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SYNTHETIC STUDIES ON MITOMYCINS. 2.[1] A SYNTHESIS OF 9a-HYDROXY-5,8-DIDEOXOMITOSANE SKELETON THROUGH A NOVEL RETROALDOL TYPE OF RING-OPENING REACTION.

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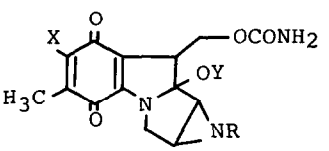
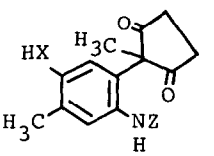
Summary: A synthesis of 9a-hydroxy-5,8-dideoxomitosanes was accomplished by the transannular cyclization of hydro-1-benzazocinone intermediates derived from 3-(2,5-dioxo-1-methylcyclopentyl)-6-methyl-p-phenylenediamine derivatives. These mitosanes were led to the 8-membered ring system by an oxidative ring-opening reaction.

In the preceding communication[1] has been described a new regiospecific Michael addition reaction, affording the compounds(2a and 2b), which are claimed by us to be the important precursors for a synthesis of mitomycins(1). We wish to report in the present communication a new biomimetic route to the synthesis of 9a-hydroxy-5,8-dideoxomitosane(3a, b) from 2a and 2b through fewer steps, which include a novel retroaldol type of ring-opening reaction, followed by a transannular cyclization.



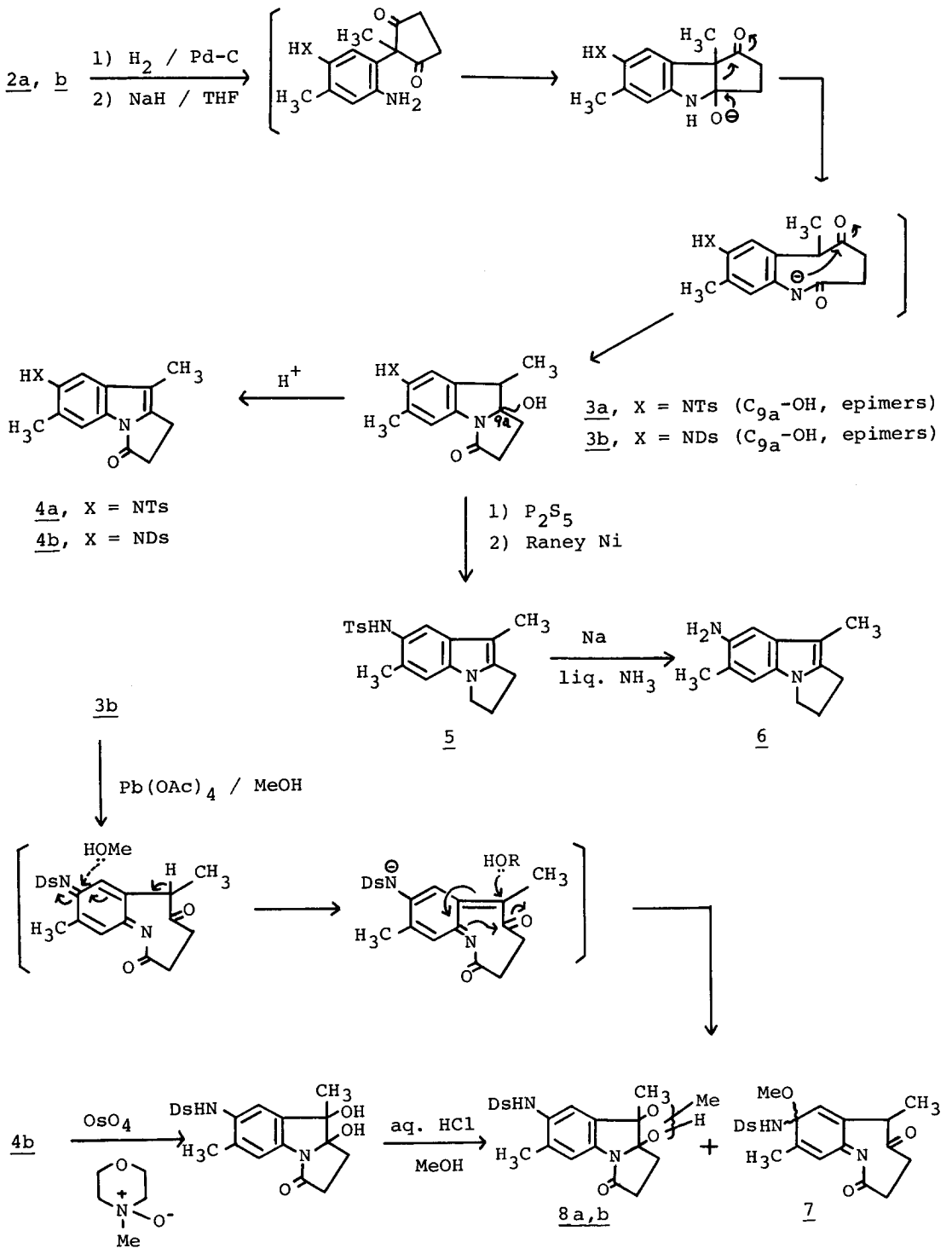
1, mitomycins

X = OCH_3, NH_2
Y = H, CH_3
R = H, CH_3



2a, X = NTs
2b, X = NDs

Ts = tosyl, Z = CO_2CH_2Ph or H
Ds = $SO_2N(CH_3)_2$


2a, b
1) H2 / Pd-C
2) NaH / THF
3a, X = NTs (C9a-OH, epimers)
3b, X = NDs (C9a-OH, epimers)
H+
4a, X = NTs
4b, X = NDs
1) P2S5
2) Raney Ni
5
Na
liq. NH3
6
3b
Pb(OAc)4 / MeOH
OsO4
aq. HCl
MeOH
8a,b
7

Removal of the carbobenzoxy group from the diketone(2a, Z = CO_2CH_2Ph) was made by hydrogenolysis with 10% Pd-C in triethylamine-aq. THF in an atmospheric pressure of hydrogen to afford the corresponding aminoketone(2a, Z = H), which was treated with sodium hydride in dry THF at a room temperature, yielding an epimeric mixture of 9a-hydroxy-5,8-dideoxomitosanes 3a[IR ν(Nujol) 1670 cm^{-1}; NMR δ(DMSO-d_6) 0.93(d, 1.5, J = 7 Hz), 1.14(d, 1.5, J = 7 Hz), 1.91(s, 1.5), 1.96(s, 1.5) and 2.37(s, 3) ppm; MS 386(M^+) and 368(M^+- H_2O): 95% yield from 2a]. In a similar manner, 2b gave 3b[IR ν(Nujol) 1675 cm^{-1}; NMR δ(acetone-d_6) 1.16 (d, 1.5, J = 7 Hz), 1.38(d, 1.5, J = 7 Hz), 2.39(s, 3) and 2.80(s, 6) ppm; MS 339(M^+) and 321(M^+- H_2O): 86% yield from 2b]. The acid-sensitive 3a and 3b were converted quantitatively to 5,8-dideoxomitosenes 4a(mp 221-4°) and 4b(mp 199-201°)[2] through dehydration reaction in glacial acetic acid at a room temperature for 5 min, respectively.

Reduction of the lactam group in 3a was carried out with phosphorous pentasulfide in THF at reflux, followed by desulfurization with Raney Ni in EtOH-THF at reflux, to afford pyrrolo[1,2-a]indole 5 (mp 217-20°)[2] which was subjected to detosylation reaction with sodium in liquid ammonia, providing the known pyrrolo [1,2-a]indole[6 , mp 95-7°(lit.[3] mp 94-5°); IR ν(KBr) 3300 and 3220 cm^{-1}; NMR δ($CDCl_3$) 2.17(s, 3), 2.29(s, 3), 2.36-2.65(m, 2), 2.85(t, 2, J = 7Hz), 3.93(t, 2, J = 7 Hz), 6.78(s, 1) and 6.90(s, 1) ppm: 64% overall yield from 3a].

Oxidation of 3b with 1.5 eq. of lead tetraacetate in triethylamine-methanol at a room temperature and the subsequent treatment with aq. ethylene glycol afforded the unstable 8-membered compound[7, mp 103-4°; IR ν($CHCl_3$) 3280, 1705, 1620 and 1560 cm^{-1}; NMR δ($CDCl_3$) 1.26(d, 3, J = 7 Hz), 2.02(d, 3, J = 1.5 Hz), 2.89(s, 6), 3.04(s, 3), 7.06(q, 1, J = 1.5 Hz) and 7.20(d, 1, J = 2 Hz) ppm; MS 369(M^+): 37% yield], monomethoxymitosanes[8a, mp 183-5°; IR ν(Nujol) 3360, 3270, 1690 and 1618 cm^{-1}; NMR δ($CDCl_3$) 1.39(s, 3), 2.34(s, 3), 2.87(s, 6), 3.36(s, 3), 3.40(s, 1), 6.00(broad s, 1) and 7.41(s, 2) ppm; MS 369(M^+): 9% yield], and [8b, mp 172-3°; IR ν(Nujol) 3320, 3180, 1670 and 1610 cm^{-1}; NMR δ($CDCl_3$) 1.59(s, 3), 2.08(s, 1), 2.34(s, 3), 2.85(s, 6), 3.25(s, 3), 5,98(broad s, 1), 7.39(s, 1) and 7.43 ppm; MS 369(M^+): 12% yield] as two isomers. The same products(8a, b) were also obtained by oxidation of 4b with a catalytic amount of osmium tetroxide-N-methylmorpholine-N-oxide[4] in aq. acetone-tert. butanol at a room temperature, followed by treatment with 10% hydrochloric acid-methanol in 70% overall yield from 4b.

Further studies are in progress to accomplish the synthesis of mitomycins and the related compounds.

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