SYNTHETIC APPROACHES TO MITOMYCINS

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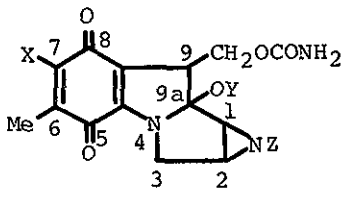
The mitocycins (1) are a family of antibiotics that possess an activity against both gram-positive and negative bacteria but are more noted for their antitumor properties. Many reports have been published on approaches to the synthesis of mitomycins.[1-7]



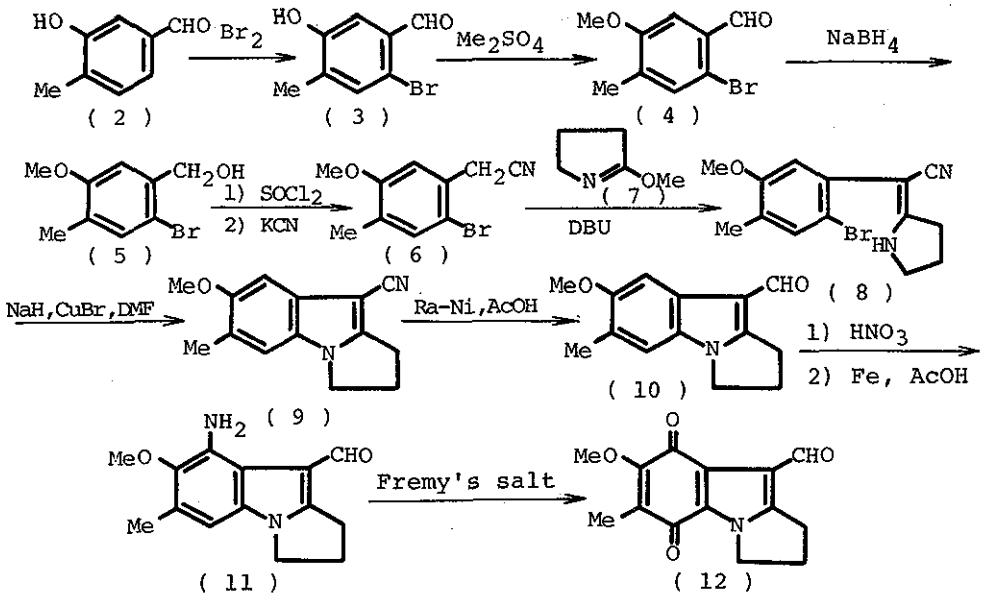
(1)

	X	Y	Z
Mitomycin A	MeO	Me	H
Mitomycin B	MeO	H	Me
Mitomycin C	NH_2	Me	H
Porfiromycin	NH_2	Me	Me

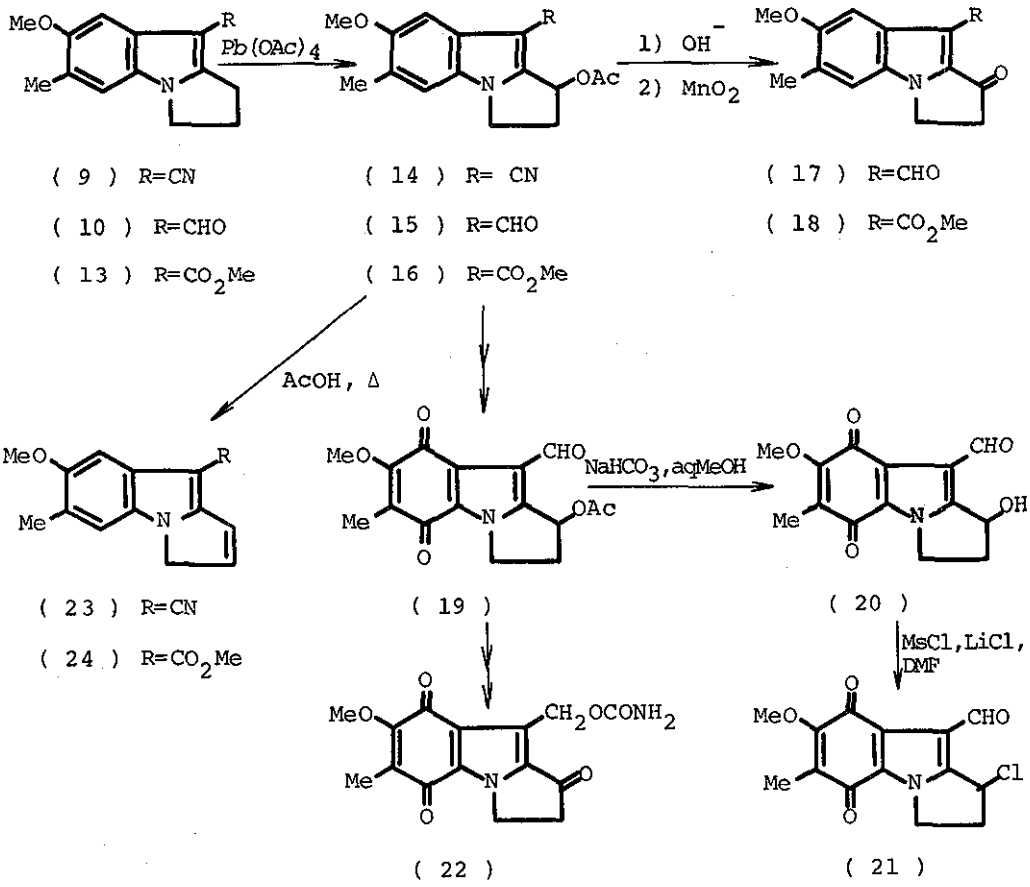
The majority of published works are concerned with the formation of the tricyclic pyrrolo[1,2-a]indoles. Our synthesis of this ring system involves an intramolecular nucleophilic aromatic substitution as follows. Bromination of 3-hydroxy-4-methyl-benzaldehyde (2) yielded the bromide (3), which was methylated with dimethyl sulphate to give the aldehyde (4). Reduction of 4 with sodium borohydride, followed by chlorination of the resulting

alcohol (5) with thionyl chloride and cyanation with potassium cyanide in the presence of sodium iodide in ethyl methyl ketone, gave the nitrile (6). Heating the nitrile (6) with 2-methoxy-Δ'-pyrroline (7) in the presence of 1,5-diazabicyclo[5.4.0]undec-5-ene furnished the corresponding α-pyrrolidine-2-ylideneacetonitrile (8).

The cyclisation of 8 to the pyrrolo[1,2-a]indole (9) was accomplished by stirring at room temperature in the presence of sodium hydride and cuprous bromide in dimethylformamide. Refluxing the nitrile (9) with nickel-aluminium alloy in 50 % aqueous acetic acid gave the aldehyde (10), which was transformed into the quinone (12) according to the usual method, namely nitration, followed by reduction and oxidation of the resulting amino-compound (11) with Fremy's salt.[8]



Introduction of a functional group at C_1 position was carried out by oxidation with lead tetraacetate. Thus, stirring the nitrile (9), the aldehyde (10) and the ester (13) with an equivalent amount of lead tetraacetate in acetic acid at room temperature yielded



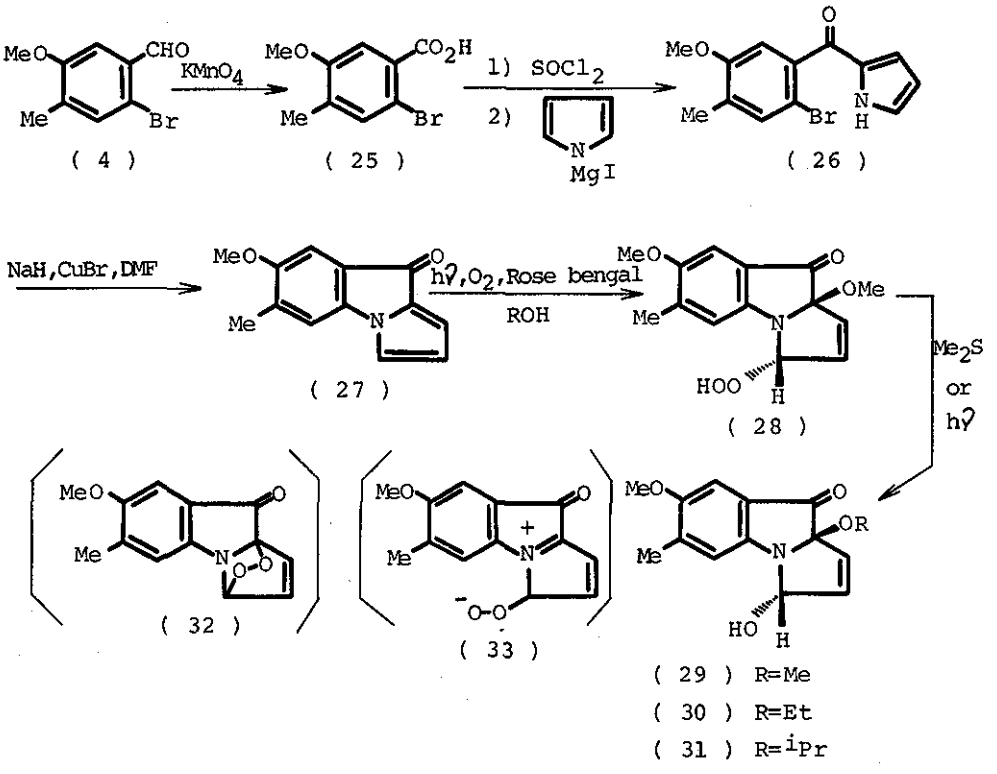
the acetates (14,15 and 16) in good yield. The acetates (15 and 16, were hydrolysed and then oxidised with manganese dioxide in methylene chloride to the ketones (17 and 18). The formyl-acetate (15) was converted, according to a known procedure[6], to the quinone

(19), which had already been transformed to desammonoapomitomycin A (22).[6] The quinone (19) was hydrolysed with sodium hydrogen carbonate in aqueous methanol to the alcohol (20), which, on treatment with methanesulphonyl chloride and lithium chloride in dimethylformamide, yielded the chloride (21), whereas heating the acetates (14 and 16) in acetic acid furnished the 3H-pyrrolo[1,2-a]indoles (23 and 24).[9]

The introduction of the oxo-substituent at the C_{9a} position seems to be one of the most difficult problems for the synthesis of mitomycins. The elimination of the hydroxyl or methoxyl group at the C_{9a} position very easily occurs under a mild acidic treatment of mitomycins. No report for building up the oxo-substituent at the angular position in the pyrrolo[1,2-a]indole ring system has appeared. On the other hand, Franck has tried the photooxidation of the 9H-pyrrolo[1,2-a]indoles but only dehydrated products were obtained.[5] Furthermore, 9-keto-9H-pyrrolo[1,2-a]-indole did not react with singlet oxygen. We expected that the presence of electron-donating groups on ring A would activate the addition of singlet oxygen to pyrrole ring C in 9-keto-9H-pyrrolo-[1,2-a]indoles. Based on this premise, 9-keto-7-methoxy-6-methyl-9H-pyrrolo[1,2-a]indole (27) was subjected to photooxidation.[10] The substrate (27) was prepared as follows. Potassium permamganate oxidation of the aldehyde (4) in aqueous acetone gave the carboxylic acid (25), which, after conversion of the acid chloride, was condensed with pyrrylmagnesium iodide. Cyclisation of the resulting 2-benzoylpyrrole (26) to 27 was carried out by treatment with sodium hydride and cuprous bromide in dimethylformamide at

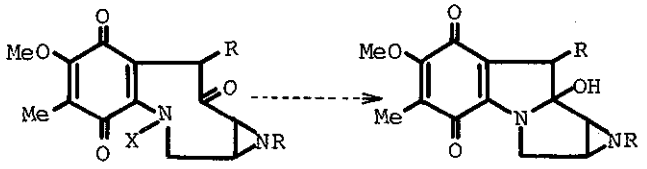
room temperature.

Irradiation of 27 in methanol under an oxygen atmosphere in the presence of Rose Bengal as sensitizer with a 200 W halogen lamp for 24 h gave 9,9a-dihydro-3α-hydroperoxy-9-keto-7,9aβ-dimethoxy-6-methyl-3H-pyrrolo[1,2-a]indole (28) and the corresponding 3α-hydroxy-compound (29). The former (28) could be converted to the latter (29) by irradiation in methanol or treatment with dimethylsulphide. Therefore after the irradidation for 24 h, the resulting mixture was irradiated for additional 24 h under the similar conditions as above except a nitrogen atmosphere and the hydroxy-compound (29) was obtained as a sole product in 71.4 % yield.

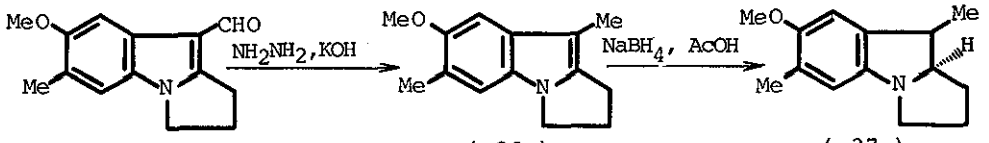


The 9aβ-ethoxy (30)- and isopropyloxy (31)-compounds were synthesised by irradiation of 27 in the corresponding alcohols, respectively. These products would be formed via the endo-peroxide (32) or the zwitterionic intermediate (33).

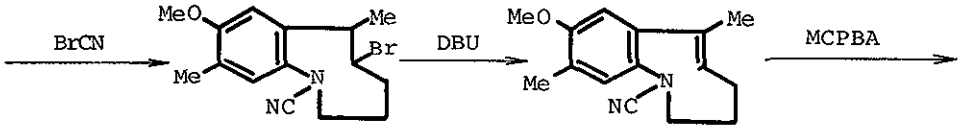
Furthermore, we considered that removing the protecting group of the eight membered ketone (34) would provide the oxo-substituted compound (35) as a stable form. Therefore, the aldehyde (10) was converted to the tetrahydro-1H-pyrrolo[1,2-a]indole (37) by Wolff-



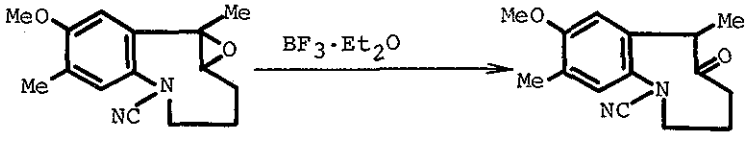
(34) (35)



(10) (36) (37)



(38) (39)



(40) (41)

Kishner reduction followed by stirring 36 with sodium borohydride in acetic acid. Treatment of 37 with cyanogen bromide selectively cleaved the bond between the nitrogen and the carbon at 9a position. Dehydrohalogenation of the resulting bromide (38) with DBU gave the olefin (39), which was transformed to the required ketone (41) by the epoxidation followed by a treatment with boron trifluoride etherate. The conversion of 41 to quinone derivative is under investigation.

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