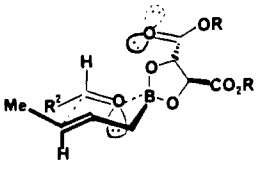
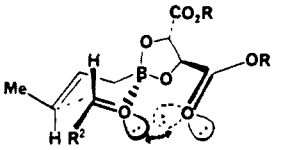
of 3,4-syn-4,5-anti diastereomers **8** and **11** that may derive from the *Z* olefin contaminant (2–4%) present in **2**. Only in the case of (+)-**2** and **3** does the amount of **8** (8%) exceed the level expected on the basis of the isomeric purity of the reagent.

It is clear from these results that reagent **2** is highly enantioselective since the stereochemistry at C(3) and C(4) of **6**, **7**, **9**, and **10** is controlled simply by selecting the appropriate enantiomer of **2**. The origin of asymmetry in these reactions is consistent with the stereoelectronic model proposed previously,[9] namely, that transition state A is favored as a consequence of n/n electronic repulsive interactions involving the indicated aldehydic oxygen atom and the β-face ester carbonyl that destabilizes B relative to A. Further studies and applications of these reagents in organic synthesis will be reported shortly.



A (favored)



B (disfavored)

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Electrophilic and Nucleophilic Character of the Carbon 10 Methylene Group in Mitosenes Revealed

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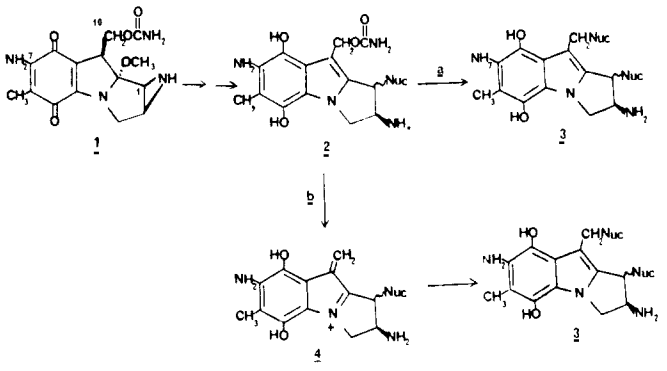
Received August 12, 1985

Mitomycin C (**1**) belongs to a class of antibiotics that exhibit potent, specific antitumor activity.[1] Recent studies[2-12] have supported the contention that the drug functions as a bioreductive alkylating agent.[13] Both carbons 1 and 10 in **1** have been invoked as the likely centers for nucleophilic attack by DNA.[1] Considerable evidence has been amassed indicating that carbon 1 is more reactive than carbon 10 toward nucleophiles at neutral pH in the presence of a reducing agent[2-12] and in dilute acid.[14-18] Moreover, isolation of both carbon 1 diastereomeric products in many of these reactions has suggested that ring opening of the aziridine moiety precedes attack by the nucleophile. In contrast to our considerable understanding of the mode of reaction at carbon 1, little is known about the corresponding mechanism for carbon 10 alkylation, a situation partly due to diminished reactivity and achirality of this site. Several possibilities can be envisioned for carbon 10 alkylation. Two of the more attractive routes are (1) S_N2 substitution of the carbamate group in **2** by the genetic material to yield **3** (Scheme I, path a) and (2) initial loss of the carbamate moiety in **2** to yield iminium ion **4**, followed by nucleophilic attack by DNA to produce the disubstituted adduct **3** (Scheme I, path b). In the second mechanism, ionization should be facilitated by delocalization of the electron pair on the indole nitrogen atom. Herein, we present evidence favoring the second pathway (route b) and demonstrate for the first time the potential nucleophilic character of carbon 10.

Scheme I



Scheme II

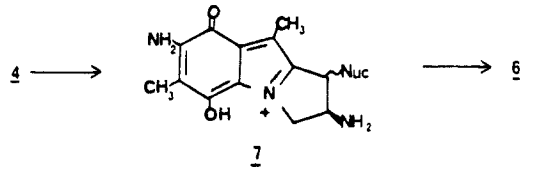


Table I. Percent Deuterium Incorporation Observed in the Conversion of **5** to **6**

entry	substrate	gas utilized	solvent utilized	% D incorporation at C-10 in **6**[a]
1	**5a**	D_2	CH_3OH	0
2	**5a**	H_2	CH_3OD	91
3	**5b**	D_2	C_2H_5OH	0
4	**5b**	H_2	C_2H_5OD	86

[a] Percent deuterium incorporation was determined by ^1H NMR. Accuracy of the measurement is ±5%.

Treatment of an 0.2 mM methanol solution of 1,2-*trans*-1-hydroxy-2,7-diaminomitosene[8,19] (**5a**) with PtO_2 and H_2 (27 °C, 7 min) led to the isolation of the carbon 10 methyl adduct **6a**[20] in approximately 80% yield after oxidative workup. No other significant products were detected by HPLC analyses.[21] A comparable result was obtained for the reduction of **5b** in etha-

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(19) Taylor, K. G.; Remers, W. A. *J. Med. Chem.* **1975**, *18*, 307–311.

(20) Compound **6a**: HPLC retention time 14.6 min; IR (KBr) 1607, 1385 cm^{-1}; ^1H NMR (300.1 MHz, CD_3OD) δ 1.70 (s, 3 H, C_6CH_3), 2.22 (s, 3 H, $C_{10}CH_3$), 3.78–3.81 (m, 1 H, C_2H), 3.87 (dd, 1 H, J = 3.8, 13.0 Hz, C_3H_β), 4.45 (dd, 1 H, J = 6.1, 13.0 Hz, C_3H_α), 4.69 (d, 1 H, J = 2.8 Hz, C_1H); ^{13}C NMR (75.5 MHz, Me_2SO-d_6) 8.47, 9.88, 53.19, 63.79, 73.26, 104.46, 113.22, 123.32, 127.11, 140.63, 147.22, 178.91 ppm (only one carbonyl carbon resonance was observed); UV (MeOH) λ_{max} 248, 309, 525 nm; field-desorption mass spectrum, m/z calcd for $C_{13}H_{15}N_3O_3$ 261.111, found 261.113.

(21) HPLC conditions: C_{18} μBondapak (ss) 3.9 mm × 15 cm; flow rate 1 mL/min at room temperature; gradient linear from 0% B to 50% B in 20 min; buffer A, aqueous 3 mM TEAP (pH 4.5); buffer B, 3 mM TEA in acetonitrile; wavelength of detection 254–312 nm.

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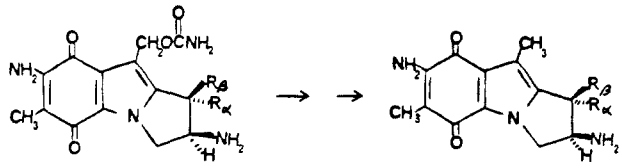
nol.[22,23] In both cases, the new carbon 10 methyl products **6a,b**



5a, R_β = H; R_α = OH
b, R_β = OH; R_α = H

6a, R_β = H; R_α = OH
b, R_β = OH; R_α = H

were readily identified by their spectroscopic properties. Of particular note, was the absence of the carbamate absorption at 1708 cm^{-1} in the infrared spectrum of **6a** and the appearance of a singlet at ~δ 2.25 in the ^1H NMR spectra of **6** for the carbon 10 methyl group.

Two mechanisms are likely for the formation of **6a,b**. One pathway (Scheme II) involves the tautomerization of **4** to **7** in the absence of an external nucleophile, followed by proton loss to produce the oxidized adduct **6**. Alternatively, catalytic hydrogenolysis of the carbamate group in **2** should generate the carbon 10 methyl derivative which then is reoxidized during the workup to yield **6**. This latter route is precedented since benzylic carbamates are readily hydrogenated to give the corresponding toluene derivatives.[24]

Substantiation for the first mechanism (Scheme II) was obtained by rerunning each of these reductions under slightly modified conditions. First, D_2 was substituted for H_2 (Table I, entries 1 and 3), while in a second experiment the O-deuterated alcohol (ROD) was used in place of the corresponding protonated solvent (ROH) (Table I, entries 2 and 4). Deuterium incorporation (86-91%) at carbon 10 was observed *only* in the second experiment, establishing solvent as the source of deuterium.[25] Notably, we obtained a similar result in an earlier study concerning the mechanism of carbon 1 ring opening in mitosenes.[7]

These results provide the first evidence for the ambidextrous (i.e., electrophilic[27] and nucleophilic) nature of the carbon 10 methylene unit in mitomycin C. Additional studies in progress are aimed at determining the generality and biological significance of this phenomenon.

Acknowledgment. We thank the National Institutes of Health (ROICA29756) and the National Institutes of Health sponsored Biomedical Research Support Grant Program at the University of Houston for their generous support of our work. We also express our appreciation to Dr. Gary Martin (College of Pharmacy) and Ed Ezell of this department for running the high-field NMR spectra and Dr. Stephen Reynolds (Exxon Research and Engineering Co.) for obtaining the field-desorption mass spectra. Grateful acknowledgment is made to both Dr. W. T. Bradner, Bristol-Myers Laboratories, Syracuse, NY, and Dr. I. Matsubara, Kyowa Hakko Kogyo Co., Ltd., Tokyo, Japan, for gifts of mitomycin C.

(22) Compound **6b**: HPLC retention time 16.4 min; ^1H NMR (300.1 MHz, CD_3OD) δ 1.75 (s, 3 H, C_6CH_3), 2.27 (s, 3 H, $C_{10}CH_3$), 3.68 (dd, 1 H, J = 8.5, 12.2 Hz, C_3H_β), 3.77-3.86 (m, 1 H, C_2H), 4.44 (dd, 1 H, J = 7.2, 12.2 Hz, C_3H_α), 4.72 (d, 1 H, J = 5.3 Hz, C_1H); UV (MeOH) λ_{max} = 248, 309, 350 (sh), 525 nm.

(23) Reduction of **5b** was run in ethanol (37 °C, 7 min) rather than methanol due to the enhanced solubility of the starting material in the former solvent. Although HPLC analysis indicated that the reaction proceeded cleanly, lower isolated yields for **6b** were observed in these reactions.

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(25) ^1H NMR spectroscopy provided a convenient method to monitor these reactions. Monodeuteration at carbon 10 led to an appearance of a 1:1:1 multiplet (J_{HD} ~ 2.07 Hz) upfield (~0.02 ppm) from the singlet normally associated with the carbon 10 methyl group. Both the upfield shift and the observed coupling constant are diagnostic of deuterium incorporation at this site.[26]

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(27) This property should be modulated by the type of substituent present at carbon 7.

Organometallic Derivatives of the Tetrathiometallates: Syntheses, Structures, and Reactions of $MS_4[Rh(COD)]_2$ and $MS_4[(C_5H_5)Ru(PPh_3)]_2$ (M = Mo, W)

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We wish to describe experiments which demonstrate that the tetrathiometallate(VI) compounds[1] can function as ligands for reactive low-valent, organometallic complexes.[2] Previous work on the coordination chemistry of MoS_4^{2-} and WS_4^{2-} has focused almost exclusively on their inorganic coordination compounds.

The complex $WS_4Rh_2(COD)_2$ (**1**) (COD = 1,5-cyclooctadiene) was readily prepared by the reaction of stoichiometric quantities of $(Ph_4P)_2WS_4$ with $[Rh(COD)Cl]_2$ in acetonitrile. After 18 h, the product was collected and recrystallized from CH_2Cl_2/CH_3CN to give **1** in 80% yield as dark red crystals (eq 1).[3] The inter-

$$Rh_2Cl_2(COD)_2 + WS_4^{2-} \rightarrow (COD)RhS_2WS_2Rh(COD) + 2Cl^- \quad (1)$$

mediate in this synthesis, $WS_4Rh(COD)^-$, could be isolated as its tetraphenylphosphonium salt by the addition of a second equivalent of $(Ph_4P)_2WS_4$ to $WS_4Rh_2(COD)_2$.[4] $WS_4Ir_2(COD)_2$ and $MoS_4Rh_2(COD)_2$ may also be prepared in an analogous manner, although the $MoRh_2$ complex is somewhat unstable in solution. Compound **1** was further characterized by X-ray diffraction (Figure 1).[5]

Compound **1** is a versatile synthetic intermediate as evidenced by its substitution chemistry (Scheme I). Addition of 4 equiv of PPh_3 to a CH_2Cl_2 solution of **1** results in the formation of a deep purple solution from which we isolated $WS_4Rh_2(PPh_3)_4$ (**2**).[6] Similarly, addition of 2 equiv of 1,2-bis(diphenylphosphino)ethane (dppe) results in the formation of the bis-chelated $WS_4Rh_2(dppe)_2$ (**3**).[7] Although **1** gives intractable products when treated with CO, $WS_4[Rh(PPh_3)CO]_2$ (**4**) could be prepared by carbonylation of **2** or by treatment of **1** with CO in the presence of 2 equiv of

(1) Müller, A.; Diemann, E.; Jostes, R.; Bögge, H. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 934. Coucouvanis, D. *Acc. Chem. Res.* **1981**, *14*, 201. Holm, R. H. *Chem. Soc. Rev.* **1981**, *10*, 455.

(2) Organometallic derivatives of the tetrathiometallates have been prepared previously (Adam, G. J. S.; Green, M. L. H. *J. Organomet. Chem.* **1981**, *208*, 299. Ruffing, C. J.; Rauchfuss, T. B. *Organometallics* **1982**, *1*, 400) but only once has their reactivity been examined: Kovacs, J. A.; Bashkin, J. K.; Holm, R. H. *J. Am. Soc.* **1985**, *107*, 1784.

(3) All new compounds were isolated in analytically pure form and were characterized by ^1H and ^{31}P NMR and mass spectrometry. $WS_4Rh_2(COD)_2$: IR (Nujol) 434, 403 cm^{-1}.

(4) $(PPh_4)[WS_4Rh(COD)]$: FAB^- MS 523 ($WS_4Rh(COD)^-$); FAB^+ MS 339 (Ph_4P^+); IR (Nujol) 492, 484, 448 cm^{-1}.

(5) A crystal was obtained by cleavage of a twinned specimen. Systematic absences uniquely defined the space group as $P2_1/c$. Crystal parameters of a = 7.314 (2) Å, b = 10.774 (2) Å, and c = 25.323 (5) Å; β = 91.51 (2)°; V = 1994.8 (9) Å^3; Z = 4 were determined. The data were collected on a Nicolet R3 diffractometer at ambient temperatures with monochromatized Mo Kα (λ = 0.71073 Å) radiation. Of the 3610 reflections collected 2594 unique reflections with $F_c \geq 3\sigma(F_o)$ were used in the structure solution and refinement. The W, Rh, and S atoms were located by direct methods (SOLV-SHELXTL). Anisotropic temperature factors were used for the refinement (blocked cascade) of all non-hydrogen atoms. Hydrogen atoms were refined isotropically. Final structure refinement converged to R_F = 3.6% and R_{wF} = 3.7%.

(6) $WS_4Rh_2(PPh_3)_4$: ^{31}P NMR (all ^{31}P NMR spectra were measured at 101 MHz on CH_2Cl_2 solutions and are quoted in ppm vs. 85% H_3PO_4 external standard) 43.9 (d, $|J(^{103}Rh,^{31}P)|$ = 173 Hz).

(7) $WS_4Rh_2(dppe)_2$: ^{31}P NMR 71.55 (d, $|J(^{103}Rh,^{31}P)|$ = 164 Hz); FAB^+ MS 1316(MH^+).

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