Rossi and J. F. Bunnett, *ibid.*, **38**, 3020 (1973); (c) J. V. Hay, T. Hudlicky, and J. F. Wolfe, *J. Am. Chem. Soc.*, **97**, 374 (1975); (d) M. F. Semmelhack, B. P. Chong, R. D. Stauffer, T. D. Rogerson, A. Chong, and L. D. Jones, *ibid.*, **97**, 2507 (1975).
(3) The ^{1}H NMR spectra of **3** and **4** are consistent with the assigned stereochemistry: **3** (CCl_4, TMS), δ 7.1 (br s, 5 H), 6.3 (d, J = 12, 1 H), 5.5 (d, J = 12, 1 H), 3.6 (q, J = 6.5, 2 H), 1.3 (s, 6 H), 1.0 (t, J = 6.5, 3 H); **4** (CCl_4, TMS), δ 7.1 (br s, 5 H), 6.2 (s, 2 H), 4.1 (q, J = 6.8, 2 H), 1.3 (s, 6 H), 1.2 (t, J = 1.3, 3 H). Final assignment of stereochemistry is based on FSO_3H-catalyzed isomerization of either **3** or **4** to an equilibrium mixture containing 95% of isomer assigned trans stereochemistry (**4**).
(4) (a) M. W. Rathke and D. F. Sullivan, *Tetrahedron Lett.*, 4249 (1972). (b) Katzenellenbogen has reported increased amounts of γ-alkylation associated with copper enolates of certain α,β-unsaturated esters: J. A. Katzenellenbogen and A. L. Crumrine, *J. Am. Chem. Soc.*, **96**, 5662 (1974).
(5) Ester enolate solutions were prepared by addition of the appropriate ester to THF solutions of lithium diisopropylamide at dry ice temperature. The resultant solutions were maintained at −78 °C and transferred to the catalyst suspension by Teflon tubing and argon pressure.
(6) For a recent review of the stereochemical features of vinylic radical processes, see L. A. Singer in "Selective Organic Transformation", Vol. II, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N.Y. 1970, p 269.
(7) For example, a classical nucleophilic aromatic substitution mechanism[7a] is postulated for substitution reactions of the halogen in π-(halobenzene)chromium tricarbonyl complexes.[7b] The observed dependence of yield and reactivity on leaving group is F > Cl > I.[7c] (a) Cf. J. F. Bunnett, *Quart. Rev., Chem. Soc.*, **12**, 1 (1958). (b) M. F. Semmelhack and H. T. Hall, *J. Am. Chem. Soc.*, **96**, 7092 (1974). (c) M. F. Semmelhack and H. T. Hall, *ibid.*, **96**, 7091 (1974).
(8) (a) M. F. Semmelhack, R. D. Stauffer, and T. D. Rogerson, *Tetrahedron Lett.*, 4519 (1973); (b) K. Tamao, M. Zembayashi, Y. Kiso, and M. Kumada, *J. Organomet. Chem.*, **55**, C91 (1973); (c) L. Cassar, *ibid.*, **54**, C57 (1973); (d) J. P. Corriu and J. P. Masse, *J. Chem. Soc., Chem. Commun.*, 144 (1972).
(9) (a) G. W. Parshall, *J. Am. Chem. Soc.*, **96**, 2360 (1974); (b) D. G. Morrell and J. K. Kochi, *ibid.*, **97**, 7262 (1975).
(10) Tetrakis(tri-*n*-butylphosphine)nickel(0) was prepared essentially as described by M. Aresta, C. F. Nobile, and A. Sacco, *Inorg. Chim. Acta*, **12**, 167 (1975).
(11) Alfred P. Sloan Fellow, 1975-1977.

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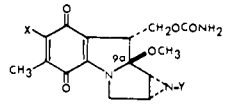
Synthetic Studies toward Mitomycins. 1. Total Synthesis of Deiminomitomycin A

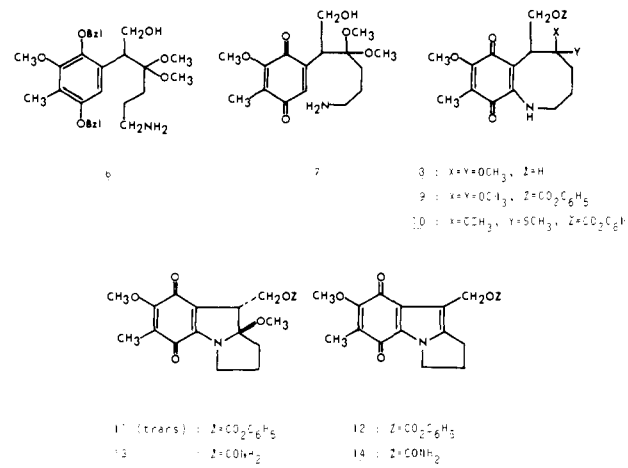
Sir:

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.[1] Since their structures were first elucidated in 1962,[1] numerous synthetic approaches to the mitomycins have been reported.[2] However, the mitomycins



1a : mitomycin A; X=OCH$_3$, Y=H
1b : mitomycin B; see reference 5.
1c : mitomycin C; X=NH$_2$, Y=H
1d : porfiromycin; X=NH$_2$, Y=CH$_3$
1e : methylmitomycin; see reference 5.

themselves have not yet been synthesized. It seemed to us that the most difficult problem in synthesizing the naturally occurring mitomycins is related to introducing the 9a methoxy group since this is known to be the most labile functionality present in the target molecules.[3] In this communication, we wish to report a total synthesis of deiminomitomycin A (**13**). This synthesis involves two key cyclizations: the intramolecular Michael reaction used to construct the eight-membered ring of **8** and the trans-annular cyclization of **10** to **11** under conditions mild enough to introduce and preserve the 9a methoxy group.

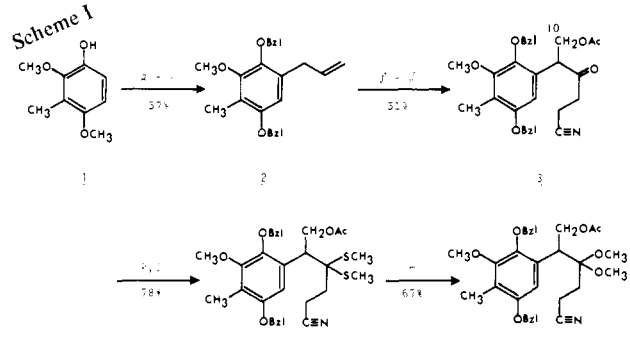


6 **7** **8** : X=Y=OCH$_3$, Z=H
9 : X=Y=OCH$_3$, Z=CO$_2$C$_6$H$_5$
10 : X=CH$_2$, Y=SCH$_3$, Z=CO$_2$C$_6$H$_5$
11 (trans) : Z=CO$_2$C$_6$H$_5$ **12** : Z=CO$_2$C$_6$H$_5$
13 : Z=CONH$_2$ **14** : Z=CONH$_2$

Scheme I summarizes the 13-step synthesis of nitrile **5** from 2,4-dimethoxy-3-methylphenol (**1**)[6,7] readily available from 2,6-dimethoxytoluene. Although the carbon atom at the 10 position[8] could be introduced directly by Claisen rearrangement (i.e., $ArOCH_2CH{=}CHCH_2OCH_2C_6H_5 \rightarrow Ar'CH(CH_2OCH_2C_6H_5)CH{=}CH_2$), we found the route shown to be more practical. All the steps in Scheme I proceeded straightforwardly except for the ketallization of **3** (or the corresponding primary alcohol) to **5**. Owing to difficulties encountered in avoiding the elimination of acetic acid (or water) under various ketallization conditions, the 3-step transformation of **3** to **5** was used. The product of step *k* was the thioketal thioiminoether which was converted to thioketal nitrile **4** by brief treatment with triethylamine in methanol at room temperature.

Lithium aluminum hydride reduction of **5** in ether gave amine **6**[9] (mp 60–62 °C), which was subjected to hydrogenolysis (1 atm of H_2, Pd on C/CH_3OH, room temperature, 15 min) followed by treatment with oxygen (1 atm of O_2, CH_3OH, room temperature, 20–40 h) to afford the eight-membered quinone **8**[9] (red needles; mp 110–112 °C; UV (CH_3OH) 218 nm (log ϵ 4.36), 304 (4.05), 509 (3.15); ^{1}H NMR ($CDCl_3$) 1.87 (3 H, s), 3.20 (3 H, s), 3.27 (3 H, s), 4.07 ppm (3 H, s)) in 40–50% yield. Clearly, an intermediate in this transformation was benzoquinone **7**, the primary amino group of which cyclized intramolecularly to the quinone moiety in the Michael fashion. Although an eight-membered ring was formed, the Michael reaction was extremely facile and **8** was

Scheme I



1 **2** **3** **4** **5**

[a] $CH_2{=}CHCH_2Br/K_2CO_3$/acetone, reflux, mp 32–33 °C.[9] [b] $C_6H_5N(CH_3)_2$, reflux, oil.[10] [c] 70% HNO_3/HOAc, room temperature, oil.[10] [d] Zn/HOAc, 0 °C, mp 110–113 °C.[9] [e] $C_6H_5CH_2Br/K_2CO_3$/DME–DMF, reflux, mp 41–42 °C.[9] [f] $H_2O_2/C_6H_5CN/K_2CO_3/CH_3OH$–dioxane, room temperature, mp 56–57 °C.[9] [g] LDA/CH_3CN, −30 °C, oil.[10] [h] CrO_3/H_2SO_4/aqueous acetone, mp 99–101 °C.[9] [i] $NaOCH_3/(CH_2O)_3/CH_3OH$–THF, 0 °C, mp 86–87 °C.[9] [j] Ac_2O/Py, 0 °C, oil.[10] [k] $CH_3SH/BF_3{\cdot}2AcOH$, −30 °C, oil.[10] [l] Et_3N/CH_3OH, room temperature, mp 103–104 °C.[9] [m] $HgCl_2/Et_3N/CH_3OH$, mp 88–89 °C.[9]

the only isolable product. Phenyl chloroformate treatment of **8** in methylene chloride containing pyridine gave phenylcarbonate **9**[10] (red amorphous solid; M^+ obsd 445.1745, calcd for $C_{23}H_{27}O_8N$ 445.1736) in 85% yield. Careful treatment of **9** with methanethiol containing a catalytic amount of boron trichloride etherate at -45 °C afforded hemithioketal **10**[10] (red amorphous solid; M^+ obsd 461.1521, calcd for $C_{23}H_{27}O_7SN$ 461.1508; ^1H NMR ($CDCl_3$) 1.88 (3 H, s), 1.91 (3 H, s), 3.40 (3 H, s), 4.06 ppm (3 H, s)) in 73% yield. The ^1H NMR spectrum indicated that **10** was a single substance; however, its stereochemistry was not established.

The crucial transannular cyclization of **10** was effected by mercuric chloride in methylene chloride containing a small amount of triethylamine. The product (**11**)[10] (purple amorphous solid; M^+ obsd 413.1485, calcd for $C_{22}H_{23}O_7N$ 413.1474) was isolated as about 1:1 mixture[11] of cis-trans isomers by preparative layer chromatography (Merck Al_2O_3 Type T, 1:4 EtOAc-CH_2Cl_2) in 67% yield.[12] Upon contact with weak acid such as a catalytic amount of acetic acid in methylene chloride or thin layer chromatography on silica gel, **11** was smoothly and quantitatively converted to the known indolequinone **12**[9,13] (mp 137–138 °C).

Brief ammonia treatment of **11** (as a 1:1 cis-trans mixture) gave deiminomitomycin A (**13**) in over 90% yield. The ^1H NMR spectrum showed that the initially isolated product was about a 1:1 mixture of cis-trans isomers. The ^1H NMR signal of the 9a methoxy group appears at 3.14 ppm in one isomer, while at 3.32 ppm in the other isomer. The trans stereochemistry was assigned to the isomer with the chemical shift of 3.14 ppm because the 9a methoxy group signal appears at 3.20 ppm in the ^1H NMR spectrum of mitomycins A.[14] During attempted separation of the isomer by preparative layer chromatography (Merck Al_2O_3 Type T, 2:98 CH_3OH-CH_2Cl_2), most of the cis isomer decomposed to the known indolequinone **14**[9,14] (mp 204–206 °C), while the bulk of the trans isomer remained intact. Thus, deiminomitomycin A (**13**)[10] (purple amorphous solid; M^+ obsd 336.1329, calcd for $C_{16}H_{20}O_6N_2$ 336.1321; UV (CH_3OH) 219 nm (log ϵ 4.26), 319 (4.04), 525 (3.18); ^1H NMR ($CDCl_3$) 1.87 (3 H, s), 3.14 (3 H, s), 4.07 ppm (3 H, s)) could be isolated in 30–35% yield from **11**.[12] The observed difference in stability supports the stereochemistry assignment based on the ^1H NMR spectrum. Deiminomitomycin A (**13**) could be quantitatively converted to indolequinone **14** under such weakly acidic conditions as a catalytic amount of acetic acid in methylene chloride or even thin layer chromatography on silica gel. It is interesting to note that deiminomitomycin A is *much less* stable than the naturally occurring mitomycins.

Application of these methods to a total synthesis of the mitomycins is in progress in our laboratories.

Acknowledgment. Financial assistance from National Science Foundation, Milton Fund, and Hoffmann-La Roche Co. is gratefully acknowledged.

References and Notes

(1) See, for example, "The Merck Index 9th Edition, M. Windholz, Ed., Merck & Co. Inc., Rahway, N.J., 1976, p 6060 ff, and references cited therein.
(2) For those synthetic approaches reported before spring, 1974, see G. J. Siuta, R. W. Franck, and R. J. Kempton, *J. Org. Chem.*, **39**, 3739 (1974), and references cited therein; G. Leadbetter, D. L. Fost, N. N. Ekwurlbe, and W. A. Remers, *ibid.*, **39**, 3580 (1974); T. Takada, Y. Kosugi, and M. Akiba, *Tetrahedron Lett.*, 3283 (1974); J. W. Lown and T. Itoh, *Can. J. Chem.*, **53**, 960 (1975); T. Kametani, K. Takahashi, M. Ihara, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 389 (1976); T. Kametani, T. Ohsawa, K. Takahashi, M. Ihara, and K. Fukumoto, *Heterocycles*, **4**, 1637 (1976); T. Kametani, K. Takahashi, Y. Kigawa, M. Ihara, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 28 (1977); D. R. Crump, R. W. Franck, R. Gruska, A. A. Ozorio, M. Pagnotta, G. Suita, and J. G. White, *J. Org. Chem.*, **42**, 105 (1977).
(3) See, for example, S. Kinoshita, K. Uzu, K. Nakano, M. Shimizu, T. Takahashi, and M. Matsui, *J. Med. Chem.*, **14**, 103 (1971).
(4) 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).
(5) G. O. Morton, G. E. Van Lear, and W. Fulmor, *J. Am. Chem. Soc.*, **92**, 2588 (1970).
(6) R. Royer, P. Demerseman, A.-M. Laval-Jeantet, J.-F. Rossignol, and A. Cheutin, *Bull. Soc. Chim. Fr.*, 1026 (1968).
(7) We considerably improved the overall yield of **1** from 2,6-dimethoxytoluene by the following sequence of reactions, i.e., (1) $Cl_2CHOCH_3/TiCl_4/CH_2Cl_2$, 0 °C, (2) MCPBA/$CH_2Cl_2$, 0 °C, (3) $NaOCH_3$ (0.1 equiv), CH_3OH, 0 °C. The overall yield was 95% yield or better in 100-g scale experiments.
(8) Numbering in this paper corresponds to that of the mitomycins.
(9) Satisfactory spectroscopic and analytical data were obtained for this substance.
(10) Satisfactory spectroscopic data including exact mass spectrum were obtained for this substance.
(11) The transannular cyclization of the acetate (i.e., X = OCH_3; Y = SCH_3; Z = $COCH_3$ in the structure **10**) yielded a mixture of trans (three parts) and cis (two parts) isomers.
(12) This substance was always contaminated with a trace amount of the corresponding indolequinone resulting from decomposition during the work-up.
(13) G. R. Allen, Jr., J. F. Poletto, and M. J. Weiss, *J. Org. Chem.*, **30**, 2897 (1965).
(14) We are indebted to Dr. J. S. Webb, Lederle Laboratories, for providing the spectroscopic data of mitomycin A.

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Stannylation/Destannylation. New Syntheses of Carbonyl Compounds via Organotin Intermediates

Sir:

Recent experiments in our laboratory indicate that alkyltin compounds are valuable intermediates for organic synthesis.[1] This generalization is based in part on our observations that (1) easily prepared trialkyltin anions undergo high yield conjugate addition[2] to α,β-enones to give useful regiospecific enolates of 3-stannyl ketones; and (2) alkylstannanes are smoothly oxidized by chromic anhydride/pyridine to the corresponding ketones. These two reactions provide a number of useful snythetic transformations. In particular, a dialkylative enone transposition is described and illustrated by a short synthesis of dihydrojasmone.

Trialkylstannyllithium reagents may be conveniently prepared by a procedure similar to the one that we recently reported for the preparation of trimethylsilyllithium.[3,4] Thus, treatment of a tetrahydrofuran solution of hexamethyldistannane or hexabutyldistannane with methyllithium or butyllithium (−20 °C, 15 min) yields the corresponding trialkylstannyllithium and inert tetraalkylstannane in >95% yield.[5] A more economical, but somewhat less convenient procedure, involves titration of ~0.5 M solutions of lithium in liquid ammonia (−70 °C) with a 0.5 M tetrahydrofuran solution of hexaalkyldistannane (yield of R_3SnLi, >95%) or trialkylhalostannane (yield of R_3SnLi, 70–80%).[6]

Regardless of the method of preparation, THF or THF-NH_3 solutions of trialkylstannyllithium react with most α,β-unsaturated carbonyl compounds via the 1,4 mode of addition. Thus 2-cyclohexenone reacts with trimethylstannyllithium or tributylstannyllithium (−78 °C, 5 min) to give 3-stannylcyclohexanones **1a** (96% yield;[7] IR (neat) 1710, 770 cm^{-1}; NMR (δ^{CCl_4}) 0.07 (9 H, s))[8] and **1b** (89% yield; IR (neat) 1710 cm^{-1}), respectively. None of the corresponding 1,2 adduct could be detected. The addition appears to proceed axially with cyclohexenones as evidenced by formation of the *cis*-dimethylcyclonexanone **2** (93% yield) from 3,5-dimethylcyclohexenone.[9] These results parallel our previous observations with trimethylsilyllithium, but the similarities stop here. While trimethylsilyllithium was ineffective at addition to isophorone and $\Delta^1(9)$-2-octalone, trimethylstannyllithium gave the adducts **3** and **4** in 77 and 94% yields, respectively. The success of this reagent at addition to hindered enones is prob-