calculation of the difference of free energy of activation ($\Delta\Delta G^{\ddagger}$) for the two diastereotopic reactions of 0.20 kcal/mol (20 °C).

These results are of interest both from theoretical and practical viewpoints. Although the degree of resolution achieved in these preliminary experiments is low, the relatively large difference in rate of reaction of the two enantiomers has encouraged further experiments designed to explore the potential and origin of this phenomenon.

Acknowledgment. The authors gratefully acknowledge helpful discussions with Dr. F. A. Johnson.

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(4) Based on $[\alpha]_D^{25}$ +17.45° reported by H. H. Zeiss, *J. Am. Chem. Soc.*, **73**, 2391 (1951).
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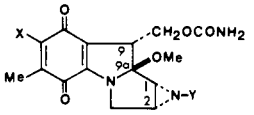
Synthetic Studies toward Mitomycins. 2.[1] Total Synthesis of *dl*-Porfiromycin[2]

Sir:

The mitomycins (**1a–e**) are a class of antibiotics with activity against gram-positive and gram-negative bacteria and also against several kinds of tumors.[3] Since their structures were first elucidated in 1962,[3] numerous synthetic approaches to the mitomycins have been reported.[4] However, the mitomycins themselves have not yet been synthesized. In this communication, we wish to report the first total synthesis of *dl*-porfiromycin (**1d**) by the synthetic route that we recently used for the synthesis of deiminomitomycin A.[1]



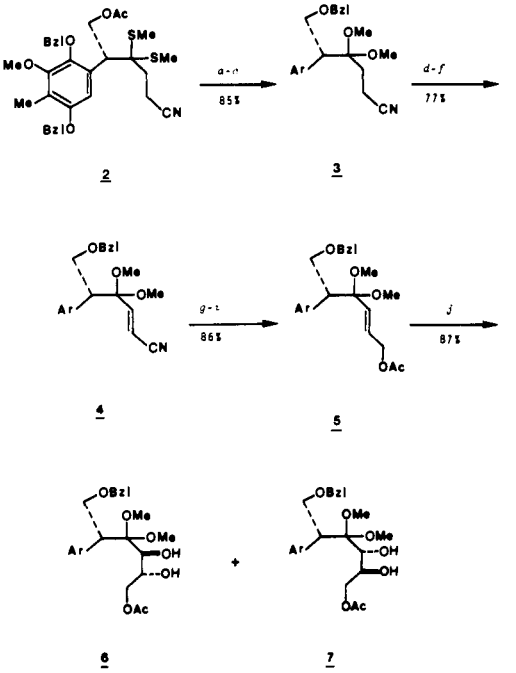
1a, mitomycin A, X = OCH_3, Y = H
b, mitomycin B[5]
c, mitomycin C, X = NH_2, Y = H
d, porfiromycin, X = NH_2, Y = CH_3
e, mitiromycin[6]

Scheme I summarizes the synthesis of diols **6** and **7** from nitrile **2**.[1] The ^{1}HNMR spectra clearly showed that the olefinic bonds of **4** and **5** were exclusively trans. Osmium tetroxide oxidation of **5** yielded about a 1:1 mixture of diastereomeric diols **6**[7] (oil; ^{1}H NMR ($CDCl_3$) δ 1.96 (3 H, s), 2.21 (3 H, s), 2.91 (3 H, s), 3.28 (3 H, s), 3.80 ppm (3 H, s)) and **7**[7] (oil; ^{1}H NMR ($CDCl_3$) δ 1.96 (3 H, s), 2.21 (3 H, s), 3.08 (3 H, s), 3.41 (3 H, s), 3.83 ppm (3 H, s)) which could be separated by silica gel chromatography.[8] The stereochemistry assignments of **6** and **7** were made from the experiments discussed later.

Scheme II summarizes the transformation of **6** into dibenzylamino-*N*-methylaziridine **10**[7] (oil; ^{1}H NMR ($CDCl_3$) δ 2.18 (6 H, s), 3.01 (3 H, s), 3.15 (3 H, s), 3.76 ppm (3 H, s)). The high regio- and stereospecificity realized in this transformation is mainly due to the fact that the C-1 position[9] is sterically hindered by the adjacent dimethyl ketal group.

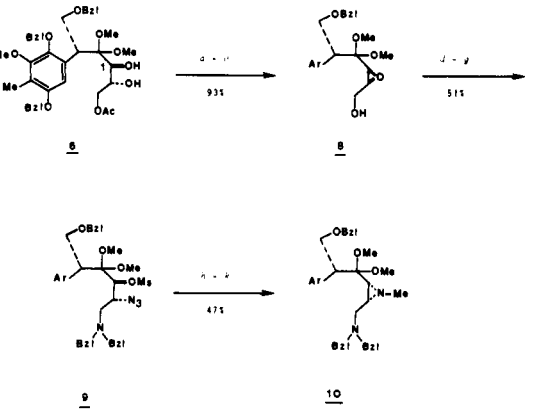
The eight-membered quinone **11**[7] (deep red needles; mp 165–168 °C; M^+ obsd 352.1641, calcd for $C_{17}H_{24}O_6N_2$ 352.1634; ^{1}H NMR ($CDCl_3$) δ 1.85 (3 H, s), 2.41 (3 H, s), 3.13 (3 H, s), 3.36 (3 H, s), 4.01 (3 H, s); UV (CH_3OH) λ_{max} 220 nm (log ϵ 4.37), 305 (4.24), 505 (3.25)) was obtained from **10** in 35–40% yield by the procedure which we had previously developed.[1] An analogous synthetic route starting with the diastereomeric diol **7** resulted in the eight-membered quinone **12**[7] (deep red needles; mp 104–105 °C dec; M^+ obsd 352.1639, calcd for $C_{17}H_{24}O_6N_2$ 352.1634; ^{1}H NMR ($CDCl_3$) δ 1.81 (3 H, s), 2.44 (3 H, s), 3.14 ($^3/_5 \times$ 3 H,[10] s), 3.38 (3 H, s), 3.46 ($^2/_5 \times$ 3 H,[10] s), 4.01 (3 H, s); UV (CH_3OH) λ_{max} 221 nm (log ϵ 4.44), 306 (4.24), 500 (3.27)). On addition of 1 drop of 0.1 N hydrochloric acid, the UV spectrum (methanol) of **11** changed smoothly to a new spectrum, characteristic of the mitosene (**13** or its degradation products) chromophore.[11] However, under the same conditions, the UV spectrum of **12** was unchanged. This observed reactivity difference suggests a cis relationship between the aziridine ring and the hy-

Scheme I

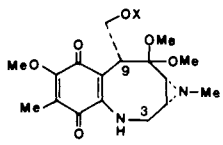


[a] $NaOCH_3/CH_3OH-CH_2Cl_2/25$ °C. [b] $C_6H_5CH_2Br/KH/DMF/25$ °C. [c] $HgCl_2/CH_3OH/25$ °C. [d] LDA/THF/−78 °C. [e] $C_6H_5SeBr/THF/-78$ °C. [f] $H_2O_2/THF-EtOAc/25$ °C.[20] [g] DIBAL/$CH_2Cl_2-C_6H_5CH_3/0$ °C. [h] $NaBH_4/CH_3OH-CH_2Cl_2/0$ °C. [i] Ac_2O–Py/25 °C. [j] OsO_4/Py–THF/25 °C.

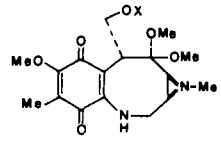
Scheme II



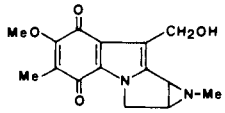
[a] $MsCl/Et_3N/CH_2Cl_2/0$ °C. [b] NaH/DMF/25 °C. [c] $NaOCH_3/CH_3OH-CH_2Cl_2/25$ °C. [d] LiN_3/DMF/150 °C. [e] Ms_2O/Py/25 °C. [f] $C_6H_5CH_2NH_2/150$ °C. [g] $C_6H_5CH_2Br/K_2CO_3$/acetone/reflux. [h] $P(OCH_3)_3$/THF/reflux. [i] NaH/THF/25 °C. [j] $LiAlH_4/Et_2O/0$ °C. [k] CH_3I/K_2CO_3/acetone/reflux.



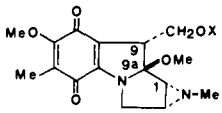
11, X = H
14, X = $CO_2C_6H_5$
16, X = C_6H_5



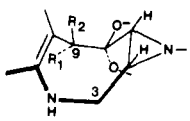
12, X = H
15, X = $CO_2C_6H_5$



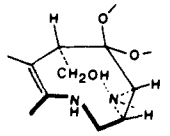
13



17, X = H
18, X = $CONH_2$



11a, R_1 = CH_2OH, R_2 = H
12a, R_1 = H, R_2 = CH_2OH



11b

droxymethyl group in the eight-membered quinone which cyclizes to the mitosene **13.** The following argument is proposed. Two tub conformations[12] **11a** and **11b** (slightly twisted) are considered as possible preferred conformations for **11.** There is no serious increase in steric hindrance in bringing **11a** or **11b** to the transition state for the transannular cyclization. Examination of a molecular model suggests that the preferred conformation of the trans compound **12** is most likely the tub conformation **12a** corresponding to **11a,** because the other tub conformation corresponding to **11b** experiences considerable steric compression between the aziridine and quinone rings, and also between the hydroxymethyl and amide NH groups. There is a serious increase in steric hindrance in bringing **12a** to the transition state for the transannular cyclization.

We anticipated that the preferred conformation of **11** would be **11b** because of the hydrogen-bond stabilization indicated. Valuable information was obtained from the difference in stability of phenyl carbonates **14**[7] and **15,**[7] synthesized, respectively, from **11** and **12** under standard conditions ($ClCO_2C_6H_5$/Py/0 °C). *cis*-Phenyl carbonate **14** decomposed to phenyl ether **16**[7] on standing at room temperature for 2 days, while *trans*-phenyl carbonate **15** was stable under the same conditions. Furthermore, a strong peak corresponding to (M^+ − 44) was observed in the mass spectrum of **14,** while no such peak was observed in the mass spectrum of **15.**[13] These results can be rationalized in terms of an intramolecular interaction between the aziridine and phenyl carbonate groups which is *only* possible in the conformation corresponding to **11b.** Thus, this conformation must exist at least to some extent even for **14.** All of the ^1H NMR signals of **11** in $CDCl_3$ are sharp, suggesting that **11** exists in one preferred conformation; i.e., **11b,** or that interconversion between two conformations **11a** and **11b** is rapid. The second possibility is unlikely because a serious interaction between the hydrogen atoms at C-3 and C-9 occurs during the interconversion. This analysis suggested that the transannular cyclization of **11** would result in the desired stereochemistry with respect to the C-1, C-9a, and C-9 positions.[14]

Trityl tetrafluoroborate[15,16] (CH_2Cl_2/25 °C) smoothly effected the transannular cyclization of **11** to yield exclusively decarbamoyl-*N*-methylmitomycin A (**17**)[7] (deep purple needles; mp 99–101 °C dec; M^+ obsd 320.1387, calcd for $C_{16}H_{20}O_5N_2$ 320.1372; ^1H NMR ($CDCl_3$) δ 1.84 (3 H, s), 2.26 (3 H, s), 3.16 (3 H, s), 4.04 ppm (3 H, s); UV (CH_3OH) λ_{max} 216 nm (log ϵ 4.20), 320 (3.97), 530 (3.08)) in 90% yield. The synthetic substance was identical with an authentic sample prepared from mitomycin A (**1a**)[17] in two steps (1, $NaOCH_3$/CH_3OH–C_6H_6/25 °C;[18] 2, CH_3I/K_2CO_3/acetone/reflux[11,19]) in all respects (^1H NMR, UV, mass spectrum, IR, and TLC). Decarbamoyl-*N*-methylmitomycin A (**17**) was converted to *N*-methylmitomycin A (**18**)[7,11] (mp 172–174 °C dec) in two steps (1, $COCl_2/C_6H_5N(CH_3)_2/CH_2Cl_2$–$C_6H_5CH_3$/25 °C; 2, NH_3/CH_2Cl_2–$C_6H_5CH_3$/0 °C) in 85% yield. The transformation of *N*-methylmitomycin A (**18**) to porfiromycin (**1d**) has been previously reported.[11]

The total synthesis of mitomycins A, B, and C by the route reported is in progress in our laboratory.

Acknowledgment. Financial assistance from National Institutes of Health, National Science Foundation, and Hoffmann-La Roche is gratefully acknowledged.

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(1) F. Nakatsubo, A. J. Cocuzza, D. E. Keeley, and Y. Kishi, *J. Am. Chem. Soc.*, **99,** 4835 (1977).
(2) This paper was presented at the 25th National Organic Chemistry Symposium, Morgantown, W. Va., June 19–23, 1977, by Y. Kishi.
(3) See, for example, "The Merck Index", M. Windholz, Ed., 9th ed, Merck & Co., Rahway, N.J., 1976, p 807 ff and references cited therein.
(4) See the references cited in part I of this series.
(5) The structure of mitomycin B including its absolute configuration was recently confirmed by x-ray crystallography: R. Yahashi and I. Matsubara, *J. Antibiot.*, **29,** 104 (1976).
(6) G. O. Morton, G. E. Van Lear, and W. Fulmor, *J. Am. Chem. Soc.*, **92,** 2588 (1970).
(7) Satisfactory spectroscopic data were obtained for this substance.
(8) We have recently developed a method to transform diol **7** into epoxide **8** in six steps (1, $NaOCH_3/CH_3OH$/25 °C; 2, MsCl/Py–CH_2Cl_2/25 °C; 3, K_2CO_3/CH_2Cl_2/25 °C; 4. Ms_2O/Py/25 °C; 5. KOAc/18-crown-6/DMF/120 °C; 6, $NaOCH_3/CH_3OH$–CH_2Cl_2/25 °C). The overall yield was 56%.
(9) Numbering in this paper corresponds to that of the mitomycins.
(10) Apparently **12** exists as a mixture of two conformers.
(11) J. S. Webb, D. B. Cosulich, J. H. Mowat, J. B. Patrick, R. W. Broschard, W. E. Meyer, R. P. Williams, C. F. Wolf, W. Fulmor, C. Pidacks, and J. E. Lancaster, *J. Am. Chem. Soc.*, **84,** 3185 (1962).
(12) See, for example, *Top. Stereochem.*, **7,** 128 (1973).
(13) The corresponding phenyl carbonate in the deiminomitomycin A series is also stable, and does not give a peak of (M^+ − 44) in the mass spectrum.[1]
(14) One can reach the same conclusion about the stereochemistry outcome of the transannular cyclization of **11,** even for the second possibility.
(15) D. H. R. Barton, P. D. Magnus, G. Smith, G. Streckert, and D. Zurr, *J. Chem. Soc., Perkin Trans. 1,* 542 (1972).
(16) We have recently discovered that HBF_4 (CH_2Cl_2/25 °C) or $HClO_4$ (CH_2Cl_2/25 °C) effects the transannular cyclization of **11** as well as $(C_6H_5)_3CBF_4$ does. The effective reagent under the trityl tetrafluoroborate conditions is most likely HBF_4 liberated from $(C_6H_5)_3CBF_4$ and moisture since 0.4 equiv of this reagent gave the best result. Hydrogen chloride or boron trifluoride etherate in methylene chloride at room temperature gave less satisfactory results because elimination of methanol from the produced mitosane **17** could not be controlled under these conditions. The conditions for the transannular cyclization used in the synthesis of deiminomitomycin A[1] could not be applied to **11,** because transketalization of **11** (and **14**) to the corresponding hemithioketal was unsuccessful under a variety of conditions. The trityl tetrafluoroborate condition was not successful for the synthesis of deiminomitomycin A because elimination of methanol from the produced deiminomitomycin A could not be controlled under these conditions.
(17) We are indebted to Dr. J. S. Webb, Lederle Laboratories, for a sample of mitomycin A.
(18) S. Kinoshita, K. Uzu, K. Nakano, and T. Takahashi, *J. Med. Chem.*, **14,** 109 (1971).
(19) S. Kinoshita, K. Uzu, K. Nakano, M. Shimizu, T. Takahashi, and M. Matsui, *J. Med. Chem.*, **14,** 103 (1971).
(20) D. W. Brattesani and C. H. Heathcock, *Tetrahedron Lett.*, 2279 (1974).

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On the Regioselectivity of the Catalyzed and Uncatalyzed Diels–Alder Reaction

Sir:

We wish to report that the regioselectivity of the Diels–Alder reaction can be varied dramatically by a combination of the competing orientating influences of sulfur and oxygen on