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A Convergent Approach to the Mitomycin Ring System

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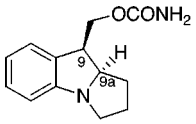
ABSTRACT



A novel stereoselective approach to the ring system of the mitomycins is described. The synthesis was based on a convergent strategy involving a stereocontrolled addition of a *β*-phenyl silyl enol ether to a pyrroline *N*-acyliminium ion followed by an intramolecular palladium-catalyzed aryl triflate amination to afford the (9*R,9a*R**)-tetrahydropyrrolo[1,2-*a*]indole ring system.**

The mitomycin family of antitumor agents, typified by the most well studied member mitomycin C, have been the focus of a large body of synthetic and mechanistic work[1] in the 45 years since their discovery.[2] The mechanism of action of these clinically important chemotherapeutic agents has been elucidated in a detailed series of investigations.[3] Bioreduction of the quinone system precedes amine-promoted loss of methanol to the corresponding indole. Consequent activation of the now benzylic carbamate and aziridine electrophilic carbons leads to the eventual formation of a covalent cross-link of duplex DNA.[4] Several total syntheses have been described[5] along with an amazingly diverse set of studies describing synthetic approaches to the highly functionalized and intricate ring system characteristic of these deceptively simple natural products. We now report our initial contribution to the development of a general synthetic approach to the mitomycin family of antitumor agents (Figure 1).

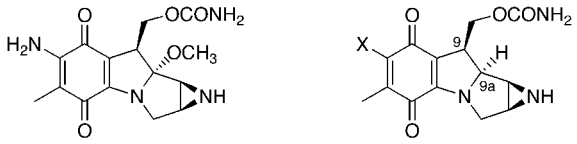


Figure 1. Structure of mitomycin C and the mitosane system.

Many synthetic approaches to the mitomycins and related systems are effective at construction of the target heterocyclic ring system but may lack generality and convergency. Even with the extensive synthetic literature on the mitomycins, certain deficiencies remain with respect to the use of more modern organometallic methods and with issues of stereocontrol in the construction of the parent heterocyclic ring system, in particular, the C9 and C9a stereogenic centers. Herein, we describe a potentially general and conceptually simple synthetic strategy for the construction of the pyrrolo[1,2-*a*]indole ring system of the mitomycins that is illustrated by the stereocontrolled synthesis of the mitosane skeleton.[6]

(1) Mitomycins and Porfiromycin. In *The Chemistry of Antitumor Antibiotics*; Remers, W. A.; Wiley-Interscience: 1979.

(2) Hata, T.; Sano, Y.; Sugawara, A.; Matsune, A.; Kanamori, K.; Shima, T.; Hoshi, T. *J. Antiobiot., Ser. A* **1956**, *9*, 141 (mitomycins A and B). Wakaki, S.; Marumo, H.; Tomioka, K.; Shimizu, G.; Kato, E.; Kamada, H.; Kudo, S.; Fujimoto, Y. *Antiobiot. Chemother.* **1958**, *8*, 288 (mitomycin C).

(3) Tomasz, M.; Lipman, R.; McGuinness, B. F.; Nakanishi, K. *J. Am. Chem. Soc.* **1988**, *110*, 5892−5896. Tomasz, M. *Chem. Biol.* **1995**, *2*, 575.

(4) Tomasz, M. Mitomycin C: DNA Sequence Specificity of a Natural DNA Cross-Linking Agent. I *Advances in DNA Sequence Specific Agents*; Hurley, L. H., Ed.; JAI Press: Greenwich, CT, 1992; Vol. 1, pp 247−261. Franck, R. W.; Tomasz, M. The Chemistry of Mitomycins. In *Chemistry of Antitumor Agents*; Wilman, D. E. V., Ed.; Blackie & Son: New York; 1990; Chapter 15, pp 379−394.

(5) Waldmann, H. *Org. Synth. Highlights II* **1995**, 309−314. Fukuyama, T.; Yang, L. Total Synthesis of Mitomycins. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier, 1993; Vol. 13, pp 433−471.

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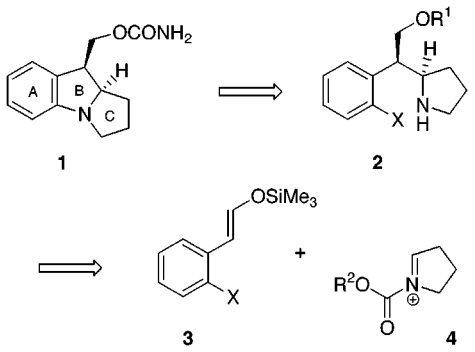
The basis of our synthetic plan is to incorporate the intact pyrrolidine C-ring in a two-reaction process of palladium-catalyzed intramolecular aryl amination proceeded by a stereoselective addition of a β-aryl enol ether to a pyrrolidinone-derived *N*-acyliminium ion (Scheme 1). This strategy

Scheme 1. Retrosynthetic Plan

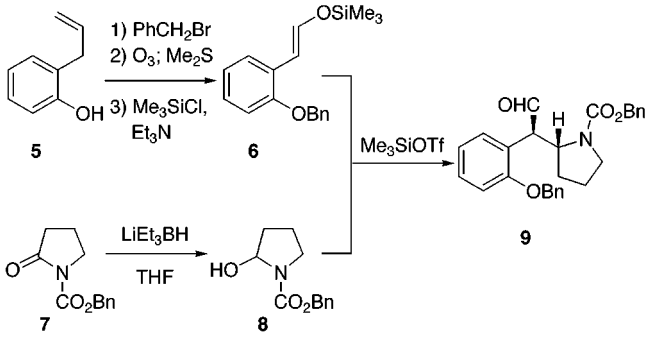


converges intact A- and C-ring precursors in a B-ring annulation sequence. Stereochemical control in the *N*-acyliminium ion addition sets the relative stereochemistry of the two stereogenic centers of the target system **1**.

There are a number of earlier synthetic strategies en route to pyrrolo[1,2-*a*]indole systems that are superficially similar to ours,[7] but only in that an intact pyrrolidine or pyrrole ring is appended onto a benzenenoid system. Of particular note is the work of Kametani,[7f] although in this early route to the simpler mitosene skeleton[8] the important issue of stereocontrol in the formation of the C9 and C9a centers was not addressed.

This plan was put into practice as illustrated in Scheme 2. Silyl enol ether **6** was synthesized from *o*-allylphenol (**5**)

Scheme 2. Iminium Ion Addition

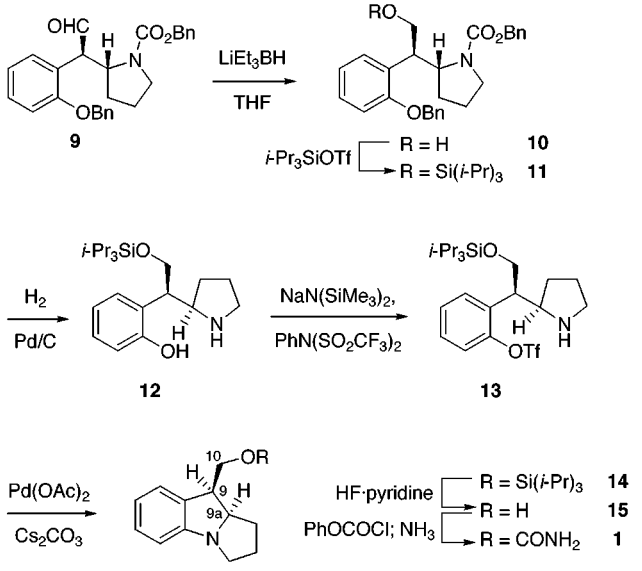


by benzylation (BnBr, K_2CO_3, acetone, 58 °C, 18 h), ozonolysis (O_3, CH_2Cl_2, −78 °C, 30 min, then Me_2S, 25 °C, 6 h), and silylation (Me_3SiCl, Et_3N, CH_3CN, 0 °C, 12 h)[9] in an overall yield of 54% from the starting phenol. *N*-Acyliminium ion precursor **8** was synthesized from *N*-CBz pyrrolidinone (**7**)[10] by reduction with $LiEt_3BH$ (THF, −78 °C, 1 h, 92%).[11] Trimethylsilyl triflate promoted addition of **6** to the *N*-acyliminium generated from **8** (Me_3SiOTf, CH_2Cl_2, −78−25 °C, 2 h) afforded **9** in excellent yield (96%). Establishment of relative stereochemistry or reaction stereoselectivity was not possible at this juncture due to the slowly interconverting rotamers about the carbamate N−CO bond in **9** that obscured ^1H NMR signals by line broadening, rather it was established by following cyclization to the pyrroloindole (vide infra).

The aldehyde of **9** was reduced to the corresponding alcohol most effectively with SuperHydride ($LiEt_3BH$, THF, −78 °C, 30 min, 99%), which in turn was protected as the triisopropylsilyl ether (*i*-Pr_3SiOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 6 h, 92%). Removal of the *O*-benzyl and *N*-CBz groups by hydrogenolysis (1 atm H_2, Pd/C, MeOH, 12 h) afforded the corresponding aminophenol **12**, which was acylated selectively on the phenolic oxygen by deprotonation (1 equiv of NaHMDS, THF, 0 °C) followed by addition of *N*-phenyltriflimide ($PhNTf_2$, 0 °C, 1 h) to afford **13** (83% from carbamate **11**) as a >6:1 ratio of spectroscopically distinguishable but chromatographically inseparable diastereomers. Acylation occurred selectively on the reactive sodium phenolate in preference to the amino group. The use of a lithium counterion or other sodium bases (NaH) was unsuccessful in providing useful O- vs *N*-selectivity in this reaction.

Intramolecular palladium-catalyzed aryl amination[12] (Scheme 3) using the conditions of Buchwald and co-workers[13] (Pd-

Scheme 3. Palladium-Catalyzed Cyclization



$(OAc)_2$, BINAP, Cs_2CO_3, toluene, 100 °C, 18 h, 44%) afforded the pyrrolo[1,2-*a*]indole **14** in moderate yields.[14] Desilylation (HF·pyridine, 25 °C, 48 h, 83%) and carbamoylation following literature protocol[6b] (PhOCOCl, pyridine,

(6) For previous syntheses of mitosane systems, see: (a) Jones, G. B.; Guzel, M.; Mathews, J. E. *Tetrahedron Lett.* **2000**, *41*, 1123−1126. (b) Dijksman, W. C.; Verboom, W.; Egberink, R. J. M.; Reinhoudt, D. N. *J. Org. Chem.* **1985**, *50*, 3791. (c) Danishefsky, S.; Regan, J.; Doehner, R. *J. Org. Chem.* **1981**, *46*, 5255−5261.

25 °C, 18 h then liquid NH_3, CH_2Cl_2, 6 h, 59% overall) afforded the mitosane system (9*R**,9a*R**)-**1**.[15] The minor diastereomer (9*R**,9a*S**)-**1** could be separated by preparative thin-layer chromatography.[16]

The relative stereochemistry of the C9 and C9a stereogenic centers of the major diastereomer of **1** was determined to be 9*R**,9a*R** by correlation with published ^1H and ^{13}C NMR spectral data.[6b,17] In addition, nuclear Overhauser enhancement studies on both diastereomers were consistent with and confirmed unequivocally the proposed stereochemical assignments. Figure 2 shows energy-minimized structures

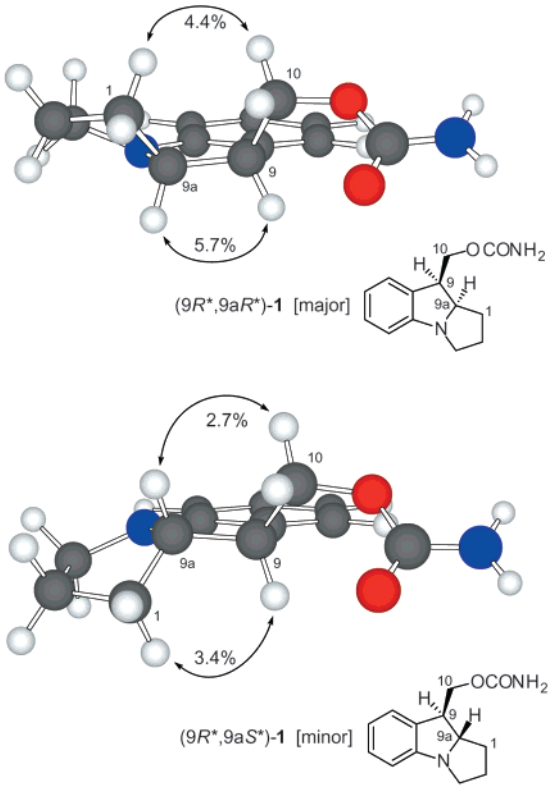
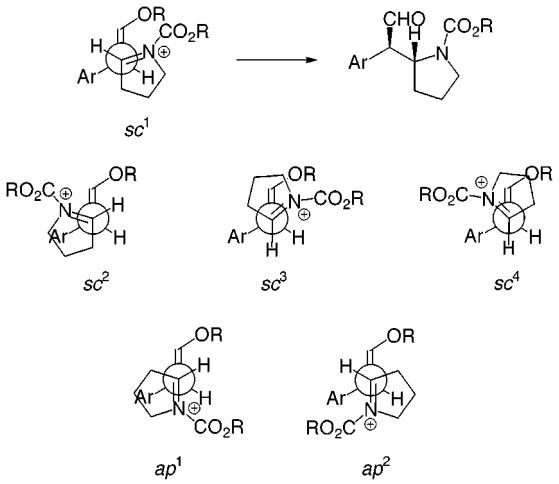


Figure 2. Relative stereochemistry assignment by NOE.

(MMX force field) of the major and minor diastereomers of **1**. In the major stereoisomer [(9*R**,9a*R**)-**1**], the most definitive enhancements were between C10−H and C1−H_β (4.4%) and between C9−H and C9a−H (5.7%). Notably absent were enhancements between C9−H and either C1−H and between the C10−H's and C9a−H. In the minor diastereomer [(9*R**,9a*S**)-**1**], the definitive enhancements were between C9−H and C1−H_α (3.4%) and between C9a−H and C10−H (2.7%). Completely absent were enhancements between C10−H's and either C1−H_α or C1−H_β. These nuclear Overhauser enhancement studies served to definitively establish the relative stereochemistry at the C9 and C9a stereogenic centers.

A rationale for the observed diastereoselection in the addition of enol ether **6** with the iminium ion derived from **8** is shown in Scheme 4.[18] Considering the possible orienta-

Scheme 4. Origin of Diastereoselection



tions of the two reactive π-systems, the least sterically crowded arrangement is the synclinal orientation *sc*^{1} that leads to the desired stereochemical array in the addition product. The alternative synclinal orientations *sc*^{2}, *sc*^{3}, and *sc*^{4} place the pyrrolinium ring over the aromatic ring or silyl

(7) (a) Yamada, Y.; Matsui, M. *Agr. Biol. Chem.* **1971**, *35*, 282−284. (b) Takada, T.; Kosugi, Y.; Akiba, M. *Tetrahedron Lett.* **1974**, 3283−3286. (c) Kametani, T.; Takahashi, K.; Ihara, M.; Fukumoto, K. *Heterocycles* **1975**, *3*, 691−695. (d) Kametani, T.; Ohsawa, T.; Takahashi, K.; Ihara, M.; Fukumoto, K. *Heterocycles* **1976**, *4*, 1637−1644. (e) Crump, D. R.; Franck, R. W.; Gruska, R.; Ozorio, A. A.; Pagnotta, M.; Siuta, G. J.; White, J. G. *J. Org. Chem.* **1977**, *42*, 105−108. (f) Kametani, T.; Takahashi, K.; Ihara, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1976**, 389.

(8) The mitosenes have a double bond between C9 and C9a (i.e., they possess a dihydropyrrolo[1, 2-*a*]indole ring system) and thus lack these important stereogenic centers.

(9) Duhamel, P.; Hennequin, L.; Poirier, J. M.; Tavel, G.; Vottero, C. *Tetrahedron* **1986**, *42*, 4777.

(10) Louwrier, S.; Tuynman, A.; Hiemstra, H. *Tetrahedron* **1996**, *52*, 2629.

(11) Fisher, M. J.; Overman, L. E. *J. Org. Chem.* **1990**, *55*, 1447. Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1973**, *95*, 1669.

(12) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046.

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(14) Not surprisingly, the dihydroindole ring system of **14** was sensitive to air oxidation, and the modest isolated yield for the cyclization of **13** to **14** is in part due to this sensitivity.

(15) The major stereoisomer (9*R**,9a*R**)-**1** was characterized: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.11 (app t, 1H, J = 8.5, 7.9 Hz), 7.07 (d, 1H, J = 7.9 Hz), 6.74 (dd, 1H, J = 7.9, 7.3 Hz), 6.56 (d, 1H, J = 7.9 Hz), 4.64 (br s, 2H, NH_2), 4.55 (dd, 1H, J = 6.1, 5.5 Hz, C10−H), 4.29 (dd, 1H, J = 8.5, 5.5 Hz, C10−H), 3.96 (ddd, 1H, J = 9.8, 8.5, 5.5 Hz, C9a−H), 3.71 (ddd, 1H, J = 9.6, 8.5, 6.1 Hz, C9−H), 3.44 (ddd, 1H, J = 10.7, 8.8, 3.7 Hz, C3−H), 3.12 (ddd, 1H, J = 10.7, 8.5, 7.7 Hz, C3−H), 1.78−1.95 (m, 2H, C2−H), 1.68 (m, 1H, C1−H), 1.36 (m, 1H, C1−H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.58, 154.81, 128.98, 128.41, 124.03, 119.35, 110.76, 68.64, 64.94, 51.80, 41.78, 26.00, 25.07; HRMS (FAB), *m/e* 233.1294 (calcd for $C_{13}H_{16}N_2O_2$ + H, 233.1290).

(16) The minor stereoisomer (9*R**,9a*S**)-**1** was characterized: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.12 (m, 1H, 2H), 6.75 (app t, 1H, J = 7.3 Hz), 6.56 (d, 1H, J = 7.9 Hz), 4.60 (br s, 2H, NH_2), 4.23 (dd, 1H, J = 10.4, 6.4 Hz, C10−H), 4.13 (dd, 1H, J = 11.9, 6.4 Hz, C10−H), 3.71 (ddd, 1H, J = 9.5, 6.4, 3.1 Hz, C9a−H), 3.50 (m, 1H, C9−H), 3.40 (m, 1H, C3−H), 3.13 (m, 1H, C3−H), 1.91 (m, 1H, C1−H), 1.84 (m, 2H, C2−H), 1.35 (m, 1H, C1−H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.65, 154.91, 129.60, 128.77, 125.25, 119.40, 111.35, 68.82, 67.82, 51.98, 46.55, 30.83, 25.68.

enol ether, making all of these orientations nonviable energetically. Both antiperiplanar orientations suffer steric crowding, severely in ap^1 between pyrrolinium and aromatic rings, or to a lesser degree in ap^2 between the carbamoyl group and the *O*-benzyl phenol on the aromatic ring. Thus, from this analysis, it would appear that the two least crowded orientations are sc^1 and ap^2, where the sc^1 orientation predominates to afford the observed diastereoselection. The minor diastereomer presumably arises from orientation ap^2.

The synthetic strategy developed as a stereoselective route to tetrahydropyrrolo[1,2-*a*]indole **1** provides a unique and convergent entry into the mitomycin ring system. Further work on more elaborated systems, both the aromatic and pyrrolidine synthons, is under investigation.

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Supporting Information Available: Experimental procedures and spectral characterization of synthetic intermediates and products. This information is available free of charge via the Internet at http://pubs.acs.org.

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(17) The stereochemical series with a *cis* relationship between C9-H/C9a-H is denoted *trans* by Chemical Abstracts Service. Before 1983, the 9*R**,9a*R** series with a *cis*-relationship between C9-H/C9a-H was denoted as *cis*. Because of this confusing reversal of notation, we have avoided using *cis* and *trans* altogether in naming our compounds. Thus, the 9*R**,9a*R** stereoisomer has the C9-H and C9a-H on the same face of the molecule, wereas the 9*R**,9a*S** stereoisomer has them on opposite sides.

(18) Russowsky, D.; Petersen, R. Z.; Godoi, M. N.; Pilli, R. A. *Tetrahedron Lett.* **2000**, *41*, 9939. Maldaner, A. O.; Pilli, R. A. *Tetrahedron Lett.* **2000**, *41*, 7843. Pilli, R. A.; Russowsky, D. *Trends Org. Chem.* **1997**, *6*, 101−123. Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Org. Chem.* **1985**, *50*, 3115−3121.