THE TOTAL SYNTHESIS OF MITOMYCINS[1]

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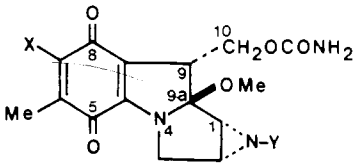
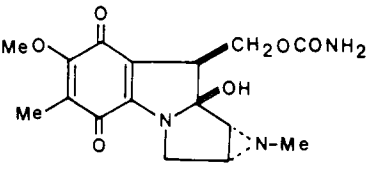
It was 1956 when Hata and his co-workers at Kyowa Hakko Company first succeeded in the isolation of two new antibiotics, mitomycins A and B, from a culture broth of *Streptomyces caesipitosus* (1). It soon became evident that the mitomycins were active against gram positive and gram negative bacteria, and also against several kinds of tumor cells in both animals and humans. Wakaki and his co-workers at Kyowa Hakko later isolated the third member of this antibiotic group, mitomycin C, from the same *Streptomyces* strain (2). Mitomycin C was shown to have the strongest and broadest activity against tumors and has been used in cancer chemotherapy.

In 1962, Webb and his colleagues at the Lederle Laboratories reported the beautiful structure elucidation of mitomycin A and its interconversion with mitomycin C and porfiromycin (3). Tulinsky confirmed the structure proposed for mitomycin A by X-ray analysis (4). The relative stereochemistry of mitomycin B was shown to be different from that of mitomycin A by Yahashi and Matsubara,

Scheme 1





1 : mitomycin A

X = OMe, Y = H

2 : mitomycin B

3 : mitomycin C

X = NH_2, Y = H

4 : porfiromycin

X = NH_2, Y = Me

and the absolute configuration assigned for the aziridine ring of mitomycin B was opposite to that of mitomycin A. They later corrected this to be the same (5).

The structure of mitomycins A, B, C, and porfiromycin is summarized in scheme 1 (6).

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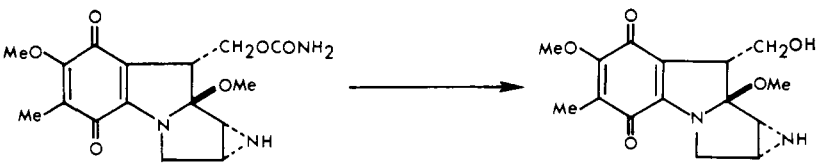
[1]Presented as a plenary lecture at the 20th Annual Meeting of the American Society of Pharmacognosy at Purdue University, West Lafayette, Indiana, July 30–August 3, 1979.

The unique structure of the mitomycins, coupled with their great medicinal value, offers a formidable challenge to the synthetic chemist. Indeed, numerous synthetic approaches to the antibiotics and also their degradation products have been reported from the time their structures were first elucidated (7). However, the naturally occurring mitomycins themselves had never been synthesized until 1977 when we succeeded in the first total synthesis of the antibiotics (8). In this article, we would like to review our synthetic efforts in this area.

The mitomycin skeleton is known to be stable under basic conditions. For example, Kinoshita and his co-workers were successful in hydrolyzing mitomycin A (**1**) into decarbamoylmitomycin A (**5**) with sodium methoxide in benzene at room temperature (9). Further, the hydroxy group of **5** was shown to behave normally toward acylating reagents.

Scheme 2



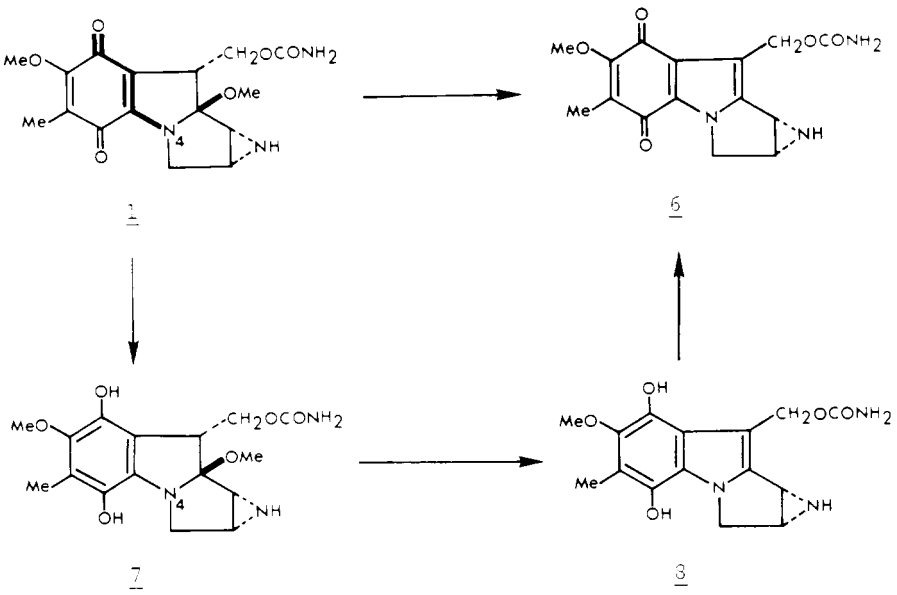
1 **5**

Contrary to the base stability, mitomycins are known to be extremely acid-labile. For example, a brief treatment of mitomycin A in methylene chloride containing a small amount of a mineral or organic acid causes elimination of methanol to yield an unstable, so-called mitosene derivative **6**. Since the carbon-nitrogen bond of the aziridine ring is located at the benzylic position, **6** is solvolyzed further (3, 9).

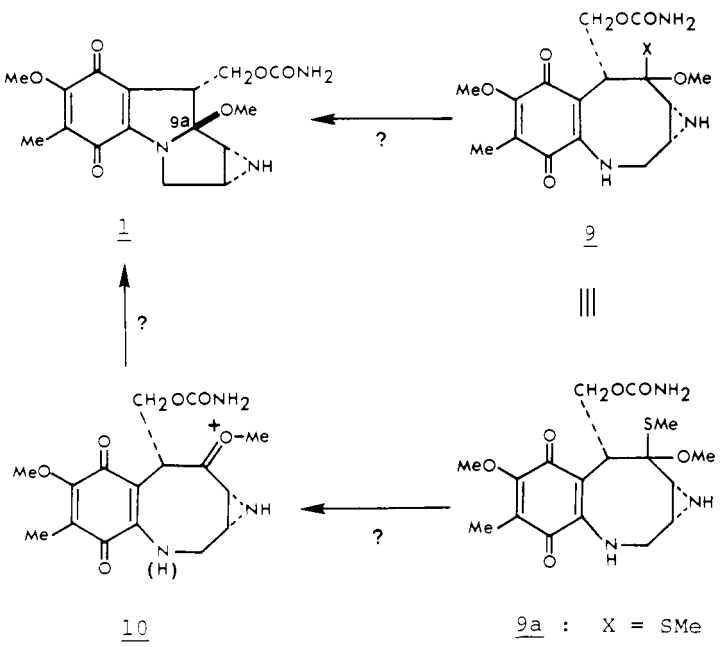
The aforementioned instability of mitomycins is further intensified under reducing conditions. Thus, when mitomycin A was subjected to hydrogenation conditions in methanol at room temperature, the major product isolated, after air-oxidation, was the mitosene **6** or its degradation product(s) (3, 9). The observed difference in stability between mitomycins and their dihydroderivatives could be attributed to the difference in the nucleophilicity of the N-4 nitrogen atoms (10)—note the vinylogous amide group of **1**, indicated by heavy lines in scheme 3.

These analyses suggest that the following two points are important in designing the synthesis of mitomycins: 1. as the least stable functionality of mitomycins is the C-9a methoxy group, it would be wise to introduce this functionality to a synthetic intermediate at as late a stage as possible; and 2. once this is realized, the oxidation level of the compounds must be kept at that of the indole quinone. One interesting possible method to introduce the C-9a methoxy group which meets with these criteria is shown in scheme 4, whereby the C-9a methoxy group might be introduced by a transannular cyclization reaction via the oxonium ion **10**. There are at least four good reasons for considering this transannular reaction. First, the C-9a methoxy group could be introduced to a synthetic intermediate at a very late stage in the synthesis in this manner. Second, no reducing conditions

Scheme 3



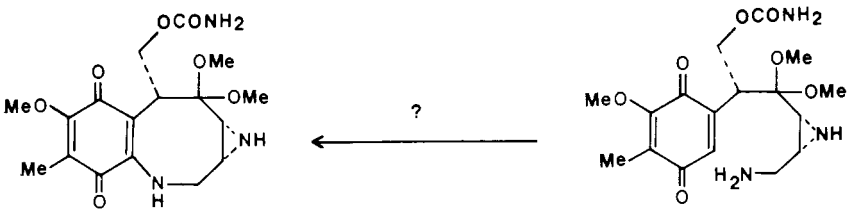
Scheme 4



are necessary to force this cyclization reaction. Third, it might be possible to realize the reaction under neutral or even basic conditions by choosing the proper protecting group as X in **9**. One obvious choice for this purpose would be the dimethyl hemithioketal **9a** which is expected to be activated to **10** in the presence of a metal ion such as Hg^{2+}. Fourth, as discussed later (see pages 560–61), the outcome of the stereochemistry of this cyclization is expected to give the product with the desired stereochemistry.

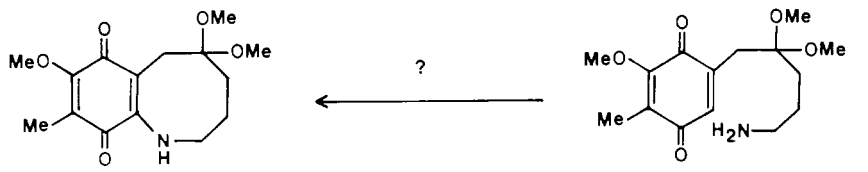
Generally speaking, the synthesis of an eight-membered compound is rather difficult, and hence it is not wise to propose a synthesis using an intermediate with such a ring system. However, the four reasons described previously were too attractive to allow us to discard this plan. One possible synthetic route to the eight-membered quinone is shown in scheme 5. Inspection of molecular models revealed that the transition state for the expected eight-membered ring formation seemed reasonable mainly because of the existing quinone and aziridine rings. Nevertheless, we felt that the feasibility of this key step should first be verified, and chose the compound **13** for this purpose.

Scheme 5



9b : X = OMe

11

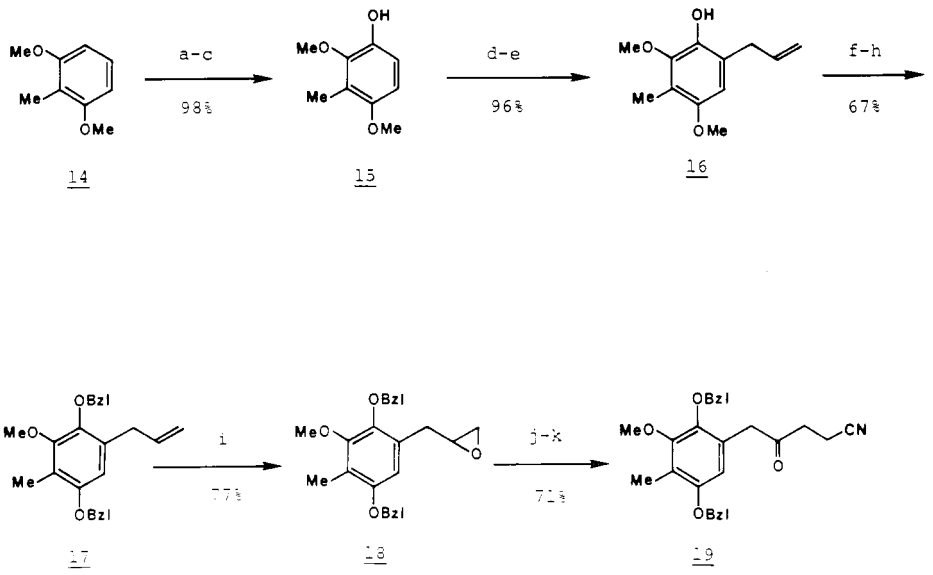


12

13

Commercially available 2,6-dimethoxytoluene (**14**) was used as the starting material for the synthesis of **13**. Scheme 6 summarized the straightforward 11-step synthesis of the keto nitrile **19** from **14**. This route was suitable for a large scale experiment and its overall yield was very high; over 100 g of crystalline keto nitrile **19** could be prepared from 100 g of **14** in about 10 days by one person.

Scheme 6

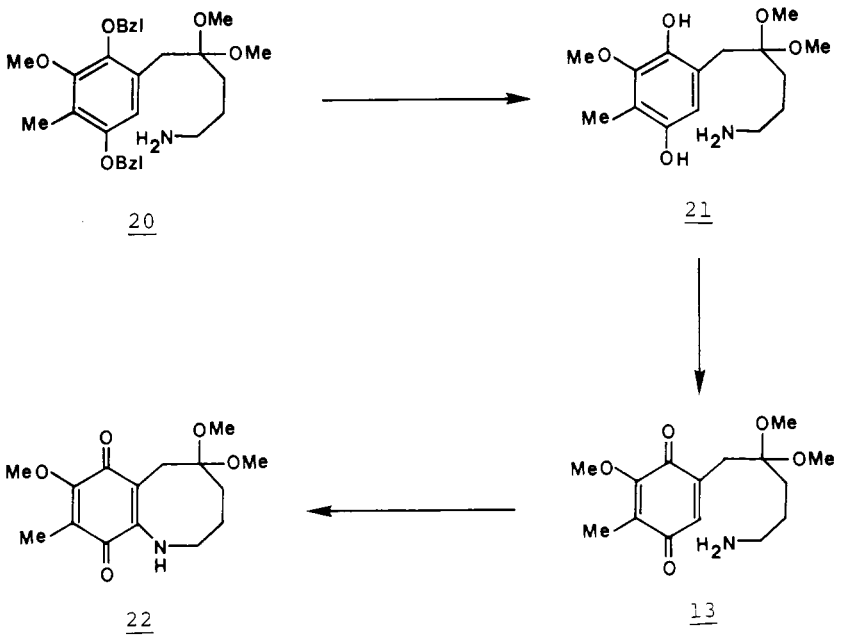


Reagents a: $Cl_2CHOCH_3/TiCl_4/CH_2Cl_2/0°C$. b:MCPBA/$CH_2Cl_2$/0°C. c: $NaOCH_3/CH_3OH$/0°C. d: $CH_2=CHCH_2Br/K_2CO_3$/acetone/reflux. e: $C_6H_5N(CH_3)_2$/reflux. f: HNO_3/AcOH/RT. g: Zn/AcOH/0°C. h: $C_6H_5CH_2Br/K_2CO_3$/DME–DMF/reflux. i.: $H_2O_2/C_6H_5CN/K_2CO_3$/CH_3OH-dioxane/RT. j. LDA/CH_3CN/−30°C. k: CrO_3/H_2SO_4/aq. acetone.

After protection of the keto group as its dimethyl ketal, **19** was reduced by lithium aluminum hydride to the amine **20**, which was directly subjected to hydrogenolysis (Pd-C/methanol/rt) and then air-oxidation (O_2/methanol/rt), to yield the desired eight-membered quinone **22**. Clearly, an intermediate in this transformation was the benzoquinone **13**, the primary amino group of which cyclized intramolecularly to the quinone moiety in the Michael fashion. Thus, it was established that the proposed intramolecular Michael reaction was suitable for the synthesis of a compound like **9**. Although some reasonable alternative modes for the cyclization reaction exist, the compound **22** was the only isolable product of this sequence of reactions. The overall yield of the eight-membered quinone **22** from the keto nitrile **19** was 40–50%.

The eight-membered quinone **22** was found to be extremely sensitive to acids; for example, a trace amount of hydrochloric acid in methanol at room temperature, a trace amount of acetic acid in methanol at room temperature, or even silica gel tlc plates are acidic enough to convert **22** into the indole quinone **23** almost instantaneously. This transformation could also be effected under thermal conditions. The intermediate of these reactions must be the compound **24**. However, all efforts to detect the existence of **24** by spectroscopic or chromatographic techniques were fruitless. These situations could be summarized as follows. Although the feasibility of the proposed transannular cyclization reaction, i.e., **9**→**1**, was well demonstrated, it was still necessary to develop a special method to control an unstable intermediate like **24**.

Scheme 7

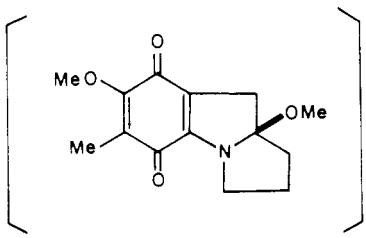


Under these circumstances, the investigation to transform **22** into the dimethyl hemithioketal **25** was undertaken. Taking into account the relative stability of the oxonium ion over the sulfonium ion, it should be possible to synthesize **25** by a methyl mercaptan–acid combination. However, the most serious reservation for this proposal was the fact that the oxonium ion necessary for this transketallization could also provide the transannular cyclization. In other words, the real question in our minds was how to avoid the transannular cyclization reaction under transketallization conditions. Our hope, though it seemed very small, was that at a low enough temperature the oxonium ion might take a conformation in which the amide nitrogen would stay far enough away from the oxonium ion center and thus allow it to be neutralized by methyl mercaptan. In any event, the dimethyl ketal **22** was treated with *neat* methyl mercaptan at −45°C in the presence of a catalytic amount of borontrifluoride etherate, with extremely careful monitoring of the reaction by tlc. A remarkably clean transformation was observed under these conditions, and the desired dimethyl hemithioketal **25** was isolated in almost quantitative yield.

The dimethyl hemithioketal **25** thus synthesized was then subjected to a reaction with mercuric chloride in methylene chloride containing triethylamine at room temperature, to afford cleanly the methoxy compound **24**, which was successfully isolated by basic aluminum oxide tlc and fully characterized by spectroscopic methods. Compound **24** was found, as expected, to be extremely sensitive to acids, and thus yielded the indolequinone **23** quantitatively.

Scheme 3

22 23



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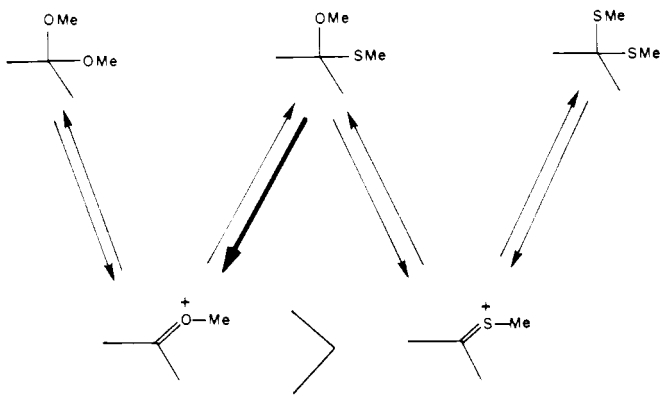
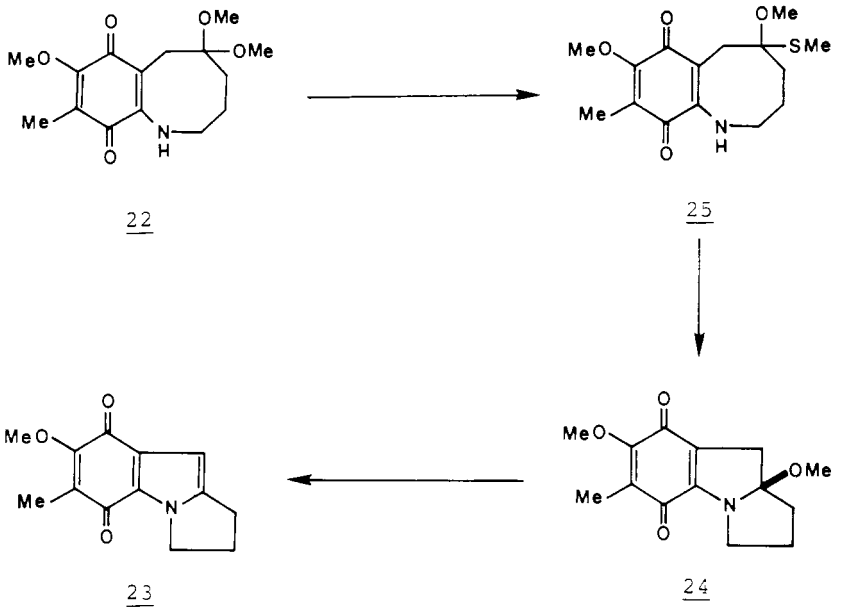
Scheme 4



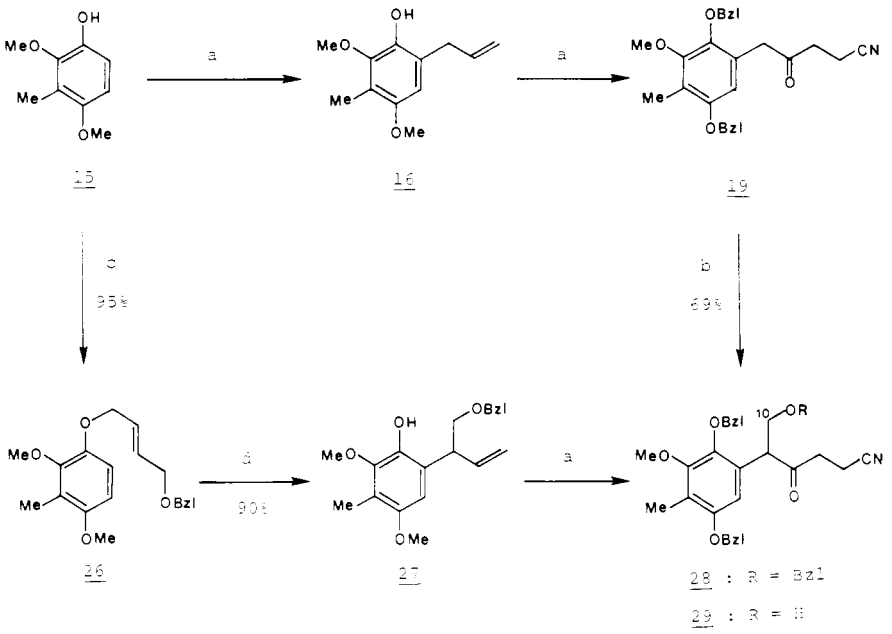
Scheme 10



Let us now turn our attention to the introduction of the C–10 hydroxymethyl group. Scheme 11 summarizes two methods developed to achieve this using the aforementioned 2,4-dimethoxy-3-methylphenol (**15**) as the starting material. Both methods worked equally well, but the sequence involving hydroxymethylation of **19** was used for further studies, simply because all intermediates of this sequence had already been well characterized in the model series.

The next required transformation was protection of the keto group of **28** or **29** as its dimethyl ketal. Under standard conditions, the major product isolated was the dimethyl ketal of the α,β-unsaturated ketone formed from **28** or **29**. Almost all methods known to effect ketallization, including newly developed ones, were attempted unsuccessfully. Hydroboration of the aforementioned dimethyl ketal of the α,β-unsaturated ketone in boiling xylene, followed by hydrogen peroxide work-up, did afford the desired primary alcohol, but the overall yield was too low and, more seriously, the reproducibility varied too widely to use it for further studies. After many unsuccessful attempts, the method summarized in scheme 12 was established to effect the necessary transformation. The key step of this transformation was the smooth dimethyl thioketallization of the acetate **30** (prepared from **29** under standard conditions) with neat methyl mercaptan in the presence of boron trifluoride–acetic acid complex at $-30°C$. Under these conditions, however, the nitrile group of **30** was also transformed into the thioiminoether group, which was converted back to the nitrile upon brief treatment with triethylamine–methanol at room temperature. The protecting group of the hydroxymethyl group of **32** was transferred to the benzyl group by two steps. Then, the dimethyl thioketal group was converted to the dimethyl ketal

Scheme 11



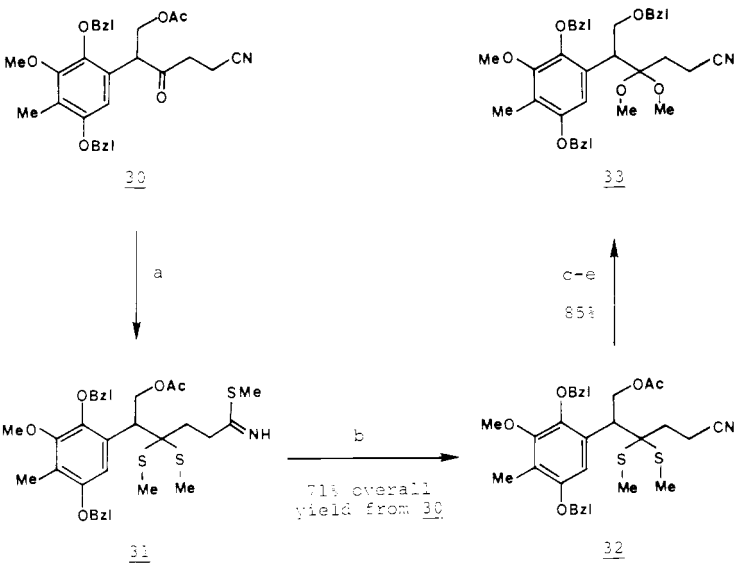
Reagents a: See Scheme 6. b: $H_2CO/NaOCH_3/CH_3OH$ 0°C. c: $BzlOCH_2CH=CHCH_2Br/K_2CO_3$/acetone/reflux. d: $C_6H_5N(CH_3)_2$/reflux.

by treatment with methanol in the presence of mercuric chloride and triethylamine. The overall yield of **33** from **29** was about 60%.

It was necessary to raise the oxidation level of the side chain of **33**, which was easily achieved by one of the known methods; namely, the carbanion generated from **33** was quenched with phenylselenyl bromide, followed by hydrogen peroxide treatment, to yield the α,β-unsaturated nitrile (11). This nitrile was then converted to the acetate **34** in a 3-step procedure. The ^1H nmr spectra clearly showed that the olefinic bonds of the α,β-unsaturated nitrile and the olefinic acetate **34** were exclusively trans. The reactivity of the olefinic bond of the α,β-unsaturated nitrile of the acetate **34** was found to be extremely poor. The only reagent which successfully reacted with this functionality was osmium tetroxide; it took over one week to complete the osmium tetroxide oxidation of **34** using 3 equivalents of the oxidant at room temperature. About a 1:1 mixture of diastereomeric diols was isolated which could fortunately be separated by chromatographic techniques. One of the two diols had to correspond to structure **35** and the other to **36**, although at this stage it was not yet established which was which.

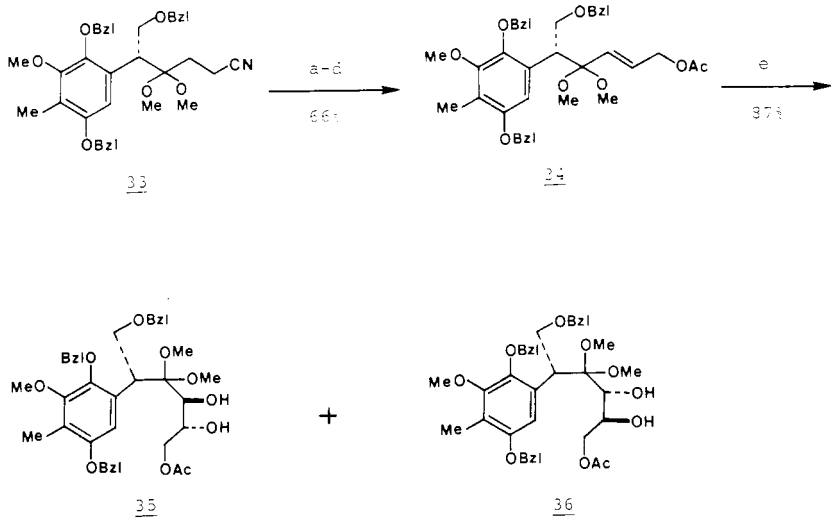
Scheme 14 summarizes the transformation of the diol **35** to the eight-membered quinone **41**. A parallel synthetic route starting with the diol **36** resulted in the eight-membered quinone **42** (see scheme 16). The high regio- and stereoselectivity realized in this transformation is mainly due to the fact that the C-1 position is sterically hindered by the adjacent dimethyl ketal group.

Scheme 12



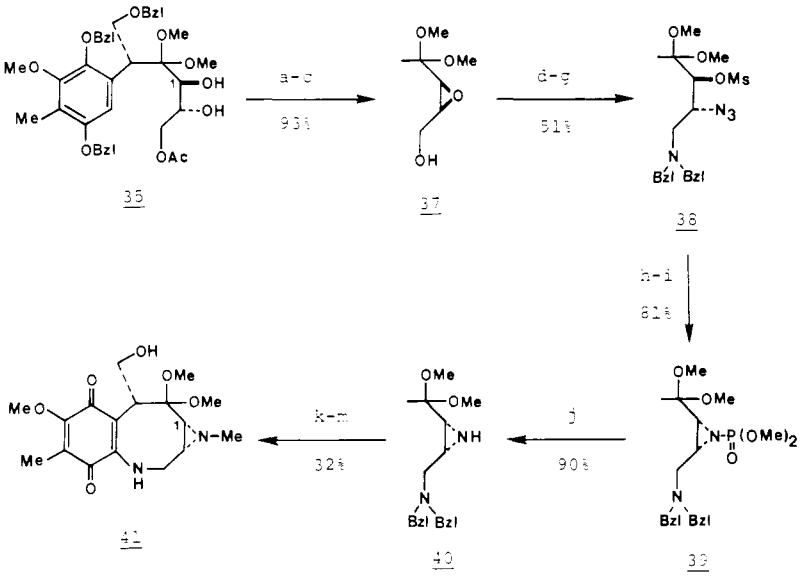
Reagents a: $CH_3SH/BF_3{\cdot}2AcOH/-30°C$. b: $(C_2H_5)_3N/CH_3OH/RT$. c: $NaOCH_3/CH_3OH$–CH_2Cl_2/RT. d: $C_6H_5CH_2Br/KH/DMF/RT$. e: $HgCl_2/(C_2H_5)_3N/CH_3OH$–THF/RT.

Scheme 13



Reagents a: 1. LDA/THF/−78°C. 2. C_6H_5SeBr/THF/−78°C. 3. 30% H_2O_2/EtOAc-THF/0°C. b: DIBAL/CH_2Cl_2/0°C. c: $NaBH_4/CH_3OH$–CH_2Cl_2/0°C. d: Ac_2O-Py/RT. e: OsO_4/Py/THF/RT.

Scheme 14

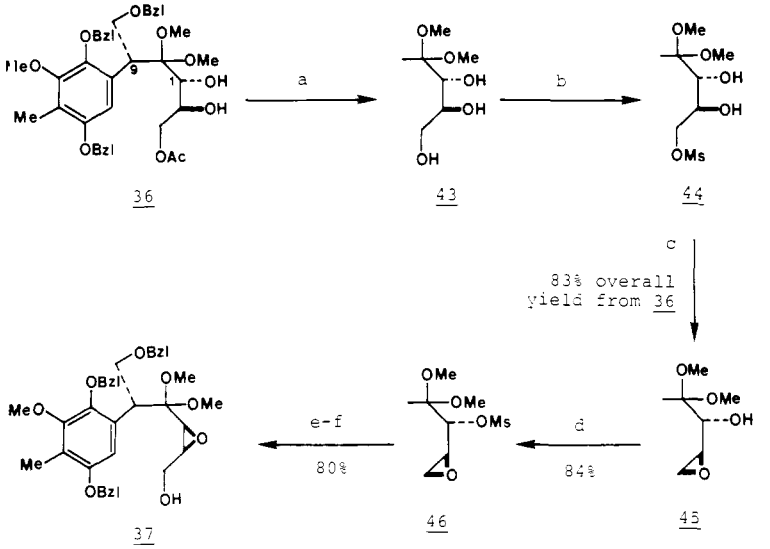


Reagents a: $MsCl$-$(C_2H_5)_3N$/CH_2Cl_2/0°C. b: NaH/DMF/RT. c: $NaOCH_3$/CH_3OH-CH_2Cl_2/RT. d: LiN_3/DMF/150°C. e: Ms_2O-Py/0°→RT. f: $C_6H_5CH_2NH_2$/150°C. g: $C_6H_5CH_2Br$/K_2CO_3/acetone/reflux. h: $(CH_3O)_3P$/reflux. i: NaH/THF/RT. j: LAH/Et_2O/0°C. k: CH_3I/K_2CO_3/acetone/reflux. l: H_2/Pd-C/AcOH/RT. m: O_2/CH_3OH/RT.

Scheme 15 summarizes a method to convert the diol **36** to the epoxy alcohol **37**, which is identical with the one derived from the diol **35** (see scheme 14). The key step of this transformation is the epoxide opening-closing reaction of **46**. Thus, diols **35** and **36** were equally useful for the synthesis of the mitomycin A series, and also for the mitomycin B series as well—note the relative stereochemistry of the C-1 and C-9 centers of mitomycin A (**1**) and B (**2**). At this stage, however, it was not yet established which eight-membered quinone, **41** or **42**, corresponded to which structure of the two.

A dramatic reactivity difference between the two eight-membered quinones, **41** and **42**, was observed. On addition of one drop of 0.1 *N* hydrochloric acid in methanol, the uv spectrum of one of the two quinones changed smoothly to a new spectrum characteristic of the mitosene chromophore, while under the same conditions the uv spectrum of the other eight-membered quinone was unchanged. Much stronger acidic conditions such as 3–5 drops of concentrated hydrochloric acid were necessary to change its uv spectrum to that of the mitosene chromophore. This observed reactivity difference suggested that the eight-membered quinone more sensitive to the transannular cyclization reaction would correspond to structure **41**. Two tub conformations **A** and **B** (slightly twisted forms due to the stabilization of the possible hydrogen bond indicated) are considered as possible preferred conformations for **41** (12). There is no serious increase in steric hindrance in bringing **A** or **B** to the transition state for the transannular cyclization reaction, since the C-10 hydroxymethyl group swings toward the outer side of the molecule in this process. Examination of molecular models suggests that the

Scheme 15



36 43 44 45 46 37

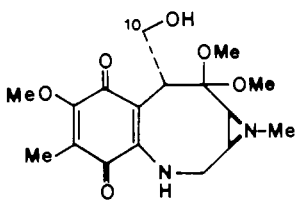
Reagents a: $NaOCH_3/CH_3OH$/RT. b: MsCl-Py/CH_2Cl_2/RT. c: K_2CO_3/CH_2Cl_2/RT. d: Ms_2O-Py/RT. e: KOAc/18-crown-6/DMF/120°C. f: $NaOCH_3/CH_3OH$-CH_2Cl_2/RT.

preferred conformation of **42** is most likely the tub conformation corresponding to **A**, because the other tub conformation corresponding to **B** experiences considerable steric compression between the aziridine and quinone rings, and also between the hydroxy methyl and amine NH groups—note there is no stabilization by the hydrogen bond in this series. There is a serious increase in steric hindrance in bringing **42** to the transition state for the transannular cyclization reaction since the C–10 hydroxymethyl group swings toward the inner side of the molecule in this process.

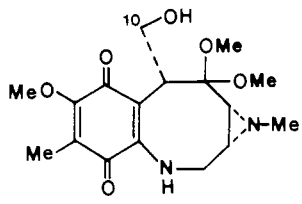
We anticipated that the most preferred conformation of **41** would be **B** because of the aforementioned hydrogen-bond stabilization. Valuable information regarding the conformation of the eight-membered quinones was obtained from the stability difference between the phenyl carbonates **47** and **49**, synthesized under standard conditions from **41** and **42** respectively. *cis*-Phenyl carbonate **47** decomposed to the phenyl ether **48** on standing in methylene chloride at room temperature for 2 days, while *trans*-phenyl carbonate **49** was stable under the same conditions. Furthermore, a strong peak corresponding to (M^+-44) was observed in the mass spectrum of **47**, while no such peak was observed in the mass spectrum of **49**. The phenyl carbonate **50**, belonging to the deimino series, behaved exactly like the *trans*-phenyl carbonate **49**. The instability observed only for **47** can be rationalized in terms of an intramolecular interaction between the aziridine and phenyl carbonate groups, which would only be possible in a conformation corresponding to **B**. Thus, this conformation must exist at least to some extent even in the *cis*-phenyl carbonate **47**.

Let us consider the stereochemical outcome of the transannular cyclization of **41**. All of the ^1H nmr signals of **41** in $CDCl_3$ at room temperature are sharp, sug-

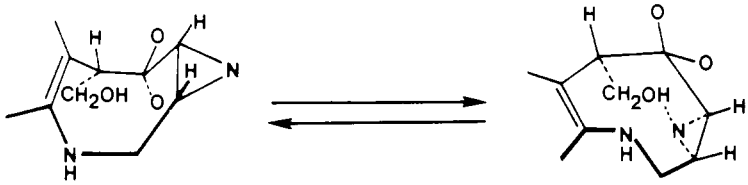
Scheme 16



42



41



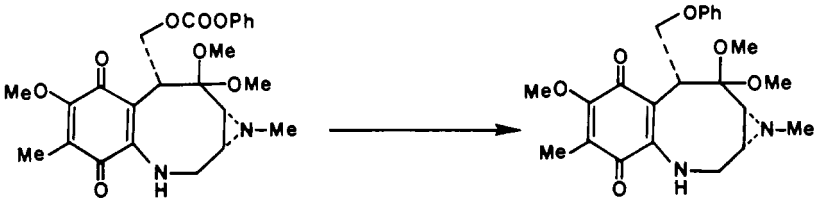
A B

gesting that **41** exists entirely in the one preferred conformation, namely **B**, or that interconversion between the two conformations **A** and **B** is rapid in the nmr time scale. In the former case, the transannular cyclization reaction proceeds through the oxonium ion **D**, which yields the desired stereochemistry at the C–1, C–9a, and C–9 positions. In the latter case, it would be safe to assume that interconversion between the oxomium ions **C** and **D** is also rapid, and hence the transannular cyclization proceeds through the oxonium ion **D**, since it yields the sterically less crowded product. Examination of molecular models reveals that the latter case is unlikely because a serious steric interaction between the hydrogen atoms at C–3 and C–9 occurs during the interconversion between **B** and **A**.

Encouraged by these considerations, transformation of the dimethyl ketal **41** or **47** to the corresponding dimethyl hemithioketal **51** or **52** was attempted under the conditions previously successful for the transformation of **22** to **25** (see scheme 10), but both of them were recovered unchanged. Reactivity differences found between the model and real systems might be attributed to the electronic effect of the aziridine ring or most likely of its protonated form. This would be interesting information for the future design of mitomycin analog syntheses, hopefully with better antitumor activity. In any event, unsuccessful transketallization of **41** to **51** made this synthesis seemingly caught at a dead end.

Under these circumstances, we decided to reinvestigate the transannular cyclization reaction under acidic conditions. Trityl tetrafluoroborate (13) in methylene chloride at room temperature was found to effect the cyclization reaction of **41** smoothly, to yield *exclusively* decarbamoyl-*N*-methylmitomycin A (**53**)

Scheme 17



47 48

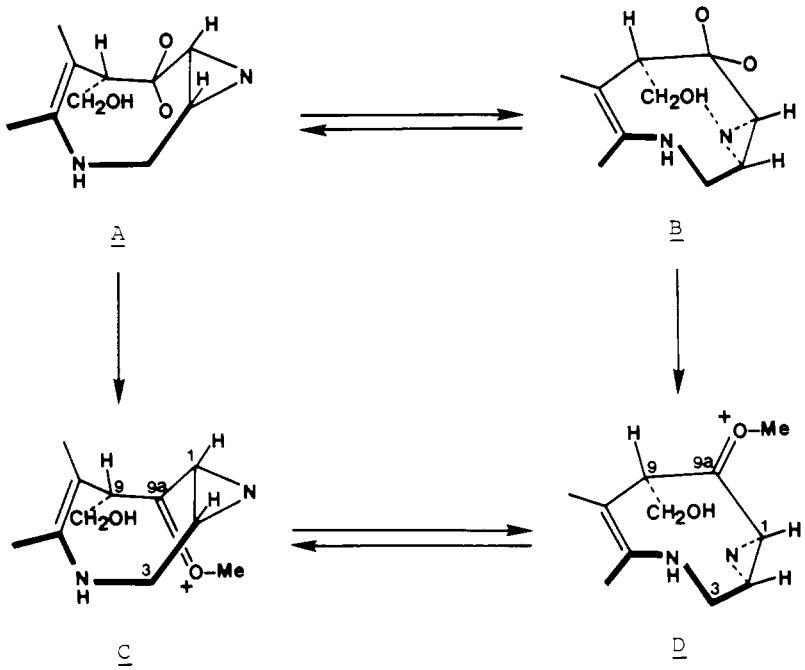
49 50

in high yield. Later, tetrafluoroboric acid and perchloric acid in methylene chloride at room temperature were also found to be equally as effective as trityl tetrafluoroborate. The effective reagent under trityl tetrafluoroborate conditions was probably tetrafluoroboric acid liberated from trityl tetrafluoroborate and moisture since 0.4 equivalents of this reagent produced the best result. It is interesting that no elimination of methanol from decarbamoylmitomycins and mitomycins was observed under these acidic conditions. The stereochemistry of **53** was confirmed from comparison with an authentic decarbamoyl-*N*-methylmitomycin A prepared from natural mitomycin A (**1**) (9).

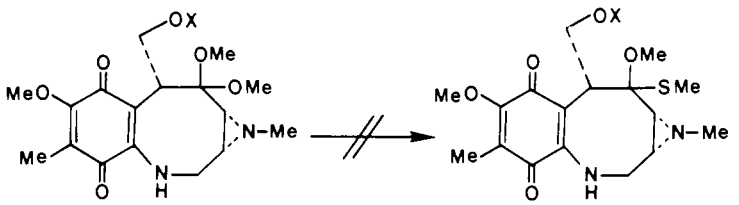
Synthetic decarbamoyl-*N*-methylmitomycin A (**53**) was converted to *N*-methylmitomycin in two steps and then transformed into porfiromycin (**4**) by the method previously established by Webb and his co-workers (3). The synthetic porfiromycin (**4**) was identical in every respect with natural porfiromycin.

Let us examine the total synthesis of mitomycins A (**1**) and C (**3**). On attempting the Michael reaction on the aziridine **40** under the same conditions as previously used, the formation of two products in about 5:1 ratio was observed. The minor product was found to be the desired eight-membered quinone; i.e., the product with H instead of $(CH_2)_3OAc$ in structure **57**, while the major product was most likely formed via an interaction of the aziridine nitrogen and the C-8 carbonyl group. Thus, protection of the aziridine nitrogen of **40** became necessary. The 3-acetoxypropyl group was used for the present purpose, since conventional protecting groups such as acetyl, benzoyl, ethoxycarbonyl, methoxy-

Scheme 18



Scheme 19



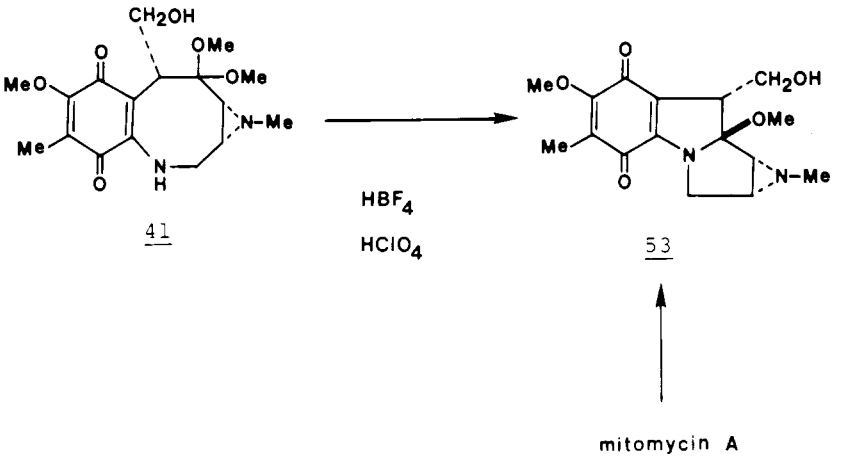
41 : X = H

47 : X = $CO_2C_6H_5$

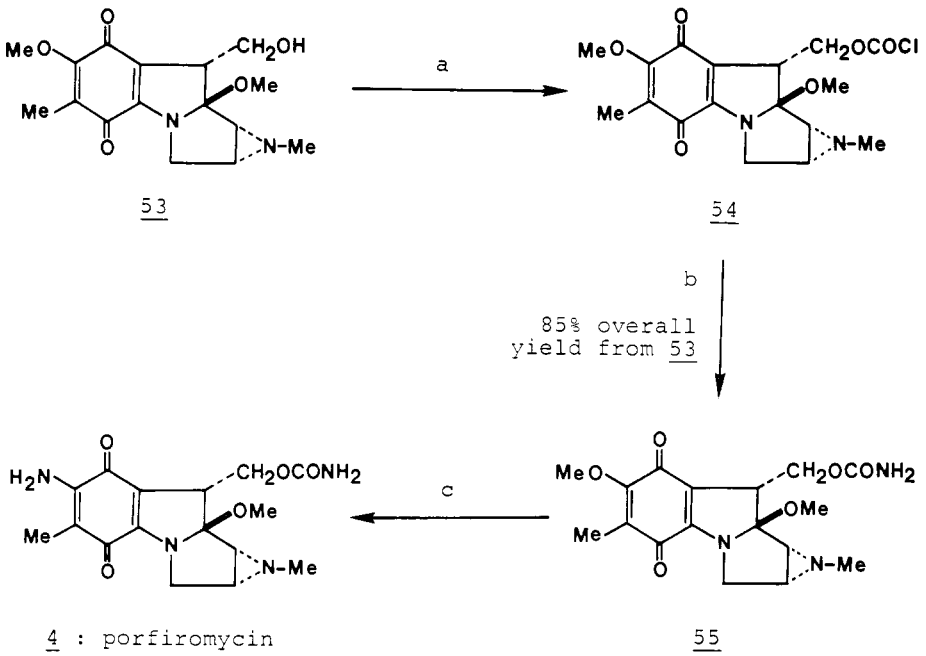
51 : X = H

52 : X = $CO_2C_6H_5$

Scheme 20



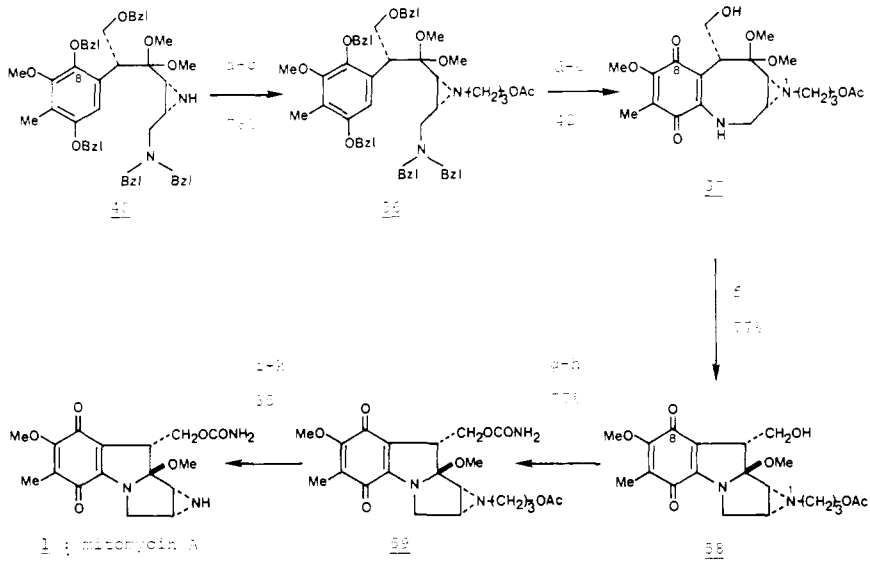
Scheme 21



Reagents a: $COCl_2$–$C_6H_5N(CH_3)_2$/CH_2Cl_2–$C_6H_5CH_3$/RT. b: NH_3/CH_2Cl_2–$C_6H_5CH_3$/0°C. c: See references 3 and 9.

methyl, etc. proved unsuccessful at some stage of the following synthetic sequence. The 3-acetoxypropyl group was put on **40** by a Michael reaction with acrolein, followed by diborane reduction and then by acetylation. The eight-membered quinone **57** was cleanly formed under the same conditions previously used. The transannular cyclization reaction of **57** was effected with tetrafluoroboric acid in methylene chloride at room temperature to yield exclusively the decarbamoyl-*N*-(3-acetoxypropyl)mitomycin A (**58**), which was converted to *N*-(3-acetoxypropyl)-mitomycin A (**59**) in the 2-step procedure used previously. The protecting group was removed in a 3-step procedure: first, hydrolysis of the acetyl group; second, oxidation of the resultant alcohol group; and third, retro-Michael reaction, to give *d,l*-mitomycin A (**1**). The synthetic substance was found to be identical with natural mitomycin A in all respects. The transformation of mitomycin A (**1**) to mitomycin C (**3**) was carried out by the method previously developed by Webb and his co-workers (3).

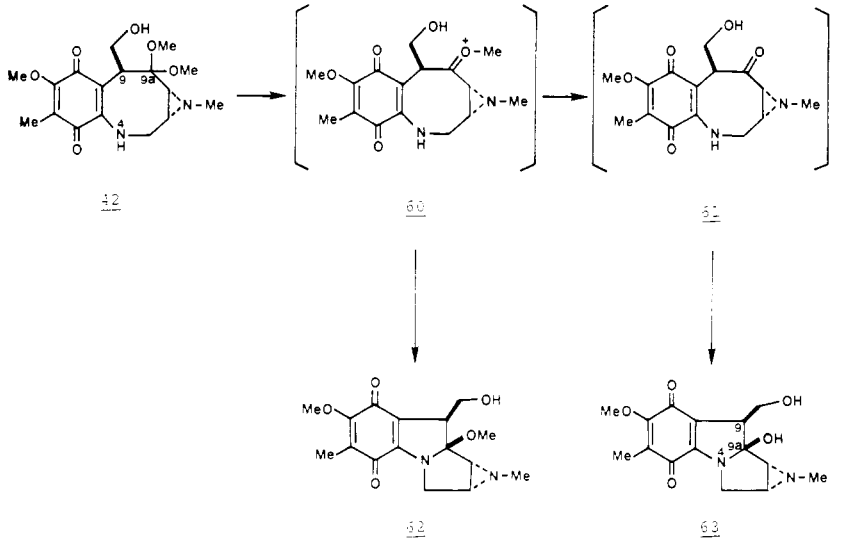
Scheme 23



Reagents a: CH_2=CHCHO/CH_2Cl_2/RT. b: B_2H_6/CH_2CL_2–THF/−78°C→RT. c: Ac_2O–Py/RT. d: H_2/Pd-C/AcOH/RT. e: O_2/CH_3OH/RT. f: HBF_4/CH_2Cl_2/RT. g: $COCl_2$–$C_6H_5N(CH_3)_2$/CH_2Cl_2/RT. h: NH_3/CH_2Cl_2/0°C. i: $NaOCH_3$/CH_3OH–CH_2Cl_2/RT. j: DMSO–DCC/TFA–Py/RT. k: $HClO_4$–$C_6H_5(CH_3)_2$/CH_2Cl_2/RT.

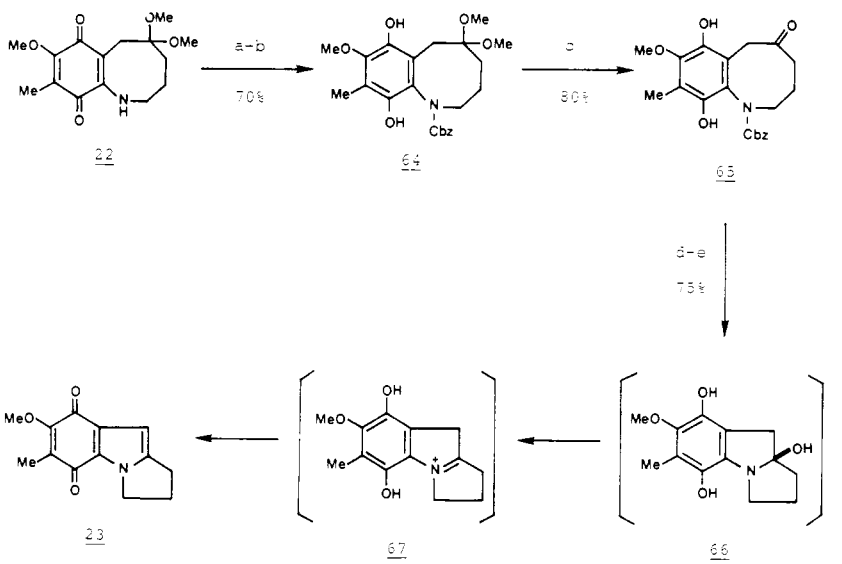
Let us now turn our attention to the total synthesis of mitomycin B (**2**), whose relative stereochemistry at the C–9 and C–9a positions is different from that of other mitomycins. The eight-membered ketone **61**, which should exist as decarbamoylmitomycin B (**63**), seemed for us the most logical intermediate for this synthesis. Since the eight-membered dimethyl ketal **42** was already available in our laboratory, the problem remaining was to establish a method to hydrolyze the dimethyl ketal group of **42** to the keto without the transannular cyclization reaction at the hemiketal or its equivalent stage, i.e., no **60**→**62**. Based on our pre-

Scheme 23



vious experience in this area, we felt that there would be little chance to avoid the transannular cyclization at the undesired stage as long as hydrolysis was attempted on the eight-membered quinone with the free NH group at the N-4 position.

Scheme 24



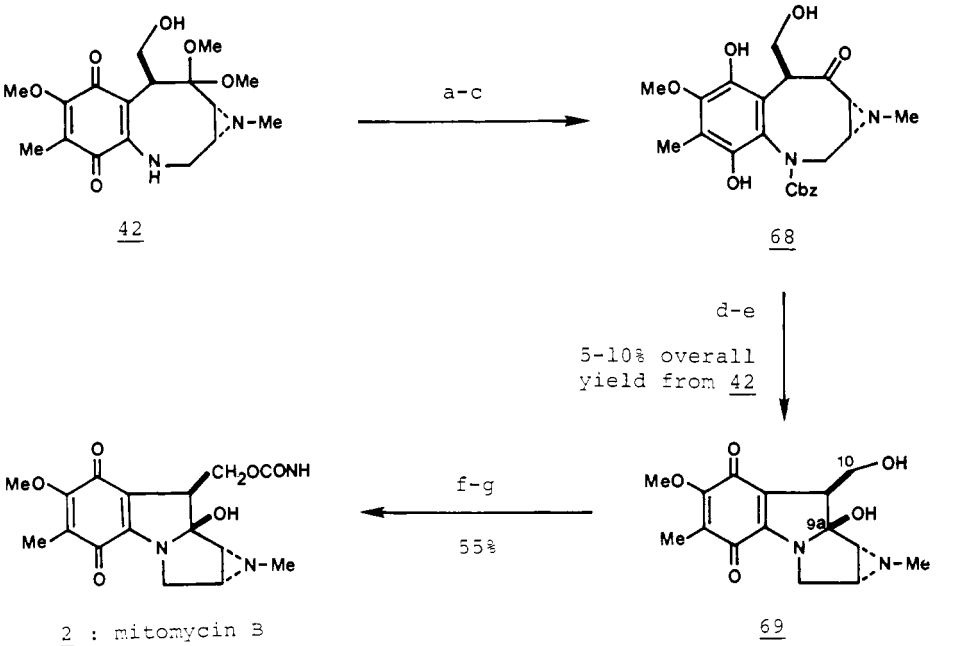
Reagents a: H_2/Pd-C/Py/RT b: $C_6H_5CH_2OCOCl$-Py/RT. c: 3N HCl/CH_2Cl_2/RT. d: H_2/Pd-C/CH_3OH/RT/5 minutes. e: O_2/CH_3OH/RT.

Therefore, investigation was initiated on a method to protect the NH group, using the eight-membered quinone **22** as a model compound.

N-Carbobenzoxylation of **22** was effected under standard conditions, after its quinone moiety had been reduced to the corresponding hydroquinone. The crude product thus obtained was subjected to acid-hydrolysis, using dilute hydrochloric acid in methylene chloride (heterogeneous conditions) at room temperature, to yield the ketone **65** in high yield. Hydrogenolysis of **65** (Pd-C/methanol/rt/*5 minutes*), followed by air-oxidation (O_2/methanol/rt), gave the indole quinone **23**, which was presumably formed from the desired carbinolamine **66** via the immonium salt **67**. The formation of the immonium salt was not expected to present a serious problem for the real system, since we could confirm that at least 50% of mitomycin B (**2**) was recovered after it had been treated under the exact same conditions as in the above two steps. The stability difference observed between the carbinol **66** and mitomycin B (**2**) is similar to the cases previously discussed (see pages 554 and 561).

Guided by the results obtained in the model system, the dimethyl ketal **42** was reduced to the hydroquinone, carbobenzyoxylated, and then hydrolyzed with acid to yield the desired ketone **68**. The ketone **68** was then subjected to hydrogenolysis (Pd-C/methanol/rt/*5 minutes*), followed by air-oxidation, to give decarbamoylmitomycin B (**69**), which was found to be identical with the authentic substance

Scheme 25



42 68 69

Reagents a: H_2/Pd-C/Py/RT. b: $C_6H_5CH_2OCOCl$-Py/RT. c: 3N HCl/CH_2Cl_2/RT. d: H_2/Pd-C/CH_3OH/RT/5 minutes. e: O_2/CH_3OH/RT. f: $Cl_3CCONCO$/CH_2Cl_2/RT. g: K_2CO_3/CH_3OH/RT.

prepared from natural mitomycin B (**2**) in every respect (9). The overall yield of **69** from **42** varied in the range of 5% to 10%.

Transformation of decarbamoylmitomycin B (**69**) to mitomycin B (**2**) was much more difficult than anticipated. The method successfully used for this purpose in the synthesis of the mitomycin A series was unsuccessful, probably because of the formation of a cyclic carbonate between the C-9a and C-10 positions. After many fruitless attempts, the necessary conversion was cleanly achieved in a 2-step procedure shown in scheme 25. The synthetic mitomycin B (**2**) was confirmed to be identical with natural mitomycin B in every respect.

Thus, the successful completion of the first total synthesis of racemic mitomycins A, B, C, and porfiromycin was accomplished. However, there are still two major problems remaining in this area; i.e., the synthesis of optically active mitomycins, and the development of a shorter, more efficient synthetic route. It would not require much imagination to propose a convergent synthetic route to some key intermediates such as **35** from readily available, naturally occurring carbohydrates. We are currently examining this possibility with the hope that the above two problems will be solved in this manner.

ACKNOWLEDGMENT

It is my greatest pleasure to acknowledge the devotion and skill of Drs. Fumiaki Nakatsubo, Donald E. Keeley, Anthony J. Cocuzza, Tohru Fukuyama, and Thomas M. Barger, who brought the syntheses to their successful conclusion. We wish to thank Dr. K. Nakano, Kyowa Hakko Kogyo Company for a sample of mitomycins A, B, C, and porfiromycin, and the late Dr. J. S. Webb, Lederle Laboratories, for a sample of mitomycin A. Financial support from the National Cancer Institute, DHEW (Grant No. CA 22215), and the National Science Foundation (Grant No. CHE 75-15768) is gratefully acknowledged.

LITERATURE CITED AND FOOTNOTES

1. T. Hata, Y. Sano, R. Sugawara, A. Matsumae, K. Kanamori, T. Shima and T. Hoshi, *J. Antib.*, Tokyo, Ser. A, **9**, 141 (1956).
2. S. Wakaki, H. Marumo, K. Tomioka, G. Shimizu, E. Kato, H. Kamada, S. Kudo and Y. Fujimoto, *Antibiotics and Chemotherapy*, **8**, 228 (9158).
3. J. S. Webb, D. B. Cosulich, J. H. Mowat, J. B. Patrick, R. W. Broschard, W. E. Meyer, R. P. Williams, C. F. Wolf, W. Fulmor and C. Pidacks, *J. Am. Chem. Soc.*, **84**, 3185 and 3187 (1962).
4. A. Tulinsky, *J. Am. Chem. Soc.*, **84**, 3188 (1962); A. Tulinsky and J. H. van den Hende, *J. Am. Chem. Soc.*, **89**, 2905 (1967).
5. R. Yahashi and I. Matsubara, *J. Antib.*, Tokyo, **29**, 104 (1976) and **31**, 78-69 (1978).
6. For a review on mitomycins, see W. A. Remers, "The Chemistry of Antitumor Antibiotics", Volume 1, page 221 ff.
7. For example, see T. Kametani and K. Takahashi, *Heterocycles*, **9**, 293 (1978). Also see the references cited in this paper under reference 8.
8. F. Nakatsubo, A. J. Cocuzza, D. E. Keeley and Y. Kishi, *J. Am. Chem. Soc.*, **99**, 4835 (1977); F. Nakatsubo, T. Fukuyama, A. J. Cocuzza and Y. Kishi, *J. Am. Chem. Soc.*, **99**, 8115 (1977); T. Fukuyama, F. Nakatsubo, A. J. Cocuzza and Y. Kishi, *Tetrahedron Lett.*, 4295 (1977).
9. S. Kinoshita, K. Uzu, K. Nakano and T. Takahashi, *J. Med. Chem.*, **14**, 109 (1971); S. Kinoshita, K. Uzu, K. Nakano, M. Shimizu, T. Takahashi and M. Matsui, *J. Med. Chem.*, **14**, 103 (1971).
10. Numbering in this paper corresponds to that of mitomycins.
11. D. W. Brattesani and C. H. Heathcock, *Tetrahedron Lett.*, 2279 (1974).
12. See, for example, *Top. Stereochem.*, **7**, 128 (1973).
13. D. H. R. Barton, P. D. Magnus, G. Smith, G. Streckert and D. Zurr, *J. Chem. Soc. Perkin Trans. I*, 542 (1972).