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SYNTHESIS OF 4,9-DIETHOXY-5,6,(7),8-TRIMETHOXY-1,3-DIHYDRONAPHTHO-(2,3-C)-FURAN-1-ONE : A KEY SYNTHON OF FREDERICAMYCIN A

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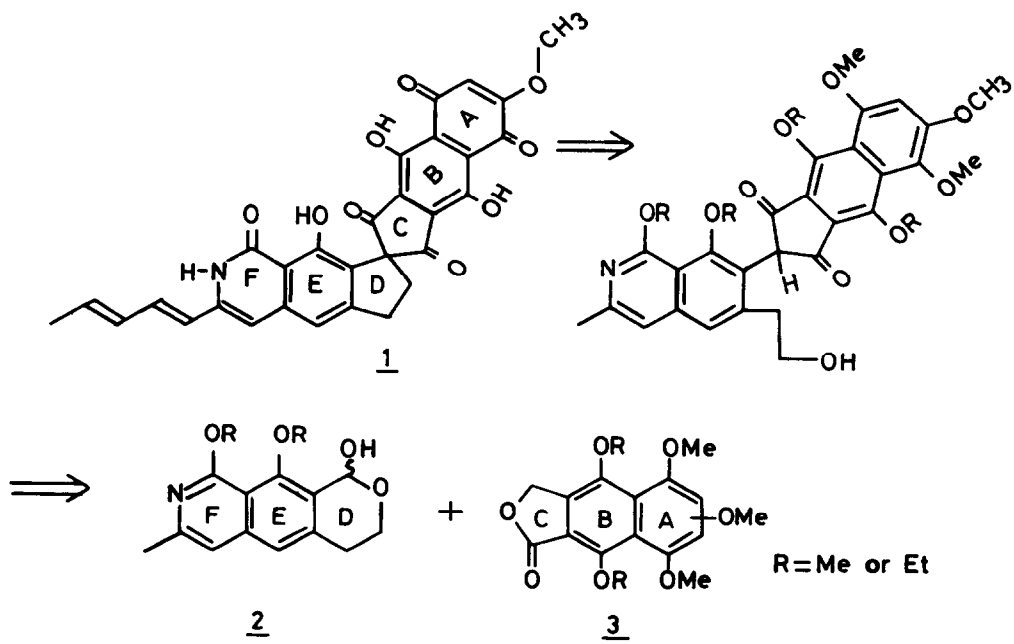
Summary : The synthesis of 4,9-diethoxy-5,6,(7),8-trimethoxy-1,3-dihydronaphtho-(2,3-C)-furan-1-one (ABC ring synthon) for fredericamycin A has been described by involving cycloaddition reactions.

Interest in the synthesis of fredericamycin A arose because of the potent anticancer activity and interesting structural features[1]. For instance, the presence of a novel and hitherto unknown spiro (4,4) nonane system, undoubtedly makes this molecule unique for this class of antibiotics.

As a part of the programme on the total synthesis of fredericamycin A (1), we were the first to develop a strategy for the construction of spiro (4,4) nonane system[2]. Based on our methodology we realized that the substituted benz-phthalide (ABC ring synthon) 3 and isoquinoline (DEF ring synthon) 2 would be our target synthons (Scheme 1). Herein we report the construction of the benz-phthalide segment 3 by involving successive cycloaddition reactions.

Scheme 1



1

2

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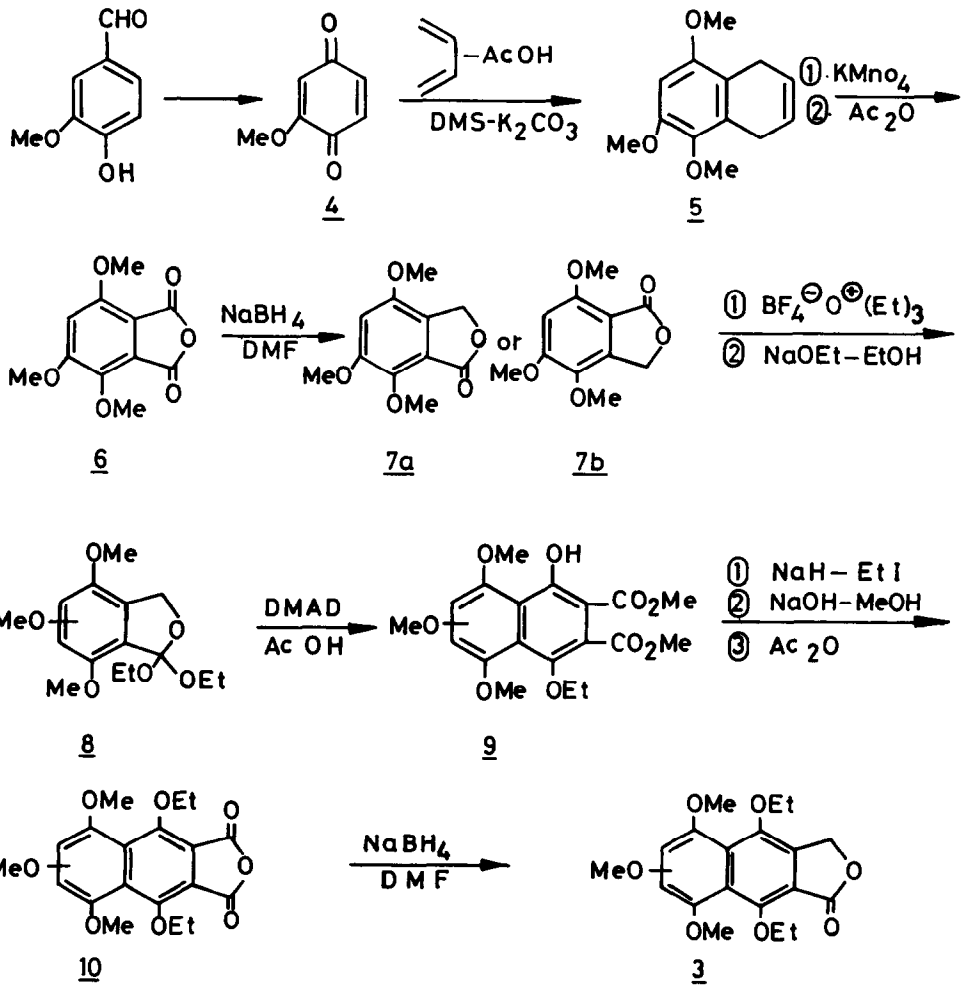
Re-examination of benz-phthalide synthon 3 suggested that the structure dimethyl 1-ethoxy-4-hydroxy-5,6,(7),8-trimethoxynaphthalene-2,3-dicarboxylate (9) is a suitable precursor. In principle, compound 9 could be prepared by cycloaddition reaction of dimethyl-acetylenedicarboxylate and a diene, generated in situ from a suitably substituted 1,1-di-alkoxy isobenzofuran by acid catalysed elimination of an alkoxy group of the orthoester (8). The requisite compound 8 has been prepared from vanillin (Scheme 2).

Scheme 2



Successive oxidation of vanillin with alkaline hydrogen peroxide followed by sodium dichromate gave 2-methoxy-1,4-benzoquinone (4)[3] in 69% yield. Diels-Alder reaction of 4 with 1,3-butadiene in glacial acetic acid was performed (R.T; 12 hr) and then the expected adduct was methylated with dimethylsulfate in presence of anhydrous potassium carbonate and acetone (reflux temperature; 12 h) to give 5 in 70% yield[4]. Oxidation of 5 with aqueous potassium permanganate (2.5 eq; 100°) during 2 hr addition followed by 1 hr further refluxing gave rise to the diacid (40% yield) which on treatment with an excess acetic anhydride (155°; 6 hr) afforded the required anhydride 6 in 70% yield. Selective reduction[5] of the anhydride 6 with 1.2 eq. of sodium borohydride in dimethylformamide (R.T; 1 hr with acid work up) afforded 4,5,(6),7-trimethoxy-1(3H)-isobenzofuranone (7a or 7b) in 80% yield. Although the spectral studies of 7 indicated that it was a single isomer, the correct regiostructure could not be ascertained.

Compound 7 was converted into the orthoester 8 (82% yield) by treating with triethyloxoniumtetrafluoroborate[6] (1.2 eq; R.T; 48 hr) in ethylene dichloride followed by the addition of the resulting mixture to a cooled solution of sodium ethoxide in ethanol (2 eq. Na in 14 eq. of ethanol; -30°; 1.5 hr) and usual work up[7]. In the PMR spectrum of 8, an upfield shift of 0.18 ppm for the resonances due to methylene protons was observed when compared with the PMR spectrum of the phthalide 7, in addition, resonances due to two ethoxy groups were also revealed, thus confirming the structure 8. The cycloaddition reaction of the diene, generated[8] *in situ* from the orthoester 8 and glacial acetic acid (catalytic amount) with dimethylacetylenedicarboxylate in refluxing chlorobenzene afforded dimethyl 1-ethoxy-4-hydroxy-5,6,(7),8-trimethoxynaphthalene-2,3-dicarboxylate (9) in 84% yield. The free hydroxyl group in 9 was protected as ethyl ether in 76% yield by the reaction of sodium hydride and ethyliodide (THF refluxing; 2 h). The resulting product was hydrolysed with 10% methanolic sodium hydroxide (reflux 12 hr) to the diacid which was converted to the anhydride 10 by treatment with acetic anhydride under reflux in 84% yield. Compound 10 constitutes the ABC ring synthon for the synthesis of fredericamycin A by the methodology reported by Braun *et al*[2e] for the spiro system. Reduction of 10 to the corresponding 4,9-diethoxy-5,6,(7),8-trimethoxy-1,3-dihydronaphtho-(2,3-C)-furan-1-one was effected by the above procedure ($NaBH_4$ - DMF; R.T; 2 hr) in 55% yield. It is pertinent to mention that the position (C-6 or C-7) of the methoxyl group in compound 3 would not deter our overall synthetic plan because at later stages coupling of 3 with isoquinoline synthon 2 would result the same product.

The synthesis of the isoquinoline (DEF synthon) 2 and its coupling with the benzphthalide (ABC synthon) 3 for the total synthesis of fredericamycin A is being purused.

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