Synthesis of 9a-Deoxymitomycin Congeners [1]

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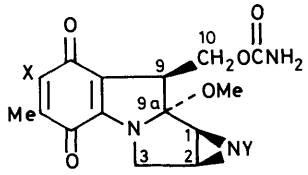
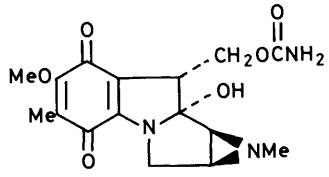
The protected mitosane (**23**) is prepared in stereospecific manner. The key reactions included in the synthetic scheme are (i) Lewis acid-mediated Claisen-type rearrangement of the penta-2,4-dienyl aryl ether (**10**) to the penta-2,4-dienylphenol (**11**), (ii) the regioselective incorporation of the alkoxymethyl group at the 1-position of the pentadienyl side-chain in the protected pentadienylhydroquinone (**12**), and (iii) the stereospecific copper-catalysed double cyclization of the azido(penta-2,4-dienyl)quinone (**15**) to the 3*H*-pyrrolo[1,2-*a*]indole-5,8-dione (**16**) in one step. Subsequent stereospecific introduction of the aziridine ring furnishes the target compound (**23**).

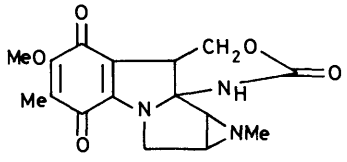
Mitomycins (**1a**—**e**) are a group of excellent antibiotics against both gram-positive and gram-negative bacteria and also against a broad spectrum of solid tumours.[2] In particular, mitomycin C (**1c**) was shown to have the strongest and broadest activity against tumours and has been used in medical practice in cancer chemotherapy, regardless of its relative high toxicity. These clinical uses have stimulated research into both the synthesis[3] and the mechanistic action[4] of these compounds. After the appearance of the total synthesis of mitomycins by Kishi,[5] many reports on synthetic approaches which use shorter and flexible routes toward these compounds were published.[3f–h] We have developed an original and efficient route towards mitomycin precursors[6] and disclose here the detailed synthesis of the protected 9a-deoxymitomycin derivative (**2**).



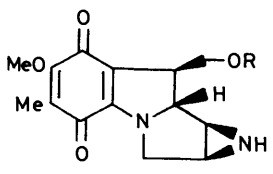
(**1a**) Mitomycin A X = OMe, Y = H
(**1c**) Mitomycin C X = NH_2, Y = H
(**1d**) Porfiromycin X = NH_2, Y = Me



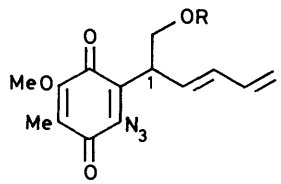
(**1b**) Mitomycin B



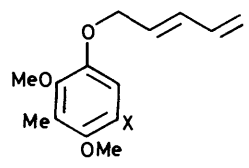
(**1e**) Mitiromycin



(**2**)



(**3**)



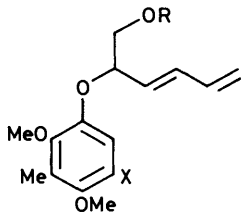
(**4**)

Scheme 1.

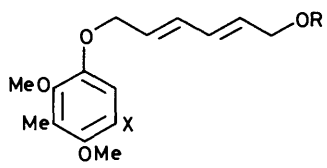
For accomplishment of the synthesis of compound (**2**) according to our strategy (Scheme 1), two new reactions are required, *i.e.* (i) regioselective rearrangement of a penta-2,4-dienyl group to an aromatic ring for the preparation of the precursor required in the next cyclization, and (ii) the double cyclization of the azidodienylquinone to the 3*H*-pyrrolo[1,2-*a*]indole-5,8-dione (a '1,2-deiminomitosane'†). The former reaction was accomplished by Lewis acid-mediated Claisen-type rearrangement of an aryl dienyl ether (**4**),[7] and the latter reaction was successfully attained by means of copper-catalysed reaction of the azidodienylquinone (**3**).[6a,b,8] This cyclization not only gives the required dihydropyrroloindole ring but also synchronously forms an olefinic double bond at the C-1 position. This double bond is very convenient for the introduction of the required aziridine ring in the natural products. These two reactions were coupled and an original and efficient synthetic route to the protected form of 9a-deoxymitomycin was established.

The initial problem encountered was the introduction of an alkoxymethyl group at the 1-position of the pentadienyl side-chain of compound (**3**). According to our strategy with the Claisen-type rearrangement,[7] if pentadienyl aryl ethers with an alkoxymethyl group, e.g. (**5**) or (**6**), can be selectively rearranged to the *ortho* position, this route would be the most efficient one. From a mechanistic study, however, hexadienyl aryl ethers with a pentasubstituted aromatic moiety showed only fragmentation under Lewis acid-mediated conditions.[7] Furthermore, since our initial approach[6b] to the synthesis of (**3**; R = $PhCH_2$) requires

† For the definition of mitosane, see Ref. 3*b*, p. 415.



(5)

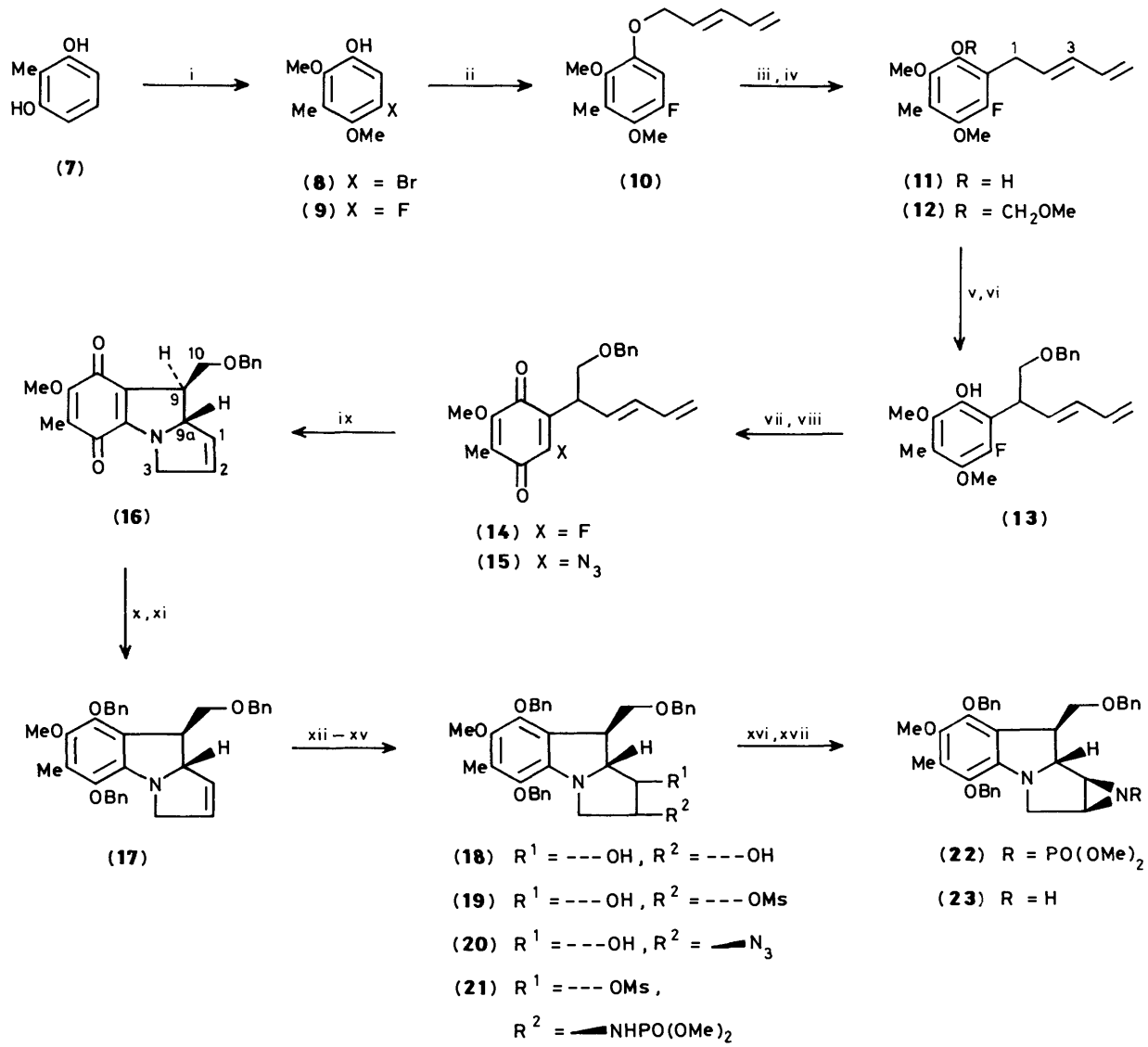


(6)

a multi-step sequence, we decided on the introduction of the alkoxymethyl group to the pentadienylhydroquinone diether (**12**), which can be easily obtained in quantity by the established rearrangement (Scheme 2).

A fluorine atom was incorporated in the aromatic ring as a halogen functionality which would be unexchangeable with Bu^nLi at the stage of the synthesis of the pentadienyl anion. Based on the above analysis, the protected fluoro(penta-2,4-dienyl)hydroquinone diether (**12**) was the initial synthetic target. As the starting material, 5-bromo-2,4-dimethoxy-3-methylphenol (**8**)[7] was prepared from commercially available 2-methylresorcinol (**7**) in 56% overall yield in five steps; *i.e.* (i) methylation with MeI–NaH in dimethylformamide (DMF) (100%), (ii) formylation with $MeOCHCl_2$–$TiCl_4$ (82%), (iii) bromination with Br_2 (80%), (iv) Baeyer–Villiger oxidation with *m*-chloroperbenzoic acid, and (v) basic hydrolysis (86% yield in two steps). The bromophenol (**8**) thus obtained was converted into the fluoride derivative (**9**)[7] in 72% overall yield from (**8**) in three steps; (i) protection of the phenol (**8**) with $MeOCH_2Cl$ (MOMCl) in DMF, (ii) fluorination with perchloryl fluoride ($FClO_3$),* and (iii) deprotection of the

* Perchloryl fluoride is explosive in the presence of oxidizable substances. For safety treatment, see J. H. Peet and B. W. Rocket, *J. Organomet. Chem.*, 1974, **82**, C57: W. Adcock and T. C. Khor, *ibid.*, 1975, **91**, C20.



Scheme 2. *Reagents:* i, MeI, NaH, DMF; $MeOCHCl_2$, $TiCl_4$; Br_2; *m*-$ClC_6H_4CO_3H$; KOH, MeOH; ii, $MeOCH_2Cl$, NaH, DMF; Bu^nLi, Et_2O; $FClO_3$; HCl, acetone; iii, $AlCl_3$·OEt_2; iv, NaH, $ClCH_2OMe$; v, Bu^nLi, $ClCH_2OCH_2Ph$; vi, H_3O^+; vii, CAN; viii, NaN_3; ix, $Cu(acac)_2$; x, Zn, AcOH; xi, BnBr, K_2CO_3; xii, OsO_4, *N*-methylmorpholine oxide; then H_3O^+; xiii, MsCl, Et_3N; xiv, $Bu^n_4N^+N_3^-$; xv, MsCl, Et_3N; xvi, $P(OMe)_3$; xvii, NaH; xviii, $LiAlH_4$

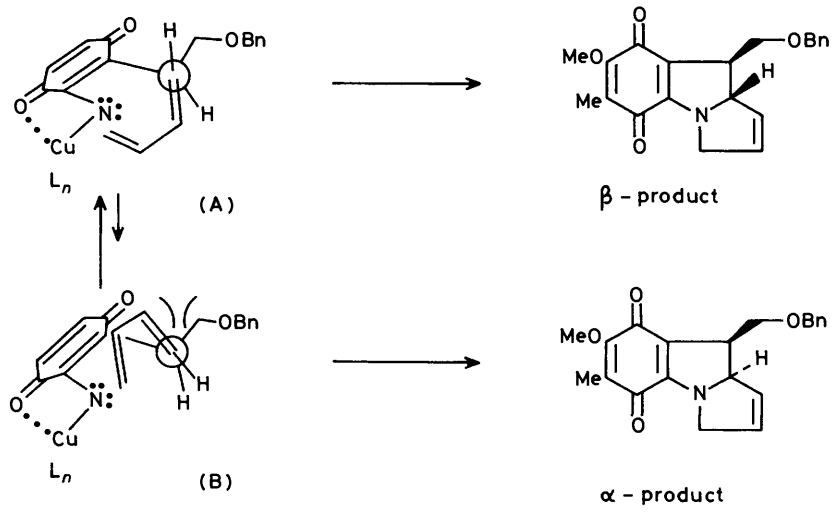
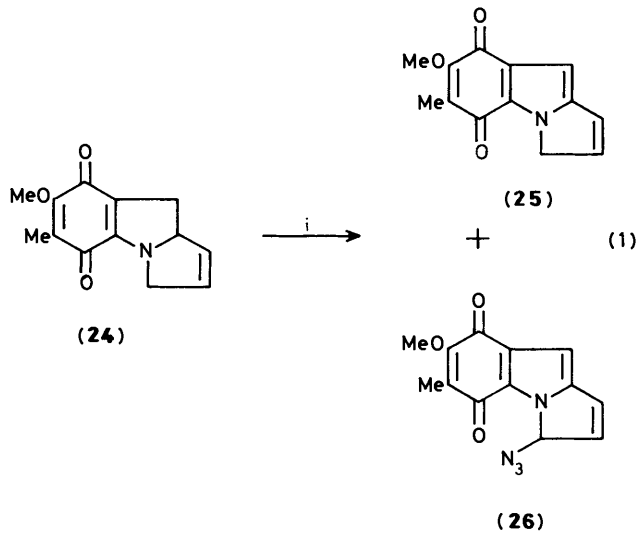


Figure.

MOM group. This phenol (**9**) was converted into the corresponding pentadienyl ether (**10**) with penta-2,4-dienyl chloride–K_2CO_3 in acetone in 83% yield. In the rather simple analogue, the Claisen-type rearrangement of a pentadienyl aryl ether can be best mediated by BF_3·Et_2O.[7] In this case, however, even use of 1.5 mol equiv. of BF_3·OEt_2 (−25 °C; 1 h) gave the required compound (**11**) in insufficient yield (39%), presumably because the electron-withdrawing fluoride group at the *ortho* position decreases the electron density at the unsubstituted carbon atom. After examination of several Lewis acids, treatment with $AlCl_3$·OEt_2 in CH_2Cl_2 (−25 °C; 1 h) afforded compound (**11**) in reasonable yield (62%).

The next problem was the regioselective introduction of an alkoxymethyl group at the side-chain C-1 position, which is the most crowded one on the pentadienyl moiety. We examined electrophilic reaction of the easily generated pentadienyllithium obtained by treatment of compound (**12**) with Bu^nLi. Anhydrous formaldehyde as an electrophile gave two isomeric adducts at the 1- and 3-position in almost equivalent amounts in 32% overall yield. On the other hand, benzyloxymethyl chloride gave the desired adduct in 55% isolated yield in preference to the 3-adduct (22%); they were easily separated by silica gel chromatography. After deprotection of the MOM group, the obtained phenol (**13**) was oxidized with cerium(IV) ammonium nitrate (CAN) to give almost exclusively the corresponding *p*-quinone (**14**), with very little of the *o*-quinone.*

The following double cyclization of the azidodienylquinone (**15**), which was obtained from quinone (**14**) by exchange of the halogen with azide, with $Cu(acac)_2$ catalyst (acac = acetylacetonate) afforded the desired product (**16**). This reaction exhibited an appreciable effec due to substrate concentration. A similar azidoquinone with a simple penta-2,4-dienyl group showed the highest yield (59%) at rather lower concentration (0.005M),[8] while the optimum yield (49%) of compound (**16**) was obtained with 0.01M-(**15**). The product (**16**) showed the ^1H n.m.r. coupling constant J_{9-9a} 5.2 Hz. Since this value is analogous to the corresponding coupling constant ($J_{9\alpha-9a}$ 6.9 Hz) of the unsubstituted product at the 9-position, in comparison with $J_{9\beta-9a}$ 11.5 Hz,[6a,†] the stereochemistry of compound (**16**) was assigned to be 9β. The counter-isomer, the α form, was not detected either by chromatographic or by ^1H n.m.r. methods. This high stereoselectivity is explained in terms of the intermediate's configuration (Figure). The intermediate (A) giving the β product is considered to possess higher stability than the (B) form owing to lower steric repulsion between the benzyloxymethyl group and the butadienyl one.



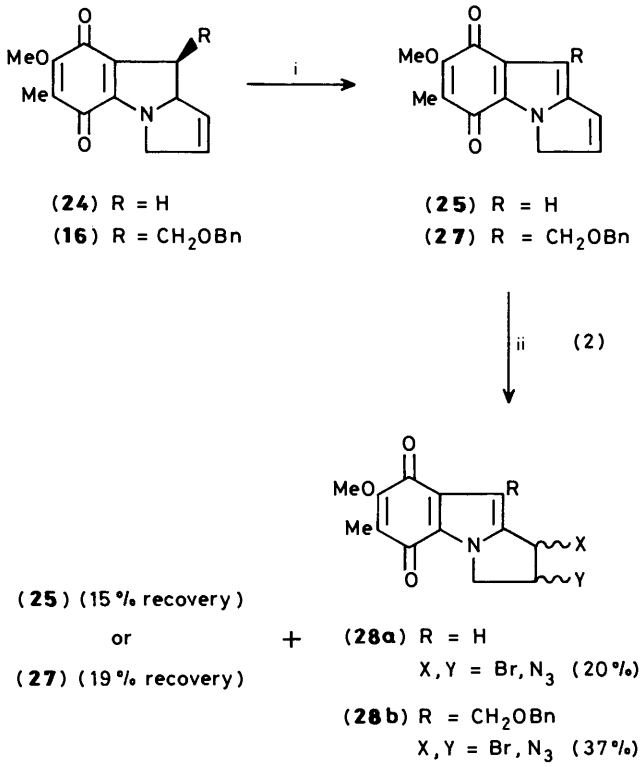
Reagent and conditions: i, BrN_3, −50 °C

For the formation of an aziridine ring from the unactivated C-1–C-2 double bond of compound (**24**), addition of halogenoazide, *e.g.* BrN_3[10] or IN_3,[11] and subsequent reduction[12] is thought to be one of the simplest procedures because it is not necessary to protect the quinone during these reactions. We examined the reaction of the indoloquinone (**24**) with BrN_3 in CH_2Cl_2 at −50 °C. Despite its excellent reactivity with C=C

* When the analogous 1-bromo derivative of (**11**) was oxidized with CAN, the corresponding quinone isomers were obtained in the ratio *ortho*:*para* = 3:2.

† The reduced forms of the isomeric analogues of (**16**) were reported to show J_{9-9a} 4 Hz for the β isomer and J_{9-9a} 11.4 Hz for the α one.[9]

double bonds, however, aromatization preferentially occurred to give the corresponding indoloquinones (**25**) and (**26**) [equation (1)]. Mitosene (**29**) is known to be the active form of mitomycins.[13] To examine the formation of the aziridine functionality from the double bond of the indoloquinones (**25**) and (**27**), these quinones were directly treated with 1 mol equiv. of BrN_3 at −75 °C for 0.5 h to give a regioisomeric mixture of the adducts (**28a**) (20%) and (**28b**) (37%), respectively [equation (2)].



(**24**) R = H
(**16**) R = CH_2OBn

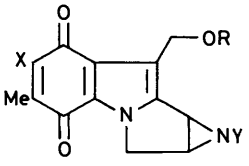
(**25**) R = H
(**27**) R = CH_2OBn

(**25**) (15% recovery)
or
(**27**) (19% recovery)

\+ (**28a**) R = H
X,Y = Br, N_3 (20%)

(**28b**) R = CH_2OBn
X,Y = Br, N_3 (37%)

Reagents: i, DDQ; ii, BrN_3 (1 mol equiv.)



(**29**)

However, owing to the instability of these products under the reduction conditions, further conversion was not examined.

The multistep procedure was applied to the preparation of the protected form (**23**) of mitosane (Scheme 2). The tribenzyl ether (**17**), which was prepared from the quinone (**16**) by reductive benzylation, was treated with OsO_4–*N*-methylmorpholine oxide to afford diol (**18**), which was then converted into the aziridine as follows; (i) esterification of the 2-OH to the monosulphonate (**19**) with MsCl–Et_3N; (ii) conversion of the ester (**19**) into the corresponding azide (**20**) with $Bu_4N^+N_3^-$; (iii) esterification of the 1-OH to the corresponding mesyl ester with MsCl–Et_3N and phosphorylation to the phosphoramide (**21**) with Me_3P. Reductive removal of the *N*-phosphoryl group with lithium aluminium hydride gave the protected form (**23**) of the 9-demethoxymitomycin in 28% overall yield from diol (**18**). The relative stereochemistry of the introduced aziridine ring was confirmed by comparison of the spectral data with those of an authentic sample derived from natural mitomycin C.* The obtained product (**23**) is a promising precursor for the synthesis of mitomycins A, C, and porfiromycin because all four compounds have the same relative stereochemistry. The remaining problem in the total synthesis is the introduction of an oxygen functionality at the 9a-position. This is now under study in our laboratory.

Experimental

M.p.s were determined with a Yanagimoto micromelting-point apparatus. I.r. spectra were recorded on a JASCO IRA-1 spectrometer. ^1H N.m.r. spectra were obtained using CCl_4 or $CDCl_3$ solutions incorporating tetramethylsilane as internal standard on JEOL JMN-PS-100 (100 MHz) or JMN-FX-400 (400 MHz) instruments. Mass spectra and high-resolution mass spectra were recorded on a JEOL JMS-DX-300 mass spectrometer. Column chromatography was performed on Wako-gel C-200. Microanalyses were performed by the Microanalytical Laboratory of Kyoto University. Satisfactory microanalyses of azide and aziridine derivatives were not obtained due to their inherent instability. All solvents were freshly distilled and stored under nitrogen atmosphere. Methylene dichloride was distilled from calcium hydride. Ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl and stored over sodium wire. Benzene was distilled and stored over molecular sieves 4 Å. Acetone was stored over calcium sulphate. The homogeneity of substrates was tested by t.l.c. and/or h.p.l.c.

2-(1-*Benzyloxymethylpenta*-2,4-*dienyl*)-3-*fluoro*-4,6-*dimethoxy*-5-*methylphenol* (**13**).—To a THF (34 ml) solution of 1-fluoro-2,4-dimethoxy-5-methoxymethoxy-3-methyl-6-(penta-2,4-dienyl)benzene (**12**)[6b] (1.01 g, 3.4 mmol) at −75 °C was added Bu^nLi (1.56M hexane solution; 3.28 ml, 5.13 mml) under nitrogen. After the mixture had been stirred for 0.5 h at −40 °C, benzyloxymethyl chloride (0.41 ml, 3.42 mmol) was added to the solution at −75 °C. The reaction solution was allowed to warm to 0 °C and was poured into water. The organic phase was separated, washed with water, dried over $MgSO_4$, and evaporated under reduced pressure. Column chromatography of the residue on silica gel with hexane–ether (9:1) as eluant gave the 1-*benzyloxymethyl adduct* (**13**) (697 mg, 55%) (Found: C, 71.0; H, 7.0; F, 4.8. $C_{22}H_{25}FO_4$ requires C, 71.0; H, 6.8; F, 5.1%); $\nu_{max.}$(NaCl) 3 520, 2 940, 1 460, 1 415, 1 260, 1 120, 1 060, 1 000, 780, and 750 cm^{-1}; δ_H(100 MHz; CCl_4) 1.11 (3 H, s, Me), 3.63 (5 H, OMe and CH_2OBn), 3.76 (3 H, s, OMe), 4.00—4.20 (1 H, m, 1′-H), 4.43 (2 H, s, CH_2Ph), 4.88 (1 H, d, *J* 10 Hz, 5′-H), 5.00 (1 H, d, *J* 14 Hz, 5′-H), 5.80—6.30 (2 H, m, 2′-, 3′-, and 4′-H), 6.30 (1 H, s, OH), and 7.13 (5 H, s, Ph); *m/z* 372 (M^+, 6%), 252 (76), 223 (100), and 91 (32).

2-(1-*Benzyloxymethylpenta*-2,4-*dienyl*)-3-*fluoro*-6-*methoxy*-5-*methyl*-1,4-*benzoquinone* (**14**).—To an acetonitrile (2.7 ml) solution of the fluorophenol (**13**) (432 mg, 1.2 mmol) at 0 °C was added an aqueous solution (2.7 ml) of CAN (1.39 g, 2.5 mmol). After being stirred for 3 min, the mixture was poured into water and extracted with water. Usual work-up and subsequent purification by column chromatography on silica gel gave the corresponding quinone (**14**) (293 mg, 69%); $\nu_{max.}$

* *N*-Methylmitomycin A derived from mitomycin C (M. Matsui, Y. Yamamoto, K. Uzu, and T. Hirota, *J. Antibiot.*, 1968, **21**, 189) was converted into the 9a-deoxy form (S. Kinoshita, K. Uzu, K. Nakano, M. Shimizu, T. Takahashi, and M. Matsui, *J. Med. Chem.*, 1971, **14**, 103) of which tribenzyl ether has similar n.m.r. data to those of (**23**). These values also agree with the reported ones.[9]

(NaCl) 1 660, 1 615, 1 450, 1 360, 1 305, 1 280, 1 200, 1 160, 1 100, 1 000, 980, and 780 cm^{-1}; δ_H(100 MHz; CCl_4) 1.88 (3 H, s, Me), 3.73—3.84 (2 H, m, CH_2OBn), 3.98 (4 H, OMe and 1'-H), 4.42 (2 H, s, CH_2Ph), 4.95—5.18 (2 H, m, 5'-H), 5.59—6.28 (2 H, m, 2'-, 3'-, and 4'-H), and 7.18 (5 H, m, Ph); *m/z* 356 (M^+, 5%), 326 (13), 235 (100), and 207 (51).

2-*Azido*-3-(1-*benzyloxymethylpenta*-2,4-*dienyl*)-5-*methoxy*-6-*methyl*-1,4-*benzoquinone* (**15**).—To a MeOH (6.3 ml) solution of the quinone (**14**) (293 mg, 0.82 mmol) was added an aqueous solution (1.3 ml) of NaN_3 (80 mg, 1.2 mmol) and the mixture was stirred for 1 h in the dark, and then concentrated under reduced pressure; to the residue were added water and $CHCl_3$. After usual work-up and chromatographic purification on silica gel, the corresponding azidoquinone (**15**) (274 mg, 88%) was obtained; $\nu_{max.}$(NaCl) 2 100, 1 650, 1 595, 1 360, 1 290, 1 145, 1 100, 1 000, and 960 cm^{-1}; δ_H(100 MHz; CCl_4) 1.90 (3 H, s, Me), 3.68 [3 H, m, $CH(CH_2OBn)$], 4.02 (3 H, s, OMe), 4.35 and 4.48 (2 H, ABq, *J* 12 Hz, CH_2Ph), 4.96 (1 H, d, *J* 6 Hz, 5'-H), 5.10 (1 H, d, *J* 15 Hz, 5'-H), 6.00 (2 H, m, 2'-, 3'-, and 4'-H), and 7.22 (5 H, m, Ph).

9β-*Benzyloxymethyl*-9,9aβ-*dihydro*-7-*methoxy*-6-*methyl*-3H-*pyrrolo*[1,2-a]*indole*-5,8-*dione* (**16**).—To a refluxing dry benzene (36 ml) solution of $Cu(acac)_2$ (204 mg, 0.78 mmol) was added a dry benzene (3 ml) solution of the azidoquinone (**15**) (133 mg, 0.35 mmol) and the mixture was stirred for 2 h at 80 °C. After cooling to room temperature, the mixture was filtered and the solvent was removed under reduced pressure. Usual purification gave the *dihydropyrroloindoloquinone* (**16**) (60 mg, 49%) (Found: C, 71.7; H, 5.8; N, 4.1. $C_{21}H_{21}NO_4$ requires C, 71.8; H, 6.0; N, 4.0%); $\lambda_{max.}$(MeOH) 213 (ε 20 400 dm^3 mol^{-1} cm^{-1}), 224sh, 255 (7 400), 314 (7 400), and 535 nm (1 100); $\nu_{max.}$(NaCl) 1 620, 1 575, 1 400, 1 300, 1 255, 1 133, 730, and 658 cm^{-1}; δ_H(400 MHz; $CDCl_3$) 1.86 (3 H, s, Me), 3.50 (1 H, dd, J_{gem} 16.1, $J_{10,9}$ 8.9 Hz, 10-H), 3.53 (1 H, ddd, J_{gem} 16.1, $J_{9,9a}$ 5.2, $J_{10,9}$ 2.4 Hz, 9-H), 3.94 (1 H, dd, J_{gem} 16.1, $J_{10,9}$ 2.4 Hz, 10-H), 4.02 (1 H, dddd, J_{gem} 16.4, $J_{3\beta,9a}$ 3.6, $J_{3\beta,1}$ 2.1, $J_{3\beta,2}$ 1.5 Hz, 3β-H), 4.03 (3 H, s, OMe), 4.31 (1 H, dddd, J_{gem} 16.4, $J_{3\alpha,9a}$ 3.6, $J_{3\alpha,1}$ 1.8, $J_{3\alpha,2}$ 1.8 Hz, 3α-H), 4.56 (2 H, ABq, *J* 12.2 Hz, CH_2Ph), 4.82 (1 H, m, 9a-H), 5.82 (1 H, m, 1-H), 5.86 (1 H, m, 2-H), and 7.21 (5 H, m, Ph); *m/z* 351 (M^+).

5,8-*Dibenzyloxy*-9β-*benzyloxymethyl*-9,9aβ-*dihydro*-7-*methoxy*-6-*methyl*-3H-*pyrrolo*[1,2-a]*indole* (**17**).—To zinc powder (60 mg) was added a CH_2Cl_2 (2 ml) solution of the quinone (**16**) (306 mg, 0.87 mmol) and AcOH (0.5 ml) under nitrogen and the mixture was stirred until the solution became colourless. The mixture was filtered and the filtrate was concentrated under reduced pressure. A mixture of the residue, benzyl bromide (2.1 ml, 17 mmol), and K_2CO_3 (2.39 g, 17 mmol) in DMF (5 ml) was refluxed for 12 h. After having cooled to room temperature, the mixture was poured into water, and extracted with ether. Usual work-up and chromatographic purification on silica gel gave the *benzyl ether* (**17**) (242 mg, 52%); δ_H(100 MHz; CCl_4) 2.00 (3 H, s, Me), 3.20—3.40 (1 H, m, 9-H), 3.63 (3 H, s, OMe), 3.68—4.04 (3 H, m, 10-H_2, 3-H), 4.39 (2 H, m, 3- and 9a-H), 4.48 and 4.85 (2 H, ABq, *J* 10 Hz, CH_2Ph), 4.59 and 5.14 (2 H, ABq, *J* 10 Hz, CH_2Ph), 4.87 and 5.32 (2 H, ABq, *J* 10 Hz, CH_2Ph), 5.63 (2 H, m, 1- and 2-H), and 7.18—7.22 (15 H, m, Ph); *m/z* 533 (M^+) (Found: M^+, 533.2567. $C_{35}H_{35}NO_4$ requires *M*, 533.2566).

5,8-*Dibenzyloxy*-9β-*benzyloxymethyl*-2,3,9,9a-*tetrahydro*-7-*methoxy*-6-*methyl*-1H-*pyrrolo*[1,2-a]*indole*-1α,2α-*diol* (**18**).—To a THF (2.1 ml) solution of the benzyl ether (**17**) (363 mg, 0.68 mmol) and *N*-methylmorpholine oxide (75 mg, 0.75 mmol) was added a catalytic amount of OsO_4 in Bu^{t}OH (1.3 ml) and water (0.15 ml), and the solution was stirred for 12 h. The mixture was poured into water and extracted with ether. Usual work-up and purification gave the *diol* (**18**) (294 mg, 76%) (Found: C, 74.3; H, 6.5; N, 2.4. $C_{35}H_{37}O_6$ requires C, 74.1; H, 6.6; N, 2.5%); $\nu_{max.}$($CHCl_3$) 3 400, 1 440, 1 190, and 1 090 cm^{-1}; δ_H(400 MHz; $CDCl_3$) 2.12 (3 H, s, Me), 2.53 (1 H, br s, OH), 2.89 (1 H, br s, OH), 3.18 (1 H, dd, *J* 6.4 and 10.1 Hz, 10-H), 3.43 (1 H, t, *J* 8.9 Hz, 3-H), 3.65 (1 H, dd, *J* 10.8 and 5.8 Hz, 3.75 (3 H, s, OMe), 3.95 (1 H, m, 2-H), 4.01 (1 H, t, *J* 5.5 Hz, 9-H), 4.08 (1 H, m, 3-H), 4.10 (1 H, m, 1-H), 4.30 (1 H, m, 9a-H), 4.48 and 4.54 (2 H, ABq, *J* 12.2 Hz, CH_2Ph), 4.67 and 5.13 (2 H, ABq, *J* 11 Hz, CH_2Ph), 4.96 and 5.05 (2 H, ABq, *J* 11 Hz, CH_2Ph), and 7.40 (15 H, m, Ph).

2-*Azido*-5,8-*dibenzyloxy*-9-*benzyloxymethyl*-2,3,9,9a-*tetrahydro*-7-*methoxy*-6-*methyl*-1H-*pyrrolo*[1,2-a]*indol*-1-*ol* (**20**).—To a CH_2Cl_2 (1 ml) solution of the diol (**18**) (114 mg, 0.2 mmol) at 0 °C were added Et_3N (43 μl, 0.46 mmol) and methanesulphonyl chloride (MsCl) (17 μl, 0.22 mmol) under nitrogen. After being stirred for 2 h, the mixture was poured into water and extracted with CH_2Cl_2. After usual work-up, the monomesyl ester (**19**) was obtained; δ_H(400 MHz; $CDCl_3$) 2.10 (3 H, s, Me), 2.96 (3 H, s, Ms), 3.46—3.49 (3 H, m, 10-H_2 and 3-H), 3.74 (3 H, s, OMe), 4.05 (3 H, m, 9a-, 9-, and 3-H), 4.36 (1 H, m, 1-H), 4.46 and 4.53 (2 H, ABq, *J* 12 Hz, CH_2Ph), 4.68 and 5.07 (2 H, ABq, *J* 11 Hz, CH_2Ph), 4.94 and 5.03 (2 H, ABq, *J* 11 Hz, CH_2Ph), 5.11 (1 H, m, 2-H), and 7.24—7.41 (15 H, Ph).

To a dry benzene solution of the monomesyl ester (**19**) (103 mg, 0.16 mmol) was added $Bu^n_4NN_3$ (820 mg, 2.8 mmol) and the solution was refluxed for 3 h. The mixture was poured into water and the benzene solution was washed with water five times. After usual work-up, the azido alcohol (**20**) was obtained in 56% yield, $\nu_{max.}$($CHCl_3$) 3 400, 2 100, 1 460, and 1 100 cm^{-1}.

4,7-*Dibenzyloxy*-8β-*benzyloxymethyl*-1,1aα,2,8,8aβ,8b-*hexahydro*-6-*methoxy*-5-*methylazirino*[2',3';3,4]*pyrrolo*[1,2-a]*indole* (**23**).—To a CH_2Cl_2 (0.5 ml) solution of the azido alcohol (**20**) (53 mg, 0.89 mmol) at 0 °C were added Et_3N (40 μl, 0.29 mmol) and MsCl (20 μl, 0.24 mmol) under nitrogen. After being stirred for 2 h, the mixture was poured into water and extracted with CH_2Cl_2. Usual work-up gave the corresponding mesyl ester.

To a THF (15 ml) solution of the mesyl ester was added trimethyl phosphite (38 μl, 0.33 mmol) and the mixture was refluxed for 4 h. After the solvent was removed under reduced pressure, the crude phosphoramide (**21**) was obtained.

To a THF (1 ml) suspension of NaH (60 wt%; 36 mg, 0.89 mmol) at 0 °C was added a THF (1 ml) solution of the phosphoramide (**21**) under nitrogen and the mixture was stirred for 4 h, poured into water, and extracted with ether; usual work-up gave compound (**22**).

To an ethereal (1.5 ml) solution of compound (**22**) at 0 °C was added an ethereal suspension of $LiAlH_4$ (1M; 0.16 ml) under nitrogen and the mixture was stirred for 2 h. To the mixture at 0 °C was added 20% aqueous NaOH (0.32 ml) and the product was extracted with ether. After usual work-up and purification, the *aziridine derivative* (**23**) was obtained in 28% yield from the diol (**18**); δ_H(400 MHz; $CDCl_3$) 2.19 (3 H, s, Me), 2.95 (1 H, m, 1a-H), 3.05 (1 H, m, 8b-H), 3.31 (1 H, dd, *J* 4.9 and 11 Hz, C*H*HOBn), 3.46 (1 H, m, 2-H), 3.65 (1 H, m, CH*H*OBn), 3.71 (1 H, d, *J* 11 Hz, 2-H), 3.74 (3 H, s, OMe), 4.20 (1 H, m, 8a-H), 4.22 (1 H, m, 8-H), 4.45 and 4.92 (2 H, ABq, *J* 11 Hz, CH_2Ph), 4.53 and 4.65 (2 H, ABq, *J* 11 Hz, CH_2Ph), 4.99 and 5.20 (2 H, ABq, *J* 11 Hz, CH_2Ph), and 7.37 (15 H, m, Ph); *m/z* 548 (M^+, 10%) and 457 (100) (Found: M^+, 548.2679. $C_{35}H_{36}N_2O_4$ requires *M*, 548.2674).

Reaction of the Dihydropyrroloindoloquinone (**24**) *with* BrN_3.—To a CH_2Cl_2 (2 ml) solution of the quinone (**24**) (46 mg, 0.2 mmol) at −50 °C was added a CH_2Cl_2 solution of BrN_3[10] (1M; 0.6 ml) under nitrogen and the mixture was stirred for 1 h.

The mixture was poured into water and extracted with CH_2Cl_2. Usual work-up and purification gave the corresponding indoloquinone (**25**) (30%) and the 3-azido derivative (**26**) (35%).

Compound (**25**): red needles, m.p. 151—152 °C (Found: C, 68.0; H, 4.6; N, 6.3. $C_{13}H_{11}NO_3$ requires C, 68.1; H, 4.8; N, 6.1%); $\nu_{max.}$ 1 670, 1 640, 1 610, 1 320, 1 080, and 1 010 cm^{-1}; δ_H(400 MHz; $CDCl_3$) 1.97 (3 H, s, Me), 3.99 (3 H, s, OMe), 4.72 (2 H, m, 3-H_2), 6.36 (1 H, s, 9-H), 6.57 (1 H, ddd, *J* 5.8, 2.1, and 1.8 Hz, 2-H), and 6.67 (1 H, ddd, *J* 5.8, 2.1, and 1.8 Hz, 1-H); *m/z* 229 (M^+, 100), 214 (34), 200 (58), and 186 (37).

Compound (**26**): $\nu_{max.}$(KBr) 2 100, 1 660, 1 630, and 1 310 cm^{-1}; δ_H(400 MHz; $CDCl_3$) 1.99 (3 H, s, Me), 4.02 (3 H, s, OMe), 6.40 (1 H, s, 9-H), 6.54 (1 H, dd, *J* 5.8 and 1.5 Hz, 2-H), 6.60 (1 H, dd, *J* 5.8 and 0.9 Hz, 1-H), and 6.76 (1 H, dd, *J* 1.5 and 0.9 Hz, 3-H); *m/z* 228 ($M - N_3$).

Reaction of the Indoloquinones (**25**) *and* (**27**) *with* BrN_3.—To a MeOH (20 ml) solution of the quinone (**24**) (67 mg, 0.29 mmol) was added a MeOH solution of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (77 mg, 0.35 mmol) and the mixture was stirred for 1.5 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to give the indoloquinone (**25**) in 67% yield.

To a CH_2Cl_2 (6 ml) solution of the indoloquinone (**25**) was added a CH_2Cl_2 solution of BrN_3 (1M; 0.31 ml) at −75 °C for 2 min. After being stirred at this temperature for 0.5 h, the mixture was poured into aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2. After usual work-up and purification, compounds (**28a**) (22 mg, 20%) and (**25**) (15% recovery) were obtained. The pyrroloindole (**28a**) was a mixture of two regioisomers (A and B).

A isomer of (**28a**) had δ_H(400 MHz; $CDCl_3$) 1.96 (3 H, s, Me), 4.03 (3 H, s, OMe), 4.37 (1 H, dd, *J* 13.7 and 1.3 Hz, 3-H), 4.55 (1 H, dd, *J* 13.7 and 5.1 Hz, 3-H), 4.88 (1 H, dd, *J* 5.1 and 1.3 Hz, 2-H), 5.29 (1 H, s, 1-H), and 6.57 (1 H, s, 9-H).

B isomer of (**28a**) had δ_H(400 MHz; $CDCl_3$) 1.97 (3 H, s, Me), 4.03 (3 H, s, OMe), 4.69 (1 H, d, *J* 14.5 Hz, 3-H), 4.78 (1 H, dd, *J* 4.3 and 14.5 Hz, 3-H), 5.04 (1 H, d, *J* 4.3 Hz, 2-H), 5.45 (1 H, s, 1-H), and 6.60 (1 H, s, 9-H).

The mixture of both isomers showed $\nu_{max.}$(NaCl) 2 100, 1 660, 1 640, and 1 320 cm^{-1}.

The indoloquinone (**27**) was prepared in 94% yield from the dihydroindoloquinone (**16**) in the same manner as for the synthesis of the indoloquinone (**25**), and gave *red needles*, m.p. 155—157 °C (Found: C, 72.4; H, 5.6; N, 4.2. $C_{21}H_{19}NO_4$ requires C, 72.2; H, 5.5; N, 4.0%); $\nu_{max.}$(KBr) 1 650, 1 630, 1 600, 1 500, 1 310, and 1 100 cm^{-1}; δ_H(400 MHz; $CDCl_3$) 1.97 (3 H, s, Me), 4.00 (3 H, s, OMe), 4.64 (2 H, s, CH_2OBn), 4.71 (2 H, s, 3-H_2), 4.84 (2 H, s, CH_2Ph), 6.53 (1 *H*, d, *J* 6 Hz, 2-H), 6.77 (1 H, d, *J* 6.1 Hz, 1-H), and 7.32—7.46 (10 H, m, Ph).

The indoloquinone (**27**) was treated with BrN_3 by the same procedure as was the quinone (**25**) to afford compounds (**28b**) and (**27**) in 37% yield and 19% recovery, respectively. The pyrroloindole (**28b**) was a mixture of two regioisomers (C and D).

C isomer of (**28**) showed $\nu_{max.}$($CHCl_3$) 2 100, 1 660, 1 640, and 1 100 cm^{-1}; δ_H(400 MHz; $CDCl_3$) 1.94 (3 H, s, Me), 4.00 (3 H, s, OMe), 4.18 (1 H, dd, *J* 12 and 8.5 Hz, 3-H), 4.67 (1 H, ddd, *J* 5.6, 7.3, and 8.5 Hz, 2-H), 4.68 (2 H, ABq, *J* 11 Hz, 10-H_2), 4.73 (1 H, dd, *J* 12 and 7.3 Hz, 3-H), 4.83 (2 H, ABq, *J* 14 Hz, CH_2Ph), 5.08 (1 H, d, *J* 5.6 Hz, 1-H), and 7.38 (5 H, s, Ph).

D isomer of (**28**) showed $\nu_{max.}$(KBr) 2 100, 1 660, 1 640, 1 500, and 1 100 cm^{-1}; δ_H(400 MHz; $CDCl_3$) 1.96 (3 H, s, Me), 4.02 (3 H, s, OMe), 4.59 (1 H, d, *J* 4.7 Hz, 2-H), 4.64 (1 H, d, *J* 14.1 Hz, 3-H), 4.69 (2 H, ABq, *J* 11.5 Hz, 10-H_2), 4.69 (1 H, d, *J* 4.7 and 14.1 Hz, 3-H), 4.87 (2 H, ABq, *J* 14.1 Hz, CH_2Ph), 5.23 (1 H, s, 1-H), and 7.39 (5 H, s, Ph).

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