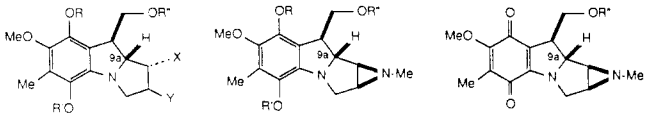
On the Reaction of Leucomitosenes with Osmium Tetraoxide: A Route to Novel Mitomycins

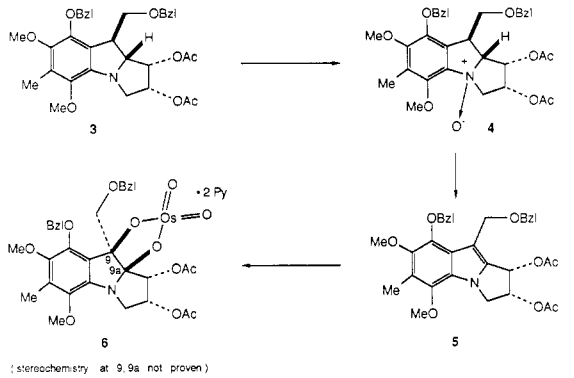
Summary: Remarkably stable osmate esters are obtained from the reaction of osmium tetraoxide with indolic systems related to mitomycins.

Sir: A synthetic entry to the 9a-deoxy family of mitomycins,[1,2] i.e., mitosanes, has been accomplished in our laboratory.[3,4] Our synthetic route to mitosanes passed through intermediates of the type **1**, where X is an oxygen-based group (OH, OAc) and Y is either an α-oxygen function (OH, OAc, OSO_2R) or a β-nitrogen-based group (N_3, $NHP(O)(OMe)_2$). We also prepared leucoaziridinomitosanes (**2**)[3] and aziridinomitosanes[3] by total synthesis.[4]

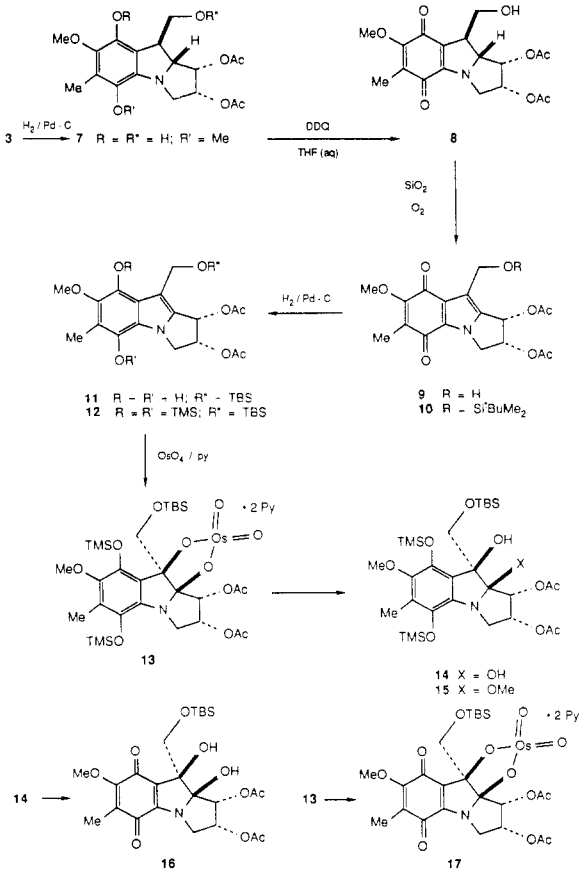


An attempt to achieve C_{9a} functionalization on a type **1** substrate (i.e., compound **3**) via a Polonovski reaction on its derived *N*-oxide **4** was recently described.[5] The most promising result in this regard was the conversion of **4** to the leucomitosene **5**, albeit in modest (ca. 25%) yield. We now describe a study directed toward the possibilities of oxidizing an indole of this type. Treatment of **5** with OsO_4 (10 equiv) in pyridine afforded a single stereoisomer of the remarkably stable osmate ester **6** in 97% yield.[6,7] Though it seems likely that osmylation had occurred on the least hindered (β) face of the indole, the stereochemistry cannot rigorously be assigned with the data in hand.[8]

It was hoped to extend the osmylation reaction to an indole which would be better poised for conversion to a quinone (of mitomycins). A key finding in this regard was that mitosane **8**, obtained via **3** and **7** as shown, undergoes oxidative transformation to indoloquinone **9** (43% yield) upon exposure to silica gel in the presence of air.[9] Protection of the primary alcohol as its TBS ether was smoothly accomplished. The quinone function in **10** was



reduced to the hydroquinone **11**, which was converted to the bis TMS protected derivative **12** upon reaction with trimethylsilyl triflate in pyridine (92% yield from **10**).



Treatment of **12** with OsO_4 in pyridine gave an 89% yield (after chromatography) of osmate ester **13** (stereochemistry not rigorously known). Deosmylation of **13** was accomplished through the action of hydrogen sulfide in THF affording **14**. Desilylation and concurrent oxidation via *n*-Bu_4NF–O_2–Pd/C afforded quinone diol **16** in 58% overall yield. Exchange of the C_{9a} hydroxyl by methoxyl was accomplished by reaction of diol **14** with *p*-TsOH in methanol for 1 h. Again, a single stereoisomer, **15** (stereochemistry not rigorously known), was obtained. Finally, in this diacetoxy series we note that reaction of **13** with *n*-Bu_4NF in the presence of air gave the novel quinone–osmate ester **17** in 54% overall yield.

During the course of our experiments to probe the mechanism of action of mitomycins by identifying labile intermediates in the activation cascade,[10,11] we recently

(1) For key sources on various aspects of mitomycins, see: (a) Franck, R. *Prog. Chem. Org. Nat. Prod.* **1979**, *38*, 1. (b) Remers, W. *The Chemistry of Antitumor Antibiotics*; Wiley-Interscience: New York, 1979; Vol. 1. (c) Zein, N.; Kohn, H. *J. Am. Chem. Soc.* **1986**, *108*, 296.

(2) For the total syntheses of naturally occurring mitomycins, see: (a) Kishi, Y. *J. Nat. Prod.* **1979**, *42*, 549. (b) Nakatsubo, F.; Fukuyama, T.; Cocuzza, A. J.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, *99*, 8115. (c) Fukuyama, T.; Nakatsubo, F.; Cocuzza, A. J.; Kishi, Y. *Tetrahedron Lett.* **1977**, 4295. (d) Fukuyama, T.; Yang, L. *J. Am. Chem. Soc.* **1987**, *109*, 7880.

(3) The following descriptors have been introduced to facilitate communication in the still-developing area of mitomycin chemistry. The prefix "leuco" or its absence defines whether the A ring is hydroquinonoidal or quinonoidal. The suffix "mycin" is reserved for systems bearing an oxygen heterofunction at C_{9a}. The suffix "sene" describes the presence of a 9–9a double bond. The suffix "sane" indicates that C_{9a} is in the reduced form, i.e., bears a hydrogen. We further suggest that the presence or absence of a 1,2-aziridine be clearly specified by the presence or absence of the aziridino descriptor.

(4) Danishefsky, S. J.; Berman, E.; Ciufolini, M.; Etheredge, S. J.; Segmuller, B. E. *J. Am. Chem. Soc.* **1985**, *107*, 3891.

(5) Danishefsky, S. J.; Feigelson, G. B. *Heterocycles* **1987**, *25*, 301.

(6) The assignment of two pyridine units per molecule of ester is based on integration of the NMR spectrum.

(7) Cf.: Ockenden, D. W.; Schofield, K. *J. Chem. Soc.* **1953**, 3440.

(8) For two examples of surprising stereochemical results arising for osmylation of related systems, see ref 4 and ref 16.

(9) The simplest mechanistic proposal is that under these conditions the indolinoquinone is directly dehydrogenated to the indoloquinone. Alternatively, it could be the consequence of isomerization of the indolinoquinone to an indolohydroquinone with subsequent air oxidation of the hydroquinone moiety to the indoloquinone.

(10) Danishefsky, S. J.; Egbertson, M. *J. Am. Chem. Soc.* **1986**, *108*, 4648.

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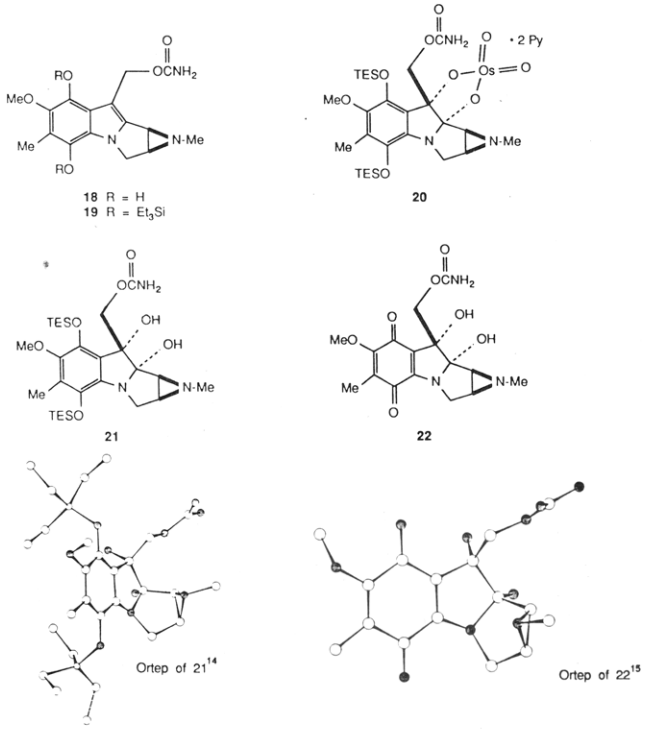
described the first preparation of the leucoaziridinomitosene **18**, which upon silylation under Mitscher's conditions generated the bis TES derivative **19**.[12] We now describe the first transformation (other than silylation) of a leucoaziridinomitosene.



Osmylation of **19**, carried out as above, afforded a 20–30% overall yield[13] of the osmate ester **20**. By the protocol described above, **20** was converted to the C_9 α-hydroxyleucoaziridinomitomycin derivative **21**. The stereochemistry of **21** was established through crystallographic means (see ORTEP drawing).[14] Cleavage of the silyl groups and concurrent oxidation of the hydroquinone afforded the 9α-hydroxylated mitomycin B derivative **22**. That there had been no alteration in stereochemistry in going from the indole series to the final product was verified by a single-crystal determination of the latter (see ORTEP drawing).[15]

In summary, these results demonstrate the feasibility of the conversion of mitosanes (cf. **8**) to mitosenes (cf. **9**) and the usefulness of the osmylation of leucomitosenes (**5** and **12**), *including a leucoaziridinomitosene* (**19**) for installing novel functionality patterns in this important skeleton. An application of these newly won capabilities to the synthesis of the intriguing 10-decarbamoyloxy-9-dehydro series is described in the accompanying paper.[16]

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Supplementary Material Available: ORTEP drawings and tables containing fractional coordinates, temperature factors, bond distances, torsional angles, and anisotropic temperature factors for compounds **21** and **22** (20 pages). Ordering information is given on any current masthead page.

(11) Egbertson, M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1987**, *109*, 2204.

(12) Veysoglu, T.; Mitscher, L. A. *Tetrahedron Lett.* **1981**, *22*, 1303.

(13) This yield includes the synthesis of the preparation of the unstable leuco compound **19**[11] and its osmylation product, **20**.

(14) The structure of compound **21** was determined by X-ray crystallography using a crystal that measured 0.30 × 0.15 × 0.10 mm. Diffraction measurements were made on an Enraf-Nonius CAD-4 fully automated diffractometer using graphite-monochromated Cu Kα radiation (λ = 1.541 84 Å). Preliminary indications of the unit cell based on 25 randomly selected reflections revealed monoclinic symmetry with the following lattice parameters: a = 12.060 (3) Å, b = 9.708 (3) Å, and c = 15.027 (3) Å with β = 107.0 (2)°. The space group, based on the observed systematic extinctions, was assigned as $P2_1$ (No. 4), Z = 2 with one molecule of composition $C_{25}H_{49}O_7N_3Si_2$ forming the asymmetric unit. The volume was 1682 (1) Å^3, and the calculated density was 1.176 g/cm^3. There were 2547 relections collected with $2\theta \leq 112°$; of those reflections, 2200 (86%) with $I \geq 3\sigma(I)$ were adjudged observed.

The structure was solved by using MULTAN 80. The phasing of 310 E values ≥ 1.423 resulted in an electron density map that revealed the heavy atoms. Multiple iterations of refinement and the weighted Fourier option in MULTAN 80 resulted in solution of the entire structure. The TES groups exhibit severe disorder, and those atoms (C14, C14A, C15, C15A, C18, C18A, C22, and C22A) were refined isotropically. Hydrogen atoms were calculated by using SDP program HYDRO and added to the structure calculations. The following full-matrix refinement of the non-hydrogen atoms and addition of the hydrogen atoms to the structure factor calculations, without refinement to their positions, resulted in convergence to an unweighted residual of 0.075 and a weighted residual of 0.083. Tables containing fractional coordinates, temperature factors, bond distances, torsional angles, and anisotropic temperature factors are available in the supplementary material.

(15) The structure of compound **22** was determined by X-ray crystallography using a crystal that measured 0.25 × 0.10 × 0.05 mm. Diffraction measurements were made by a Rigaku AFC5S fully automated diffractometer using graphite-monochromated Cu Kα radiation (λ = 1.541 78 Å). Preliminary indications of the unit cell based on 25 randomly selected reflections revealed monoclinic symmetry with the following lattice parameters: a = 7.869 (4) Å, b = 7.572 (3) Å, and c = 13.864 (4) Å with β = 102.02 (3)°. The space group, based on the observed systematic extinctions, was assigned as $P2_1$ (No. 4), Z = 2 with one molecule of composition $C_{16}H_{19}O_7N_3$ forming the asymmetric unit. The volume was 807.9 (5) Å^3, and the calculated density was 1.50 g/cm^3. There were 1316 reflections collected with $2\theta \leq 120°$; of those reflections, 885 (67%) with $I \geq 3\sigma(I)$ were adjudged observed.

The structure was solved by using MITHRIL. The hydrogens were calculated for. The full-matrix refinement of the non-hydrogen atoms and inclusion of the hydrogen scattering factor resulted in convergence of the crystallographic reliability factors to the following values: unweighted residual of 0.044 and a weighted residual of 0.051. Tables containing fractional coordinates, temperature factors, bond distances, torsional angles, and anisotropic temperature factors are available in the supplementary material.

(16) Feigelson, G. B.; Danishefsky, S. J. *J. Org. Chem.* following paper in this issue.

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On the Synthesis and Extraordinary Configurational Stability of the C_{9a}-Hydroxylated Mitomycins in the 10-Decarbamoyloxy-9-dehydro Series: Fully Synthetic Routes to Novel Mitomycin Congeners

Summary: An aziridinomitosene bearing an aldehyde function at C_{10} has been synthesized. Osmylation of this compound leads to cleavage of C_{10} and formation of a C_9-ketonic product, which was converted to the title series. The stereoisomeric 9a-hydroxy compounds do not interconvert.

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