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MODEL STUDIES TOWARDS FREDERICAMYCIN A. PROTOCOL FOR THE RAPID CREATION OF THE SPIROCYCLIC CENTRE

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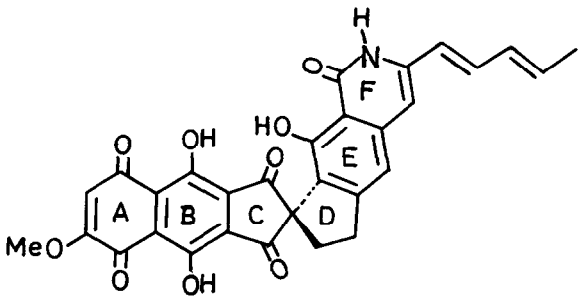
Summary : A novel, two step, photochemical approach towards the dibenzospiro[4.4]nonane ring system 5 present in fredericamycin A is delineated.

Fredericamycin A 1, produced by the strains of streptomyces greseus, represents a new structural-type among the natural products and is notable for the appreciable antitumour and antibiotic properties it exhibits.[1] The high biological activity profile of 1 as well as its structural complexity and unique L-like molecular shape have drawn synthetic chemists all over into a hot chase towards this formidable target.[2] The core of the fredericamycin A molecule is the dibenzo-1,4-diketospiro[4.4] nonane sub-unit and all synthetic efforts, to-date, have focussed on the creation of 2 or its closely related derivatives.[2] We wish to describe here an exceptionally simple, two step approach for the generation of the spiro centre present in 1 from commercially available precursors. Further elaboration to 2 and related dibenzospiro[4.4]nonane dione 7 and trione 8 is also described, Scheme 1.

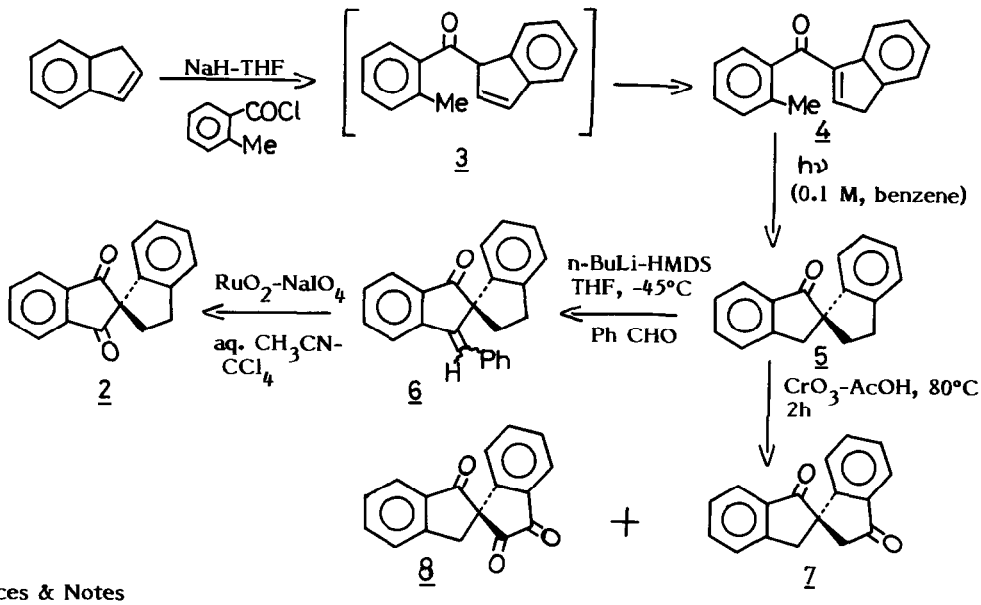


1

Reaction of indenyl anion with 2-methylbenzoyl chloride furnished the intermediate 3 which readily isomerized to 1-(2-methylbenzoyl)-3H-indene 4[3], mp 85°C (60%). Irradiation (< 3600 Å) of 3 with a 450 W Hanovia lamp in a quartz vessel led to the formation of 5[3], mp 88-90°C (65%) via a 1,6-hydrogen abstraction from the methyl group and spirocyclisation.[5] The spiro[4.4]nonanone derivative 5 was conveniently transformed into the required dione 2[2a,f,h,5] through the benzylidene derivative

6 and oxidative cleavage (50%), Scheme 1. Related spiro-dione **7**[3] and trione **8**[3] (3:1, 65%) were obtained from **2** by direct chromic acid oxidation. The special feature of our approach is that it can be readily adapted for the union of two highly functionalised halves (AB + DEF) for the creation of **1** as well as for the preparation of analogues with the oxygenation pattern present in **7** & **8**. Further work is in progress.[6]

SCHEME 1



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3. Compound **4** : IR (KBr): 1640, 1590, 1560, 760 cm^{-1}; ^1H NMR: δ 2.39 (3H, s), 3.52 (2H, d, J=2Hz), 6.92(1H, dd, J=2Hz), 7.0-7.6(7H, m), 8.18(1H, m). **5**: IR(KBr): 1695 cm^{-1}; ^1H NMR: δ 1.9-3.5(6H, m), 6.72(1H, d, J=8Hz), 6.9-7.8(7H, m); ^{13}C NMR: δ 31.7(t), 37.4(t), 48.7(t), 61.9(s), 208.2(s) and 12 aromatic C's between 122.1-157.0. **7**: IR(KBr): 1700 cm^{-1}; ^1H NMR: δ 2.94(2H, ABq, J=18Hz), 3.56(2H, ABq, J=18Hz), 6.8-7.8(8H, m); ^{13}C NMR: δ 42.2, 47.4, 55.7, 204.6, 205.5 and aromatic C's. All the new compounds gave satisfactory analytical data.
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5. We thank Dr. A.V. Rama Rao and his colleagues for comparison spectra of **2**.
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