INTRODUCTION OF ALL FUNCTIONAL GROUPS FOUND IN THE BENZENE PART OF MITOMYCIN C TO PYRROLO[1,2-*a*]INDOLE DERIVATIVE

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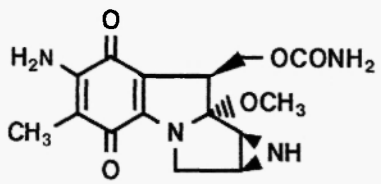
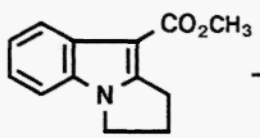
Abstract : All functional groups on the benzene part of mitomycin C were directly introduced on pyrrolo[1,2-*a*]indole 2 by Friedel-Crafts alkylation, oxidative introduction of *p*-quinone moiety *etc*.

Introduction of substituents on the benzene part (4~7 position) of indole ring is one of the most difficult problems in the organic syntheses (1). We have developed several useful methods to resolve the problem and applied those to the syntheses of natural products (2~4). We have been reported efficient method for the synthesis of indoloquinone (4b) and applied them for the synthesis 7-methoxymitosene starting from 6-methylindole (4d, e). In this paper, we report the synthesis of pyrroloindoloquinone 3 by direct introduction of the functional groups found in mitomycin C 1 (5~7) from simple pyrrolo[1,2-*a*]indole 2.



Mitomycin C (1)



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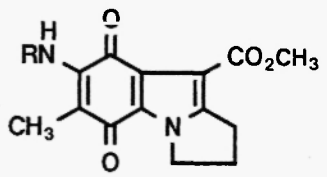


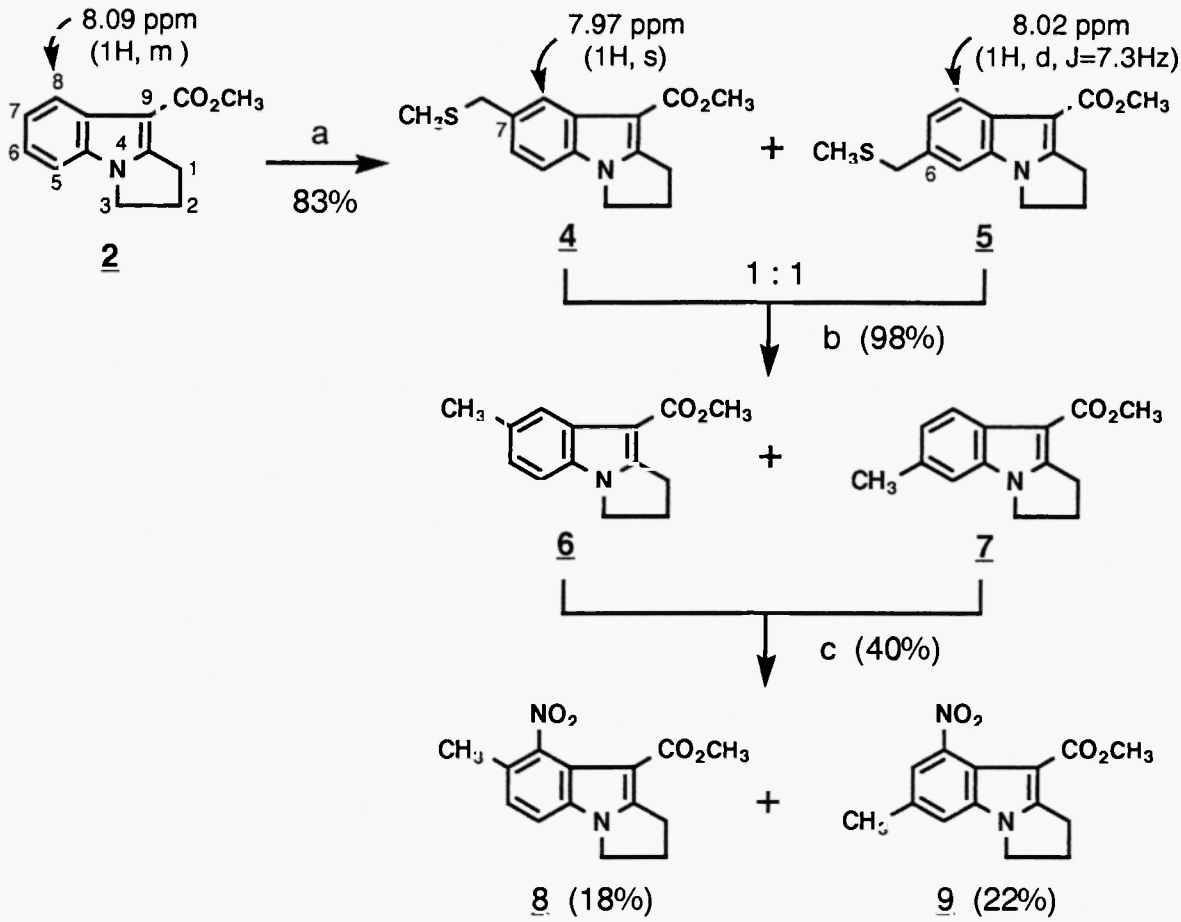
3 R=Bn

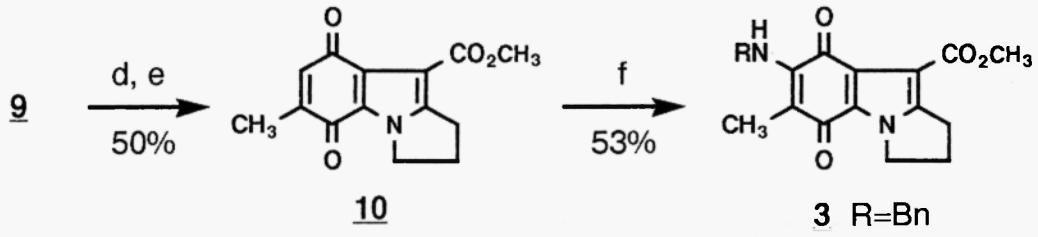
Although Friedel-Crafts methylation [$CH_3Br/AlCl_3$, $(CH_3)_2SO_4/AlCl_3$ *etc.*] of pyrrolo[1,2-*a*]indole 2 gave no methylated product, alkylation with $ClCH_2SCH_3/AlCl_3$ in CH_2Cl_2 at -20°C for 30min gave monomethylthiomethyl derivatives 4 and 5 in 83% yield(1:1). Those could not be seperated on silica gel TLC or column, but were seperated with HPLC[Namsil NA-10 (8), 3%AcOEt in Hex] in small scale and those structures were determined as 7-substituted 4 and 6-substituted 5 by comparison of those ^{1}H-NMR-spectra. 4; ^{1}H NMR ($CDCl_3$) δ(ppm) 2.00 (3H, s), 2.66 (2H, m), 2.29 (2H, t, J=7.6Hz), 3.83 (2H, br.s), 3.91 (3H, s), 4.11 (2H, t, J=7.2Hz), 7.22 (2H, m), 7.97 (1H, s). 5; ^{1}H NMR ($CDCl_3$) δ(ppm) 2.00 (3H, s), 2.66 (2H, m), 2.29 (2H, t, J=7.6Hz), 3.82 (2H, br.s), 3.90 (3H, s), 4.11 (2H, t, J=7.2Hz), 7.16 (1H, d, J=7.3Hz), 7.22 (1H, s), 8.02 (1H, d, J=7.3Hz).

Reduction of a mixture of 4 and 5 with Raney Ni in methanol at 25°C gave corresponding methyl derivatives 6 and 7, in 98% yield. Separation of 6 (9) and 7 (4d) were also difficult in large scale, but each structure was determined after separation with HPLC(ODS-3, 50%MeOH in H_2O) and comparison with authentic samples.

A mixture of 6 and 7 were nitrated with sodium nitrate in the presence of 2.5% conc. H_2SO_4 in acetic acid at 40°C for 50min to afford mono-nitro-derivatives 8 and 9, which were easily separated on silica gel column (14% and 22% yields respectively). 8; mp 192°C, ^{1}H NMR ($CDCl_3$) δ(ppm) 2.42 (3H, br.s), 2.68 (2H, m), 3.32 (2H, t, J=7.6Hz), 3.82 (3H, s), 4.16 (2H, t, J=7.3Hz), 7.07 (1H, d, J=8.5Hz), 7.26 (1H, d, J=8.3Hz). 9; mp 178~179°C, ^{1}H NMR ($CDCl_3$) δ(ppm) 2.50 (3H, br.s), 2.69 (2H, m), 3.31 (2H, t, J=7.6Hz), 3.82 (3H, s), 4.15 (2H, t, J=7.2Hz), 7.26 (1H, s), 7.39 (1H, s). Compounds 8 and 9 were also obtained by nitration of purified 7-methyl derivative 6 and 6-methyl derivative 7, respectively, and those structures were easily determined by their ^{1}H-NMR-spectra. In both case, the nitrating position of 6 and 7 was favoured at the 8-position (3a, d, e).

Hydrogenation of compound 9 with H_2/Pd-C in methanol gave a 8-amino derivative in 90% yield and subsequent oxidation of the amino-derivative with Fremy's salt [$\cdot ON(SO_3K)_2$] gave *p*-quinone 10 (10) in 56% yield. Amination of 10 with benzylamine afforded 3 (11) which contains all functional groups on the benzene part of mitomycin C 1. Thus we developed novel method directly introducing all substituents, found in benzene part of mitomycin C, on the benzene part of pyrrolo[1,2-*a*]indole 2 in 6 steps(4.8% over all yield).





Reagents: a) $ClCH_2SCH_3$, $AlCl_3$ (4 and 5, 83%); b) Raney Ni (6 and 7, 98%);
c) $NaNO_3$, H_2SO_4 (8, 22%); d) H_2, Pd-C (90%);
e) $\bullet ON(SO_3K)_2$, Phosphate Buffer (56%); f) $BnNH_2$, pyridine (53%).

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(8) Packed column of 10μ normal phase silicagel, Nam Res. Lab.

(9) 6; ^{1}H NMR ($CDCl_3$) δ(ppm) 2.47 (3H, br.s), 2.64 (2H, m), 3.28 (2H, t, J=7.6Hz), 3.89 (3H, s), 4.09 (2H, t, J=7.0), 7.05 (1H, d, J=8.5Hz), 7.14 (1H, d, J=8.2Hz), 7.90 (1H, s)

(10) 10; mp 172~173°C(decomp.), ^{1}H NMR ($CDCl_3$) δ(ppm) 2.05 (3H, d, J=1.8Hz), 2.61 (2H, m), 3.14 (2H, t, J=7.6Hz), 3.88 (3H, s), 4.33 (2H, t, J=7.5Hz), 6.46 (1H, d, J=1.3Hz)

(11) 3; ^{1}H NMR ($CDCl_3$) δ(ppm) 2.08 (3H, br.s), 2.56 (2H, m), 3.09 (2H, t, J=7.6Hz), 3.85 (3H, s), 4.31 (2H, t, J=7.3Hz), 4.71 (2H, d, J=6.1Hz), 6.30 (1H, br.s), 7.26~7.35 (5H, m)

Received November 24, 1994