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SYNTHESIS OF SPIROCYCLIC DIKETONES RELATED TO FREDERICAMYCIN A

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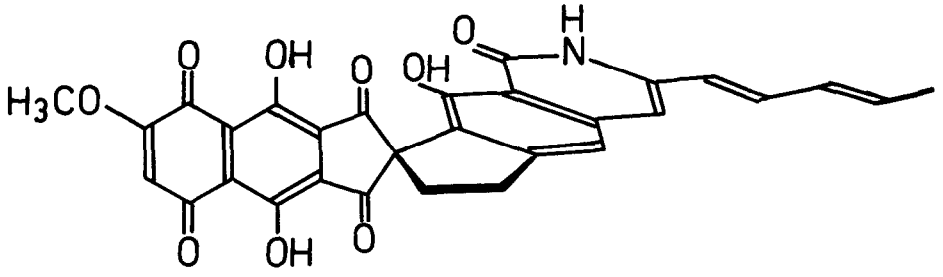
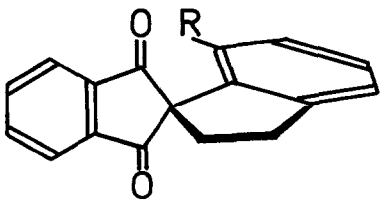
Abstract: An intramolecular Friedel-Crafts type reaction of the thioacetals 7a and 7b is the key step in a simple synthesis of the diketones 2a and 2b.

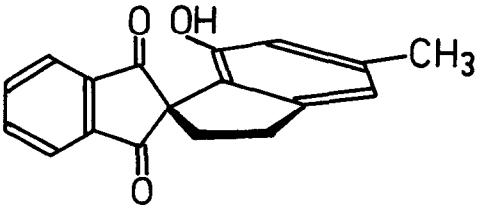
Fredericamycin A (1), an antitumor antibiotic produced by Streptomyces griseus, has a novel spiro ring system, previously unknown in this class of natural products[1]. Obviously, the synthesis of this unusual quinone is felt to be a challenge by several research groups. Preliminary reports[2] on the preparation of the tetracyclic compounds 2a and 3 prompt us to communicate our simple synthesis of the spirocyclic diketones 2a and 2b.



1



2a: R=H, 2b: R=OCH$_3$



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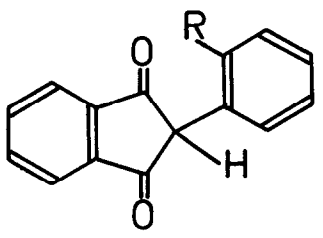
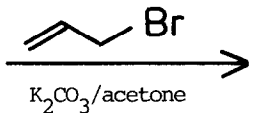
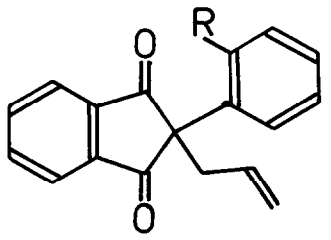
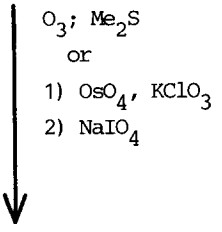


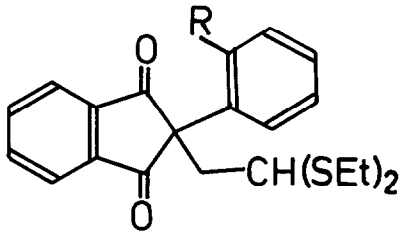
4a,b



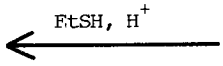


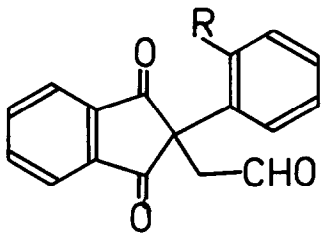
5a (95%)
5b (78%)



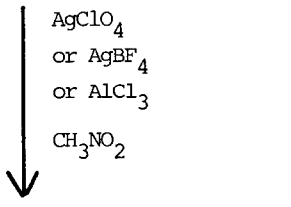


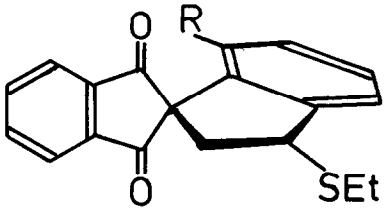
7a (78%)
7b (93%)



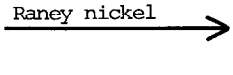


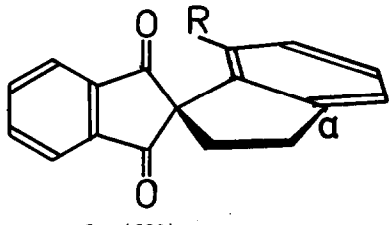
6a (87%)
6b (64%)





8a (35-44%)
8b (36%)

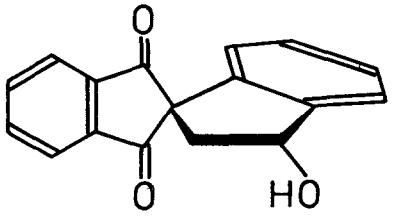




2a (62%)
2b (45%)

2, 4 - 8: a: R = H
b: R = OCH_3

The indandiones 4a and 4b, easily available from phthalic anhydride and phenyl- or 2-methoxy phenyl acetic acid[3], are alkylated with allyl bromide to give the alkenes 5a and 5b respectively. The cleavage of the olefinic double bond is accomplished either directly by ozonolysis or gradually by hydroxylation and subsequent treatment with sodium periodate. Since all attempts to convert the aldehyde 6a into the spirocyclic alcohol 9 were unsuccessful, we tried to cyclize the thioacetal 7a[4], which is conventionally available from 6a. Indeed, heating 7a with silver perchlorate or silver tetrafluoroborate in anhydrous nitromethane effects the desired ring closure to give the spirocyclic compound 8a. This Friedel-Crafts type reaction also occurs, when the thioacetal 7a is treated with aluminum chloride. The subsequent desulfurization with Raney nickel affords the tetracyclic diketone 2a. The yields refer to the isolated and purified products (chromatography or recrystallization). In a completely analogous manner, the methoxy spirodione 2b is prepared from the indandione 4b[5]. As the carbon-carbon bond a (formula 2) is formed in the end of the reaction sequence, the formation of regioisomers 10 is avoided. The application of this concept to the preparation of fredericamycin (1) is in progress in our laboratory.



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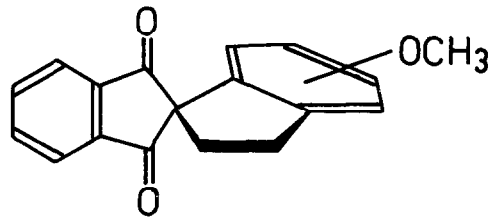

10

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References and Notes

1) For isolation and determination of the structure, see R. Misra, R. C. Pandey, J. V. Silverton, J. Am. Chem. Soc. 104 (1982) 4478 and references cited therein.

2) A. V. Rama Rao, D. Reddeppa Reddy, V. H. Deshpande, J. Chem. Soc. Chem. Commun. 1984,1119; A. S. Kende, F. H. Ebetino, T. Ohta, Tetrahedron Lett. 1985, 3063. - For preparation of a benzindandione in a model sequence for the synthesis of 1, see K. A. Parker, K. A. Koziski, G.Breault, Tetrahedron Lett. 1985, 2181.

3) S. Gabriel, Ber. Dtsch. Chem. Ges. 18 (1885) 3470; F. Nathanson, Ibid. 26 (1893) 2576; S. L. Shapiro, K. Geiger, L. Freedman, J. Org. Chem. 25 (1960) 1861; J. Rotbergs, V. Strautina, V. Oskaja, Latv. PSR Zinat. Akad. Vestis, Kim. Ser. 1974, 75; Chem. Abstr. 80 (1974) 145861t.

4) Sulfur stabilized carbocations, generated from other precursors, are known to attack arenes: A. Eschenmoser, Quart. Rev. 24 (1970) 366; E. R. de Waard, H. R. Reus, H. O. Huisman, Tetrahedron Lett. 1973, 4315.

5) Satisfactory C, H analyses and spectral data were obtained for the new compounds.

8a: ^{1}H NMR ($CDCl_3$; 250 MHz) δ = 1.3 (t, J = 8 Hz; 3 H), 2.60 - 2.95 (m; 4 H), 4.63 (t, J = 8 Hz; 1 H), 6.62 (d, J = 8 Hz; 1 H), 7.12 (t, J = 8 Hz; 1 H), 7.32 (t, J = 8 Hz; 1 H), 7.53 (d, J = 8 Hz; 1 H), 7.92 - 7.95 (m; 2 H), 8.03 - 8.15 (m; 2 H).

8b: ^{1}H NMR: δ = 1.3 (t, J = 8 Hz; 3 H), 2.55 - 2.90 (m; 4 H), 3.40 (s; 3 H), 4.79 (t, J = 8 Hz; 1 H), 6.70 (d, J = 8 Hz; 1 H), 7.21 (d, J = 8 Hz; 1 H), 7.40 (t, J = 8 Hz; 1 H), 7.96 - 8.01 (m; 2 H), 8.08 - 8.19 (m; 2 H).

2a: Schmp. 127 - 129 °C; ^{1}H NMR: δ = 2.57 (t, J = 8 Hz; 2 H), 3.31 (t, J = 8 Hz; 2 H), 6.63 (d, J = 7.5 Hz; 1 H), 7.06 (t, J = 7.5 Hz; 1 H), 7.23 (t, J = 7.5 Hz; 1 H), 7.35 (d, J = 7.5 Hz; 1 H), 7.9 (mc; 2 H), 8.06 - 8.11 (m; 2 H).

2b: ^{1}H NMR: δ=2.55 (t, J = 8 Hz; 2 H), 3.18 (t, J = 8 Hz; 2 H), 3.48 (s; 3 H), 6.67 (d, J = 8 Hz; 1 H), 7.00 (d, J = 8 Hz; 1 H), 7.53 (t, J = 8 Hz; 1 H), 7.71 - 7.90 (m; 4 H).

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