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A Total Synthesis of (±)-Mitomycin K. Oxidation of the Mitosene C9-9a Double Bond By (Hexamethylphosphoramido)oxodiperoxomolybdenum (VI) (MoO_5 · HMPA).

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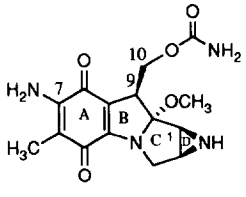
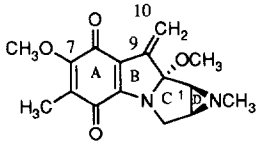
Abstract: A synthesis of (±)-Mitomycin K has been achieved in thirteen steps from commerically available 2,5-dimethylanisole in a 1.36% overall yield. One of the key steps is the oxidation of the C9-9a double bond of **1** by (hexamethylphosphoramido)oxodiperoxomolybdenum (VI) to give **5a** and **b**. This allows for the facile introduction of the C-9a methoxy group into the mitomycin skeleton.

The mitomycins are a class of natural products, which exhibit potent antitumor activities under reductive conditions.[1] Mitomycin C is the least toxic of the mitomycins and has proven to be a useful chemotherapeutic agent.[2] Two total syntheses of this important natural product have been accomplished by Kishi *et al.*[3] and by Fukuyama *et al.*[4] In addition, a total synthesis of a related natural product, mitomycin K, has been reported by Danishefsky *et al.*[5] Our explorations into mitomycin chemistry have also resulted in a synthesis of mitomycin K.



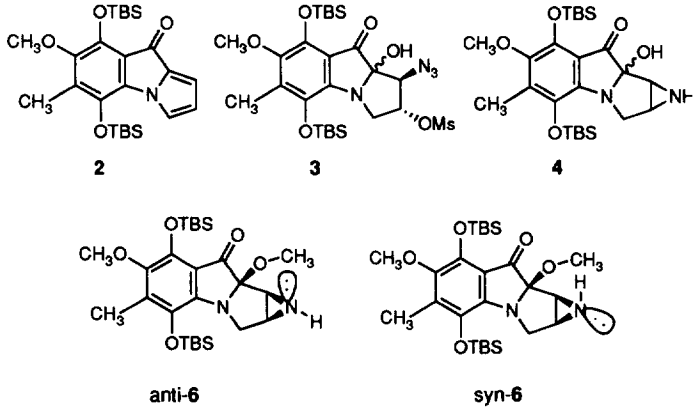
Mitomycin C



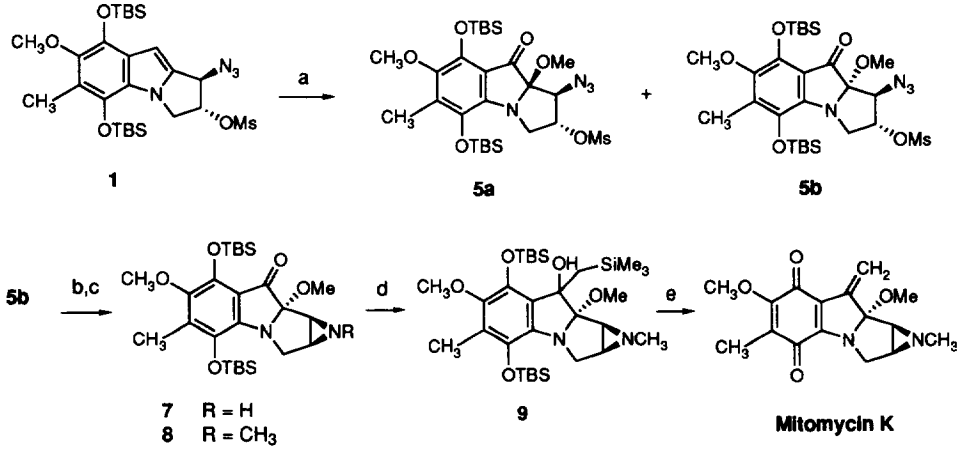
Mitomycin K

We had previously synthesized azidomitosene **1**[6] and were interested in finding a method to oxidize the C9-9a double bond of **1** in order to introduce the labile methoxy group of the mitomycins at C-9a. Our initial attempts to effect this oxidation with 2-phenylsulfonyl-3-phenyloxaziridine (Davis' reagent) failed, which was disappointing in view of the fact that this reagent had readily reacted with an unsubstituted analog.[7] In this case, Davis' reagent proved to be completely inert towards **1**, even at elevated temperatures. Treatment with 30% hydroperoxide also proved to be unreactive towards **1**, while *t*-butyl hydroperoxide in methanol produced the benzopyrrole **2**. Reaction with *m*-chloroperbenzoic acid resulted in removal of the TBS protecting groups and oxidation of the hydroquinone to give the corresponding quinone. Our first positive results came with the reaction of **1** with OXONE® in 1:1 acetone:sat. $KHCO_3$ to give an approximately 30% yield of **3** and 50% yield of **2**.[8] The hydroxy ketone **3** could be converted into **4** by treatment with triphenylphosphine in the presence of triethylamine in 10:1 THF:H_2O. Better results were obtained by treatment of **1** with (hexamethylphosphoramido)oxodiperoxomolybdenum (VI) (MoO_5 · HMPA) to give **5a** and **b** (**5a**: 46%, **5b**: 25%)[9] as a mixture of diastereomers (Scheme 1).[10] Both **5a** and **5b** (stereochemistry proven by its ultimate conversion to mitomycin K) react with triphenylphosphine in the presence of triethylamine to give the coresponding aziridine compounds **6** and **7**. The two diastereomers reach an approximately 1:1 equilibrium after three days in 0.2M HCl in MeOH. This allows for the partial conversion of **5a** into the more useful

diastereomer **5b**. Compound **7**[11] appears to exist as a mixture of invertomers (isomers by inversion at the aziridine center) by its ^1H and ^{13}C NMR spectra.[12] Compound **6**[13] also appears to exist as an approximately 5:2 mixture of syn and anti invertomers. The aziridine hydrogen of syn-**6** may form a hydrogen bond with the C-9a methoxy oxygen, resulting in different chemical shifts for the hydrogens on carbons 1-3.



The synthesis of both mitomycin K and its epimer at C-9a have been accomplished previously starting from a tricyclic 9-ketopyrroloindole derivative.[5,14] We modified the earlier route so as to convert **6** into mitomycin K, in order to confirm that the methoxy group at C-9a is *trans* to the aziridine ring. Methylation of **6** with methyl triflate resulted in the formation of **8**[15], which appears to exist as only one invertomer by its ^1H and ^{13}C NMR spectra. Compound **8** was converted into **9**[16] by reaction with trimethylsilylmethyllithium in



Scheme 1. (a) 2.0 equiv. $MoO_5 \cdot HMPA$, MeOH, 5-10°C, 3 d; **5a**, 25%; **5b**, 46%. (b) 1.5 equiv. PPh_3, 2.0 equiv. NEt_3, 10:1 THF:H_2O, rt, 10 h; 70%. (c) 30 equiv. CH_3OTf, 30 equiv. pyridine, CH_2Cl_2, 0°C, 22h; 78%. (d) 15 equiv. of 1.0 M $(CH_3)_3SiCH_2Li$, THF, −10°C, 10 min; 76%. (e) 3.0 equiv. PCC, CH_2Cl_2, 0°C, 10 min; 63%.

THF, a key step used by *Danishefsky* in his synthesis.[5,14] Oxidative cleavage of the *t*-butyldimethylsilyl (TBS) groups of **9** with pyridinium chlorochromate (PCC) led to concomitant Peterson elimination to form mitomycin K.[17]

In conclusion, a facile method for transforming mitosenes into mitomycins by introducing the C-9a methoxy group via a $MoO_5 \cdot$ HMPA oxidation of the C9-9a double bond has been developed, and has led to a 13-step synthesis of mitomycin K in a 1.4% overall yield from commercially available 2,5-dimethylanisole. Further studies towards the synthesis of mitomycin C are planned.

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9. For **5a**: ^{1}H NMR ($CDCl_3$): δ 0.09 (s, 3H), 0.19 (s, 3H), 0.20 (s, 3H), 0.30 (s, 3H), 1.03 (s, 9H), 1.05 (s, 9H), 2.16 (s, 3H), 3.03 (s, 3H), 3.28 (s, 3H), 3.46 (dd, 1H, $J_1 = 6.9$, $J_2 = 11.9$), 3.56 (d, 1H, $J = 8.2$), 3.66

(s, 3H), 4.06 (dd, 1H, J_1 = 6.9, J_2 = 11.9), 5.20-5.30 (m, 1H). IR (neat) υ 2116 (N_3), 1721(C=O) cm^{-1}. MS (EI 70ev) m/z 642 (M^+), 585 ($M^+ - C(CH_3)_3$). High-resolution MS (EI) m/z calcd for $C_{27}H_{46}N_4O_8Si_2S$: (M^+) 642.2575, found 642.2574. For **5b:** ^1H NMR ($CDCl_3$): δ 0.08 (s, 3H), 0.19 (s, 3H), 0.22 (s, 3H), 0.29 (s, 3H), 1.04 (s, 18H), 2.17 (s, 3H), 3.08 (s, 3H), 3.20 (s, 3H), 3.66 (s, 3H), 4.02 (dd, 1H, J_1 = 6.2, J_2 = 13), 4.08 (dd, 1H, J_1 = 6.2, J_2 = 13), 4.32 (d, 1H, J = 6.2), 4.72-4.80 (m, 1H). IR (neat) υ 2115 (N_3), 1722 (C=O) cm^{-1}. MS (EI 70ev) m/z 642 (M^+), 585 ($M^+ - C(CH_3)_3$). High-resolution MS (EI) m/z calcd for $C_{27}H_{46}N_4O_8Si_2S$: (M^+) 642.2575, found 642.2581.

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11. ^1H NMR ($CDCl_3$): δ 0.07 (s, 3H), 0.18 (s, 3H), 0.20 (s, 3H), 0.27 (s, 3H), 1.03-1.04 (broad s, 18H), 2.12 (s, 3H), 2.85-2.95 (m, 1H), 2.95-3.05 (m, 1H), 3.26 (s, 3H), 3.47 (d, 1H, J = 12.9), 3.64 (s, 3H), 3.98 (d, 1H, J = 12.9). ^{13}C NMR ($CDCl_3$): δ -4.59, -4.32, -3.39, 1.01, 12.08, 18.40, 18.61, 25.78, 25.92, 37.12, (38.54 and 38.72), (44.69 and 44.85), 51.71, 59.94, 100.69, (114.51 and 114.74), 136.12, (140.76 and 141.03), 144.26, (150.89 and 151.18), 166.75, 194.35. MS (EI) m/z 520 (M^+), 463 ($M^+ - C(CH_3)_3$). High-resolution MS m/z calcd for $C_{27}H_{44}N_2O_5Si_2$: (M^+) 520.2789, found 520.2788.
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13. 40% yield; ^1H NMR ($CDCl_3$): δ –0.08 (s, 3H), 0.09 (s, 3H), 0.21 (s, 3H), 0.30 (s, 3H), 1.06 (s, 18H), 2.18 (s, 3H), 2.75-2.80 (m, 1H, minor invertomer), 2.95-3.10 (m, 2H, minor invertomer), 3.2-3.30 (m, 1H, minor invertomer), 3.27 (s, 3H), 3.46 (dd, 1H, J = 4.0, 13.0, major invertomer), 3.67 (s, 3H), 3.79 (d, 1H, J = 13.0, major invertomer), 4.25-4.40 (m, 2H, major invertomer). MS (EI) m/z 520 (M^+), 488 (M^+ - OCH_3 - H), 463 ($M^+ - C(CH_3)_3$), 431 ($M^+ - C(CH_3)_3$ - OCH_3 - H), 416 ($M^+ - C(CH_3)_3$ - OCH_3 - CH_3 - H). MS (CI) m/z 521 (M + 1)$^+$, 489 (M^+ - OCH_3), 463 ($M^+ - C(CH_3)_3$), 431 ($M^+ - C(CH_3)_3$ - OCH_3 - H), 417 ($M^+ - C(CH_3)_3$ - OCH_3 - CH_3).
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15. ^1H NMR ($CDCl_3$): δ 0.07 (s, 3H), 0.20 (s, 3H), 0.23 (s, 3H), 0.28 (s, 3H), 1.02-1.06 (broad s, 18H), 2.12 (s, 3H), 2.13 (s, 3H), 2.23 (dd, 1H, J_1 = 2.1, J_2 = 4.4), 2.38 (d, 1H, J = 4.4), 3.24 (s, 3H), 3.36 (dd, 1H, J_1 = 2.1, J_2 = 12.2), 3.66 (s, 3H), 3.85 (d, 1H, J = 12.2). ^{13}C NMR ($CDCl_3$): δ -4.63, -4.26, 3.34, 0.02, 12.06, 18.28, 18.66, 25.79, 25.96, 43.95, 46.46, 48.26, 51.48, 52.12, 59.93, 100.35, 115.31, 134.41, 135.52, 140.78, 144.06, 151.33, 196.30. MS (EI 70ev) m/z 534 (M^+), 477 ($M^+ - C(CH_3)_3$). High-resolution MS m/z calcd for $C_{27}H_{44}N_2O_5Si_2$: (M^+) 534.2945, found 534.2945.
16. ^1H NMR ($CDCl_3$): ^1H NMR ($CDCl_3$): δ -0.20 (s, 9H), 0.05 (s, 3H), 0.20 (s, 3H), 0.26-28 (broad s, 6H), 1.04 (s, 18H), 1.61 (d, 1H, J = 13.6), 1.90 (d, 1H, J = 13.6), 2.07 (s, 3H), 2.25 (s, 3H), 2.27-2.38 (m, 2H), 3.34 (s, 3H), 3.51 (s, 3H), 3.47-3.57 (m, 1H), 3.67 (d, 1H, J = 11.7). MS (EI 70eV): m/z 622 (M^+). High-resolution MS m/z calcd for $C_{31}H_{58}N_2O_5Si_3$: (M^+) 622.3654, found 622.3648.
17. mp 123-125°C; ^1H NMR ($CDCl_3$) δ: 1.86 (s, 3H), 2.22 (s, 3H), 2.21-2.28 (m, 1H), 2.28 (d, 1H, J = 4.5), 3.06 (s, 3H), 3.42 (dd, 1H, J_1 = 12.6, J_2 = 1.7), 4.08 (d, 1H, J =12.6), 4.09 (s, 3H), 5.45 (s, 1H), 6.28 (s, 1H). MS (EI 70eV): m/z 302 (M^+). High-resolution MS m/z calcd for $C_{16}H_{18}N_2O_4$: (M^+) 302.1267, found 302.1267.

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