SYNTHESIS OF (±) FREDERICAMYCIN A§

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Abstract - A total synthesis of fredericamycin A (**1**) is described, in which a novel radical cyclisation approach is used to build the spiro[4.4]nonane system. The supporting studies with experimental details are reported.

In recent times, fredericamycin A (**1**)[1] has evoked a lot of interest among chemists and biologists in light of its potent antitumour and antibiotic activity. Besides its complex structural features comprising an array of highly substituted aromatic rings and an unique spirosystem offers a challenge in organic synthesis. Various methods[2] have been adopted for the skeletal construction of **1** and three total syntheses,[3] including one from our group have been accomplished.[3c] Reported, herein, our findings and experiences encountered during the total synthesis of this molecule. Systematic synthetic analysis of fredericamycin A (Scheme 1) reveals that a suitable approach for the construction of spiro unit is very much essential for the success of its total synthesis. The first task was therefore to work out a methodology to obtain a model spiro[4.4]nonane system. Another important point is that the spiro system should be built at the later stages of the synthesis, because the strained spiro unit may not withstand the drastic reaction conditions, employed for preparing substituted aromatic rings. Disconnection of **1** showed that indandione (**2**) is a key intermediate which can be synthesised from benzphthalide (**4**) and corresponding aldehyde (**7**) or (**8**) using Shapiro's conditions.[4] This intermediate can later be elaborated to the spiro unit through intramolecular alkylation.

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§ This paper is dedicated to Prof. Alan R. Katritzky on the occasion of his 65th birthday with our best wishes.

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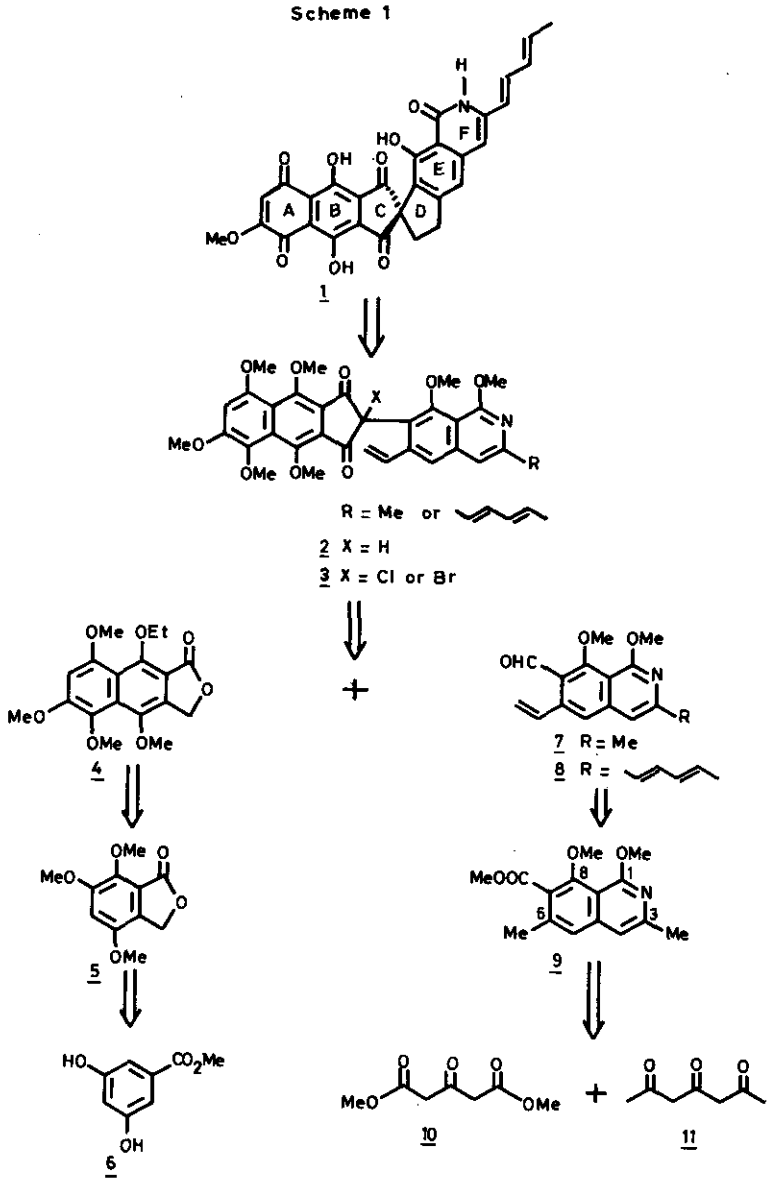
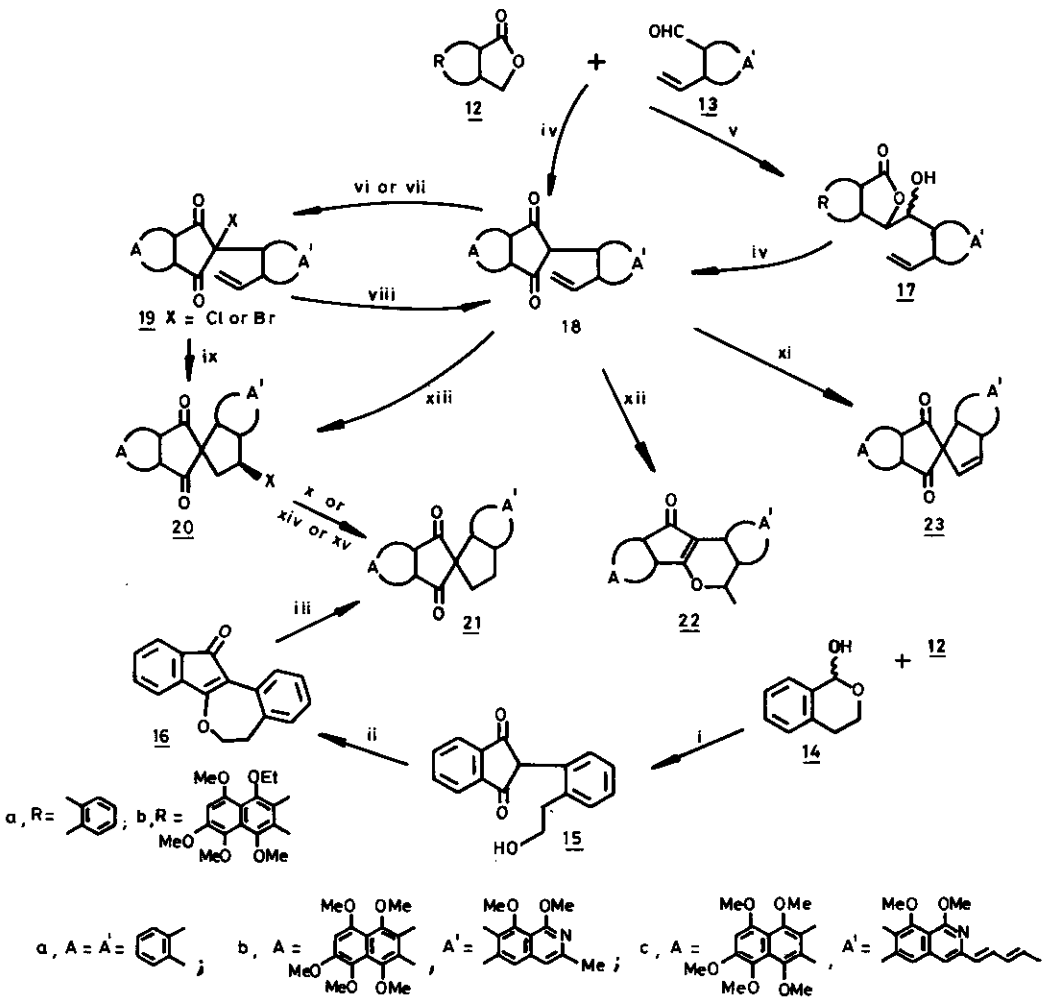
Scheme 1



The intermediate (**15**) was obtained by condensation of phthalide (**12a**) with 1-hydroxyisochroman (**14**) in the presence of sodium methoxide in methanol. Attempts to convert **15** to **21** chemically were unsuccessful as each reaction resulted in the formation of the cyclic enol ether (**16**). Therefore thermal isomerization (Scheme 2) was resorted to, where compound (**15**) was heated to 290-300°C for 5 h followed by trituration of the crude reaction mixture with hexane yielding crystalline spiro[4.4]nonane system (**21a**) (40%). The structure (**21**) was unequivocally established by means of X-ray crystallographic studies.[2a] Although the spiro system, could be built, by ther-

Scheme 2



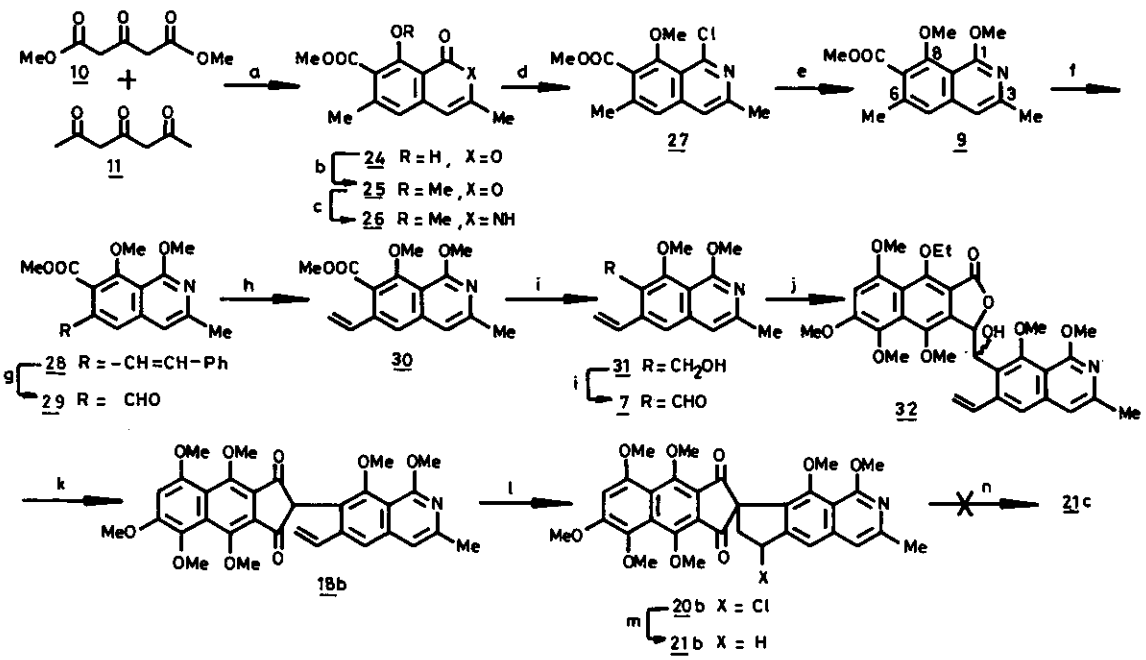
Reagents and conditions : i) NaOMe, MeOH; ii) *p*-Toluenesulphonic acid, CH_2Cl_2, room temperature, 30 min; iii) Δ, 290-300°C, 5 h; iv) NaOMe, MeOH, ethyl propionate, reflux, 1.5 h; v) LDA, THF, HMPA, -78°C, 1.5 h; vi) $CuCl_2$ or $CuBr_2$, acetic acid, room temperature, 1-2 h; vii) $CuCl_2$ or $CuBr_2$, Mn(III) acetate, acetic acid , room temperature, 15 min; vii) Ph_3SnH (2 eq.), AIBN (0.03 eq.), benzene, reflux, 4 h; ix) Ph_3SnH (1 eq.), AIBN (0.03 eq.), benzene, 80°C, 10 h, slow addition; x) Ph_3SnH (1.1 eq.), reflux, 2 h; xi) Mn(III) acetate (1 eq.) Cu(II) acetate (1 eq.), acetic acid, room temperature, 30 min; xii) cat. HCl, $CHCl_3$, room temperature; xiii) Mn(III) acetate (1 eq.), Cu(II) acetate (1 eq.), $CHCl_3$ (1 eq.), acetic acid; xiv) Bu_3SnH, AIBN (0.03 eq.), benzene, reflux, 12 h; xv) 10% Pd/C, MeOH, 4 h.

mal means the conditions employed were, rather drastic to apply to target molecule. Hence it was decided to generate a new but milder methodology[20] in order to avoid any unforeseen problems. After an extensive study a radical-mediated reaction was decided upon for spiro formation (Scheme 2), since it is well known that radicals are least influenced by steric and to a certain

degree only by electronic effects of substituents.

The model indandione (**18a**) was obtained in good yield from phthalide (**12**) and ortho-styrene aldehyde (**13**) using Shapiro's conditions.[3] The compound (**18a**) on being treated with Mn(III) acetate and Cu(II) acetate in AcOH produced the olefinic spiro system (**23a**) which on reduction over palladised charcoal yielded the required spiro system (**21**). Interestingly, the treatment of **18a** with Mn(III) acetate, Cu(II) acetate and chloroform (1 eq.) at room temperature for 30 min resulted in the formation of chloro derivative (**20a, X=Cl**). Reduction of halogen with Bu_3SnH or Pd/C gave the spiro system (**21**) in good yields. The latter method has an advantage over the former since the chlorine atom can easily be reduced with different reagents other than Pd/C. This eliminates the risk of saturating the diene part when dealing with the actual system.

Scheme 3



Reagents and conditions : a) NaOH (2N), MeOH, room temperature, 24 h; b) DMS, K_2CO_3, acetone, reflux, 48 h; c) NH_3 aq. 45°C, 24 h; d) $POCl_3$, reflux 3 h; e) NaOMe, reflux 6 h; f) benzaldehyde, HMPA, $NaNH_2$, 7 h; MeI, K_2CO_3, 8 h; g) OsO_4-$NaIO_4$, H_2O-THF (1:4, v/v), room temperature, 4 h; h) Ph_3PMeI, $NaNH_2$, ether, room temperature, 2 h; i) DIBAL-H, CH_2Cl_2, -78°C, 1 h; MnO_2, $CHCl_3$, 4 h; j) LDA, 4, HMPA-THF (1:6, v/v); k) NaOMe, methanol, ethyl propionate, reflux, 1.5 h; l) Mn(III) acetate (1 eq.), Cu(II) acetate (1 eq.), chloroform (1 eq.), acetic acid, room temperature, 30 min; m) 10% Pd/C, methanol, 4 h; n) NBS, CCl_4, benzoyl peroxide, light.

Based on this methodology ABC[5] and DEF[6] segment were chosen as key fragment to accomplish the task. All the phenolic hydroxyls are protected as methyl ethers for operational convenience.

A good yielding method for ABC segment was developed and we resorted to the Diels-Alder approach for the synthesis of ABC segment starting from isobenzofuran as the diene.[5b]

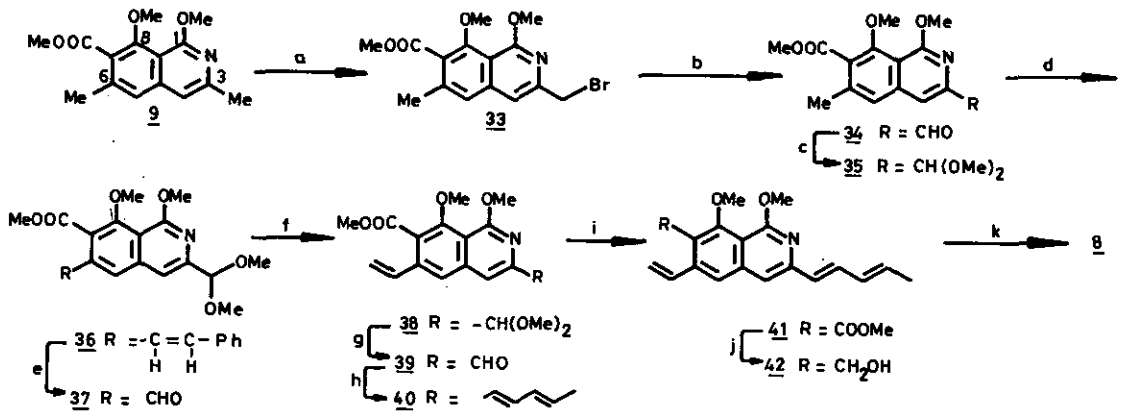
After the successful completion of the synthesis of the ABC fragment the next challenge was to synthesise the DEF fragment. A high yielding route for the construction of highly substituted isoquinoline is very much desired to complete the goal. Although several approaches for the synthesis of simple isoquinoline have been reported over the years, the synthesis of a molecule such as **8** having diverse functionalities have rarely been attempted. To accomplish this task, we designed a new approach where two polyketide units, were condensed to give the pentasubstituted benzene as shown in Scheme 3.

Condensation of 2,4,6-heptatrione with dimethyl 1,3-acetonedicarboxylate in presence of sodium hydroxide in methanol followed by methylation gave isocoumarin (**25**).[7] Conversion of isocoumarin to isoquinolone was concieved by heating with aq. ammonia at 60°C. Compound (**26**) was converted to chloro derivative using $POCl_3$, followed by treatment with sodium methoxide to give required intermediate (**9**) in 70% overall yield.

Having pivotal intermediate (**9**) where two methyl groups are present at C-3 and C-6 positions now it was decided to functionalise regioselectively the C-6 methyl and C-3 methyl groups for pentadienyl side chain and radical trap respectively (Scheme 3). The benzaldehyde was condensed regioselectively on **9** at the 6 position to produce **28** in 82% yield. Treatment of **28** with osmium tetroxide and $NaIO_4$ in H_2O-THF (1:4, v/v) afforded the aldehyde (**29**) (59%) which on further subjected to Wittig reaction gave olefinic compound (**30**) (88%). Subsequent transformation of **30** into the aldehyde (**7**) was accomplished by reduction with DIBAL-H followed by oxidation with MnO_2 in chloroform (83% yield). The Shapiro's conditions (MeONa, MeOH, ethyl propionate) failed to yield dione (**18b**) from ABC and DEF segments. Therefore a modified approach was developed to get this crucial intermediate (**18b**). The aldol reaction between **4** and **7** in presence of LDA, HMPA in THF at -78°C gave the adduct (**32**) (62%). Refluxing **32** with NaOMe and ethyl propionate in methanol for 1.5 h furnished the dione (**18b**) in 61% yield. Conversion of **18b** (X=Cl, 73%) was accomplished by using our Mn(III) mediated radical cyclisation method.[2o] Removal of chlorine atom from **20b** with Pd/C in methanol gave the correspond compound (**21b**) (80%). Attempts to functionalise the methyl group in **21b** for extending pentadienyl side chain were unsuccessful. Therefore it was decided to make isoquinoline with pentadienyl side chain (**8**) and

then proceed further as shown in Scheme 4.

Scheme 4



Reagents and conditions : a) NBS, CCl_4, benzoyl peroxide (cat.), 6 h, light; b) hexamine, acetic acid-H_2O (1:1, v/v), 80°C, 30 min; c) MeOH, PPTS, reflux 1 h; d) $NaNH_2$, PhCHO, HMPA, room temperature, 8 h; K_2CO_3, MeI, 12 h; e) OsO_4-$NaIO_4$, buffer pH 7, 0°C, 5 h; f) Ph_3PMeBr, $NaNH_2$, THF-ether (1:20, v/v), 0°C, 10 min; g) DDQ, H_2O-MeCN (1:9, v/v), 1.5 h, room temperature; h) $Ph_3P^+CH_2$-CH=CH-MeCl$^-$, BuLi, THF, -78°C, 45 min, -45°C, 45 min; i) PTS, NaBr, I_2, MeOH, reflux 45 min; j) DIBAL-H, CH_2Cl_2, 1 h, -78°C; k) PDC, CH_2Cl_2, molecular seives, 45 min, room temperature.

For this purpose compound (**9**) was treated with NBS (1 eq.) to get the monobromo derivative (**33**) which on hydrolysis gave the aldehyde (**34**). The compound (**34**) obtained in good yields was directly oxidised to the aldehyde using the hexamine method. Treatment of the aldehyde with acidic solution of methanol afforded the dimethyl acetal (**35**) (98%). The next step in the sequence was to arrange for a radical trap at the C-6 position. For this, the C-6 methyl has to be oxidised to aldehyde and extended by one carbon unit. As direct conversion of a methyl group to aldehyde function which requires harsh reaction conditions would not be appropriate for this compound, the C-6 methyl was first condensed with benzaldehyde in presence of $NaNH_2$ in HMPA to obtain the stilbene derivative (**36**) which on oxidative cleavage with OsO_4-$NaIO_4$ in buffered condition afforded required aldehyde (**37**) in 61% yield. Wittig reaction of it with triphenylmethylenephosphorane in ether gave the styrene derivative (**38**) in 73% yield.

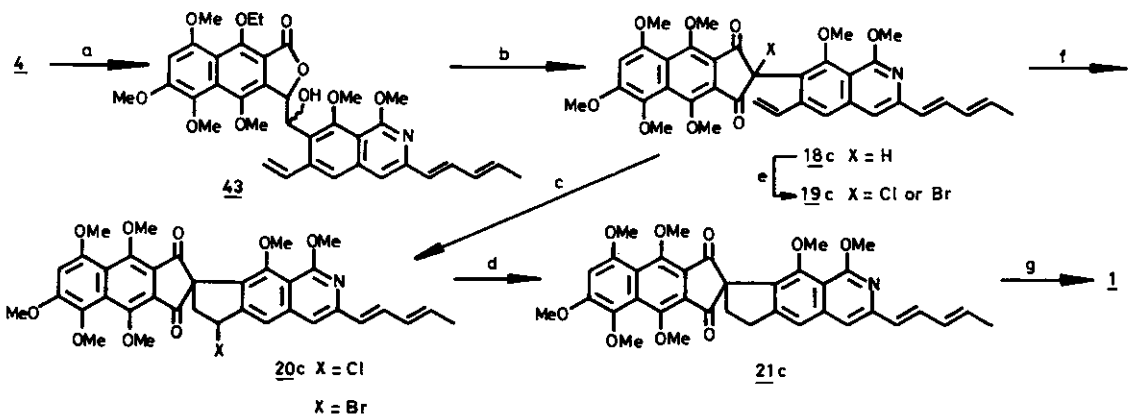
With these building blocks in hand, there were two options to complete a total synthesis 1) to form the spiro system first followed by pentadienyl side chain extension or 2) to build the pentadienyl isoquinoline before fabricating the spiro skeleton by coupling with ABC segment. We preferred the second approach which minimises the risk of interference from other functionalities

in pentadienyl chain extension step.

Based on the above strategy, the dimethyl acetal (**38**) was hydrolysed to the aldehyde (**39**) which on Wittig olefination with crotyltriphenylphosphonium chloride and butyllithium gave ester (**40**) (1:1, cis-trans:trans-trans) in 60% yield. Isomerization to more trans-trans form (84:16) was achieved using iodine. Reduction of the ester functionality of **41**, followed by oxidation gave DEF segment (**8**) required for coupling.

Aldol reaction between **4** and **8** in presence of LDA furnished the adduct (**43**). Sodium methoxide in methanol rearranged the adduct (**43**) to 1,3-dione (**18c**) in good yield. Spiro annulation of 1,3-dione was carried out following our methodology[2o] (Scheme 5) wherein **18c** treated with Mn(III) acetate, Cu(II) acetate in chloroform (1 eq.) gave chloro compound (**19c**) in 60% yield. Reductive

Scheme 5



Reagents and conditions : a) LDA, 8, THF, HMPA, -78°C, 1.5 h; b) NaOMe, MeOH, ethyl propionate, reflux, 2 h; c) Mn(III) acetate (1 eq.), Cu(II) acetate (1 eq.), $CHCl_3$ (1 eq.), acetic acid, room temperature, 30 min; d) tributyltin hydride, AIBN, benzene, reflux 12 h; e) $CuBr_2$, Mn(III) acetate, acetic acid, room temperature, 15 min; f) Ph_3SnH (1 eq.), AIBN (0.03 eq.), benzene, 50°C, 10 h, slow addition; Ph_3SnH (1.1 eq.), reflux, 2 h; g) BBr_3, CH_2Cl_2.

removal of chlorine atom of **19c** with tributyltin hydride gave a mixture of products, which on chromatographic seperation resulted hexamethyl ether of fredericamycin A (**21c**) in less than 10% yield. Because of the low yields in spiro annulation stage, a modified radical method[2v] was developed as shown in Scheme 2. Treatment of dione (**18c**) with $CuBr_2$, Mn(III) acetate in AcOH at room temperature for 15 min resulted in the formation of the bromo derivative (**19c, X=Br**) in 85% yield. Radical cyclisation of **19c** (**X=Br**) with slow addition of Ph_3SnH (1 eq.), AIBN (0.03 eq.) in benzene at 50°C followed by reductive elimination of bromine (**20c, X=Br**) (not isolated) by adding Ph_3SnH (1.1 eq.) at reflux temperature for two more hours, gave hexamethyl

ether of fredericamycin A (**21c**) in 55% yield after chromatographic separation. Subjecting **21c** with BBr_3 in DCM at -78°C and warm it slowly to 0°C, gave fredericamycin A (**1**) in 29% identical with the natural product[8] in all respects.

EXPERIMENTAL

Melting points were determined on Fisher-Johns melting point apparatus and are uncorrected. Nmr spectra were obtained with a Varian Gemini (200 MHz) instrument. Tetramethylsilane was used as an internal reference and deuteriochloroform as solvent. J-Values are given in Hz. Ir spectra were recorded on a Shimadzu IR-470 spectrophotometer. Mass spectra were obtained by EI at 70 eV with Finnigan mat 1020B instrument. Elemental analyses were performed on a Perkin Elmer 2400 Elemental Analyser. Flash chromatography was performed on Merck silica gel (200 mesh) and the solvents ethyl acetate, pet. ether (bp 40-60°C) was redistilled before use. All reactions were monitored by tlc on Merck silica gel $60F_{254}$ precoated glass plate (layer thickness 0.25 mm) and were visualised with UV light and then with phosphomolybdic acid solution. Organic extracts were dried over anhydrous Na_2SO_4 and solvents were removed on a Buchi rotary evaporator. Routinely dry organic solvents were stored under nitrogen. Organic solvents were dried by distillation from the following benzene and tetrahydrofuran (THF) (sodium benzophenone ketyl), CaH_2, methanol (magnesium methoxide), ethyl propionate ($CuSO_4$) and HMPA (CaH_2). Where necessary, reactions requiring anhydrous conditions were performed in a flame or oven dried apparatus under nitrogen.

8-Hydroxy-7-methoxycarbonyl-3,6-dimethylisocoumarin (24). To a suspension of 2,4,6-heptatrione (**11**) (75 g, 528 mmol) in methanol (260 ml) was added dimethyl 1,3-acetonedicarboxylate (**10**) (120 g, 690 mmol) and 2N NaOH solution (260 ml) over 1 h. The reaction mixture was stirred for 24 h at room temperature, refrigerated for 1 h and filtered, washed with methanol (2x50 ml) to afford a tan solid. The solid was stirred with 2N HCl for 30 min followed by filtration and drying gave crude isocoumarin product. Recrystallization with methanol gave **24** (58 g) in 44% yield as yellow crystalline material : mp 156-158°C (methanol): ^{1}H-Nmr (200 MHz, $CDCl_3$): δ 2.40 (3H, s), 2.62 (3H, s), 3.93 (3H, s), 6.17 (1H, s), 6.80 (1H, s), 11.4 (1H, s); ir ($CHCl_3$) ν : 1720, 3400 cm^{-1}.

8-Methoxy-7-methoxycarbonyl-3,6-dimethylisocoumarin (25). A mixture of **24** (58 g, 234 mmol), DMS (74 g, 587 mmol) and potassium carbonate (125 g, 906 mmol) in acetone (600 ml) was heated

at reflux for 48 h. Acetone was distilled and the reaction mixture was taken in water (200 ml). It was filtered, washed with water (2x100 ml) and dried in vacuum to give **25** (60 g) in 98% yield as a white crystalline solid : mp 152°C (acetone/pet. ether): ^{1}H-Nmr (200 MHz, $CDCl_3$): δ 2.25 (3H, s), 2.35 (3H, s), 3.95 (6H, s), 6.15 (1H, s), 6.90 (1H, s); ir ($CHCl_3$) ν: 1710, 1730 cm^{-1}; ms m/z: 262 (M^+). Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.11; H, 5.38. Found: C, 64.15; H, 5.27.

8-Methoxy-7-methoxycarbonyl-3,6-dimethyl-1(2*H*)-isoquinolone (26). Compound (**25**) (60 g, 229 mmol) suspended in aqueous NH_3 (25%, 200 ml) was heated at 60°C for 1 h. An additional amount of aqueous NH_3 (25%, 200 ml) was added and heating continued for one more hour. Reaction mixture was cooled and filtered to afford compound (**26**) (54.6 g) in 91% yield as a white crystalline solid : mp 245°C (methanol/pet. ether): ^{1}H-Nmr (200 MHz, $CDCl_3$): δ 2.40 (6H, s), 3.95 (3H, s), 4.05 (3H, s), 6.20 (1H, s), 7.00 (1H, s); ir ($CHCl_3$) ν: 1720, 1730 cm^{-1}; ms m/z: 261 (M^+). Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.14; H, 5.61; N, 5.24.

1-Chloro-8-methoxy-7-methoxycarbonyl-3,6-dimethylisoquinoline (27). Compound (**26**) (23 g, 88.12 mmol) in phosphorous oxychloride (230 ml, 2.468 mol) was refluxed for 3 h. 3/4th volume of $POCl_3$ was distilled. The cooled reaction mixture was poured into crushed ice and left overnight. It was neutralized with 4N NaOH solution and extracted with CH_2Cl_2 (2x200 ml). The organic layer was dried (Na_2SO_4) and concentrated to give compound (**27**) (21.3 g) in 87% yield as a solid : mp 88.6°C (methylene chloride/pet. ether): ^{1}H-Nmr (200 MHz, $CDCl_3$): δ 2.40 (3H, s), 2.60 (3H, s), 3.85 (3H, s), 3.95 (3H, s), 7.20 (2H, s); ir ($CHCl_3$) ν: 1730 cm^{-1}; ms m/z: 279 (M^+). Anal. Calcd for $C_{14}H_{14}NO_3Cl$: C, 60.11; H, 5.05; N, 5.01. Found: C, 59.82; H, 5.06, N, 5.20.

1,8-Dimethoxy-7-methoxycarbonyl-3,6-dimethylisoquinoline (9). To a freshly prepared sodium methoxide, prepared from sodium (11.25 g, 489 mmol) and methanol (640 ml), compound (**27**) (10 g, 35.7 mmol) was added and refluxed for 6 h. Methanol was distilled off completely and water (250 ml) was added. The separated solid was filtered, washed with water (2x50 ml) and dried. The crude product was recrystallised from methanol to give compound (**9**) (8 g) in 80% yield as a solid : mp 119.2°C (methanol): ^{1}H-Nmr (200 MHz, $CDCl_3$): δ 2.35 (3H, s), 2.45 (3H, s), 3.86 (3H, s), 3.87 (3H, s), 4.05 (3H, s), 6.90 (1H, s), 7.19 (1H, s); ir ($CHCl_3$) ν: 1720 cm^{-1}; ms m/z: 275 (M^+). Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.15; H, 6.28; N, 5.02.

1,8-Dimethyoxy-7-methoxycarbonyl-3-methyl-6-(2'-phenylethelene)isoquinoline (28). A mixture of compound (**9**) (1 g, 3.63 mmol) and sodium amide (0.29 g, 7.43 mmol) in HMPA (10 ml) was stirred at room temperature for 15 min and treated with benzaldehyde (0.384 g, 3.63 mmol). After 7 h, methyl iodide (1.13 g, 8 mmol) and potassium carbonate (1 g, 7.24 mmol) were added and stirred for an additional 8 h. Reaction mixture was diluted with water (50 ml) and extracted with ethyl acetate (2x50 ml). The organic layer was washed with water (2x50 ml), dried (Na_2SO_4) and concentrated. The residue was purified by chromatography (acetone-pet. ether; 1.5:8.5, v/v) to give ester (**28**) (1.04 g) in 82% yield as a pale yellow solid : mp 103-105°C (acetone/pet. ether): ^{1}H-Nmr (200 MHz, $CDCl_3$): δ 2.50 (3H, s), 3.90 (3H, s), 3.95 (3H, s), 4.10 (3H, s), 6.95 (1H, s), 7.00-7.60 (8H, m); ir ($CHCl_3$) ν: 1730 cm^{-1}; ms m/z 363 (M^+). Anal. Calcd for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85. Found: C, 72.63; H, 5.94; N, 3.61.

6-Formyl-1,8-dimethoxy-7-methoxycarbonyl-3-methylisoquinoline (29). To a stirred solution of compound (**28**) (0.85 g, 2.34 mmol) in H_2O-THF (1:4, v/v, 25 ml) was added osmium tetroxide (0.003 g, 0.012 mmol) at room temperature. Sodium periodate (1.6 g, 7.5 mmol) was added in 30 min and left at room temperature for 4 h. The reaction mixture was filtered and washed with ether (2x50 ml). The organic layer was dried (Na_2SO_4), concentrated under reduced pressure and purified by chromatography (acetone-pet. ether; 0.5:9.5, v/v) to give aldehyde (**29**) (0.4 g) in 59% yield as a solid : mp 118.2°C (acetone/pet. ether): ^{1}H-Nmr (200 MHz, $CDCl_3$): δ 2.40 (3H, s), 3.95 (3H, s), 4.05 (3H, s), 4.20 (3H, s), 7.00 (1H, s), 7.90 (1H, s), 10.30 (1H, s); ir (Nujol) ν: 1700, 1710 cm^{-1}; ms m/z 289 (M^+). Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.32; H, 5.19; N, 4.86.

6-Ethenyl-1,8-dimethoxy-7-methoxycarbonyl-3-methylisoquinoline (30). A mixture of methyltriphenylphosphonium iodide (240 mg, 0.594 mmol) and sodium amide (30 mg, 0.77 mmol) in ether (20 ml) was stirred for 2 h under nitrogen at room temperature. The ethereal solution of phosphorane was siphoned out into compound (**29**) (40 mg, 0.138 mmol) in ether (5 ml) under nitrogen and stirred at room temperature for 15 min. Reaction mixture was poured into water (2 ml) and extracted with ethyl acetate (2x15 ml). The organic layer was dried (Na_2SO_4), concentrated and purified by chromatography (acetone-pet. ether; 0.5:9.5, v/v) to give olefinic compound (**30**) (35 mg) in 88% yield as a solid : mp 113.8°C (acetone/pet. ether): ^{1}H-Nmr (200 MHz, $CHCl_3$): δ 2.52 (3H, s), 3.90 (3H, s), 3.93 (3H, s), 4.15 (3H, s), 5.45 (1H, dd, J=11.0 and 1.4 Hz), 5.85

(1H, dd, J=16.5 and 1.4 Hz), 6.75 (1H, dd, J=11.0 and 16.5 Hz), 7.00 (1H, s), 7.53 (1H, s); ir ($CHCl_3$) ν : 1720 cm^{-1}; ms m/z : 287 (M^+). Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.73; H, 6.33; N, 4.71.

6-Ethenyl-7-formyl-1,8-dimethoxy-3-methylisoquinoline (7). To a stirred and cooled (-78°C) solution of compound (**30**) (70 mg, 0.244 mmol) in dry CH_2Cl_2 (3 ml) was added DIBAL-H solution (0.4 ml, 20% solution in hexane) slowly. After 1 h reaction mixture was quenched with methanol (0.5 ml) and allowed to warm to room temperature. The reaction mixture was diluted with saturated potassium sodium tartrate solution (2 ml), stirred for 15 min at room temperature and extracted the aqueous layer with CH_2Cl_2 (2x15 ml). The organic layer was dried (Na_2SO_4) and concentrated to give crude mixture of alcohol (**31**) and aldehyde (**7**), which was treated with MnO_2 (1 g, 11.5 mmol) in dry chloroform (6 ml) for 4 h. It was filtered over celite and washed with hot $CHCl_3$ (2x15 ml). Combined organic layers were concentrated to give aldehyde (**7**) (52 mg) in 83% yield as a solid : mp 117.7°C (chloroform/pet. ether): ^{1}H-Nmr (300 MHz, $CDCl_3$): δ 2.46 (3H, s), 3.88 (3H, s), 4.08 (3H, s), 5.29 (1H, dd, J=10.14 and 1.69 MHz), 5.55 (1H, dd, J=16.90 and 1.69 Hz), 6.88 (1H, s), 7.29 (1H, s), 7.34 (1H, dd, J=16.90 and 10.14 Hz), 10.38 (1H, s); ir ($CHCl_3$) ν: 1680 cm^1; ms m/z 257 (M^+). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.09; H, 5.68; N, 5.32.

Aldol adduct (32). To a freshly prepared LDA [(0.57 mmol, generated from diisopropylamine (0.08 ml, 0.57 mmol) and butyllithium (0.2 ml, 2.9N solution in hexane)] in THF (9 ml) a solution of phthalide (**4**) (200 mg, 0.574 mmol) in HMPA-THF (1:6, v/v, 7 ml) was added at -78°C. Reaction mixture was stirred at -78°C for 10 min and treated with aldehyde (**7**) (150 mg, 0.58 mmol) in THF (3 ml). After an additional 10 min reaction mixture was quenched with ammonium hydroxide buffer (pH 8, 1 ml) at -78°C warmed to room temperature and stirred for 5 min. Reaction mixture was diluted with water (1 ml) and extracted with ethyl acetate (2x15 ml). The organic layer was washed twice with water (2 ml), dried (Na_2SO_4) and concentrated. The residue obtained was purified by chromatography (triethylamine-acetone-pet. ether; 0.05:0.95:9.00, v/v) to give adduct (**32**) as a viscous oil (217 mg) in 62% yield : ^{1}H-Nmr (300 MHz, $CDCl_3$): δ 1.50 (3H, t, J=6.7 Hz), 2.40 (3H, s), 3.50-4.02 (6x3H, s), 4.20-4.30 (2H, m), 5.10-6.30 (5H, m), 6.77 (1H, s), 6.99 (1H, s), 5.76-7.59 (2H, m); ir ($CDCl_3$) ν: 1765, 3450 cm^{-1}; ms m/z : 348 (M^+ -$C_{15}H_{15}$-O_3N), 256 (M^+ -$C_{18}H_{21}O_7$). Anal. Calcd for $C_{33}H_{35}NO_{10}$: C, 65.44; H, 5.83; N, 2.31. Found:

C, 65.50; H, 5.62; N, 2.30.

Dione (18b). To a mixture of sodium methoxide (564 mg, 24.5 mmol), compound **(32)** (165 mg, 0.272 mmol) in methanol (4 ml) was added ethyl propionate (1 ml, 8.73 mmol) and refluxed for 1.5 h under nitrogen atmosphere. Reaction mixture was cooled and quenched with ammonium hydroxide buffer (pH 8, 1 ml). The reaction mixture was extracted with chloroform (2x15 ml) and the organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (triethylamine-acetone-pet. ether; 0.01:1.99:8.00, v/v) to give 1,3-dione **(18b)** as an oil (95 mg) in 61% yield : ^{1}H-Nmr (300 MHz, $CDCl_3$): δ 2.43 (3H, s), 3.78 (3H, s), 3.84 (3H, s), 3.90 (3H, s), 3.93 (3H, s), 3.98 (3H, s), 4.00 (3H, s), 4.01 (3H, s), 4.60 (1H, s), 5.21 (1H, d, J=11.0 Hz), 5.75 (1H, d, J=17.0 Hz), 6.86 (1H, s), 6.93-7.00 (2H, m), 7.62 (1H, s); ir ($CHCl_3$) ν: 1705, 1734 cm^{-1}; ms m/z : 573 (M^+). HRms calcd for $C_{32}H_{31}NO_9$: 573.6052, found : 573.6050.

6'-Chloro-6',7'-dihydro-4,5,7,8,9,1',9'-heptamethoxy-3'-methylspiro[2 *H*-benz[*f*]indene-2,8'-[8*H*]-cyclopent[*g*]isoquinoline]-1,3-dione (20b, X=Cl). To a solution of compound **(18b)** (35 mg, 0.061 mmol) in acetic acid (0.5 ml), a mixture of Mn(III) acetate (14 mg, 0.061 mmol) and Cu(II) acetate (11 mg, 0.061 mmol) was added followed by chloroform (5 μ l). Reaction mixture was stirred at room temperature for 30 min and acetic acid was removed under vacuum at room temperature. The crude reaction mixture was taken in 10% triethylamine in ethyl acetate (10 ml), filtered through a small pad of silica gel and washed with 10% triethylamine in ethyl acetate (10 ml). The combined organic layers were concentrated and purified by chromatography (triethylamine-acetone-pet. ether; 0.02:0.98:9.00, v/v) to give chloro compound **(20b)** as an oil (27 mg) in 73% yield : ^{1}H-Nmr (300 MHz, $CDCl_3$): δ 2.42 (3H, s), 2.80 (1H, dd, J=16.0 and 6.0 Hz), 2.95 (1H, dd, J=16.0 and 6.0 Hz), 3.41 (3H, s), 3.78 (3H, s), 3.85 (3H, s), 3.90-4.04 (4x3H, s), 5.80 (1H, t, J=6.0 Hz), 6.86 (1H, s), 6.99 (1H, s), 7.48 (1H, s); ms m/z : 608 (M^+). HRms calcd for $C_{32}H_{30}NO_9Cl$: 608.0502, found : 608.0501.

6',7'-Dihydro-4,5,6,8,9,1',9'-heptamethoxy-3'-methylspiro[2 *H*-benzy[*f*]indene-2,8'[8 *H*]cyclopent[*g*]-isoquinoline]-1,3-dione (21b). To a suspension of 10% Pd/C (5 mg) in methanol (5 ml) was added compound **(20b, X=Cl)** (10 mg, 0.0164 mmol) in methanol (1 ml) and stirred under hydrogen atmosphere at room temperature for 4 h. Reaction mixture was filtered through a small pad of silica gel, washed with 10% triethylamine in ethyl acetate (10 ml) and combined organic layer was concentrated to give compound **(21b)** as an oil (75 mg) in 80% yield : ^{1}H-Nmr (300

MHz, $CDCl_3$): δ 2.47 (3H, s), 2.54 (2H, t, J=7.5 Hz), 3.40 (2H, t, J=7.5 Hz), 3.48 (3H, s), 3.90 (3H, s), 4.00 (3H, s), 4.06 (2x3H, s), 4.07 (3H, s), 4.08 (3H, s), 6.93 (1H, s), 6.96 (1H, s), 7.32 (1H, s), irradiation at δ 2.55 resulted a singlet at δ 3.39; ms m/z : 573 (M^+). HRms calcd for $C_{32}H_{31}NO_9$: 573.6052, found : 573.6053.

3-Bromomethyl-1,8-dimethoxy-7-methoxycarbonyl-6-methylisoquinoline (33). To a mixture of compound **(9)** (6 g, 21.8 mmol) and benzoyl peroxide (0.01 g, 0.0412 mmol) in CCl_4 (120 ml), NBS (3.92 g, 22 mmol) was added and refluxed with the aid of 500 watts bulb for 6 h. Reaction mixture was cooled, filtered and washed with CCl_4 (2x50 ml). The combined organic extracts were concentrated to give **33** (7.75 g) in 99% yield as a solid: mp 129.5°C (carbon tetrachloride/ pet. ether): ^{1}H-Nmr (200 MHz, $CDCl_3$): δ 2.40 (3H, s), 3.85 (3H, s), 4.00 (3H, s), 4.60 (2H, s), 7.15 (1H, s), 7.30 (1H, s); ms m/z : 354 (M^+). Anal. Calcd for $C_{15}H_{16}NO_4Br$: C, 50.86; H, 4.55; N, 3.95. Found: C, 50.35; H, 4.34; N, 4.03.

3-Formyl-1,8-dimethoxy-7-methoxycarbonyl-6-methylisoquinoline (34). To the compound **(33)** (15 g, 42.38 mmol), in AcOH-water (1:1, v/v, 100 ml) was added hexamine (11.88 g, 84.74 mmol) and kept for 5 min in preheated oil bath (70°C). The reaction mixture was cooled to room temperature, extracted with CH_2Cl_2 (2x200 ml). The combined organic layer was washed with sodium bicarbonate solution (10%, 2x15 ml) and concentrated under vacuo. The residue was purified by chromatography (acetone-pet. ether; 1:9, v/v) to give aldehyde **(34)** (10.72 g) in 65% yield as a solid : mp 125.3°C (acetone/pet. ether): ^{1}H-Nmr (200 MHz, $CDCl_3$): δ 2.45 (3H, s), 3.95 (3H, s), 4.00 (3H, s), 4.25 (3H, s), 7.55 (1H, s), 7.90 (1H, s), 10.70 (1H, s); ir ($CHCl_3$)ν : 1700, 1730 cm^{-1}; ms m/z : 289 (M^+). Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.32; H, 5.19; N, 4.80.

1,8-Dimethoxy-3-dimethoxymethyl-7-methoxycarbonyl-6-methylisoquinoline (35). A solution of aldehyde **(34)** (2 g, 6.92 mmol) in methanol (50 ml) containing PPTS (0.1 g, 0.4 mmol) was refluxed under nitrogen for 2 h. Methanol was removed under vacuum and residue was diluted with chloroform (30 ml). It was washed with water (2x5 ml), aqueous sodium bicarbonate solution (10%, 2x5 ml), dried (Na_2SO_4) and concentrated to give compound **(35)** (2.27 g) in 98% yield as a solid : mp 85°C (chloroform/pet. ether): ^{1}H-Nmr (200 MHz, $CDCl_3$): δ 2.42 (3H, s), 3.42 (6H, s), 3.87 (3H, s), 3.91 (3H, s), 4.10 (3H, s), 5.31 (1H, s), 7.35 (2H, s); ir ($CHCl_3$) ν : 1720 cm^{-1}; ms m/z : 335 (M^+). HRms calcd for $C_{17}H_{21}NO_6$: 335.1369, found: 335.1370.

1,8-Dimethoxy-3-dimethoxymethyl-7-methoxycarbonyl-6-(2'-phenylethenyl)isoquinoline (36). A mixture of acetal derivative (**35**) (2 g, 5.97 mmol) and sodium amide (0.468 g, 12 mmol) in HMPA (20 ml) under nitrogen was stirred at room temperature for 15 min. Benzaldehyde (0.64 g, 6 mmol) was added slowly and allowed to stir for 7 h. Then potassium carbonate (2 g, 14.48 mmol) followed by methyl iodide (1.7 g, 12 mmol) was added. After 7 h, the reaction mixture was poured into water (10 ml) and extracted with ethyl acetate (2x50 ml). The ethyl acetate layer was washed with water (2x10 ml), dried (Na_2SO_4), concentrated and purified through chromatography (triethylamine-acetone-pet. ether; 0.02:0.98:9.00, v/v) to give stilbene derivative (**36**) (2.06 g) in 82% yield as a solid : mp 138.4°C (acetone/pet. ether): ^{1}H-Nmr (200 MHz, $CDCl_3$): δ3.42 (6H, s), 3.87 (3H, s), 4.00 (3H, s), 4.10 (3H, s), 5.38 (1H, s), 7.07-7.70 (8H, m), 7.73 (1H, s); ir ($CHCl_3$) ν : 1730 cm^{-1}; ms m/z : 423 (M^+). HRms calcd for $C_{24}H_{25}NO_6$: 423.1682, found: 423.1683.

6-Formyl-1,8-dimethoxy-3-dimethoxymethyl-7-methoxycarbonylisoquinoline (37). To a stirred and cooled (0°C) solution of **36** (1.5 g, 3.55 mmol) in aqueous THF [buffer (pH 7) - THF; 1:5, v/v, 30 ml] was added catalytic amount of osmium tetroxide (0.005 g) and sodium bicarbonate (0.50 g). After 15 min sodium periodate (1.5 g, 7 mmol) was added to the reaction mixture in 30 min and stirred for an additional 4 h. Reaction mixture was filtered and washed with ethyl acetate (2x15 ml). The organic layer was dried (Na_2SO_4) and concentrated to give a residue which was purified by column chromatography (triethylamine-acetone-pet. ether; 0.02:0.98:9.00, v/v) to give aldehyde (**37**) (0.755 g) in 61% yield as a solid: mp 81.6°C (acetone/pet. ether): ^{1}H-Nmr (200 MHz, $CDCl_3$): δ 3.5 (6H, s), 4.00 (3H, s), 4.05 (3H, s), 4.21 (3H, s) 5.46 (1H, s), 7.66 (1H, s), 8.10 (1H, s), 10.17 (1H, s); ms m/z: 349 (M^+). Anal. Calcd for $C_{17}H_{19}NO_7$: C, 58.45; H, 5.48; N, 4.01. Found: C, 58.30; H, 5.41; N, 4.00.

6-Ethenyl-1,8-dimethoxy-3-dimethoxymethyl-7-methoxycarbonylisoquinoline (38). To a suspension of methyltriphenylphosphonium iodide (2.3 g, 5.7 mmol) in dry ether (10 ml), sodium amide (0.240 g, 6.15 mmol) was added and the mixture was stirred at room temperature for 4 h. The supernatant layer was added to aldehyde (**37**) (0.50 g, 1.43 mmol) dissolved in dry THF (3 ml) at 0°C. After 15 min ethereal layer was decanted and the residue was washed with chloroform (2x15 ml). The combined organic washings were concentrated in vacuo to afford crude residue which was purified by column chromatography (triethylamine-acetone-pet. ether; 0.05:0.95:9.00,

v/v) to give olefin (**38**) as an oil (0.365 g) in 73% yield : ^{1}H-Nmr (200 MHz, $CDCl_3$): δ 3.40 (6H, s), 3.92 (3H, s), 3.96 (3H, s), 4.15 (3H, s), 5.34 (1H, s), 5.42 (1H, d, J=11.0 Hz), 5.88 (1H, d, J=16.5 Hz), 6.72 (1H, dd, J=11.0 and 16.5 Hz), 7.42 (1H, s), 7.65 (1H, s); ms m/z : 347 (M^+). HRms calcd for $C_{18}H_{21}NO_6$: 347.1369, found: 347.1370.

6-Ethenyl-3-formyl-1,8-dimethoxy-7-methoxycarbonylisoquinoline (39). To the compound (**38**) (17 mg, 0.049 mmol) in 90% acetonitrile (2 ml) was added DDQ (1.1 mg, 0.0049 mmol) and stirred for 1 h at room temperature. Acetonitrile removed under reduced pressure and was extracted with ethyl acetate (2x10 ml), dried (Na_2SO_4) and purified through column chromatography (acetone-pet. ether; 1:9, v/v) to give compound (**39**) as an oil (13.9 mg) in 95% yield: ^{1}H-Nmr (200 MHz, $CDCl_3$): δ 3.88 (3H, s), 3.92 (3H, s), 4.18 (3H, s), 4.60 (1H, d, J=11.0 Hz), 5.88 (1H, d, J=17.0 Hz), 6.64 (1H, dd, J=11.0 and 17.0 Hz), 7.75 (1H, s), 7.82 (1H, s), 9.98 (1H, s); ms m/z : 301 (M^+). HRms calcd for $C_{16}H_{15}NO_5$: 301.0950, found: 301.0951.

6-Ethenyl-1,8-dimethoxy-7-methoxycarbonyl-3-(1,3-pentadienyl)isoquinoline (40). To a stirred and cooled (0°C) suspension of crotyltriphenylphosphonium chloride (126 mg, 0.358 mmol) in THF (5 ml), n-BuLi (0.10 ml, 3N in hexane) was added dropwise and stirred for 1 h. It was cooled (-78°C) and treated with cold (-78°C) solution of aldehyde (**39**) (90 mg, 0.299 mmol) in THF (2.5 ml) dropwise. After 90 min the reaction mixture was quenched with methanol (1 ml) and warmed to room temperature. The reaction mixture was concentrated and the residue obtained was purified by chromatography (acetone-pet. ether; 0.2:9.8, v/v) to give **40** as an oil (60 mg) in 60% yield.

Isomerization of 40. A mixture of anhydrous sodium bromide (350 mg, 3.4 mmol), PTSA (70 mg, 0.368 mmol), compound (**40**) (70 g, 0.206 mmol) and a small crystal of iodine were refluxed in methanol (3 ml) for 45 min under nitrogen. Reaction mixture was cooled, concentrated and diluted with chloroform (20 ml). The organic layer was washed with 5% sodium thiosulphate solution (1 ml), saturated bicarbonate solution (2x5 ml), dried (Na_2SO_4) and concentrated to give **41** as a viscous oil (65 mg) in 93% yield. Hplc analysis (silica column, chloroform-heptane; 1:9, v/v), cis-trans, trans-trans forms, 16:84 : ^{1}H-Nmr (200 MHz, $CDCl_3$): δ 1.88, 1.90 (3H, d, J=7.1 Hz, two sets), 3.92, 3.93 (3H, s, two sets), 3.96 (3H, s), 4.20, 4.22 (3H, s, two sets), 5.44 (1H, d, J=11.0 Hz), 5.85 (1H, d, J=17.0 Hz), 5.90-6.02 (2H, m), 6.31 (1H, m), 6.47, 6.53 (1H, d, J=15.0 Hz, two sets), 6.72 (1H, dd, J=11.0 and 17.0 Hz), 7.06, 7.12 (1H, s, two sets), 7.53,

7.54 (1H, s, two sets), irradiation at δ 1.85 resulted doublet at δ 6.00; ms m/z : 339 (M^+). HRms calcd for $C_{20}H_{21}NO_4$: 339.1470, found: 339.1470.

6-Ethenyl-7-formyl-1,8-dimethoxy-3-(1,3-pentadienyl)isoquinoline (8). A stirred and cooled (-78°C) solution of compound (**41**) (100 mg, 0.295 mmol) in CH_2Cl_2 (2 ml) was treated slowly with DIBAL-H (0.42 ml of 20% hexane). After 3 h, the reaction mixture was quenched with methanol (1 ml) and allowed to reach room temperature. The reaction mixture was treated with saturated potassium sodium tartarate solution (1 ml) for 10 min and the mixture was extracted with CH_2Cl_2 (2x15 ml). The organic layer was dried (Na_2SO_4) and concentrated. The crude product was taken in CH_2Cl_2 (6 ml) and stirred with PDC (240 mg, 0.6 mmol) and freshly grinded molecular sieves (250 mg) for 1 h. Reaction mixture was filtered through celite and washed with CH_2Cl_2 (2x10 ml). The combined organic layers were concentrated and purified through chromatography (triethylamine-acetone-pet. ether; 0.2:3.8:6.00, v/v) to give aldehyde (**8**) as an oil (59 mg) in 65% yield: ^{1}H-Nmr (200 MHz, $CDCl_3$): δ1.92, 1.98 (3H, d, J=7.3 Hz, two sets), 4.01, 4.02 (3H, s, two sets), 4.24, 4.26 (3H, s, two sets), 5.45 (1H, d, J=11.0 Hz), 5.70 (1H, d, J=17.0 Hz), 5.90-6.40 (3H, m), 6.45, 6.53 (1H, d, J=15.1 Hz, two sets), 7.00, 7.08 (1H, s, two sets), 7.40, 7.60 (1H, dd, J=11.0 and 17.0 Hz, two sets), 7.51, 7.53 (1H, s, two sets), 10.63, 10.65 (1H, s, two sets); ms m/z : 309 (M^+). HRms calcd for $C_{19}H_{19}NO_3$: 309.1366, found: 309.1373.

Aldol adduct (43). To freshly prepared LDA (0.29 mmol) (generated from diisopropylamine, 0.04 ml and n-BuLi (0.1 ml, 2.9N solution in hexane) in THF (5 ml) was added phthalide (**4**) (100 mg, 0.287 mmol) in HMPA-THF (1:6, v/v, 3.5 ml) at -78°C and stirred for 10 min. A solution of aldehyde (**8**) (89 mg, 0.288 mmol) in THF (2 ml) was added slowly and stirring was continued for an additional 10 min. The resulting mixture was quenched with ammonium hydroxide buffer (pH 8, 2 ml) at -78°C, warmed to room temperature, and stirred for 5 min. The reaction was diluted with saturated NaCl solution (1 ml) and extracted with ethyl acetate (2x15 ml). The organic phase was washed with saturated NaCl solution (2x5 ml), dried (Na_2SO_4) and concentrated. Chromatography on silica gel with triethylamine-acetone-pet. ether (0.05:0.95:9.00, v/v) as eluent afforded 100 mg of product (**43**) as an oil (53%): ^{1}H-Nmr (200 MHz, $CDCl_3$): δ1.43, 1.47 (3H, t, J=6.7 Hz, two sets), 1.80, 1.86 (3H, d, J=7.1 Hz, two sets), 3.70, 3.72 (3H, s, two sets), 3.74, 3.80 (3H, s, two sets), 3.83, 3.86 (3H, s, two sets), 3.89, 3.93 (3H, s, two sets), 3.96, 3.99 (3H, s, two sets), 4.03, 4.06 (3H, s, two sets), 4.20-4.24 (2H, m), 5.25-6.02

(6H, m), 6.20-6.50 (3H, m), 6.68, 6.72 (1H, s, two sets), 6.95, 7.19 (1H, s, two sets), 7.32 (1H, m), 7.47, 7.50 (1H, s, two sets); ir ($CHCl_3$) ν: 1760 cm^{-1}. Anal. Calcd for $C_{37}H_{39}NO_{10}$: C, 67.57; H, 5.98; N, 2.13. Found: C, 67.48; H, 6.03; N, 2.10.

Dione (18c). To a solution of sodium methoxide, prepared from sodium (130 mg, 5.7 mmol) and methanol (1 ml), was added compound (**43**) (50 mg, 0.076 mmol) in methanol (1 ml) followed by ethyl proprionate (0.3 ml). The mixture was refluxed for 1.5 h under nitrogen blanket. The reaction mixture was concentrated under vacuo, diluted with saturated NaCl solution (1 ml), extracted with chloroform (3x5 ml). Drying over sodium sulphate and evaporation gave the crude product. Flash chromatography (triethylamine-acetone-methanol-methylene chloride-pet. ether; 0.1:5:5:5:10:74.9, v/v) of the residue provided 20 mg of **18c** as an oil (43%): ^{1}H-Nmr (200 MHz, $CDCl_3$): δ 1.80, 1.82 (3H, d, J=7.1 Hz, two sets), 3.70, 3.72 (3H, s, two sets), 3.82, 3.90 (3H, s, two sets), 3.93-3.98 (2x3H, s, two sets), 4.01-4.05 (2x3H, s, two sets), 4.15, 4.17 (3H, s, two sets), 4.60 (1H, s), 5.21 (1H, d, J=11.0 Hz), 5.50 (1H, m), 5.75 (1H, d, J=17.0 Hz), 5.92 (1H, m), 6.30 (1H, m), 6.42, 6.51 (1H, d, J=15.1 Hz, two sets), 6.67 (1H, s), 6.95 (1H, s), 7.00 (1H, m), 7.61, 7.63 (1H, s, two sets); ir ($CHCl_3$)ν: 1705, 1730 cm^{-1}; ms m/z : 625 (M^+). Anal. Calcd for $C_{36}H_{35}NO_9$: C, 69.11; H, 5.64; N, 2.24. Found: C, 69.20; H, 5.45; N, 2.20.

[*E*, *E*]-6',7'-Dihydro-6'-chloro-4,5,6,8,9,1',9'-heptamethoxy-3'-(1,3-pentadienyl)spiro[2*H*-benz-[*f*]-indene-2,8'-[8*H*]cyclopent[*g*]isoquinoline]-1,3-dione (20c, X=Cl). A solution of compound (**18c**) (15 mg, 0.024 mmol) in acetic acid (0.4 ml) was treated with a mixture of Mn(III) acetate (5.6 mg, 0.024 mmol) and Cu(II) acetate (4.3 mg, 0.024 mmol) followed by chloroform (2.0 μl, 0.024 mmol). Reaction mixture was stirred at room temperature for 30 min. Acetic acid was removed under vacuum worked up the reaction as mentioned earlier (**20b, X=Cl**) and purified on preparative tlc (triethylamine-acetone-methanol-ethyl acetate-methylene chloride-pet. ether; 0.1:5:5:5:10:74.9, v/v) to give **20c, X=Cl** as an oil (8 mg) in 48% yield, (diastereomeric mixture): ^{1}H-Nmr (300 MHz, $CDCl_3$): δ 1.87, 1.91 (3H, d, J=7.0 Hz, two sets), 2.83 (1H, dd, J=16.0 and 7.0 Hz), 3.00 (1H, dd, J=16.0 and 7.0 Hz), 3.47, 3.51 (3H, s, two sets), 3.88, 3.92 (3H, s, two sets), 4.08, 4.11 (3H, s, two sets), 4.12, 4.19 (4x3H, s, two sets), 5.84, 5.90 (1H, t, J=7.0 Hz, two sets), 6.00 (1H, m), 6.30 (1H, m), 6.45, 6.50 (1H, d, J=15.0 Hz, two sets), 6.95, 7.00 (1H, s, two sets), 7.10, 7.15 (1H, s, two sets), 7.35, 7.41 (1H, d, J=15.0 Hz, two sets), 7.60, 7.65 (1H, s, two sets), irradiation at δ 5.84 resulted two doublet at δ 2.83 and 3.00; ms m/z : 660 (M^+) . HRms calcd

for $C_{36}H_{34}NO_9Cl$: 660.1267, found : 660.1268.

Bromo compound (19c, X=Br). A solution of **18c** (125 mg, 0.2 mmol) in acetic acid (0.4 ml) was treated with Mn(III) acetate (53.7 mg, 0.2 mmol) followed by $CuBr_2$ (44.7 mg, 0.2 mmol). The mixture was stirred at room temperature for 15 min. The solvent was removed in vacuo and the residue was purified by flash chromatography ($CHCl_3$). The yield of purified bromo **19c** was 119.7 mg as an oil in 85% yield : ^{1}H-Nmr (200 MHz, $CDCl_3$): δ1.70, 1.75 (3H, d, J=7.0 Hz, two sets), 3.45, 3.50 (3H, s, two sets), 3.85-4.05 (6x3H, s, two sets), 5.40-6.30 (6H, m), 6.70, 6.72 (1H, s, two sets), 6.92, 6.94 (1H, s, two sets), 7.20 (1H, m), 7.60, 7.65 (1H, s, two sets); ms m/z : 703, 705 (M^+). HRms calcd for $C_{36}H_{34}NO_9Br$: 704.5827, found : 704.5829.

Hexamethyl ether of fredericamycin A (21c). To a solution of bromo compound (**20c**) (105.6 mg, 0.15 mmol) in benzene (5 ml) at 50°C under nitrogen was added a solution of triphenyltin hydride (52.7 mg, 0.15 mmol) and AIBN (0.6 mg, 0.0044 mmol) in benzene (10 ml) by syringe pump over 10 h. The mixture was stirred at the same temperature for an additional 2 h. Further added Ph_3SnH (57.9 mg, 0.165 mmol) and the mixture was refluxed for 2 h. The solvent was removed in vacuo and the residue was chromatographed (triethylamine-acetone-methylene chloride; 1:5:94, v/v) to give **21c** as an oil (51.6 mg) in 55% yield : ^{1}H-Nmr (200 MHz, $CDCl_3$): δ 1.87, 1.95 (3H, d, J=7.0 Hz, two sets), 2.55 (2H, t, J=7.5 Hz), 3.40 (2H, t, J=7.5 Hz), 3.49, 3.52 (3H, s, two sets), 3.95, 3.96 (3H, s, two sets), 4.05-4.15 (5x3H, s, two sets), 5.95 (1H, m), 6.30 (1H, m), 6.50, 6.55 (1H, d, J=15.0 Hz, two sets), 6.95, 6.98 (1H, s, two sets), 7.10, 7.15 (1H, s, two sets), 7.35 (1H, dd, J=15.0, 10.0 Hz), 7.60, 7.65 (1H, s, two sets), irradiation at δ 2.55 resulted singlet at δ 3.40 and vice versa; ir ($CHCl_3$) ν : 1700, 1730 cm^{-1}; ms m/z 625 (M^+). HRms calcd for $C_{36}H_{35}NO_9$: 625.6817, found : 625.6812.

Fredericamycin A (1). To the cooled solution of **21c** (5 mg, 0.008 mmol) in methylene chloride (1 ml) at -78°C was added boron tribromide (18.38 mg, 72.8 µl from 1.0M solution in methylene chloride, 0.0728 mmol). The reaction was stirred at -78°C for 15 min and warm it slowly to 0°C over a period of 4 h. The resulting mixture was cooled to -78°C, quenched with water (300 µl), stirred 10 min at same temperature and 15 min at room temperature. The solvent was removed in vacuo and the crude residue was separated on a tlc plate (acetic acid-acetone-methanol-chloroform; 1:3:3:93, v/v) afforded **1** as solid (acetone/methanol/chloroform) (1.2 mg) in 29% yield, whose nmr data superimposible to the natural product: ^{1}H-Nmr (400 MHz, $CDCl_3$):

δ 1.85 (3H, d, J=6.5 Hz), 2.56 (2H, t, J=7.6 Hz), 3.33 (2H, t, J=7.6 Hz), 4.00 (3H, s), 5.96 (1H, dq, J=17.7 and 6.9 Hz), 6.18 (1H, dd, J=15.6 and 10.0 Hz), 6.11 (1H, d, J=15.6 Hz), 6.31 (1H, s), 6.37 (1H, s), 6.52 (1H, dd, J=15.6 and 10.0 Hz), 6.90 (1H, s).

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