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SYNTHESIS OF 2,2-DISUBSTITUTED 4,9-DIHYDROXY-1H-BENZ(f)INDENE-1,3(2H)DIONES. A MODEL SEQUENCE FOR THE SYNTHESIS OF FREDERICAMYCIN

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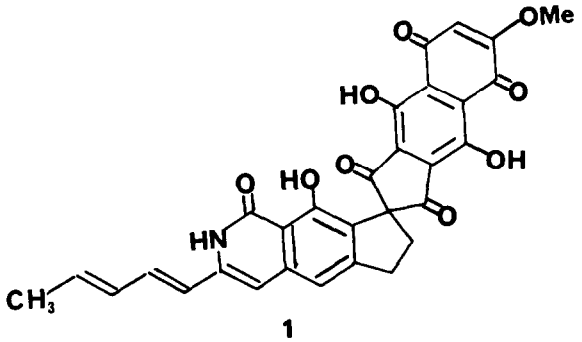
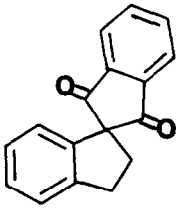
Benzindenedione 3 was prepared as a model for fredericamycin.

Among the known antitumor compounds, a unique structural feature is the spiro ring system of fredericamycin A *(1)*.[1] Recently, Rama Rao *et al.* prepared the model spiro(4,4) nonane *2*[2] from a 2-aryl 1,3-indanedione.[3] The report of that conversion prompts our communication of an alternative approach to joining the two perpendicular moieties of fredericamycin; our strategy led to the construction of the fredericamycin model *3*.



1



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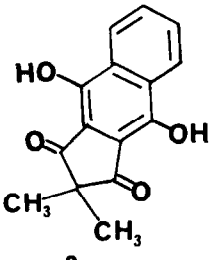
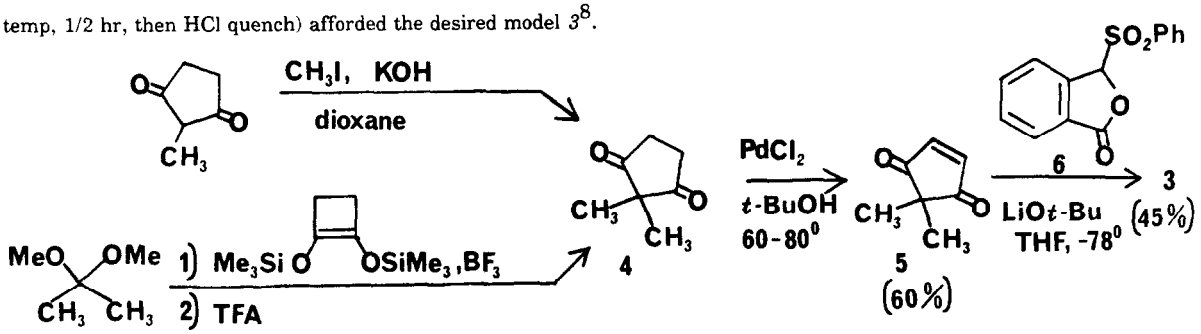


3

Our inspection of the structure of fredericamycin led us to focus on the 2,2-disubstituted cyclopentane-1,3-dione as a key feature. We imagined that the introduction of this moiety might be achieved by the Kuwajima aldol/ring expansion procedure[4] (see below). Elaboration of a cyclopentanedione to a benz(f)indene-1,3(2H)-dione would then be required. This ring system is relatively rare; a search of the literature revealed only three 2,2-disubstituted examples[5] and no 4,9-dihydroxy or dialkoxy compounds.

Our approach was to extend Hauser's elegant quinone annelation methodology, previously developed and used with cyclohexenones and butenolides,[6] to cyclopentenediones. 2,2-Dimethylcyclopentanedione *(4)* could be prepared by the literature method[7] or by the Kuwajima annelation of 2,2-dimethoxypropane (1 equiv. disiloxycyclobutene, 1 equiv $BF_3 \cdot OEt_2$, THF, -78°, 1 hr and room temp, 1 hr; adduct is dissolved in TFA at 50° and stirred at room temp 1 hr;

kugelrohr distillation, flash chromatography with EtOAc/C_6, 1:2, 40% yield). The required olefinic bond was introduced by treatment with NBS[7] or with $PdCl_2$ (1 equiv in *t*-BuOH, 60–80°, overnight, filter, concentrate). The latter procedure was superior in our hands; it gave a very clean product and, because the conditions required are very mild, it seems promising for application to more sensitive and elaborate systems. Treatment of the lithium enolate of the phthalide sulfone *6* (from 1 equiv of sulfone and 3 equiv Li*O*t-Bu in THF, -78°, 5 min) with enedione *5* (2 1/2 equiv, -78° to room temp, 1/2 hr, then HCl quench) afforded the desired model *3*[8].



Preparations of more oxygenated analogs of *3* and of spiro compounds more closely related to fredericamycin are underway.

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   (b) The 2-phenyl, 2-benzyl and 2-phenyl, 2-allyl substituted 1H-benz(f)indene-1,3(2H)diones from the Perkin-type condensation of phenylacetic acid and naphthalene-2,3-dicarboxylic anhydride followed by benzylation or allylation: Janson, S., Vanags, G., *Latv. PSR Zinat. Akad. Vestis, Kim. Ser., 1964,* 571, cited *Chem. Abstr.. 1965, 62,* 9079b.
   (c) Some phenyl substituted derivatives are known. An interesting example is the 2-hydroxymethyl-2,4-diphenyl derivative prepared by aldol condensation with formaldehyde: Jansons, S., *Latv. PSR Zinat. Akad. Vestis, Kim. Ser., 1969,* 212, cited *Chem. Abstr., 1969, 71,* 61031y.

6. Both a cyclohexenone annelation and a butenolide annelation are described in Hauser, F. M., Prasanna, S., *J. Org. Chem., 1981, 103,* 6378.

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8. Purified by preparative tlc on silica gel, eluent 1:4 EtOAc/C_6. IR ($CHCl_3$): 3360, 1700, 1675, 1605 cm^{-1}. NMR ($CDCl_3$): 8.77 (br, 2H, exch D_2O), 8.42 (dd, J=7,3 Hz, 2H), 7.76 (dd, J=7,3 Hz, 2H), 1.37 (s, 6H) ppm. M.p. 172–174° from Et_2O/Hexane. M^+ calcd for $C_{15}H_{12}O_4$ 256.0735; found 256.0734.

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