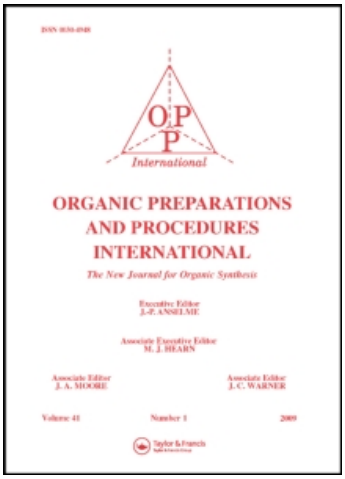

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SYNTHESIS OF DIMETHYL 1,4-DIHYDROXY-5,6,8-TRIMETHOXYNAPHTHALENE-2,3-DICARBOXYLATE, A KEY INTERMEDIATE FOR FREDERICAMYCIN A

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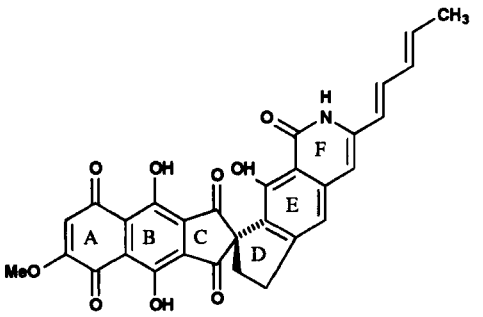
Fredericamycin A (**1**) is unique among the recently isolated[1] antitumor and antibiotic compounds in that it contains a spiro ring system. Most of the approaches[2] to **1** describe the synthesis of either the spiro ring junction or ABC or DEF ring synthons. Kelly *et al.*[3] and Clive *et al.*[4] have recently completed the total syntheses of racemic **1**.



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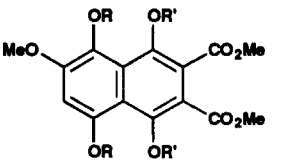
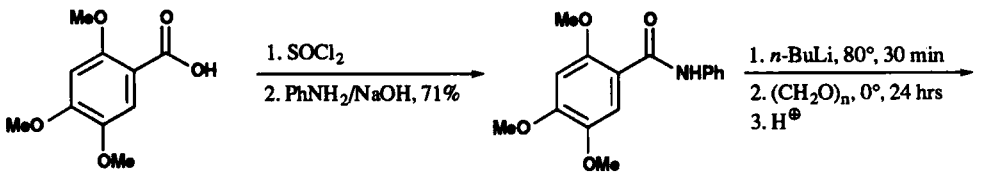


2

a) R = R' = Bn b) R = Bn, R' = H c) R = Me, R' = Et d) R = Me, R' = H

Although a number of methods are available for the synthesis of functionalised naphthalenes,[5] only two approaches[3,6] describe the synthesis of pentaoxygenated naphthalene-2,3-dicarboxylates (**2a-c**) which could be used for the synthesis of **1**. This communication reports a convenient synthesis of **2d**, which has the requisite functionality required for the construction of the ABC ring system of fredericamycin A (**1**).

In our approach the phthalide **5a** is obtained from amide **4**, using a heteroatom directed lithiation reaction[7,8] Treatment of **5a** with LDA in THF at -78° is followed by quenching with TMSCi to obtain isobenzofuran [6]. Reaction of [6] with dimethylacetylene dicarboxylate in THF at -78° for 3 hrs, followed by acidic workup gave the desired naphthalene derivative **2d** in 36% yield.



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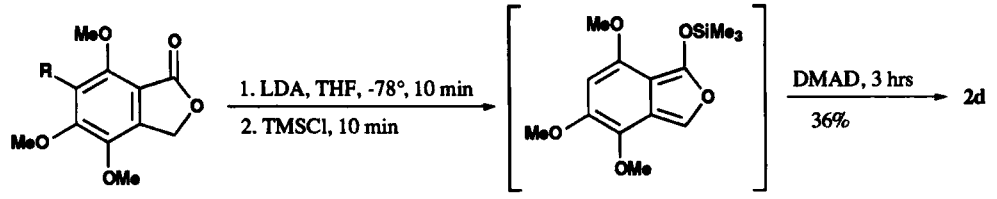
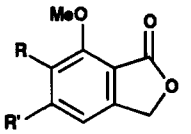


5 6

5a, R = H (36%)
b, R = –CH_2OH (3%)



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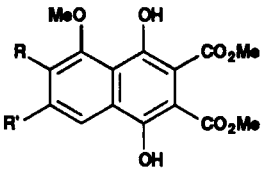

8

7, 8	R	R'
a	H	H
b	OMe	H
c	OMe	OMe

The naphthalene derivatives **8a-c** were also synthesised from the corresponding phthalides **7a-c**[9,10] in 30, 41 and 31% yields respectively. These compounds are of interest for the synthesis of fredericamycin A analogues.

The yields obtained for the naphthalenes 2d and 8a-c are far superior to the earlier reported[3] yields.

EXPERIMENTAL SECTION

All melting points are uncorrected. ^1H NMR spectra were recorded on Jeol FX 90 Q instrument in $CDCl_3$ using TMS as an internal standard. IR Spectra were obtained as nujol mulls on a Perkin-Elmer-337 spectrophotometer. Analyses were obtained using Hosli's rapid carbon-hydrogen analyser.

2,4,5-Trimethoxy-N-phenylbenzamide (4).- A solution of 2,4,5-trimethoxybenzoic acid (**3**, 5.0 g, 23 mmol.) in thionyl chloride (3.1 mL, 70 mmol.) was refluxed at 80° for 6 hrs. Excess thionyl chloride was removed under reduced pressure. The semi-solid thus obtained was dissolved in CH_2Cl_2 (15 mL) and added dropwise to a mixture of aniline (2 mL, 33 mmol.) in NaOH (2N, 15 mL) during a period of 30 min. at 0°. Stirring at 0° was continued for 2 hrs and the organic layer was separated. The

aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined CH_2Cl_2 layer was washed with aqueous $NaHCO_3$, water and brine. It was dried (Na_2SO_4) and evaporated to give a solid, which on recrystallization from CH_2Cl_2 - hexane furnished **4** (4.8 g, 71%), mp. 154-156°; NMR: δ 3.97, 4.02 and 4.11 (s, 3H each, 3 x OMe), 6.58 (s, 1H, ArH), 7.2 - 7.88 (m, 5H, -Ph), 7.83 (s, 1H, ArH), 9.85 (bs, 1H, -NH, exchangeable with D_2O); IR: 1670 and 3350 cm^{-1}.

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.94; N, 4.88. Found : C, 66.95; H, 5.94; N, 4.92

4,5,7-Trimethoxyphthalide (5a).- A solution of *n*-butyllithium (10 mmol., prepared from 0.2 g lithium and 1.5 mL *n*-butyl bromide) in ether (50 mL) was added to a refluxing solution of amide (**4**, 0.86 g, 3 mmol) in THF (40 mL) over 15 min. The burgundy red reaction mixture was cooled to 0° and paraformaldehyde (3.0 g) was added portionwise over 15 min. The white reaction mixture thus obtained was stirred overnight at room temperature and quenched by addition of water (20 mL). THF was removed under reduced pressure and the residue was acidified with HCl (1:1) and extracted with CH_2Cl_2 (2 x 20 mL). The CH_2Cl_2 layer was washed with water, dried (Na_2SO_4) and evaporated to give a thick oily product which was purified on silica gel chromatography using $CHCl_3$ as an eluent. The initial fractions contained a solid which was recrystallized from ethyl acetate-hexane to give phthalide **5a** (0.24 g, 36%), mp. 135 136° (lit.[11] 134 -135°), NMR: δ 3.85 (s, 3H, OMe), 4.00 (s, 6H, 2 x OMe), 5.26 (s, 2H, -CH_2-), 6.50 (s, 1H, ArH); IR: 1750 cm^{-1}.

Anal. Calcd for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40. Found : C, 59.10; H, 5.22

Further elution with the same solvent gave **5b** (0.025 g, 3%); mp 104°; NMR: δ 2.36 (s, 1H, -OH, exchangeable with D_2O), 3.94, 4.05 and 4.16 (s, 3H each, 3 x OMe), 4.78 (s, 2H, CH_2-OH), 5.32 (s, 2H, -CH_2-); IR: 1760 and 3400 cm^{-1}.

Anal. Calcd for $C_{12}H_{14}O_6$: C, 54.54; H, 5.83. Found : C, 54.70; H, 5.48

General Procedure for Dimethyl 1,4-Dihydroxynaphthalene-2,3-dicarboxylate (2d, 8a-c).- To a solution of LDA in THF (1.5 mmol, prepared from 0.26 mL, 1.9 mmol. diisopropylamine and 1 mL, 1.5 M solution of *n*-butyl lithium in hexane) was added a solution of phthalide **5a** or **7a-c** (1.2 mmol.) in THF (15 mL) at -78° over 5 min. The reaction mixture was stirred for 10 min. and chlorotrimethylsilane (0.24 mL, 1.9 mmol.) was added while maintaining the temperature at -78°. Stirring was further continued for 10 min and a solution of dimethylacetylene dicarboxylate (0.24 mL, 1.6 mmol.) in THF (5 mL) was added dropwise to the reaction mixture in 5 min. After complete addition the reaction mixture was warmed to room temperature over 3 hrs. Water (10 mL) was added and the THF was removed under reduced pressure, hydrochloric acid (12 N, 10 mL) was added to the residue and it was extracted with CH_2Cl_2 (3 x 25 mL). The organic layer was washed with water (2 x 20 mL), brine and dried (Na_2SO_4). On evaporation it gave a crude product which was purified via silica gel chromatography using ethyl acetate - hexane (1:1) as an eluent. Recrystallization from CH_2Cl_2-hexane provided naphthalenes **2d** and **8a-c**.

Compound 2d: Yield 0.16 g, 36%; mp. 173-174°; NMR: δ 3.94, 4.00 and 4.02 (s, 3H each, 3 x OMe), 4.04 (s, 6H, 2 x CO_2Me), 6.80 (s, 1H, ArH), 10.45 and 11.60 (s, 1H each, 2 x -OH, exchangeable with D_2O); IR: 1670, 1740 and 3250 cm^{-1}.

Anal. Calcd for $C_{17}H_{18}O_9$: C, 55.74; H, 4.95. Found: C, 55.78; H, 4.98

Compound 8a: Yield 0.12 g, 30%; mp. 162-163°; NMR: δ 4.00 (s, 3H, OMe), 4.11 (s, 6H, 2 x CO_2Me), 7.08-8.22 (m, 3H, 3 x ArH), 9.42 and 11.88 (s, 1H each, 2 x OH, exchangeable with D_2O); IR: 1670, 1740 and 3350 cm^{-1}.

Anal. Calcd for $C_{15}H_{14}O_7$: C, 58.82; H, 4.61. Found: C, 58.64; H, 4.64

Compound 8b: Yield 0.17 g, 41%; mp. 124-125°; NMR: δ 3.94 and 4.00 (s, 3H each, 2 x OMe), 4.11 and 4.17 (s, 3H each, 2 x CO_2Me), 7.34 (δ, 1H, J = 8 Hz, ArH), 8.34 (δ, 1H, J = 8 Hz, ArH) 9.71 and 12.05 (s, 1H each, 2 x OH, exchangeable with D_2O); IR: 1670, 1740 and 3320 cm^{-1}.

Anal. Calcd for $C_{16}H_{16}O_8$: C, 57.14; H, 4.80. Found: C, 57.34; H, 4.77

Compound 8c : Yield 0.14 g, 31%; mp. 167-168°; NMR: δ 3.64, 4.00, 4.05 and 4.14 (s each, 15H, 3 x OMe and 2 x CO_2Me), 7.65 (s, 1H, ArH), 9.54 and 11.88 (s, 1H each, 2 x OH, exchangeable with D_2O); IR: 1670, 1735 and 3320 cm^{-1}.

Anal. Calcd. for $C_{17}H_{18}O_9$: C, 55.74; H, 4.95. Found: C, 55.96; H, 4.86

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