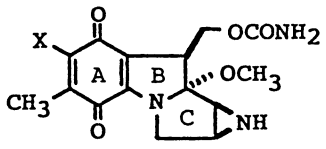
CHEMISTRY LETTERS, pp. 1225-1228, 1987.

Efficient Synthesis of 7-Methoxymitosene from 6-Methylindole[1)]

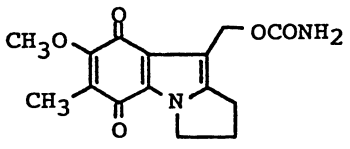
Shin-ichi NAKATSUKA,* Osamu ASANO, and Toshio GOTO
Laboratory of Organic Chemistry, Faculty of Agriculture,
Nagoya University, Chikusa, Nagoya 464

An efficient synthesis of 7-methoxymitosene from easily available 6-methylindole was achieved by 17 steps in 3.0% overall yield.

Mitomycins[2)] are an important class of antitumor antibiotics and especially mitomycin C (2) has been clinically used. Numerous synthetic studies[3)] toward them have been done since their structure elucidations.[4)] We have reported selective introducing method of functions (such as alkyl[5-8)]-acyl[9)] moiety, oxygen,[10,11)] nitrogen,[12,13)] etc.) to the benzene part of indole derivatives and established a novel synthetic method of indoloquinone derivatives,[10)] which contains the same quinone ring (A-ring) as mitomycin A (1). As further application of the method to the synthesis of mitomycins, we reported a synthesis of 7-methoxymitosene (3) from easily obtained 6-methylindole (7) in the previous paper.[1)] But the more efficient synthetic method was required because the overall yield of 3 in the previous route was rather low. Here we describe the efficient synthesis of 3 from 6-methylindole (7).



Mitomycin A ; X=OCH_3 (1)
Mitomycin C ; X=NH_2 (2)



7-Methoxymitosene (3)

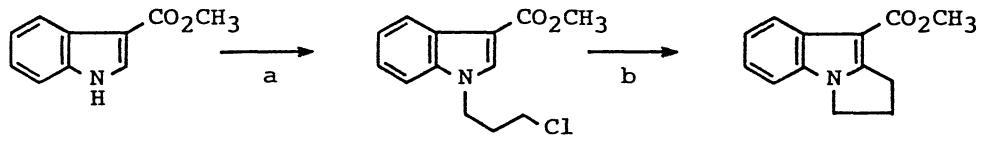
In the previous paper, we reported a new method for C-ring construction of mitomycins by anion formation at 2-position of indole nucleus by four steps (43% overall yield) and we succeeded in development of the more efficient method by two steps as shown in Scheme 1. Methyl indole-3-carboxylate 4 was derived to 5,[14] which contains C_3 unit for the C-ring [NaH/$Br(CH_2)_3Cl$]. To a cooled solution of 5 in THF at -78 °C was added 1.0 equiv. n-BuLi gradually. After 20 min, the solution was warmed up to 25 °C and stirred for 30 min. The cyclization of C-ring proceeded smoothly to give a desired pyrrolo[1,2-a]indole derivative 6[15] in 63% overall yield from 4.

Improvement of synthetic route for 7-methoxymitosene 3 was achieved as shown in Scheme 2. Although in the synthesis of simple indoloquinone system an oxygen function could be introduced in over 59% yield, a hydroxy group was introduced in only 17% overall yield in the case of pyrrolo[1,2-a]indole derivatives, 6 etc. So, an alternate route, in which C-ring was cyclized after oxidative functionalization of the benzene part, was investigated.

The N-chloropropyl derivative 8,[16] which was obtained by alkylation of 7 with NaH/$Br(CH_2)_3Cl$, was derived to 9[17] in three steps [1) $(COCl)_2$, 2) 120 °C, 3) MeOH] in 52% overall yield. The 5-position of 9 was selectively acylated to 10[18] with $ClCH_2COCl/AlCl_3$ in 96% yield. Treatment of 10 with m-CPBA in the presence of Na_2HPO_4 and subsequent hydrolysis with 1 M NaOH gave the corresponding 5-hydroxy derivative 11[19] in 67% overall yield. The derivation of 11 to 5-methoxy-4-hydroxy derivative 12 was achieved by the previous procedure[1] [1) $\cdot O\text{-}N(SO_3K)_2$, 2) H_2/Pd-C, 3) CH_3I/aq.KOH; 42% overall yield].

C-ring construction was achieved as follows. To a cooled THF solution of 12[20] at -78 °C was carefully added 2.2 equiv. LDA and the reaction mixture was warmed up and kept for 30 min at 25 °C. The phenoxy anion was quenched with AcOH and extracted with dichloromethane to afford the desired pyrrolo[1,2-a]indole derivative in 71% yield. Subsequent oxidation of the product with $\cdot O\text{-}N(SO_3K)_2$ gave pyrrolo[1,2-a]indoloquinone 13 in 58% yield.

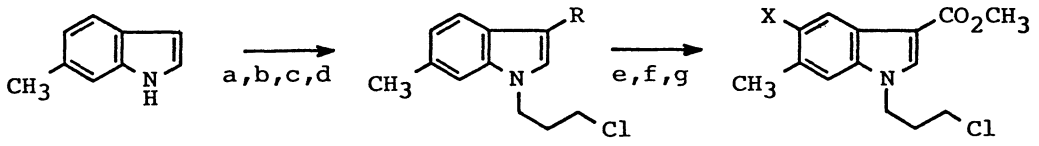
The overall yield of 13 from 7 was improved to 5.8% from 0.5% by the previous route.[1] The conversion of 13 to 3 was reported in the previous paper(5 steps, 52% overall yield). Thus, we succeeded in an efficient synthesis of 7-methoxymitosene 3 from simple 6-methylindole 7 by 17 steps in 3.0% overall yield. Further synthetic studies on mitomycins are now in progress.



4 5 6

Scheme 1. Synthesis of pyrrolo[1,2-a]indole derivative 6.

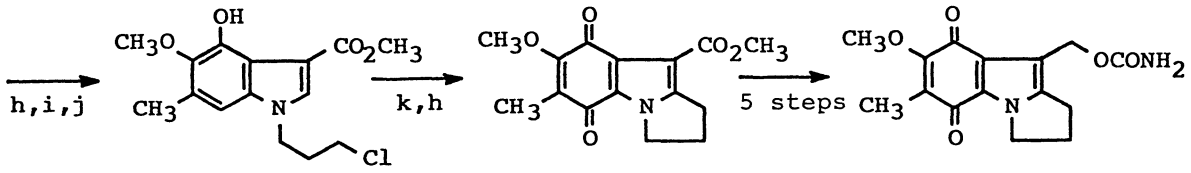
Reagents: a) NaH/$Br(CH_2)_3Cl$, b) n-BuLi



7

8 R=H
9 R=CO_2CH_3

10 X=$COCH_2Cl$
11 X=OH



12 13 3 7-methoxymitosene

Scheme 2. Synthesis of 7-methoxymitosene 3 from 6-methylindole 7.

Reagents: a) NaH/$Br(CH_2)_3Cl$, b) $(COCl_2)_2/Et_2O$, c) 120 °C, d) MeOH, e) $ClCH_2COCl/AlCl_3$, f) mCPBA/Na_2HPO_4, g) 1 M NaOH/MeOH, h) $\cdot ON(SO_3K)_2$, i) H_2/Pd-C, j) CH_3I/aq. KOH, k) 2 equiv. LDA,

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14) 5: oil, MS m/z 253 and 251(M^+), ^{1}H-NMR $\delta(CDCl_3)$ ppm 2.23(2H,m),3.41(2H,t,J=6.5 Hz), 3.90(3H, s), 4.28(2H, t, J=7.0 Hz),7.04-7.41(3H,m),7.78(1H,s),8.15(1H,m).

15) 6: mp 87-88 °C, MS m/z 215(M^+), ^{1}H-NMR $\delta(CDCl_3)$ ppm 2.66(2H, m), 3.31(2H, t, J=7.3 Hz), 3.86(3H, s), 4.08(2H, t, J=7.5 Hz), 7.04-7.32(3H, m), 8.06(1H, m).

16) 8: oil, MS m/z 209 and 207(M^+).

17) 9: mp 88-89 °C, MS m/z 267 and 265(M^+).

18) 10: mp 147-148 °C, MS m/z 285 and 283(M^+), ^{1}H-NMR $\delta(CDCl_3)$ ppm 2.30(2H, m), 2.67(3H, s), 3.48(2H, t, J=6.0 Hz), 3.92(3H, s), 4.37(2H, t, J=7.0 Hz), 4.80 (2H, s), 7.24(1H, s), 7.83(1H, s), 8.52(1H, s).

19) 11: mp 198-198.5 °C, MS m/z 283 and 281(M^+), ^{1}H-NMR $\delta(CDCl_3:CD_3OD=2:1)$ ppm 2.30(2H, m), 2.36(3H, s), 2.44(2H, t, J=6.0 Hz), 3.84(3H, s), 4.28(2H, t, J= 7.0 Hz), 7.08(1H, s), 7.42(1H, s), 7.66(1H, s).

20) 12: mp 110.5-111.5 °C, MS m/z 313 and 311(M^+), ^{1}H-NMR $\delta(CDCl_3)$, ppm 2.30(2H, m), 2.39(3H, s), 3.47(2H, t, J=6.0 Hz), 3.88(3H, s), 3.92(3H, s), 4.25(2H, t, J=7.0 Hz), 6.60(1H, s), 7.60(1H, s), 10.76(1H, s).

(Received March 25, 1987)