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SYNTHETIC APPROACH TOWARD MITOMYCINS. SYNTHESIS OF 9-BENZYLOXYMETHYL-5-METHOXY-4-METHYL-3*H*-PYRROLO[1,2-*a*]INDOL-4,5-DIONE [1)]

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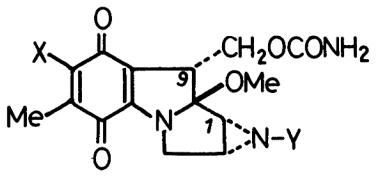
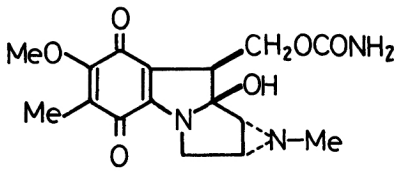
2-Azido-3-(1'-benzyloxymethyl-2',4'-pentadienyl)-5-methoxy-6-methyl-1,4-benzoquinone is prepared and its thermal decomposition under the presence of $Cu(acac)_2$ affords the corresponding 3*H*-pyrrolo[1,2-*a*]indol-5,8-dione, which is the important precursor for mitomycin synthesis.

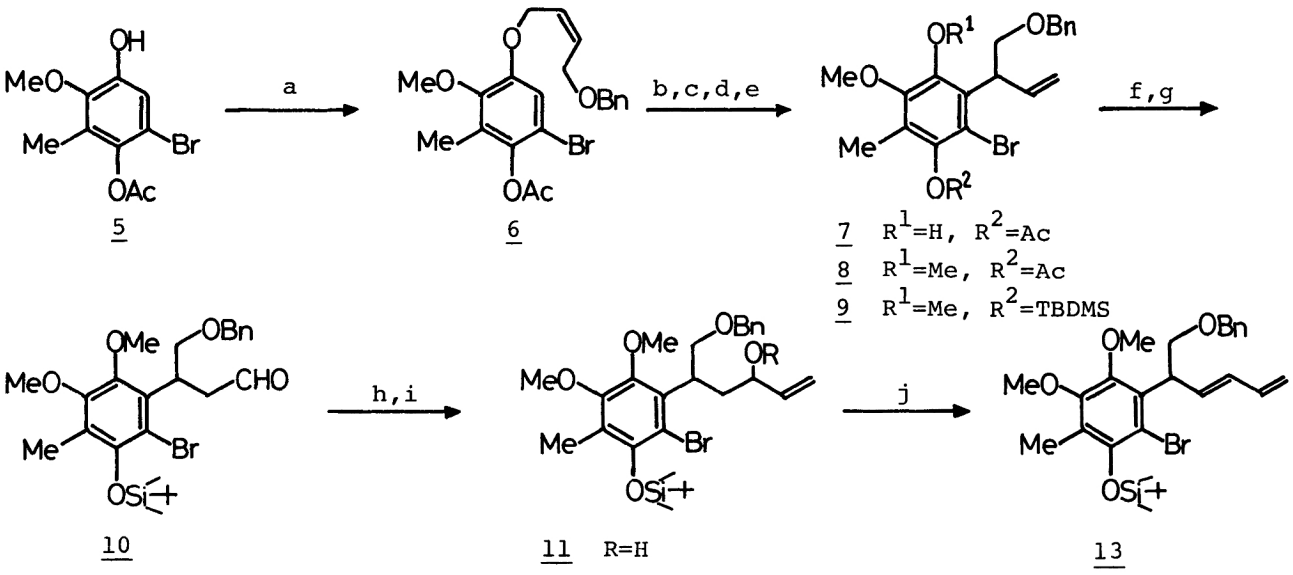
Mitomycins are known to be a member of antitumor antibiotics which have demonstrated activities against a variety of human malignancies.[2)] Many synthetic efforts have been made for recent twenty years.[3)] In our previous paper,[1)] we reported one step cyclization of 2-azido-3-(2',4'-pentadienyl)-1,4-quinones to 3*H*-pyrrolo[1,2-*a*]-indols by means of copper metal catalyzed thermal decomposition. This method is thought to be one of the most promising route to the construction of mitomycins, because it is easily accessible and their double bond at C-1 has potentiality to be converted to the corresponding aziridine. The obtained mitosan analogues, however, lack carbamoyloxymethyl group at 9 position. From the DNA cross-linking ability, this group, which cooperates with aziridino group, plays an essential role for the development of strong activities toward DNA as a bioreductive alkylating agent.[2b-d)] So, we aimed to synthesize 16, which possesses hydroxymethyl group at C-9. In our synthesis of key precursor 15, we had to conquer sterical dif-





1 mitomycin A: X=OMe, Y=H
2 mitomycin B
3 mitomycin C: X=NH_2, Y=H
4 porfiromycin: X=NH_2, Y=Me

Scheme 1



5 6

7 R^1=H, R^2=Ac
8 R^1=Me, R^2=Ac
9 R^1=Me, R^2=TBDMS

10 11 R=H 12 R=Ms 13

14 X=Br
15 X=N_3

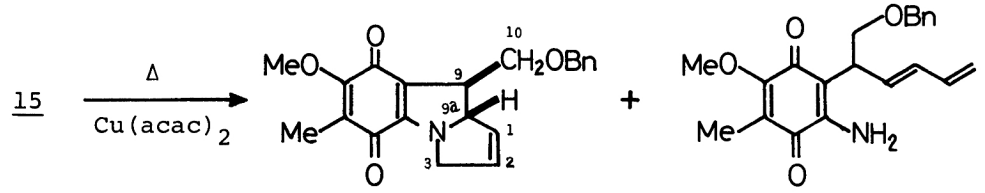
Reaction

a: $BnOCH_2CH=CHCH_2Br$, K_2CO_3, acetone, Δ.
b: N,N-Dimethylaniline, 200°C, 3h. c: MeI, K_2CO_3, acetone.
d: KOH, MeOH, 0°C. e: TBDMS-Cl, imidazole, DMF.
f: $BH_3 \cdot SMe_2$, Et_2O; H_2O_2, NaOH. g: PCC, CH_2Cl_2.
h: $CH_2=CHMgBr$, THF. i: MsCl, Et_3N, 0°C. j: Al_2O_3, Et_2O.
k: CAN, CH_3CN. l: NaN_3, EtOH.

ficulties which may arise between benzyloxymethyl group at position 1' and near-by substituent X(X=Br,N_3). However, we have overcome the difficulties as described bellow. We report successful synthesis of the desired pyrroloindolquinone 16.

Preparation of 15 was performed in the following reaction sequense (Scheme 1). 4-Acetoxy-5-bromo-3-methyl-2-methoxyphenol (5)[4,5] was treated with 4-bezyloxy-1-bromo-cis-2-butene[6] and K_2CO_3 in acetone to afford the corresponding allyl ether 6[5] (88%), which was heated at 200°C in N,N-dimethylaniline under argon atmosphere. This Claisen rearrangement proceeded rather slow and after 3 h most of the starting material disappeared to afford the corresponding phenol 7[5] in an 84% yield. After methylation (MeI/K_2CO_3/acetone) of 7, methyl ether 8 was obtained in a quantitative yield. In this stage, two routes were examined for construction of 2,4-pentadienyl side chain. First, we applied Wittig reaction; by ozonolysis (O_3/AcOEt/-78°C then Me_2S) 8 was converted to the corresponding aldehyde, which was treated with $Ph_3P=CH-CH=CH_2$. Unexpectedly, the desired diene was not obtained.[7] So, another route was tried as follows. The acetate 8 was converted to the corresponding t-$BuMe_2Si$(TBDMS) ether 9[5] by two step procedures (KOH/MeOH/0°C; TBDMS-Cl/imidazole/DMF) in a 95% overall

yield. Hydroboration of 9 ($BH_3 \cdot SMe_2/Et_2O/0°C$ then 30% H_2O_2/NaOH/EtOH) was followed by oxidation with pyridinium chlorochromate (PCC) in CH_2Cl_2 to afford aldehyde 10,[8] in which the side chain was elongated with vinyl Grignard reagent (THF/0°C) to give alcohol 11[5] in a 51% overall yield from 9. The alcohol 11 was quantitatively converted to the corresponding mesylate 12[5] (MsCl / excess Et_3N / 0°C / 1 h). Eliminatin of this leaving group with various amine bases, such as 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU),was unsuccessful. Treatment of 12 with activated alumina (Woelm neutral, akt 1) in dry ether for 4 h afforded the desired diene 13[8] in a 78% yield. According to the previous method,[1] the bromoquinone was converted to the corresponding azidoquinone 15[5] (58%), which was added to the refluxed solution of benzene under the presence of $Cu(acac)_2$[9] (2 equiv. to 15) under argon atmosphere. The solution was continued to reflux for 3 h until the starting quinone disappeared.



16 17

Products were separated by preparative LC (hexane/ether eluted),and 9-benzyloxymeth-yl-6-methyl-7-methoxy-3*H*-pyrrolo[1,2-*a*]indol-5,8-dione (16)[8] and aminoquinone 17[5] were obtained in the respective yields of 40% and 5%. This cyclization proceeded stereoselectively to afford only β-bezyloxymethyl derivative (from NMR analysis). Thus, the cyclization reaction proceeded smoothly and substituent at 1' position of the side chain showed no intensive effect to our cyclization. The obtained quinone 16 is the important precursor in the mytomycin synthesis.

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References

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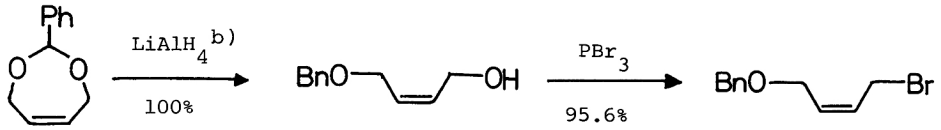
4) Compound 5 was prepared by a modified method of our previous one from 2-hydroxy-6-methoxytoluene, i.e. (i) Br_2-dioxane/Et_2O/-20°C to r.t., (ii) Ac_2O/Py/r.t., (iii)$Cl_2CHOCH_3/TiCl_4/CH_2Cl_2$/-5-0°C, (iv) H_2O_2/HCO_2H.

5) These substances gave satisfactory MS,IR,and ^{1}H-NMR spectra consisted with assigned structures.

6) This allylic bromide is prepared by the following route from 2-phenyl-4,7-dihydro-1,3-dioxepin.[a)]



bp 80°C/ 0.13Pa
(Kugelrohr)

a) H.-D.Scharf and H.Frauenrathe, Chem. Ber., 133, 1472 (1980);
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7) In the present time, the reason was not clear, while steric hindrance around formyl group may prevent attack of bulky phosphonium ylide together with its essential low reactivity.

8) Spectroscopic data of typical compounds; 10: ^{1}H-NMR(CCl_4) δ 0.12(s,6H,Me_2Si), 1.00(s,9H,t-Bu), 2.08(s,3H,ring Me), 2.80(t,2H,J=7, 2Hz,$C\underline{H}_2CHO$), 3.4-3.7(m,2H, CH_2O), 3.66 and 3.72(each s,3H,MeO), 4.22(m,1H,C<u>H</u>-Ar), 4.42(s,2H,$C\underline{H}_2Ph$), 7.16(s, 5H,Ph), 9.54(t,1H,J=2Hz,CHO); IR 2920, 1720, 1450, 1400, 1100, 825, 770cm^{-1}; MS m/e 538(M^+-2), 536(M^+).
12: ^{1}H-NMR(CCl_4) δ 0.14(s,6H,Me_2Si), 1.04(S,9H,t-Bu), 2.09(s,3H,ring Me), 2.1(m, 2H,CH_2), 2.75 and 2.78(each s,3H,$\underline{Me}SO_3$), 3.6-3.9(m,8H), 4.44(s,2H,$C\underline{H}_2Ph$), 4.90 (m,1H,C<u>H</u>-Ar), 5,0-6.0(m,3H,olefinic H), 7.16(s,5H,Ph); IR 2930, 2860, 1450, 1405, 1360, 1170, 1110, 830, 770cm^{-1}; MS m/e 644(M^+-2), 642(M^+).
16: 400MHz ^{1}H-NMR($CDCl_3$) δ 1.86(s,3H,ring CH_3), 3.50(dd,1H,J=16.1,8.8Hz, diastereotopic C^{10}-H), 3.53(ddd,1H,J=8.8,5.8,2.4Hz,$H^{9\alpha}$), 3.94(dd,1H,J=16.1,2.4Hz, diastereotopic C^{10}-H), 4.02(dddd,1H,J=16.4,3.6,2.1,1.5Hz,$H^{3\beta}$), 4.03(s,3H,MeO), 4.31(dddd,1H,J=16.1,3.6,1.8,1.8Hz,$H^{3\alpha}$), 4.56(AB q,2H,J=12.2Hz,$C\underline{H}_2Ph$), 4.82(m,1H, H^{9a}), 5.82 and 5.86(m,2H,olefinic H), 7.32(m,5H,arom. H); IR 1620, 1575, 1405, 1300, 1255, 1100, 730, 658cm^{-1}; MS m/e 351(M^+); UV(MeOH) λ_{max}(log ε) 213(4.31), 224(sh), 255(3.87), 314(3.87), 535(3.04). Dark purple oil.

9) From our recent study, $Cu(acac)_2$ is active toward decomposition of azidoquinone as well as activated Cu powder and it suppresses aminoquinone formation. Other metal acetylacetonates (M=V, Mn, Fe, Co, Ni) were almost ineffective to this reaction.

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