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SYNTHESIS OF (±) FREDERICAMYCIN A

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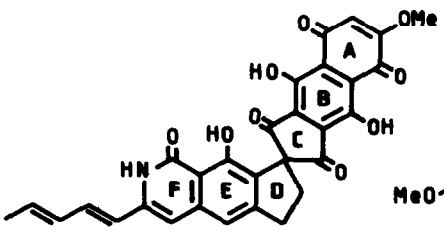
Abstract : The synthesis of Fredericamycin A (**1**) has been achieved by subjecting the 1,3-dione (**14**) to an unusual 5-endo trigonal radical cyclization followed by reductive elimination of the halogen in **15** and subsequent demethylation.

Fredericamycin A (**1**) an antitumor antibiotic produced by Streptomyces griseus[1] has been the target of much synthetic interest not only due to its antitumor properties[2] but also because of its structural complexity. Various approaches[3,4] have been devised for the skeletal construction of **1**, including two total syntheses, first by Kelly[5a] and recently by Clive[5b]. We wish to report our findings leading to the synthesis of **1**, in which the key step involves building the spiro system by an unusual 5-endo trigonal radical cyclisation.

On the basis of our earlier model reactions[3] for building the spiro system, the two main segments, the pentamethoxy benzphthalide (ABC segment **2**)[6] and the isoquinoline part (DEF segment **3**)[7] were chosen for completing the goal. All the phenolic hydroxyls in **2** and **3** were protected in the form of methyl ethers for operational convenience.



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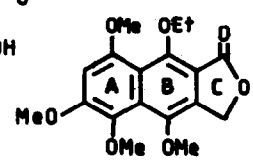

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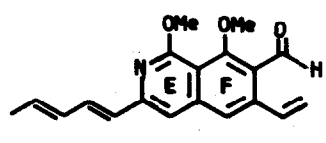

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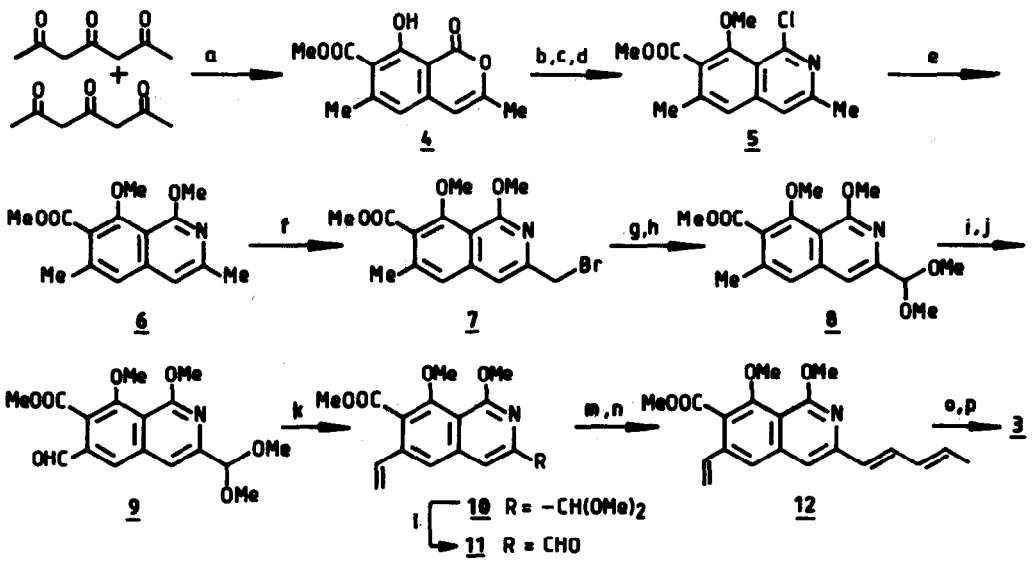
A good yielding process for the ABC segment (**2**) has already been established[6a,b]. Two elegant approaches for the synthesis of **3** have been developed, but the overall yields were low[7a,b]. However, we preferred a simplified approach which took advantage of the condensing of two polyketide units as summarized in scheme 1.

Isocoumarine (**4**)[8] was converted to the pivotal intermediate (**6**) through a standard set of reactions. The two methyl groups at C-3 and C-6 of isoquinoline have to be functionalized separately for introduction of pentadienyl side chain and radical trap respectively. For this purpose compound **6** was treated with NBS to give exclusively monobromo derivative (**7**). Oxidation of compound **7**, after treating the resultant aldehyde with acidic solution of methanol, afforded dimethyl acetal derivative (**8**). Condensation of **8** with benzaldehyde followed by oxidative cleavage of olefinic group furnished the required aldehyde (**9**) which was

later transformed to the styrene derivative (**10**). Regeneration of aldehyde at C-3 and further treatment with crotyltriphenylphosphoniumchloride and butyllithium in THF gave diene ester (**12**) as a mixture of geometrical isomers[9]. Compound **12** was isomerized to a more trans-trans form under iodine catalysed conditions (cis-trans and trans-trans forms, 16:84; from HPLC and NMR).

Scheme-1

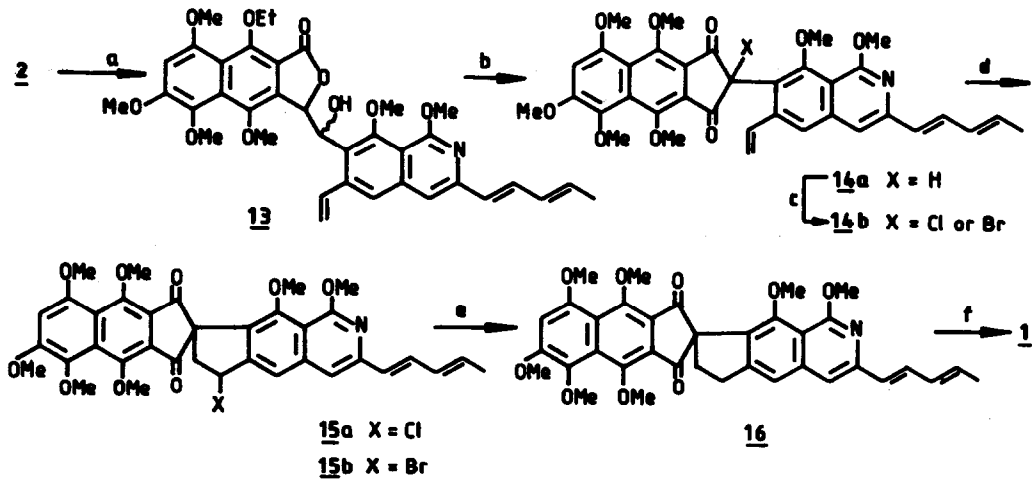


a) NaOH(2N), MeOH, rt, 24 h (65%), b) DMS, K_2CO_3, acetone, reflux 3.5 days (98%), c) NH_3 aq, 45°C, 24 h (70%), d) $POCl_3$, reflux 5 h (87%), e) NaOMe, reflux 6 h (80%), f) NBS, CCl_4, Benzoyl peroxide (cat), 6 h, light (95%), g) Hexamine, acetic acid-H_2O (1:1, v/v), 80°C, 30 min (65%), h) MeOH, PPTS, reflux 1 h (98%), i) $NaNH_2$, PhCHO, HMPA, rt, 8 h; K_2CO_3, MeI, 12 h (82%), j) OsO_4, $NaIO_4$, buffer pH 7, 0°C, 5 h (60%), k) $Ph_3P^+CH_3Br^-$, $NaNH_2$, ether-THF (20:1, v/v), 0°C, 10 min (78%), l) DDQ, CH_3CN-H_2O (9:1 v/v), 1.5 h, rt (95%), m) Ph_3P^+-CH_2-CH=CH-$MeCl^-$, BuLi, THF, -78°C, 45 min, -45°C, 45 min (78%), n) PTS, NaBr, I_2, MeOH, reflux 45 min (93%), o) DIBAL, CH_2Cl_2, 1 h, -78°C (92%), p) PDC, CH_2Cl_2, molecular seives, 45 min, rt (70%).

Aldol reaction between **2** and **3** in presence of LDA furnished the adduct (**13**) (Scheme 2). Sodium methoxide mediated rearrangement to the 1,3-dione (**14a**) was accomplished under careful experimental conditions. Model experiments to synthesize **14a** directly from **2** and **3** under Shapiro's conditions[10] were unsuccessful. Spiro annulation of dione (**14a**) was first carried as per our earlier approach[3c], wherein **14a** was treated with Mn (III) acetate, Cu (II) acetate and chloroform in acetic acid at room temperature for 30 min, resulting in the

formation of chloro derivative (**15a**) in 60% yield. Reductive elimination of chlorine with Bu_3SnH gave a mixture of products, which on chromatographic separation gave the hexamethyl ether of fredericamycin A (**16**) in less than 10% yield. However, treatment of **14a** with $CuBr_2$, Mn (III) acetate and acetic acid at room temperature for 15 min resulted in the formation of the bromo derivative (**14b**) in 80% yield[11]. Radical cyclization of **14b** with slow addition

Scheme-2



a) LDA, **3**, THF, HMPA, -78°C, 3 h (54%), b) NaOMe, MeOH, ethylpropionate, reflux 1.5 h (58%), c) $CuBr_2$, Mn(III)acetate, AcOH, 15 min, rt (80%), d) Ph_3SnH (1 eq), AIBN (0.03 eq), benzene, slow addition 12 h, 50°C, e) Ph_3SnH (1.1 eq), benzene, reflux 2 h (55%), f) BBr_3, CH_2Cl_2, -78°C, 30 min, 0°C, 10 min.

of Ph_3SnH (1 eq), AIBN (0.03 eq) in benzene at 50°C for 12 h followed by reductive elimination of bromine in **15b** (not isolated) by adding Ph_3SnH (1.1 eq) and refluxing the mixture for additional 2 h gave the hexamethyl ether of fredericamycin A (**16**) in 55% yield after chromatographic separation[11]. The NMR spectrum of **16** is fully in agreement with the assigned structure[12]. Subjecting **16** with BBr_3 in CH_2Cl_2, -78°C, and bringing it slowly to 0°C gave Fredericamycin A (**1**) which is identical with the natural sample[13].

References:

1. Isolation - Pandey, R.C.; Toussaint, M.W.; Stroshane, R.M.; Kalita, C.C.; Aszalos, A.A.; Garretson, A.L.; Wei, T.T.; Byrne, K.M.; Geoghegan, Jr. R.F.; White, R.J. *J. Antibiot.*, **1981**, *34*, 1389; Structure - Misra, R.; Pandey, R.C.; Silverton, J.V. *J. Am. Chem. Soc.*, **1982**, *104*, 4478; Misra, R.; Pandey, R.C.; Hilton, B.D.; Roller, P.P.; Silverton, J.V. *J. Antibiot.*, **1987**, *40*, 786; Biosynthesis - Byrne, K.M.; Hilton, B.D.; White, R.J.; Misra, R.; Pandey, R.C. *Biochemistry*, **1985**, *24*, 478.

2. Warnick-Pickle, D.J.; Byrne, K.M.; Pandey, R.C.; White, R.J. *J. Antibiot.* **1981**, *34*, 1402; Misra, R. *J. Antibiot.*, **1988**, *41*, 976; Dalal, N.S.; Shi, X. *Biochemistry*, **1989**, *28*, 748; Latham, M.D.; King, C.K.; Gorycki, P.; Macdonald, T.L.; Ross, W.E. *Cancer Chemother. Pharmacol.*, **1989**, *24*, 167.

3. a) Rama Rao, A.V.; Reddy, D.R.; Deshpande, V.H. *J. Chem. Soc. Chem. Commun.*, **1984**, 1119; b) Rama Rao, A.V.; Reddy, D.R.; Rao, B.V. *Indian J. Chem. Sec. B*, **1988**, *27*, 1065; c) Rama Rao, A.V.; Rao, B.V.; Reddy, D.R.; Singh, A.K. *J. Chem. Soc. Chem. Commun*, **1989**, 400; d) Rama Rao, A.V.; Rao, B.V.; Reddy, D.R. *Indian J. Chem. Sec. B*, **1991**, *30*, 723.

4. Other approaches for constructing spiro system, see a) Clive, D.L.J.; Khodabocus, A.; Vernon, P.G.; Angoh, A.G.; Bordeleau, L.; (in part) Middleton, D.S.; Lowe, C.; Kellner, D. *J. Chem. Soc. Perkin Trans. 1*, **1991**, 1443; b) Boger, D.L.; Jacobson, I.C. *J. Org. Chem.*, **1991**, *56*, 2115.

5. a) Kelly, T.R.; Bell, S.H.; Ohashi, N.; Armstrong-Chong, R.J. *J. Am. Chem. Soc.*, **1988**, *110*, 6471; b) Clive, D.L.J.; Tao, Y.; Khodabocus, A.; Wu, Y.-J.; Angoh, A.G.; Bennett, S.M.; Boddy, C.N.; Bardeleau, L.; Kellner, D.; Kleiner, G.; Middleton, D.S.; Nicholos, C.J.; Richardson, S.R.; Vernon, P.G. *J. Chem. Soc. Chem. Commun.* **1992**, 1489.

6. ABC Segment - a) Rama Rao, A.V.; Reddy, D.R.; Annapurna, G.S.; Deshpande, V.H. *Tetrahedron Lett.*, **1987**, *28*, 451; b) Rama Rao, A.V.; Sreenivasan, N.; Reddy, D.R.; Deshpande, V.H. *Tetrahedron Lett.*, **1987**, *28*, 455; c) Parker, K.A.; Spero, D.M.; Koziski, K.A. *J. Org. Chem.*, **1987**, *52*, 183; d) Tanoue, Y.; Terada, A.; Tsuboi, T.; Hayashida, T.; Tsuge, O. *Bull. Chem. Soc. Jpn*, **1987**, *60*, 2927.

7. DEF Segment - a) Rama Rao, A.V.; Reddy, D.R. *J. Chem. Soc. Chem. Commun*, **1987**, 574; b) Pulla Reddy, S. Ph.D. Thesis, Pune University, India, **1986**; c) Parker, K.A.; Breault, G.A. *Tetrahedron Lett.*, **1986**, *27*, 3835; d) Clive, D.L.J.; Sedgeworth, J. *J. Heterocyclic. Chem.*, **1987**, *24*, 509.

8. Bertz, S.H. *Synthesis*, **1980**, 708.

9. a) Bohlmann, F.; Mannhardt, H.-J. *Chem. Ber.* **1956**, *89*, 1307; b) Hug, R.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta.*, **1972**, *55*, 1828.

10. Shapiro, S.L.; Geiger, K.; Youlus, J.; Freedman, L. *J. Org. Chem.* **1961**, *26*, 3580.

11. Details of this methodology will be published separately.

12. Spectroscopic data of **16**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.87, 1.95 (3H, d, J = 7.0 Hz, CH_3, two sets), 2.55 (2H, t, J = 7.5 Hz), 3.40 (2H, t, J = 7.5 Hz), 3.49, 3.52 (3H, s, CH_3, two sets), 3.95, 3.96 (3H, s, CH_3, two sets), 4.05-4.15 (15H, s, $5CH_3$), 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 2.55 ppm resulted singlet at 3.40 ppm and vice versa; IR ν_{max} ($CHCl_3$): 1730, 1700 cm^{-1}; Ms m/z : 625 (M^+).

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