

Mitomycin Synthetic Studies: Stereocontrolled and Convergent Synthesis of a Fully Elaborated Aziridinomitosane

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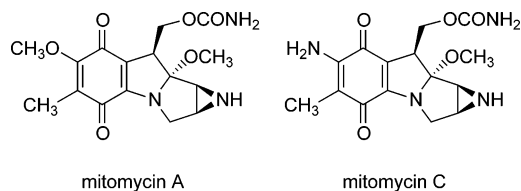
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Full details of a stereocontrolled and convergent synthetic route to 9a-desmethoxymitomycin A (**1**) are reported. The target molecule possesses the parent tetrahydropyrrolo[1,2-*a*]indole ring system characteristic of the mitomycin family of antitumor agents. The synthesis was based on the diastereocontrolled addition of a fully elaborated cinnamylstannane to a pyrrolidine-based *N*-acyliminium ion as the key convergent step, which resulted in the installation of the C9 and C9a stereogenic centers.

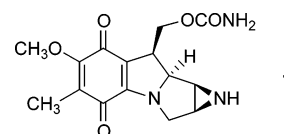
Introduction

Mitomycins A and B were isolated from *Streptomyces caespitosus* by Hata and co-workers and were found to possess potent antitumor and antibiotic activity.¹ The isolation of mitomycin C from the same fermentation broth was reported subsequently. These antitumor agents have been studied in detail with respect to mechanism of action and clinical utility,² and the synthetic literature describing approaches to the total synthesis of the mitomycins is extensive and well-appreciated.³



Mitomycin C is used clinically as a cancer chemotherapeutic agent against a variety of solid tumors. This agent forms covalent cross-links with duplex DNA⁴ by alkylating deoxyguanosine at the C2-amino group within the DNA minor groove in 5'-d(CG)-3' sequences.^{5,6} These agents require bioreduction from the quinone to hydroquinone oxidation state to generate the active form of the drug.⁷

Numerous efforts at the total synthesis of mitomycins and related compounds have been reported, and novel synthetic approaches are still being reported after nearly half a century of extensive research.⁸ Starting with the first total synthesis of mitomycins A and C reported in 1977 from the Kishi group,⁹ there have been several subsequent successful total syntheses¹⁰ and an innumerable variety of synthetic approaches to the mitomycins and the structurally¹¹ and functionally¹² related natural products FR900482 and FR66979. The sustained and vigorous interest in this family of natural products is testament to their relevance as synthetic targets. The densely and diversely functionalized ring system of these natural products presents an attractive and challenging objective for the practitioner of targeted organic synthesis. In this article, we report the full details of a novel synthetic route to the highly elaborated aziridinomitosane **1**¹³ that provides a strategically unique, synthetically efficient, and convergent ring entry to the tricyclic tetrahydropyrrolo[1,2-*a*]indole ring system of the mitomycins.



The central premise of our synthetic approach to the ring system of the mitomycins (**2**) was based on a

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(3) Remers, W. A. *Mitomycins and porfiromycin*. In *The Chemistry of Antitumor Antibiotics*; Wiley-Interscience: New York, 1979; pp 221–276.

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(5) (a) Tomasz, M.; Lipman, R.; Chowdary, D.; Pawlak, J.; Verdine, G. L.; Nakanishi, K. *Science* **1987**, *235*, 1204. (b) Tomasz, M.; Lipman, R.; McGuinness, B. F.; Nakanishi, K. *J. Am. Chem. Soc.* **1988**, *110*, 5892.

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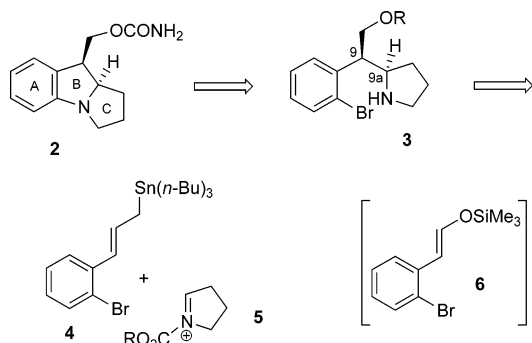
(8) (a) Coleman, R. S. *Curr. Opin. Drug Discovery Dev.* **2001**, *4*, 435. (b) Danishefsky, S. J.; Schkeryantz, J. M. *Synlett* **1995**, 475. (c) Fukuyama, T.; Yang, L. *Total Synthesis of Mitomycins*. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: New York, 1993; pp 433–471.

(9) (a) Fukuyama, T.; Nakatsubo, F.; Cocuzza, A. J.; Kishi, Y. *Tetrahedron Lett.* **1977**, 4295. (b) For a review of work from the Kishi group, see: Kishi, Y. *J. Nat. Prod.* **1979**, *42*, 9388.

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(11) (a) Uchida, I.; Takase, S.; Kayakiri, H.; Kiyoto, S.; Hashimoto, M.; Tada, T.; Koda, S.; Morimoto, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4108. (b) Shimomura, K.; Hirai, O.; Mizota, T.; Matsumoto, S.; Mori, J.; Shibayama, F.; Kikuchi, H. *J. Antibiot.* **1987**, *40*, 600.

proposed diastereofacial selective addition of cinnamylstannane **4** to a pyrrolidine-derived *N*-acyliminium ion **5** for introduction of the C9 and C9a stereogenic centers in the addition product **3**. In our preliminary studies on the development of this conceptually simple strategy,¹⁴ we found that the silyl enol ether **6** was more effective than stannane **4** as a nucleophilic partner in the addition to iminium ion **5**. The key bond could be formed by the addition of **6** to **5** to provide **3** in near quantitative yield with a favorably disposed 6:1 ratio of diastereomers at the newly formed C9 and C9a stereogenic centers. Final cyclization of the B-ring was achieved by a Buchwald-Hartwig coupling¹⁵ of the pyrrolidine nitrogen with the aryl bromide. Determination of relative stereochemistry of **2** was made by detailed nuclear Overhauser effect studies.



We now report the full details of our successful efforts to implement this strategy using more highly elaborated cinnamylstannanes and pyrrolidine constructs and describe the stereochemical details of the key *N*-acyliminium ion addition reaction as a function of substitution of the pyrrolidine ring. These studies have resulted in a stereocontrolled and convergent synthesis of aziridinomitosane **1** starting from the simple aromatic and carbohydrate precursors 2,6-dimethoxytoluene and D-ribose.

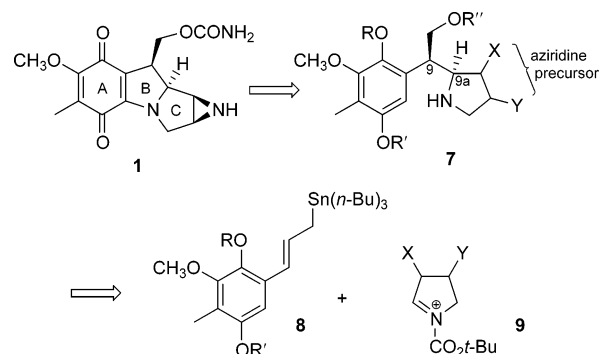
Introduction of the central B-ring of **1** would rely on the well-established chemistry of quinones using an intramolecular Michael addition by the pyrrolidine nitrogen of **7** followed by air oxidation.¹⁶ The quinone precursor, protected hydroquinone **7**, would need to possess functionalities X and Y that could serve as precursors for introduction of the aziridine ring. The identities of X and Y and the relative configuration of the carbon atoms that bear them provided us with considerable flexibility in the timing and strategy for aziridine introduction. The key C9–C9a bond in **7** is an ideal connection point, maximizing convergence in the coupling of a fully elaborated γ -aryl allylstannane **8** and appropriately functionalized *N*-acyliminium ion **9**. De-

spite validating the feasibility and stereochemical outcome of this convergent bond construction step in our preliminary studies, there remained several important issues with respect to successfully implementing the proposed synthetic strategy for construction of fully elaborated systems:

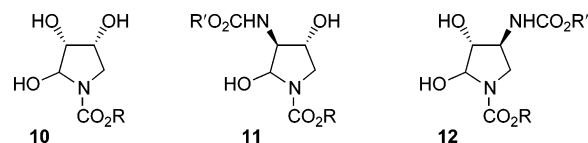
1. At what stage of the synthesis would the aziridine be introduced and by which array of functional groups X and Y in **7**?

2. Could we formulate a viable and orthogonal protecting group scheme for the various oxygen- and nitrogen-based functional groups in both **8** and **9**?

3. What would be the effect of substituents X and Y in **9** on the diastereofacial selectivity of the allylstannane addition reaction?



Retrosynthetically, mapping the mitomycin aziridino-[2,3-*c*]pyrrolidine C-ring of target **1** onto an appropriate iminium ion precursor led us to three potential pyrrolidine systems bearing appropriate functionality for late-stage aziridine introduction. In the case of **10**, the *cis*-1,2-diol could serve in a bidirectional manner as an aziridine precursor depending upon which hydroxyl group is inverted upon displacement with a nitrogen nucleophile. Analysis of the diastereofacial selectivity in the iminium ion addition led us to the prediction that the α -hydroxyl groups of **10** would direct stannane addition from the desired β -face. The two amine-containing pyrrolidines **11** and **12** have the advantage of earlier introduction of what will ultimately become the aziridine nitrogen, thereby leading to greater convergency; however, **11** bears a protected amino group adjacent to the nascent iminium ion, and β -face diastereoselectivity in the addition of allylstannane **8** was potentially problematic. With pyrrolidine **12**, the protected amino group could still provide a steric impediment to β -face approach of the allylstannane, but being distal to the iminium ion may make this substituent less of a factor in control of diastereoselectivity.



Preparation of Mitosane C-Ring Precursors. Our initial work in developing this synthetic strategy started with the preparation of an *N*-acyliminium ion precursors based on the pyrrolidine diol construct **10**, where the *cis*-1,2-diol of **10** was mapped onto the C2/C3 diol of D-ribose. One-pot acetonide formation and glycosylation of D-ribose

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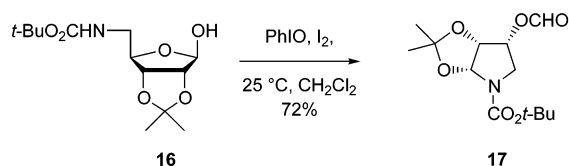
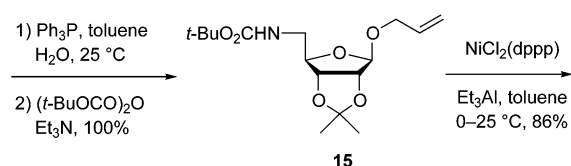
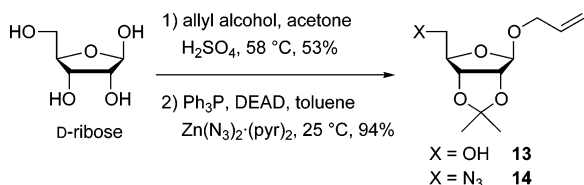
(13) (a) Ziegler, F. E.; Berling, M. Y. *Tetrahedron Lett.* **1998**, *39*, 2455. (b) Danishefsky, S.; Berman, E. M.; Ciufolini, M.; Etheredge, S. J.; Segmuller, B. E. *J. Am. Chem. Soc.* **1985**, *107*, 3891. (c) Kinoshita, S.; Uzu, K.; Nakano, K.; Shimizu, M.; Takahashi, T. *J. Med. Chem.* **1971**, *14*, 103.

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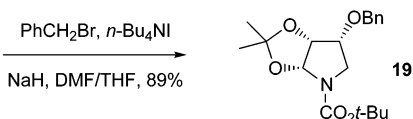
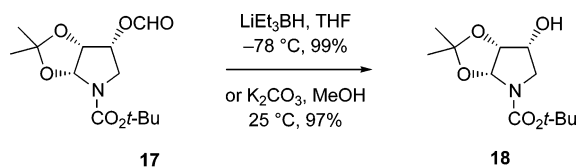
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(16) Finley, K. T. The addition and substitution chemistry of quinones. In *Chemistry of the Quinonoid Compounds*; Patai, S., Ed.; Wiley: New York, 1974; Vol. 2, pp 877–1144.

with allyl alcohol provided the corresponding allyl glycoside/2,3-acetonide **13**, which was converted to the 5-azido-5-deoxyribose **14** in high yield using zinc azide under Mitsunobu conditions.¹⁷ Conversion of the azide of **14** to the corresponding *tert*-butyl carbamate **15** proceeded in 88% yield for the two-step sequence of reduction and acylation. Allyl deprotection of **15** was affected using nickel chloride and triethylaluminum¹⁸ to afford **16**. At this stage, the furanose ring was fragmented by treatment with iodosobenzene and iodine, which afforded pyrrolidine **17** in good yields for this efficient rearrangement process.¹⁹



Two methods proved effective for removing the formate ester of **17**: (1) reduction with lithium triethylborohydride and (2) methanolysis under basic reaction conditions. The resulting alcohol **18** was protected as the corresponding benzyl ether to afford **19** in essentially quantitative yield. We intended that the acetonide would serve as a source of the corresponding iminium ion and the Lewis acid complex of the ring-opened acetal would serve as a steric block of the α -face, directing approach of the allyl stannane. This system was now at the point of convergence after seven synthetic operations from D-ribose (27% overall).

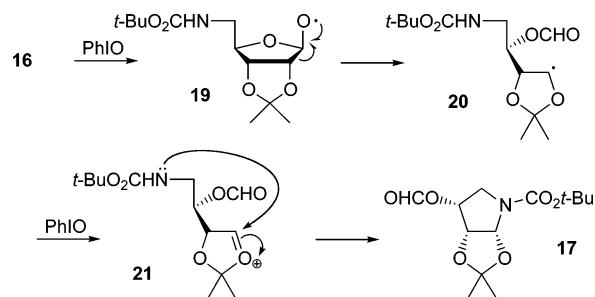


This iodosobenzene-induced furanose fragmentation reaction developed by Suarez and co-workers proved to

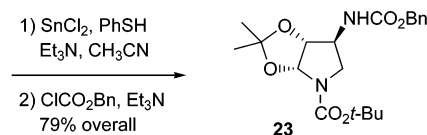
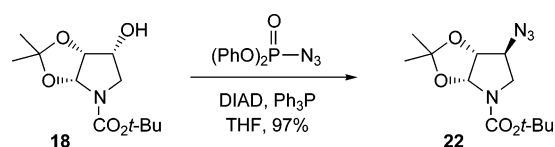
(17) Viaud, M. C.; Rollin, P. *Synthesis* **1990**, 130.

(18) Taniguchi, T.; Ogasawara, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 1136.

be the ideal method for pyrrolidine ring formation. This reaction presumably proceeds by two sequential one-electron oxidations from **16**, first to afford the glycosyl radical **19**, which fragments to afford carbon-centered radical **20**, which is further oxidized to oxonium ion **21**, which in turn is trapped by the carbamate nitrogen to afford **17** after loss of a proton.



The pyrrolidine system bearing nitrogen-containing functionality at C4 was prepared by the same route as for **19**. Alcohol **18** was converted to the corresponding azide **22** in excellent yield by reaction with diphenylphosphoryl azide.²⁰ The azide of **22** was reduced, and the resulting amine was acylated to afford benzyl carbamate **23**. Azide **22** and carbamate **23** are seven and eight steps, respectively, from D-ribose.



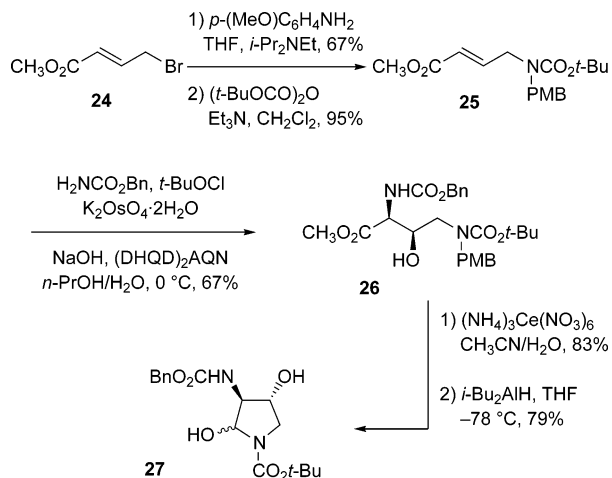
The pyrrolidine system bearing nitrogen-containing functionality at C3 was synthesized by a different route using a Sharpless asymmetric aminohydroxylation.²¹ *p*-Methoxybenzylamine was alkylated with methyl 4-bromocrotonate (**24**), and the resulting secondary amine was acylated to afford bis-protected amine **25**. Double protection of the amine group was essential for subsequent success in the Sharpless aminohydroxylation. Using literature reaction conditions with benzyl urethane and (DHQD)₂AQN, **25** afforded the protected amino alcohol **26** in good yields and with the desired regioselectivity. Removal of the *p*-methoxybenzyl (PMB) group and reduc-

(19) (a) Armas, P.; Francisco, C. G.; Suarez, E. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 772. (b) Armas, P.; Francisco, C. G.; Suarez, E. *Tetrahedron Lett.* **1992**, *33*, 6687. (c) Armas, P.; Francisco, C. G.; Suarez, E. *J. Am. Chem. Soc.* **1993**, *115*, 8865. (d) Francisco, C. G.; Freire, R.; Gonzalez, C. C.; Suarez, E. *Tetrahedron: Asymmetry* **1997**, *8*, 1971.

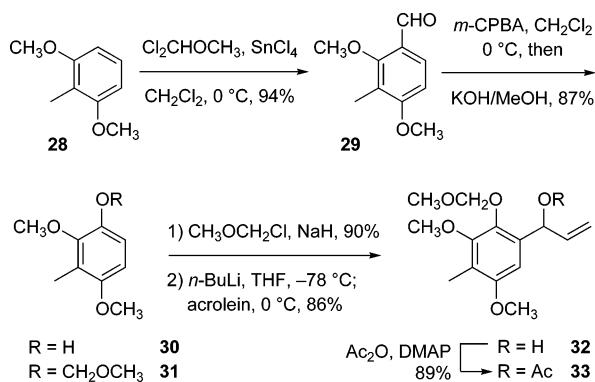
(20) (a) Lal, B.; Pramanik, B.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, 1977. (b) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203.

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tion of the ester to the aldehyde was accompanied by spontaneous cyclization to pyrrolidine **27**. The enantiomeric excess of the Sharpless product was determined by chiral HPLC to be 92%, after removal of the *p*-methoxybenzyl group of **26**. Pyrrolidine **27** was synthesized in five steps from methyl 4-bromocrotonate (28% overall).

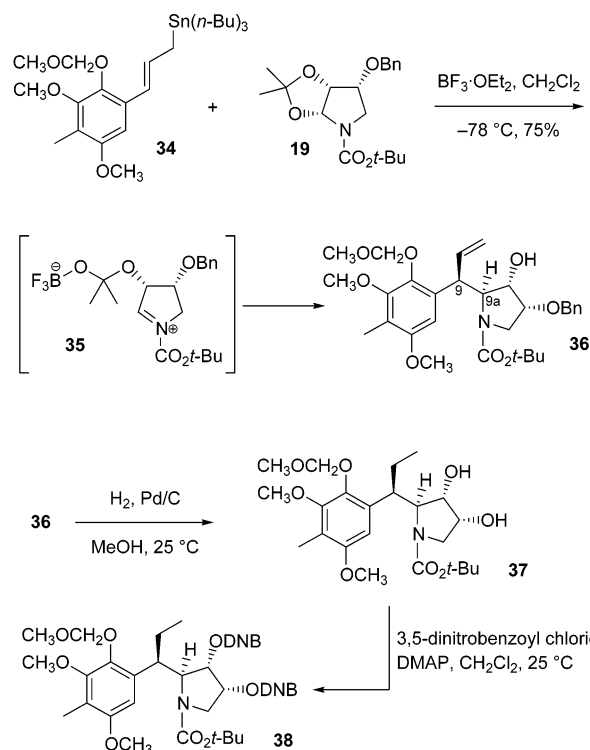


Preparation of A-Ring Cinnamylstannane. In a manner similar to a number of previously reported approaches to the mitomycins, we constructed an A-ring precursor from 2,6-dimethoxytoluene (**28**). Friedel–Crafts alkylation²² of **28** with dichloromethyl methyl ether in the presence of tin(IV) chloride afforded aryl aldehyde **29** in excellent yield. Baeyer–Villiger oxidation²³ with *m*-CPBA and subsequent KOH hydrolysis of the resulting formate ester afforded phenol **30**, which was protected as the corresponding methoxymethyl ether to afford **31**. (This sequence of reactions was exceptionally convenient to perform on a large scale, as benzaldehyde **29** could be recrystallized from hexane and both phenol **30** and methoxymethyl ether **31** could be distilled.) Directed *ortho*-lithiation of **31** with *n*-butyllithium and reaction of the resulting aryllithium intermediate with acrolein afforded allylbenzene **32** in good yield. No



lithiation *meta* to the methoxymethyl ether was noted. Acetate ester formation afforded allylic acetate **33**, and reductive stannylation²⁴ occurred to afford *trans*-cinnamylstannane **34** with complete regio- and stereocontrol in good chemical yield. [The originally reported methodology was developed for allylic halides and occurred without thermodynamically driven double bond migration; our application of this protocol has expanded the scope of the method.] Cinnamylstannane **34** was synthesized from **28** in six steps and in 43% overall yield.

Allylstannane/Iminium Ion Additions. Generation One Approach. The convergent coupling of stannane **34** with pyrrolidine **19** proceeded smoothly with allylic transposition in the presence of boron trifluoride etherate, presumably by way of iminium ion **35**. The coupled product **36** could be isolated in good yield and as a single diastereomer. Stoichiometric Lewis acid was critical to prevent deprotection of the phenolic methoxymethyl ether of **34**. A single diastereoisomer was clearly present in the product **36**, but line broadening in the ¹H NMR caused by slow interconversion of *tert*-butyl carbamate conformers prevented determination of the relative or absolute configuration at the C9 and C9a stereogenic centers at this point in the synthesis. This problem plagued us throughout the work, and high-resolution mass spectrometry proved to be exceptionally useful in the absence of useful high-resolution ¹H NMR data.²⁵



Absolute and relative stereochemistry of the addition product **36** was demonstrated by X-ray crystallography of the corresponding bis-dinitrobenzoate. Hydrogenolysis of the benzyl ether and hydrogenation of the vinyl group

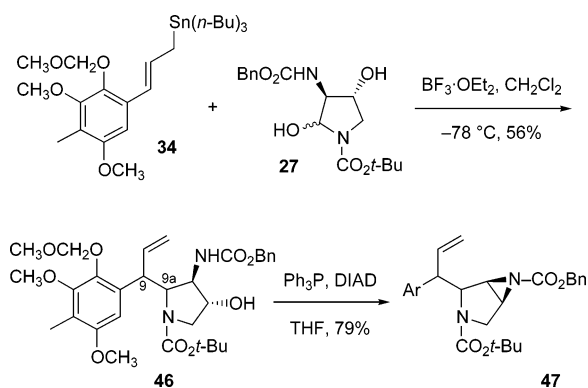
(22) Fleming, I. *Chemtracts* **2001**, *14*, 405 and references therein.

(23) Renz, M.; Meunier, B. *Eur. J. Org. Chem.* **1999**, 737.

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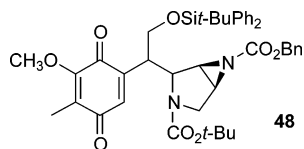
Two alternatives to this unsuccessful approach toward aziridine introduction appeared reasonable: (1) introduction of the requisite nitrogen by displacement at the benzyloxy carbon of **45**, which would require a significant investment in protecting group manipulations, or (2) introduction of the emergent aziridine nitrogen at an earlier juncture of the synthesis, prior to coupling of the two fragments. Because we wished to avoid a potentially troublesome series of protecting group manipulations on a late intermediate, we chose the option of using a nitrogen-functionalized pyrrolidine in the iminium ion addition reaction.

Allylstannane/Iminium Ion Additions. Generation Two Approach: 3-Aminopyrrolidine. With a bulky benzyl carbamate now proximal to the iminium ion formed by treatment of **27** with boron trifluoride, addition of cinnamylstannane **34** occurred with poor diastereoselectivity, affording a 1:1 mixture of stereoisomers **46** of unidentified configuration at C9/C9a. Although aziridine **47** could readily be formed in good yield by Mitsunobu cyclization of the amino alcohol of **46**, this entire route proved unworkable as a result of the lack of stereocontrol in the key addition reaction between **27** and **34**.²⁶

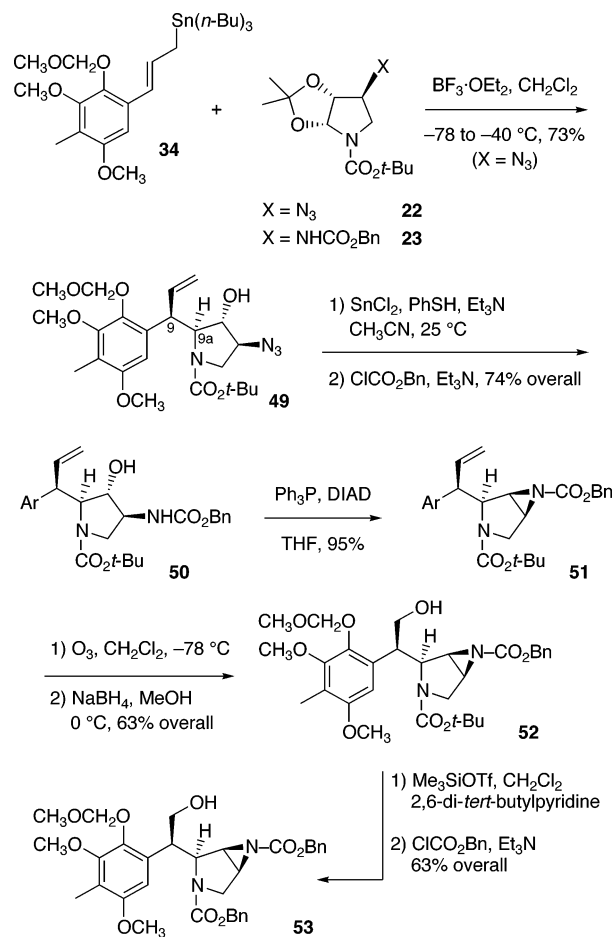


Allylstannane/Iminium Ion Additions. Generation Three Approach: 4-Aminopyrrolidine. Addition of cinnamylstannane **34** to 4-azidopyrrolidine **22** now afforded a favorably disposed 7:3 diastereomeric ratio of addition products **49** in 73% yield, where the major diastereomer corresponded to that shown. [A similar result was obtained in the addition of cinnamylstannane to the protected 4-aminopyrrolidine **23**, where the corresponding addition product was formed, albeit in only 54% yield but as a 3:1 ratio of diastereomers favoring the desired isomer.] At the stage of azide **49**, we had introduced essentially all of the molecular complexity of the target molecule in 14 total synthetic steps (six steps to **34** from 2,6-dimethoxytoluene plus seven steps to azide

(26) Aziridine **47** could be carried forward as a stereoisomeric mixture without complications [(1) O_3 , MeOH , -78°C , then NaBH_4 , 0°C , 55%; (2) $t\text{-BuPh}_2\text{SiCl}$, Et_3N , DMAP , 96%; (3) $(\text{NH}_4)_3\text{Ce}(\text{NO}_3)_6$, $\text{CH}_3\text{-CN}/\text{H}_2\text{O}$, 25°C , 87%] to afford the quinone **48**, thereby validating the feasibility of maintaining the integrity of the aziridine ring system through this reaction sequence.



22 from D-ribose, plus the coupling step). The remainder of the synthesis required two cyclization reactions, an unveiling of protecting groups, and adjustment of the oxidation state of the aromatic A-ring.

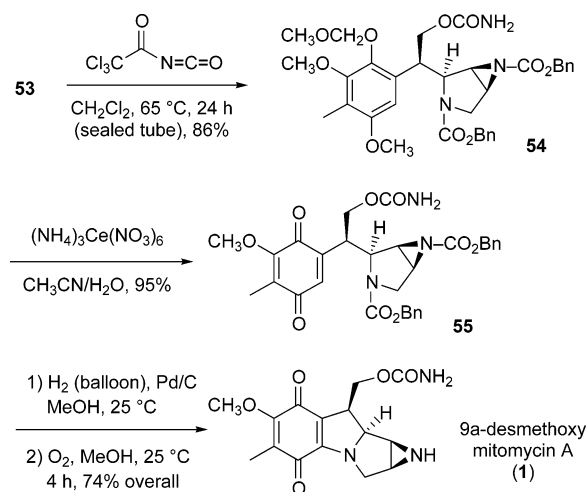


Reduction of the azide of **49** occurred smoothly and in good yield upon treatment with stannous chloride and thiophenol in the presence of triethylamine, which afforded the corresponding amine. Acylation with benzyl chloroformate afforded carbamate **50**. The use of triphenylphosphine as a reductant effected only 25% yield in the two-step sequence. Cyclization to the aziridine occurred with essentially quantitative conversion under Mitsunobu reaction conditions, and aziridine **51** was isolated in 95% yield from **50**. Using previously established conditions for ozonolysis with reductive workup, the alkene of **51** was transformed to the desired alcohol **52** by treatment with ozone at -78°C followed by NaBH_4 at 0°C . This reaction routinely proved difficult to achieve in reasonable yields, and other protocols (e.g., $\text{OsO}_4/\text{NaIO}_4$) were unsuccessful in the presence of the electron-rich aromatic system. The endgame of the synthesis from **52** proved straightforward, although it required an unfortunate change of nitrogen protecting groups prior to quinone formation.²⁷ Cleavage of the *tert*-butyl carbamate of **52** with trimethylsilyl triflate and reprotection

(27) It proved impossible to remove a pyrrolidine *tert*-butyl carbamate once the C10 carbamate and/or the quinone were installed; intermediates possessing a benzyl carbamate protecting the pyrrolidine nitrogen could be converted to a quinone bearing system.

as the benzyl carbamate afforded **53** in 63% unoptimized yield.

The side chain carbamate was installed onto **53** using trichloroacetyl isocyanate to afford **54** in 86% yield. Deprotection and oxidation of the aromatic ring occurred directly upon treatment of **54** with ceric ammonium nitrate, which afforded *p*-quinone **55** in essentially quantitative yield (95% isolated yield). Removal of the benzyl carbamates protecting the aziridine and pyrrolidine nitrogens occurred under standard hydrogenolysis conditions from **55** to afford the corresponding aziridino[1,2-*c*]pyrrolidine with the aromatic ring in the hydroquinone oxidation state. Direct exposure of this compound to atmospheric oxygen, following removal of traces of palladium by filtration through a 45- μ m filter to prevent oxidation of the pyrrolidine ring, affected a slow reoxidation to the quinone accompanied by cyclization of the B-ring, afforded mitosane **1** (9a-desmethoxy mitomycin A) in good yield (74% for two steps), and completed the synthesis of the target molecule.



Difference NOE spectroscopy with **1** demonstrated the correct stereochemistry had been obtained at the synthetically installed C9 and C9a stereocenters (Figure 2). Relevant nuclear Overhauser effect enhancements are listed in Table 1 and are consistent with the stereoisomer shown in Figure 2, clearly demonstrating that the absolute configuration at the C9 and C9a stereogenic centers is the same as that found in mitomycin A and C. Although NOE measurements appear to be consistent with the third structure in Table 1 where C9-H and C9a-H are *cis* and α , this structure is highly unlikely because it would require allylstannane **34** to approach the iminium ion generated from **22** from the α -face that bears the bulky alkoxy groups. Precedent suggests that this is disfavored (see addition of **34** to **19**). The remaining two structures, where C9-H and C9a-H are *trans*, are inconsistent with observed NOE enhancements.

One synthetic problem that has yet to be seriously addressed is the issue of the C9a angular methoxy group. It is widely appreciated by those chemists who have chosen the mitomycins as synthetic targets that an alkoxy or hydroxy group at this position is highly labile. It is exceptionally difficult to manipulate compounds bearing an oxygen at C9a when the intact tetracyclic ring system is in the hydroquinone oxidation state. This is,

TABLE 1. Calculated Proton–Proton Distances and Nuclear Overhauser Enhancements for Stereoisomeric Products

¹ H- ¹ H pair	Distance (Å) ^a	% NOE observed ^b	Diastereoisomer
C9-C9a	2.3	1.5	
C9-C10	2.5	4.0	
C9a-C1	2.6	1.4	
C2-C3 α	2.7	1.5	
C1-C10	2.9	0.8	
C9a-C3 α	3.2	*	
C10-C9a	3.6	–	
C9-C1	3.7	–	
C9a-C10	2.4	–	
C9-C10	2.5	4.0	
C9a-C1	2.5	1.4	
C9-C9a	3.1	1.5	
C9-C3 β	3.2	–	
C9-C1	3.6	–	
C9-C9a	2.3	1.5	
C9-C10	2.6	4.0	
C1-C10	2.9	0.8	
C9a-C1	3.0	1.4	
C9a-C3 β	3.0	–	
C9-C1	3.6	–	
C9a-C10	3.8	–	
C9-C10	2.5	4.0	
C9-C1	2.5	–	
C9a-C10	2.8	–	
C9-C9a	2.8	1.5	
C9a-C3 β	2.9	–	
C9a-C1	3.1	1.4	
C9a-C2	4.1	–	
C1-C10	4.9	0.8	

^a Calculated from energy minimized (MM3) structures generated in CHCl₃ using MacroModel (v 6.0). ^b Key: minus = not observed; asterisk = impossible to observe because of spectral overlap.

in fact, what happens in vivo as the quinone is reduced to the hydroquinone, and the B-ring undergoes elimination and aromatization to set up the system for DNA cross-linking. Successful synthetic routes to the mitomycins have sidestepped this issue by avoiding hydroquinone (indoline) systems altogether or by placement of a carbonyl group next to the bridgehead nitrogen, where amide resonance prevents elimination. In the context of the present work, early introduction of the angular methoxy group is not feasible, and so a chemoselective oxidation at this position will be necessary for completion of the total synthesis of the mitomycin C.

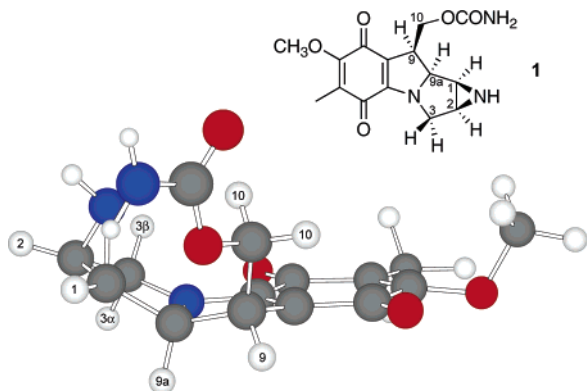


FIGURE 2. Representation of the energy minimized (MM2) structure of **1** with relevant protons numbered (mitomycin numbering).

Such oxidations are preceded in the context of natural products synthesis.²⁸

The convergent and diastereoselective synthesis of **1** was achieved in 23 total synthetic operations from D-ribose and 2,6-dimethoxytoluene. The longest linear

sequence of reactions was 16 steps,²⁹ making this synthesis of the mitomycin system among the more efficient reported to date. The key step in this reaction sequence, coupling of cinnamylstannane **34** with the iminium ion derived from pyrrolidine **22**, occurred in good chemical yield with useful diastereoselectivity.

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Supporting Information Available: Full details on the preparation, characterization of synthetic intermediates and products, and crystallographic data in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(29) Comparable syntheses of **1** or a closely related compound have required 32 total steps (20 linear)^{13a} or 27 steps (27 linear).^{13b}