SYNTHESIS OF 1,2-AZIRIDINO-2,3-DIHYDRO-1H-PYRROLO[1,2-a]INDOLE DERIVATIVES SIMILAR TO THE ACTIVATED FORMS OF MITOMYCIN[1]

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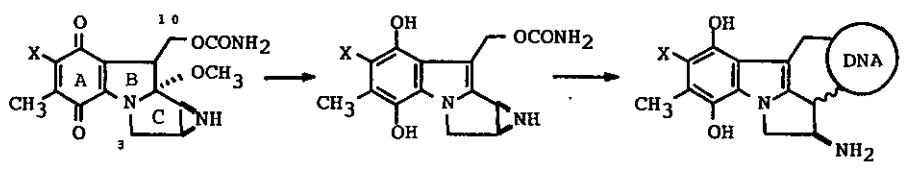
Abstract——Titled compounds, 8 and 12, were efficiently synthesized from 2,3-dihydro-1H-pyrrolo[1,2-a]indole derivatives by closure of the aziridine ring.

Mitomycins A[2] (1), C[2] (2) etc. form a group of one of the most popular anti-cancer agents, and mitomycin C has been used clinically. After many studies on the mechanism[3] responsible for the binding of mitomycins to DNA, it was found that aziridinopyrrolo[1,2-a]indoles (Form I), produced via reduction to the semiquinone radical anion and subsequent loss of methanol, are the activated form to be attacked by the DNA molecule and plays a very important role in the mode of action of these drugs (Scheme 1).

The chemical derivation of natural mitomycins to such activated aziridinopyrroloindoles has recently been achieved by several groups.[4] However, only a few successful synthetic approaches[5] toward them have been appeared in the stabilized cases (for instance, the electron density of the B ring was diminished by conjugation with a carbonyl group at the 10- or 3-position, etc.). The further application of this approach for the synthesis of mitomycins has not been attempted. The first elegant total synthesis of mitomycins was achieved by Kishi's group[5c]

Scheme 1



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

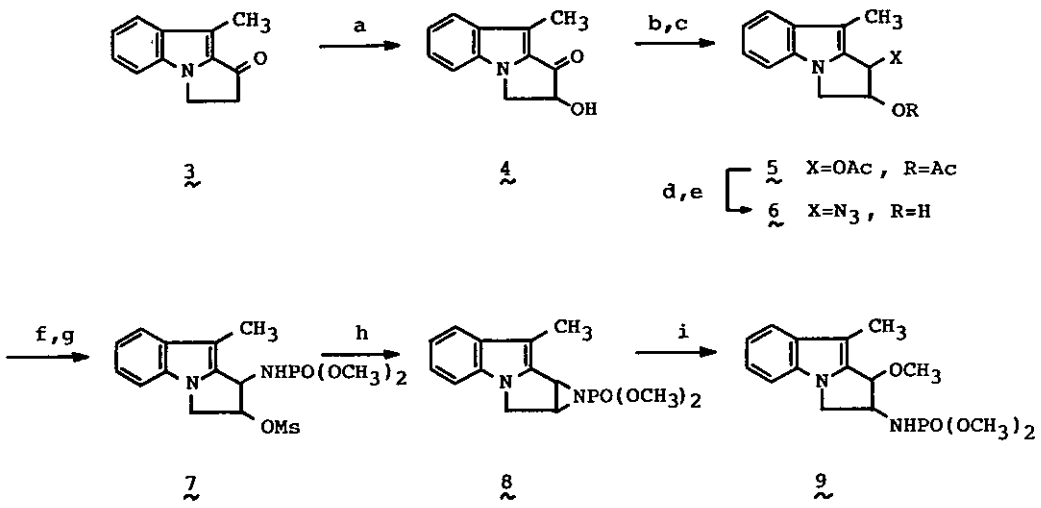
via ring closure of the eight-membered ring derivative containing the aziridine ring prepared at the acyclic early stage. Subsequently, aziridine ring closure after the ring construction of mitomycins has been avoided in most synthetic studies. In this paper, we report a novel method synthesizing the aziridinomitosene derivatives (Type I) starting from pyrroloindole derivatives (Schemes 2 and 3).

Pyrroloindole 3[6] was oxidized with MoOPH after formation of its anion in THF with LDA at -78°C to afford the corresponding hydroxy derivative 4, mp 155-158 °C, in 56% yield. Compound 4 was converted to diacetate 5 in two steps [1) $NaBH_4$ /MeOH-THF, 2) Ac_2O/Py] in 71% overall yield. Introduction of nitrogen function was achieved by treatment of 5 with sodium azide in AcOH-H_2O (2:1) at 60 °C, followed by hydrolysis of its acetoxy group with 1 N NaOH to give 1-azido-2-hydroxy derivatives 6a,b. These were easily separated on a silica gel TLC plate to the trans- and cis-isomers (6a[7]:6b[8]=3:1). After mesylation of the trans-isomer 6a (MsCl/Py; 98%), the azido group was converted to phosphoryl amide 7 with $P(OMe)_3$ in 67% yield.

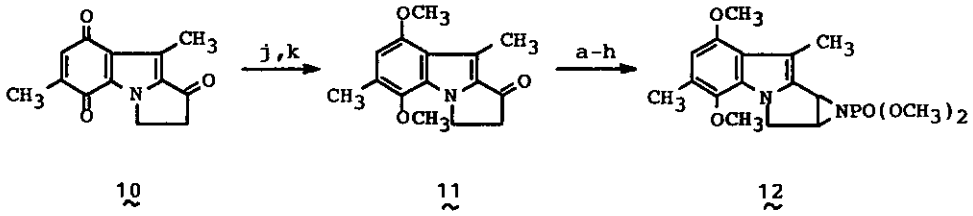
After treatment of 7 with 1.2 equiv. NaH in THF at 25°C for 10 min, the reaction mixture was checked by chromatography on a silica gel TLC plate. Although a new major spot was detected on the TLC plate, preparative TLC separation of the extracted reaction mixture (at this stage, no decomposition of the product was observed) gave the other polar compounds. These results indicated that the initial product obtained by treatment 7 with NaH was very unstable. We therefore measured the ^{1}H-nmr spectrum of the reaction mixture (over 90% recovery) without purification by silica gel TLC. The spectrum in $CDCl_3$ indicated that the reaction mixture contained the desired phosphorylaziridino derivative 8[9] in over 80% purity. The ms spectrum [m/z 292 (M^+)] also supported the structure of 8. No signal assignable to 8 in the ^{1}H-nmr spectrum of 8 in CD_3OD was observed at all, but signals of ring-opened compounds similar to 9 were observed. A methanol solution of the crude 8 at 25°C for 10 min gave ring-opened products 9a[10] and 9b[11] (1:1) in quantitative yield. The structures of 9a,b were determined by measurements of their spectroscopic data to be 9a (trans-isomer) and 9b(cis-isomer). It should be noted that the ratio of the cis- and trans-isomers was 1:1, since acid-catalyzed ring opening of aziridinomitosene or mitomycins is known to give cis-amino alcohol as a major product (cis: trans=3:1-5:1).[12]

These methods were further studied for the synthesis of aziridinopyrroloindole 12

Scheme 2



Scheme 3



Reagents: a) LDA/MoOPH, b) $NaBH_4$/MeOH-THF, c) Ac_2O/Py, d) NaN_3/aq. AcOH, e) 1N NaOH/MeOH, f) MsCl/Py, g) $P(OCH_3)_3$/THF, h) NaH/THF, i) MeOH, j) H_2/Pd-C, k) CH_3I/LiOH

(Scheme 3). Pyrroloindoloquinone 10,[13] synthesized from indole previously, was reduced with H_2/Pd-C and followed by methylation with CH_3I/LiOH to afford the protected hydroquinone derivative 11[14] in 64% overall yield.

The aziridine ring was introduced into 11 in 8 steps by application of the previous ring closure method to give 12[15] in 17% overall yield. Aziridine 12 was also a very reactive compound, especially under acidic conditions even on a silica gel plate, similarly to 8. These reactivities of 8 and 12 are very reasonable because their structures are very similar to those of activated mitomycins [type I] and their B-ring is not stabilized as in the case of earlier syntheses.[5]

REFERENCES AND FOOTNOTES

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7. 6a: IR(KBr) 3400, 2950, 2120 cm^{-1}, ms m/z 228(M^+), ^{1}H-nmr $\delta(CDCl_3)$ ppm 2.40(3H, s), 3.96(1H, dd, J=11.0 and 2.5 Hz), 4.39(1H, dd, J=11.0 and 5.2 Hz), 4.79(1H, m), 4.89(1H, d, J=2.5 Hz), 7.04-7.32(3H, m), 7.57(1H, m).
8. 6b: ms m/z 228(M^+), ^{1}H-nmr $\delta(CDCl_3)$ ppm 2.42(3H, s), 3.83(1H, dd, J=10.0 and 7.2 Hz), 4.40(1H, dd, J=10.0 and 7.0 Hz), 4.84(1H, m), 5.14(1H, d, J=5.0 Hz), 7.04-7.32(3H, m), 7.58(1H, m).
9. 8: ms m/z 292(M^+), ^{1}H-nmr $\delta(CDCl_3)$ ppm 2.38(3H, s), 3.79(3H, s), 3.85(3H, s), 3.94-4.14(3H, m), 5.23(1H, d, J=11.2 Hz), 7.00-7.32(3H, m), 7.53(1H,m).
10. 9a(trans isomer): ms m/z 324(M^+), ^{1}H-nmr $\delta(CDCl_3)$ ppm 2.40(3H, s), 2.89 (1H, d, J=10.5 Hz), 3.41(3H, s), 3.73(3H, d, J=3.3 Hz), 3.79(3H, d, J=3.3 Hz), 3.89 (1H, dd, J=10.8 and 1.8 Hz), 4.40(1H, m), 4.42(1H, dd, J=10.8 and 5.0 Hz), 4.65(1H, d, J=1.5 Hz), 7.06-7.36(3H, m), 7.57(1H, m).
11. 9b(cis isomer): ms m/z 324(M^+), ^{1}H-nmr $\delta(CDCl_3)$ ppm 2.41(3H, s), 3.41(3H, s), 3.77(3H, d, J=1.5 Hz), 3.80(1H, t, J=7.5 Hz), 3.83(3H, d, J=1.5 Hz), 3.88(1H, br.t, J=11.5 Hz), 4.24(1H, m), 4.37(1H, dd, J=9.0 and 7.5 Hz), 4.60(1H, d, J=5.0 Hz), 7.06-7.25(3H, m), 7.57(1H, m).
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13. Compound 10 was prepared from 6-methylindole.
14. 11: ms m/z 259(M^+), ^{1}H-nmr $\delta(CDCl_3)$ ppm 2.38(3H, s), 2.67(3H, s), 2.33(2H, t, J=7.0 Hz), 3.82(3H, s), 3.87(3H, s), 4.52(2H, t, J=7.0 Hz), 6.14(1H, s).
15. 12: ms m/z 366(M^+), ^{1}H-nmr $\delta(CDCl_3)$ ppm 2.34(3H, s), 2.41(3H, s), 3.78(3H, s), 3.83(3H, s), 3.58-3.90(4H, m), 6.16(1H, s).

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