SYNTHETIC STUDIES ON MITOMYCIN I. SYNTHESIS OF 7-METHOXYMITOSENE FROM 6-METHYLINDOLE BY SELECTIVE OXIDATION OF BENZENE PART

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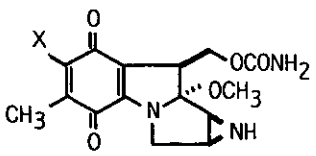
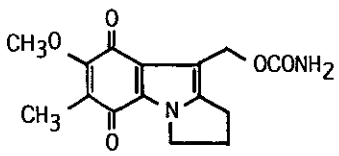
Abstract —— Synthesis of 7-methoxymitosene 3, one of the mitosene analog containing common carbon skeleton in mitomycin series was achieved in 19 steps from 6-methylindole 4 by oxidative functionalization methods.

The mitomycins are a class of antibiotics with activity against gram-positive and gram-negative bacteria and also against several kinds of tumors. Mitomycin C is also used clinical anticancer agents. Structures[1,2,3] of mitomycins were first elucidated in 1962. Since then a lot of synthetic studies[4] toward mitomycins have been studied and many synthetic methods for mitosene, mitosane analog and so on have been reported. However, the total synthesis of mitomycins was reported only by Kishi and his coworkers.[5]

Although mitomycins have a highly oxidized indole nucleus, there is no useful approach for the synthesis of mitomycins by oxidative functionalization of simple indole. Recently, we have succeeded in the introduction of substituent(s)[6-9] on the benzene part of indole derivatives and also in the synthesis of a simple indoloquinone[10] from 6-methylindole. Here, we report the synthesis of 7-methoxymitosene 3 starting from 6-methylindole (4).



mitomycin A : X=OCH_3 (1)
mitomycin C : X=NH_2 (2)



7-methoxymitosene (3)

6-Methylindole 4 was alkylated with NaH and 3-bromopropyl acetate in DMF to afford 5[11] in 89% yield. Carbomethoxy group was introduced at 3-position of 5 in three steps [1) $(COCl)_2$ in Et_2O, 2) 120°C in tetrachloroethane, 3) MeOH] to give 6[12] in 52 % overall yield. Acetoxy group of 6 was converted to corresponding tosylate 7[13] by two steps [1) 1N NaOH /MeOH, 2) TsCl/Py] in 82 % overall yield. Construction of mitomycin's skeleton was achieved by anion formation at 2-position of 7 with BuLi in THF and intramolecular cyclization to obtain pyrroloindole derivative 8[14] in 90 % yield. Chloroacetyl group was selectively introduced at 7-position of 8 by treatment with chloroacetyl chloride and $AlCl_3$ in dichloroethane to afford 9[15] in 76 % yield. Conversion of chloroacetyl group of 9 to 5-hydroxy compound 11[16] was achieved by Baeyer-Villiger oxidation of 9 and subsequent hydrolysis of chloroacetoxy group of 10 [1) m-CPBA/Na_2HPO_4/$CHCl_3$, 2)1N NaOH in MeOH) in 20 % overall yield.

Phenol 11 was oxidized to o-quinone 12[17] with Fremy's salt [$\cdot O\text{-}N(SO_3K)_2$] in acetone-$H_2O$ in 36 % yield. Compound 12 was selectively derived to monomethyl hydroquinone 13[18] in two steps [1) H_2/10% Pd-C, 2) MeI,K_2CO_3/DMF] in 61% overall yield. Compound 13 was reoxidized with Fremy's salt to produce desired p-quinone 14 in 55 % yield. Thus obtained 14 has the mitomycin's skeleton and the same indoloquinone ring system. Methyl ester group of 14 was converted to carbamate by published procedure[4] to obtain 7-methoxymitosene 3 [2,3-dihydro-9-hydroxymethyl-7-methoxy-6-methyl-1H-pyrrolo[1,2-a]indole-5,8-dionecarbamate] in 52 % overall yield. The spectroscopic data of 3 were completely identical to those of reported 7-methoxymitosene. Thus we could synthesize 7-methoxymitosene 3, in 19 steps from simple 6-methylindole 4. Further synthetic studies on mitomycins are under investigation.

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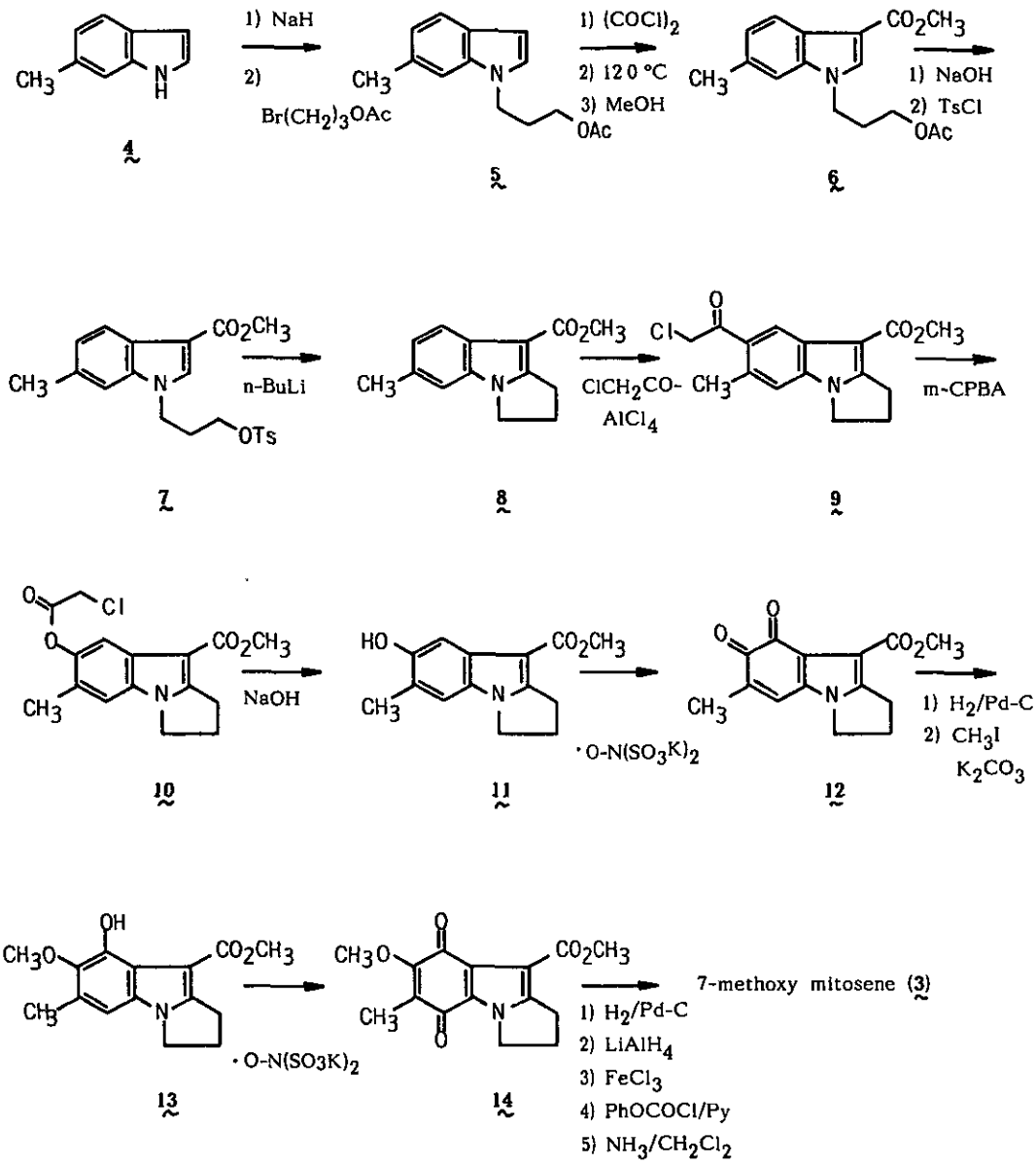

Recently the absolute configuration of mitomycins have been revised.

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11. 5: oil; ^{1}H-NMR δ($CDCl_3$) ppm 2.03(3H, s), 2.09 (2H, m), 2.46(3H, s), 4.00(2H, t, J=7 Hz), 4.13(2H, t, J=7 Hz), 6.39(1H, d, J=3 Hz), 6.93(1H, d, J=3 Hz), 6.94(1H, d, J=8 Hz), 7.06(1H, br.s), 7.45(1H, d, J=8Hz)].

12. 6: mp 75.5-76.0°C; ^{1}H-NMR δ($CDCl_3$) ppm 2.03(3H, s), 2.15(2H, m), 2.47(3H, s), 3.87(3H, s), 4.03(2H, t, J=7 Hz), 4.18(2H, t, J=7 Hz), 7.06(1H, d, J=9 Hz), 7.09(1H, s), 7.70(1H, s), 7.99(1H, d, J=9 Hz)].

13. 7: mp 112°C; ^{1}H-NMR δ($CDCl_3$) ppm 2.20(2H, m), 2.43(3H, s), 2.47(3H, s), 3.88(3H, s), 3.97(2H, t, J=7 Hz), 4.19(2H, t, J=7 Hz), 6.74(1H, s), 7.07(1H, d, J=9 Hz), 7.30(2H, d, J=8 Hz), 7.60(1H, s), 7.72(2H, d, J=8 Hz), 7.98(1H, d, J=9 Hz)].

14. 8: mp 150.5-151.5°C; ^{1}H-NMR δ($CDCl_3$) ppm 2.46(3H, s), 2.62(2H, m), 3.26(2H, t, J=8 Hz), 3.88(3H, s), 4.08(2H, t, J=8 Hz), 7.01(1H, s), 7.04(1H, d, J=9 Hz), 7.94(1H, d, J=9 Hz)].

15. 9: mp 173°C; ^{1}H-NMR δ($CDCl_3$) ppm 2.64(3H, s), 2.68(2H, m), 3.29(2H, t, J=7 Hz), 3.90(3H, s), 4.12(2H, t, J=7 Hz), 4.82(2H, s), 7.11(1H, s), 8.46(1H, s)].

16. 11: mp 264-265°C; ^{1}H-NMR δ($CDCl_3$-CD_3OD 5:1) ppm 2.35(3H, s), 2.64(2H, m), 3.24(2H, t, J=8 Hz), 3.85(3H, s), 4.07(2H, t, J=7 Hz), 7.00(1H, s), 7.40(1H, s)].

17. 12: mp 207-208°C; ^{1}H-NMR δ($CDCl_3$) ppm 1.96(3H, d, J=1 Hz), 2.60(2H, m), 3.21(2H, t, J=7 Hz), 3.83(3H, s), 3.98(2H, t, J=7 Hz), 6.83(1H, q, J=1 Hz)].

18. 13: mp 190-192°C: ^{1}H-NMR δ($CDCl_3$) ppm 2.35(3H, s), 2.61(2H, m), 3.15 (2H, t, J=7 Hz), 3.85(3H, s), 3.88(3H, s), 3.96(2H, t, J=7 Hz), 6.46(1H, s)].

19. 14: mp 208.5-210°C; ^{1}H-NMR δ($CDCl_3$) ppm 1.93(3H, s), 2.58(2H, m), 3.10(2H, t, J=7.5 Hz), 3.85(3H, s), 4.04(3H, s), 4.29(2H, t, J=7.2 Hz)].

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