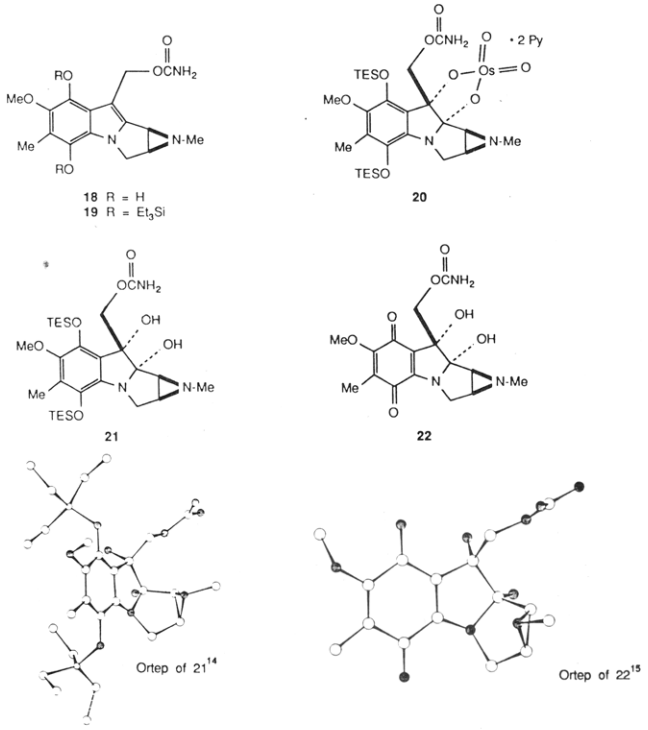
described the first preparation of the leucoaziridinomitosene **18**, which upon silylation under Mitscher's conditions generated the bis TES derivative **19**.[12] We now describe the first transformation (other than silylation) of a leucoaziridinomitosene.



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]

Acknowledgment. This work was supported by PHS Grant CA28824. An American Chemical Society Graduate Fellowship (Division of Organic Chemistry) to M.E. is gratefully acknowledged. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE7916210.

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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Sir: In previous reports we have described a prototype scheme for the oxidative conversion of a leucomitosane (**1**) to a leucomitosene (**2**)[1,2] and of a mitosane (**3**) to a mitosene (**4**)[2,3] (Figure 1). Systems **1** and **3** were generated by fully synthetic routes.[4,5] We have also described the partial synthesis of leucoaziridinomitosenes **7** and **7a** via naturally derived **5** and aziridinomitosene (**6**).[6]

Complicating our attempts to achieve a fully synthetic route to natural mitomycins[7,8] and novel derivatives thereof was the failure to achieve conversion of **8** and **10**, each obtained by total synthesis,[4] to **9** and **11**, respectively. In each instance only noncharacterizable products were obtained in attempting to achieve the "ane" to "ene" oxidation, under conditions that were well tolerated in the model systems, **1** and **3**.[1,2] *The presence of the aziridine ring had imposed some serious limitations on the feasibility of formation and orderly reactions of C_{9a} iminium equivalents.*

Fortunately, an interesting way of achieving the required overall result was discovered. Reaction of **8** with DDQ resulted in a 35% yield of the stable leucoaziridinomitosene (**12**).[9,10] *No doubt the stability of **12** accrues from the C_{10} aldehyde, which attenuates the "internal nucleophilicity" of the indolic nitrogen.* There is a parallelism between the stabilizing effect of this C_{10} aldehyde and the stabilization provided by indolinoquinone and indoloquinones relative to indolines and indoles (cf. inter alia mitomycins vs leucomitomycins and aziridinomitosenes vs leucoaziridinomitosenes).[3]

The osmylation of the indole aldehyde system was investigated with surprising results.[11] Treatment of **12** with 10 equiv of OsO_4 in pyridine led to a very slow reaction. *Workup after several days afforded a 46% yield of the C_{10} nor compound, **13**.* A formalism to account for this degradative transformation is provided in Figure 2, where the precise nature of the nucleophile, Nu, is unspecified. Although the stereochemistry at C_{9a} was not rigorously known at this stage, the hydroxyl group was expected to be α, since osmylation would be presumed to have occurred anti to the β-disposed aziridine.[12] Methylation of the tertiary hydroxyl group was accomplished in high yield with sodium hydride–dimethyl sulfate to give **13a**.[13]

Access to compounds **13** and **13a** allowed us to focus on the naturally occurring decarbamoyloxy mitomycins (**17** and **17a**) as synthetic targets.[14] Hydrogenolysis of the benzyl ether of either **13** or **13a** was achieved with H_2–Pd/C. The phenolic functions were protected with the Mitscher silylating agent,[15] yielding **14** and **14a**.

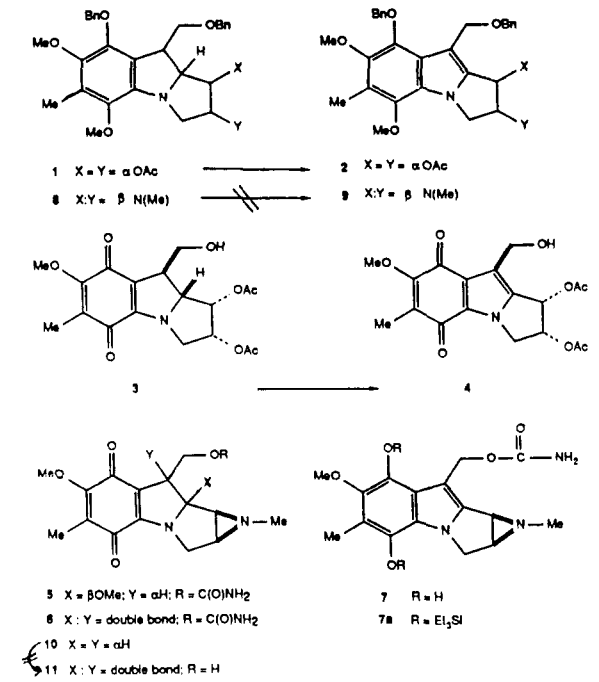

Figure 1.

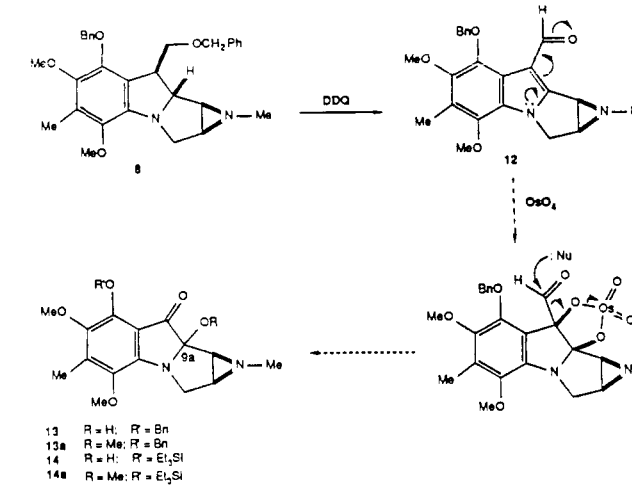

Figure 2.

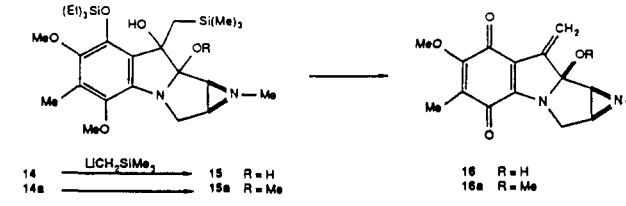

Figure 3.

Each of these compounds reacted in high yield with [(trimethylsilyl)methyl]lithium[16] in ether to afford the

(1) Danishefsky, S. J.; Feigelson, G. B. *Heterocycles* **1987**, *25*, 301.
(2) Feigelson, G. B.; Egbertson, M.; Danishefsky, S. J.; Schulte, G. *J. Org. Chem.*, preceding paper in this issue.
(3) For a statement of the nomenclature descriptors we use to indicate mitomycin structural types, see ref 2 (footnote 3).
(4) Danishefsky, S. J.; Berman, E.; Ciufolini, M.; Etheredge, S. J.; Segmuller, B. E. *J. Am. Chem. Soc.* **1985**, *107*, 3891.
(5) For a complete description of the background studies pertinent to this work, see: Feigelson, G. B. Thesis, Yale University, 1988.
(6) For the "ascorbic acid route" to aziridinomitosane, see: Danishefsky, S. J.; Egbertson, M. *J. Am. Chem. Soc.* **1986**, *108*, 4648.
(7) For the total syntheses of mitomycins by the Kishi school, see: Kishi, Y. *J. Nat. Prod.* **1979**, *42*, 549. Nakatsubo, F.; Kukuyama, T.; Cocuzza, A. J.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, *99*, 8115. Fukuyama, T.; Nakatsubo, F.; Cocuzza, A. J.; Kishi, Y. *Tetrahedron Lett.* **1977**, 4295.
(8) For a recent highly concise synthesis of the mitomycins, see: Fukuyama, T.; Yang, L. *J. Am. Chem. Soc.* **1987**, *109*, 7880.
(9) Leucoaziridinomitosenes lacking the C_1 aldehyde are quite unstable.[10] Only the aldehyde could account for the stability of compound **12**. Therefore it seems likely that products in which the indole is elaborated first would not survive. We believe that the aldehyde must be in place when the leucoaziridinomitosene is formed for the product to be stable. This situation is probably responsible for the relatively modest yield, since oxidation to the indole is probably competitive as the first step.
(10) Egbertson, M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1987**, *109*, 2204.
(11) For the osmylation of indoles, see: Ockenden, D. W.; Schofield, K. *J. Chem. Soc.* **1953**, 3440.
(12) This is in fact the case in the presence of a C_1 carbamoyloxy group (see ref 2).
(13) While it need necessarily be the case that the configuration at C_{9a} does not change upon base-induced methylation, in fact, there is no change of stereochemistry in the conversion of either **14** to **14a** or **17** to **17a**.[14]
(14) Urakawa, C.; Tsuchiya, H.; Nakano, K.-I. *J. Antibiot.* **1981**, *34*, 243. Urakawa, C.; Tsuchiya, H.; Nakano, K.-I.; Nakamura, N. *J. Antibiot.* **1981**, *34*, 1152.
(15) Veysoglu, T.; Mitscher, L. A. *Tetrahedron Lett.* **1981**, *22*, 1303.

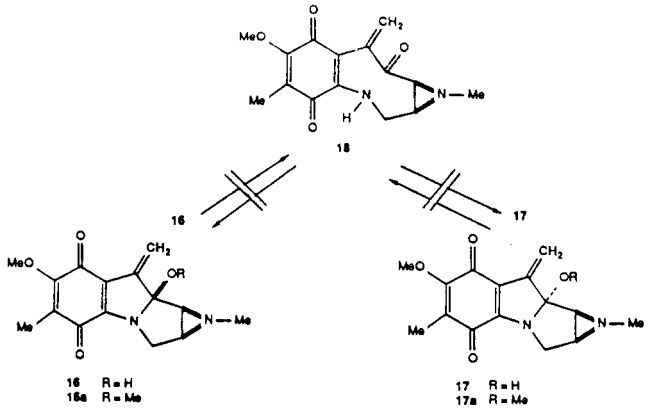

Figure 4.

adducts **15** and **15a** (Figure 3), which were surprisingly stable to spontaneous Peterson type elimination.[17] Cleavage of the silyl protecting group followed by oxidation (with DDQ–aqueous THF) and stirring for 30–40 min at room temperature led to the exocyclic methylene group in nearly quantitative yield. While the NMR spectra of **16** and **16a** indicate them to have the same gross structures as the corresponding natural products **17** and **17a**, there are small but clear differences in chemical shifts of various resonances.[18] The infrared and mass spectra of the two sets of stereoisomers are very similar. The TLC chromatographic properties of the two sets of compounds are also discernibly different. Given the previously derived 9a α-configuration of the oxygen functions of the natural products **17** and **17a**,[14,19] we are obliged to formulate the stereochemistry of the synthetic racemates as shown in **16** and **16a**.

Two features of this situation are most surprising. First, osmylation of **12** had occurred syn to the aziridino nitrogen, a result that stands in direct contrast to the previously described and rigorously proven α-osmylation of compound **7a**.[2] This difference may be a consequence of the much-reduced nucleophilicity of the indolic double bond of vinylogous formamide **13**. *Thus it might be that the only possibility for 13 to react at all with osmium tetraoxide is through a pathway where the osmylating species is directed by the cis proximal aziridino nitrogen.* In contrast, the indolic nitrogen atom of **7**, which is more basic than the corresponding center in **13**, may provide a ligating site for the oxidizing agent. Ligation by the indolic nitrogen could well occur anti to the aziridine for steric reasons, thus accounting for the observed results.

No less remarkable is the configurational stability of the hydroxy compounds **16** and **17**. A variety of attempts to effect interconversion of these compounds in either direction, under acidic or basic conditions, were unsuccessful. Starting with either substrate, there was no indication for interconversion, even at the very sensitive TLC level of analysis which would certainly have detected trace levels of crossover. We can only take these results to imply a very high barrier to opening of the carbinolamine, from either **16** or **17**, to what would have been the common ring chain tautomer **18** (Figure 4). This stands in sharp contrast to the reported accessibility of the corresponding system in the mitomycin B series.[20] Thus the exomethylene linkage seems to stabilize the carbinolamine relative to the amino ketone.[20]

Barring an enzymatically facilitated ring opening, it seems very unlikely that the in vivo bioactivity of **17** arises from its accession to the highly electrophilic **18**. Studies involving the mechanism of biological action of **17** (or **16**) are planned.

Acknowledgment. This work was supported by PHS Grant CA28824. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210.

(16) Ager, D. J. *Synthesis* **1984**, 384.
(17) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780.
(18) For instance: for compound **16** ($CDCl_3$), δ 5.94 and 5.33 (C_{10} olefinic protons); for **17**, δ 6.20 and 5.57 (C_{10} olefinic protons); for **16a**, δ 6.24 and 5.33 (C_{10} olefinic protons); for **17a**, δ 6.28 and 5.46 (C_{10} olefinic protons).
(19) The stereochemistry of the naturally derived compounds was inferred[14] from the interconversion of various carbamoyloxymitomycins into decarbamoyloxymitomycins. Thus, mitomycin B, upon direct elimination of the C-10 functionality, provided **17**. Base-induced methylation of **17** afforded **17a**. Compound **17a** could also be derived from the angular (C_{9a}) methoxy compound *N*-methylmitomycin A in a more circuitous sequence[20] which presumably could not have involved perturbation of the stereochemistry at C_{9a}.
(20) It had been concluded[14] that the barrier for carbinolamine → amino ketone conversion is accessible in the case of mitomycin B. The basis for the surmise was the finding that elimination of the 10-carbamoyloxy function occurs with mitomycin B in basic medium to produce **17**. By contrast, in the angular methoxy series (cf. *N*-methylmitomycin A), conversion to **17a** through elimination requires the use of a stronger leaving group (sulfonate) at C_{10}. The argument has been made that this difference is rationalized via the amino ketone form of mitomycin B, which is prone to eject carbamic acid to form **18** and thence **17**. Our data do not exclude this interpretation, but they would add the proviso that **18** must kinetically convert to **17** to the exclusion of **16**, since **16** does not suffer transformation to **17**. Similarly, the data per se do not rigorously exclude the possibility that either **16** (or **17**) does suffer transformation to **18** which kinetically returns to its precursor. They do exclude the possibility that **18** is accessible from both precursors, since in that case there would have been crossover between **16** and **17**.

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Spontaneous Stepwise Reduction of an Organic Peroxide by Ascorbic Acid[1]

Summary: Ascorbic acid (**1**) reacts spontaneously with dilauroyl peroxide (**2**) to produce dehydroascorbic acid (**3**), carbon dioxide, lauric acid, and undecane.

Sir: The broad spectrum of physiological activity exhibited by vitamin C (L-(+)-ascorbic acid, **1**) may be attributed in part to the redox activity of the "reductone" functional group.[2] It is important that the reactivity of ascorbic acid toward simple organic functional groups be delineated.[3] We have begun exploring the chemistry of ascorbic acid and organic peroxides. In this paper we report the spontaneous, uncatalyzed, nonenzymatic reduction of dilauroyl

(1) A partial account of this work was presented to the 195th meeting of the American Chemical Society, New Orleans, LA, September 3, 1987.
(2) For a discussion of the nonenzymatic physiological effects of ascorbic acid, see: Brin, M. In *Ascorbic Acid: Chemistry, Metabolism, and Uses*; Seid, P. A.; Tolbert, B. M., Eds.; American Chemical Society: Washington, DC, 1982; pp 369–377.
(3) For reviews of ascorbic acid chemistry, see: (a) *Ascorbic Acid: Chemistry, Metabolism, and Uses*; Seid, P. A., Tolbert, B. M., Eds.; American Chemical Society: Washington, DC, 1982. (b) "Second Conference on Vitamin C" In *Annals of the New York Academy of Sciences*; King, C. G., Burns, J. J., Eds.; New York Academy of Sciences: New York, 1975; Vol. 258, pp 1–552. (c) "Vitamin C" In *Annals of the New York Academy of Sciences*; Burns, J. J., Ed.; New York Academy of Sciences: New York, 1961; Vol. 92, pp 1–332.

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