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STRATEGIES AND INTERMEDIATES FOR FREDERICAMYCIN A SYNTHESIS:

A 3-SUBSTITUTED 9-ALKOXY CYCLOPENTA(g)ISOQUINOLINE-1,8(2H)-DIONE

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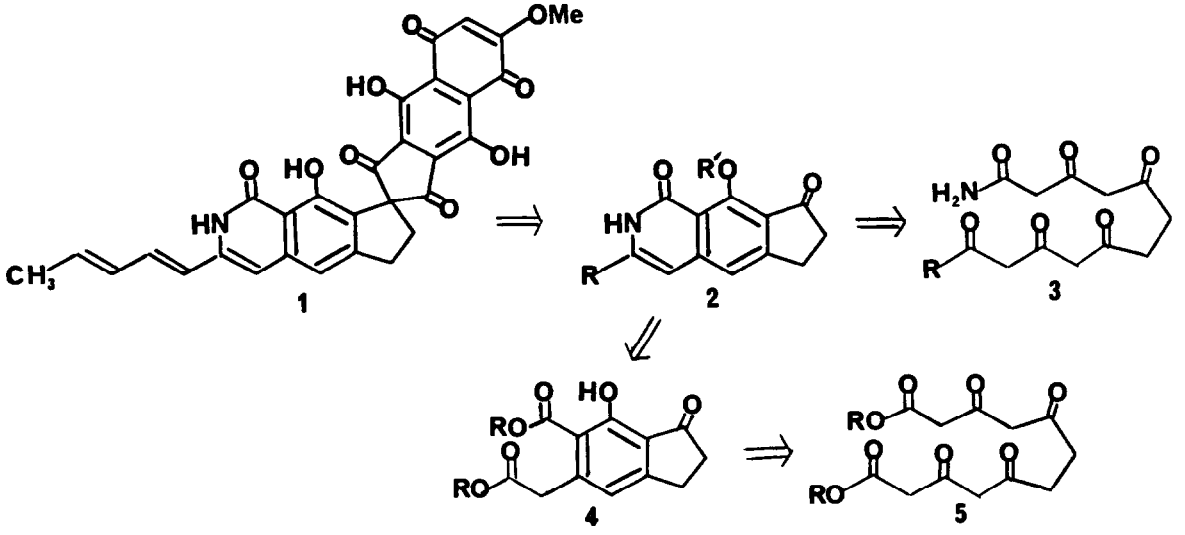
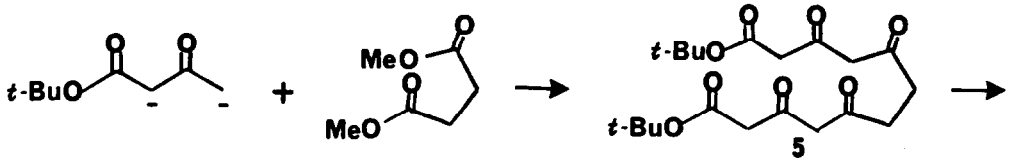
Summary. A polyketide condensation affords a key intermediate for fredericamycin synthesis. Subsequent reactions yield a model for the "lower ring system" of this antitumor antibiotic.

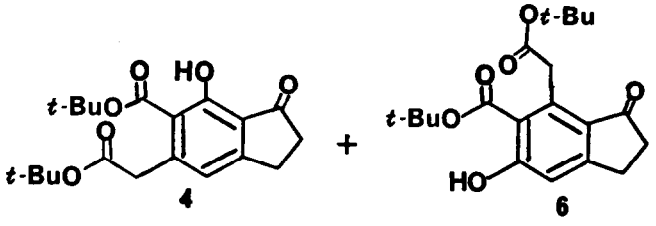
The unusual *spiro* structure of fredericamycin A,[1] *1*, has been the object of several recent model studies.[2] Our strategy for construction of the *spiro* ring system is based on a retrosynthetic disconnection in which the quaternary center is derived from a ketone.[2b] Therefore, a possible synthetic route could be built on the fully substituted tricyclic compound *2* (R = CH=CH-CH=CHCH$_3$, R′ = H or protecting group).

The key intermediate *2*, a 3-alkyl 9-hydroxycyclopenta(g)isoquinoline-1,8(2H)-dione, is in principle the aldol condensation product of an acyclic polyketide *3*.[3] Recognizing the potential difficulties in the synthesis and regioselective cyclization of the unsymmetrical *3*,[4] we chose to attempt the preparation of structures *2* by modification of the homophthalic ester *4*, envisioned as the condensation product of the symmetrical polyketide *5*. We are now pleased to report the successful use of this strategy for the synthesis of the model isoquinolone *2* (R,R′=CH$_3$).



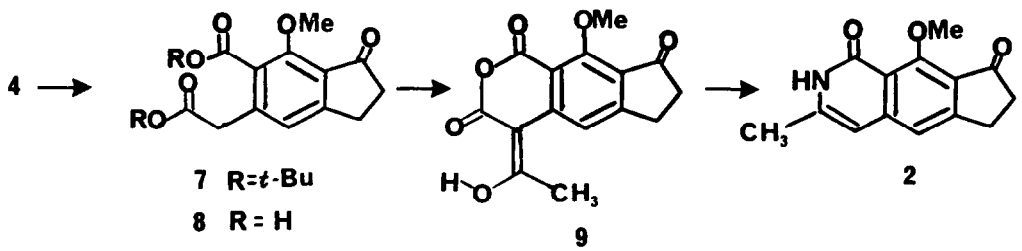
The required polyketide *5* (R = *t*-Bu) was prepared by condensation of four equivalents of the dianion of *t*-butyl acetoacetate with dimethyl succinate in THF (94% yield).[5,6] Cyclization was accomplished by treatment with sodium hydride in the presence of 18-crown-6[7,8] in refluxing benzene; under these conditions, a 65% yield of a mixture of the desired *4* (R = *t*-Bu) and the alternative aldol product *6* was obtained. The isomeric diesters[9] were easily separated by silica gel chromatography. The structure of the major product (78% of the mixture; isolated in 51% yield from *5*) was assigned as *4*[10] by a nuclear Overhauser experiment. Irradiation of the signal at 3.95 ppm (the benzylic methylene adjacent to the ester group) led to a 20% enhancement (approx.) of the aromatic signal.





Treatment of homophthalic diester *4* (R = *t*-Bu) with methyl iodide and anhydrous potassium carbonate in DMF gave the methyl ether *7*[9] in 63% yield. Conversion to diacid *8*[11] (mp 200°C d) was effected in 93% yield by treatment with trifluoroacetic acid in refluxing dichloromethane.

The reaction sequence of Tirodkar and Usgaonkar[12] was used to transform diacid *8* to the model pyridone *2* (R,R′ = CH_3). Thus, treatment with acetic anhydride at room temperature gave the acylated anhydride *9*[11] (mp 208–210° C) in 75% yield. X-ray crystallographic analysis of *9*[13] revealed the enolic nature of the acyl anhydride (Figure 1); also, by implication, elucidation of this structure confirmed the regiochemical assignment of the major aldol product as *4*. Conversion of *9* to the isoquinolone *2* (R,R′ = CH_3,[9] mp 223–225°C d) was accomplished in 31% yield by treatment with concentrated aqueous ammonia in refluxing THF.



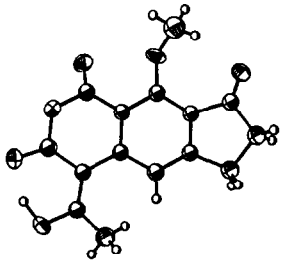


Figure 1. Structure of *9* [12]

Application of this approach to the synthesis of the appropriately substituted isoquinolone *2* (R = CH=CH-CH=CHCH$_3$) and elaboration of the intact "lower" ring system to fredericamycin A are being pursued.

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NMR spectra were acquired with a Bruker WM250 spectrometer, purchased with funds from the National Science Foundation and from Montedison, SPA (Milan, Italy). The structure of *9* was determined with a Nicolet R3m/E diffractometer purchased with funds from the National Science Foundation; we are grateful to John D. Higgins and to Professors Gene B. Carpenter and Paul G. Williard for their expert assistance in carrying out the X-ray diffraction experiment.

References

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2. (a) Rama Rao, A. V., Reddy, D. R., Deshpande, V. H., *J. Chem. Soc., Chem. Commun., 1984,* 1119.

   (b) Parker, K. A., Koziski, K. A., Breault, G., *Tetrahedron Lett., 1985, 26,* 2181.

   (c) Kende, A. S., Ebetino, F. H., Ohta, T., *Tetrahedron Lett., 1985, 26,* 3063.

   (d) Braun, M., Veith, R., *Tetrahedron Lett., 1986, 27,* 179.

   (e) Bach, R. D., Klix, R. C., *J. Org. Chem., 1986, 51,* 749; Bach, R. D., Klix, R. C., *Tetrahedron Lett., 1986, 27,* 1983.

3. For a review of biomimetic syntheses based on polyketides, see Harris, T. M., Harris, C. M., *Tetrahedron, 1977, 33,* 2159.

4. For a recent synthesis of an unsymmetrical polyketide, see Kirkemo, C. L., White, J. D., *J. Org. Chem., 1985, 50,* 1316.

5. The procedure for generating the dianion of *t*-butyl acetoacetate is that of Huckin, S. N., Weiler, L., *Can. J. Chem., 1974, 52,* 2157.

6. A solution of 34.4 g (217 mmol) of *t*-butyl acetoacetate in 60 mL of THF was added dropwise to a suspension of 9.6 g (200 mmol) of hexane-washed NaH in 40 mL of THF (0^0 C, argon). When the addition was complete, the reaction mixture was allowed to stir until no further evolution of gas could be observed. The reaction mixture was cooled to -78^0 C and then 76 mL of *n*-BuLi (2.65 M in hexane, 201 mmol) was added dropwise. After 30 min at -78^0 C, the bath was removed for 20 min and then the reaction mixture was cooled again to -78^0 C. A solution of 6.5 mL (7.26 g, 49.7 mmol) of dimethyl succinate in 30 mL of THF was added over 20 min. The reaction mixture was allowed to stir at -78^0 for 40 min and at -23^0 for 1 h. Then it was quenched with 20% HCl (pH 1) and diluted with ether. The aqueous phase was extracted with CH_2Cl_2 (2 x 150 mL) and the combined organic solution was dried over $MgSO_4$ and concentrated to afford 30.7 g of a yellow oil. Excess *t*-butyl acetoacetate was removed by Kugelrohr distillation, leaving 18.7 g (94%) of a dark yellow oil. The infrared spectrum of this material showed a broad carbonyl centered at 1730 cm^{-1}; the ^1H nmr spectrum showed singlets at 5.62, 3.23, 2.62, 1.65, and 1.50 ppm and several minor signals. Polyketide *5* could be purified by chromatography (silica gel; EtOAc:hexanes, 1:2); however, because this resulted in significantly decreased yields, the crude material was used in the next step.

7. Under an argon atmosphere, 57 mg (1.18 mmol) of NaH (50% dispersion) was washed with cyclohexane (3 x 1 mL) and suspended in 5 mL of benzene. To this were added 29 mg (0.111 mmol) of 18-crown-6 in 2 mL of benzene and 413 mg (1.04 mmol) of polyketide *5* in 10 mL of benzene. The reaction mixture was allowed to stir at room temperature until the evolution of gas had subsided and then at reflux overnight. Aqueous HCl was added to quench the reaction. The aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic solution was dried over $MgSO_4$ and concentrated to give 560 mg of a red oil. Flash chromatography with hexanes/EtOAc (2:1) afforded two yellow oils: 192 mg (51%) of the major product and 55 mg (14%) of a minor product. These regioisomers could be distinguished by their ^1H NMR spectra: major isomer, 11.17 (s, 1H, exch D_2O), 6.77 (s, 1H), 3.95 (s, 2H), 3.05 (m, 2H), 2.68 (m, 2H), 1.59 (s, 9H), 1.43 (s, 9H); minor isomer, 11.30 (s, 1H), 6.93 (s, 1H), 4.62 (s, 2H), 3.2-2.9 (m, 2H), 2.8-2.45 (m, 2H), 1.72 (s, 9H), 1.55 (s, 9H).

8. The use of 15-crown-5 led to comparable yields of the cyclization mixture and comparable ratios of *4*:*6*.

9. These new compounds had ir and nmr spectra consistent with the structures assigned. The high resolution mass spectrum of each showed a molecular ion.

10. Yamaguchi and coworkers recently reported a similar scheme which afforded a condensation product derived from polyketide *5* (dimethyl ester). They assigned structure *4* (dimethyl ester) to this product; comparison of their chemical shift data with those of each of our condensation products confirms their structure assignment. See M. Yamaguchi, K. Shibato, I. Hirao, *Chem. Lett., 1985,* 1145.

11. These new compounds had ir and nmr spectra consistent with the structures assigned. Each gave a satisfactory C,H analysis.

12. Tirodkar, R. B., Usgaonkar, R. N., *J. Ind. Chem. Soc., 1969, 46,* 935; Tirodkar, R. B., Usgaonkar, R. N., *Ind. J. Chem., 1972, 10,* 1060.

13. The anhydride *9* crystallized in the triclinic space group $P\bar{1}$. The unit cell parameters were determined to be a = 8.078 (3) Å, b = 8.528 (3) Å, c = 9.614 (4) Å, α = 76.14 (3)°, β = 79.20 (3)°, γ = 76.20 (3)° by least squares fitting to the positions of 25 independent reflections in the range $24° \leq 2\theta \leq 26°$. The unit cell contained two asymmetric units of molecular formula $C_{15}H_{12}O_6$ in a volume of 619.2 (0.4) $Å^3$ which produces a calculated density of 1.55 g/cm^3. A total of 1827 reflections were recorded in the range $3.5° \leq 2\theta \leq 45°$ with a Nicolet R 3m/E crystallographic system with the θ:2θ scan routine and graphite monochromated MoK α radiation (γ = 0.71069 Å). A total of 1469 unique reflections with the criterion [$F_o \geq 2.5\ \sigma\ (F_o)$] were observed. After Lorentz polarization corrections, the structure was solved by the SHELXTL programs. All non-hydrogen atoms were refined anisotropically. The locations of all hydrogen atoms were determined by Fourier difference synthesis. In the final stages of refinement the hydrogen atoms were placed in calculated positions and allowed to ride on the atom to which they are attached. The final agreement factors are R = 0.044 and R_w = 0.075 for 196 independent parameters where $R_w = [\ E(w \cdot \Delta^2)/E(w \cdot F_o^2)]^{1/2}$; $\Delta = |\ F_o - F_c|$ and the weighting scheme w = $1/[\ \sigma^2(F_o) + 0.0049\ F_o^2]$. Crystallographic parameters have been deposited with the Cambridge Crystallographic Data Center, Lensfield Road, Cambridge, England.

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