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# A Synthesis of (+)-9a-Desmethoxymitomycin A via Aziridinyl Radical Cyclization

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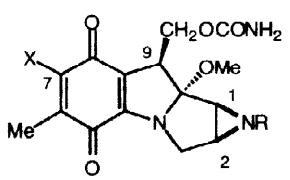
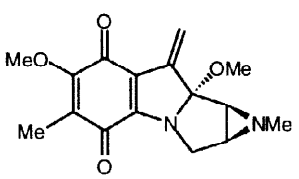
**Abstract:** A synthesis of (+)-desmethoxymitomycin A is described. The critical step is a highly stereoselective cyclization of an aziridinyl radical to afford a tetracycle having the same relative and absolute stereochemistry as mitomycin A and C. © 1998 Elsevier Science Ltd. All rights reserved.

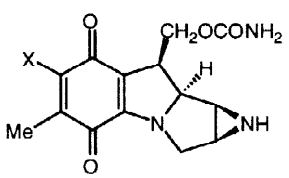
The antitumor activity[1] and the densely functionalized structure of the mitomycins have made these natural products a target of synthetic efforts over the past twenty years. Notable accomplishments in the field have included the total synthesis of porfiromycin (**1a**),[2,3] mitomycins A (**1b**) [4,3] and C (**1c**),[4,3,5,6] and mitomycin K (**2**).[7-9] These syntheses resulted in racemic material; few studies[10] have addressed the synthesis of this class of compounds as their enantiomers. We have developed a protocol for the generation of chiral aziridinyl radicals,[11] which we have applied to the synthesis of the nucleus of FR-900482.[12] In this Letter we describe a synthesis of (+)-9a-desmethoxymitomycin A (**3a**) by this general strategy.




**1a**, R = Me, X = $NH_2$
**b**, R = H, X = OMe
**c**, R = H, X = $NH_2$




**2**




**3a**, X = OMe
**b**, R = $NH_2$

m-Nitrophenol **4a** was prepared from 2,6-dimethoxytoluene as previously described by Fukuyama (Scheme 1).[13] Claisen rearrangement of aniline **5** afforded the hexa-substituted aniline **6a**, which was produced in 51% overall yield from 2,6-dimethoxytoluene. Attempts to effect rearrangement prior to nitro group reduction were unsuccessful. The free-amino group of **6a** required protective acetylation to effect $OsO_4/HIO_4$ cleavage of the double bond. This process afforded an ~1:1 mixture of uncyclized aldehyde **7** and cyclized alcohol **8**. When the mixture was heated in acetic acid at 80 °C followed by deacetylation with base, indole **9b** was produced in 91% yield from aniline **6a**.

Vilsmeier-Haack formylation of indole **9b** was achieved without incident (Scheme 2). Alkylation of the indole carboxaldehyde **10** was accomplished with the previously described[11] chiral aziridinyl triflate **15b** in 78%

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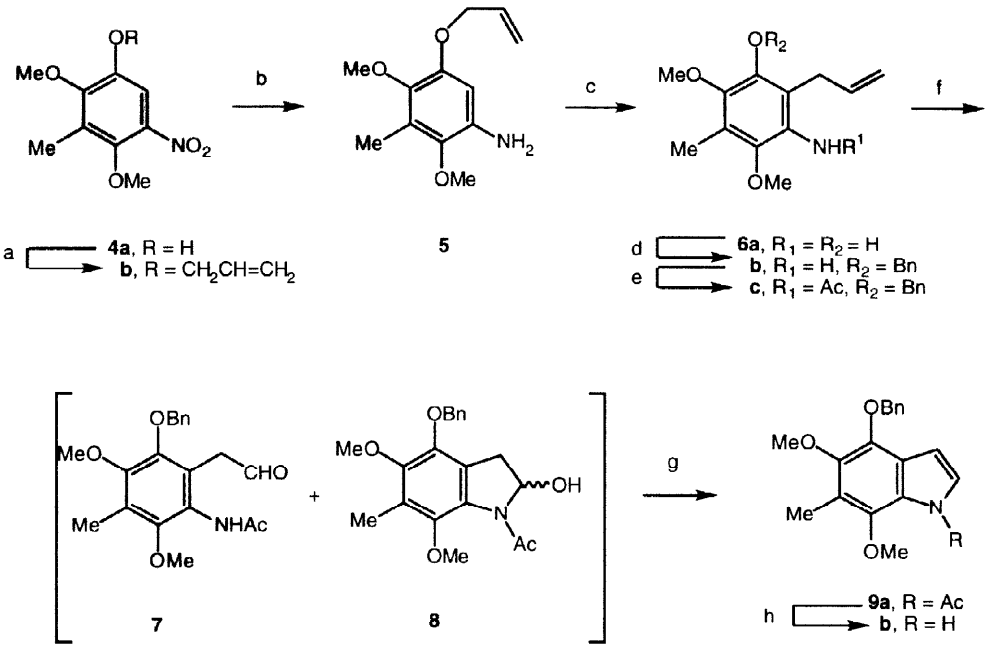
**Scheme 1**



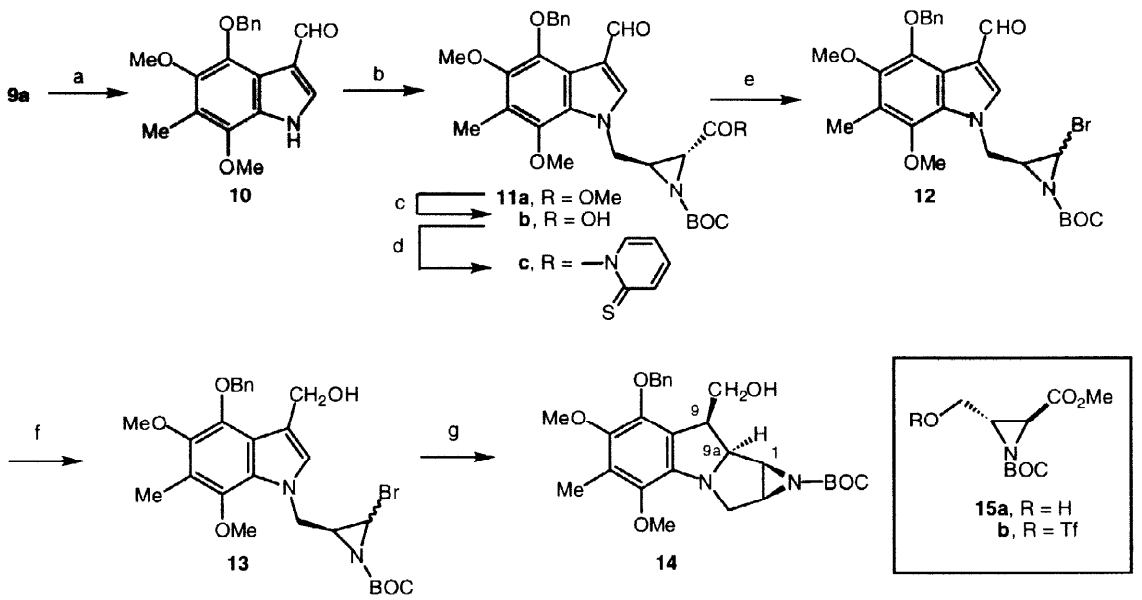

a) $CH_2$=$CHCH_2Br$, $K_2CO_3$, acetone, reflux. b) Zn, HCl, MeOH, 25-50 °C. c) xylenes, 200 °C; 51% from 2,6-dimethoxytoluene. d) BnBr, NaH, $Bu_4N^+I^-$ (cat.), THF, 25 °C. e) $Ac_2O$, pyr., 25 °C. f) $NaIO_4$, $OsO_4$ (cat.), aq. acetone, 25 °C. g) AcOH, 80 °C. h) $K_2CO_3$, MeOH; 91% from **6a**.

yield based on aziridinol **15a**. Activation of the ester group as the thiohydroxamate **11c**[14] and subsequent irradiation in the presence of $CBrCl_3$ led to a 4:1 mixture of bromoaziridines **12** in 62% yield. The major stereoisomer was assigned to the cis isomer ($^1H$ NMR, J = 5.0 Hz) while the minor component was assigned the trans stereochemistry (J = 1.7 Hz). The preponderance of the cis isomer presumably reflects the greater steric bulk of the BOC group over the indole moiety in the reaction of the intermediate aziridinyl radical with $CBrCl_3$. Although the stereoisomers **12** were separable, there was no preparative need to do so. The mixture of bromoaziridines **12** was subjected to reduction with $NaBH_4$ to provide the 3-indolylmethanols **13**. Subsequent reductive radical cyclization of the mixture **13**, or either of its stereoisomers, in the presence of n-$Bu_3SnH$ led to the single tetracyclic alcohol **14** in 55% yield.[15]

The relative stereochemistry of alcohol **14** was assigned on the basis of NOE studies ($H_{9a}$ ---> $H_1$, 10.8%; $H_{9a}$ ---> $H_9$, 13.3%) and chemical evidence. In an attempt to prepare the triflate of alcohol **14**, intramolecular displacement of the triflate by the BOC group occurred with concomitant loss of the *tert*-butyl group forming the bridged carbamate. This substance can be formed only with the stereochemistry present in **14**. The stereochemistry, relative and absolute, is the same as that found in the mitomycins **1** and it is in accord with previous cyclizations of aziridinyl[11,12] and oxiranyl[16,17] radicals.

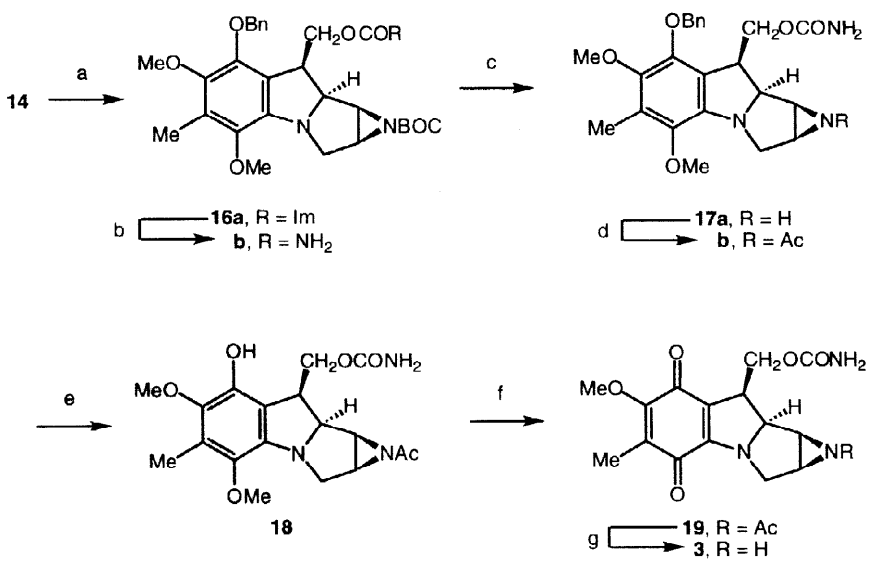
Introduction of the carbamate moiety at $C_{10}$ of alcohol **14** was accomplished in a two-step process without isolation of the intermediate imidazolide **16a** (Scheme 3). Selective removal of the tert-butylcarbamate protecting group over the $C_{10}$ carbamate moiety was accomplished through the use of buffered TMSOTf.[18] Owing to the lability of the unprotected aziridine nitrogen in **17a** toward subsequent oxidation, the nitrogen was reprotected as its

**Scheme 2**




a) $POCl_3$, DMF, 35 °C; 99%. b) KHMDS, THF, **15b**; 78% from **9a**. c) LiOH, aq. THF, 25 °C.
d) 2,2'-dithiobis(pyridine N-oxide), $Bu_3P$, $CH_2Cl_2$. e) $CBrCl_3$, 500-W tungsten lamp; 62% from **11a**.
f) $NaBH_4$, aq. dioxane. g) 0.018 M (**13**), $Bu_3SnH$ (1.8 equiv.) , ACCN (0.4 equiv.), toluene, reflux; 55% from **12**.

**Scheme 3**




a) $Im_2C{=}O$, THF, 73 °C. b) $NH_3$, EtOH-THF, 25 °C; 92% from **14**. c) TMSOTf, 2,6-di-*tert*-butylpyridine, $CH_2Cl_2$, 25 °C.
d) $Et_3N$, $Ac_2O$, $CH_2Cl_2$, 25 °C; 98% from **16b**. e) $H_2$, Pd/C, EtOAc. f) DDQ, aq. acetone, -78 °C --> 25 °C; 62% from **17b**.
g) $NH_3$ (2 equiv.), MeOH; 36%.

acetyl derivative **17b**. Catalytic debenzylation and DDQ oxidation produced the purple quinone **19** [$\lambda_{max}$ (MeOH): 220 (22,200), 319 (12,100), 554 (3,200) nm].

Conversion of mitomycin A (**1b**) to mitomycin C (**1c**)[19] and deacetylation[20] of the N-acetylaziridine moiety are standard protocols achieved through ammonolysis in the mitomycin series. Treatment of quinone **19** with a large excess of $NH_3$/MeOH failed to give rise to 9a-desmethoxymitomycin C (**3b**). However, the use of two equivalents of $NH_3$ permitted the isolation of the product of deacetyation, (+)-9a-desmethoxymitomycin A [$[\alpha]_D^{23}$ = +704° (c, 0.095, MeOH)] in 36% yield. Clearly, the presence of the 9a-methoxy group in mitomycin A affords a stability to that series of compounds that is lacking in the seemingly less complex 9a-desmethoxy series.

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