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Synthesis of analogs of biologically important compounds

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Synthesis of analogs of biologically important compounds

by

Hak Won Kim

A Dissertation Submitted to the

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For the Graduate College

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DEDICATION

To my parents, wife and son.

GENERAL INTRODUCTION

The synthesis of natural products and their analogs has been an important and active area of organic chemistry. There are many new strategies and methodologies of synthesis waiting to be discovered. We have been involved in the synthesis of analogs of biologically important compounds, and the development of new methodology for this synthesis.

This dissertation is divided into three parts. The first part will deal with the synthesis of cyclopropane analogs of glutamic acid. The second part will describe the synthetic approaches to novel ion chelating tetracycline analogs. The third part will deal with the synthetic approaches to mitomycin analogs.

Explanation of Dissertation Format

This dissertation presents an alternate format and is divided into three parts preceded by a general introduction and followed by a general summary. Each of the parts is related to the others in that they are concerned with the synthesis of analogs of biologically important compounds. The three parts are intended to be separate, publishable articles. The numbering scheme adopted for the compounds and references is independent in each section.

PART I.

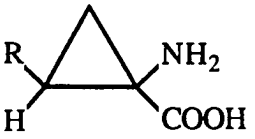
SYNTHESIS OF ANALOGS OF GLUTAMIC ACID

HISTORICAL

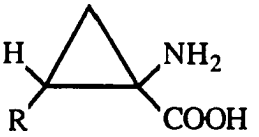
There is considerable interest in unnatural and uncommon amino acids from a synthetic and a biological perspective. Some of these novel amino acids have potential as suicide enzyme inhibitors.[1] These inhibitors are defined as a class of irreversible inactivators of specific target enzymes. Suicide enzyme inhibitors differ from the common irreversible inhibitors in that the reactive functional group is latent in the molecules in solution. Only after binding to the target enzyme and after the enzyme begins catalysis is the reactive chemical grouping uncovered. The particular chemical reaction sequence of the enzyme is required to unravel the inactivator. This activation occurs in a precise microenvironment only, the active site of the target enzyme. If covalent capture is efficient, then only the conscripted enzyme molecule is modified and its catalytic activity destroyed. The term suicidal inhibition conveys the role of the enzyme molecule in catalyzing its own destruction.

A subclass of suicide enzyme inhibitors is the cyclopropane-containing amino acids. These amino acids are particularly interesting because they constitute a unique form of "conformationally constrained" amino acids, which have been found in nature, generally in the unbound form or as simple dipeptides. Also, as a consequence of the severe carbon-carbon bond angle deformation demanded by the cyclopropane ring, a latent instability is incorporated into the peptide, which if unmasked in vivo, will form reactive entities capable of capturing nucleophiles or electrophiles present in a receptor or an enzyme active site.

Many cyclopropane amino acid analogs exist in diastereomeric E- and Z-forms in which the characteristic functionality at the β-carbon of the specific amino acid is *cis* to the carboxyl or *cis* to the amino function. Of course, each of these diastereomers consists of an enantiomeric pair.

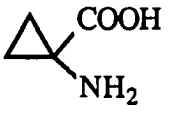


Z-Isomer
1



E-Isomer
2

There are some naturally occurring cyclopropane amino acids,[2] such as 1-aminocyclopropane carboxylic acid (Acc) (**3**), hypoglycin A (**4**), coronamic acid (**5**), carnosadine (**6**), and 3,4-methanoglutamic acid (**7**).



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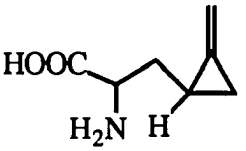

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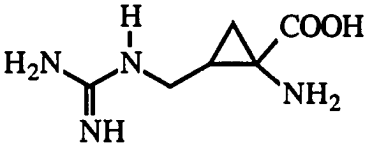

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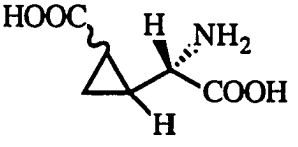
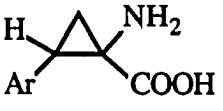


7

Several synthetic cyclopropane amino acids have been reported, such as aromatic 2,3-methano amino acid **8**, 2,3-methano valine (**9**), and 2,3-methanoproline (**10**).



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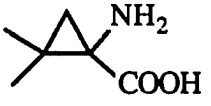

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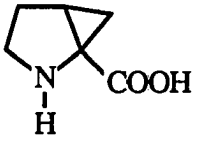
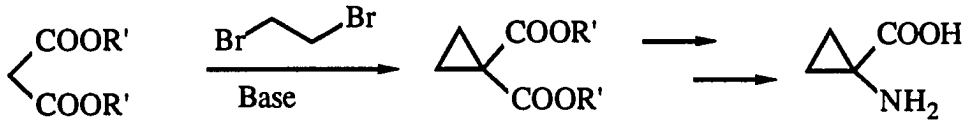


10

Many different approaches to the chemical synthesis of natural and unnatural cyclopropane amino acids are worth reviewing for their chemical content and bearing on important biological investigation.

1-Aminocyclopropane carboxylic acid (Acc) (**3**) was first isolated from cider apples and perry pears by Burroughs in 1957.[3] It has been found to be the biosynthetic precursor to the plant hormone ethylene[4] and is a substrate to the PLP-linked enzyme ACPC deaminase, which converts Acc to ammonia and 2-ketobutyrate.[5]

One of the earliest and straightforward synthetic methods entails the alkylation of a glycine derivative or congener with ethylene dibromide or its equivalent. Alkylation of the diester **11**[6] gave the cyclopropane diester **12**, which was followed by conversion of one ester function into an amino group. Further transformation afforded the free amino acid **3**.

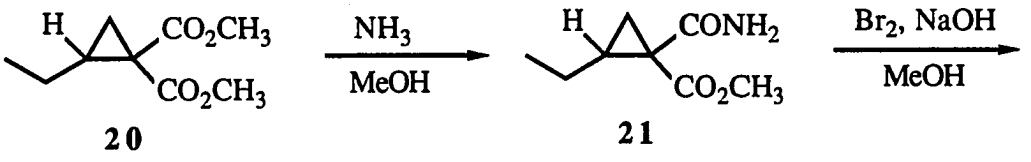


11 **12** **3**

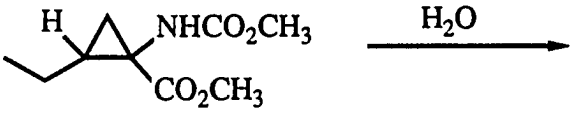
A second synthetic approach to Acc **3** is the "diazo addition" method in which diazomethane is added to an α-substituted acrylic acid derivative **13**, forming a pyrazoline **14**. Intermediate **14** can be converted into the desired cyclopropane **15** by light or heat. Bregovec[7] and Hiyama[8] used this method for the synthesis of Acc **3**.

Coronatine, a toxin produced by *Pseudomonas corona-facience*, which induces chlorosis in Italian ryegrass, contains coronamic acid (**5**). Coronamic acid (**5**) is N-acylated by coronafacic acid to give coronatine.

Ichihara and his coworkers reported the first synthesis of **5** in 1977.[13] Their synthesis of **5** began with the diester **20**, prepared by dialkylation of dimethyl malonate with 1,4-dibromo-2-butene followed by hydrogenation of the remaining vinyl groups. Aminolysis of the less hindered ester gave the amide **21** which was converted into the urethane **22** by Hofmann rearrangement. Hydrolysis of **22** gave racemic **5**.

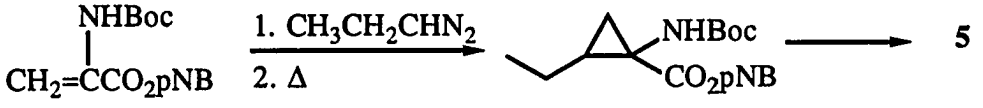


20 **21**



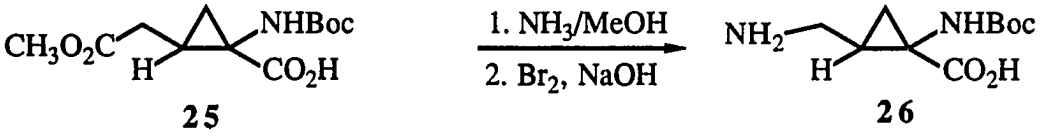
22 **5**

A later synthesis of racemic **5** in Stammer's group was accomplished by the addition of diazoethane to a dehydroalanine derivative followed by pyrolysis and deblocking.[7b]

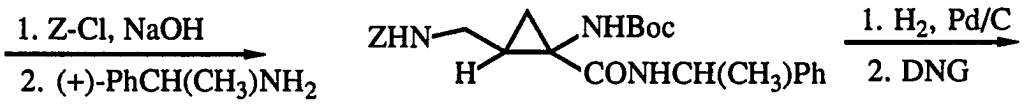


23 **24**

In 1984, carnosadine (**6**) was isolated from a red algae, *Grateloupia carmosa* [14], by Wakamiya *et al.* They also reported the synthesis of **6** which proceeded by way of the 2,3-methanoglutamic acid derivative **25**.[15] Conversion of the γ-ester function of **25** into an amino group by Hofmann rearrangement of the corresponding amide gave **26**. The DCC coupling of compound **26** with (R)-(+)-α-methylbenzylamine gave the separable amide **27**. Deprotection of the γ-amino group, guanidation, deblocking, and hydrolysis gave carnosadine (**6**).



25 **26**



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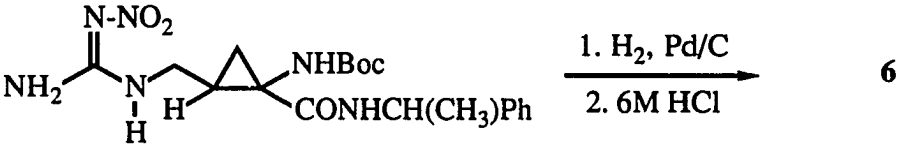


28

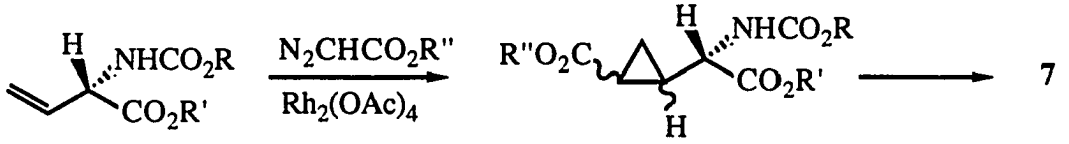
* Z = benzyloxycarbonyl

DCC-HOBt = N,N'-dicyclohexylcarbodiimide - 1-hydroxybezotriazole

DNG = 3,5-dimethyl-1-nitroguanylpyrazole

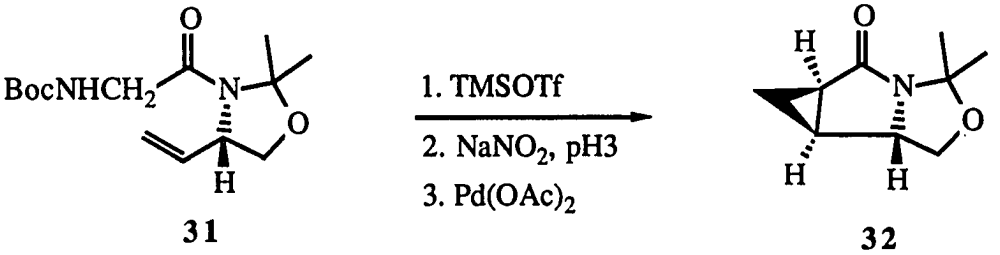
In 1969, *cis*- and *trans*-3,4-methanoglutamic acids (**7**) were isolated and identified.[16] The first synthesis of these amino acids **7** proceeded by rhodium acetate catalyzed addition of

diazoacetic ester to (2S)-vinyl glycine **29** which gave four chromatographically separable diastereomers of **30**. Deprotection of **30** gave the desired amino acid **7**.[17]

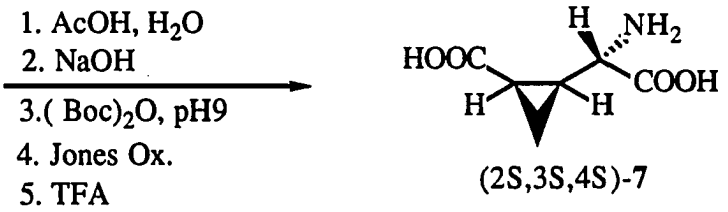


29 **30**

Yamanoi and Ohfune reported the enantioselective synthesis of **7** in 1988.[18] Deblocking of the alkene **31** (prepared from (2S)-2-amino-3-butenol), diazotization, and ring-closure gave the desired isomer **32** in a 6:1 ratio. Removal of the ketal and hydrolysis of the amide, followed by the necessary N-blocking, oxidation, and N-deblocking afforded enantioselectively the natural isomer of **7**.



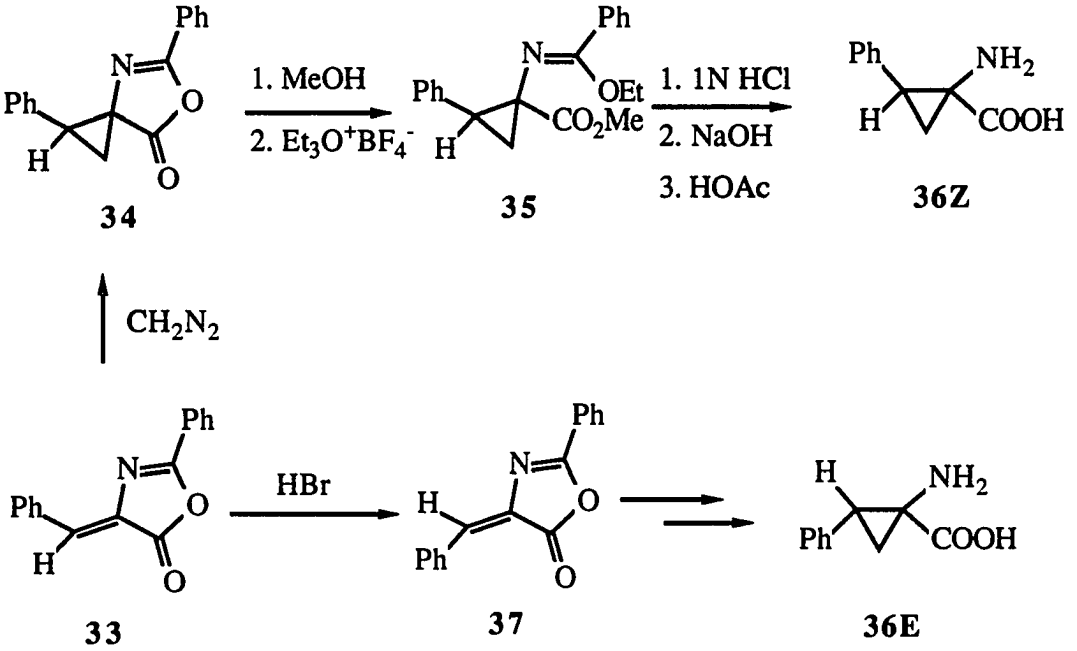
31 **32**



(2S,3S,4S)-7

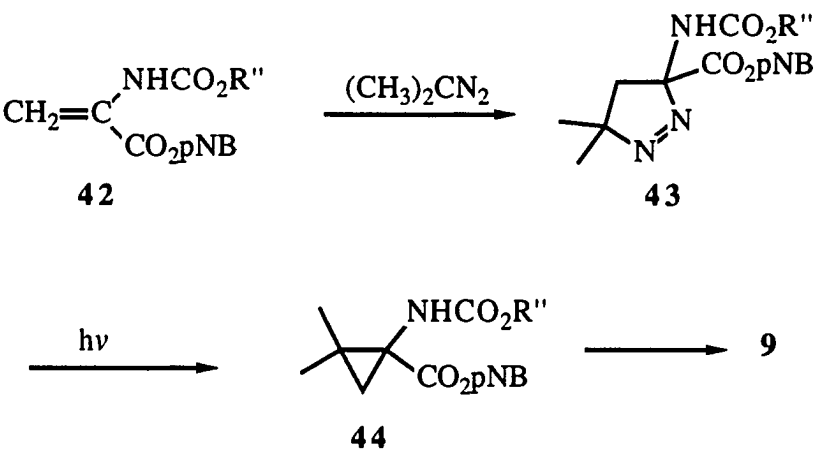
Several methods have been used to prepare synthetic cyclopropane-containing amino acids which may have significant biological activities, such as antibiotic and enzyme inhibitory activity. Some aromatic cyclopropane amino acids have been synthesized.

Stammer and coworkers reported the first synthesis of the (E)- and (Z)-isomers of racemic 2,3-methanophenylalanine **36** from **33**.[19] They used mild hydrolysis of imino ester intermediate **35** which was formed from the N-benzoyl group by treatment with Meerwein's reagent. Hydrolysis of the remaining methyl ester or hydrogenolysis of the benzyl ester afforded the free amino acid **36**. Isomerization of **33**[20] with hydrogen bromide gave the E-oxazolone **37** which was converted into the E-amino acid by the same procedure as was used for the Z-isomer. Also, recently, a chiral synthesis of **36** was reported by Fernandez et al.[21]

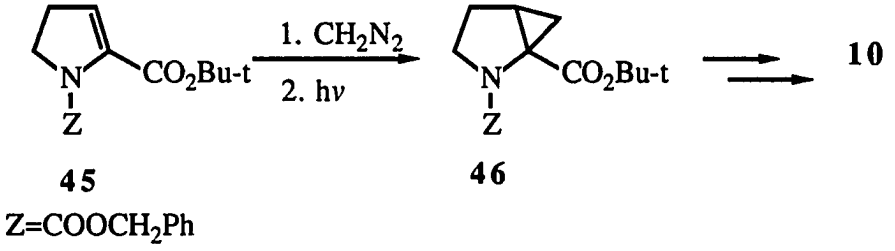


A number of the 2,3-methanophenylalanines **36**, prepared by this method, were shown to be reversible time-dependent inhibitors of both 3',4'-dihydroxyphenylalanine (DOPA) decarboxylase and tyrosine aminotransferase.

(Z)-2,3-Methanohistidine has also been synthesized by diazomethane cyclopropanation of the appropriate oxazolone.[22] This cyclopropane analog of histidine had a weak inhibitory effect on histidine decarboxylase.



The synthesis of racemic 2,3-methanoproline (**10**) has been accomplished by diazomethane cyclopropanation of the 2,3-dehydroproline derivative **45** followed by deblocking.[24]



45
Z=COOCH$_2$Ph

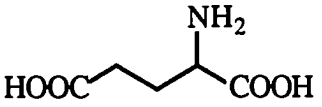
46

This cyclopropane analog, racemic 2,3-methanoproline (**10**), was found to be a weak inhibitor of an ethylene-forming enzyme in cucumber cotyledons and squash seeds.

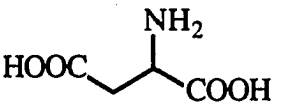
Other cyclopropane analogs of aliphatic amino acids, such as 2,3-methanoleucine (**47**)[2], 2,3-methanohomoserine (**48**)[25], and 2,3-methanomethionine (**49**)[25], were prepared by the diazoalkane method.

RESULTS AND DISCUSSION

We have been interested in the cyclopropane amino acids because of our research in the development of novel suicide inhibitors of glutamate decarboxylase (GAD) and aspartate aminotransferase (AAT).



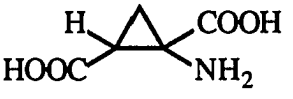
glutamic acid



aspartic acid

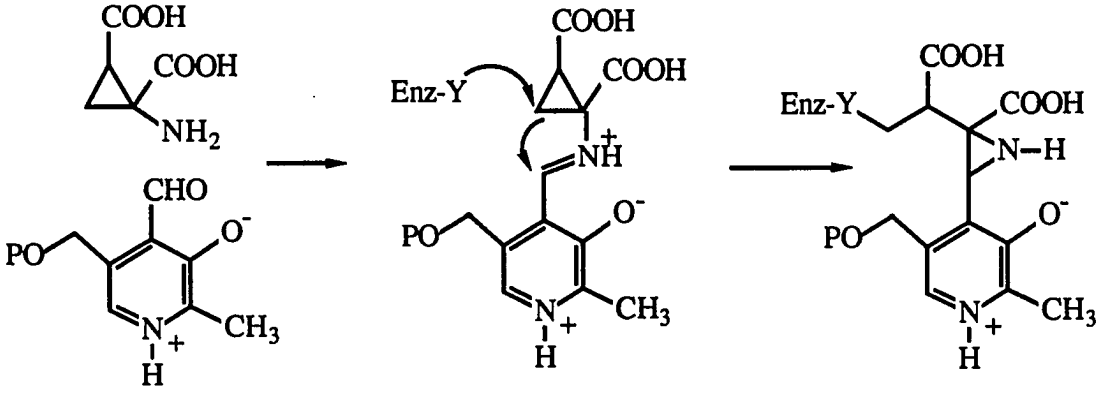
We proposed cyclopropane diacids **52** and **53**, which represent cyclic single-conformation analogs of glutamic acid, as enzyme-activated inhibitors.

52



53

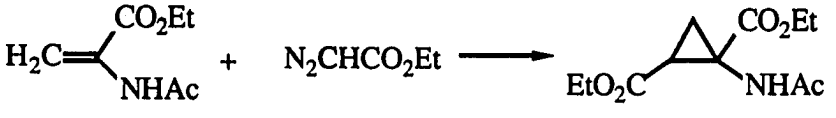
Our rationale for considering **52** and **53** as possible enzyme inhibitors is shown below.



54 **55**

In analogy with the facile opening of doubly activated cyclopropanes demonstrated by Stewart[27] and the Danishefsky group,[28] we speculated that pyridoxal phosphate adduct **54** would be reactive to nucleophiles and that it might form a covalent bond with a proximate amino or phenol group of the enzyme. The resulting dipolar intermediate would rapidly close to form the aziridine **55**, thus making the addition irreversible. An X-ray determination of the adduct of AAT with 2-methylaspartate indicated that the nucleophile could be the phenol oxygen of tyrosine **70***.[29] Indeed, the Walsh group[5] has recently postulated that nucleophilic attack on a cyclopropane methylene group is involved in the mechanism by which a bacterial deaminase converts Acc (**3**) into 2-oxobutyrate.

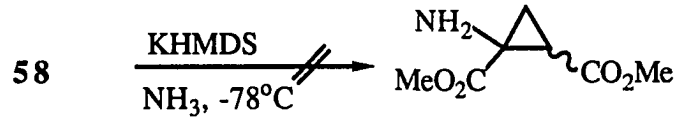
As the introduction indicated, a survey of literature methods for the synthesis of cyclopropane carboxylic acids revealed that there were two primary strategies : dipolar cycloadditions of diazo compounds and alkylation of 1,2-dihalides. The dipolar additions of diazo compounds to dehydroalaninates, followed by thermolysis or photolysis of the resulting dipolar addition product, constitute an effective method for the synthesis of many cyclopropane-containing amino acids.[8, 23] However, the yields are poor when the dipolarophile has bulky beta substituents or when ethyl diazoacetate is employed. Notably, diester **56**, the closest literature analog to amino acids **52** and **53**, is produced in only 12.5% yield.[30]



56

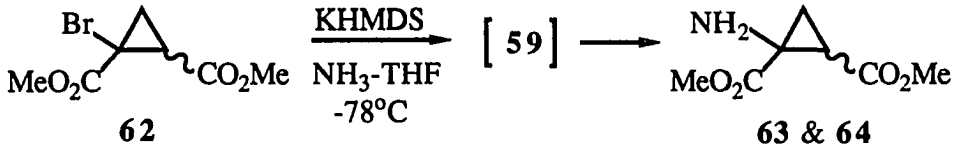
to yield the highly reactive intermediate, dimethyl Δ'-cyclopropene-1,2-dicarboxylate (**59**), followed by addition of the alcohol to the strained double bond.

Initially, we tried to make the cyclopropane amino diester **63** and **64** from **58** by the McDonald method. Reaction of **58** with potassium hexamethyldisilazane (KHMDS, 1.0 M in toluene) in liquid ammonia at -78°C did not give the desired products **63** and **64.**



63 & 64

We found that in this reaction, debromination of **62** might be crucial. So, we attempted a two step reaction for making **63** and **64.** Bromocyclopropane compound **62** was obtained from McDonald's method. The rapid addition of KHMDS (1M, toluene) to **62** in liquid ammonia and THF at -78°C gave a mixture of **63** and **64** in 35% to 50% yield after purification by silica gel chromatography.

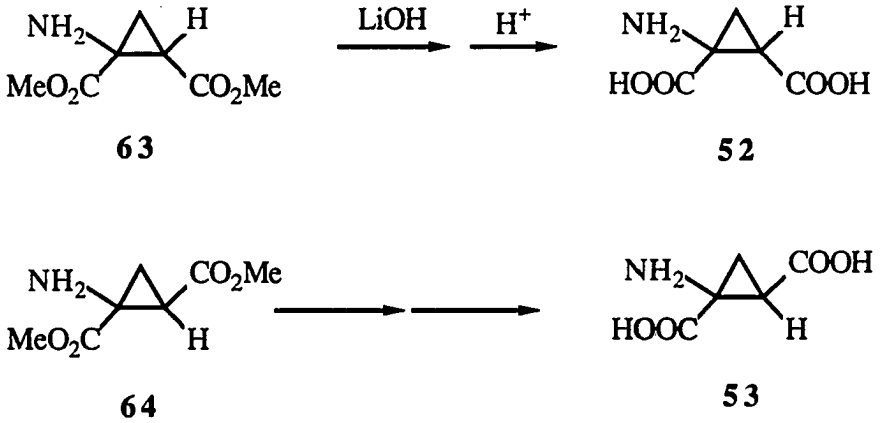


62 **63 & 64**

The relative amounts of diesters **63** and **64** produced in each experiment were variable. The structures of the diesters **63** and **64** were assigned after comparison of their NMR spectra with that of **60**.[31b]

In order to accomplish the synthesis of **52** and **53**, mild hydrolysis conditions were applied to each diester. Hydrolysis of each diester **63** and **64** with lithium hydroxide in THF-H_2O (4:1) at room temperature for 1 day, followed by acidification with 2N HCl

solution at 0°C, gave the crude amino acids, **52** and **53**, respectively. Each crude diacid was separated by preparative HPLC by a gradient elution using TFA in acetonitrile.



63 **52**

64 **53**

With samples of **52** and **53** in hand, the enzyme inhibition experiments were performed by Metzler's group.[32] Unfortunately, our amino diacids **52** and **53** do not show any inhibition of AAT. However, the facile preparation of these amino diacids by way of the cyclopropene **59** will make possible the synthesis of many other analogs, some of which may be enzyme inhibitors.

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Diethyl ether and tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. N,N-Dimethylformamide (DMF) was dried by azeotropic distillation with benzene, followed by vacuum distillation. Dichloromethane (CH_2Cl_2) and methyl alcohol were distilled from calcium hydride. All reactions were conducted under a nitrogen atmosphere, and all extracts were dried over anhydrous sodium sulfate or anhydrous magnesium sulfate. Apparatuses for experiments requiring anhydrous conditions were flame-dried under a stream of nitrogen or were dried in a 150°C oven for 12 h. Flash chromatography was performed on Kieselgel 60, mesh 230 - 400. Infrared spectra were obtained on a Perkin-Elmer 1320 spectrophotometer. Proton nuclear magnetic resonance spectra (300 MHz) were obtained using a Nicolet Magnetics Cooperation NT-300 spectrometer. All chemicals shifts are reported in δ relative to tetramethylsilane as an internal standard. Splitting patterns are designated as a s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Carbon-13 NMR spectra were determined on a Nicolet NT-300 spectrometer and are reported in δ relative to $CDCl_3$ (77.06 ppm). High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer. Low resolution mass spectra were recorded on a Finnegan 4023 mass spectrometer. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories Inc. The purity of all title compounds was judged to be >90% by ^1H NMR spectral determinations.

Dimethyl 1-aminocyclopropane-1,2-dicarboxylate (63 and 64). To a solution of bromo diester **58** (180 mg, 0.76mmol) in liquid ammonia (5 ml) and THF (5 ml)

52: ^{1}H NMR ($CDCl_3$) δ 1.66 (dd, J = 6.0, 9.9 Hz, 1H), 1.96 (dd, J = 6.0, 8.4 Hz, 1H), 2.39 (dd, J = 8.4, 9.9 Hz, 1H); ^{13}C NMR (DMSO-D_6) δ 18.75, 56.32, 65.12, 169.17, 170.47; IR ($CHCl_3$) 2930, 1720 cm^{-1}. Compound **52** was found to be greater than 98% pure using a Beckmann 110B HPLC eluting with 0.1% TFA in water. At a flow rate of 1 ml/min, the product had a retention time of 8.21 min.

53: ^{1}H NMR ($CDCl_3$) δ 1.77 (dd, J = 5.7, 9.0 Hz, 1H), 1.98 (dd, J = 5.7, 7.8 Hz, 1H), 2.58 (dd, J = 7.8, 9.0 Hz, 1H); ^{13}C NMR (DMSO-D_6) δ 29.13, 56.85, 64.38, 168.72, 171.96.

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PART II.

SYNTHESIS OF NOVEL ION CHELATING TETRACYCLINE ANALOGS

INTRODUCTION

The tetracyclines are a well established class of antibiotics. They have a wide spectrum of antibiotic activity and also chelate various metal ions to form complexes. We have been interested in the synthesis of novel ion chelating analogs of tetracyclines.

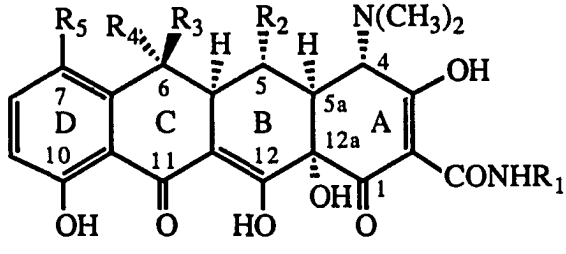
This manuscript will describe the synthetic approaches to several promising chelating analogs, such as monocyclic, bicyclic, and tricyclic analogs.

HISTORICAL

The tetracyclines are a family of broad spectrum antibiotics which have a common perhydronaphthacene skeleton. Tetracycline antibiotics have played an important role in human and veterinary medicine, and in animal nutrition.

I. General Aspects of Tetracyclines[1]

Duggar isolated the first tetracycline **1**, chlorotetracycline (CTC, aureomycin), in 1948 from the culture filtrate of *Streptomyces aureofaciens*.[1] In 1950, Kane, Finlay and Sobin of Pfizer Laboratories reported the discovery of another broad spectrum tetracycline antibiotic, oxytetracycline (**2**) (OTC, terramycin), from the fermentation liquors of *Streptomyces rimosus*.[3] Woodward and coworkers elucidated its structure.[4] The prototype compound tetracycline **3** (TC) was first prepared by catalytic hydrogenation of chlorotetracycline (**1**).[5] In 1957, McCormick *et al.*[6] discovered 6-demethylchlorotetracycline (**4**), a metabolite of a *S. aureofaciens* mutant.



1 - 8

Table 1. Therapeutically important tetracyclines

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1. Chlorotetracycline (Aureomycin, CTC), R_1=R_2=H, R_3=OH, R_4=CH_3, R_5=Cl

2. Oxytetracycline (Terramycin, OTC), R_1=R_5=H, R_2= R_3=OH, R_4=CH_3

3. Tetracycline (TC), R_1=R_2=R_5=H, R_3=OH, R_4=CH_3

4. Demethylchlorotetracycline (DMCT), R_1=R_2=R_4=H, R_3=OH, R_5=Cl

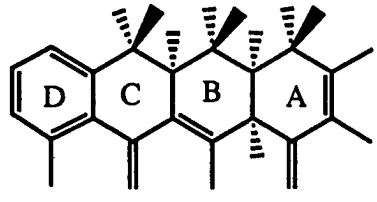
5. Rolitetracycline, Pyrrolidino- (PMT), R_1=CH_2-pyrrolidino, R_2=R_5=H, R_3=OH, R_4=CH_3

6. Methacycline (MOTC), R_1=R_5=H, R_2=OH, R_3,R_4=(CH_2=)

7. Deoxycycline (DOOTC), R_1=R_3=R_5=H, R_2=OH, R_4=CH_3

8. Minocycline (MITC), R_1=R_2=R_3=R_5=H, R_4=$N(CH_3)_2$

As the name indicates, tetracyclines are derived from a system **9** of four linearly annelated six-membered rings, and a characteristic arrangement of double bonds. Two distinct chromophoric regions A and BCD are separated by the sp^3 carbon atom 12a.



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The tetracyclines opened a new era of antibacterial chemotherapy. They are active orally and parenterally, and are relatively well tolerated. Also, their antimicrobial spectrum was broader than that of any other antibiotic then known. In accord with their mutual chemical

similarity, all tetracyclines have a very similar activity, e.g., activity against gram positive and negative bacteria.

Tetracyclines inhibit many enzyme reactions important for vital processes of bacterial and mammalian cells, e.g. oxidative phosphorylation and electron transfer.[1a] The tetracyclines are actively transported into the cells of susceptible bacteria and exert a bacteriostatic effect by inhibiting protein biosynthesis after binding to the 30S ribosomal subparticle.[1b] The binding apparently results in an inhibition of translocation of amino acid-laden transfer RNA (comprising the growing peptide chain) from the donor to acceptor site. Cessation of protein biosynthesis results and the cells stop multiplying and eventually die. The 80S ribosomes of eukaryotes, including yeasts and man, are much less sensitive to the effect of tetracyclines. This accounts for the useful selective toxicity of these drugs.

The tetracyclines also have a great tendency to form reversible complexes with cations and anions as well as with substances of low or high molecular weight.[1a] Theses properties are important for understanding their antibiotic activity, pharmacokinetics, and side effects. A selection of complex forming agents is shown in Table 2.

Table 2. Complexing agents for tetracyclines

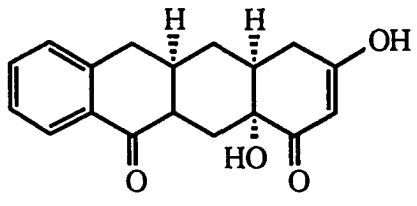
Metal cations	Fe^{3+}, Fe^{2+}, Cu^{2+}, Ni^{2+}, Co^{2+}, Zn^{2+}, Mn^{2+}, Mg^{2+}, Ca^{2+}, Be^{2+}, Al^{3+}, Zr^{4+}.
Anions	Phosphate, citrate, salicylate, p-hydroxybenzoate, saccharin anion.
Neutral compounds	caffein, urea, thiourea, polyvinylpyrrolidone.
Biopolymers	serum albumin, lipoproteins, globulins, RNA.

the asymmetric centers C-4, C-4a and C-12a is essential, whereas the configurations at C-5, C-5a and C-6 may be altered. The amide hydrogen may be substituted by a methyl group, but large groups have a deleterious effect except for those that are eliminated spontaneously in water. The dimethylamino group may be replaced by a primary amino group without loss of in-vitro activity, but all other changes so far lead to a decreased bacteriostatic action. The hydrophobic part of the molecule from C-5 to C-9 may be altered in various ways. Modifications of C-6 and C-7 in particular afforded products having greater chemical stability, increased antibiotic activity, and more favorable pharmacokinetics.

II. Synthesis of Tetracyclines

In spite of their broad spectrum of activity, tetracyclines are by no means ideal chemotherapeutic agents for the cure of all bacterial infections. Therefore, the structures of these molecules have been modified by chemical or enzymatic methods to correlate the individual structural elements with biological activity. Also, since the structures of the first tetracylines were determined, their total synthesis was considered. Because of the complicated stereochemisty and substitution, few total syntheses have been reported. In this dissertation, only some synthetic approaches to tetracyclines and their analogs are described.

In 1959 - 1961, Fields, Kende and Boothe *et al.*[7-10] succeeded in synthesizing **10** and **11**, which could be precursors of tetracyclines. At the same time, Muxfeldt's group synthesized the precursors **12**, **13**, and **14**.[11]



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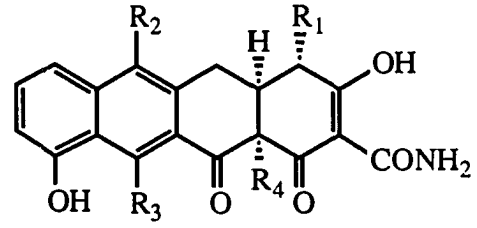
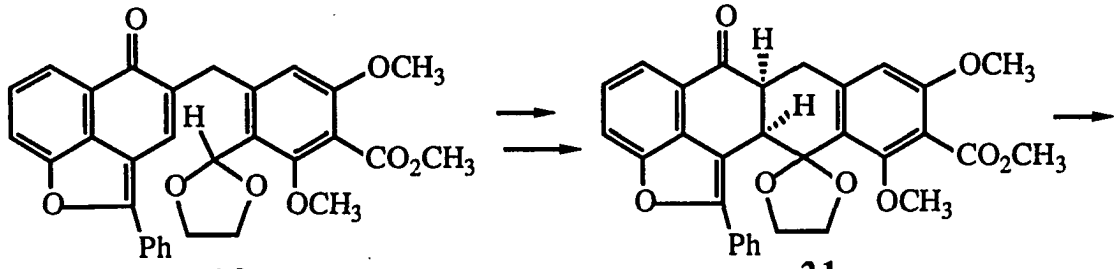
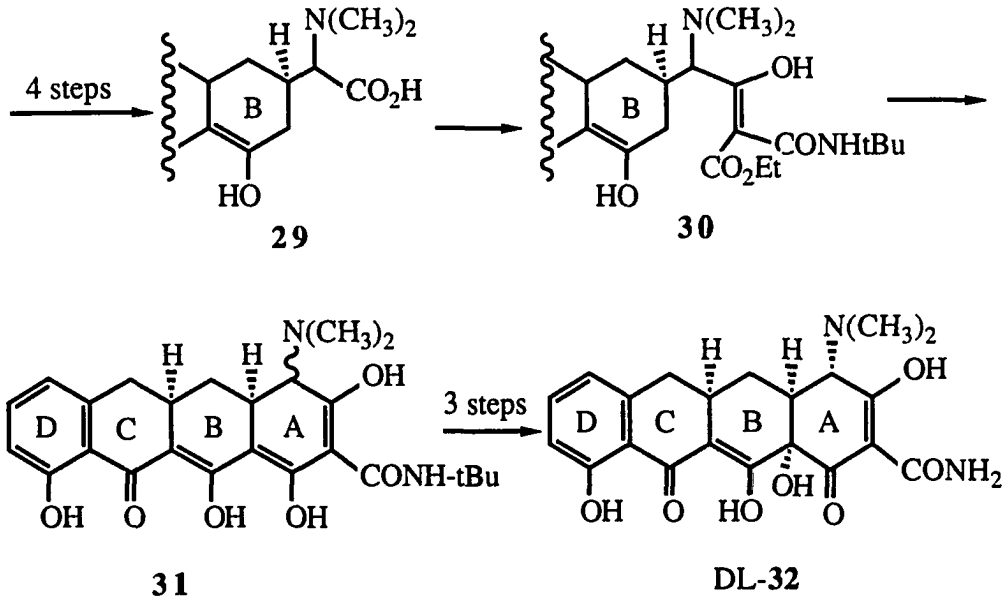


16, $R_1=R_2=R_3=R_4=H$
17, $R_1=R_3=R_4=H$, $R_2=CH_3$
18, $R_1=N(CH_3)_2$,$R_2=CH_3$,$R_3=OH$,$R_4=H$
19, $R_1=H$,$R_2=CH_3$,$R_3=R_4=OH$

In 1957, Barton's group began preliminary work on the total synthesis of tetracycline.[13] Their strategy was to build up a four-ring system in which rings A and D are aromatic. Later, ring A was hydrogenated. After many unsuccessful attempts, it was found that the easily accessible acetal **20** furnished the tetracycline **21** upon proton-catalyzed photocyclization. Further transformations afforded compound **22** which contains the structural elements of tetracycline except for ring A. Deprotection of **22** gave the fully aromatic 6-methylpretetramide **23**, which is the first isolable intermediate in the biosynthesis of tetracycline. Recently, Barton and coworkers reported that base-catalyzed photocyclization provided an efficient route to the fully substituted linear tetracyclic acetate from the naphthofuran.[14]



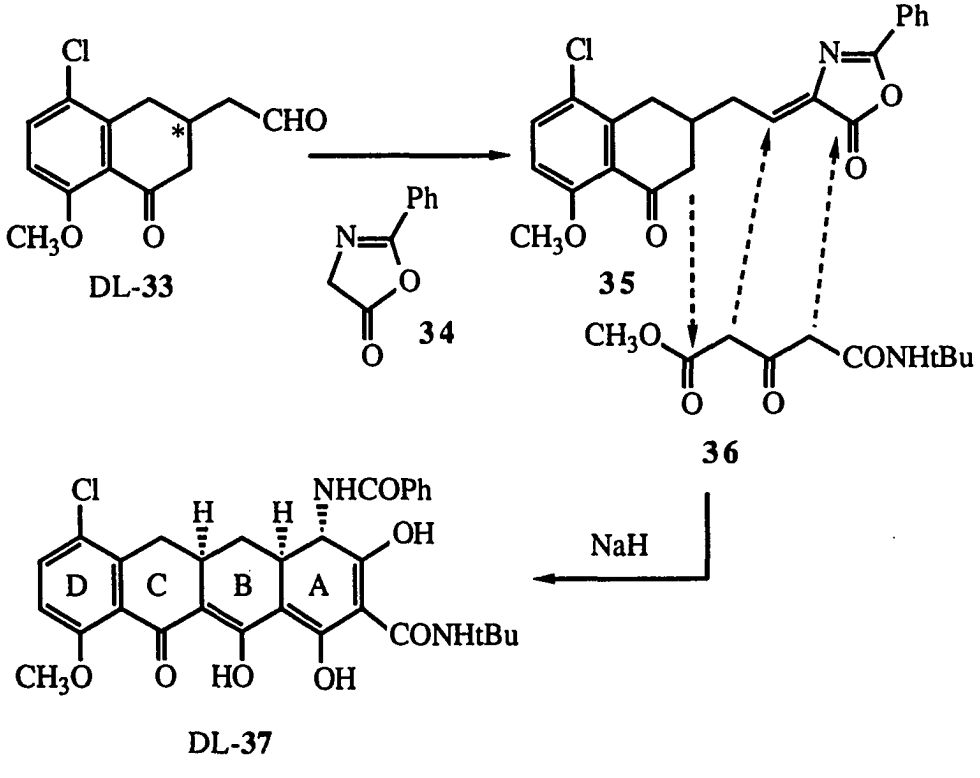
20 **21**



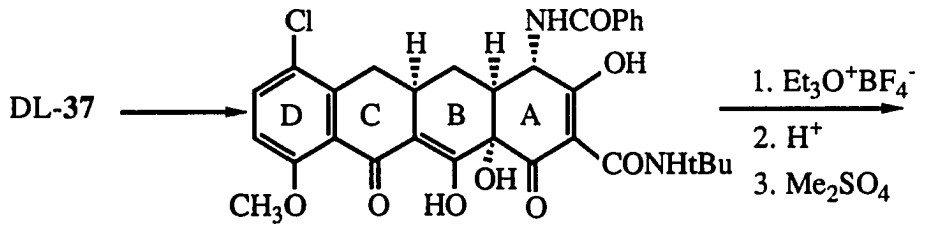
The Woodward/Pfizer synthesis began with the aromatic ring D, onto which rings C, B and A were built stepwise by condensation reactions. Methyl *m*-methoxybenzoate **24** was converted in nine steps into the tetralone **25**. Condensation of **25** with oxalic ester and sodium hydride gave the tricycle **26**. Stepwise construction of the A ring was the most difficult problem. *n*-Butyl glyoxylate was condensed with **26** to afford **27**. Stereospecific introduction of dimethylamine to the exocyclic double bond gave **28**. Reduction of the keto group in ring B and hydrolysis of the ester afforded the acid **29**. Reductive dehalogenation and reaction with ethyl N-(*tert*-butyl)malonamate gave the corresponding compound **30**, which was cyclized to give the tetracycline **31**. Stereospecific introduction of a hydroxyl group at C-12a led to inversion of the 4-dimethylamino group from β– to the natural α-configuration. Removal of the protecting groups then afforded DL-**32**. The overall yield of the 22-step synthesis was 10^{-3}%.

After many years of intensive preliminary experiments, Muxfeldt and his coworkers developed an extremely useful method by which not only natural tetracyclines, e.g. the

complicated teramycin with its six asymmetric centers, but also new types of tetracyclines could be prepared. The strategy of Muxfeldt was utilized for the synthesis of DL-1,6-demethyl-6-deoxychlorotetracyline **40**,[16] which was built from the easily pre-prepared fragments **33**, **34**, and **36**. Condensation of the aldehyde **33** and the oxazolone **34** gave the condensation product **35**. The reaction of compound **35** with the glutaramate **36** afforded the tetracycle **37** by a double ring closure. This elegant condensation in which three new C-C bonds were produced in a single step was the key step of the synthesis. Epimerization of the 4-benzoylamino group and purification by fractional crystallization or by chromatography gave the desired pair of enantiomers **37**.



Introduction of the 12a-hydroxyl group to give **38** was effected smoothly by autoxidation in DMF in the presence of sodium hydride. Debenzoylation of compound **38**, followed by methylation of the amino group, provided the compound **39**. Finally, removal of the protecting groups by hydrogen bromide gave product **40** as its hydrobromide.



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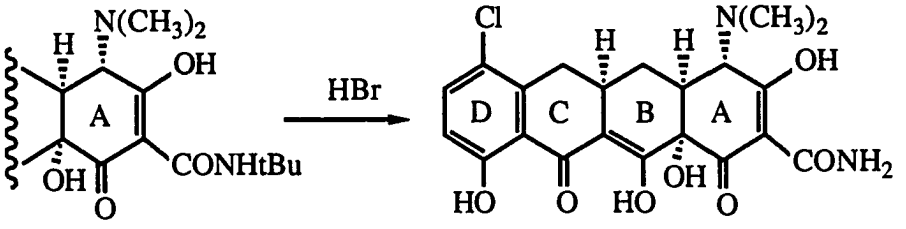
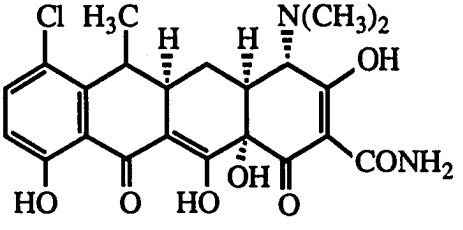
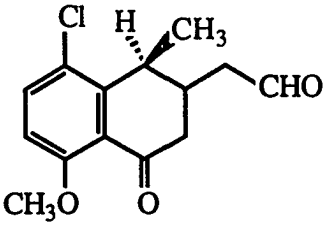


39 **DL-40**

This synthesis could be set up to yield many different products by using differently substituted starting units. For example, Muxfeldt *et al.* synthesized oxytetracycline (**2**) in racemic form in 1968[17], and also DL-anhydroaureomycin (**41**)[18] by this method.

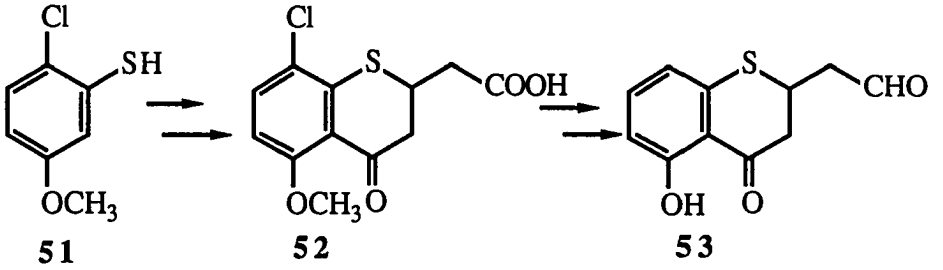


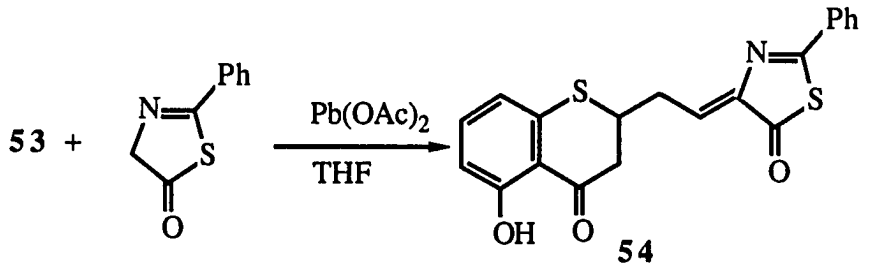
DL-41

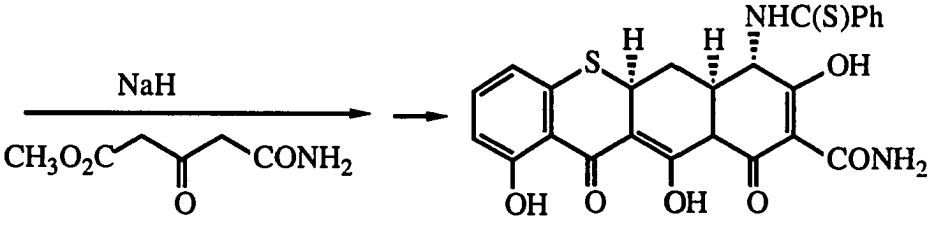


DL-42

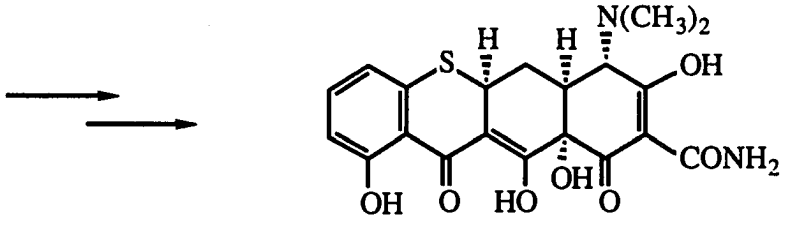
In 1985, the Merck group reported a total synthesis of 6-thiatetracycline (**56**), a new synthetic tetracycline, which showed activity against tetracycline-resistant organisms.[21] Their synthesis was based on the general strategy of Muxfeldt.







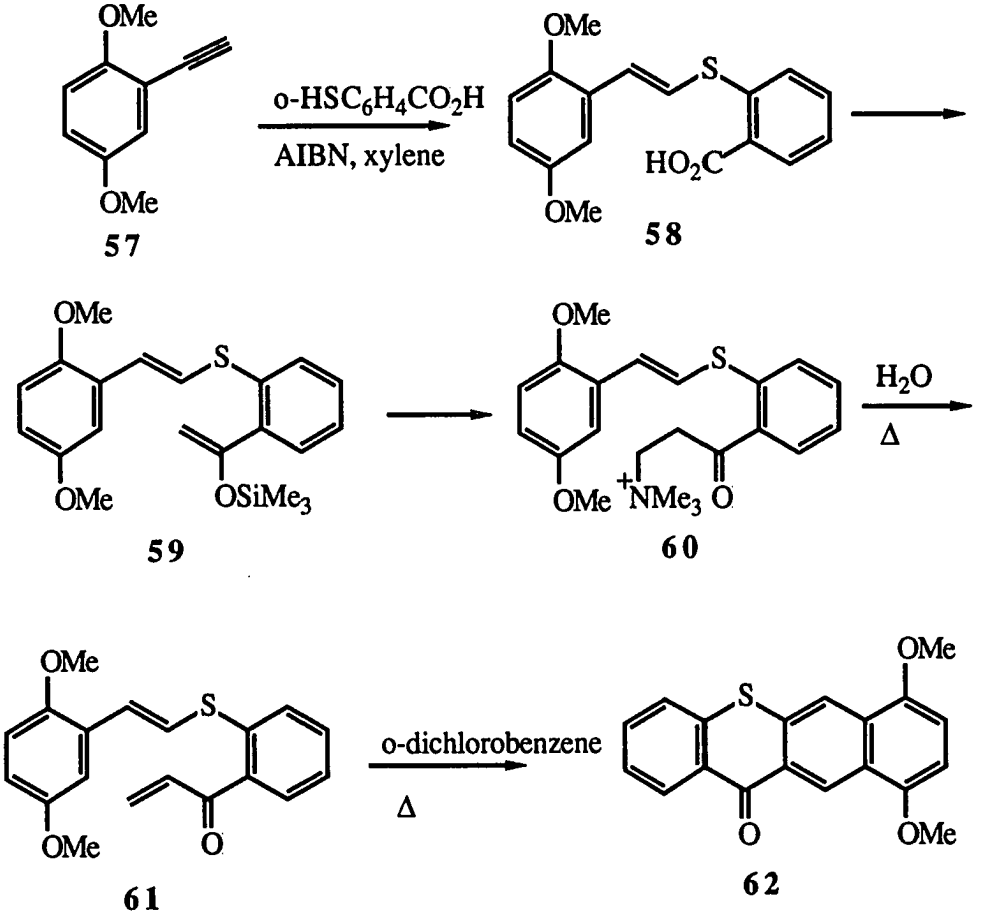
DL-**55**



DL-**56**

Reaction of the thiol **51** with dimethylglutaconate, followed by saponification, provided the corresponding diacid, which was cyclized in liquid hydrogen fluoride to give the carboxylic acid **52**. Demethylation with HBr/CH_3CO_2H, dechlorination, and acylchlorination followed by Rosenmund reduction gave the aldehyde **53**. Condensation with the thiazolone afforded **54**. Reaction of **54** with methyl 3-oxoglutaramate and subsequent cyclization with sodium hydride yielded the tetracyclic compound which was epimerized to the desired isomer **55**. Further transformation of **55** gave thiatetracycline **56** as a racemic mixture.

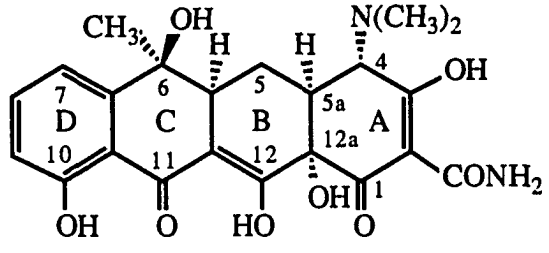
Parsons and coworkers also reported new routes to thiatetracycline analogs, via an intramolecular Diels-Alder approach.[22]



Treatment of the ethynyl compound **57** with thiosalicylic acid in hot xylene containing a catalytic amount of azoisobutyronitrile (AIBN) gave the sulphide **58**. Addition of methyl lithium to **58**, followed by silylation with TMS-Cl, gave the silyl enol ether **59**. Reaction of **59** with N,N-dimethylmethyleneammonium chloride, followed by basic workup and subsequent methylation, afforded the quaternary ammonium salt **60**. Conversion of **60** to **61** and intramolecular Diels-Alder reaction of **61** gave the thiatetracycline analogs **62**.

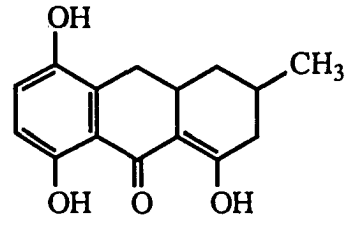
RESULTS AND DISCUSSION

The tetracyclines are a well established class of antibiotics. They have a wide spectrum of antibiotic activity and also chelate various metal ions to form complexes. Their high affinity for calcium ions has led to dietary modifications for patients who use these tetracyclines. The separation of antibiotic activity from chelating ability would enable researchers to study the biological effects of metal ion chelation without interference from other effects. The tetracycline **3** is shown below.

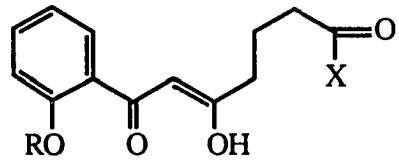


3

The dimethylamino group at C-4 and the chromophoric keto-enol systems in ring A and BCD are essential for antibiotic activity. Since the chromophoric keto-enol systems in rings A and BCD are likely responsible for the ion chelation effects, we have attempted to synthesize simple chelating analogs (bicyclic, tricyclic compounds) without the dimethylamino group. We proposed several chelating analogs of tetracyclines which are shown below.

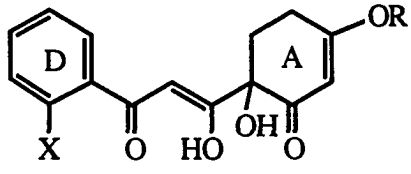


63



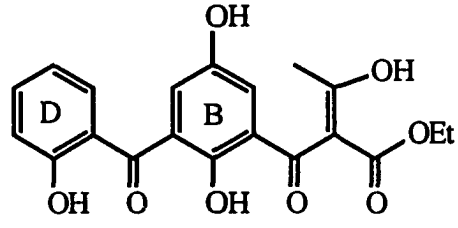
64

{a, R=H,X=OH
b, R=H,X=NHOH



65

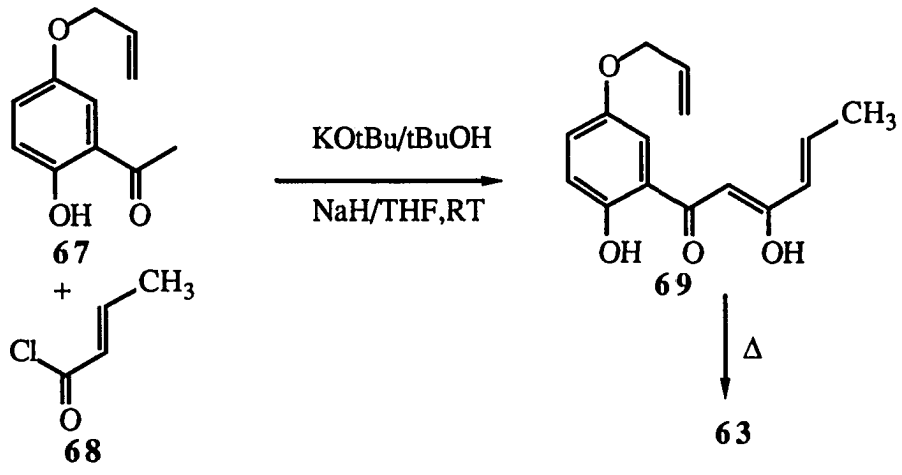
{a, X=H,R=CH_2OCH_3
b, X=OH,R=H



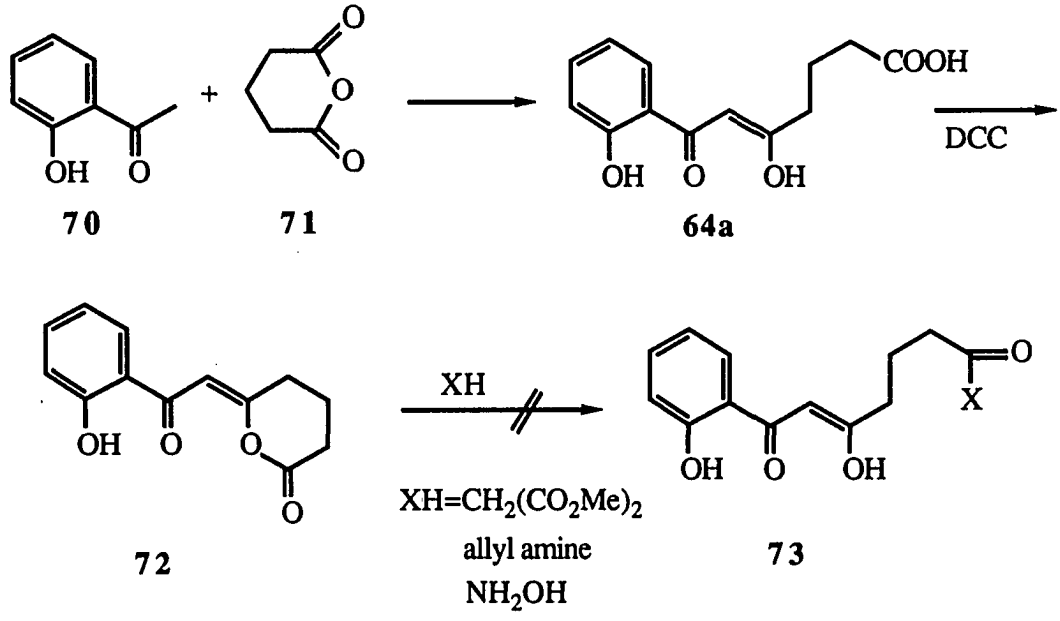
66

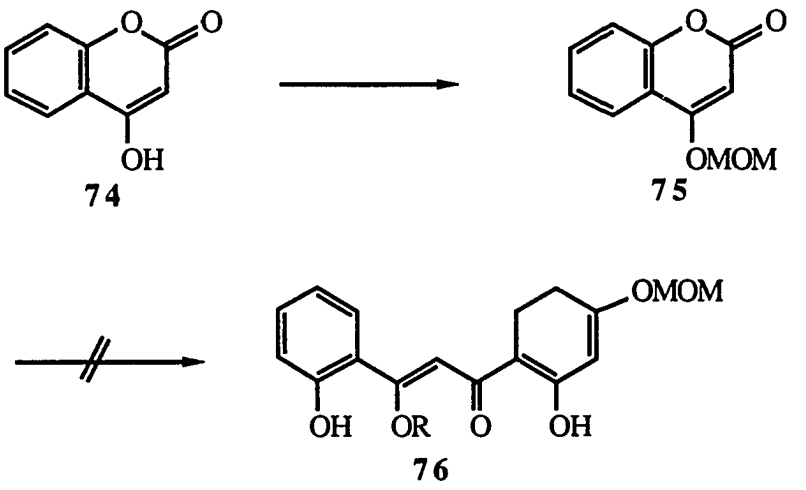
I. Synthetic approaches to the tricyclic analog 63 and the monocyclic analogs 64

The tricyclic analog **63** was prepared by the tandem Claisen-Diels-Alder methodology developed in our research group.[23]

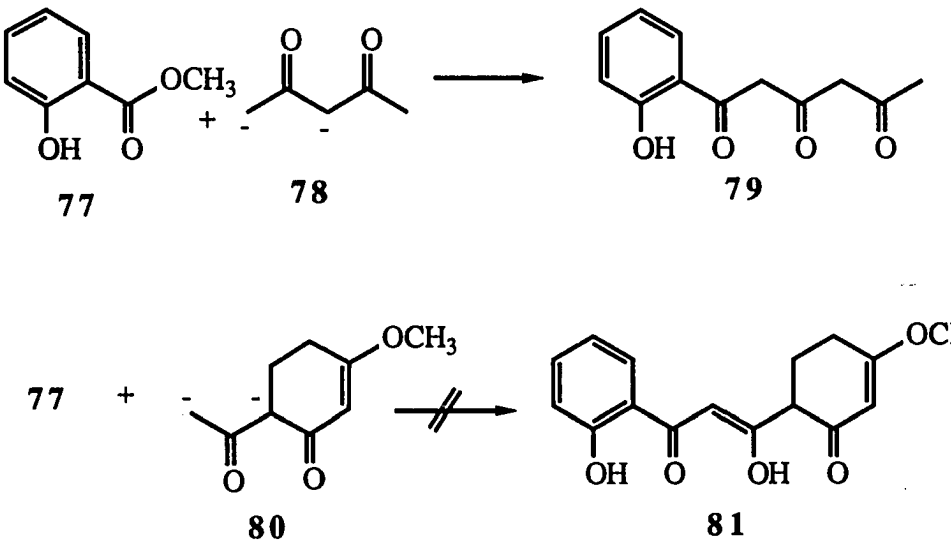


However, the tricyclic analog **63** did not show a chelating activity with calcium ion. A possible problem was that the tricyclic ring system constrained the movement of the functional group in the analog. Monocyclic analog **64** is far more flexible. Unfortunately, acid **64a** did not exhibit useful activity. However, the hydroxamic acid **64b** might show useful activity and became our next synthetic objective. Lactone intermediate **72** was generated by treatment of **64a** with DCC.

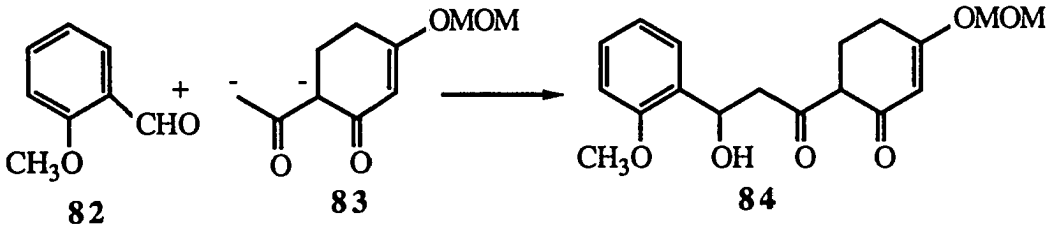




Our second approach involved the reaction of the dianion of a beta-diketone with an ester or an activated acyl group. The simple model study with the dianion of acetylacetone **78** was very successful.[24] However, when the desired diketone dienolate **80** was employed, only starting material were recovered.

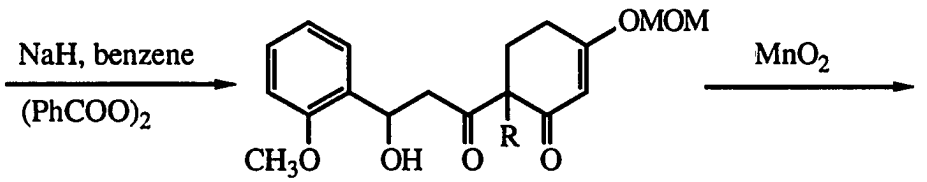


Reaction of the dianion of the diketone **83** with ortho-methoxybenzaldehyde (**82**) afforded the aldol product **84** in 90% yield. Reaction of the dianion of the aldol product **84** with dibenzoyl peroxide afforded **85** as two diastereomers.[25] Both diastereomers reacted slowly with manganese dioxide to provide triketone **86**.



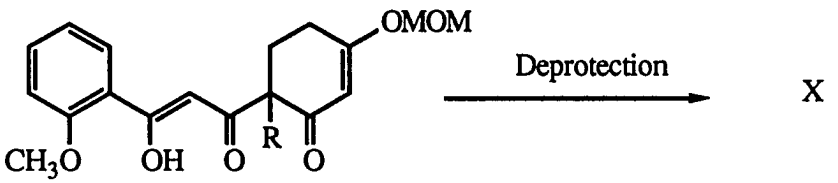
82 **83** **84**

Keto & enol forms



85

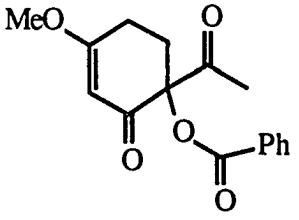
R=PhCOO-



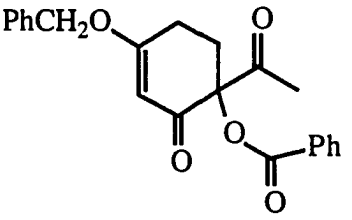
86

Unfortunately, deprotection of the MOM group, the methoxy group, and the benzoyl group did not occur. Even though we had an aldol adduct **84** from the intermolecular aldol condensation, many problems were encountered in this route. Therefore, we next examined an intramolecular acylation example.

However, neither removal of the MOM protecting group in **91** nor the rearrangement of the triketone **90** was successful. The rearrangement of **93** and **94** also failed.



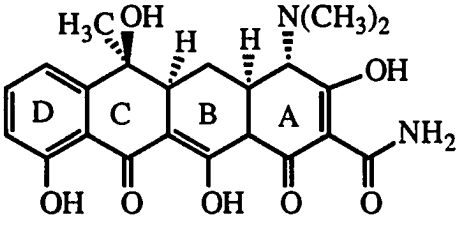
93



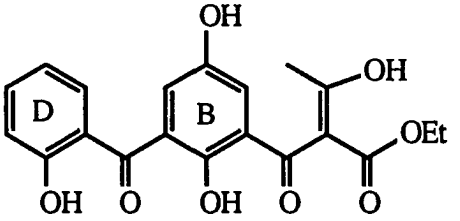
94

III. Synthetic approaches to analog 66

After several attempts to synthesize novel ion chelating analogs of tetracyclines, we decided to prepare the promising bicyclic analog **66**.



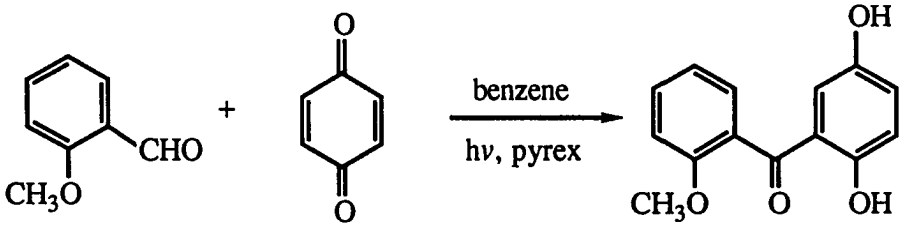
3



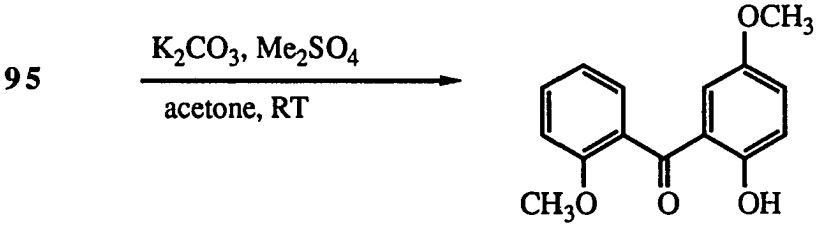
66

Our proposed analog **66** has the chromophoric keto-enol systems which can be found in the natural tetracycline **3**. Also, analog **66** has a hydroxy group at C-5 which could be an additional ligand for complex formation. In contrast to the previously proposed analog **65** which contains the A and D rings, the bicyclic analog **66** contains the B and D rings which might be more rigid and stable under some deprotecting conditions. Our synthesis started from the readily available compound **95**, which was prepared by a photochemical process

developed in our research group.[27] Irradiation of a mixture of an excess *o*-methoxy benzaldehyde and *p*-quinone in degassed benzene gave the corresponding photoadduct **95** in ~ 60% yield. Selective methylation of compound **95** afforded the monomethylated compound **96** in 88% yield by treatment with potassium carbonate and 1 equivalent of dimethyl sulfate in acetone under ambient temperature for 1 day. When the reaction was heated at reflux, the reaction was complete after 2 or 3 hours, but the yield was lower (60 - 70%).

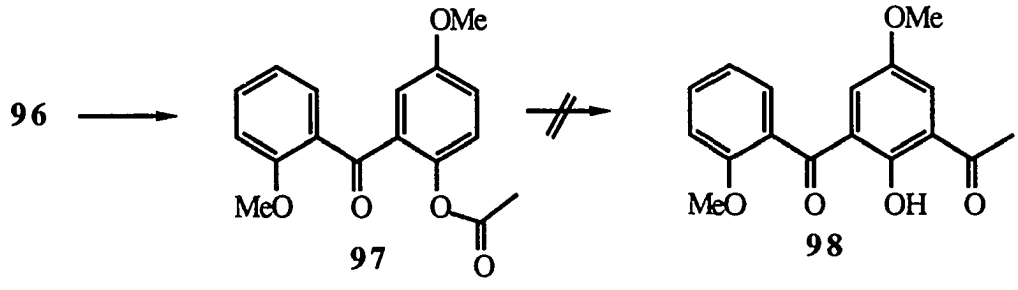


95

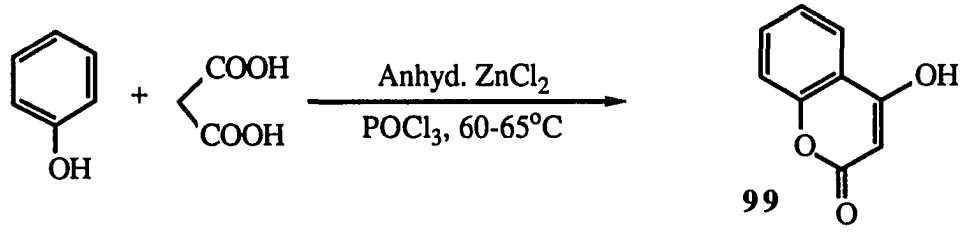


96

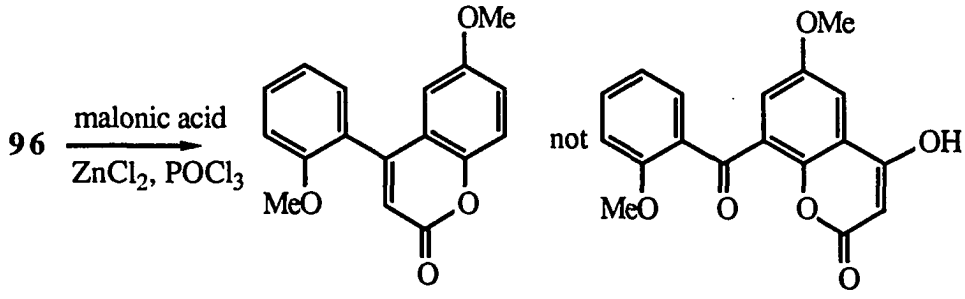
To introduce a carbonyl ortho to the free hydroxyl group in compound **96**, we examined the Fries rearrangement with various O-acylated derivatives of **96**. The O-acylated compounds were prepared and then examined for rearrangement. Lewis acid catalyzed or photocatalyzed Fries rearrangements did not provide the desired product **98**.



After several experiments, we decided to prepare the lactone intermediate **101**, which might be converted to our desired compound after hydrolysis. From a literature survey, we found that 4-hydroxycoumarin **99** was prepared by treatment of phenol with malonic acid, anhydrous zinc chloride and phosphorous oxychloride at 60 - 75°C.[28] It proceeded via intramolecular Friedel-Crafts acylation.



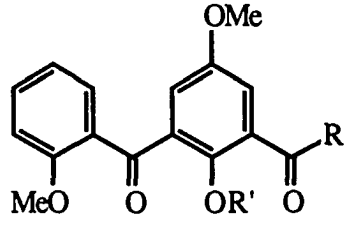
We expected that this method could be applied to our synthesis of the lactone intermediate **101**. However, this reaction gave the undesired compound **100** instead of the lactone intermediate **101**.



100 **101**

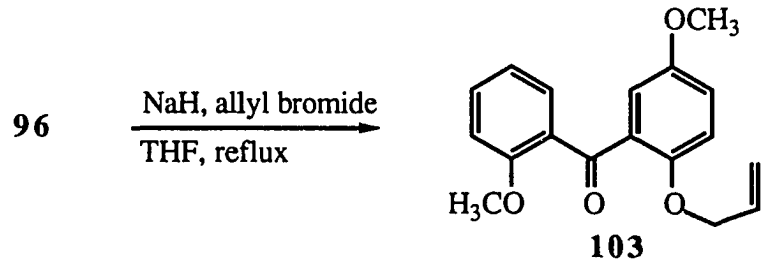
We assumed that the existing carbonyl group could be causing the problem in the Fries rearrangement and the intramolecular Friedel-Craft reactions. We therefore decided to try another pathway.

The next attempt to prepare compound **102** was successful.



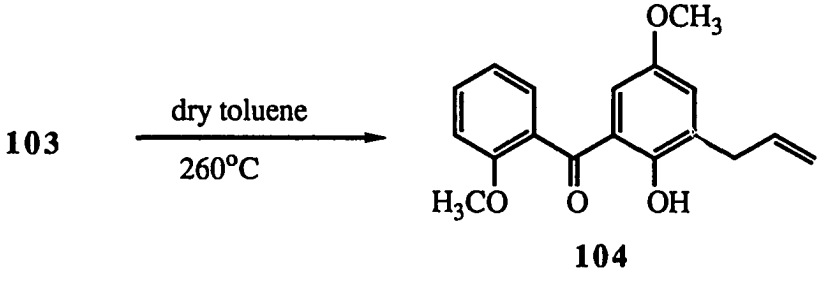
102

A five step synthesis of **102** (R' = CH_3, R = H) from compound **96** provided a highly efficient route. Allylation of **96** afforded the allylic ether **103**. The treatment of **96** with sodium hydride and allyl bromide in boiling THF gave **103** in quantitative yield after silica gel chromatography.



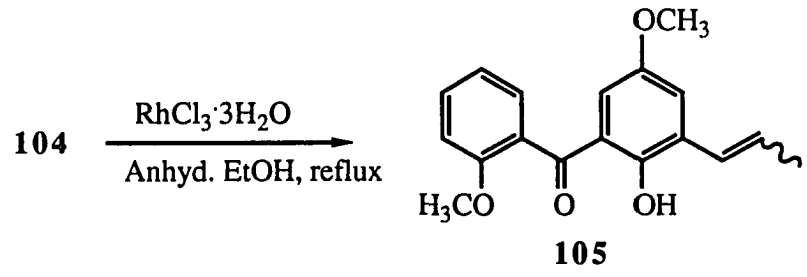
103

Heating **103** at 260°C for 18 hours in a sealed tube gave the Claisen rearrangement product **104** in quantitative yield.



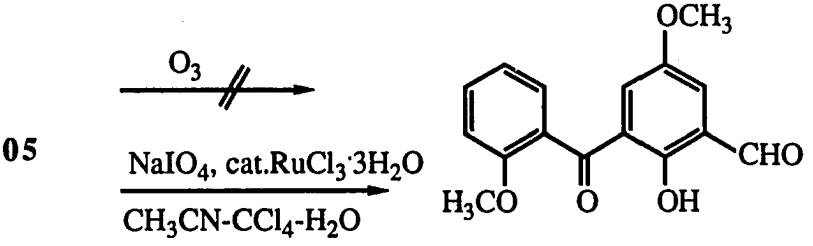
104

We then performed the conversion of **104** to **105**. Initially, this conversion was done by treatment with potassium *tert*-butoxide in boiling ether to give the desired product **105** in a high yield.[29] However, this method was not reproducible. We found that the purity of the potassium *tert*-butoxide was crucial in this reaction. Another synthetic method was necessary, which should be general and reproducible. Rhodium catalyzed isomerization gave the solution.[30] Addition of a catalytic amount of rhodium(III) chloride to a solution of **104** in hot ethanol afforded **105**, reproducibly in quantitative yield. Since the reaction could not



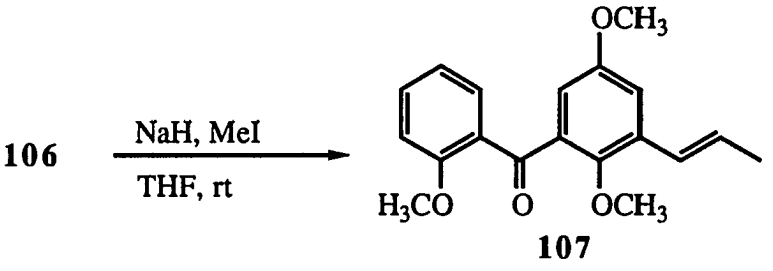
105

be monitored by TLC because the R_f values of both the starting material and the product were the same, the reaction was monitored by taking NMR spectra of the aliquot from the reaction mixture. NMR and GC showed that the resulting product included a mixture of *cis*- and *trans*-**105**, with the trans isomer as the major product. Oxidative cleavage of the alkene moiety in **105** to give the aldehyde **106** was the next task. The ozonolysis of **105,** followed by reductive cleavage with dimethyl sulfide at -78°C, should have given the desired aldehyde **106**. However, **105** decomposed under ozonolysis conditions to give unidentifiable products. We next attempted oxidative cleavage by the ruthenium-catalyzed periodate method. Treatment of **105** with 6 equivalents of sodium periodate in mixed solvents (CH_3CN-CCl_4-H_2O), followed by addition of a catalytic amount of ruthenium trichloride hydrate, afforded the corresponding aldehyde **106** in only 9.5% yield after silica gel chromatography.



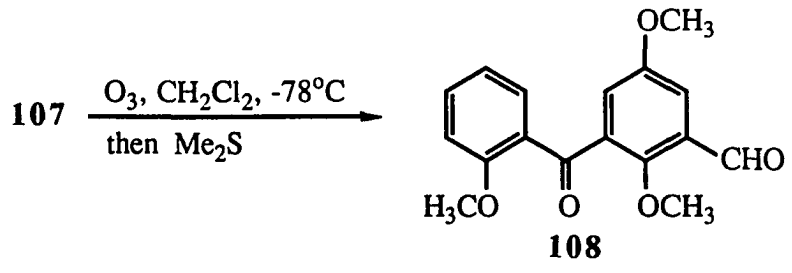
106

Due to the problem encountered in the oxidative cleavage of **105**, we reinvestigated the stability of our starting material **105** under oxidative conditions. We felt that the free hydroxyl group might be causing the problem in the oxidative cleavage step. We expected that protection of the hydroxyl group prior to ozonolysis, might give a solution. Protection of **106** was achieved by treatment with methyl iodide and sodium hydride in dry THF at ambient temperature. The methylated compound **107** was obtained in 98% yield.



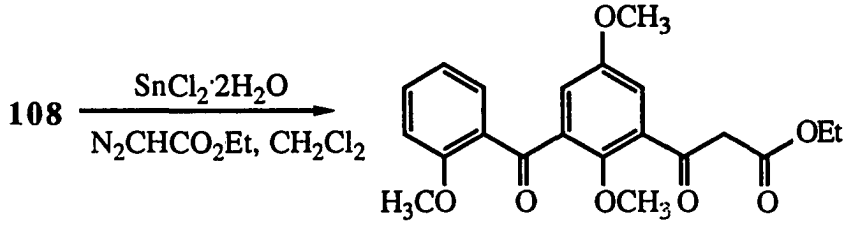
107

Now ozonolysis of **107** was examined. Excess ozone was bubbled into the dichloromethane solution of **107** at -78°C for 30 min. Quenching with 6 equivalents of dimethyl sulfate and warming to room temperature, followed by aqueous workup, afforded the desired aldehyde **108** in a modest yield (~ 40%). After several runs to increase the yield of the ozonolysis, we postulated that the excess ozone might be the problem with this reaction. We bubbled ozone through the solution until excess ozone from the solution made the color of a saturated potassium iodide solution turn from colorless to dark orange. Bubbling an equivalent of ozone into a solution of **107** gave the aldehyde **108** in increased yield (63 - 85%).



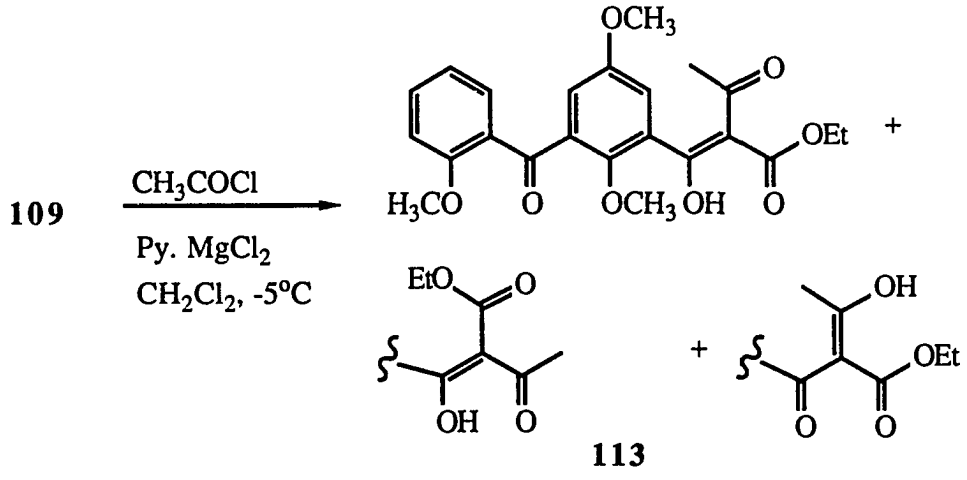
108

The aldehyde **108** was converted into the β-keto ester **109** by the Roskamp method.[31] A dichloromethane solution of the aldehyde **108** was added slowly to a solution of tin(II) chloride dihydrate and ethyl diazoacetate. Aqueous workup and purification afforded a 21% of the β-keto ester **109**.

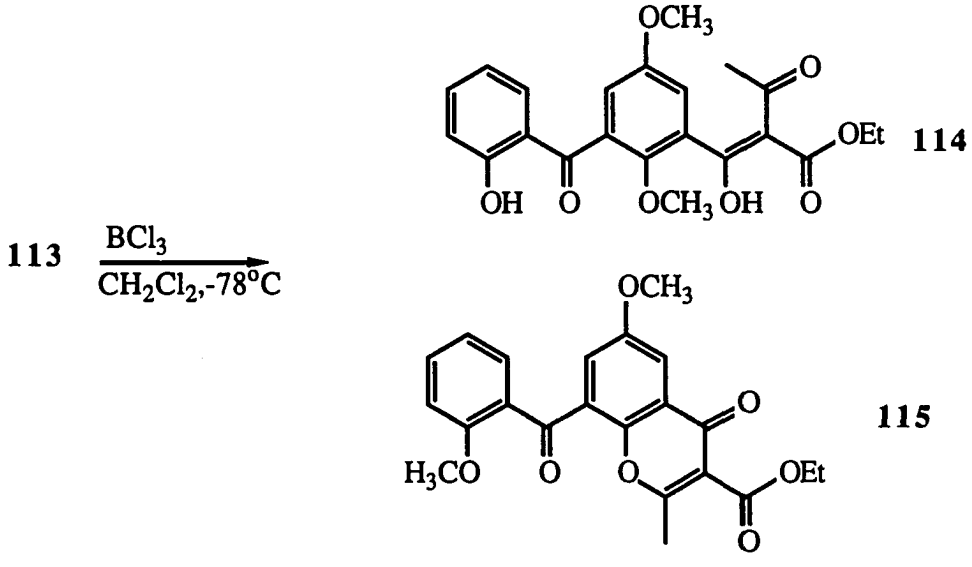


& enol form **109**

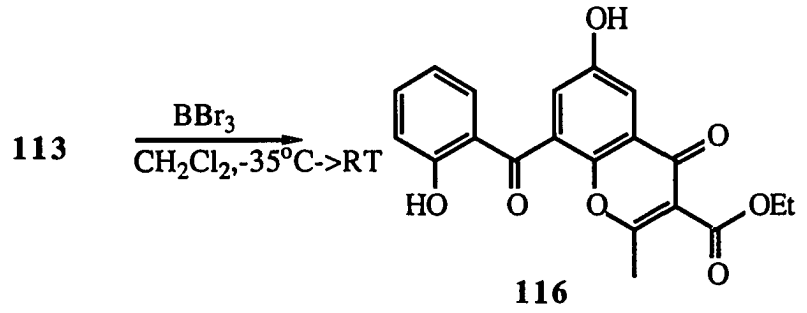
Due to the low yield and the lack of reproducibilty of the reaction, we needed another synthetic method. The work of Pelliciari and coworkers[32] provided the answer. A solution of LDA at 0°C was added dropwise to a -78°C cooled solution of **108** and ethyl diazoacetate in THF. In situ deprotonation of the diazoester and attack of the aldehyde made an α-diazo-β-hydroxy ester. Quenching at -78°C with acetic acid and aqueous workup afforded a 90% yield of **110** after chromatography. Dilution of **110** in dry dimethoxyethane and addition of catalytic rhodium(II) acetate at room temperature caused nitrogen extrusion and hydride transfer to give the desired β-keto ester **109** in 94% yield.



Finally, we attempted to deprotect the methoxy groups in compound **113**. Initially, **113** was treated with boron trichloride to effect deprotection. Treatment of **113** with 1.0M solution of boron trichloride in dichloromethane at -78°C afforded two monodemethylated products, **114** in 21% yield and **115** in 25% yield, both of which might show chelating ability.

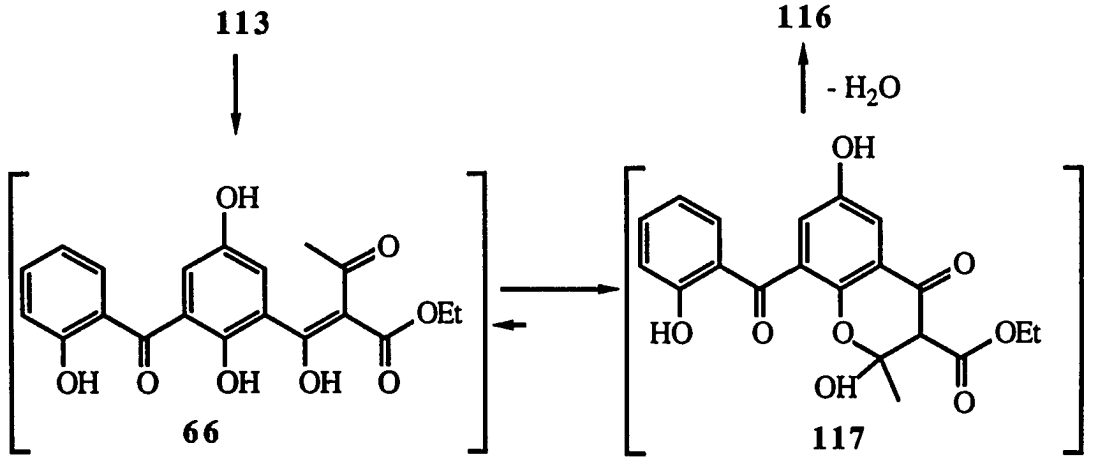


Boron tribromide, which is stronger than boron trichloride, was also examined. Addition of 1.0M boron tribromide to **113** in dry dichloromethane at -35°C, followed by warming to room temperature, gave a single compound in 54% yield.



116

We expected the bicyclic analog **66** as the product from this deprotection; however, compound **116** was obtained instead. Formation of **116** could be explained as shown below.



Deprotection of **113** gave the bicyclic compound **66** which could be converted to the hemiacetal **117**.[24] The hemiacetal **117** might lose water to give the resulting compound **116**.[34] Therefore, we concluded that isolation of compound **66** was not possible. We proposed that **116** might be converted into **66** under enzymatic hydrolysis to form a complex with metal ions. Compound **116** itself could be a novel ion chelating analog, and a new antibiotic agent.

In conclusion,we have synthesized four possible chelating analogs, **113**, **114**, **115**, and **116**. These analogs will be tested for novel ion chelating ability. Also, we have developed a synthetic method for the preparation of the aldehyde **108** from compound **96**. This method might be extended to the synthesis of other aromatic carbonyl compounds which are not available by Friedel-Crafts acylation and Fries rearrangement.

Preparation of diketone 88. To a -78°C solution of LDA (16.5 mmol) in 5 mL of THF was added MOM-protected cyclohexanedione (1.04 g, 6.6 mmol) in 3 mL of THF. After stirring for 30 min at -78°C, pyruvonitrile (1.4 mL, 19.8 mmol) was added rapidly. The solution was warmed to 0°C, and quenched with acetic acid (10 mL). Water was added, and the aqueous layer was extracted with CH_2Cl_2, washed, dried (Na_2SO_4) and concentrated. Purification by flash chromatography with 2:1 hexane-ethyl acetate gave 1.06 g of **88** (82% yield). The resulting product was a mixture of keto and enol tautomers: Rf 0.29 (2:1 = H:EA); ^1H NMR ($CDCl_3$) δ 2.04 (s), 2.28 (s), 2.36 - 2.46 (m), 2.54 - 2.70 (m), 3.41 - 3.45 (m), 3.46 (s), 3.47 (s), 5.01 - 5.09 (m), 5.44 (s), 5.51 (s); IR (film) 2960, 1780, 1770, 1650, 1600 cm^{-1}; CI-MS m/e 199 (M+1), 216 (M+18).

Preparation of diketo ester 89. To a 0°C suspension of 60% NaH (0.12 g, 2.99 mmol) in 8 mL of dry benzene was added a solution of diketone **88** (0.54 g, 2.72 mmol) in 7 mL of dry benzene. The reaction mixture was stirred for 1 h at room temperature. A solution of dibenzoyl peroxide (0.59 g, 2.45 mmol) in 5 mL of dry benzene was added to the above solution at 0°C, and the resulting solution was stirred for 1 h at room temperature. The reaction mixture was cooled to 0°C, quenched with water, extracted with ether, washed with water, dried (Na_2SO_4), and concentrated. Purification by flash chromatography with 2:1 hexane-ethyl acetate provided 0.72 g (84% yield) of pure diketo ester **89**; Rf 0.36 (2:1 = H:EA); ^1H NMR ($CDCl_3$) δ 2.35 (s, 3H), 2.52 (tt, J = 4.8, 17.7 Hz, 1H), 2.65 - 2.69 (m, 2H), 2.97 - 3.03 (m, 1H), 3.48 (s, 3H), 5.08 - 5.13 (m, 2H), 5.62 (s, br, 1H), 7.47 (t, J = 7.8 Hz, 2H), 7.61 (t, J = 7.5 Hz, 1H), 8.07 (d, J = 7.5 Hz, 2H); CI-MS (NH_3) m/e 319 (M+1), 336 (M+18).

Allylation of monomethylated compound 96. To a 0°C suspension of NaH (0.0324 g, 0.81 mmol) in 3 mL of THF was added a solution of **96** (0.10 g, 0.39 mmol) in 1 mL of THF. The reaction mixture was stirred for 15 min at room temperature. Freshly distilled allyl bromide (0.04 mL, 0.46 mmol) was added dropwise, and the resulting solution was heated to reflux for 4 h. The reaction mixture was cooled to 0°C and quenched with water. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4) and concentrated. Purification by flash column chromatography with 4:1 hexane-ethyl acetate afforded 0.12 g of **103** (100% yield): Rf 0.40 (4:1 = H:EA); ^{1}H NMR ($CDCl_3$) δ 3.66 (s, 3H), 3.80 (s, 3H), 4.27 (dd, J = 1.5, 6.6 Hz, 2H), 4.88 - 5.00 (m, 2H), 5.50 - 5.62 (m, 1H), 6.82 (d, J = 9.0 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.95 - 7.00 (m, 2H), 7.15 (d, J = 3.3 Hz, 1H), 7.41 (dt, J = 1.8, 7.8 Hz, 1H), 7.50 (dd, J = 1.8, 7.5 Hz, 1H); IR (film) 3035, 3000, 2940, 2915, 1650, 1590 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 55.48, 55.58, 69.62, 111.30, 114.26, 114.39, 116.31, 118.41, 120.14, 129.96, 130.34, 131.06, 132.39, 132.56, 151.45, 153.45, 158.14, 194.81; CI-MS (NH_3) m/e 259, 276, 299 (M+1), 316 (M+18). Colorless oil.

Claisen rearrangement of allylated compound 103. A solution of allylated compound **103** (1.59 g, 5.33 mmol) in 45 mL of toluene was deoxygenated and sealed in a glass tube. The tube was heated at 260°C for 18 h. The color of the solution changed from colorless to yellow. The tube was cooled, the reaction mixture was concentrated, and the residue was purified by flash chromatography with 4:1 hexane-ethyl acetate to afford 1.59 g (100%) of rearranged product **104**: Rf 0.40 (5:1); ^{1}H NMR ($CDCl_3$) δ 3.46 (d, J = 6.6 Hz, 2H), 3.61 (s, 3H), 3.77 (s, 3H), 5.09 - 5.17 (m, 2H), 5.96 - 6.09 (m, 1H), 6.68 (d, J = 3.0 Hz, 1H), 6.98 - 7.06 (m, 2H), 7.28 (dd, J = 1.5, 7.2 Hz, 1H), 7.48 (dt, J = 1.5, 8.7 Hz, 1H), 12.18 (s, 1H); IR (film) 3035, 3000, 2940, 2915, 1590, 1490, 1460 cm^{-1}; ^{13}C

6.20 - 6.31 (m, 1H), 6.62 (dd, J = 1.5, 15.9 Hz, 1H), 6.88 (d, J = 3.0 Hz, 1H), 6.92 - 7.00 (m, 2H), 7.10 (d, J = 3.0 Hz, 1H), 7.45 (dt, J = 1.2, 8.4 Hz, 1H), 7.53 (dd, J = 1.5, 7.5 Hz, 1H); IR (film) 3000, 2940, 2915, 1660, 1590 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 18.75, 56.52, 56.62, 62.56, 111.58, 112.67, 114.33, 120.10, 124.74, 127.64, 129.25, 130.48, 132.45, 133.00, 135.46, 149.59, 156.18, 158.52, 195.36; CI-MS (NH_3) m/e 313 (M+1), 314, 330 (M+18); HRMS m/e calcd for $C_{19}H_{20}O_4$: 312.13616. Found: 312.13599; m/e 77, 135, 176, 191, 312.

Ozonolysis of 107 to prepare the aldehyde 108. A solution of the olefin **107** (0.90 g, 2.88 mmol) in 60 mL of CH_2Cl_2 was cooled to -78°C and ozone was bubbled into the solution through a glass tube at -78°C(~ 4 min). The outlet gas from the reaction mixture passed through a saturated KI solution until the color of the KI solution changed from colorless to dark orange. The reaction mixture was purged with N_2 for 15 min and then dimethyl sulfide (0.84 mL, 11.52 mol) was added. The mixture was allowed to warm up to room temperature and stirred overnight. After washing with water (three times), the solution was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography with 4:1 hexane-ethyl acetate to afford 0.73 g (85% yield) of the aldehyde **108**: Rf 0.38 (3:1 = H:EA); ^1H NMR ($CDCl_3$) δ 3.67 (s, 3H), 3.69 (s, 3H), 3.84 (s, 3H), 6.96 (d, J = 8.4 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 7.26 (d, J = 3.3 Hz, 1H), 7.44 (d, J = 3.3 Hz, 1H), 7.52 (dt, J = 1.5, 9.3 Hz, 1H), 7.63 (dd, J = 1.5, 7.8 Hz, 1H), 10.36 (s, 1H); IR (film) 3030, 3000, 2940, 1650(br), 1590, 1570 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 55.54, 55.78, 64.99, 111.62, 112.97, 120.42, 122.65, 128.07, 129.60, 130.67, 133.87, 136.76, 155.32, 155.70, 157.73, 189.08, 193.69; CI-MS (NH_3) m/e 301 (M+1), 318 (M+18), 335 (M+35); HRMS m/e calcd $C_{17}H_{16}O_5$: 300.09977. Found: 300.10048; m/e 77, 92, 105, 121, 135, 151, 165, 179, 300; UV-Vis (CH_2Cl_2) λmax 242, 332.

(CH_2Cl_2) λmax 248, 324; EI-MS m/e 77, 91, 121, 135, 177, 219, 299, 340, 386; HRMS m/e calcd for $C_{21}H_{22}O_7$: 386.13655. Found: 386.13586.

Acylation of the keto ester 109. To a solution of dry magnesium chloride (0.007 g, 0.073 mmol) and keto ester **109** (0.0278 g, 0.072 mmol) in 2 mL of dry CH_2Cl_2 at -5°C was added pyridine (0.0117 mL, 0.145 mmol) dropwise. After the reaction mixture was stirred for 15 min at -5°C, freshly distilled acetyl chloride (0.0051 mL, 0.072 mmol) was added. The resulting mixture was stirred for 15 min at 0°C and 4 h at room temperature. After being cooled at 0°C, the reaction was quenched with 6N HCl, and diluted with water. The aqueous layer was extracted with CH_2Cl_2, dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography with 2:1 hexane-ethyl acetate containing with 10 drops of acetic acid to afford 0.0247 g (80% yield) of **113**: Rf 0.45 (2:1 = H:EA); ^1H NMR ($CDCl_3$) δ 0.95 (t, J = 8.7 Hz), 0.96 (t, J = 6.6 Hz), 2.30 (s), 2.44 (s), 3.41 (s), 3.43 (s), 3.72 (s), 3.74 (s), 3.80 (s), 3.82 (s), 3.96 (q, J = 7.2 Hz), 4.05 (q, J = 6.9 Hz), 6.93 - 6.99 (m), 7.01 (d, J = 3.0 Hz), 7.07 (d, J = 3.0 Hz), 7.44 - 7.53 (m), 13.82 (s), 17.60 (s); IR(film) 2980, 2940, 1710, 1660, 1595 cm^{-1}; UV-Vis (CH_2Cl_2) λmax 256, 294; CI-MS (NH_3) m/e 360, 432; HRMS m/e calcd for $C_{22}H_{22}O_8$: 414.13147. Found: 414.13225; m/e 121, 179, 253, 337, 383, 414.

Deprotection of compound 113 to prepare dimethoxy compounds 114 and 115. To a solution of **113** (0.1372 g, 0.32 mmol) in 5 mL of dry CH_2Cl_2 at -78°C was added a 1.0 M BCl_3 solution (3.2 mL, 3.2 mmol) in CH_2Cl_2. After the reaction mixture was stirred for 1 h at -78°C, the reaction was quenched with water, and warmed to room temperature. The aqueous layer was extracted with CH_2Cl_2,

dried (Na_2SO_4), and concentrated. Purification with 2:1 hexane-ethyl acetate with 10 drops of acetic acid gave two pure compounds in a 46% combined yield.

114: 0.0282 g (21% yield); Rf 0.51 (2:1 = H:EA); IR(film) 3040, 2960, 2920, 1720, 1630, 1600 cm^{-1}; EI-MS m/e 77, 121, 135, 177, 219, 261, 299, 351, 382, 397, 428; HRMS m/e calcd for $C_{23}H_{24}O_8$: 428.14712. Found 428.14745; UV-Vis (CH_2Cl_2) λmax 264, 294, 332.

115: 0.0315 g (25% yield); Rf 0.24 (2:1 = H:EA); ^1H NMR ($CDCl_3$) δ 1.38 (t, J = 7.2 Hz, 3H), 2.08 (s, 3H), 3.56 (s, 3H), 3.92 (s, 3H), 4.39 (q, J = 7.2 Hz, 2H), 6.93 (d, J = 8.4 Hz, 1H), 7.64 (dd, J = 1.2, 7.2 Hz, 1H), 7.71 (d, J = 3.3 Hz, 1H); IR (film) 2960, 2940, 1730, 1640, 1595 cm^{-1}; CI-MS (NH_3) m/e 397 (M+1); ^{13}C NMR ($CDCl_3$) δ 14.21, 18.88, 55.68, 56.13, 61.79, 108.96, 111.29, 117.15, 120.83, 123.45, 124.20, 129.06, 130.51, 132.00, 133.88, 147.79, 156.55, 158.53, 164.90, 166.14, 173.73, 191.81; UV-Vis (CH_2Cl_2) λmax 242, 334; EI-MS m/e 77, 121, 135, 177, 216, 253, 293, 324, 337, 396; HRMS m/e calcd for $C_{22}H_{20}O_7$: 396.12090. Found: 396.12052.

Preparation of 116. To a solution of **113** (0.020 g, 0.0467 mmol) in 2 mL of dry CH_2Cl_2 at -35°C was added 1.0M BBr_3 solution (0.37 mL, 0.37 mmol) in CH_2Cl_2. The reaction mixture was warmed to room temperature. After the reaction mixture was stirred for 4 h, the reaction was quenched with water at 0°C. The aqueous layer was extracted with CH_2Cl_2, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography with 2:1 hexane-ethyl acetate with 8 drops of acetic acid to afford 0.0092 g of demethylated compound **116** (54%); Rf 0.36 (2:1 = H:EA); ^1H NMR ($CDCl_3$) δ 1.40 (t, J = 7.2 Hz, 3H), 2.38 (s, 3H), 4.41 (q, J = 7.2 Hz, 2H), 6.85 (t, J = 7.5 Hz, 1H), 7.10 (d, J = 8.7 Hz, 1H), 7.30 (dd, J = 1.2, 8.1 Hz, 1H), 7.35 (d, J = 2.1 Hz, 1H), 7.55 (dt, J = 1.2, 8.4 Hz, 1H), 8.23 (d, J = 1.2 Hz, 1H), 11.88 (s, 1H); IR (film) 3320(br), 3040, 2980,

2920, 1730, 1630, 1600 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 14.23, 19.76, 62.13, 112.69, 117.06, 118.56, 119.25, 119.58, 123.17, 124.45, 129.18, 133.32, 137.54, 146.30, 154.51, 163.12, 164.64, 168.30, 174.70, 197.71; CI-MS (NH_3) m/e 346, 360, 369 (M+1), 383; HRMS m/e calcd for $C_{20}H_{16}O_7$: 368.08960. Found: 368.08960; m/e 67, 121, 143, 212, 239, 279, 323, 336, 353, 368; UV-Vis (CH_2Cl_2) λmax 240, 264, 336; mp 178 - 180°C. Yellow solid.

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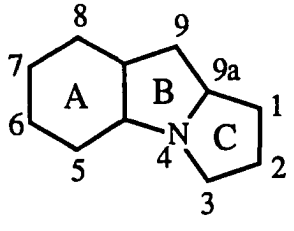
PART III.

SYNTHETIC APPROACHES TO MITOMYCIN ANALOGS

HISTORICAL

The chemistry of the pyrrolo[1,2-a]indole **1** has progressed extensively since the structures of mitomycins **2**, **3**, and **4** were determined by Webb and coworkers in 1962.[1] The mitomycins were isolated by Hata and coworkers in 1956.[2] They have attracted much attention, not only because of their unique structures, but also because of their antibiotic activity against both gram-positive and gram-negative bacteria and their activity against a broad spectrum of solid tumors.[3]



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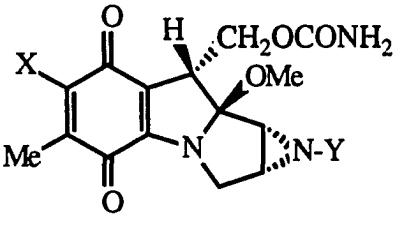
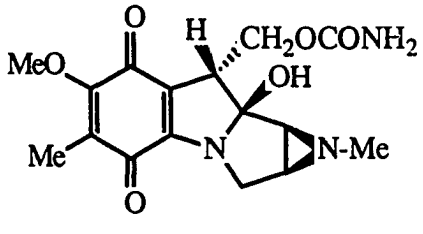


2, Mitomycin A, X=OCH_3, Y=H

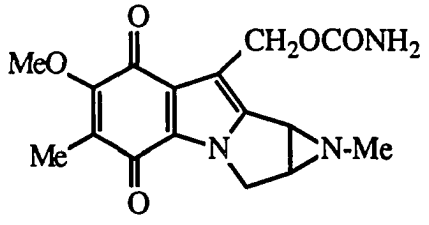
3, Mitomycin C, X=NH_2, Y=H

4, Porfiromycin, X=NH_2, Y=CH_3



5, Mitomycin B

Webb and coworkers prepared the aziridinopyrrolo[1,2-a]indoloquinone **6**, the 1,2-disubstituted mitosene **7**, and the desammono-apomitomycin A **8** from the natural mitomycins.[1]



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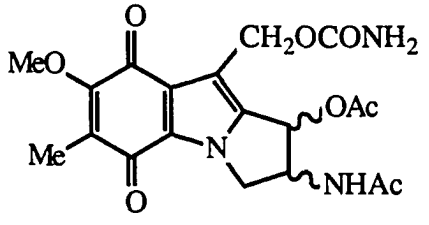

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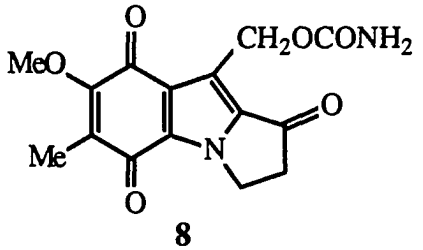
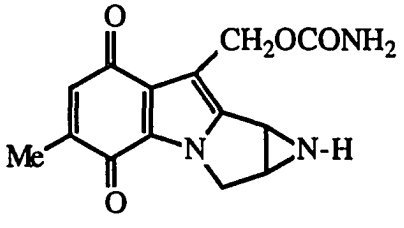


8

Since these compounds were found to possess antibacterial activity, numerous compounds related to mitosane **9** and mitosene **10** have been synthesized.[4] Webb proposed the names mitosane for the structure **9** and mitosene for the structure **10**, which are the structural components common to all mitomycins.[1]



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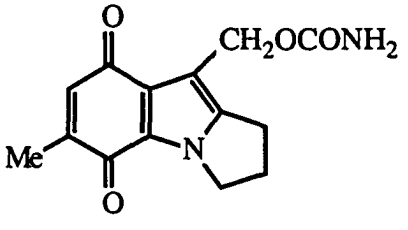
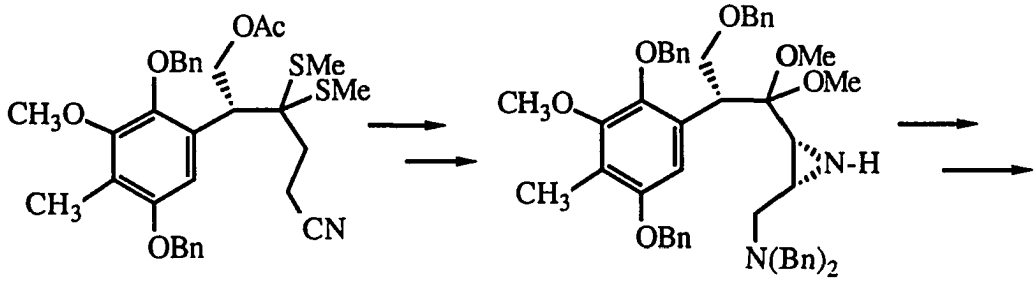
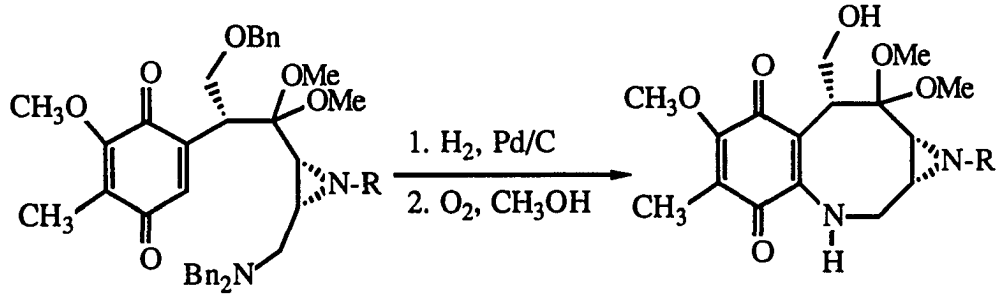


10

A variety of synthetic approaches to mitomycins and related compounds has been reported.[5] However, only a few syntheses of the mitomycins themselves have been reported. In 1977, Kishi and coworkers reported the first total synthesis of mitomycins A (**2**) and C (**3**), and porfiromycin (**4**).[6] His strategy focused on the construction of the eight-membered quinone **14** by the intramolecular Michael reaction of **13** and the transannular cyclization of **14**.



11 12



13

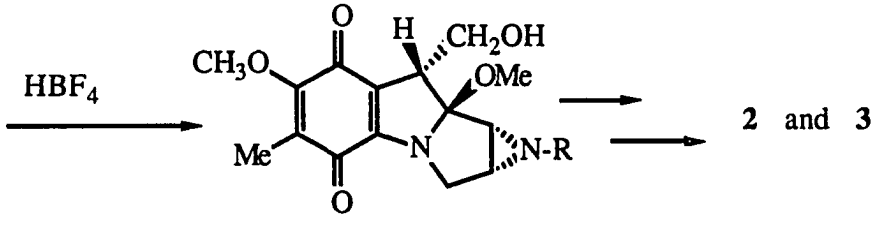
a, R=H

b, R=$CH_2CH_2CH_2OAc$

14

a, R=H

b, R=$CH_2CH_2CH_2OAc$



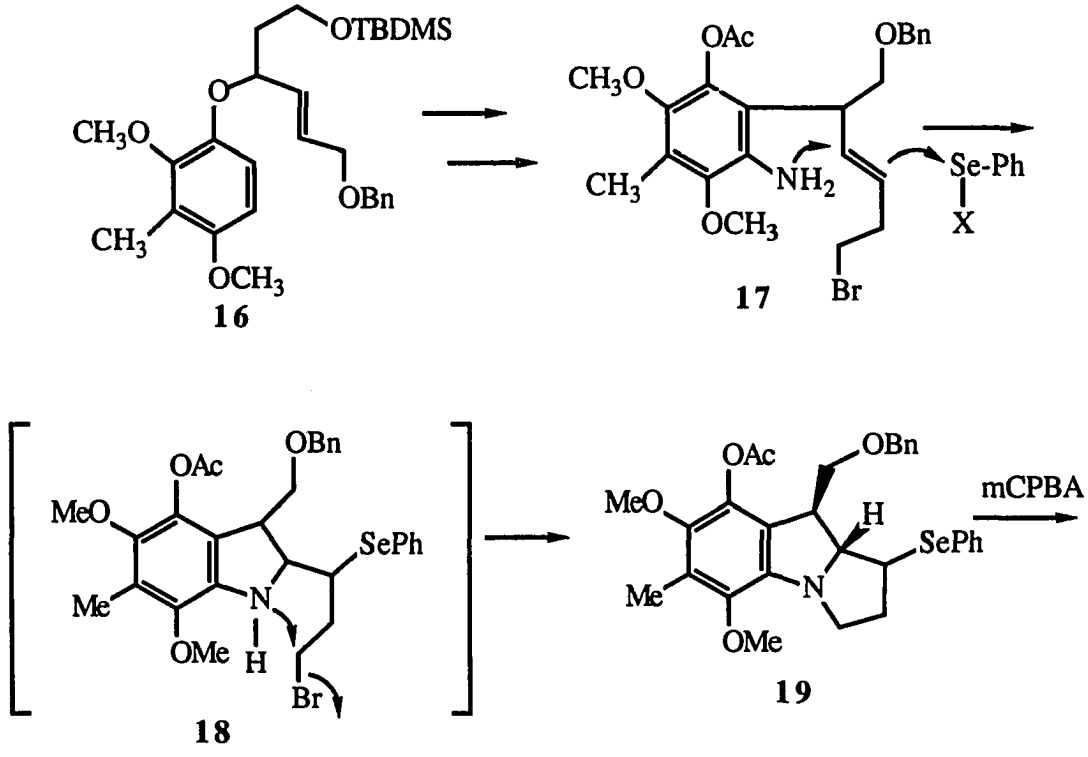
15

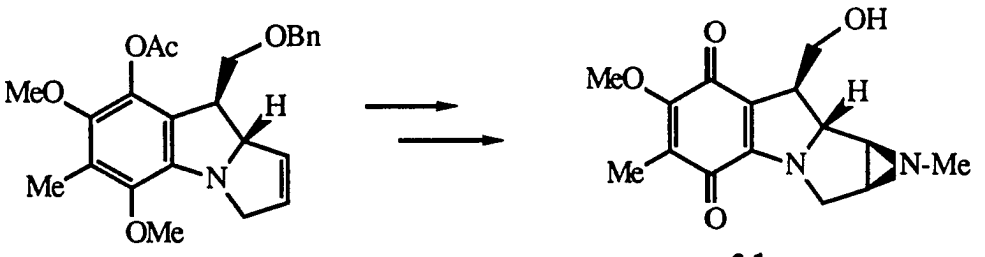
R=$CH_2CH_2CH_2OAc$

His synthesis began from the nitrile **11**. Transformation of **11** to **12** and conversion of **12** to **13** provided the precursor for the intramolecular Michael reaction. On attempting the Michael reaction on the unprotected aziridine **13a**, he observed the formation of two products. The minor product was the desired eight-membered quinone **14a**, while the major product was most likely formed by an interaction of the aziridine nitrogen with the C-1

carbonyl group. Thus, protection of the aziridine nitrogen was required in order to apply this cyclization reaction. The 3-acetoxypropylaziridine **13b** was subjected to hydrogenolysis followed by treatment with oxygen to afford the eight-membered quinone **14b** in 42% yield. Clearly, the free amino group, an intermediate in this transformation, cyclized intramolecularly to the quinone moiety in the Michael fashion. The next crucial transannular cyclization was effected by tetrafluoroboric acid in methylene chloride at room temperature. This reaction afforded exclusively decarbamoyl-N_1-(3-acetoxypropyl)mitomycin A (**15**). Further transformation provided mitomycin A (**2**) as a racemic mixture. Compound **2** has been converted to mitomycin C (**3**) and porfiromycin (**4**).[1]

Danishefsky *et al.* have developed a methodology directed toward the total synthesis of mitomycins[7], and have also synthesized other novel mitomycin congeners.[8] The intermolecular selenium-mediated alkylation of a suitably functionalized aniline gave the mitosene **20** which was converted to the desired mitomycin congeners **21**.

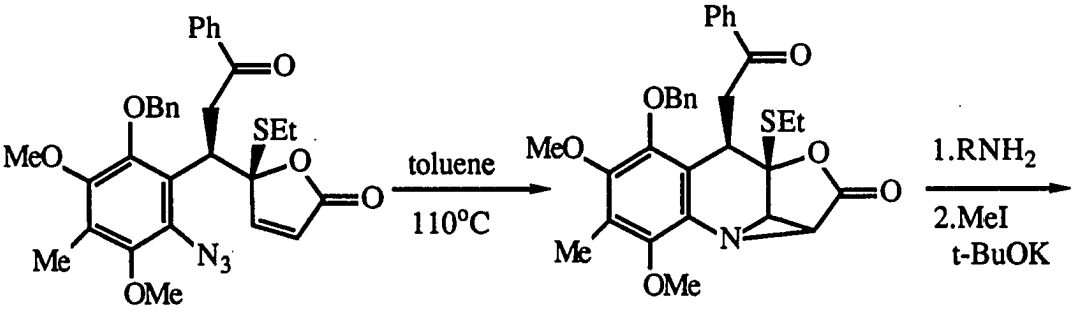




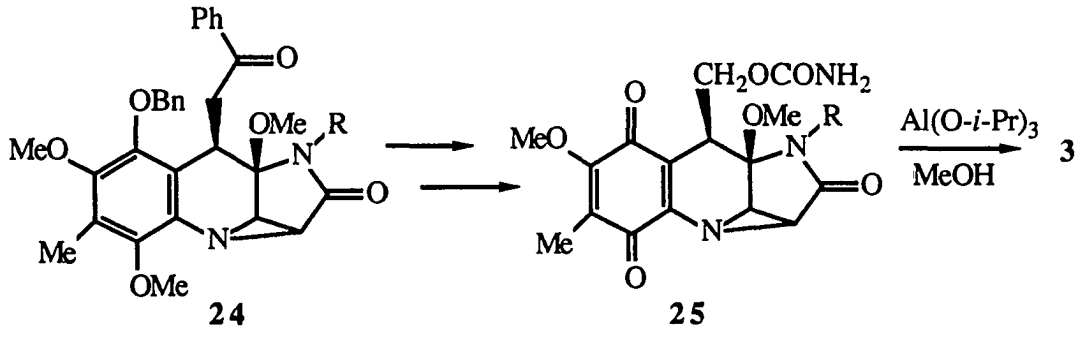
20 **21**

Toward this goal, olefin **17** was prepared from the allylic ether **16** by a Claisen rearrangement followed by further functional group transformation. Treatment of **17** with N-phenylselenophthalimide (N-PSP) provided the single tricyclic selenide **19**, which upon oxidation gave the mitosene **20**. The overall yield of **20** from **16**, without chromatography of any of the intermediates, was 31%. Further transformation of **20**, which involved the installation of the aziridine and the quinone formation, provided the aziridinomitosane **21** which is related in stereochemistry to the major classes of mitomycins. To reach the actual mitomycins, Danishefsky and coworkers have studied the C-9a functionalization of **21**.[7]

In 1987, Fukuyama and Yang reported a total synthesis of D,L-mitomycin by the rearrangement of the corresponding isomitomycin **25**.[9]

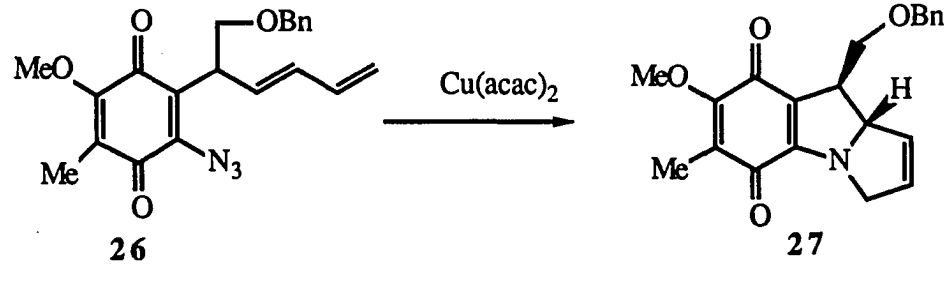


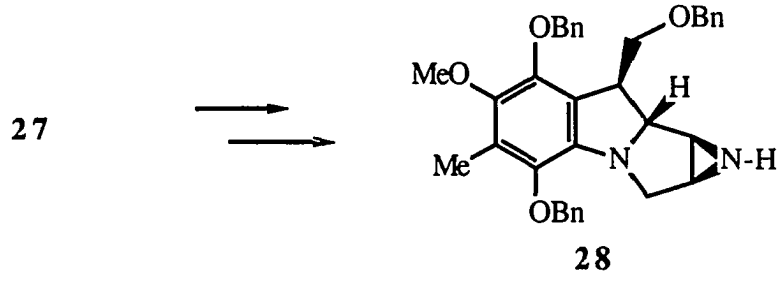
22 **23**



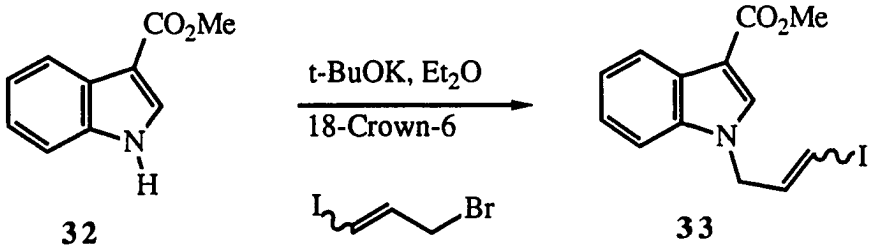
The facile intramolecular azide-olefin cycloaddition of the azido butenolide **22** gave the tetracyclic aziridine **23**. Aminolysis of the strained lactone **23** followed by methylation afforded the methoxy lactam **24**. Further transformation of **24** gave the novel antitumor, antibiotic isomitomycin A **25**. In 1987, Kono *et al.* found that **3** and **25** form an equilibrium mixture in which mitomycin A (**3**) is the predominant isomer.[10] Therefore, Fukuyama utilized **25** as a synthetic equivalent of mitomycins **2** and **3**. Equilibration of synthetic **25** with Al(O-*i*-Pr)$_3$ furnished mitomycin A (**3**) in 91% yield, which was subsequently converted to mitomycin C (**2**) by aminolysis (NH_3, MeOH).

In 1988, Naruta and coworkers reported a synthesis of a 9a-deoxymitomycin congener.[11] Their strategy focused on the stereospecific copper-catalyzed double cyclization of the azide quinone **26** to the tricyclic quinone **27** in one step. Subsequent stereospecific introduction of the aziridine ring to **27** furnished the desired compound **28**, which is a promising precursor for the synthsis of mitomycins.

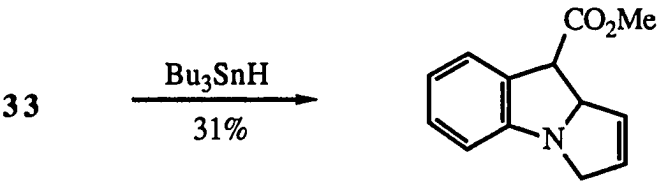




Although a variety of clever syntheses and synthetic approaches have been reported, more efficient routes are still needed.



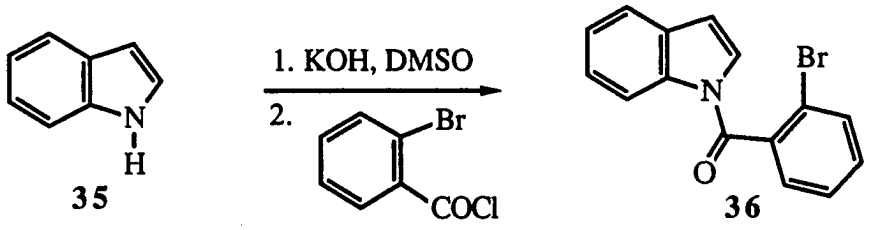
32 33



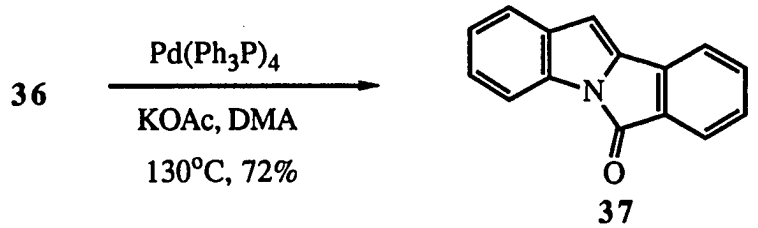
34

involves the intramolecular radical cyclization of a 3-iodopropenyl indole **33**. The product of the reaction of **33** with tributyltin hydride was the dihydro pyrrolo[1,2-a]indole **34**, an important substructure for the synthesis of mitomycins.

Kozikowski examined the same bond disconnection, but studied an organopalladium mediated reaction. He successfully generated five- and seven-membered rings from a palladium-catalyzed cyclization reaction.

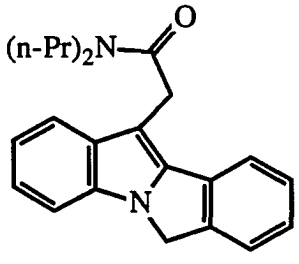


35 36

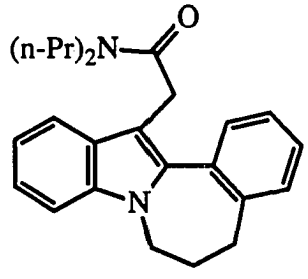


37

Among the compounds formed by this palladium-catalyzed cyclization reaction, both compound **38** and its more flexible counterpart **39** showed high affinity for the peripheral benzodiazepine receptor.

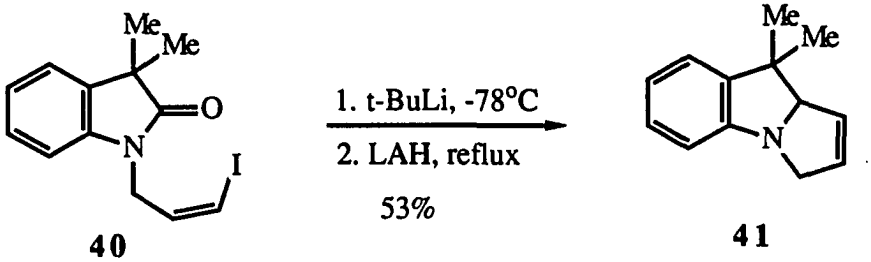


38



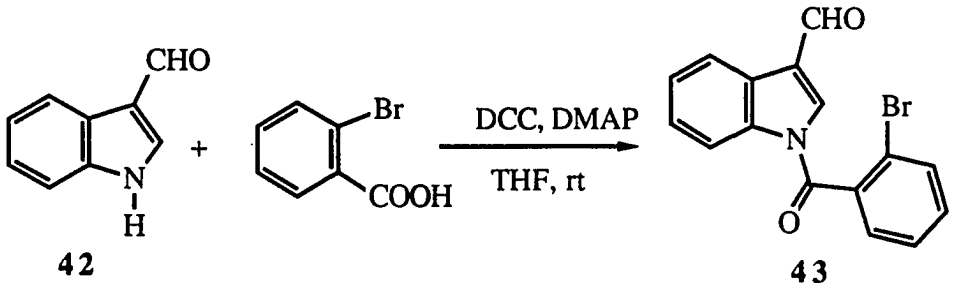
39

Additionally, Jones and coworkers recently reported the cyclization of 3-iodopropenyl oxindole **40**.[14] The treatment of **40** with tert-butyllithium gave the vinyl lithium derivative which reacted with the carbonyl group of the oxindole. Reduction with $LiAlH_4$ gave the pyrroloindoline **41** in 53% yield. They also prepared a six-membered ring compound, pyridino[1,2]indolenine, by this method.



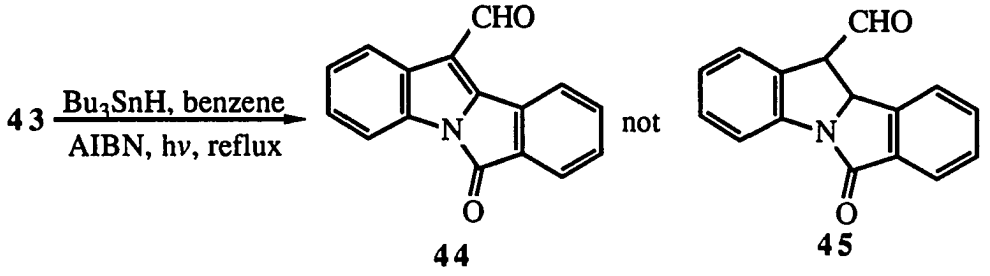
40 **41**

Our study began with the readily available indole derivative **43**. Owing to the ready availability of the indole nucleus and the ease with which it is N-acylated, we chose to explore the intramolecular cyclization of several indole derivatives. The acylation of commercially availabe indole-3-carboxaldehyde (**42**) with 2-bromobenzoic acid in the presence of DCC and DMAP (cat.) led to the N-acylated indole derivative **43** in 98% yield.



42 43

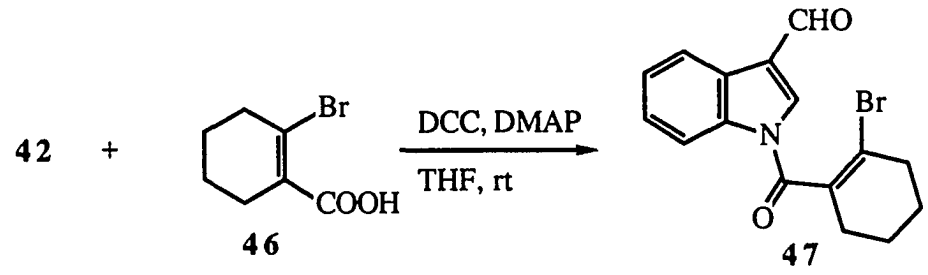
Initially, intramolecular radical cyclization of **43** was examined. Treatment of **43** with tributyltin hydride and AIBN in dry benzene under irradiation with a sun lamp afforded the aldehyde **44** in 35% yield after flash chromatography. Interestingly, we did not detect any of the dihydroindole-type product **45**.



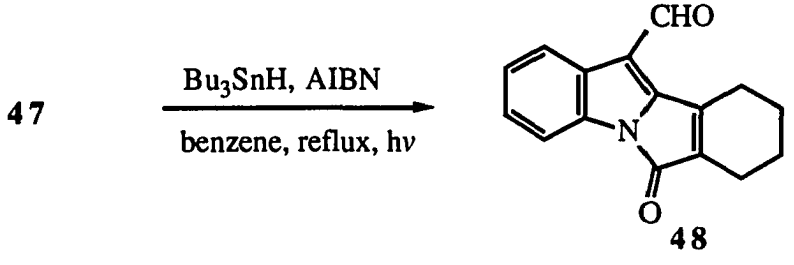
44 45

Various other reaction conditions were examined ($Bu_3SnCl/NaBH_3CN$, Ph_3SnH, $Bu_3SnSnBu_3/h\upsilon$), but aldehyde **44** was the only indole-containing product formed. The formation of aldehyde **44** at this stage was not a serious concern, since we eventually intended to study the cyclization with 2,3-disubstituted indoles wherein rearomatization would not present a problem.

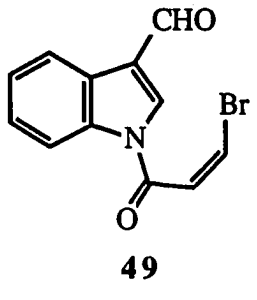
Compound **47** was next prepared from **42** and 2-bromocyclohexenecrboxylic acid (**46**).[15] DCC coupling of **42** and **46** afforded **47** in 77% yield.



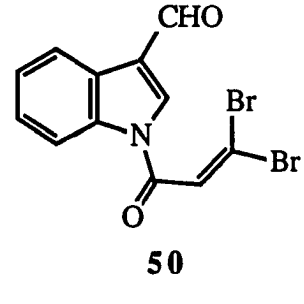
A solution of **47** in dry benzene was treated with tributyltin hydride and AIBN in refluxing benzene. This radical cyclization yielded the cyclized indole derivative **48** in 42% yield.



In an effort to increase the yield, the reaction was repeated using an initial concentration of substrate of 0.01M and slow addition of n-Bu3SnH and AIBN over four hours by syringe pump. The yield of **48** from the modified procedure was 53%. After the initial successful results from the intramolecular radical reaction with the cyclic indole precursors **43** and **47**, several other precursors (**49**, **50**) were examined in radical reactions.



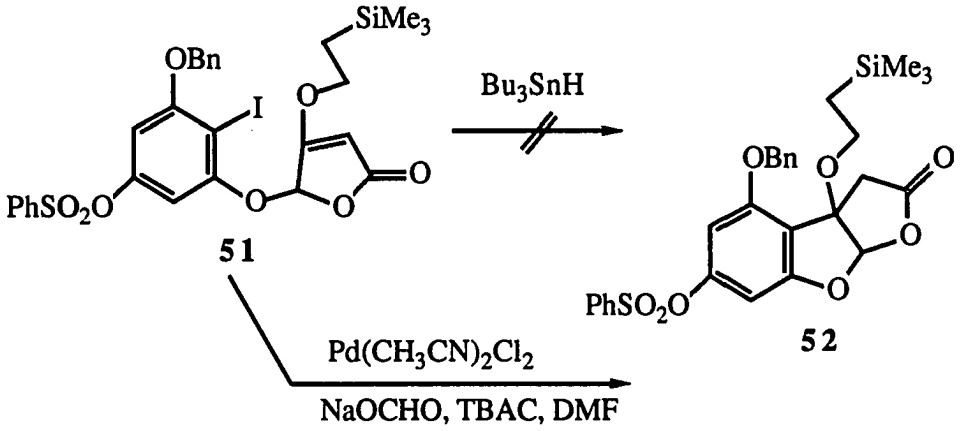
49



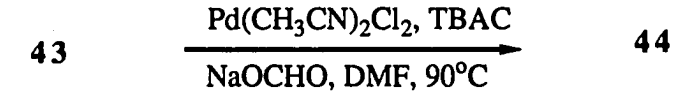
50

Unfortunately, we did not obtain any of the desired cyclized products. We assumed that cyclization did not occur in these cases because cleavage of the amide bond happened preferentially. Due to the unsuccessful results of the intramolecular radical cyclization of an acyclic precursor, we needed another method for cyclization.

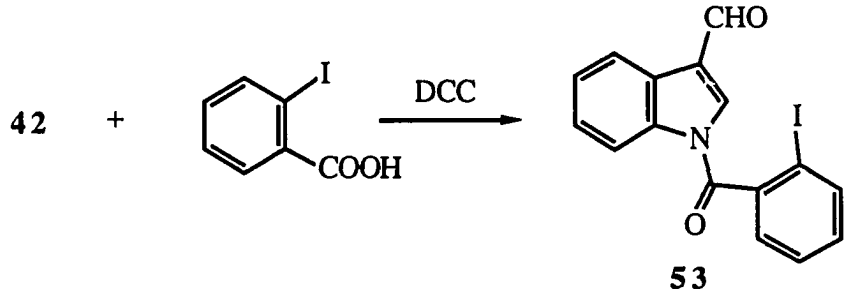
In 1989, Martin and coworkers studied intramolecular cyclizations in their synthesis of an aflatoxin M_1 precursor.[16] They found that the palladium-induced intramolecular cyclization afforded **52** in 57% yield. However, the radical cyclization of **51** failed.



We applied this palladium-mediated cyclization to our system. Compound **43** was examined. A solution of **43**, sodium formate, and tetra-n-butylammonium chloride (TBAC) in anhydrous DMF was treated with 10 mole percent bis (acetonitrile) palladium dichloride at 90°C to give the cyclized product **44** in 48% yield.



Due to the low yield of **44** from the bromide **43**, we made the iodide **53** by the DCC coupling reaction of **42** and the commercially available *o*-iodobenzoic acid in 95% yield.



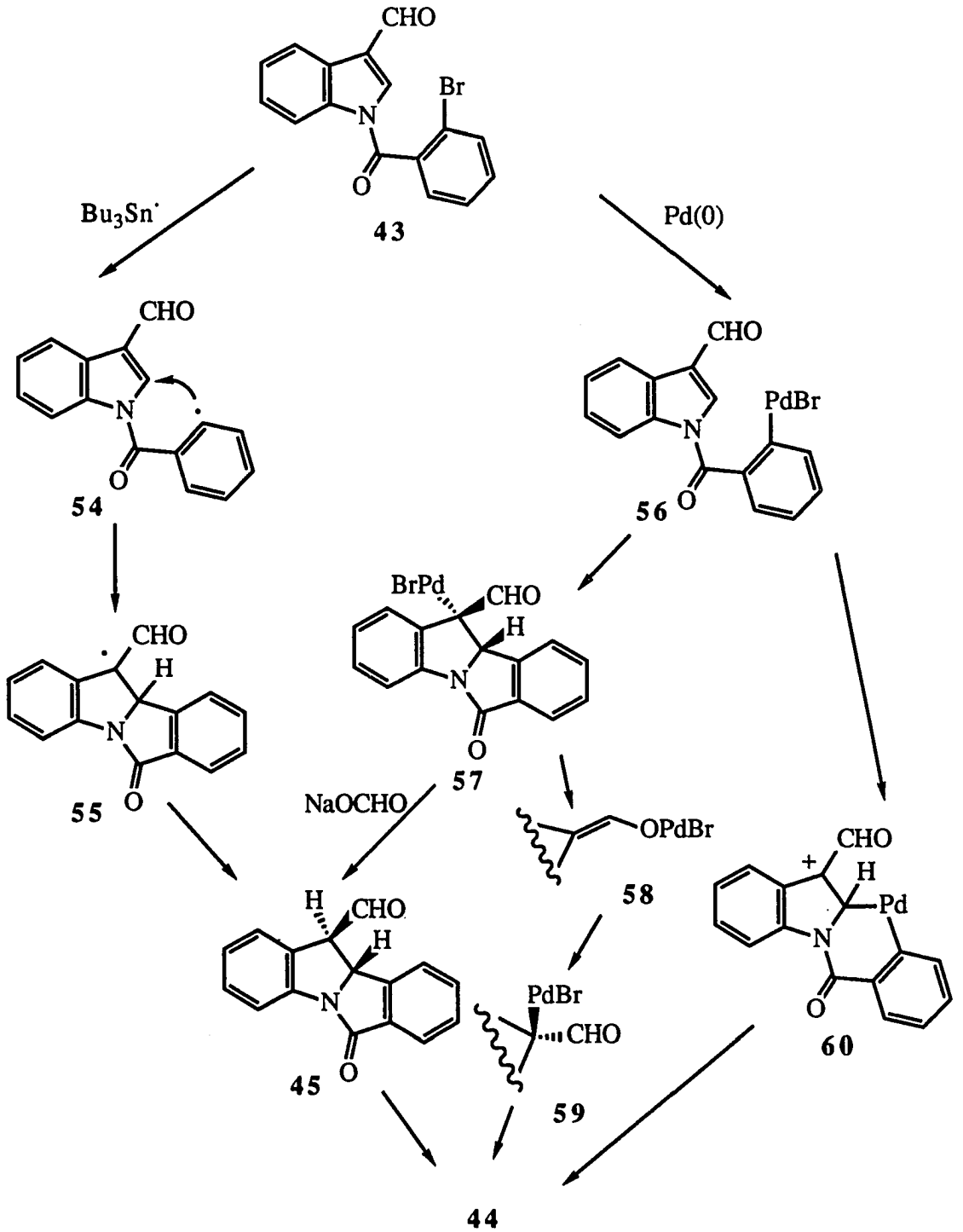
53

Palladium-mediated cyclization of the iodide **53** gave **44** in 70% yield. Palladium-mediated cyclization of the indole **47** also provided **48** in 60% yield. However, several attempts at the palladium-mediated cyclization of **49** and **50** failed. From both the intramolecular radical- and palladium-mediated cyclization, we obtained two cyclized products **44** and **48**. We propose the following mechanisms for these reactions.

Presumably, dihydropyrrolo indole intermediate **45** was first formed, and in situ dehydrogenation of the labile compound **45** gave the resulting product **44**.

In conclusion, we have developed two convenient and relatively efficient methods for the preparation of the pyrroloindole nucleus based on the intramolecular cyclization of vinyl and aryl radicals- and the palladium-mediated cyclization of vinylic and aryl halides. Additionally, resulting tetracyclic compound **44** could be an analog of the compound **38**, which showed biological importance.

* Our proposed mechanism



EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. N,N-Dimethylformamide (DMF) was dried by azeotropic distillation with benzene, followed by vacuum distillation. Benzene was distilled from lithium aluminum hydride. Dichloromethane (CH_2Cl_2), ethyl alcohol, and acetonitrile were distilled from calcium hydride. All reactions were conducted under a nitrogen atmosphere, and all extracts were dried over anhydrous sodium sulfate or anhydrous magnesium sulfate. Apparatus for experiments requiring anhydrous conditions was flame-dried under a stream of nitrogen or was dried in a 150°C oven for 12 h. Flash chromatography was performed on Kieselgel 60, mesh 230 - 400. Infrared spectra were obtained on a Perkin-Elmer 1320 spectrophotometer. Proton nuclear magnetic resonance spectra (300 Mhz) were obtained using a Nicolet Magnetics Cooperation NT-300 spectrometer. All chemicals shifts are reported in δ relative to tetramethylsilane as an internal standard. Splitting patterns are designated as a s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Carbon-13 NMR spectra were determined on a Nicolet NT-300 spectrometer and are reported in δ relative to $CDCl_3$ (77.06 ppm). High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer. Low resolution mass spectra were recorded on a Finnegan 4023 mass spectrometer. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories Inc. The purity of all title compounds was judged to be >90% by ^1H NMR spectral determinations.

General procedure for the preparation of the vinyl and aryl halides. N-(o-Bromobenzoyl)indole-3-carboxaldehyde (43). To a solution of indole-3-carboxaldehyde (0.20 g, 1.38 mmol) in dry THF (10 mL) were added *o*-bromobenzoic acid (0.31 g, 1.52 mmol), 4-dimethylaminopyridine (DMAP, 8.5 mg, 0.069 mmol), and 1,3-dicyclohexylcarbodiimide (DCC, 0.31 g, 1.52 mmol) at room temperature under nitrogen. This solution was stirred overnight. The THF was removed in vacuo. The residue was diluted with ether, the precipitate was filtered off, and the filtrate was concentrated in vacuo. The residue was purified by silica gel flash chromatography (3:1 = hexane: ethyl acetate) to afford 0.44 g (98%) of pure **43**: R_f 0.36 (3:1 = H:EA); ^{1}H NMR ($CDCl_3$) δ 7.46 - 7.50 (m, 3H), 7.52 - 7.55 (m, 2H), 7.60 (s, 1H), 7.74 (d, J = 6.3 Hz, 1H), 8.24 - 8.32 (m, 1H), 8.38 (d, J = 7.5 Hz, 1H), 10.02 (s, 1H); IR (Nujol) 1665, 1715 cm^{-1}; MS: m/e 328, 329, 330, 346, 347, 362, 363, 364; ^{13}C NMR ($CDCl_3$) δ 116.30, 119.67, 122.11, 123.15, 125.93, 126.53, 126.96, 127.98, 129.04, 132.55, 133.52, 135.59, 136.17, 136.32, 166.74, 185.65.

N-(o-Iodobenzoyl)-indole-3-carboxaldehyde (53). The procedure employed for the preparation of **43** was followed with indole-3-carboxaldehyde (0.30 g, 2.07 mmol), *o*-iodobenzoic acid (0.67 g, 2.69 mmol), DMAP (0.03 g, 0.269 mmol), and DCC (0.55 g, 2.69 mmol) in THF (20 mL). The crude product obtained after workup was chromatographed, using hexane-ethyl acetate (2:1), to give pure **53** (0.73 g, 95%): Rf 0.48 (2:1 H:EA) ; ^{1}H NMR ($CDCl_3$) δ 6.91 (d, J = 8.4 Hz, 1H), 7.10 - 7.20 (m, 1H), 7.27 - 7.33 (m, 2H), 7.40 -7.57 (m, 2H), 7.94 (d, J = 8.1Hz, 1H), 7.98 - 8.04 (m, 1H), 8.29 (d, J = 7.8Hz, 1H), 10.35 (s, 1H); IR (Nujol) 1660, 1710 cm^{-1}; CI-MS (NH_3) m/e 375, 376, 377, 393, 394, 395, 410, 411, 412; ^{13}C NMR ($CDCl_3$) δ 92.46, 116.38, 122.18, 123.20,

125.97, 126.58, 127.01, 128.60, 128.86, 132.41, 136.26, 139.70, 139.92, 168.14, 185.61.

N-(2-Bromo-1-cyclohexenecarboxyl) indole-3-carboxaldehyde (47). The procedure used for the preparation of **43** was followed with indole-3-carboxaldehyde (0.30 g, 2.07 mmol), 2-bromocyclohexene carboxylic acid (0.445 g, 2.17 mmol), DMAP (0.0122 g, 0.10 mmol), and DCC (0.45 g, 2.17 mmol) in THF (12 mL) to give the pure **47** (0.53 g, 77%) after purification by silica gel flash chromatography (4:1 = hexane:ethyl acetate): Rf 0.35 (3:1 H:EA); ^{1}H NMR ($CDCl_3$) δ 1.82 - 1.93 (m, 4H), 2.49 (d, br, 2H), 2.66 - 7.50 (m, 2H), 7.98 (s, 1H), 8.28 (d, J = 7.8Hz, 1H), 8.43 (d, J = 7.8Hz, 1H), 10.14 (s, 1H). ; IR (Nujol) 1705, 1680 cm^{-1}; CI-MS (NH_3) m/e 332, 333, 334, 349, 350, 351, 352, 366, 367, 368; ^{13}C NMR ($CDCl_3$) δ 21.12, 23.85, 29.44, 35.45, 116.25, 121.90, 123.14, 124.50. 125.69, 126.57, 126.81, 133.16, 135.65, 136.16, 168.14, 185.67.

General procedure for the radical cyclization of 47. A solution of the bromide **47** (0.08 g, 0.24 mmol) in dry benzene (4 mL) was heated to reflux, using a 275-W sun lamp. A solution of n-Bu_3SnH (0.078 mL, 0.29 mmol) and AIBN (0.0118 g, 0.07 mmol) in benzene (1 mL) was added to the stirred solution of **47** over 15 min. Heat from the sun lamp was used to keep the solution at reflux for 4 h. After removal of the benzene, the residue was stirred rapidly for 1 h with 5 mL of ether and 5 mL of saturated aqueous KF solution. The mixture was extracted with ether and the combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel flash chromatography (3:1 = hexane:ethyl acetate) to give the pure product **48** (25 mg, 42%): Rf 0.49 (3:1 H:EA); ^{1}H NMR ($CDCl_3$) δ 1.79 - 1.92 (m, 4H), 2.35 - 2.40 (m, 2H), 2.64 - 2.68 (m, 2H), 7.16 - 7.21 (m, 1H), 7.29 - 7.34 (m, 1H), 7.67 (d, J = 7.9Hz, 1H), 8.05 (d,

J = 7.8Hz, 1H), 10.18 (s, 1H); IR (Nujol) 1740, 1675 cm^{-1}; CI-MS (NH_3) m/e 252, 269; EI-MS m/e 70, 116, 143, 167, 195, 22, 251; HRMS m/e calcd for $C_{16}H_{13}O_2N$: 251.09463. Found: 251.09438; ^{13}C NMR ($CDCl_3$) δ 20.34, 21.26, 21.66, 23.92, 112.01, 117.18, 123.62, 124.25, 127.80, 123.62, 124.25, 127.80, 129.66, 133.64, 138.08, 143.61, 148.42, 164.99, 184.15; Anal. calcd for $C_{16}H_{13}O_2N$: C, 76.53; H, 5.22; N, 5.58. Found: C, 73.54; H, 5.34; N, 4.96; mp. 160 -164 °C; yellow solid.

In order to increase the yield of the radical cyclized product, the reaction was repeated, using an initial concentration of substrate of 0.01M and slow addition of n-Bu_3SnH and AIBN over 3 h by syringe pump. The pure cyclized product was obtained in 53% yield.

Radical cyclization of 43. The procedure used for the preparation of **48** was followed with bromide **43** (0.18 g, 0.549 mmol), Bu_3SnH (0.18 mL, 0.659 mmol), and AIBN (0.027 g, 0.165 mmol) in dry benzene (11 mL). The crude product obtained after workup was purified by silica gel flash chromatography (3:1 = hexane:ethyl acetate) to afford the pure cyclized product **44** (48 mg, 35%): Rf 0.63 (3:1 H:EA); ^1H NMR ($CDCl_3$) δ 7.29 (dd, J = 0.9, 7.5Hz, 1H), 7.37 (dd, J = 0.9, 7.5Hz, 1H), 7.48 (ddd, J = 0.6, 7.5Hz, 1H), 7.62 (ddd, J = 0.9, 7.5Hz, 1H), 7.80 (d, J = 7.5Hz, 1H), 7.90 (d, J = 7.8Hz, 1H), 8.00 - 8.05 (m, 2H), 10.49 (s, 1H); IR (Nujol) 1735, 1670 cm^{-1}; EI-MS m/e 70, 95, 143, 163, 190, 219, 247; HRMS m/e calcd for $C_{16}H_9O_2N$: 247.06333. Found: 247.06331; ^{13}C NMR ($CDCl_3$) δ 113.36, 116.47, 122.00, 124.56, 125.26, 125.91, 127.40, 130.88, 131.09, 132.93, 133.12, 133.36, 134.80, 144.53, 162.76, 184.14; Anal. calcd for $C_{16}H_9O_2N$: C, 77.72; H, 3.67; N, 5.67. Found: C, 77.63; H, 3.69; N, 5.61; mp. 224 -226 °C; yellow solid.

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GENERAL SUMMARY

This dissertation has described the synthesis of analogs of glutamic acid, tetracycline and mitomycin. Cyclopropane analogs of glutamic acid have been synthesized by way of the reactive cyclopropene intermediate, and several possible chelating analogs of tetracyclines to test for novel ion chelating ability were prepared. We have also developed two methods for the preparation of the pyrroloindole nucleus based on the intramolecular cyclization of vinyl and aryl radicals- and the palladium-mediated cyclization of vinylic and aryl halides.