Synthesis of Quinone Pyrano-γ-lactone Antibiotics. 1. Synthesis of 9-Deoxykalafungin

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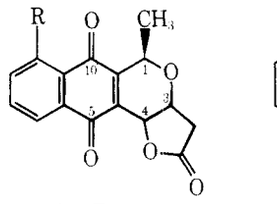
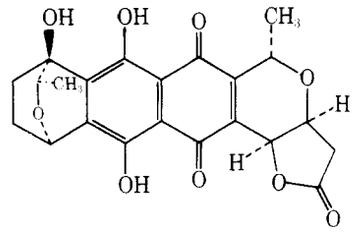
An efficient synthesis of 9-deoxykalafungin (**1b**) in six steps from readily available starting materials is described. The key step, in which all of the carbon atoms present in the target molecule are assembled, is the addition of 2-*tert*-butoxyfuran to 2-acetyl-1,4-naphthoquinone. Hydride reduction, followed by removal of the *tert*-butyl protecting group and addition of the C-1 alcohol to the unmasked butenolide, affords intermediate **13**, which can be oxidized with argentic oxide to **1b** in 17% overall yield.

Kalafungin (**1a**),[1] grantican B (**2**),[2] and the nanaomycins A, B, and C (**3a, 3b,** and **4**)[3] are members of a growing family



1a, R = OH
b, R = H



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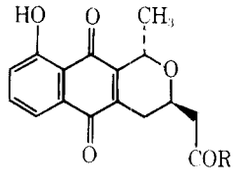
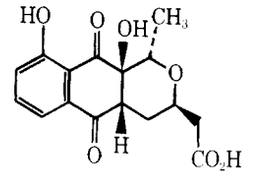


3a, R = OH
b, R = NH_2



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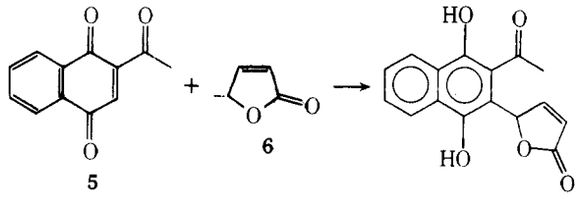
of naturally occurring antibiotics containing quinones fused to a pyrano-γ-lactone moiety.[4-6] Clinical testing has shown kalafungin to be inhibitory in vitro against a variety of pathogenic fungi, yeasts, protozoa, and gram-positive and gram-negative bacteria.[7] To date, no synthetic approaches to this interesting class of natural products have appeared. We have embarked upon a program directed toward the construction of this ring system and wish to report herein a short, efficient total synthesis of 9-deoxykalafungin (**1b**), a close analogue of the natural product.

Results and Discussion

Retrosynthetic analysis of **1b** based on work previously accomplished in this laboratory[8] indicated that the most efficient means of assembling the carbon framework would involve Michael addition of butenolide anion **6** to readily available 2-acetyl-1,4-naphthoquinone (**5**).[9]

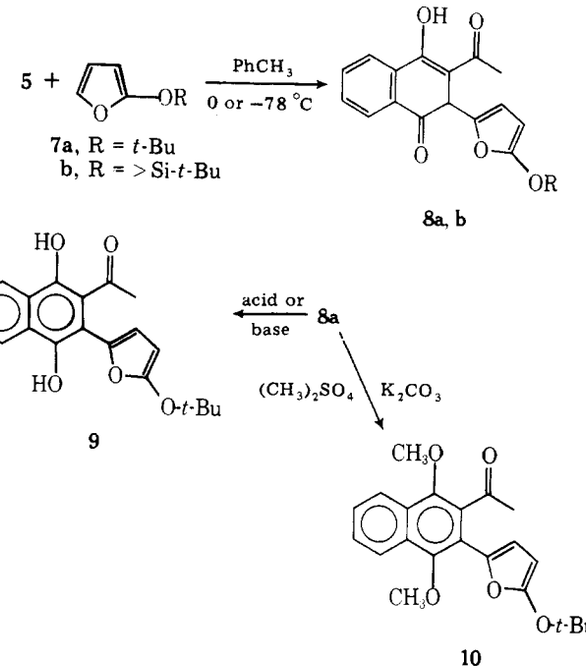


5 **6**

Unfortunately, addition of **5** to a solution of anion **6** generated via the deprotonation of $\Delta^{\alpha,\beta}$-butenolide by a complex of lithium diisopropylamide and hexamethylphosphoramide led only to intractable materials.

Having found success with 2-alkoxyfurans as butenolide anion equivalents,[10] we then turned to 2-*tert*-butoxyfuran (**7a**) and 2-(*tert*-butyldimethylsiloxy)furan (**7b**) as possible synthons (Scheme I).[11a,b] Addition of alkoxyfurans **7a** or **7b**

Scheme I



to a 0 °C toluene solution of **5** led to instantaneous formation of Michael adduct **8**,[12,13] which was readily tautomerized to hydroquinone **9**.[14] The reaction was best run by the addition of **7** to a solution of **5** at −78 °C and allowing the solution to warm slowly to ambient temperature. Under these conditions, **8** was the sole product by NMR and TLC.

Although **8b** could not be methylated with potassium carbonate and dimethyl sulfate without loss of the silyl-protecting group, **8a** was readily methylated after 8 h in boiling acetone to give **10** in an overall yield of 62% from **5**. In practice, **8** and **9** were not isolated and the transformation of **5** into **10** was conducted without purification of intermediates.

To define the generality of this reaction, we attempted the addition of **7** to unactivated quinones. Under no conditions, including Lewis acid catalysis, could **7** be induced to react with 1,4-napthoquinone, juglone, or benzoquinone.

Compound **10** already possesses the carbon skeleton of the target molecule. Transformations to unmask the butenolide and to adjust the oxidation states at carbons 1, 5, and 10 are illustrated in Scheme II.

Lithium aluminum hydride reduction of **10** afforded **11** in >95% yield. Attempts to deprotect **11** with trimethylsilyl iodide[15] yielded no recognizable products, but treatment of **11** with 1 equiv of trifluoroacetic acid in methylene chloride gave a mixture of $\Delta^{\beta,\gamma}$-unsaturated butenolide **12**,[16] readily identified by its characteristic infrared absorption at 1800 cm^{-1}, and cyclized product **13** in moderate yield. Butenolide **12** could be isomerized to the $\Delta^{\alpha,\beta}$-butenolide, which cyclized in situ

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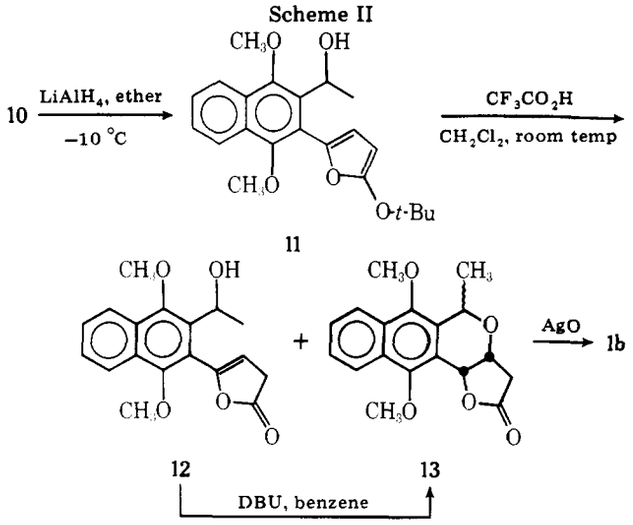
Scheme II



to **13**, by treatment with an equivalent of diazobicyclononane in benzene.

Experimentally, **13** could be prepared in 32% overall yield from **10** without any purification of intermediates. Compound **13** is an inseparable mixture of C-1 epimers (approximately 2.7:1 based on NMR). Although no control over the stereochemistry at C-1 was possible in this approach, epimerization to the natural configuration has been reported in similar systems with a catalytic amount of anhydrous acid.

Oxidative demethylation employing Rapoport's procedure[17] afforded **1b** as a mixture of epimers, the structures of which were completely consistent with all spectral data (IR, NMR, UV, combustion analysis), in 95% yield.[18]

In summary, 9-deoxykalafungin has been synthesized in six steps from 2-acetyl-1,4-naphthoquinone in an overall yield of 17%, thus demonstrating the feasibility of our approach to the fused quinone pyrano-γ-lactone antibiotics.

Further work toward the synthesis of the natural product and other related compounds is now in progress in these laboratories.

Experimental Section

General. Diethyl ether and THF were distilled from lithium aluminum hydride. All organic extracts were dried over Na_2SO_4. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorredted. Infrared spectra were determined on a Beckman IR-4250 spectrometer. Nuclear magnetic resonance spectra were determined on a Varian EM-360 instrument in $CDCl_3$ with absorptions recorded in ppm downfield from internal Me_4Si. Ultraviolet spectra were recorded using a Cary Model 14 spectrometer. High-resolution mass spectra were recorded on an AEI MS-902 high-resolution mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc.

1,4-Dimethoxy-2-acetyl-3-(5-*tert*-butoxy-2-furyl)naphthalene (10). To a 1.0 M toluene solution of 2-acetyl-1,4-naphthoquinone (**5**) (340 mg, 1.7 mmol) at −78 °C under nitrogen was added via syringe a 1.0 M toluene solution of 2-*tert*-butoxyfuran (250 mg, 1.8 mmol). The resulting solution was allowed to warm slowly to room temperature. The solvent was removed under reduced pressure and replaced with 15 mL of anhydrous acetone. Potassium carbonate (730 mg, 5.3 mmol) and dimethyl sulfate (500 mg, 4.0 mmol) were added, and the solution was heated at reflux for 8 h. The cooled solution was filtered and the filtrate was concentrated. Silica gel chromatography (10:1 hexane–ether) yielded 390 mg (62%) of a bright red oil: IR (film) 1610, 1387, 1145 cm^{-1}; NMR ($CDCl_3$) δ 1.42 (s, 9 H), 2.53 (s, 3 H), 3.80 (s, 3 H), 3.94 (s, 3 H), 5.63 (d, 1 H, J = 3 Hz), 6.85 (d, 1 H, J = 3 Hz), 7.56 (m, 2 H), 8.15 (m, 2 H). High-resolution mass spectrum for $C_{22}H_{24}O_5$ required *m/e* 368.16238; found *m/e* 368.16171.

1,4-Dimethoxy-2-(α-hydroxyethyl)-3-(5-*tert*-butoxy-2-furyl)-napthalene (11). To a stirred solution of lithium aluminum hydride (20 mg, 0.50 mmol) in ether (1.0 mL) at −10 °C under N_2 was added **10** (390 mg, 1.06 mmol) in 1.0 mL of ether. The solution was stirred for 30 min at −10 °C and then quenched by slow addition of 5 drops of water, 5 drops of 1 N NaOH, and then 1 mL of H_2O. After stirring for a further 5 min, the solution was filtered, diluted with ether, and dried. Filtration and evaporation of the solvent yielded 350 mg (96%) of a pale yellow oil: IR (film) 3450, 2980, 2930, 2850, 775 cm^{-1}; NMR ($CDCl_3$) δ 1.41 (s, 9 H), 1.56 (d, 3 H, J = 7 Hz), 3.67 (s, 3 H), 4.06 (s, 3 H), 4.18 (br s, 1 H), 4.35 (q, 1 H, J = 7 Hz), 5.64 (d, 1 H, J = 3 Hz), 6.43 (d, 1 H, J = 3 Hz), 7.52 (m, 2 H), 8.13 (m, 2 H). High-resolution mass spectrum for $C_{22}H_{26}O_5$ required *m/e* 370.17803; found *m/e* 370.17909.

2-Oxo-5-methyl-6,11-dimethoxy-2*H*-furo[3,2-*b*]naphtho-[2,3-*d*]pyran (13). To a 0.5 M methylene chloride solution of **11** (310 mg, 0.84 mmol) at 0 °C under N_2 was added 1 equiv of trifluoroacetic acid. The ice bath was removed and the solution stirred for 30 min. Benzene was added (5 mL), and the solvents were removed at reduced pressure (repeated three times). The material remaining was dissolved in 4 mL of dry benzene, and 1 equiv of diazobicyclononane was added. After stirring for 30 min at room temperature, the solution was diluted with 20 mL of 1:1 benzene–ether and washed with 5 mL of 0.5 M HCl and then brine. The organic layer was dried and filtered, and the solvent was removed at reduced pressure. Silica gel chromatography (hexane–EtOAc) yielded **13**, 90 mg (35%), as colorless crystals. NMR data showed this material to be 3:1 mixture of epimers about C-1: IR (major) 1780 cm^{-1}; NMR ($CDCl_3$) (major) δ 1.50 (d, 3 H, J = 7 Hz), 2.57 (d, 1 H, J = 18 Hz), 3.02 (dd, 1 H, J = 18, 4.5 Hz), 3.92 (s, 3 H), 4.08 (s, 3 H), 4.72 (dt, 1 H, J = 4.5, 3.0 Hz), 5.37 (q, 1 H, J = 7 Hz), 5.58 (d, 1 H, J = 3 Hz), 7.54 (m, 2 H), 8.05 (m, 2 H). Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.57; H, 5.79.

9-Deoxykalafungin (1b). To **13** (68 mg, 0.216 mmol) and argenic oxide (110 mg, 0.9 mmol) in 2.0 mL of THF was added 0.2 mL of 6 N HNO_3. After the disappearance of the argentic oxide (approximately 5 min), the reaction was terminated by addition of 10 mL of 4:1 $CHCl_3$–H_2O. The mixture was diluted with $CHCl_3$ and washed twice with water and once with brine. The organic layer was dried and filtered, and the solvent was removed in reduced pressure. Recrystallization from ether yielded 58 mg (95%) of orange crystals: mp 181–183 °C; IR (Nujol) 1780, 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.56 (d, 3 H, J = 7 Hz), 2.65 (d, 1 H, J = 18 Hz), 3.10 (dd, 1 H, J = 18, 4.5 Hz), 4.78 (dt, 1 H, J = 4.5, 3 Hz), 5.13 (q, 1 H, J = 7 Hz), 5.39 (d, 1 H, J = 3 Hz), 7.87 (m, 2 H), 8.22 (m, 2 H); UV ($CHCl_3$) 241, 248, 255, 267 sh, 345 nm. Anal. Calcd for $C_{16}H_{12}O_5$: C, 67.40; H, 4.26. Found: C, 67.40; H, 4.34.

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Registry No.—**1b** (isomer 1), 68036-42-0; **1b** (isomer 2), 68070-03-1; **5**, 5813-57-0; **10**, 68036-43-1; **11**, 68036-44-2; **13** (isomer 1), 68036-45-3; **13** (isomer 2), 68070-04-2; 2-*tert*-butoxyfuran, 32460-41-6.

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(11) (a) R. Sornay, J. M. Meunier, and J. P. Fournari, *Bull. Soc. Chim. Fr.*, 990 (1971). (b) **7b** was prepared by trapping the anion **6** (LDA–HMPA/THF/−78 °C) with *tert*-butyldimethylchlorosilane.
(12) For other additions of furans to activated quinones, see C. H. Eugster and P. Bosshard, *Helv. Chim. Acta*, **46**, 815 (1963).
(13) Compound **8**: IR (film) 1690, 1615, 1560 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (s, 9 H), 2.34 (s, 3 H), 4.73 (s, 1 H), 5.28 (d, 1 H, J = 3.5 Hz), 5.95 (d, 1 H, J = 3.5 Hz), 7.5–8.3 (m, 4 H).
(14) Compound **9**: IR (film) 3450, 1610, 1387, 1145 cm^{-1}; NMR ($CDCl_3$) δ 1.41 (s, 9 H), 2.14 (s, 3 H), 5.75 (d, 1 H, J = 3 Hz), 6.27 (br s, 1 H, –OH), 6.60 (s, 1 H, J = 3 Hz), 7.73 (m, 2 H), 8.50 (m, 2 H), 13.74 (s, 1 H).
(15) M. E. Jung and M. A. Lyster, *J. Am. Chem. Soc.*, **99**, 968 (1977).
(16) Compound **12**: IR (film) 1800 cm^{-1}; NMR ($CDCl_3$) δ 1.67 (d, 3 H, J = Hz), 3.48 (d, 2 H, J = 2.5 Hz), 4.03 (s, 3 H), 4.17 (s, 3 H), 5.20 (q, 1 H, J = 7 Hz), 6.00 (t, 3 H, J = 2.5 Hz), 7.56 (m, 2 H), 8.15 (m, 2 H).
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(18) A comparison of the NMR spectra of **1b** with the published spectra of **1a** showed them to be essentially identical with respect to chemical shifts and coupling constants, except for differences in the aromatic region attributable to the different substituents at C-9.