brine (1 x 20 ml) before drying over MgSO₄. The solvent was removed in vacuo to yield 2.10 g (106%) of crude product. The crude product was purified by silica gel flash chromatography using an eluent gradient of 30% to 60% Et₂O / hexane to provide 1.48 g (75%) of the mono-benzyl ether 323 as a bright yellow oil, Rᵢ = .59 (80% Et₂O / hexane).

\[^1\text{H NMR} (\text{CDCl}_3):\] 7.42-7.23 (10H, m), 6.87 (4H, dd, J₁ = 7.4 Hz, J₂ = 2.9 Hz), 6.86 (1H, s, under dd), 6.80 (1H, s), 5.02 (2H, app.d, J = 2.9 Hz), 4.96 (2H, s), 4.51 (2H, app.d, J = 2.2 Hz), 4.19 (1H, B of ABdd, J₁ = 10.3 Hz, J₂ = 7.4 Hz), 4.03 (1H, B of AB, dd, J₁ = 8.8 Hz, J₂ = 8.8 Hz), 3.92 (1H, m), 3.78 (3H, s), 3.68 (1H, A of ABdd, J₁ = 8.8 Hz, J₂ = 4.6 Hz)

\[^{13}\text{C NMR} (\text{CDCl}_3):\] 158.1, 153.8, 152.2, 139.5, 137.9, 135.9, 128.2, 128.0, 127.7, 127.2, 127.2, 119.0, 115.4, 114.3, 109.6, 107.3, 72.5, 71.0, 70.2, 69.6, 63.9, 55.2, 40.4

IR: 3466, 2932, 2869, 2110, 1608, 1581, 1505, 1455, 1435, 1375, 1230, 1040, 826, 739, 699
Mono-benzyl ether alcohol 323

\begin{center}
\includegraphics[width=0.5\textwidth]{molecule.png}
\end{center}

MS (El+): \hspace{1cm} 525 (M+, 40), 497, 374, 264, 236, 162, 123, 91 (100), 65

HRMS (El+): \hspace{1cm} Calculated for C_{31}H_{31}N_{3}O_{5}: 525.2264
\hspace{1cm} Found: \hspace{1cm} 525.2267
Mono-benzyl ether alcohol 323
Mono-TBS ether alcohol 324

To a stirring solution of 197.2 mg (0.453 mmol) of azido diol 240, 28.6 mg (1.13 mmol) of 95 % NaH and 16.6 mg (0.136 mmol) of DMAP in 5 ml of THF was added 81.9 mg (0.54 mmol) of TBSCI portionwise. The reaction was monitored by TLC and when the reaction was complete the reaction was quenched with 2 ml of 0.5N HCl and diluted with 5 ml of Et₂O. The layers were separated and the aqueous layer was extracted with Et₂O (1 x 5 ml). The combined organic layers were washed with sat. NaHCO₃ (2 x 5 ml) and brine (1 x 5 ml) before drying over MgSO₄. The solvent was removed in vacuo to yield 249.0 mg (100 %) of the mono TBS ether 324 as a dull yellow oil, Rₜ = .73 (80% Et₂O / hexane). The crude product was used in the next step without further purification.

¹H NMR (CDCl₃): 7.38 (5H, s), 6.87 (4H, m), 6.803 (1H, s), 6.799 (1H, s), 5.04, (2H, s), 4.96 (2H, s), 4.29 (1H, B of AB, td, J₁ = 7.4 Hz, J₂ =2.2 Hz), 4.18 (1H, A of AB, t, J = 2.2 Hz), 3.78 (3H, s), 3.76 (3H. m), 0.86 (9H, s), -0.001 (6H, s)

¹³C NMR (CDCl₃): 158.4, 154.1, 152.5, 140.0, 138.3, 136.1, 128.7, 128.2, 127.7, 119.0, 115.8, 114.7, 109.9, 107.4, 70.7, 70.1, 65.2, 65.1, 55.7, 42.8, 25.8, 18.1, -5.55, -5.64

IR: 3392, 2929, 2856, 2111, 1740, 1580, 1509, 1463, 1434, 1377, 1231, 1044, 835, 778, 735

MS (El+): 549 (M+ + 2), 505, 468, 424, 381 (100), 338, 279, 132

HRMS (Cl+): Calculated for C_{39}H_{39}N_{3}O_{5}: 550.2737
Found: 550.2728
Mono-TBS ether alcohol 324
Mono-TBS ether alcohol 324
Diacetate 325

A round bottomed flask was charged with 890 mg (2.04 mmol) of azido diol 240. 0.41 ml (4.29 mmol) of acetic anhydride, 0.35 ml (4.29 ml) of pyridine, 74.8 mg (0.61 mmol) of DMAP and 10 ml CH₂Cl₂. The mixture was stirred until TLC revealed the absence of starting material. The solution was poured into 10 ml of 2N HCl and separated. The aqueous layer was extracted with CH₂Cl₂ (2 x 10 ml) and then the organic layers were collected and washed with sat NaHCO₃ (2 x 10 ml), brine (1 x 10 ml) and then dried over Na₂SO₄. The solvent was removed to give 1.04 g (98 %) of crude diacetate 325. Silica gel chromatography, eluting with 60% Et₂O / hexanes afforded 947 mg (89 %) of pure diacetate 325 as a thick golden oil. Rᵣ = .59 (80% Et₂O / hexane).

¹H NMR (CDCl₃): 7.42-7.34 (5H, m), 6.92-6.81 (6H, m), 5.09 (2H, s), 4.97 (2H, s), 4.48 (2H, B of AB, dd, J₁ = 11.0 Hz, J₂ = 7.4 Hz), 4.36 (2H, A of AB, dd, J₁ = 11.0 Hz, J₂ = 6.6 Hz), 3.94 (1H, bm), 3.78 (3H, s), 1.99 (6H, s)

¹³C NMR (CDCl₃): 169.9, 157.8, 153.5, 151.8, 139.4, 138.4, 135.5, 128.0, 127.5, 126.9, 117.0, 115.1, 114.0, 107.0, 76.4, 70.0, 69.1, 63.4, 54.7, 20.0

IR: 2954, 2114, 1740, 1609, 1582, 1509, 1435, 1367, 1230, 1182, 155, 1041, 828, 754, 700, 605

MS (EI+): 519 (M+, 6), 396, 340, 280, 248, 236, 146, 123, 91 (100)

HRMS (EI+): Calculated for C₂₈H₂₇N₄O₇: 519.2006
Found: 519.2013
Mono-benzyl ether aldehyde 223

\[
\begin{align*}
\text{BnO} & \quad \text{O}{\text{Bn}} \\
\text{OPMP} & \quad \text{323} & \quad \text{PCC} & \quad \text{MgSO}_4 \\
\text{CH}_2\text{Cl}_2 & \quad \text{CH}_2\text{Cl}_2 & \quad \text{BnO} & \quad \text{O}{\text{Bn}} \\
\text{OPMP} & \quad \text{223} & \quad \text{N}_3
\end{align*}
\]

A solution of 778.1 mg (1.48 mmol) of alcohol 323, 957.4 mg (4.44 mmol) of PCC, 957.4 mg of MgSO\(_4\) in 20 ml of CH\(_2\)Cl\(_2\) was stirred for 4.5 hours and then quenched with 20 ml of Et\(_2\)O. The mixture was filtered through a short plug of silica gel and washed with Et\(_2\)O. The solvent was removed \textit{in vacuo} and purified by flash chromatography using 20% Et\(_2\)O/hexanes as eluent to yield 680.0 mg (88\%) of aldehyde 223, \(R_f = 0.29\) (40% Et\(_2\)O/hexane).

\(^1\text{H} \text{NMR (CDCl}_3\text{):} \quad 9.74 \ (1\text{H, app.s}), \ 7.39-7.19 \ (10\text{H, m}), \ 6.88 \ (6\text{H, m}), \ 5.02 \ (2\text{H, s}), \ 4.99 \ (2\text{H, s}), \ 4.56 \ (1\text{H, B of AB, d, J = 12.5 Hz}), \ 4.48 \ (1\text{H, A of AB, d, J = 12.5 Hz}), \ 4.25 \ (2\text{H, m}), \ 3.78 \ (3\text{H, s}), \ 3.71 \ (1\text{H, m}).

\(^13\text{C} \text{NMR (CDCl}_3\text{):} \quad 200.5, \ 157.6, \ 154.0, \ 152.3, \ 140.0, \ 139.4, \ 138.0, \ 135.7, \ 128.4, \ 128.1, \ 127.9, \ 127.3, \ 127.2, \ 115.9, \ 115.6, \ 114.5, \ 109.5, \ 107.3, \ 72.6, \ 70.6, \ 69.8, \ 67.7, \ 55.4, \ 49.3

\text{IR:} \quad 2862, \ 2114, \ 1724, \ 1583, \ 1508, \ 1455, \ 1434, \ 1378, \ 1230, \ 1108, \ 1043, \ 1108, \ 1043, \ 910, \ 827, \ 737, \ 699

\text{MS (El+):} \quad 523 \ (M+, \ 38), \ 415, \ 374, \ 374, \ 342, \ 292, \ 264, \ 236, \ 123, \ 91 \ (100)

\text{HRMS (El+):} \quad \text{Calculated for C}_{33}\text{H}_{31}\text{N}_3\text{O}_5: \quad 523.2107
\quad \text{Found:} \quad 523.2105
Mono-benzyl ether aldehyde 223
Mono-benzyl ether aldehyde 223
Mono-tert -butyldimethylsilyl ether aldehyde 326

A solution of 536.6 mg (976 μmol) of alcohol 324, 419.5 mg (1.946 mmol) of PCC, 540 mg of MgSO₄ in 15 ml of CH₂Cl₂ was stirred for 3 hours and then quenched with 15 ml of Et₂O. The mixture was filtered through a short plug of silica gel and washed with Et₂O. The solvent was removed in vacuo and purified by flash chromatography using 30% Et₂O / hexanes as eluent to yield 390 mg (73%) of aldehyde 326, R₉ = .47 (40% Et₂O / hexane).

¹H NMR (CDCl₃): 9.81 (1H, app.s), 7.41-7.32 (5H, m), 6.91 (6H, m), 5.04 (2H, s), 4.99 (2H, s), 4.34 (1H, B of AB, dd, J₁ = 10.3 Hz, J₂ = 8.1 Hz), 4.10 (1H, app.t), 3.81 (1H, A of AB, dd, J₁ = 10.3 Hz, J₂ = 6.6 Hz), 3.78 (3H, s), 0.81 (9H, s), -0.05 and -0.08 (6H, 2 singlets)

¹³C NMR (CDCl₃): 201.6, 157.6, 54.0, 152.3, 140.1, 139.4, 135.8, 128.5, 128.0, 127.4, 116.2, 115.7, 114.5, 109.4, 107.1, 70.59, 69.8, 61.0, 55.4, 51.7, 29.6, 25.6, 18.0, -5.7

IR: 2928, 2856, 2113, 1724, 1608, 1583, 1509, 1463, 1434, 1377, 1251, 1109, 1044, 837, 778, 698

MS (EI+): 547 (M+, 1), 462, 415, 339, 248, 236, 218, 91 (100), 75
Mono-TBS ether aldehyde 326
Mono-TBS ether aldehyde 326
Mono-benzyl ether ene adduct 252

A flask was charged with 830.0 g (1.58 mmol) of aldehyde 223, 51.5 mg (48.6 µmol) of Yb(fod)$_3$, 0.49 ml (48.6 µmol) of a 0.1M solution of AcOH in CH$_2$Cl$_2$, 5.15 mg of 60 mesh silica gel and 3.04 ml (31.7 mmol) of 2-methoxypropene and stirred for 7 days at room temperature. The reaction was monitored by NMR in C$_6$D$_6$ and the reaction was deemed complete upon disappearance of the aldehyde resonance. The reaction was then poured into 5 ml of 50% sat. NaHCO$_3$ and extracted with CH$_2$Cl$_2$ (2 x 5 ml). The combined organic layers were dried over Na$_2$SO$_4$ and the solvent removed in vacuo to afford a yellow oil. The oil was dissolved in 10 ml of MeOH and 50 mg of solid K$_2$CO$_3$ was added then stirred for 30 minutes before filtering off the gummy residue. The MeOH was evaporated in vacuo to yield 961.4 mg (91%) of crude ene product 252, which was used immediately in the next reaction.

$^1$H NMR (C$_6$D$_6$): 7.23-7.00 (10H, m), 6.90-6.63 (6H, m), 4.82 (1H, m), 4.64 (2H, s), 4.61-4.48 (2H, m), 4.33 (1H, m), 4.23-4.04 (1H, m), 3.86 (1H, s), 3.62 (1H, s), 3.33 (3H, s), 3.20-3.01 (1H, m), 3.11 (3H, bs), 3.05 (3H, bs), 2.62 (1H, B of AB, dd, J = 14.7 Hz, J = 5.2 Hz), 2.49 (1H, A of AB, dd, J$_1$ = 14.7 Hz, J$_2$ = 5.9 Hz), 1.57-1.26 (2H, m), 1.20 (3H, s), 1.16 (3H, s)

$^{13}$C NMR (C$_6$D$_6$): 161.7, 159.2, 154.7, 153.2, 141.4, 139.9, 138.4, 136.9, 128.7, 128.5, 127.2, 121.4, 116.1, 115.0, 110.0, 107.1, 101.2, 81.9, 72.5, 70.8, 70.6, 70.5, 70.1, 69.6, 55.2, 54.0, 49.0, 44.9, 41.6, 25.5, 25.3
Mono-benzyl ether ene adduct 252

IR: 2938, 2110, 1652, 1602, 1581, 1508, 1455, 1434, 1379, 1230, 1152, 1041, 826, 738, 699

MS (EI+): 636 (M-31, 4), 626, 564, 536, 502, 430, 362, 322, 292, 91 (100), 73
Mono-benzyl ether ene adduct 252
Mono-benzyl ether ene adduct 252
Benzyl ether triazoline 327

In a teflon screw-capped glass tube was dissolved 374.3 mg (0.561 mmol) of ene adduct 252 and 30 mg of solid K$_2$CO$_3$ in 7 ml benzene (degassed with argon for 10 minutes) and refluxed for 9.5 hours. Reaction was monitored by NMR in C$_6$D$_6$, observing the disappearance of the olefinic proton resonances. The solution was cooled and then filtered through activated charcoal and Celite® to give 378.0 mg of crude triazoline 327. Purification by silica gel chromatography (60% Et$_2$O/hexanes) yielded 83.4 mg (22%) of triazoline 327, R$_f$ = .13 (40% Et$_2$O/hexane).

$^1$H NMR (C$_6$D$_6$): 7.87 (1H, app.s), 7.28 (5H, m), 7.17-7.03 (5H, m), 6.87 (2H, m), 6.82 (1H, app. s), 6.73 (2H, m), 4.89 (1H, m), 4.73 (2H, s), 4.68 (2H, s), 4.44 (1H, B of AB, d, J = 12.5 Hz), 4.38 (1H, A of AB, d, J = 12.5 Hz), 4.27 (1H, B of AB, d, J = 18.4 Hz), 4.18 (1H, m), 4.05 (1H, B of AB, dd, J$_1$ = 9.6 Hz, J$_2$ = 5.2 Hz), 3.97 (1H, A of AB, dd, J$_1$ = 9.6 Hz, J$_2$ = 5.9 Hz), 3.74 (1H, A of AB, d, J = 18.4 Hz), 3.32 (3H, s), 3.02 (3H, s), 2.79 (1H, B of AB, dd, J$_1$ = 14.7 Hz, J$_2$ = 4.4 Hz), 2.56 (3H, s), 2.10 (1H, A of AB, dd, J$_1$ = 14.7 Hz, J$_2$ = 5.1 Hz), 1.26 (3H, s), 1.18 (3H, s)

$^{13}$C NMR (C$_6$D$_6$): 158.6, 157.7, 154.6, 153.5, 141.2, 139.5, 138.5, 138.0, 137.6, 137.4, 125.3, 117.6, 116.1, 115.2, 115.0, 112.4, 110.1, 107.1, 101.3, 101.2, 91.1, 89.4, 80.2, 77.6, 73.0, 72.8, 71.3, 71.1, 70.7, 70.3, 69.3, 68.2, 67.8, 55.2, 49.9, 49.1, 47.9, 47.8, 44.07, 43.8, 42.9, 41.6, 25.4, 25.3, 22.1, 19.3

IR: 2935, 1611, 1583, 1508, 1455, 1435, 1378, 1291, 1230, 1182, 1152, 1100, 1066, 827, 739, 699
Benzyl ether triazoline 327

MS (Cl+): 668 (M+1, <1), 626, 536, 504, 414, 214, 186 (100), 184, 142, 125, 91, 57
Benzyl ether triazoline 327
Benzyl ether triazoline 327
Benzyl ether triazole 327
TBS ether triazoline 329

In a teflon screw-capped glass tube was dissolved 110.3 mg (0.159 mmol) of ene adduct 328 and a catalytic amount of solid K₂CO₃ in 2.0 ml benzene (degassed with argon for 10 minutes) and refluxed for 27 hours. Reaction was monitored by NMR in C₆D₆, observing the disappearance of the olefinic proton resonances. The solution was cooled and then filtered through activated charcoal and Celite® to give 95.0 mg (86 %) of crude triazoline 329. Purification by silica gel chromatography (60% Et₂O/hexanes) yielded 16.5 mg (15 %) of triazoline 329, Rₗ = .11 (40% Et₂O/hexane).

¹H NMR (C₆D₆): 7.90 (1H, app.s), 7.32-7.07 (5H, m), 6.88-6.70 (5H, m), 4.86 (1H, m), 4.73 (2H, s), 4.69 (2H, s), 4.34 (1H, B of AB, d, J = 18.4 Hz), 4.27 (1H, B of AB, d, J = 9.6 Hz), 4.19 (1H, A of AB, dd, J₁ = 9.6 Hz, J₂ = 5.9 Hz), 3.84 (1H, A of AB, J = 18.4 Hz), 3.32 (3H, s), 3.09 (1H, m), 3.00 (3H, s), 2.88 (1H, B of AB, dd, J₁ = 15.4 Hz, J₂ = 3.7 Hz), 2.62 (3H, s), 2.17 (1H, A of AB, dd, J₁ = 15.4 Hz, J₂ = 4.4 Hz), 1.25 (3H, s), 1.19 (3H, s), 0.97 (9H, s), 0.03 and -0.01 (6H, 2 singlets)

¹³C NMR (C₆D₆): 158.7, 154.6, 153.5, 141.1, 138.0, 137.5, 128.7, 116.1, 115.0, 112.7, 106.9, 101.1, 91.6, 78.0, 70.6, 68.1, 63.7, 55.2, 50.0, 49.1, 46.2, 41.6, 26.1, 25.4, 25.3, 18.4, -5.2, -5.4

IR: 2953, 2856, 1611, 1582, 1509, 1463, 1453, 1379, 1230, 1100, 1066, 837, 777

MS (EI+): 644 (M-57, 84), 602, 570, 530, 502, 464, 436, 361, 332, 270, 91 (100), 73
TBS ether triazoline 329
TBS ether triazoline 329
Imidate 330 and Amide 331

In a teflon screw-capped glass tube was dissolved 772.5 mg (1.16 mmol) of ene adduct 252 and 50 mg of solid K₂CO₃ in 30 ml toluene and purged with argon for 15 minutes before refluxing for 13 hours. Reaction was monitored by NMR in C₆D₆, observing the disappearance of the olefinic proton resonances. The solution was cooled and then filtered through activated charcoal and Celite® to give 709.0 mg of crude imidate 22. Flash chromatography yielded 265.1 mg (36%) of imidate 330, Rₗ = .51 (60% Et₂O / hexane) and 221.4 mg (31%) of amide 331.

Imidate 330

¹H NMR (C₆D₆): 7.39 (1H, s), 7.37 (1H, s), 7.22-7.02 (9H, m), 6.90 (2H, d, J = 8.8 Hz), 6.77 (1H, bs), 6.73 (2H, d, J = 8.8 Hz), 4.92 (1H, B of AB, dd, J₁ = 11.0 Hz, J₂ = 5.9 Hz), 4.82 (2H, s), 4.77 (1H, s), 4.76 (1H, s), 4.60 (1H, A of AB, dd, J₁ = 9.6 Hz, J₂ = 5.9 Hz), 4.35 (1H, B of AB, d, J = 12.5), 4.18 (1H, A of AB, d, J = 12.5), 3.71 (1H, B of AB, dd, J₁ = J₂ = 9.6 Hz), 3.58 (3H, s), 3.43 (1H, A of AB, dd, J₁ = 9.6 Hz, J₂ = 5.9 Hz), 3.32 (3H, s), 3.06 (3H, s), 2.71 (1H, B of AB, d, J = 11.8 Hz), 2.60 (1H, A of AB, dd, J₁ = 11.8 Hz, J₂ = 5.9 Hz), 1.47 (3H, s), 1.25 (3H, s)

¹³C NMR (C₆D₆): 164.4, 158.0, 154.6, 153.6, 149.0, 139.1, 138.0, 137.9, 128.5, 128.4, 127.9, 127.4, 120.0, 118.0, 116.1, 115.0, 107.7, 101.2, 75.0, 72.8, 71.0, 70.8, 70.8, 55.2, 53.3, 49.0, 42.8, 37.0, 25.6, 25.4

IR: 2943, 2360, 1656, 1610, 1572, 1508, 1455, 1428, 1368, 1332, 1229, 1113, 1073, 1030, 826, 738, 699
Imidate 330

MS (Cl+):  
626 (M+1, 100), 592, 554, 536, 502, 470, 430, 412, 322, 292, 91

HRMS (EI+):  
Calculated for $C_{58}H_{49}NO_7$: 625.3039  
Found: 625.3044
Imidate 330

[Graphical representation of two chemical spectra with ppm axes labeled at the bottom of each graph.]
Benzazocinone 254

A screw-top pyrex tube was charged with 64.4 mg (964 μmol) of triazole 327. 5 drops of sat. K₂CO₃ and 5 ml of moist THF and then degassed with argon for 10 minutes. The reaction was irradiated with a Sylvannia 275W sunlamp for 12 hours. The reaction was followed by NMR (C₆D₆) and TLC. The solution was diluted with 5 ml Et₂O and washed with 50% sat. NaHCO₃ (2 ml). The ethereal solution was dried with anhydrous MgSO₄ and removed *in vacuo* to give 51 mg of crude product. Purification by preparative TLC using 60% Et₂O / hexanes yielded 29 mg (48%) of benzazocinone 524 as a yellow film, Rₕ = .00-.17 smear (60% Et₂O / hexane).

¹H NMR (C₆D₆):  7.22-7.01 (10H, m), 6.88 (2H, app.d, J = 8.8 Hz), 6.79 (1H, s). 6.75 (2H, app.d, J = 8.8 Hz), 6.63 (1H, s), 5.18 (1H, app.t, J = 8.8 Hz), 4.71 (2H, s), 4.68 (2H, s), 4.28 (2H, s), 3.95 (2H, app.d, J = 4.4 Hz), 3.60 (1H, B of AB, dd, J = 17.6 Hz), 3.44 (1H, A of AB, d, 17.6 Hz). 3.33 (3H, s), 3.16 (3H, s). 3.15 (1H, b, under peak) 3.10 (1H, B of AB, d, J = 14.7 Hz), 2.64 (1H, A of AB, dd, J₁ = 14.7 Hz, J₂ = 8.8 Hz), 2.00 (1H, b), 1.30 (3H, s). 1.28 (3H,s)

¹³C NMR (C₆D₆):  209.6, 158.4, 154.7, 153.5, 150.0, 138.8, 138.4, 137.4, 128.7, 128.6, 128.5, 127.8, 125.1, 118.6, 116.1, 115.0, 107.7, 101.5, 73.3, 71.5, 70.8, 70.5, 67.2, 62.1, 55.2, 49.6, 47.8, 44.3, 25.6

IR:  3370, 2927, 1708, 1611, 1582, 1508, 1455, 1372, 1229, 1183, 1137, 1106, 1073, 1039, 827, 737, 699
Benzazocinone 254

MS (El+): 625 (M+, >1), 565, 535, 442, 412 (100), 371, 291, 263, 230, 172, 117, 91
Benzazocinone 254
2,4,6-Triisopropylbenzenesulfonyl hydrazone 295

To a stirring solution of 6.5 mg (10 µmol) of benzazocine 254 and 3.3 mg (11 µmol) of 2,4,6-triisopropylbenzenesulfonyl hydrazide in 0.2 ml MeOH was added a catalytic amount of SOCl₂. The solution was stirred for 1 hours and then diluted with 2 ml CH₂Cl₂ and partitioned between NaHCO₃ and dried over Na₂SO₄. After solvent removal in vacuo the 8.6 mg (100%) of crude product was purified by preparative TLC using 40% Et₂O / hexanes afforded 4.8 mg (58 %) of hydrazone 295, R₄ = .62 (60% Et₂O / hexane).

¹H NMR (C₆D₆):
10.06 (1H, s), 7.42-7.27 (8H, m), 7.20-7.13 (4H, m), 6.92-6.77 (6H, m), 5.12 -4.89 (4H, m), 4.49 (2H, m), 4.40 (1H, B of AB, d, J = 11.8 Hz), 4.31 (1H, A of AB, d, J = 11.8 Hz), 4.19 (1H, m), 3.93 (2H, m), 3.78 (3H, s), 3.60 (1H, m), 3.31 (1H, m), 2.95 -2.86 (1H, m), 1.32-1.09 (21H, m)

¹³C NMR (C₆D₆):
157.7, 156.4, 154.2, 152.6, 152.6, 151.3, 138.8, 136.7, 136.0, 132.6, 128.8, 128.7, 128.5, 128.4, 128.2, 128.1, 128.06, 127.9, 127.8, 127.7, 127.3, 123.6, 123.4, 122.5, 117.2, 115.88, 115.8, 114.7, 111.9, 108.2, 108.2, 103.8, 103.4, 75.3, 75.2, 73.8, 73.4, 73.2, 72.5, 71.1, 71.0, 70.7, 70.1, 69.9, 69.6, 66.4, 60.5, 58.2, 55.7, 46.1, 44.6, 43.6, 42.3, 36.4, 34.1, 31.9, 30.3, 30.1, 30.0, 29.9, 29.7, 29.2, 25.2, 25.0, 24.8, 24.7, 23.6, 23.47

IR:
3397, 2958, 2360, 1749, 1599, 1508, 1456, 1365, 1331, 1231, 1169, 1106, 1075, 1041, 911,827, 736, 699, 661

MS (EI+):
833 (M+, 2), 728, 712, 682, 591, 579, 537, 455, 414, 398, 291, 276, 124, 91 (100)
2,4,6-Triisopropylbenzenesulfonyl hydrazone 295
2,4,6-Triisopropylbenzenesulfonyl hydrazone 295
2,4,6-Triisopropylbenzenesulfonyl hydrazone 295
APPENDICES

Appendix A
Table 1 X-ray experimental details of triazole 248
Table 2 Final atomic coordinates and displacement parameters
Table 3 Isotropic thermal parameters
Table 4 Intramolecular bond lengths and bond angles

Appendix B
Table 5 X-ray experimental details of enamide 265
Table 6 Final atomic coordinates and displacement parameters
Table 7 Isotropic thermal parameters
Table 8 Intramolecular bond lengths and bond angles

Appendix C
Table 9 X-ray experimental details of indoline 279
Table 10 Final atomic coordinates and displacement parameters
Table 11 Isotropic thermal parameters
Table 12 Intramolecular bond lengths and bond angles

X-RAY EXPERIMENTAL

Data collection was carried out on a Enraf-Nonius Kappa-CCD diffractometer. Structures were solved using the SIR92 program package, which located all the non-hydrogen atoms. Structure refinement on F² was carried out with SHELXL-96 (G.M. Sheldrick, University of Göttingen, Germany, 1996). All the non-hydrogen atoms were refined anisotropically and the hydrogen atoms were included in calculated positions using a riding model.
APPENDIX A

Crystal structure of the p-bromobenzoyl derivative of triazole 248, C_{25}H_{22}N_{3}O_{3}Br
### Table 1

Experimental details of triazole 248

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<th>Value</th>
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<td></td>
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Table 2

Final atomic coordinates and displacement parameters (in Å²)

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APPENDIX B

Crystal structure of enamide 265, C_{13}H_{13}NO
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X-ray experimental details of enamide 265

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<td>Unit cell dimensions</td>
<td>a = 12.7820(7) Å</td>
</tr>
<tr>
<td></td>
<td>b = 8.7790(9) Å</td>
</tr>
<tr>
<td></td>
<td>c = 10.4380(12) Å</td>
</tr>
<tr>
<td></td>
<td>$\alpha = 90.00^\circ$</td>
</tr>
<tr>
<td></td>
<td>$\beta = 105.125(5)^\circ$</td>
</tr>
<tr>
<td></td>
<td>$\gamma = 90.00^\circ$</td>
</tr>
<tr>
<td></td>
<td>1130.71 Å$^3$</td>
</tr>
<tr>
<td>Volume</td>
<td>4</td>
</tr>
<tr>
<td>Z value</td>
<td>1.347 Mg/m$^3$</td>
</tr>
<tr>
<td>Density (calc)</td>
<td>0.090 mm$^{-1}$</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>488</td>
</tr>
<tr>
<td>$F_{\infty\infty}$</td>
<td>1.66 to 26.59 °</td>
</tr>
<tr>
<td>$\theta$ range for data collection</td>
<td>0 \leq h \leq 15, 0 \leq k \leq 10, -13 \leq l \leq 12</td>
</tr>
<tr>
<td>Index ranges</td>
<td>2262</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>Full-matrix least-squares on F$^2$</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>2262 / 0 / 158</td>
</tr>
<tr>
<td>Goodness-Of-Fit on F$^2$</td>
<td>1.203</td>
</tr>
<tr>
<td>$2(\theta)_{\text{max}}$</td>
<td>53.18 °</td>
</tr>
<tr>
<td>Final $R$ indices [$I_o&gt;2\sigma(I_o)$]</td>
<td>$R_i = 0.068$, $R_p = 0.2234$</td>
</tr>
<tr>
<td>Largest dif. peak and hole</td>
<td>0.21 and -0.21 eÅ$^{-3}$</td>
</tr>
<tr>
<td>Atom</td>
<td>x</td>
</tr>
<tr>
<td>------</td>
<td>---------</td>
</tr>
<tr>
<td>O(1)</td>
<td>1.0548(1)</td>
</tr>
<tr>
<td>N(2)</td>
<td>0.8729(1)</td>
</tr>
<tr>
<td>O(3)</td>
<td>0.5843(2)</td>
</tr>
<tr>
<td>C(4)</td>
<td>0.9768(2)</td>
</tr>
<tr>
<td>C(5)</td>
<td>0.7839(2)</td>
</tr>
<tr>
<td>C(6)</td>
<td>0.7021(2)</td>
</tr>
<tr>
<td>C(7)</td>
<td>0.6210(2)</td>
</tr>
<tr>
<td>C(8)</td>
<td>0.7824(2)</td>
</tr>
<tr>
<td>C(9)</td>
<td>0.7701(2)</td>
</tr>
<tr>
<td>C(10)</td>
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</tr>
<tr>
<td>C(11)</td>
<td>0.8593(2)</td>
</tr>
<tr>
<td>C(12)</td>
<td>0.6396(2)</td>
</tr>
<tr>
<td>C(13)</td>
<td>0.7011(2)</td>
</tr>
<tr>
<td>C(14)</td>
<td>0.9882(2)</td>
</tr>
<tr>
<td>C(15)</td>
<td>0.6204(2)</td>
</tr>
<tr>
<td>C(16)</td>
<td>0.6542(2)</td>
</tr>
<tr>
<td>H(8)</td>
<td>0.838(1)</td>
</tr>
<tr>
<td>H(13)</td>
<td>0.701(2)</td>
</tr>
<tr>
<td>H(15)</td>
<td>0.564(2)</td>
</tr>
<tr>
<td>H(7)</td>
<td>0.564(3)</td>
</tr>
<tr>
<td>H(14A)</td>
<td>0.927(2)</td>
</tr>
<tr>
<td>H(14B)</td>
<td>1.019(2)</td>
</tr>
<tr>
<td>H(14C)</td>
<td>1.039(3)</td>
</tr>
<tr>
<td>H(11)</td>
<td>0.92510</td>
</tr>
<tr>
<td>H(16A)</td>
<td>0.610(2)</td>
</tr>
<tr>
<td>H(10A)</td>
<td>0.654(2)</td>
</tr>
<tr>
<td>H(16B)</td>
<td>0.627(2)</td>
</tr>
<tr>
<td>H(10B)</td>
<td>0.768(2)</td>
</tr>
<tr>
<td>H(9)</td>
<td>0.780(2)</td>
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Table 7

Isotropic thermal parameters

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<th>Atom</th>
<th>U11</th>
<th>U22</th>
<th>U33</th>
<th>U12</th>
<th>U13</th>
<th>U23</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)</td>
<td>0.0477(9)</td>
<td>0.087(2)</td>
<td>0.074(1)</td>
<td>0.013(1)</td>
<td>-0.003(8)</td>
<td>0.007(1)</td>
</tr>
<tr>
<td>N(2)</td>
<td>0.046(1)</td>
<td>0.044(2)</td>
<td>0.045(1)</td>
<td>0.005(1)</td>
<td>0.0033(8)</td>
<td>0.002(1)</td>
</tr>
<tr>
<td>O(3)</td>
<td>0.090(1)</td>
<td>0.068(2)</td>
<td>0.089(1)</td>
<td>-0.020(1)</td>
<td>-0.008(1)</td>
<td>0.001(1)</td>
</tr>
<tr>
<td>C(4)</td>
<td>0.047(2)</td>
<td>0.054(2)</td>
<td>0.051(1)</td>
<td>-0.002(1)</td>
<td>0.004(1)</td>
<td>-0.014(1)</td>
</tr>
<tr>
<td>C(8)</td>
<td>0.046(1)</td>
<td>0.048(2)</td>
<td>0.042(1)</td>
<td>0.005(1)</td>
<td>0.009(1)</td>
<td>0.003(1)</td>
</tr>
<tr>
<td>C(6)</td>
<td>0.043(1)</td>
<td>0.056(2)</td>
<td>0.043(1)</td>
<td>0.003(1)</td>
<td>0.010(1)</td>
<td>0.004(1)</td>
</tr>
<tr>
<td>C(7)</td>
<td>0.048(1)</td>
<td>0.080(2)</td>
<td>0.054(2)</td>
<td>0.005(2)</td>
<td>0.010(1)</td>
<td>0.023(2)</td>
</tr>
<tr>
<td>C(9)</td>
<td>0.069(2)</td>
<td>0.057(2)</td>
<td>0.050(1)</td>
<td>0.007(2)</td>
<td>0.011(1)</td>
<td>0.001(1)</td>
</tr>
<tr>
<td>C(10)</td>
<td>0.068(2)</td>
<td>0.062(2)</td>
<td>0.054(2)</td>
<td>0.001(2)</td>
<td>0.012(1)</td>
<td>0.013(1)</td>
</tr>
<tr>
<td>C(11)</td>
<td>0.047(2)</td>
<td>0.074(2)</td>
<td>0.044(1)</td>
<td>-0.002(1)</td>
<td>0.005(1)</td>
<td>-0.006(1)</td>
</tr>
<tr>
<td>C(12)</td>
<td>0.058(2)</td>
<td>0.064(2)</td>
<td>0.046(1)</td>
<td>0.009(2)</td>
<td>0.000(1)</td>
<td>0.005(1)</td>
</tr>
<tr>
<td>C(13)</td>
<td>0.044(1)</td>
<td>0.056(2)</td>
<td>0.065(2)</td>
<td>0.006(1)</td>
<td>0.003(1)</td>
<td>0.002(1)</td>
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<tr>
<td>C(14)</td>
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<td>0.061(3)</td>
<td>0.070(2)</td>
<td>0.021(2)</td>
<td>0.032(2)</td>
<td>0.012(2)</td>
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<tr>
<td>C(15)</td>
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<td>0.068(2)</td>
<td>0.067(2)</td>
<td>-0.004(2)</td>
<td>0.015(1)</td>
<td>0.006(2)</td>
</tr>
<tr>
<td>C(16)</td>
<td>0.065(2)</td>
<td>0.076(3)</td>
<td>0.071(2)</td>
<td>0.028(2)</td>
<td>0.021(1)</td>
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Table 8

Intramolecular bond lengths (Å) and bond angles (°):

Minimum bond length = 1.10 Å  Maximum bond length = 1.65 Å

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<thead>
<tr>
<th>Bond</th>
<th>Length (Å)</th>
<th>Bond</th>
<th>Length (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1) - C(4)</td>
<td>1.223(3)</td>
<td>N(2) - C(4)</td>
<td>1.392(3)</td>
</tr>
<tr>
<td>N(2) - C(5)</td>
<td>1.446(3)</td>
<td>N(2) - C(11)</td>
<td>1.409(4)</td>
</tr>
<tr>
<td>C(6) - C(7)</td>
<td>1.398(4)</td>
<td>C(6) - C(10)</td>
<td>1.491(5)</td>
</tr>
<tr>
<td>C(7) - C(15)</td>
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<td>C(8) - C(13)</td>
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</tr>
<tr>
<td>C(9) - C(11)</td>
<td>1.332(4)</td>
<td>C(9) - C(16)</td>
<td>1.510(4)</td>
</tr>
<tr>
<td>C(10) - C(12)</td>
<td>1.526(4)</td>
<td>C(12) - C(16)</td>
<td>1.506(4)</td>
</tr>
<tr>
<td>C(13) - C(15)</td>
<td>1.384(4)</td>
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</table>

<table>
<thead>
<tr>
<th>Bond</th>
<th>Angle (°)</th>
<th>Bond</th>
<th>Angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(4) - N(2) - C(5)</td>
<td>120.5(2)</td>
<td>C(4) - N(2) - C(11)</td>
<td>118.0(2)</td>
</tr>
<tr>
<td>C(5) - N(2) - C(11)</td>
<td>121.3(2)</td>
<td>O(1) - C(4) - N(2)</td>
<td>121.0(3)</td>
</tr>
<tr>
<td>O(1) - C(4) - C(14)</td>
<td>121.6(3)</td>
<td>N(2) - C(4) - C(14)</td>
<td>117.3(3)</td>
</tr>
<tr>
<td>N(2) - C(5) - C(6)</td>
<td>120.1(3)</td>
<td>N(2) - C(5) - C(8)</td>
<td>118.9(2)</td>
</tr>
<tr>
<td>C(6) - C(5) - C(8)</td>
<td>121.0(3)</td>
<td>C(5) - C(6) - C(7)</td>
<td>117.6(3)</td>
</tr>
<tr>
<td>C(5) - C(6) - C(10)</td>
<td>121.2(3)</td>
<td>C(7) - C(6) - C(10)</td>
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<td>C(5) - C(8) - C(13)</td>
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</tr>
<tr>
<td>C(11) - C(9) - C(16)</td>
<td>130.1(3)</td>
<td>C(6) - C(10) - C(12)</td>
<td>112.4(3)</td>
</tr>
<tr>
<td>N(2) - C(11) - C(9)</td>
<td>130.5(3)</td>
<td>O(3) - C(12) - C(10)</td>
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<td>C(8) - C(13) - C(15)</td>
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<td>C(7) - C(15) - C(13)</td>
<td>120.2(3)</td>
</tr>
<tr>
<td>C(9) - C(16) - C(12)</td>
<td>112.5(3)</td>
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</tbody>
</table>
APPENDIX C

Crystal structure of 9,9a-dihydro-8-methoxy-6-methyl-2-oxo-1H-pyrrolo[1,2-a]indole, \( \text{C}_{13}\text{H}_{15}\text{NO}_2 \).\(^{58}\)
<table>
<thead>
<tr>
<th><strong>Empirical formula</strong></th>
<th>C&lt;sub&gt;13&lt;/sub&gt;H&lt;sub&gt;15&lt;/sub&gt;NO&lt;sub&gt;2&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formula weight</strong></td>
<td>217.26</td>
</tr>
<tr>
<td><strong>Crystal</strong></td>
<td>Colorless needle, 0.1 x 0.2 x 0.4 mm</td>
</tr>
<tr>
<td><strong>Temperature</strong></td>
<td>293 °K</td>
</tr>
<tr>
<td><strong>Wavelength</strong></td>
<td>Mo Kα radiation (0.71073 Å)</td>
</tr>
<tr>
<td><strong>Crystal system</strong></td>
<td>Monoclinic</td>
</tr>
<tr>
<td><strong>Space group</strong></td>
<td>P2&lt;sub&gt;1&lt;/sub&gt;/n (No. 14)</td>
</tr>
<tr>
<td><strong>Unit cell dimensions</strong></td>
<td>a = 8.662(2) Å</td>
</tr>
<tr>
<td></td>
<td>b = 9.084(2) Å</td>
</tr>
<tr>
<td></td>
<td>c = 14.509(3) Å</td>
</tr>
<tr>
<td></td>
<td>α = 90 °</td>
</tr>
<tr>
<td></td>
<td>β = 98.15(3) °</td>
</tr>
<tr>
<td></td>
<td>γ = 90 °</td>
</tr>
<tr>
<td><strong>Volume</strong></td>
<td>1130.1(4) Å³</td>
</tr>
<tr>
<td><strong>Z value</strong></td>
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</tr>
<tr>
<td><strong>Density (calc)</strong></td>
<td>1.277 Mg/m³</td>
</tr>
<tr>
<td><strong>Absorption coefficient</strong></td>
<td>0.086 mm⁻¹</td>
</tr>
<tr>
<td><strong>F&lt;sub&gt;oo0&lt;/sub&gt;</strong></td>
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</tr>
<tr>
<td><strong>θ range for data collection</strong></td>
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</tr>
<tr>
<td><strong>Index ranges</strong></td>
<td>0 ≤ h ≤ 10, 0 ≤ k ≤ 11, -18 ≤ l ≤ 18</td>
</tr>
<tr>
<td><strong>Reflections collected</strong></td>
<td>2427</td>
</tr>
<tr>
<td><strong>Refinement method</strong></td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td><strong>Data / restraints / parameters</strong></td>
<td>2427 / 0 / 164</td>
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<tr>
<td><strong>Goodness-Of-Fit on F²</strong></td>
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</tr>
<tr>
<td><strong>2(θ) max</strong></td>
<td>56 °</td>
</tr>
<tr>
<td><strong>N (hkil) unique</strong></td>
<td>2427</td>
</tr>
<tr>
<td><strong>Final R indices [I &gt; 2σ(Io)]</strong></td>
<td>R&lt;sub&gt;1&lt;/sub&gt; = 0.0488, R&lt;sub&gt;2&lt;/sub&gt; = 0.1222</td>
</tr>
<tr>
<td><strong>R indices (all data)</strong></td>
<td>R&lt;sub&gt;1&lt;/sub&gt; = 0.1111, R&lt;sub&gt;2&lt;/sub&gt; = 0.1582</td>
</tr>
<tr>
<td><strong>Largest dif. peak and hole</strong></td>
<td>0.115 and -0.152 eÅ⁻³</td>
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Table 10
Final atomic coordinates and displacement parameters (in Å²)

<table>
<thead>
<tr>
<th>Atom</th>
<th>Site</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(iso)</th>
<th>Occ.</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(2)</td>
<td>4e</td>
<td>0.6308(2)</td>
<td>0.4689(2)</td>
<td>0.7641(1)</td>
<td>0.057</td>
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<tr>
<td>H(4)</td>
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<td>0.5130(2)</td>
<td>0.2629(2)</td>
<td>0.5191(1)</td>
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<tr>
<td>H(7a)</td>
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<td>0.0622(2)</td>
<td>0.5022(3)</td>
<td>0.6180(2)</td>
<td>0.071</td>
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</tr>
<tr>
<td>H(7b)</td>
<td>4e</td>
<td>0.1443(2)</td>
<td>0.6501(3)</td>
<td>0.5940(2)</td>
<td>0.071</td>
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<tr>
<td>H(8)</td>
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<td>0.1324(2)</td>
<td>0.7031(2)</td>
<td>0.7453(2)</td>
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<td>H(9a)</td>
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<td>0.0194(3)</td>
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<td>0.6184(2)</td>
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<td>H(9b)</td>
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<td>0.5201(3)</td>
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</tr>
<tr>
<td>H(12a)</td>
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<td>0.77(1)</td>
<td>0.22(1)</td>
<td>0.581(8)</td>
<td>0.100</td>
<td>0.32(4)</td>
</tr>
<tr>
<td>H(12b)</td>
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<td>0.77(1)</td>
<td>0.21(1)</td>
<td>0.708(8)</td>
<td>0.100</td>
<td>0.32</td>
</tr>
<tr>
<td>H(12c)</td>
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<td>0.84(1)</td>
<td>0.37(1)</td>
<td>0.660(9)</td>
<td>0.100</td>
<td>0.32</td>
</tr>
<tr>
<td>H(12d)</td>
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<td>0.822(5)</td>
<td>0.299(6)</td>
<td>0.717(4)</td>
<td>0.100</td>
<td>0.68</td>
</tr>
<tr>
<td>H(12e)</td>
<td>4e</td>
<td>0.806(6)</td>
<td>0.335(6)</td>
<td>0.600(4)</td>
<td>0.100</td>
<td>0.68</td>
</tr>
<tr>
<td>H(12f)</td>
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<td>0.196(6)</td>
<td>0.635(5)</td>
<td>0.100</td>
<td>0.68</td>
</tr>
<tr>
<td>H(13a)</td>
<td>4e</td>
<td>0.1669(3)</td>
<td>0.266(3)</td>
<td>0.3634(2)</td>
<td>0.107</td>
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<td>H(13b)</td>
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<td>0.1778(3)</td>
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<td>0.107</td>
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<td>H(13c)</td>
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<td>0.3419(3)</td>
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Table 11

Isotropic thermal parameters

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<td>0.000(1)</td>
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<tr>
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<tr>
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Table 12
Intramolecular bond lengths (Å) and bond angles (°):

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<table>
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REFERENCES


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54. We thank Drs. Lawrence B. Allemany and William Wilson for their invaluable assistance with these measurements.


