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MODEL STUDIES AIMED AT THE SYNTHESIS OF FREDERICAMYCIN A.

A SIMPLE O-QUINODIMETHANE ROUTE TO THE SPIRO NAPHTHALENE PORTION

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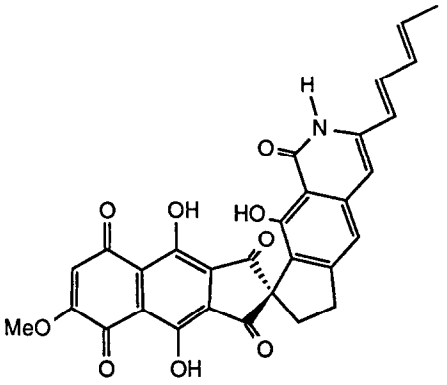
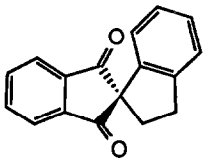
Abstract: *The three contiguous rings in the naphthalene portion of a model compound related to Fredericamycin A have been prepared by the Diels-Alder cycloaddition reaction of an α-bromo-o-quinodimethane intermediate to the carbon-carbon double bond of the spiro dienophile, spiro[4.4]non-2,3-ene-1,4-dione.*

The recent number of synthetic efforts[1] aimed at simple model compounds related to Fredericamycin A (1)[2] attests both to the significance attached to this antitumor, antibiotic compound and to the difficulty in assembing its unique spiro[4.4]nonane system. In our first report we prepared the most fundamental dibenzo[4.4]nonane 2 by a mercury induced acyl migration involving the ring expansion of a cyclobutanone.[3a] We then independently synthesized 2 employing a Diels-Alder route that utilized dienophile 3 and 1,3-butadiene.[3b]



1



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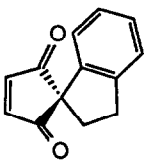


3

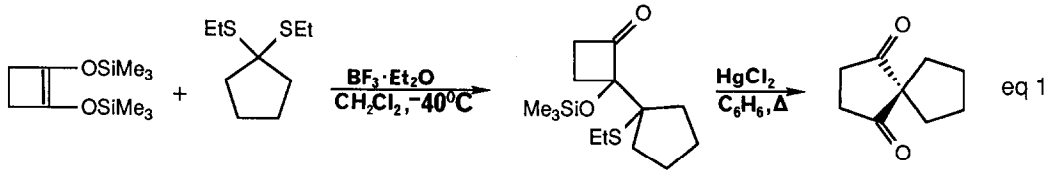
We now describe a highly efficient reaction sequence for the appendage of a naphthalene system to dienophile 3 in a "one-pot" reaction that encompasses three steps under exceptionally mild reaction conditions. Our synthetic strategy is centered on the concept of constructing the three contiguous rings in 8 and 9 by the Diels-Alder cycloaddition of the highly reactive α-bromo-o-quinodimethane intermediate 6 to the alkene portion of the novel spiro dienophiles 3

and **7**. We had previously established that the 5,5-disubstituted cyclopent-2,3-ene-1,4-dione system **3** is a relatively reactive dienophile in the thermal Diels-Alder reaction.[3b]

The recently reported method[4] for the generation of o-quinodimethane intermediates by the fluoride ion initiated trans 1,4-conjugative elimination of trimethylsilylbromide from o-[α-(bromo)-α-(trimethylsilyl)-methyl]benzyl bromide (**5**) would appear to be quite compatible with the multifarious functionality in Fredericamycin A. The reaction sequence that we now describe may therefore ultimately be applicable to a convergent synthesis of our target molecule **1**.

Metalation of o-xylene with a n-butyllithium/potassium t-butoxide mixture (Lickor-reagent)[5] and quenching with trimethylchlorosilane afforded 1-trimethylsilyl-o-xylene (**4**). Irradiation of **4** with a sunlamp in the presence of 2.0 equiv of N-bromosuccinimide in CCl_4 for 1 h afforded the dibromide **5** (74%); bp 95 °C, 0.05 mm; ^1H NMR ($CDCl_3$) δ 4.47, 4.57 (AB, J_{AB} = 9 Hz, 2 H), 4.70 (s, 1 H). The benzyl radical alpha to the trimethylsilyl group is brominated first.

Our preliminary experiments utilized spiro[4.4]non-2,3-ene-1,4-dione (**7**) as the dienophile. The double bond in **7** was readily introduced by the room temperature (CH_2Cl_2) bromination (1 equiv Br_2) and dehydrobromination (15 min) of the spiro[4.4]nonan-1,4-dione that was prepared by an adaptation of the Kuwajima[6] annelation procedure (eq 1). We prefer to



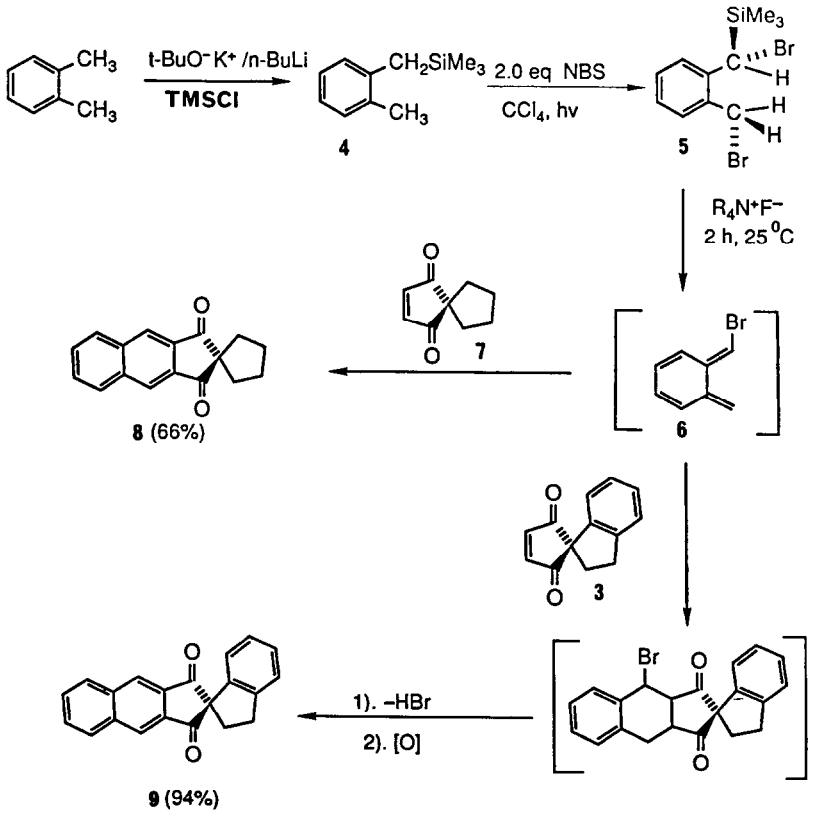
eq 1

use a thioketal in this ring expansion procedure since acyl migration to form the spiro 1,4-dione may be initiated by a mercuric salt under essentially neutral reaction conditions. In a typical reaction sequence, boron trifluoride etherate (1.95 mol) was added to a solution of 1,1-diethylthiocyclopentane (0.65 mol) in 300 mL of CH_2Cl_2 at -40 °C. After addition of the Lewis acid, 1,2-bis(trimethylsiloxy)cyclobutene (0.72 mol) in 200 mL of CH_2Cl_2 was added dropwise. The reaction was stirred for 2 h and then poured into 500 mL of saturated sodium bicarbonate. The organic layer was extracted and the aqueous layer washed with 200 mL (3X) of CH_2Cl_2. The combined organic layers were washed with water, NaCl (aq), dried ($MgSO_4$) and then concentrated affording 44% of 2-(1-ethylthiocyclopentyl)-2-trimethylsiloxycyclobutanone; bp 86-87 °C, 0.02 mm; ^{13}C NMR ($CDCl_3$) 212.7, 60.3, 41.4, 33.8, 33.7, 27.4, 25.0, 24.2, 23.8, 14.5 ppm; 1H NMR ($CDCl_3$) δ 0.13 (s, 9 H), 1.13-1.18 (t, 3 H), 1.5-2.2 (m, 8 H), 2.4-2.9 (m, 6 H); IR (neat) 1783 cm-1. The pinacol type rearrangement was readily achieved by the action of the

mild thiophile $HgCl_2$ (1.1 equiv) in refluxing benzene (15 min) affording 55% of the precursor to dienophile **7** after recrystallization. Physical data for **7**; mp 46-47 °C (pentane); ^{13}C NMR ($CDCl_3$) 208.0, 148.3, 56.1, 34.3, 27.2 ppm; ^1H NMR ($CDCl_3$) δ 1.82-1.88 (m, 8 H), 7.24 (s, 2 H); IR (KBr) 1742, 1702 cm^{-1}; MS (70 eV) calcd. for $C_9H_{10}O_2$: 150.0680, Found: 150.0671. The compound also gave a satisfactory elemental analysis.

The Diels-Alder reactions were both carried out at room temperature. To a solution of precursor **5** (1 mmol) and the spiro dienophile **7** (1.2 mmol) in 1.5 mL of CH_2Cl_2 was added 1.3 mL of 1 M tetrabutylammonium fluoride (TBAF) in 10 mL of CH_2Cl_2 over 45 min. The reaction mixture was allowed to stir for 2 h and then concentrated and the resulting residue was partioned between ether and water. The ether layer was separated, washed with NaCl (aq) and dried ($MgSO_4$). The resulting oil was chromatographed on silica gel (9:1 hexane, ethylacetate) to afford **8** in 66% yield after a subsequent recrystallization (Scheme 1); mp 128-129 °C (hexane); ^{13}C NMR ($CDCl_3$) 205.2, 136.5, 130.5, 129.4, 124.2, 61.7, 35.8, 27.6 ppm; ^1H NMR ($CDCl_3$) δ 2.00-2.03 (m, 8 H), 7.68-7.72 (m, 2 H), 8.07-8.11 (m, 2 H), 8.48 (s, 2 H); IR (KBr) 1740, 1704 cm^{-1}; MS (70 eV) calcd. for $C_{17}H_{14}O_2$: 250.0994, Found 250.1000.

SCHEME 1



The pentacyclic spiro naphthalene derivative **9** was prepared by the Diels-Alder reaction of **3** (1.2 mmol) with the α-bromo diene **6** (1 mmol) to afford 280 mg of **9** (94%) after column chromatography on silica gel (CH_2Cl_2); mp 215-216 °C (hexane-ethylacetate); ^{13}C NMR ($CDCl_3$) 201.6, 145.5, 142.4, 137.2, 136.6, 130.6, 129.7, 128.3, 126.8, 125.2, 125.0, 122.8, 68.6, 32.8, 32.1 ppm; ^1H NMR ($CDCl_3$) δ 2.61-2.66 (t, 2 H), 3.32-3.37 (t, 2 H), 6.59-6.61 (d, 1 H), 7.01-7.75 (m, 2 H), 8.12-8.15 (m, 2 H), 8.60 (s, 2 H); IR (KBr) 1726, 1710 cm^{-1}; MS (70 eV) calcd. $C_{21}H_{14}O_2$: 298.0994, Found 298.1000. The initially formed Diels-Alder adducts spontaneously lose HBr and serendipitously undergo a facile air oxidation to effect aromatization of the naphthalene rings.

This overall reaction sequence can be readily adapted to include the additional oxygen functionality in the quinone half of **1** and these experiments are now in progress. Our results to date utilizing o-quinodimethane to introduce the two aromatic rings encourages us to pursue this route to the ultimate synthesis of Fredericamycin A.

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REFERENCES

1. a) Ramo Rao, A. V.; Reddy, D. R.; Deshpanda, V. H. *J. Chem. Soc., Chem. Commun.* **1984**, 1119.
   b) Kende, A. S.; Ebentino, F. H.; Ohta, T. *Tetrahedron Lett.* **1985**, 3063.
   c) Parker, K. A.; Koziski, K. A.; Breault, G. *Tetrahedron Lett.* **1985**, 2181.
   d) Eck, G.; Julia, M.; Pfeiffer, B.; Rolando, C. *Tetrahedron Lett.* **1985**, 4723, 4725.
2. Misra, R.; Pandey, R. D.; Silverton, J. V. *J. Am. Chem. Soc.* **1982**, *104*, 4478.
3. a) Bach, R. D.; Klix, R. C. *J. Org. Chem.* accepted for publication.
   b) Bach, R. D.; Evans, J. C.; Klix, R. C. *J. Chem. Soc., Chem. Commun.* submitted for publication.
4. Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1982**, *104*, 7609.
5. Schlosser, M.; Strunk, S. *Tetrahedron Lett.* **1984**, 741.
6. Shimada, J. I. ; Hashimoto, K.; B. H.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 1759.

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