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SYNTHETIC APPROACHES TOWARD MITOMYCINS. I. STEREOSELECTIVE SYNTHESIS OF A TETRACYCLIC INTERMEDIATE.

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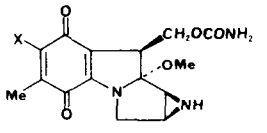
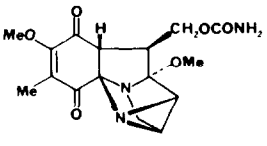
Abstract: A highly efficient synthesis of a tetracyclic intermediate 5 to the antitumor antibiotics AX-2 4, mitomycin A 2, and C 1 is described.

Mitomycin C 1 is one of the most effective antitumor agents currently used for chemotherapy.[1] Although a number of synthetic chemists have been trying to synthesize this small, yet formidable molecule, only one successful total synthesis has been reported to date.[2] Japanese chemists have recently isolated two new antitumor antibiotics, AX-1 3 and AX-2 4, from a culture broth of *Streptomyces caespitosus*.[3] They also found that mitomycin A 2, 3, and 4 form an equilibrium mixture (97:3:trace) in THF in the presence of aluminum isopropoxide. This exciting finding suggests that AX-2 4 is a synthetic equivalent of mitomycin C 1.[4] Synthesis of AX-2 4 appears to have definite advantage in that the notorious, acid-sensitive methoxy group of mitomycins is attached to the less reactive bridgehead position. In this communication we describe a facile, stereoselective synthesis of the tetracyclic intermediate 5.



1: X = NH_2

2: X = OMe



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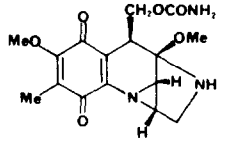

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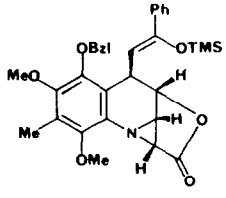

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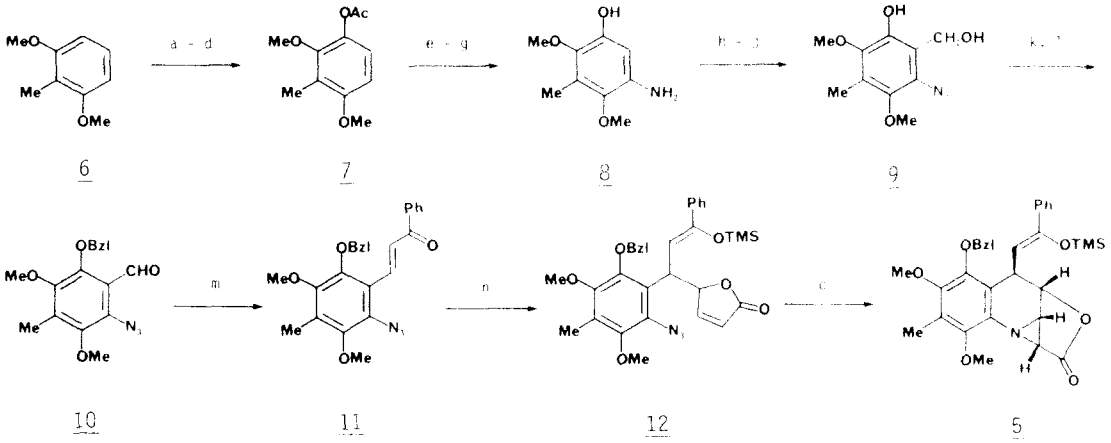
Our key intermediate 11, a highly crystalline chalcone derivative (mp 109-110° dec.), was synthesized from commercially available 2,6-dimethoxytoluene 6 in a 13-step sequence in 45% overall yield without using any chromatographic separation. Friedel-Crafts type acylation of 6 (Cl_2CHOMe, $TiCl_4$, CH_2Cl_2, 0°)[5] followed by Baeyer-Villiger oxidation of the resulting aldehyde (30% H_2O_2, SeO_2, t-BuOH, 50-60°) gave the formate. Methanolysis of the formate (Et_3N, MeOH, RT) and acetylation (Ac_2O, Py, RT) furnished the acetate 7. Nitration (90% HNO_3, Ac_2O, $Hg(OAc)_2$, AcOH, 0°),[6] hydrolysis of the acetate (3N NaOH, MeOH, RT), and catalytic hydrogenation of the nitro group (H_2 (1500 psi), 10% Pd/C, EtOH, RT) gave the aminophenol 8. Diazotization of the amine 8 ($NaNO_2$, HCl, H_2O, 0°), formation of the azide (NaN_3, H_2O, RT),[7] and hydroxymethylation of the phenol (37% HCHO, 3N KOH, t-BuOH, 80°) yielded the fully substituted aromatic compound 9. Protection of the phenol 9 ($PhCH_2Br$, K_2CO_3, DMF, 80°) and oxidation of the alcohol (PCC, CH_2Cl_2, RT) gave the aldehyde 10. Aldol condensation of the crude aldehyde 10 with acetophenone (3N NaOH, MeOH, RT) gave crystalline 11. Michael addition of 2-trimethylsiloxyfuran[8] to 11 (n-Bu_4NF, THF, -78°) gave a 2:1 mixture of the adducts 12 in 80% yield. To our great surprise, intramolecular

azide-olefin cycloaddition[9] of the mixture 12 (toluene, 110°, 2 hr) gave the desired aziridine 12[10] as the only isomer in 85% yield.[11] Stereochemistry of the side chain of 5 has been confirmed by extensive NOE studies. Application of this highly efficient route to the total syntheses of mitomycins is currently under way in our laboratories.



(a) Cl_2CHOMe, $TiCl_4$, CH_2Cl_2, 0°; (b) 30% H_2O_2, SeO_2, t-BuOH, 50-60°; (c) Et_3N, MeOH, RT; (d) Ac_2O, Py, RT; (e) 90% HNO_3, Ac_2O, $Hg(OAc)_2$, AcOH, 0°; (f) 3N NaOH, MeOH, RT; (g) H_2 (1500 psi), 10% Pd/C, EtOH, RT; (h) $NaNO_2$, HCl, H_2O, 0°; (i) NaN_3, H_2O, RT; (j) 37% HCHO, KOH, t-BuOH, 80°; (k) $PhCH_2Br$, K_2CO_3, DMF, 80° (l) PCC, CH_2Cl_2, RT; (m) PhCOMe, 3N NaOH, MeOH, RT; (n) 2-trimethylsiloxyfuran, n-Bu_4NF, THF, -78°; (o) toluene, 110°.

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References and Notes

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10. ^1H NMR (300 MHz, $CDCl_3$) of 5: δ 0.08 (9H, s), 2.22 (3H, s), 3.58 (1H, d, J=3.3), 3.78 (1H, t, J=3.3), 3.79 (3H, s), 3.86 (3H, s), 4.53 (1H, dd, J=8, 4), 4.97 (2H, AB q, J=11), 5.06 (1H, t, J=3.7), 5.09 (1H, d, J=8), 7.27-7.58 (10H, m).
11. We have not yet determined whether this high stereoselectivity is due to a mixture of rotamer 12 instead of diastereomers or due to rapid isomerization of the butenolide diastereomers under the cycloaddition conditions.

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