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The synthesis of antifungal antibiotics

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THE SYNTHESIS OF ANTIFUNGAL ANTIBIOTICS

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The synthesis of antifungal antibiotics

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GENERAL INTRODUCTION

When one plans the synthesis of a natural product or class of natural products many considerations come to mind. Typically, one tries to design a synthesis which is esthetically pleasing, yet attains the target molecule in as few operations as possible. Thus, one can avoid offending either the eye or the budget.

If the experimentor is blessed with a combination of skill and luck, the paper synthesis translates directly into the laboratory. When this occurs, one marvels at the predictive powers of theory working in consort with experimentation. Part I describes a synthesis of this sort.

Alternatively, the molecular system will laugh at the paper synthesis and defy the investigator at critical points in the synthetic scheme. He can then find himself lost in a maze where his best ideas become but junkets headed for dead ends. When this occurs, the successful synthesis becomes as much a test of character as skill. Part II describes a synthesis of this sort.

Explanation of Thesis Format

This thesis is written so that each part represents an article in a publishable form. For this reason the numbering scheme adopted for the figures and tables is independent in each section.

PART I: THE SYNTHESIS OF KALAFUNGIN

INTRODUCTION

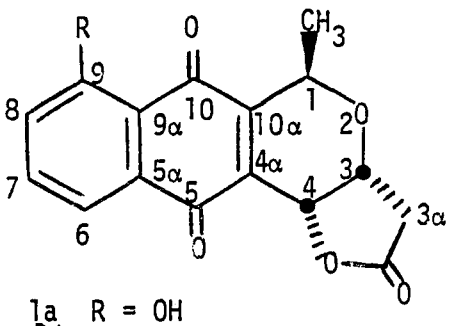
Kalafungin (1) (1a) and its enantiomer nanaomyan D (2) are part of a growing family of naturally occurring fused pyrano-naphthoquinone antibiotics. Included in this group are frenolicin (3), the griseusins A and B (4) and the nanaomycins A-C (5).

At the time this work was initiated, no total synthesis of any of these interesting natural products had been reported. This manuscript will detail the results of a program which resulted in the total synthesis of kalafungin and 9-deoxykalafungin (6, 7).

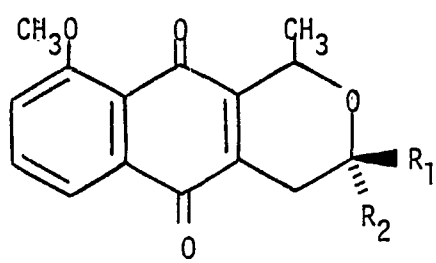
HISTORICAL

In 1968, workers at the Upjohn Company reported the isolation and clinical testing of a new antibiotic from Streptomyces tanashiensis strain Kala (UC-5063) (1). Antibiotic assay indicated high inhibitory activity in vitro against a variety of pathogenic fungi, yeasts, protozoa, gram-positive and gram-negative bacteria (1b).

The new antibiotic was designated as kalafungin and the molecular structure established as 1a by single crystal X-ray diffraction analysis (8). The absolute configuration (1R, 3R, 4R) was determined by comparison of its optical rotary dispersion curve with those of the known substances eleutherin (2a) and isoeleutherin (2b) (6).



1a R = OH
1b R = OCH_3
1c R = H

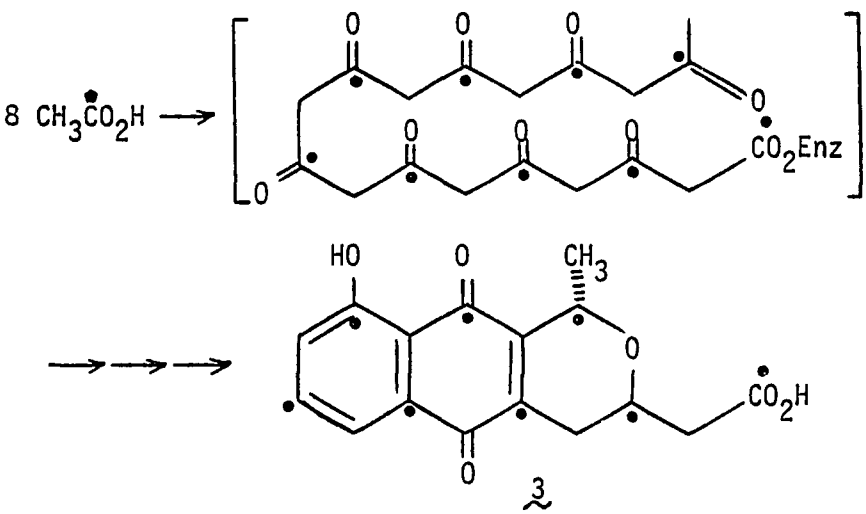


2a $R_1 = CH_3$, $R_2 = H$
2b $R_1 = H$, $R_2 = CH_3$

Omura, et al. have reported the isolation and structure determination of nanaomycin D from Streptomyces rosa var. notoensis (2). They found that all spectral properties of a chromatographed sample of nanaomycin D coincided exactly with those of kalafungin, with the exception that the direction of specific rotation of polarized light ($[\alpha]_D^{20}$ -278° (CH_3OH)) was opposite to that reported for kalafungin ($[\alpha]_D^{25}$ +159°

($CHCl_3$)). The ORD was also opposite to that reported for kalafungin, leading to the conclusion that the two were enantiomers.

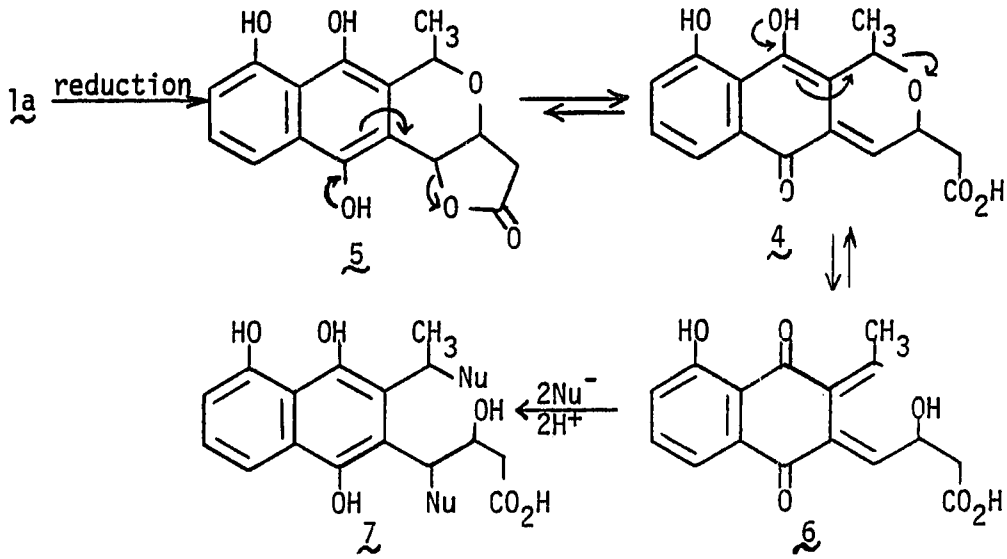
The production of two enantiomers by the genus Streptomyces poses interesting biosynthetic problems to which no ready solutions are available. By feeding labeled acetic acid to cultures of Streptomyces rosa, Tanaka, et al. established the probable biosynthetic route to be as shown below (5).



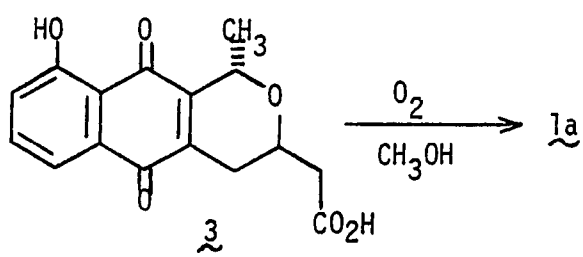
3

Although the actual mode of action of the antibiotic is unknown, Moore has postulated a bioreductive mechanism which passes through the same intermediates hypothesized by Li and Ellison in the transformation of 2 to 1a (9).

The trapping of intermediate o-quinone methides by biological nucleophiles has been postulated as the source of activity of a large number of antibiotics and antineoplastic agents, most notably, the anthracyclines and mitomycins (10, 11, 12).

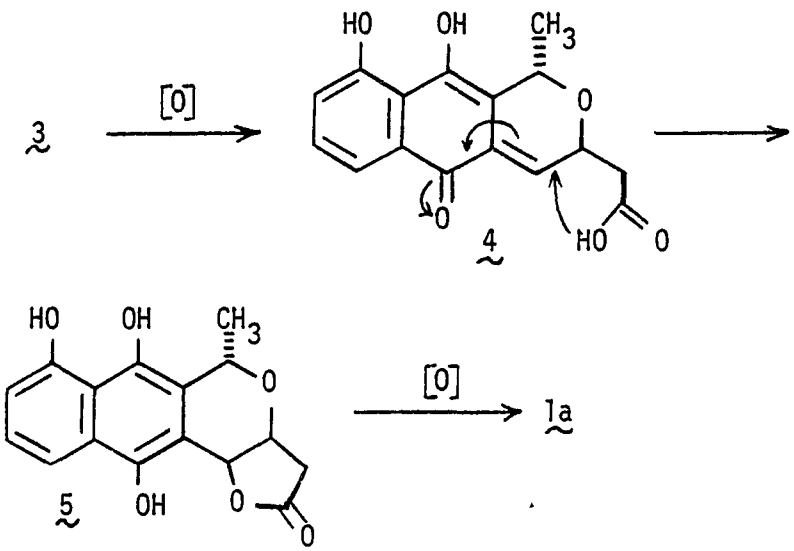


The same authors determined that nanaomycin A (3) is converted into nanaomycin D by air oxidation in methanol (2). A similar conversion of griseusin B into griseusin A by air oxidation has been reported (4). This appears to be the final biosynthetic step in the production of both kalafungin and nanaomycin D.



Li and Ellison employed this transformation as the final step in a synthesis of 1a (9). Their suggested mechanism accounts for the cis-stereochemistry at C-3 and C-4, and is detailed on the following page.

This biosynthetic dilemma, the production of both enantiomers of 1a by the genus Streptomyces, creates a unique situation for the synthetic



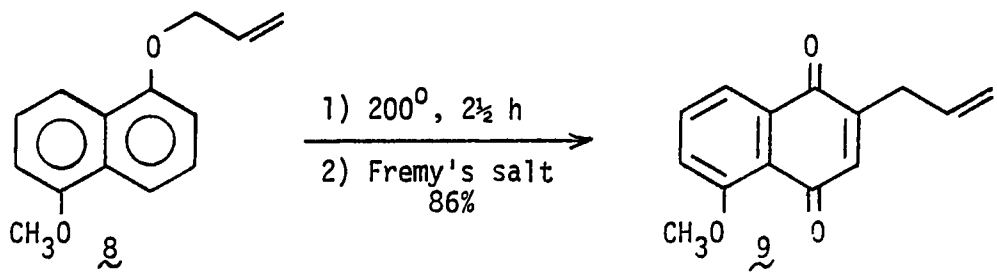
organic chemist. A racemic total synthesis of 1a furnishes not one, but two natural products.

In the year previous to our report on the total synthesis of 9-deoxykalafungin (7), one model study (13) and one total synthesis (9) of kalafungin appeared in the literature. The two were very similar, relying heavily upon a previously published synthesis of eleutherin (14). All three studies are linear in strategy, i.e., they begin with a substituted naphthoquinone and attach small pieces until they arrive at the target molecule. This type of strategy will almost always proceed in lower overall yield than a convergent synthesis, one in which large portions of the molecule are brought together in one step.

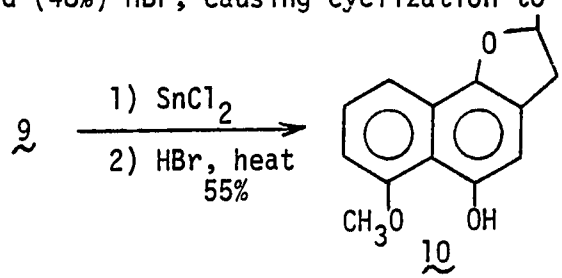
Initial synthetic studies in the area of naphtho-[2,3-c]-pyrano quinones were initiated by Eisenhuth and Schmid, approximately ten years

before the isolation of kalafungin, with the synthesis of the much simpler molecules eleutherin and isoeleutherin (14).

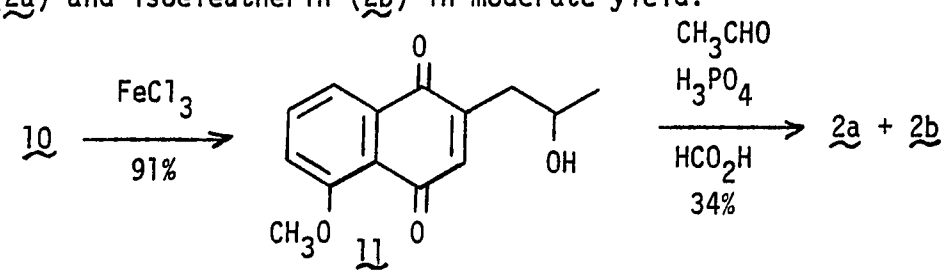
Readily available 1-allyloxy-5-methoxy naphthalene (8) was transformed by Claisen rearrangement and Fremy's salt oxidation into 2-allyl-5-methoxy-1,4-naphthoquinone (9).



Quinone 9 was reduced to the naphthydroquinone and refluxed with concentrated (48%) HBr, causing cyclization to dihydrofuran 10.

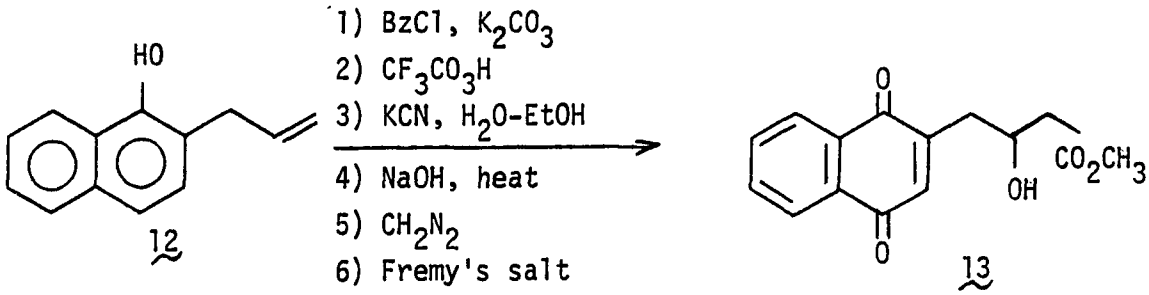


Oxidative dealkylation with ferric chloride afforded quinone 11, which was condensed with acetaldehyde to provide a mixture of eleutherin (2a) and isoeleutherin (2b) in moderate yield.

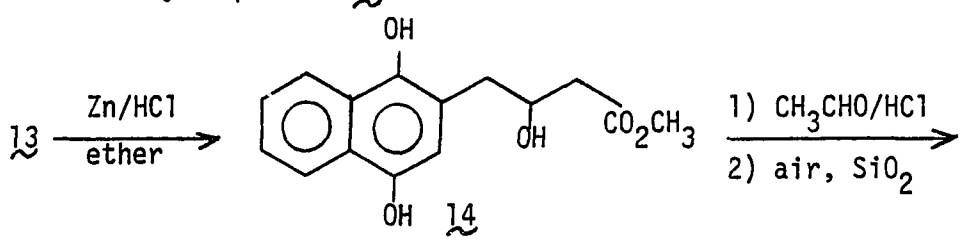


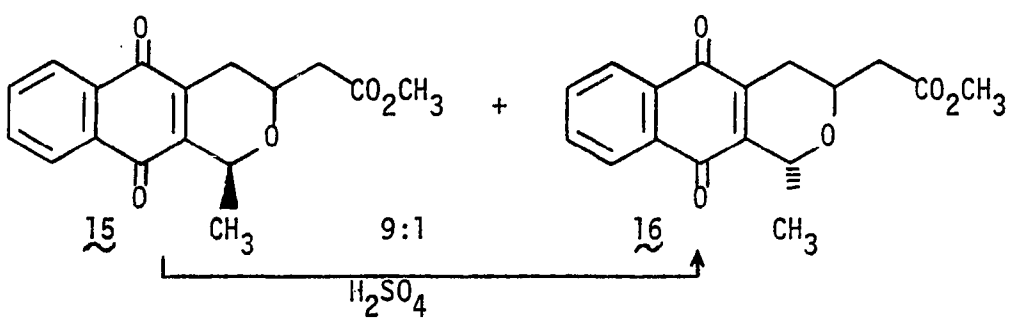
St. Pyrek, et al. have modified this route in order to synthesize 9-deoxynanaomycin A methyl ester (13). Thus, 2-allyl-1-naphthol (12)

was converted into 2-(3'-carbomethoxy-2'-hydroxypropyl)-1,4-naphthoquinone (13) in six steps.



Unfortunately, treatment of 13 with acetaldehyde, using the conditions employed in the synthesis of 2a and b, did not proceed in the desired fashion. The cyclization was successful only after reduction to hydroquinone 14.

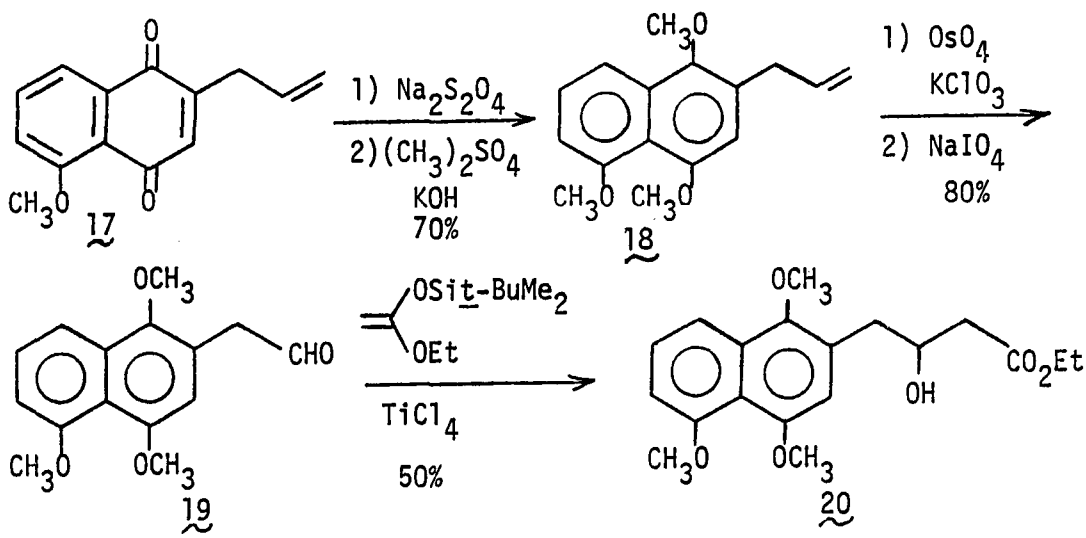




The hydroquinone formed in this cyclization is unstable and readily oxidizes to naphthoquinone 16 during silica gel chromatography. Although it is less favored thermodynamically, it is noteworthy that the cis isomer is the predominant (9:1) product. The cis isomer (15) was epimerized to 9-deoxynanaomycin A methyl ester (16) by treatment with

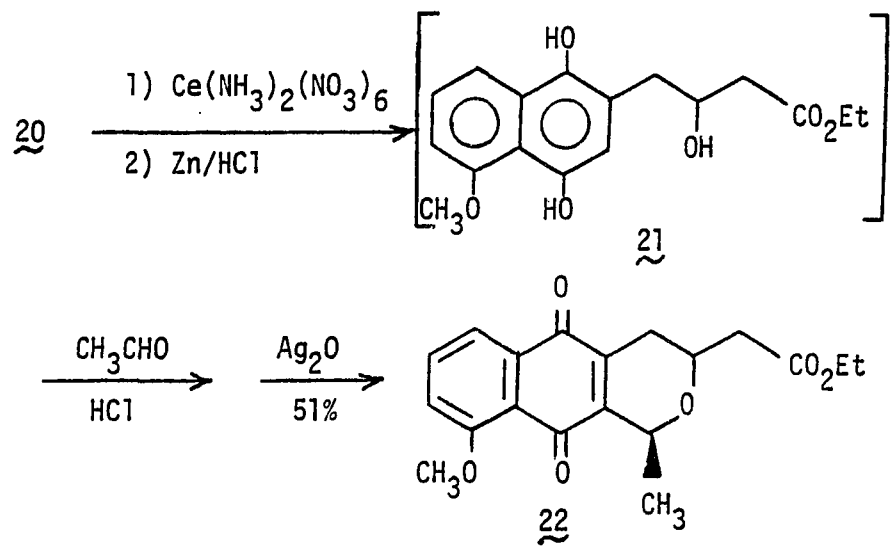
concentrated sulfuric acid. This epimerization to the more stable trans-1,3-isomer appears to be general for fused pyrano-quinones (7, 13). (The authors of this work never suggest that they have, in fact, synthesized 9-deoxynanaomycin A methyl ester. Only a careful reading of their paper uncovered this fact.)

Shortly after the publication of St. Pyrek's approach, Li and Ellison reported the total synthesis of kalafungin by a similar route (9). Reduction and methylation of 2-allyl-5-methoxy-1,4-naphthoquinone (17) produced the trimethoxy compound 18. The allyl moiety was cleaved to an aldehyde and condensed with the tert-butyldimethylsilyl ketene acetal of ethyl acetate in the presence of titanium tetrachloride. The product of this sequence, 20, although obtained somewhat more efficiently, is very similar to intermediate 13 in the synthesis by St. Pyrek, et al.

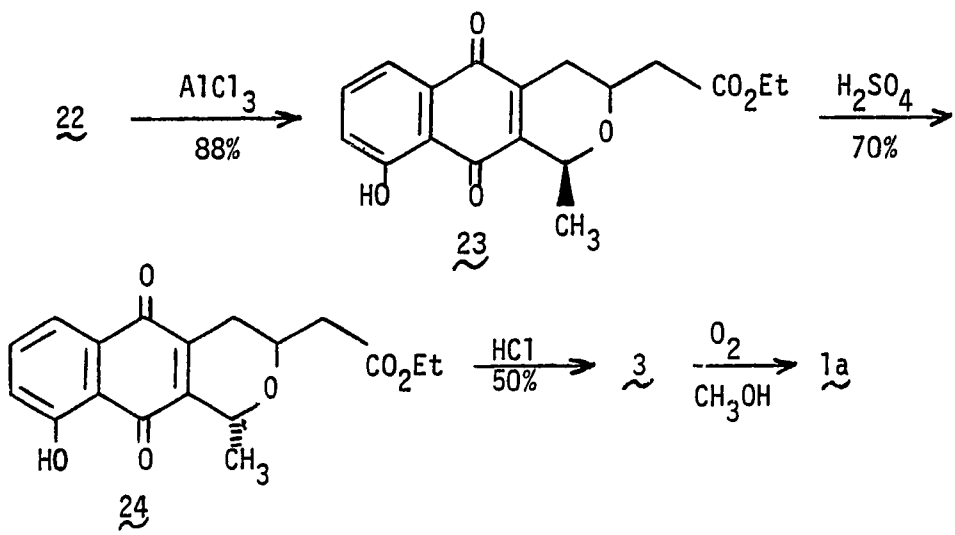


Intermediate 20 was converted to naphthydroquinone 21 by oxidative demethylation and reduction. In situ condensation with

acetaldehyde and silver oxide oxidation provided quinone 22. The relative stereochemistry between carbons 1 and 3 was assigned the cis configuration based on NMR comparison with spectra of eleutherin (2a) and isoeleutherin (2b).

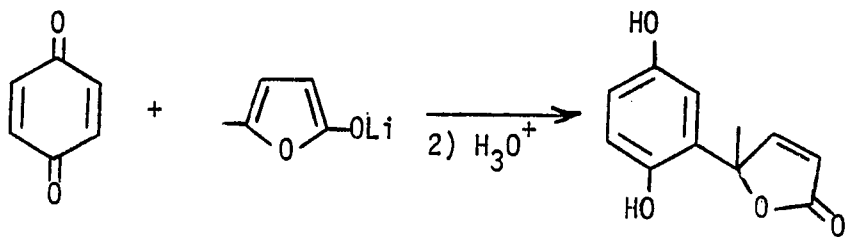


Treatment of 22 with concentrated sulfuric acid epimerized C-1 to a 2:1 mixture of nanaomycin A ethyl ester and 22. These were then separated by fractional recrystallization. The ester was hydrolyzed with concentrated hydrochloric acid to afford racemic nanaomycin A. Surprisingly, no epimerization occurred at C-1. Air oxidation in methanol provided racemic nanaomycin D (2, 5).

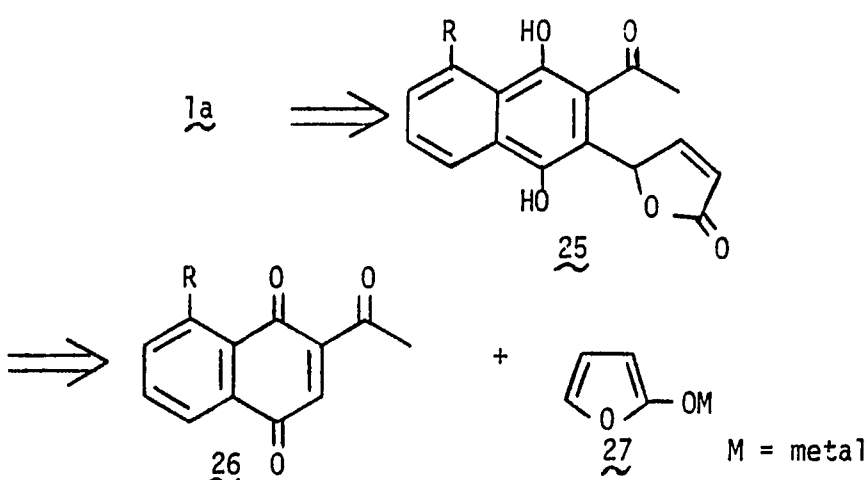

22
AlCl3
88%
HO
O
CO2Et
CH3
23
H2SO4
70%
24
HCl
50%
3
O2
CH3OH
1a

RESULTS AND DISCUSSION

Previous work from our laboratory demonstrated the facile conjugate additions of butenolide anions to unsaturated carbonyl compounds (15). The adduct derived from the addition of the anion of angelica lactone to 1,4-benzoquinone was of special interest. Thus, an attractive route

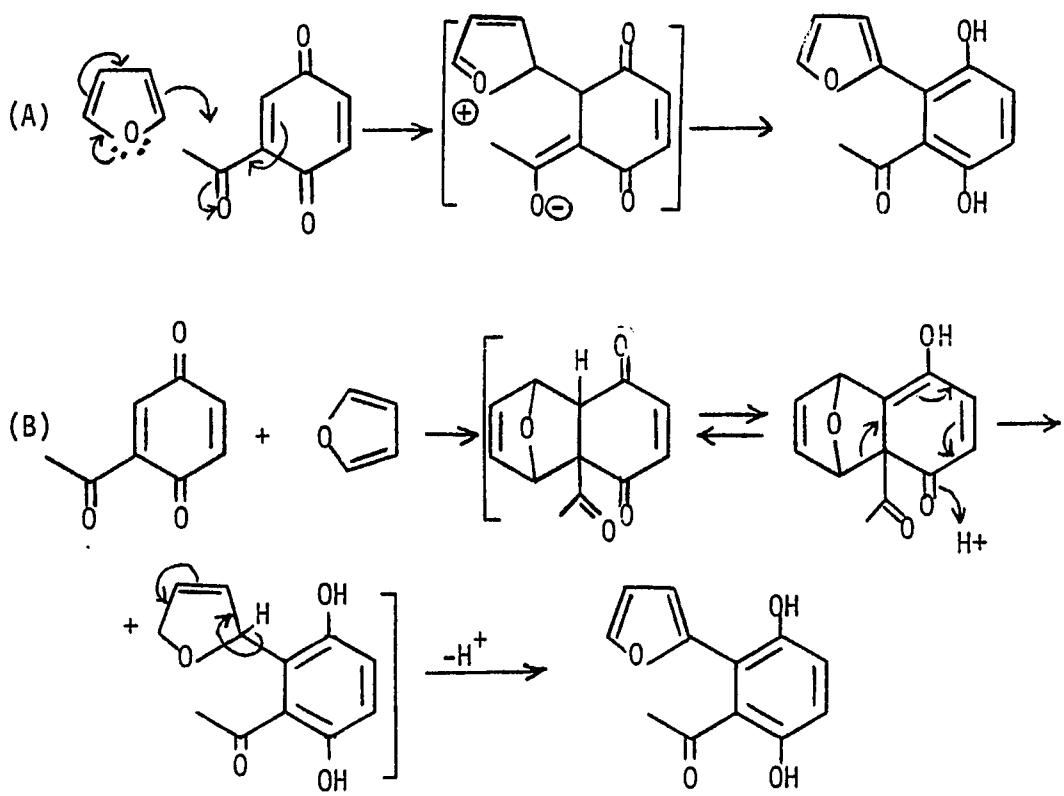


to kalafungin and related compounds would be the addition of a butenolide anion (27) to a properly substituted quinone. A strategy of this type would allow for the assemblage of all of the carbons of the target molecule in a single step. Unfortunately, all attempts to effect

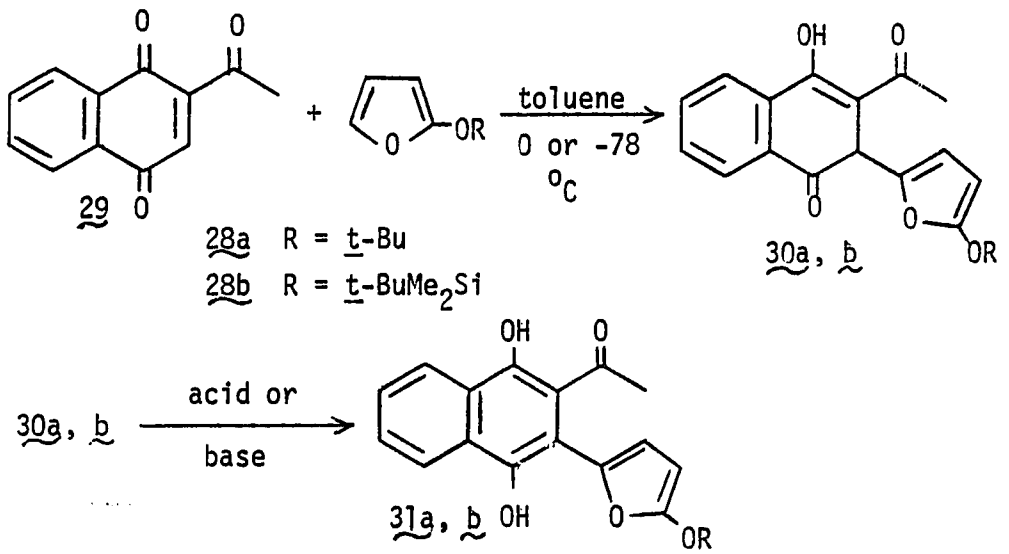


this transformation were without success, leading only to intractible materials. While searching the literature for somewhat milder approaches to compound 25, we found, much to our delight, that furans underwent an "abnormal Diels-Alder reaction" with acylquinones (16). Furan, 2-methyl furan and 3,4-dimethoxyfuran were induced to react with 2-acetyl-1,4-naphthoquinone (17), although conditions were harsh and yields were low.

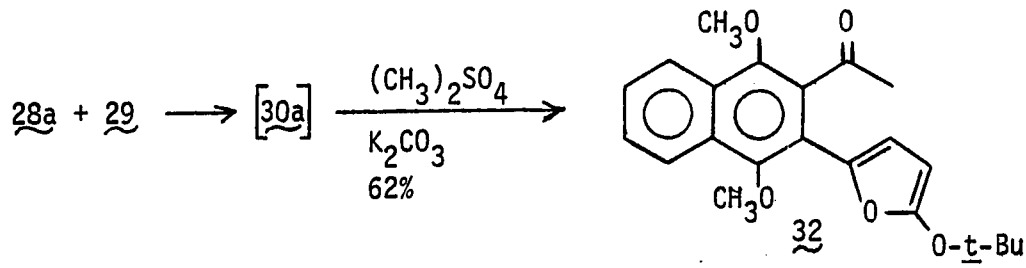
The authors postulated two possible mechanisms to explain their results. Mechanism A involved the nucleophilic addition of an electron rich furan to an electron deficient quinone. In mechanism B, it was postulated that the initial step was a Diels-Alder reaction.



We reasoned that if mechanism A was correct, the use of a more electron rich furan, such as a 2-alkoxy furan, would accelerate the rate of reaction. In fact, addition of 2-tert-butoxyfuran (28a) (18) or 2-tert-butyldimethylsilyoxy furan (28b) to a 0 °C toluene solution of 2-acetyl-1,4-naphthoquinone (29) resulted in instantaneous formation of Michael adducts 30a and b, which were readily tautomerized to the respective hydroquinones 31a and b. Highest yields were obtained when the reaction was conducted at -78 °C and allowed to warm slowly to ambient temperature.



Although 30b could not be methylated with potassium carbonate and dimethyl sulfate without loss of the silyl protecting group, 30a underwent methylation readily. In practice, 30a and 31a were not isolated and the transformation of 29 to 32 was conducted without purification of intermediates.

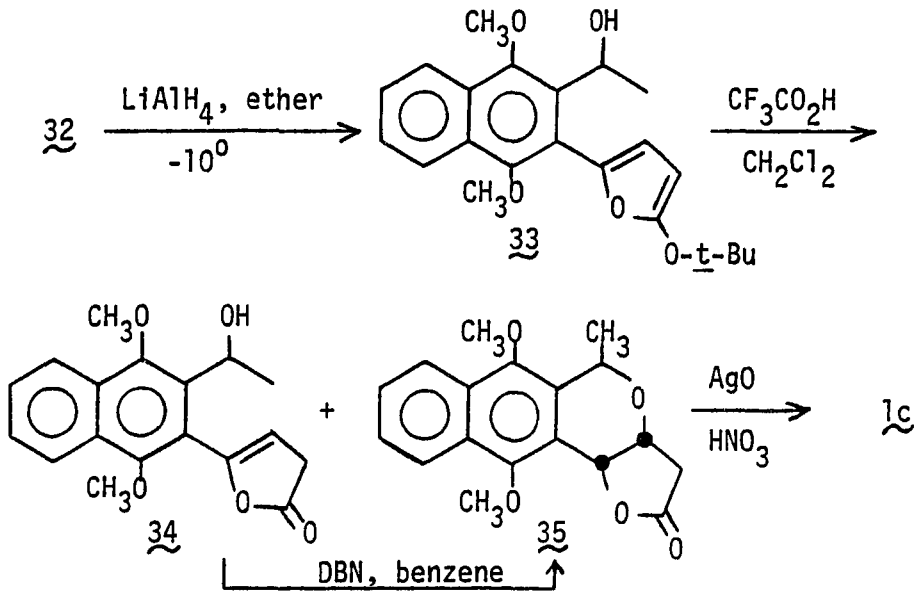


To define the generality of this reaction, we attempted the addition of 28a to unactivated quinones. Under no conditions, including Lewis acid catalysis, could 28a be induced to react with 1,4-naphthoquinone, juglone, or benzoquinone (19).

Lithium aluminum hydride reduction of 32 afforded alcohol 33 in over 95% yield. Attempts to deprotect 33 with trimethylsilyl iodide (20) yielded no recognizable products, but treatment of 33 with 1 equivalent of trifluoroacetic acid in methylene chloride afforded a mixture of $\Delta^{\beta,\gamma}$-unsaturated butenolide 34 (readily identified by its characteristic infrared absorption at 1800 cm^{-1}) and cyclized product 35 in moderate yield. Butenolide 34 could be isomerized to the $\Delta^{\alpha,\beta}$-butenolide by treatment with an equivalent of diazabicyclononane (DBN) in benzene. The intermediate $\Delta^{\alpha,\beta}$-butenolide then cyclized *in situ* to 35.

Experimentally, 35, an inseparable mixture of C-1 epimers (approximately 2.7:1 by NMR), could be prepared in 32% yield from 32 without purification of intermediates.

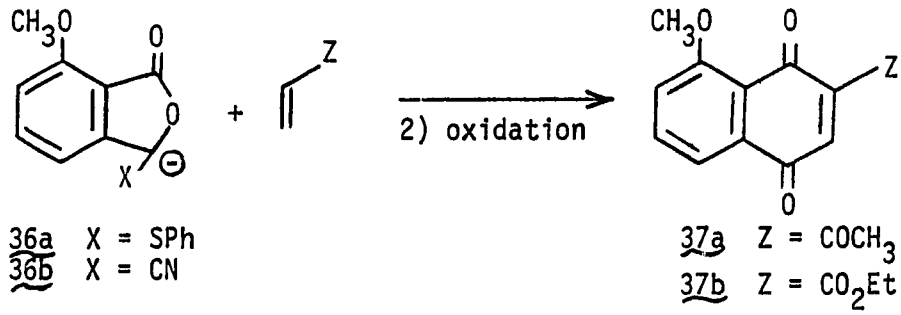
Oxidative demethylation employing Snyder and Rappoport's procedure (21) afforded 9-deoxykalafungin (1c) as a single isomer by proton and



carbon NMR, in 95% yield. Apparently, the mixture of epimers produced in the initial oxidation undergoes facile epimerization at C-1 to the thermodynamically more stable natural configuration in the presence of 6 N HNO_3. Thus, we were able to obtain racemic 9-deoxykalafungin, epimerically pure, without the unfortunate need to separate diastereomers experienced by Li and Ellison, in 17% overall yield from 2-acetyl-1,4-naphthoquinone.

Clinical testing of 9-deoxykalafungin by the Upjohn Company indicated activity very similar to that of kalafungin. (See Appendix for data of clinical testing.)

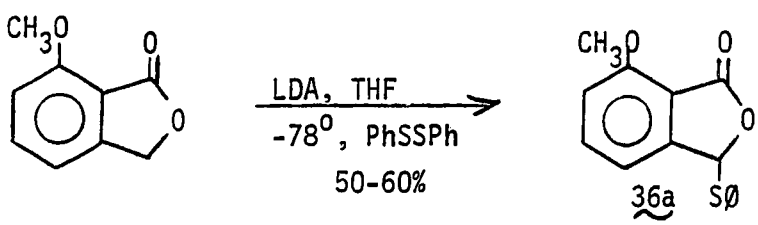
The extension of our route to kalafungin required an effective synthesis of 2-acetyl-8-methoxy-1,4-naphthoquinone (37a). One plausible strategy was the conjugate addition-annelation of substituted phthalides with unsaturated carbonyl compounds (22).



36a X = SPh
36b X = CN

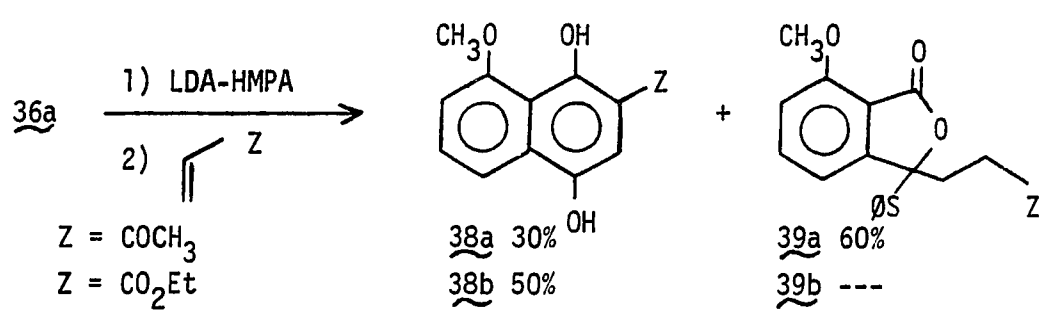
37a Z = $COCH_3$
37b Z = CO_2Et

To initiate this strategy, 7-methoxy-(3-thiophenyl)-phthalide (36a) was prepared by quenching the anion of 7-methoxyphthalide (23) with diphenyldisulfide. We then generated the anion of 36a (LDA-THF-HMPA),



36a

added ethyl acrylate or methyl vinyl ketone at -78 °C, and allowed the solution to warm to ambient temperature. This resulted in the formation of adducts 38 and 39 (24).



Z = $COCH_3$
Z = CO_2Et

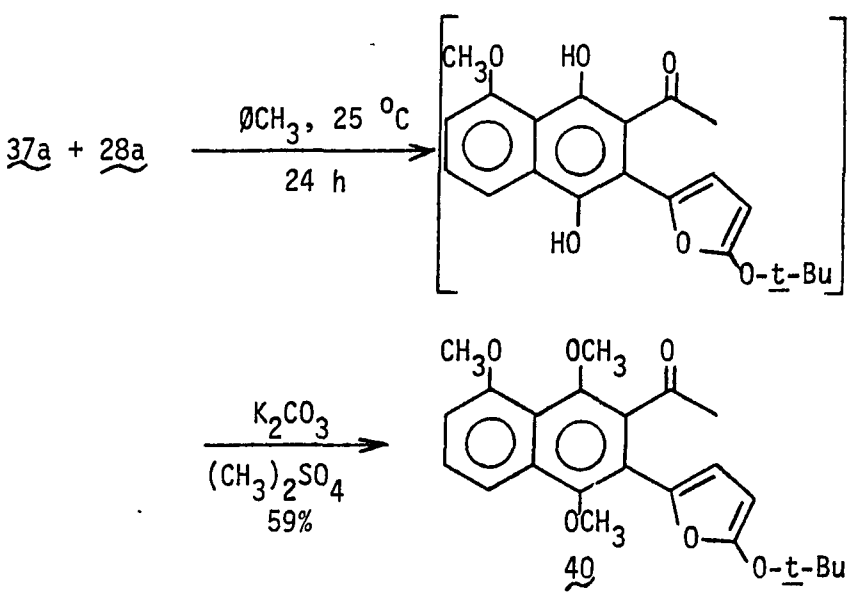
38a 30%
38b 50%

39a 60%
39b ---

Presumably, 38a arises from the anion of 39a, yet attempts to effect the transformation of 39a to 38a resulted only in recovery of

starting material. Variation of reaction parameters either lowered the yield of 38a, or had no effect (25). Treatment of 38a and b with silver oxide led quantitatively to quinones 37a and b.

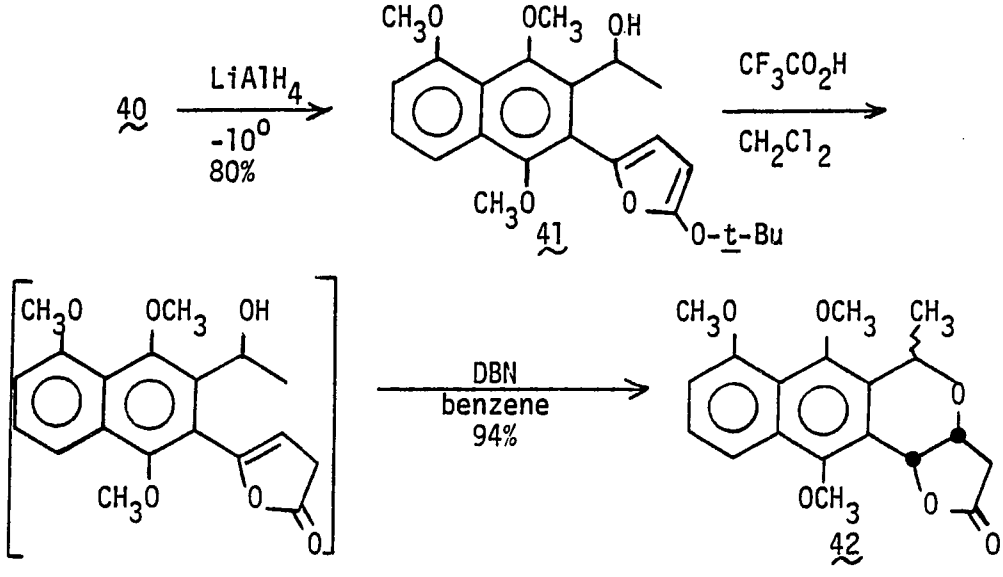
Having secured a workable route to the desired quinones (37a and b), each was treated with 2-tert-butoxyfuran. Not surprisingly, the substitution of an electron donating substituent to the quinone nucleus resulted in a decrease in reactivity (16). Although 2-carboethoxy quinone (37b) proved to be inert, even under forcing conditions (boiling toluene or Lewis acid catalysis), 2-acetyl quinone (37a) reacted slowly to yield an adduct, which could be methylated to afford compound 40 in 59% yield.



40

As expected, hydride reduction of 40 proceeded without incident, providing alcohol 41 in 80% yield. To our surprise, the

deprotection-cyclization sequence, which proceeded in only modest yield in the model system, afforded cyclized product 42 in excellent yield.



Compound 42, a mixture of C-1 epimers, when subjected to the oxidation protocol of Snyder and Rappoport, afforded 9-O-methylkalafungin (1b) as a single diastereomer (mp 203-210 °C, lit. 205-215 °C) (1b). This was determined by proton and carbon NMR (21). All other spectral data coincided with published spectra. Treatment of 1b with boron trichloride (26) at low temperature furnished synthetic (±)-kalafungin

$$\underset{\sim}{42} \xrightarrow[6\ N\ HNO_3]{AgO} \underset{\sim}{1b} \xrightarrow[\substack{CH_2Cl_2 \\ -78\ ^oC}]{BCl_3} \underset{\sim}{1a}$$

(1a) as the sole product. All spectral data for synthetic 1a were in accord with published material (1a).

EXPERIMENTAL

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 uncorrected. 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.

2-tert-Butoxyfuran (28a)

The literature procedure (18) was manipulatively awkward, affording 28a in low to moderate yield at best. Using a modified procedure, detailed below, we have been able to generate large quantities of 28a, in yields significantly higher than were possible employing the literature procedure (27).

Fifty-seven milliliters (0.125 mole) of a 2.2 M commercial hexane solution of n-butyl lithium was added dropwise to a solution of furan (13.6 g, 0.15 mole) in anhyd ether (75 mL) cooled to 0 °C under dry nitrogen. The solution was warmed to ambient temperature over 1 h to yield a white suspension of 2-lithiofuran. After it was cooled to 0 °C,

the slurry was transferred under positive nitrogen pressure, through tygon tubing having glass pipettes at each end, to a suspension of $MgBr_2$ (prepared from 3.9 g of magnesium turnings and 26.3 g of 1,2-dibromoethane) in anhyd THF (40 mL). To the resultant red-brown solution, tert-butyl perbenzoate (19.4 g, 0.10 mole) was added over approximately 30 min. Stirring was continued at 0 °C for 1 h. Then saturated aqueous bicarbonate solution (50 mL) was added with vigorous stirring. A precipitate formed, which was suction filtered (Celite), providing a two phase system. The layers were separated and the aqueous layer was extracted with ether (2 x 50 mL). The combined ether layers were washed with brine and dried (Na_2SO_4). The dried solution was filtered and distilled at 1 atmosphere pressure. The residue was distilled at reduced pressure, providing 6.38 g (45%) of 28a as a colorless liquid (bp 60-64 °C/55 mm Hg, lit. (18) 44 °C/16 mm Hg).

2-tert-Butyldimethylsilyloxy Furan (28b)

n-Butyl lithium (5.31 mL of a commercial 2.45 M hexane solution) was added to a 1.0 M tetrahydrofuran (THF) solution of diisopropyl amine (2.0 mL, 14.3 mmoles) cooled to -78 °C under dry nitrogen. After 5 min, hexamethyl phosphoramide (HMPA, 2.26 mL, 13 mmoles) was added and stirring continued until a white suspension had formed (approximately 15-30 min). When formation of the LDA-HMPA complex was complete, $\Delta^{\alpha,\beta}$-butenolide (1.0 g, 12 mmoles) was added as a 1.0 M THF solution. The resulting solution was stirred 20 min and tert-butyldimethylchlorosilane (2.0 g, 13.2 mmoles) in THF (13 mL) was added rapidly. Stirring

was continued for 10 min at -78 °C, followed by 1 h at ambient temperature. The light-yellow suspension was poured into hexanes (200 mL) and washed with water (50 mL) and brine (25 mL). The organic layer was dried, filtered, and concentrated. The crude yellow oil was filtered through silica gel (40 g, 10:1 hexanes-ether) to provide 1.97 g (84%) of 28b as a colorless oil: IR (film) 2960, 2930, 2860, 1620, 1520, 1255, 950, 850 cm^{-1}; NMR ($CDCl_3$) δ 0.25 (s, 6 H), 1.0 (s, 9 H), 5.17 (dd, J = 3 Hz, 0.5 Hz, 1 H), 6.30 (m, 1 H), 5.88 (m, 1 H).

1,4-Dimethoxy-2-acetyl-3-(5-tert-butoxy-2-furyl)naphthalene (32)

To a 1.0 M toluene solution of 2-acetyl-1,4-naphthoquinone (29) (340 mg, 1.7 mmoles) at -78 °C under nitrogen was added via syringe a 1.0 M toluene solution of 2-tert-butoxyfuran (250 mg, 1.8 mmoles). 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 mmoles) and dimethyl sulfate (500 mg, 4.0 mmoles) 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, J = 3 Hz, 1 H), 6.85 (d, J = 3 Hz, 1 H), 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)-naphthalene (33)

To a stirred solution of lithium aluminum hydride (20 mg, 0.50 mmole) in ether (1.0 mL) at -10 °C under N_2 was added 32 (390 mg, 1.06 mmoles) 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, J = 7 Hz, 3 H), 3.67 (s, 3 H), 4.06 (s, 3 H), 4.18 (br s, 1 H), 4.35 (q, J = 7 Hz, 1 H), 5.64 (d, J = 3 Hz, 1 H), 6.43 (d, J = 3 Hz, 1 H), 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-2H-furo[3,2-b]naphtho[2,3-d]pyran (35)

To a 0.5 M methylene chloride solution of 33 (310 mg, 0.84 mmole) at 0 °C under N_2 was added 1 equivalent 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 equivalent of 1,5-diazabicyclo[4.3.0]non-5-ene 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, filtered, and the

solvent was removed at reduced pressure. Silica gel chromatography (hexane-EtOAc) yielded 35, 90 mg (35%), as colorless crystals: IR (major) 1780 cm^{-1}; NMR ($CDCl_3$) (major) δ 1.50 (d, J = 7 Hz, 3 H), 2.57 (d, J = 18 Hz, 1 H), 3.02 (dd, J = 18, 4.5 Hz, 1 H), 3.92 (s, 3 H), 4.08 (s, 3 H), 4.72 (dt, J = 4.5, 3.0 Hz, 1 H), 5.37 (q, J = 7 Hz, 1 H), 5.58 (d, J = 3 Hz, 1 H), 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 (1c)

To 35 (68 mg, 0.216 mmole) and argenic oxide (110 mg, 0.9 mmole) 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, filtered, and the solvent was removed at 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, J = 7 Hz, 3 H), 2.65 (d, J = 18 Hz, 1 H), 3.10 (dd, J = 18, 4.5 Hz, 1 H), 4.78 (dt, J = 4.5, 3 Hz, 1 H), 5.13 (q, J = 7 Hz, 1 H), 5.39 (d, J = 3 Hz, 1 H), 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.

7-Methoxy-(3-thiophenyl)-phthalide (36a)

To a solution of LDA-HMPA complex (from 7.4 mmoles of diisopropylamine, 6.7 mmoles of n-butyl lithium and 6.7 mmoles of HMPA) in THF (7 mL), cooled to -78 °C under nitrogen, was added 7-methoxy phthalide in THF (12 mL). The resultant orange solution was stirred 15 min and diphenyl disulfide in 7 mL THF was added all at once. The cooling bath was removed and replaced with an ice bath. Stirring was continued at 0 °C for 30 min. Then the reaction was quenched by slow addition of 1 N HCl with vigorous stirring. Water (10 mL) was added and the whole extracted with ether (3 x 50 mL). The combined ether layers were washed with 1 N HCl (15 mL), 1 N NaOH (2 x 10 mL), water (10 mL), and brine. The dried (Na_2SO_4) solution was filtered, concentrated, and chromatographed, affording 0.81 g (2.98 mmoles, 49%) of 36a as a light-yellow solid. Recrystallization from benzene afforded off-white crystals (mp 113-116 °C): IR (KBr) 1770, 1615, 1595 cm^{-1}; NMR ($CDCl_3$) δ 4.05 (s, 3 H), 6.70 (s, 1 H), 7.0-8.0 (m, 8 H).

8-Methoxy-1,4-dihydroxy-2-naphthoic Acid, Ethyl Ester (38b)

A solution of 36a (0.27 g, 1.0 mmole) in anhyd THF (2.0 mL) was added dropwise to a suspension of LDA-HMPA complex (1.1 mmole) in 1 mL of THF cooled to -78 °C under nitrogen. Stirring was continued for 15 min and ethyl acrylate (0.10 g, 1.0 mmole) was then added as a 1 M THF solution. The mixture was allowed to warm slowly to ambient temperature over approximately 2.5 h, then quenched by addition of 2.5 mL of 1 N HCl. The whole was extracted with ether (2 x 50 mL)

and the combined ether layers were washed with water (10 mL) and brine (10 mL). The dried solution was filtered and concentrated. Silica gel chromatography (hexane-ether) provided 140 mg (0.53 mmole, 53%) of 38b as light-orange crystals: mp 143-5 °C (dec) from ether; IR (Nujol) 3500, 1670 cm^{-1}; NMR ($CDCl_3$) δ 1.40 (t, J = 7 Hz, 3 H), 4.13 (s, 3 H), 4.46 (q, J = 7 Hz, 2 H), 6.9-8.0 (m, 4 H), 12.24 (s, 1 H). High resolution mass spectrum for $C_{14}H_{14}O_5$ required m/e 262.08411; found m/e 262.08252.

2-Acetyl-8-methoxy-1,4-dihydroxynaphthalene (38a)

7-Methoxy-(3-thiophenyl)-phthalide was reacted with methyl vinyl ketone, in the manner described above, to provide 38a (Z = $COCH_3$, 30%): IR (Nujol) 3500, 1640, 1600 cm^{-1}; NMR ($CDCl_3$) δ 2.57 (s, 3 H), 4.14 (s, 3 H), 6.9-7.8 (m, 4 H), 13.60 (s, 1 H), and 39 (Z = $COCH_3$, 60%): IR 1760, 1715 cm^{-1}; NMR ($CDCl_3$) δ 2.12 (s, 3 H), 2.55 (m, 4 H), 3.97 (s, 3 H), 6.8-7.9 (m, 8 H).

Silver(I) Oxide Oxidation of Naphthydroquinones (38a and b)

The requisite hydroquinone, as a 0.2 M ether solution, was stirred with 1.5 equivalents of silver(I) oxide for 3 h. The suspension was filtered and concentrated to afford the quinones in quantitative yield.

37a: IR ($CHCl_3$) 1705, 1670, 1595, 1295, 1233 cm^{-1}; NMR ($CDCl_3$) δ 2.67 (s, 3 H), 4.12 (s, 3 H), 7.12 (s, 1 H), 7.3-7.9 (m, 3 H).

37b: IR (Nujol) 1735, 1670, 1585, 1280 cm^{-1}; NMR ($CDCl_3$) δ 1.36 (t, J = 7 Hz, 3 H), 4.10 (s, 3 H), 4.45 (q, J = 7 Hz, 2 H), 7.18 (s, 1 H), 7.3-7.9 (m, 3 H); mp 100-102 °C, lit. (28) 102-3 °C.

1,4,8-Trimethoxy-2-acetyl-3-(5-tert-butoxy-2-furyl)naphthalene (40)

A 1.0 M toluene solution of 2-tert-butoxyfuran (0.14 g, 1.0 mmole) was added to a solution of 2-acetyl-8-methoxy-1,4-naphthoquinone (37a) in 1.0 mL of toluene, at 0 °C under nitrogen. The resulting light orange solution was allowed to warm to room temperature, where it was stirred 24 h. The solvent was removed at reduced pressure and replaced with 5 mL of anhyd acetone. Potassium carbonate (0.55 g, 4 mmoles) and dimethyl sulfate (0.29 mL, 3.0 mmoles) were added, and the whole was refluxed for 8 h. The cooled solution was filtered and concentrated. Silica gel chromatography (10:1 hexane-ether) yielded 0.224 g (0.563 mmoles, 59%) of 40 as a light yellow oil: IR (film) 2980, 2940, 2850, 1710, 1610 cm^{-1}; NMR ($CDCl_3$) δ 1.48 (s, 9 H), 2.67 (s, 3 H), 3.93 (s, 3 H), 3.96 (s, 3 H), 4.17 (s, 3 H), 5.78 (d, J = 3 Hz, 1 H), 7.09 (d, J = 3 Hz, 1 H), 7.1-8.1 (m, 3 H). High resolution mass spectrum for $C_{23}H_{26}O_6$ required m/e 398.17295; found m/e 398.17565.

1,4,8-Trimethoxy-2-(α-hydroxyethyl)-3-(5-tert-butoxy-2-furyl)-naphthalene (41)

To a stirred solution of lithium aluminum hydride (15 mg, 0.40 mmole) in ether (1.0 mL), cooled to -10 °C under nitrogen, was added 40 (224 mg, 0.563 mmoles) in 1.0 mL of ether. The solution was stirred

for 30 min at -10 °C and then quenched by addition of 1 drop of water, 1 drop of 15% NaOH, and 3 drops of water. After 10 min, the solution was filtered to remove precipitated aluminum salts. The filtrate was dried and concentrated to provide 181 mg (0.45 mmoles, 80%) of 41 as a colorless oil: IR (film) 3490, 2980, 2940, 1615 cm^{-1}; NMR ($CDCl_3$) 1.45 (s, 9 H), 1.63 (d, J = 7 Hz, 3 H), 3.72 (s, 3 H), 4.02 (s, 3 H), 4.10 (s, 3 H), 4.30 (q, J = 7 Hz, 1 H), 5.2 (br s, 1 H), 5.70 (d, J = 3 Hz, 1 H), 6.48 (d, J = 3 Hz, 1 H), 6.9-8.0 (m, 3 H). High resolution mass spectrum for $C_{23}H_{28}O_6$ required m/e 400.18860; found m/e 400.18855.

9-O-Methyl Kalafungin (1b)

Trifluoroacetic acid (2 drops) was added to a solution of 41 (120 mg, 0.30 mmoles) in dichloromethane (1.0 mL), cooled to 0 °C under nitrogen. The cooling bath was removed and the red solution stirred 1 h at ambient temperature. Toluene (10 mL) was added and the solvents were removed at reduced pressure (repeated three times). The residue was dissolved in benzene (3 mL) and then cooled to 5 °C. 1,5-Diazabicyclo[4.3.0]nonene (2 drops) was added and stirring continued for 10 min. Ether (10 mL) was added and the solution transferred to a separatory funnel, where it was washed with ice cold 0.25 N HCl (2 x 5 mL) and brine (10 mL). The dried (Na_2SO_4) solution was filtered and concentrated to afford 42 (95 mg) as a yellow oil.

Crude 42 (95 mg) was dissolved in THF (3 mL) and argentic oxide (150 mg, 1.15 mmoles) was added, followed by 0.3 mL of 6 N HNO_3.

Stirring was continued for 10 min. Then 4:1 $CHCl_3$-H_2O (10 mL) was added. After transfer to a separatory funnel, it was extracted with $CHCl_3$ (2 x 50 mL) and the organic layer was then washed with water (2 x 5 mL) and brine (5 mL). The dried solution was filtered and concentrated. The residue was chromatographed (silica gel, 1:1 hexane-ethyl acetate) to afford 42 mg of 1b as an orange solid: mp 203-210 °C (dec) from acetone; R_f (1:1 hexane-ethyl acetate) = 0.15; IR (Nujol) 1780, 1665 cm^{-1}; 90 MHz NMR ($CDCl_3$) δ 1.55 (d, J = 7 Hz, 3 H), δ 2.63 (d, J = 18 Hz, 1 H), 2.98 (dd, J = 18, 5 Hz, 1 H), 4.02 (s, 3 H), 4.68 (dt, J = 5, 3 Hz, 1 H), 5.05 (q, J = 7 Hz, 1 H), 5.27 (d, J = 3 Hz, 1 H), 7.2-8.0 (m, 3 H); 90 MHz C-13 NMR ($CDCl_3$) δ 18.636, 36.947, 56.504, 66.417, 66.905, 68.909, 118.208, 119.563, 132.510, 133.865, 135.598, 151.038, 160.139, 174.062, 182.513, 203.371; UV (CH_3OH) 211, 253 nm. High resolution mass spectrum for $C_{17}H_{14}O_6$ required m/e 314.07904; found m/e 314.07856.

Kalafungin (1a)

Excess boron trichloride was added to 9-O-methyl kalafungin (1b) in 1 mL of anhyd dichloromethane cooled to -78 °C under nitrogen. When addition was complete, the cooling bath (Dry Ice-acetone) was removed and the bright purple solution was allowed to warm to ambient temperature. Ten minutes after removing the cooling bath, water was added with vigorous stirring. The yellow-orange solution was diluted with dichloromethane (50 mL) and washed with water (2 x 10 mL) and brine

(10 mL). The dried solution was filtered and concentrated to provide 1a as light orange crystals.

Attempted Additions of 2-tert-Butoxy Furan to 8-Methoxy-2-carboethoxy-1,4-naphthoquinone (37b)

Addition of 28a (70 mg, 0.50 mmoles) in toluene (1.0 mL) to a room temperature solution of 36b, followed by prolonged stirring at ambient temperature, resulted in no adduct formation by thin-layer chromatography (TLC). The solution was heated to reflux for 5 h. No reaction was observed by TLC or NMR (28).

Freshly fused zinc chloride (60 mg, 0.044 mmoles) was added to a room temperature solution of 28a (140 mg, 1.0 mmoles) and 36b (120 mg, 0.50 mmoles) in 2 mL of toluene. Stirring was continued for 12 h at ambient temperature. Ether was added and the whole was washed with water (10 mL) and brine (10 mL). Filtration and concentration of the dried solution afforded no recognizable product by NMR.

Attempted Additions of 28a to Unactivated Quinones

1,4-Naphthoquinone (0.158 g, 1.0 mmole) and 28a (180 mg, 1.3 mmoles) in benzene (10 mL) were stirred at ambient temperature for 24 h. Since no reaction was evident by TLC, the solution was refluxed for 12 h. The cooled solution was concentrated to afford a mixture of recovered 1,4-naphthoquinone and $\Delta^{\alpha,\beta}$-butenolide. The butenolide is derived from 28a by a thermal or acid catalyzed decomposition. Treatment of

benzoquinone, juglone, 1,4-benzoquinone-bis-tosylimine, or bis-chloroimine with 28a yielded similar results.

Aluminum chloride (133 mg, 1.0 mmole) was added to a solution of 28a and 1,4-naphthoquinone in benzene (2 mL) at 0 °C. The resulting solution was stirred for 15 min and then poured into ice water. The mixture was extracted with ether (2 x 50 mL). Filtration and concentration of the dried organic layer provided recovered 1,4-naphthoquinone. No trace of 28a was found. A similar reaction, employing $ZnCl_2$ as catalyst, also resulted in the destruction of 28a.

Attempted Addition of $\Delta^{\alpha,\beta}$-Butenolide Anion (27) to 1,4-Naphthoquinone

To a solution of butenolide anion 26 (generated from 168 mg, 2 mmoles of $\Delta^{\alpha,\beta}$-butenolide and 2.2 mmoles of LDA-HMPA complex) in THF (4 mL) cooled to -78 °C under nitrogen, was added a 1 M THF solution of 1,4-naphthoquinone (316 mg, 2 mmoles). A dark blue-green slurry resulted, which was stirred 15 min before 2.5 mmoles of acetic acid was added. The solution was diluted with ether and was washed with water (10 mL) and brine (10 mL). Filtration and concentration of the dried solution afforded only intractible material.

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APPENDIX

Report on clinical testing by the Upjohn Company

As per your request, we have determined the MIC's of deoxykalafungin (U-57266) and kalafungin (U-19718) vs. seventeen pathogenic fungi. The results are as follows:

Test Organisms		Minimum Inhibitory Concentration (μg/mL) Kalafungin	Deoxykalafungin
Nocardia asteroides	UC 2052	3.9	3.9
Blastomyces dermatitidis	UC 1466	≤1.0	≤1.0
Geotrichum sp.	UC 1207	3.9	3.9
Hormodendrum compactum	UC 1222	3.9	2.0
Phialophora verrucosa	UC 1807	≤1.0	≤0.5
Cryptococcus neoformans	UC 4869	2.0	2.0
Cryptococcus neoformans	UC 1139	≤1.0	1.0
Sporotrichum schenckii	UC 1364	15.6	7.8
Monosporium apiospermum	UC 1248	≤1.0	1.0
Candida albicans	UC 7163	7.8	7.8
Candida albicans	UC 7164	7.8	15.6
Microsporum canis	UC 1395	7.8	7.8
Trichophyton rubrum	UC 1458	≤1.0	≤0.5
Trichophyton violaceum	UC 1459	2.0	≤0.5
Trichophyton asteroides	UC 4775	2.0	1.0
Trichophyton mentagrophytes	UC 4797	3.9	2.0
Trichophyton mentagrophytes	UC 4860	2.0	1.0

The activity of deoxykalafungin was nearly identical to that of kalafuncin (± 1 two-fold dilution is within the error of the test). Both compounds were potent inhibitors of a wide variety of pathogenic fungi.

Notebook Reference XII-CL: 202

PART II: THE PREPARATION OF THE TRICHOTHECENE SKELETON

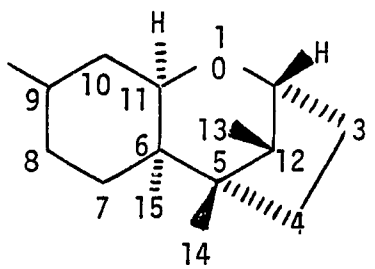
INTRODUCTION

The remarkable biological activity of certain members of the trichothecene family of terpene antibiotics has stimulated considerable interest in these natural products (1).

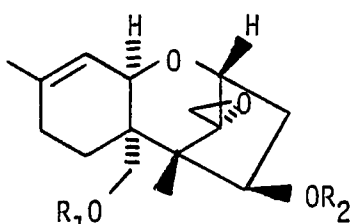
This manuscript will detail the results of a program which resulted in the first total synthesis of the trichothecene skeleton containing oxygen functionality at carbons 15 and 3.

HISTORICAL

Verrucarol (2a) and diacetoxyscirpenol (anguidin, 4a) are members of the trichothecene class of naturally occurring fungal sesquiterpenes (1). Other members of this class include the macrocyclic verrucarins and roridins, as well as the less complex trichodermol (3b). The structures of a limited number of trichothecenes are presented below.



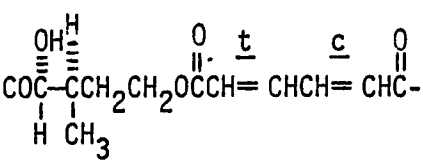
1

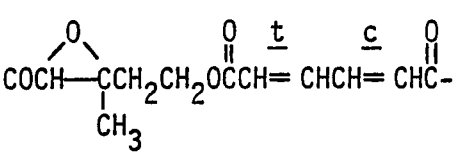


2

a $R_1 = R_2 = H$, verrucarol

b $R_1 = R_2 = Ac$, diacetoxyverrucarol (2)

c $R_1, R_2 =$  verrucarin A (3, 4)

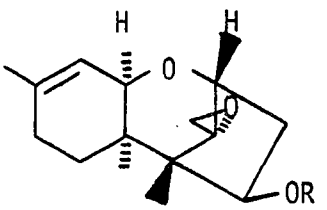
d $R_1, R_2 =$  verrucarin B (3, 5)

e ≈ R_1,R_2 = -COCH=C(CH$_3$)CH$_2$CH$_2$OC(=O)CH=CHCH=CHC(=O)- verrucarin J (3, 6)

f ≈ R_1,R_2 = -COC(=O)-C(H)(CH$_3$)CH$_2$CH$_2$OC(=O)CH=CHCH=CHC(=O)- 2'-dehydroverrucarin A (7)

g ≈ R_1,R_2 = -COC(OH)(H)-C(H)(CH$_3$)CH$_2$CH$_2$OCHCH=CHCH=CHC(=O)- roridin A (3, 8a)
CH(OH)CH$_3$

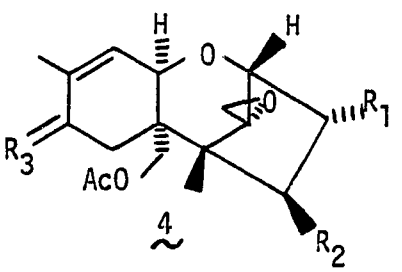
h ≈ R_1,R_2 = -COCH(O)-C(CH$_3$)CH$_2$CH$_2$OCHCH=CHCH=CHC(=O)- roridin D (3, 8b)
CH(OH)CH$_3$



3 ≈

a ≈ R = Ac, trichodermin (9)

b ≈ R = H, trichodermol (roridin C) (3)



4 ≈

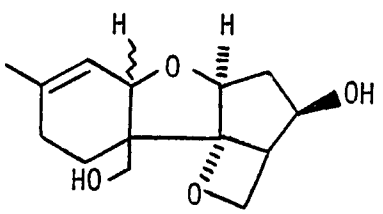
a ≈ R_1 = OH, R_2 = OAc, R_3 = H,H diacetoxyscirpenol (10, 11a-d)

b ≈ R_1 = OAc, R_2 = H, R_3 = H, H calonectrin (11e)

c ≈ R_1 = H, R_2 = OCOCH=CHCH$_3$, R_3 = O trichothecin (11f)

The verrucarins and roridins are secondary metabolites of the soil fungi Myrothecium verrucaria and Myrothecium roridum (1a-c). Verrucarol, although not actually produced by the organisms, is the sesquiterpene alcohol derived from basic hydrolysis of the macrocyclic verrucarins and roridins, with the exception of roridin C (1a).

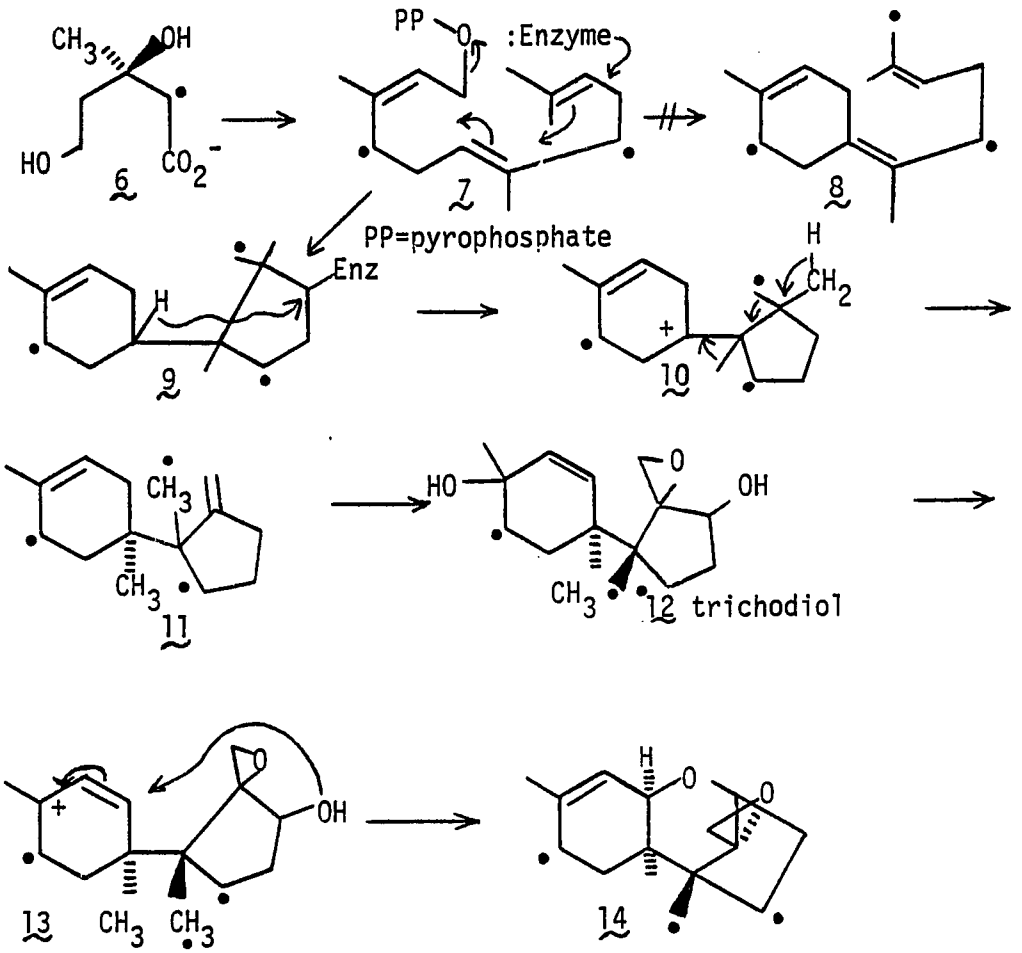
Initial investigation into the structure of verrucarol by Gutzwiller and Tamm led to their proposal of structure 5, based on ultraviolet, infrared, H^1-NMR, and combustion analysis (12).



5

The correct structure for verrucarol was established only after chemical correlation with trichodermol (3b) (13). The structure of trichodermol had been previously determined by X-ray analysis of the p-bromobenzoate (14). The structure of diacetoxyscirpenol was established by correlation with a degradation product of verrucarol (11a, b). Ironically, structure 5 corresponds to the apotrichothecene skeleton, which is produced by acid catalyzed rearrangement of the parent system (13). The elucidation of the biogenesis of the trichothecene skeleton has elicited a plethora of activity (1d, 15-19). The currently accepted biosynthetic route is shown below (1c, d).

The incorporation of geranyl pyrophosphate (7) and trichodiene (11) into the trichothecene skeleton was confirmed by feeding experiments with labeled 7 and 11 (16). Earlier proposals had postulated γ-bisabolene



(8) as a biosynthetic intermediate (17, 18), but more recent experiments resulted in low incorporations and extensive degradation when α and γ-bisabolene were administered to culture of Trichothecium roseum (16, 19). These new studies make the intervention of a bisabolene intermediate unlikely (1d).

The stimulus for the intense interest in the trichothecenes stems from the intense biological activity of these compounds. This subject has been extensively reviewed (1a) and will only be highlighted here.

Verrucarin A (2c) is the only trichothecene known to possess antibacterial activity (3c). Most trichothecenes show antifungal properties. Of those tested, verrucarin A, diacetoxyscirpenol and diacetylverrucarol were the most active (20). Trichothecin (4c) was found to be an active inhibitor of infection of bean and tobacco plants by plant viruses (21). The most significant biological property of the trichothecenes is their potent cytostatic activity. Many are under active investigation as anticancer agents.

Härri, et al. examined the verrucarins A and B and the roridins A and C for cytostatic activity against mouse tumor cells (3a). All were found to be extremely effective. Verrucarin A caused 50% inhibition at dose levels of 0.0006 µg/mL, making it one of the most potent cytostatic agents known. Diacetoxyscirpenol has also been found to be a mildly strong inhibitor of experimental tumors in mice and rats (22). The same workers found verrucarin A active against Yoshida sarcoma in higher mammals (23), and several trichothecenes have been found active against KB (human epidermal carcinoma) and L 1210 (leukemia) cells (1a, 24).

All of the trichothecenes are potent toxins and poisons. Very dilute solutions of various verrucarins and roridins caused severe local irritation, inflammation and, in some cases, lesions when applied to the skin of laboratory animals and man (10, 25-28).

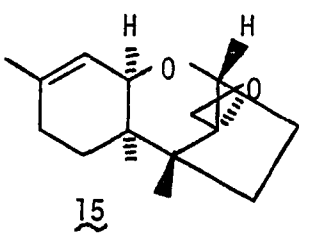
As a warning to careless investigators, Bamburg reports that brief contact with a crude ethyl acetate extract of T-2 toxin [3α,4β,8α,15-tetrahydroxy-12,13-epoxy-Δ^9-trichothecene, 8-(3-methylbutyryl)ester]

caused a severe burning sensation, followed by numbness and loss of skin (28d).

The lethal dose (LD_{50}) values for oral, intraperitoneal, intraveneous and subcutaneous administration of many trichothecenes have been reported for laboratory animals (1a, 3a, 20, 25).

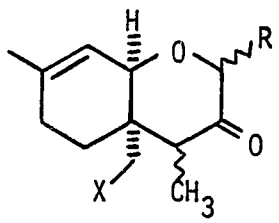
The broad range of biological properties exhibited by these natural products, together with the challenge presented by the complex tricyclic skeleton, have stimulated numerous synthetic approaches to the trichothecenes (29-37).

Due to their structural complexity, the majority of the synthetic investigations have been directed towards the least complicated trichothecenes. Successful total syntheses have been reported for (±)-12,13-epoxy-Δ^9-trichothecene (15) (32, 33) and trichodermol (3b) (29a, 35), as well as some aromatic A-ring analogues (37), but all approaches to the more complex verrucarol have met with failure (vide infra).



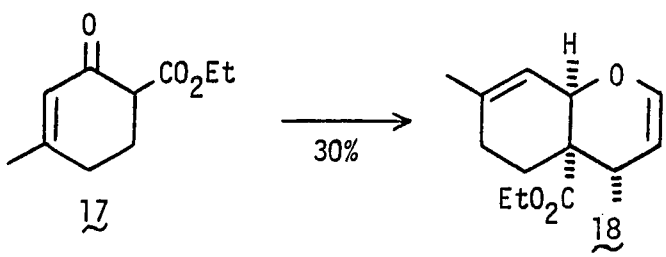
15

Two general synthetic routes have been employed to synthesize the trichothecene skeleton, one modeled broadly along biogenetic lines (33, 35) and the other passing through a functionalized isochroman derivative (16) (29, 31, 32, 36).



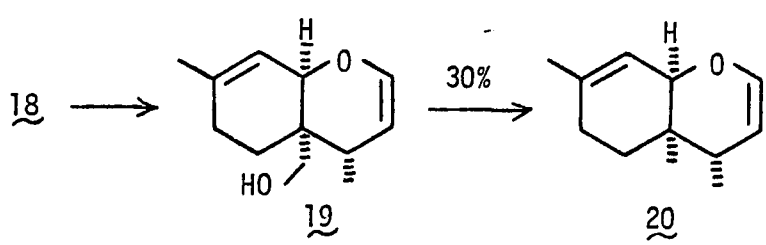
16, X = H, OH
R = H, CH_2CO_2Et, CH_2CHO

The first reported synthesis of (±)-12,13-epoxy-Δ^9-trichothecene (15) was by Fujimoto, et al. in 1974 (32). The β-keto ester 17 was condensed with crotonaldehyde and the resultant aldehyde protected as the acetal. Meerwein-Ponndorf reduction afforded the cis-fused dihydropyran 18 in low yield. The stereochemistry at the ring fusion was deduced from the proton NMR.



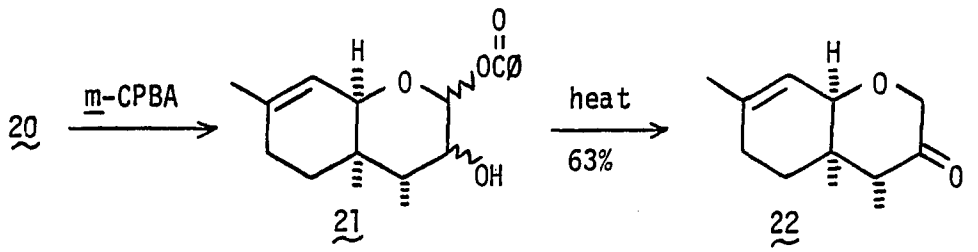
17 → 18

Reduction of 18 with lithium aluminum hydride provided alcohol 19, which was tosylated and further reduced to methyl derivative 20. The reduction of the ester at this juncture seems unnecessary and unfortunate, as 19 would appear to be a potential precursor to verrucarol (2a) and the macrocyclic trichothecenes.

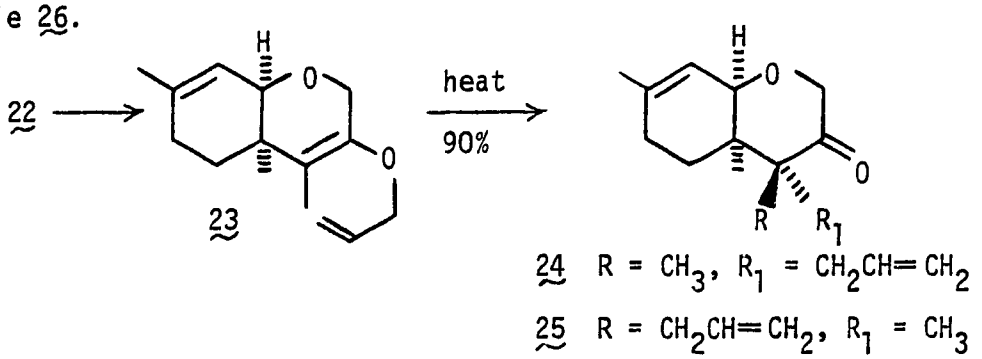


18 → 19 → 20

Treatment of 20 with m-chloroperbenzoic acid (m-CPBA) resulted in selective attack at the enol ether. The resultant mixture of diastereomeric hydroxy-esters, derived from in situ solvolytic opening of the epoxide, was pyrolyzed, providing isochromanone 22.

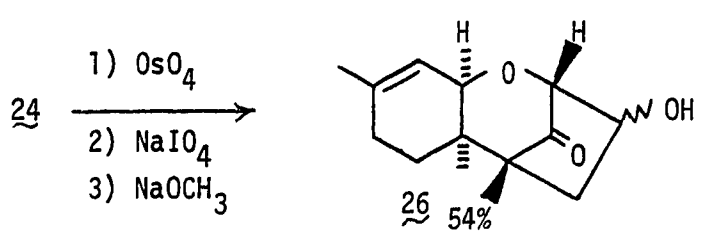


The introduction of the third ring was accomplished via a 5-step sequence. Alkylation with allyl bromide yielded an unexpected O-alkylation product (23), which was subjected to Claisen rearrangement, affording a 2:1 mixture of desired 24 to undesired 25. The mixture of diastereomers was separated and olefin 24 was converted to an aldehyde. Base catalyzed intramolecular aldol condensation furnished tricycle 26.

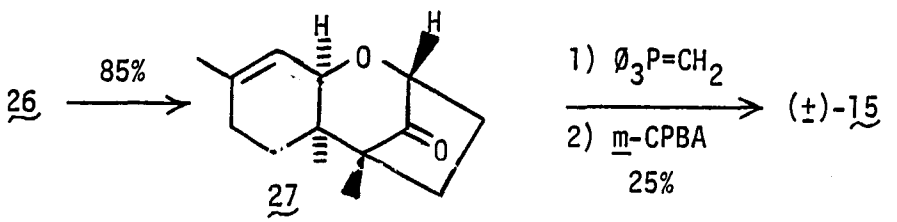


24 R = CH_3, R_1 = $CH_2CH{=}CH_2$

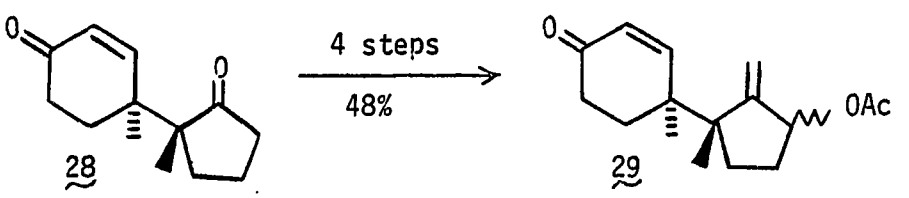
25 R = $CH_2CH{=}CH_2$, R_1 = CH_3



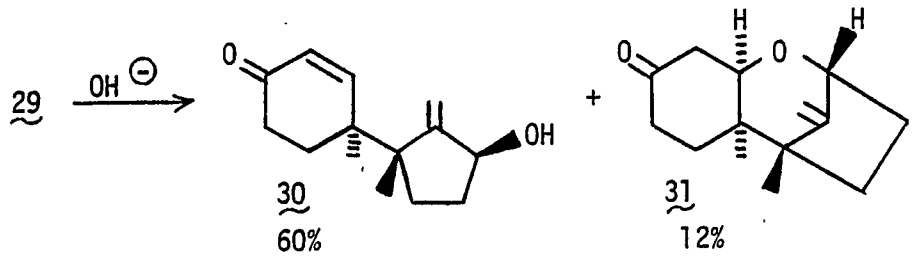
Removal of the alcohol, by conversion to the iodide and reduction, furnished ketone 27. Treatment of 27 with dimethyloxosulfonium methylide afforded the 12,13-epoxide epimeric to 15. Therefore, ketone 27 was olefinated (methylene triphenylphosphorane) and epoxidized, generating (±)-15 in low yield. The overall yield was 0.39% from β-keto ester 17.



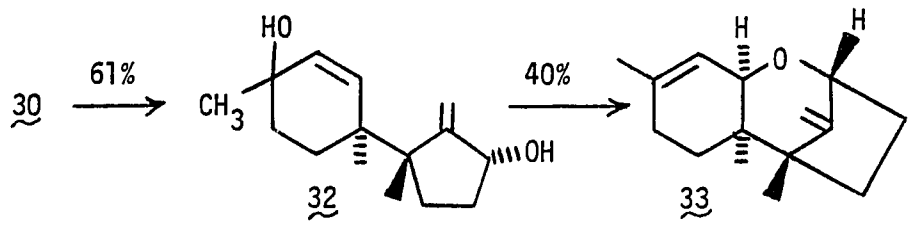
A second synthesis of (±)-15 was reported by Masuoka and Kamikawa (33). Diketone 28, available from 2-methylcyclopent-2-en-1-one and 4-methyl-cyclohex-3-en-1-one, ethylene ketal in 10% yield (photochemical dimerization, acid catalyzed rearrangement), was transformed into the diastereomeric mixture of acetoxy-ketones 29 via a four step sequence.



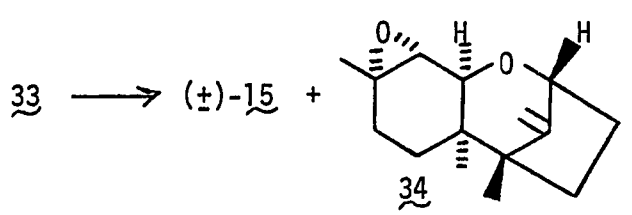
Saponification of the acetate produced alcohol 30 and, as a minor product, tricycle 31. Apparently, only the alcohol leading to the cis-fused A-B ring system can cyclize. (Oddly, no further mention of 31 is made by the authors, although it appears to be a ripe precursor to (±)-15.)



Inversion of alcohol 30 (mesyl chloride-pyridine, then tetra-ethyl-ammonium acetate) and condensation with methyl magnesium iodide afforded diol 32. When treated with acid, 32 cyclized to tricyclic olefin 33.



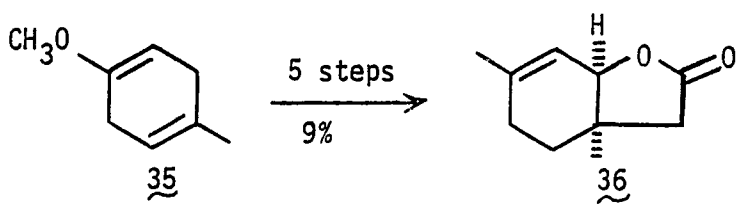
Epoxidation of 33 gave a 1:1 mixture of (±)-15 and regioisomer 34. Presumably, this lack of regiocontrol was the cause of the low yield conversion (30%) of 33 to (±)-15 by Fujimoto, et al.



This second synthesis, although shorter and somewhat more elegant than the first, proceeded in an almost identical overall yield (0.35%).

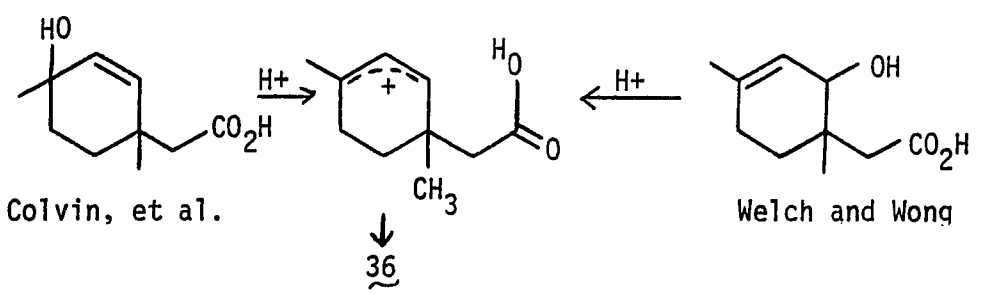
If one were to rank the trichothecenes based on the complexity of their functionality, the next degree of complexity would arise from the addition of one more functional group to (±)-12,13-epoxy-Δ^9-trichothecene. The molecule just described is trichodermol (3b), which has been synthesized twice (29a, 35).

The preparation of 3b by Colvin, et al. in 1973 was the first successful preparation of the trichothecene skeleton. Starting diene 35 was transformed by two parallel routes to key cis-fused bicyclic lactone 36. The most efficient route was 5 steps and proceeded in 9% overall yield. Welch and Wong have also prepared 36 (30).



35 36

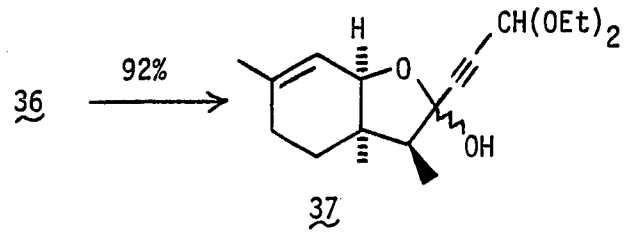
Each group of investigators generated an identical allylic carbonium ion from isomeric allylic alcohols. The intramolecular trapping of the cation by the proximate carboxylic acid insures the cis stereochemistry at the ring junction.



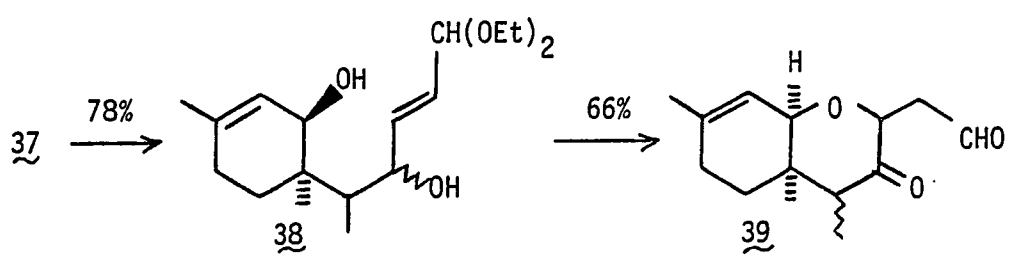
Colvin, et al. Welch and Wong

36

Lactone 36 was alkylated (lithium diisopropylamide, methyl iodide) and treated with the lithium salt of 3,3-diethoxy propyne, to provide lactol 37 in high yield.

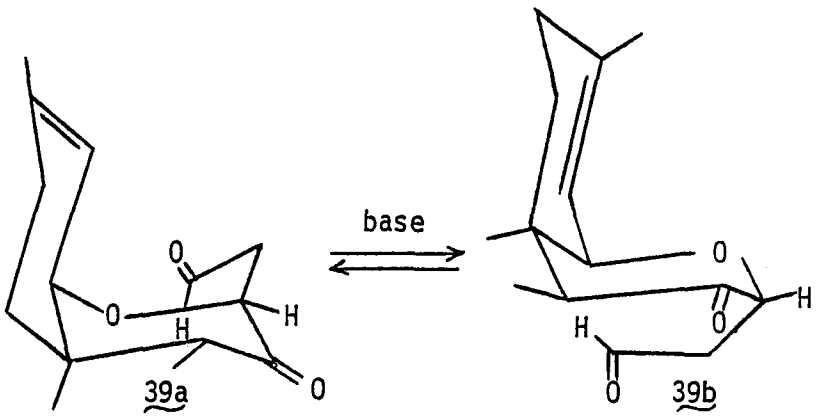


Sodium borohydride reduction afforded a diol, which was reduced with sodium in ammonia to the trans-olefin, without reduction of any of the allylic oxygen functionality. Mild acid hydrolysis effected both deprotection of the aldehyde and addition of the alcohol to the unmasked enone. Selective oxidation with chromium trioxide-pyridine provided keto-aldehyde 39, "a compound seemingly ripe for internal aldol condensation" (29a).



Although 39 was an inseparable mixture of diastereomers, the authors reasoned that of the four possible diastereomers, only two (39a and 39b) would be capable of attaining a transition state suitable for internal aldolization. Of these two remaining diastereomers, 39a would be

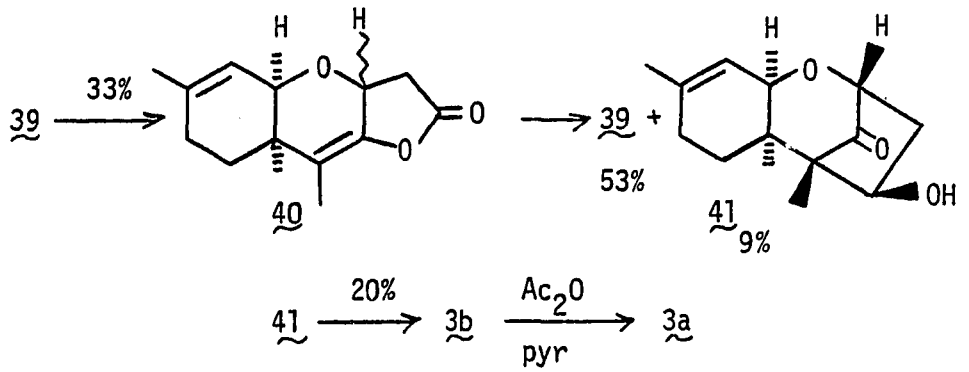
rendered less favorable due to an unfavorable steric interaction between the two carbon fragment and the A-ring. Thus, under conditions which would allow equilibration at the two centers adjacent to the ketone, intramolecular aldol condensation was expected to proceed through 39b, leading to a product with the exact stereochemistry required for trichodermol.



As fate would have it, no conditions could be found to induce 39 to undergo internal aldolization. (The authors list fifty separate sets of experimental conditions which were attempted without success.)

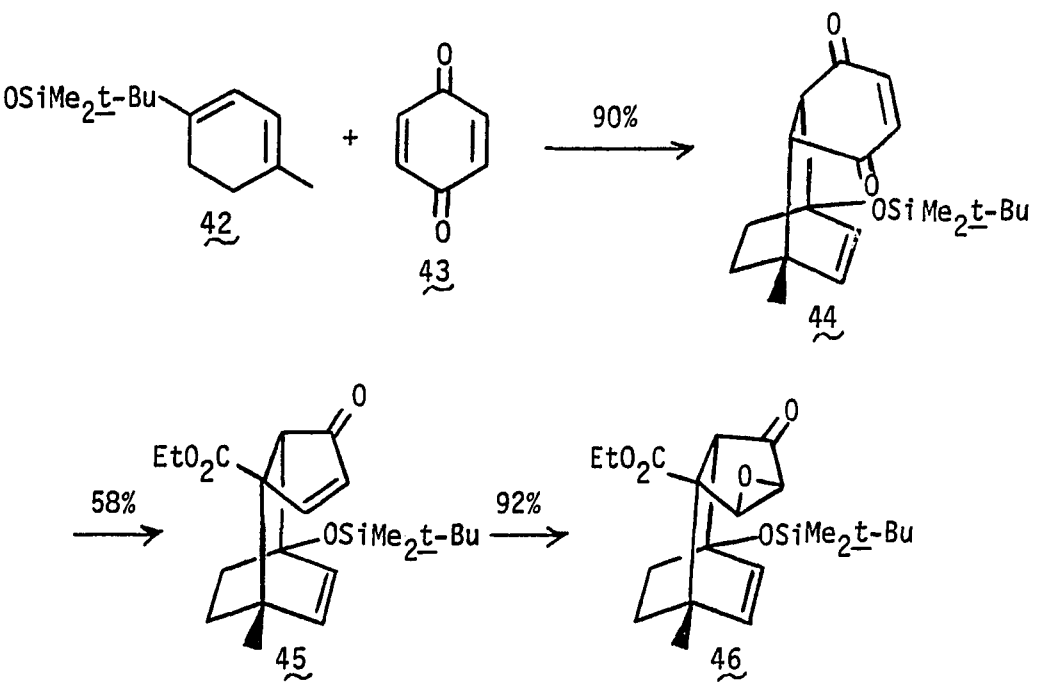
Being frustrated by this transformation, the authors sought an alternative. Oxidation to the keto-acid, followed by treatment with acetic anhydride, provided a diastereomeric mixture of enol lactones (40). Reduction with tri-tert-butoxyaluminum hydride afforded a mixture of keto-aldehyde 39 and aldol product 41 in low yield.

Acetylation, olefination and epoxidation afforded (±)-trichodermol. The overall yield was 0.025%. Trichodermol was acetylated to provide (±)-trichodermin.

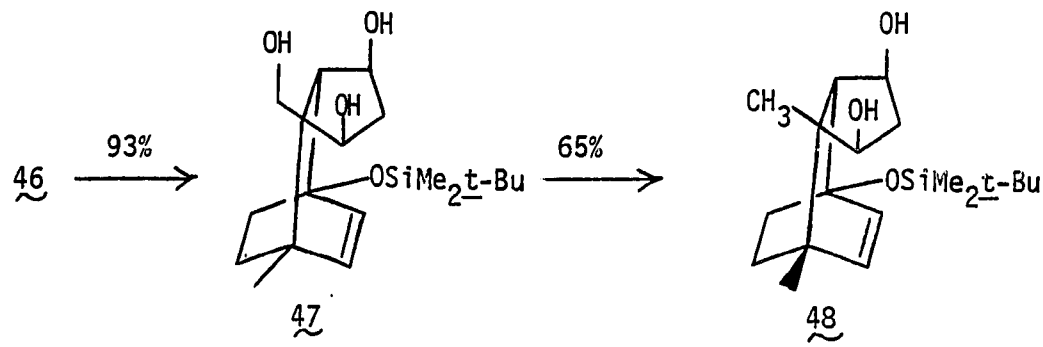


The most elegant trichothecene synthesis published to date is the trichodermol synthesis by Still and Tsai (35).

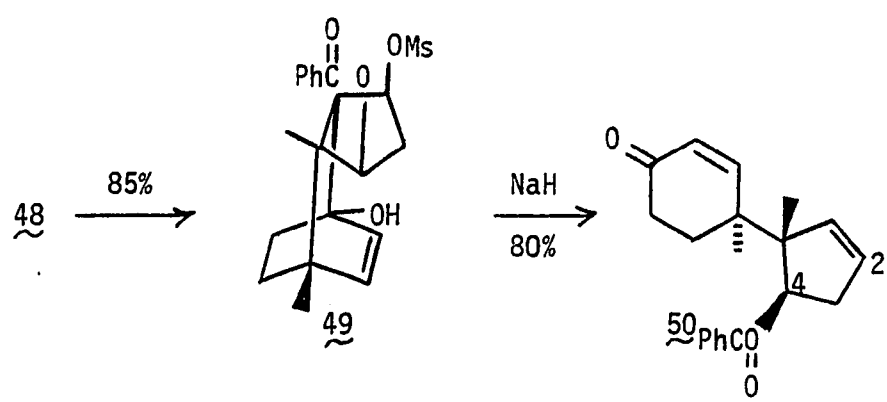
Diels-Alder reaction of diene 42 with 1,4-benzoquinone 43 afforded adduct 44 in high yield. Epoxidation (t-BuOOH, Triton B) and Herz-Favorskii ring contraction (NaOH, EtOH) provided 45 as the sole product. The regioselectivity of the ring contraction was explained by "silyl oxygen-assisted σ overlap" (35) with the proximate carbonyl, preventing attack at that center. Epoxidation (t-BuOOH, Triton B) gave 46.



The C-4 (trichothecane nomenclature) hydroxyl was introduced stereospecifically by dissolving metal reduction, to yield triol 47. The unwanted primary alcohol was selectively acetylated and removed by an unusual photochemical reaction (deoxygenated HMPA, H_2O, 450-W Hanovia, quartz).

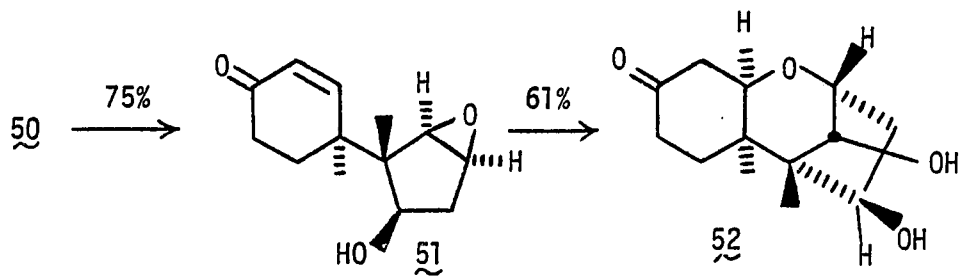


Diol 48 was converted to alcohol 49 by a four step sequence. Anionic fragmentation provided 50, in which all of the stereochemical centers have been introduced with the correct relative stereochemistry (38).

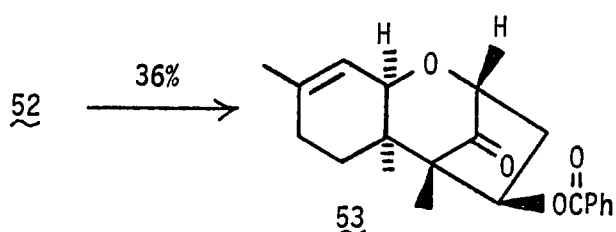


Debenzoylation and hydroxyl-directed epoxidation [t-BuOOH, $VO(acac)_2$] produced β-epoxide 51. Acid-catalyzed diol formation proceeded with

inversion at C-2. In situ hydroxyl addition afforded tricyclic product 52. The stereochemistry of the diol is that expected based on the inaccessibility of C-1 to nucleophilic attack.



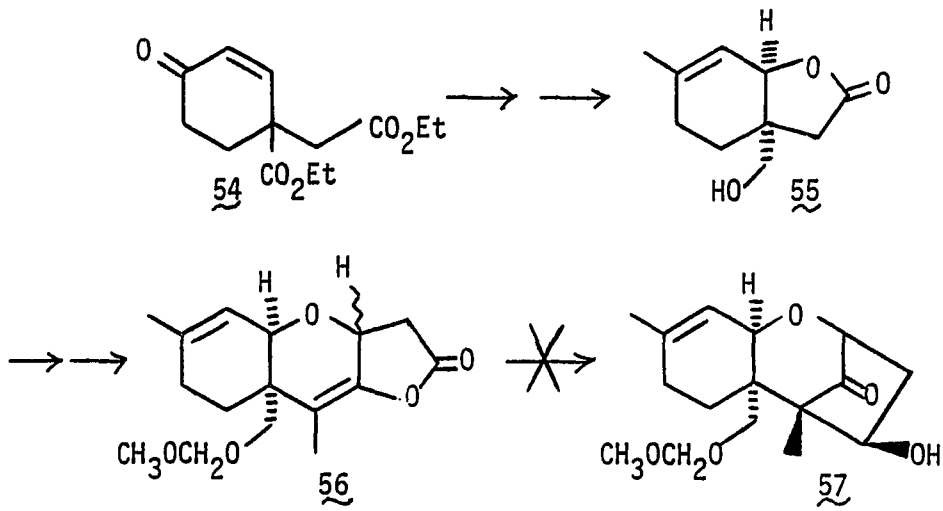
Conversion of 52 into (±)-trichodermol was accomplished by introduction of the methyl group at C-9 (CH_3Li), mono-benzylation, oxidation at C-12 and dehydration. Olefin 53 was the major isomer of a 7:1 mixture of olefins.



Keto-benzoate 53 was elaborated to (±)-3b in the manner described by Colvin, et al. for the analogous acetate (vide supra). The overall yield was 0.64%.

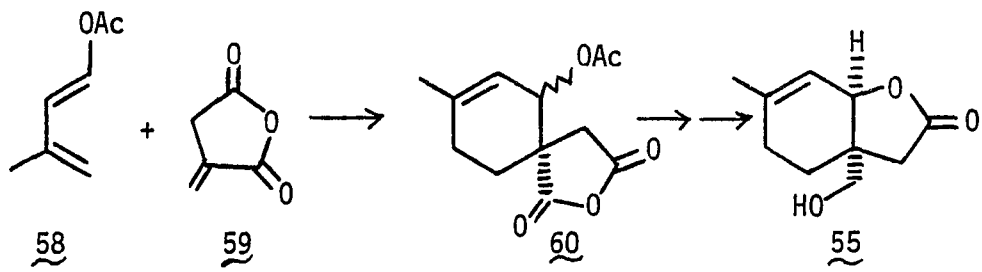
Although somewhat satisfactory routes have been devised for (±)-3b and 15, approaches to the more complex verrucarol (2a) have met with little success.

In an attempt to extend their previous work to permit the synthesis of verrucarol, Colvin, et al. synthesized the required enol lactone 56.

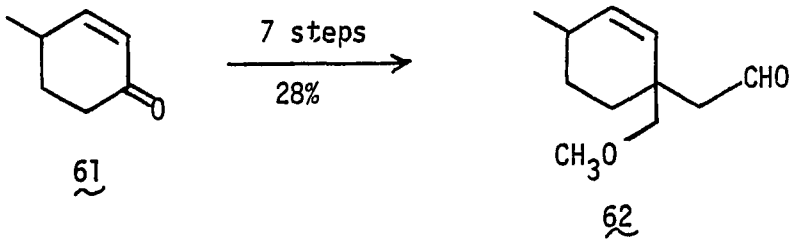


Under no conditions could 56 be induced to cyclize to aldol product 57. Their final comment was that "no crude reaction mixture, nor any of the individual components, showed the high IR carbonyl stretching frequency, ν_{max} 1760 cm^{-1}, associated with bicyclo[3.2.1]octan-8-ones, nor did NMR spectrosocpy indicate any grounds for optimism" (29b).

Snider and Amin have synthesized intermediate 55, but no further advancements have been forthcoming (34).

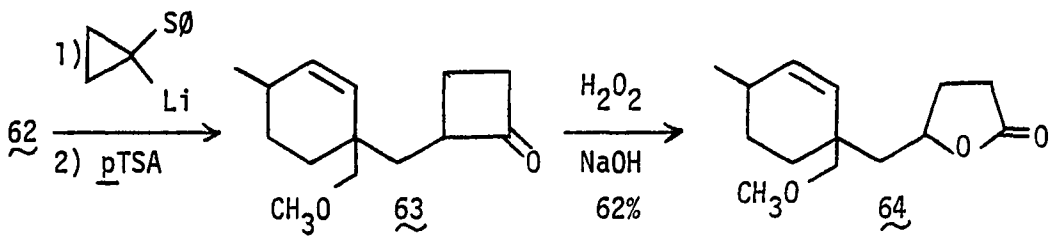


Trost and Rigby have devised a clever, but long, synthesis of a precursor to Colvin's intermediate enol lactone 56 (36). The approach began with the transformation of 4-methyl-2-cyclohexene-1-one to aldehyde 62.



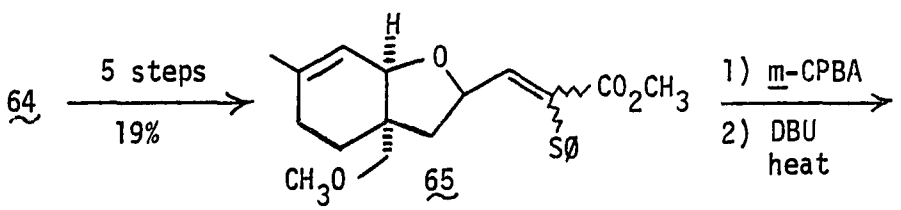
61 62

Compound 62 was further elaborated, via a cyclobutanone spiro-annulation and Baeyer-Villiger oxidation to lactone 64.

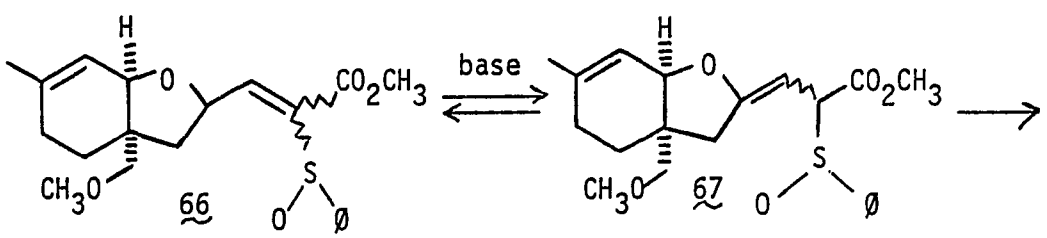


62 63 64

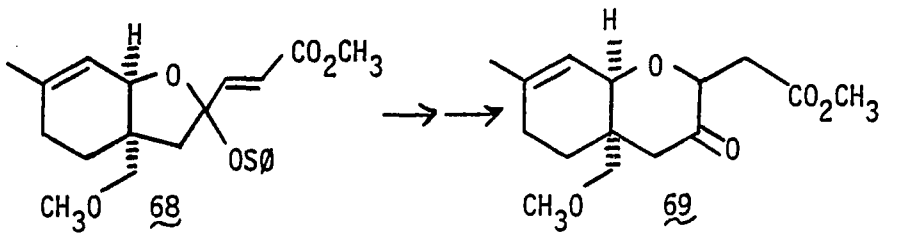
Lactone 64 was transformed to tetrahydrofuran 65 by a five step sequence, and then was rearranged to isochromanone 69 by a novel allyl sulfoxide rearrangement.



64 65



66 67

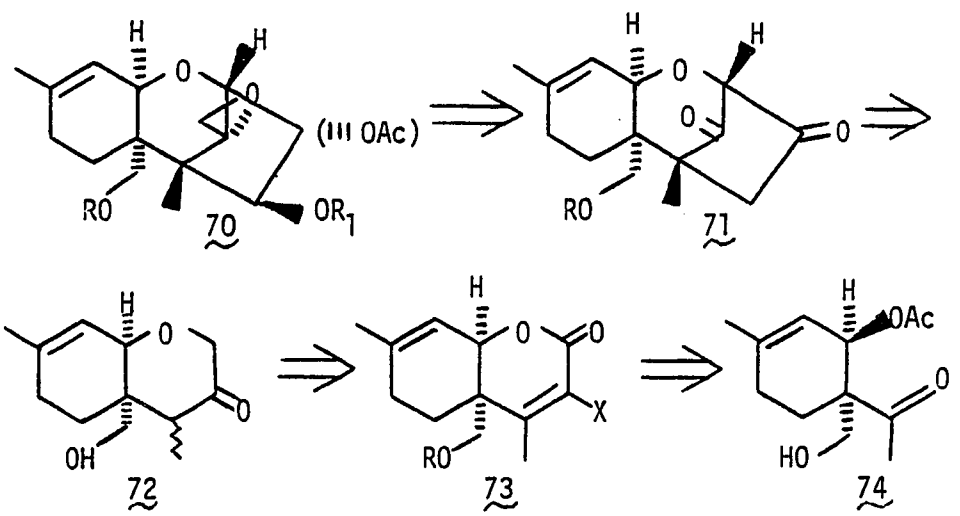


Trost and Rigby stop at this point, indicating that "Raphael (Colvin, et al.) has worked out a procedure to convert such systems to the trichothecane skeleton of verrucarol" (36). Unfortunately, Colvin, et al. have demonstrated the uselessness of this intermediate (vide supra) (29).

RESULTS AND DISCUSSION

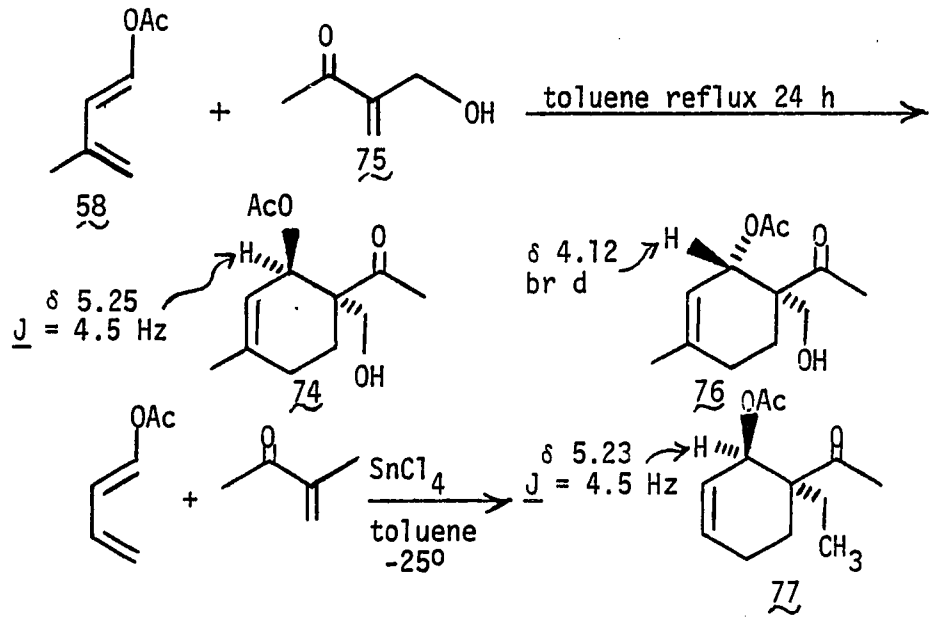
Undaunted by the difficulties encountered by other researchers, we initiated a program directed towards the total synthesis of verrucarol, diacetoxyscirpenol, and the macrocyclic trichothecenes.

A retrosynthetic outline of our approach is shown below.



Ketone 74 appeared to be perfectly suited for construction by way of a Diels-Alder reaction, if the cis-endo addition could be realized. To this end, the thermal reaction (115 °C, 24 h) of 1-acetoxy-3-methyl butadiene (34) (58) with 3-hydroxymethyl-3-buten-2-one (39) (75) was attempted, and afforded a 2:1 mixture of diastereomeric acetoxy-ketones. The stereochemistry of the major and minor products were tentatively assigned as structures 76 and 74, respectively, by comparison with the NMR spectrum of compound 77. Ketone 77 was the exclusive product from

the tin tetrachloride catalyzed Diels-Alder reaction of 1-acetoxybutadiene and isopropenyl methyl ketone (40). Further transformations confirmed this assignment (vide infra).



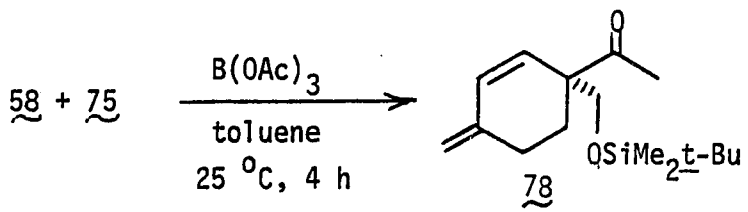
In light of the excellent selectivity found in the preparation of 77, the reaction of 58 with 75 under Lewis acid catalysis was studied.

After considerable experimentation, it was determined that the highest yields of 74 and 76 were obtained when 58 and 75 were reacted in the presence of boron triacetate (41) at low temperature. More importantly, the desired diastereomer (74) was now the predominant isomer (3.5:1) formed in the reaction. The sensitive allylic acetates 74 and 76

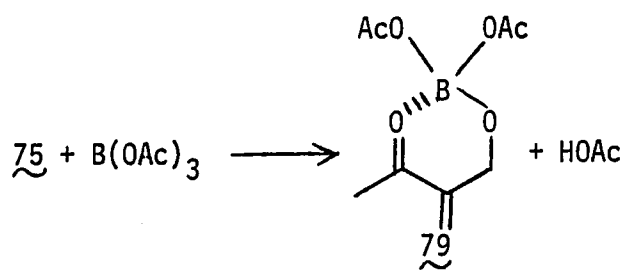
$$58 + 75 \xrightarrow[\text{toluene}\\ 5\ ^{o}C,\ 48\ h]{B(OAc)_3} \underset{3.5:1}{74 + 76}$$

were obtainable only within a narrow range of experimental conditions. At lower temperatures, the reaction proceeded sluggishly, whereas at higher

temperatures (25 °C), extensive decomposition occurred. The major product at room temperature was diene 78. Small amounts of 78 were also formed at 5 °C.

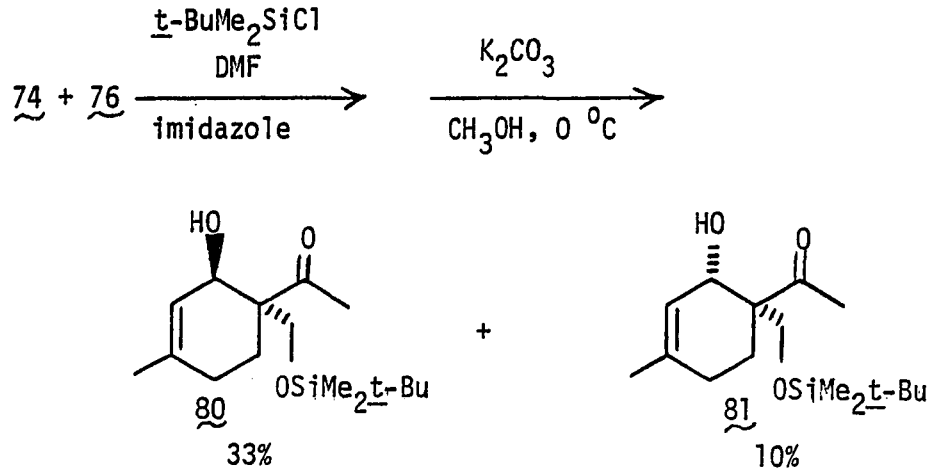


Other catalysts, such as tin tetrachloride and boron trifluoride etherate, led to tarry materials. It is also noteworthy that boron triacetate did not catalyze the addition of diene 58 to isopropenyl methyl ketone. This is understandable if the catalyst must form a chelate ring (79) with the dienophile for effective catalysis. Without this complexation, boron triacetate is probably too weak a Lewis acid to be an effective catalyst.



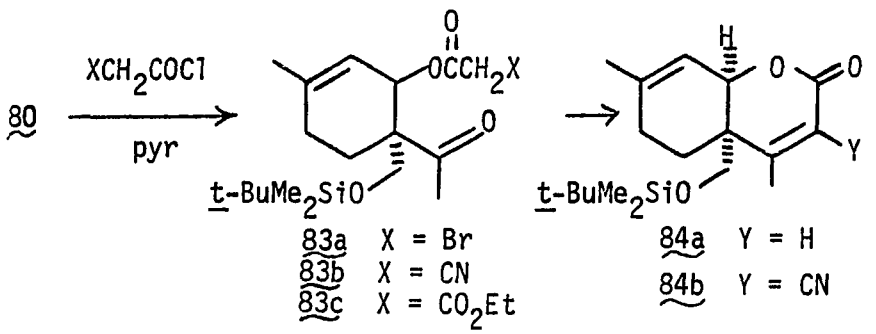
The crude mixture of alcohols 74 and 76 were then protected as tert-butyldimethylsilyl ethers by employing the procedure of Corey and Venkateswarlu (42). Saponification of the acetates afforded the mixture of diastereomers 80 and 81.

The two diastereomers were separated at this juncture by careful silica gel chromatography or, more conveniently, by preparative scale



high pressure liquid chromatography. The undesired isomer (81) could then be epimerized to a 50:50 mixture of 80 and 81 with a catalytic amount of benzyltrimethyl ammonium hydroxide. Presumably, the epimerization occurred by a process which involved an initial retroaldol followed by realdolization. In this manner, the overall yield of 80 could be raised to 38% from 3-hydroxymethyl-3-butene-2-one. Attempted epimerization of 81 using triphenylphosphine, diethylazodicarboxylate, and formic acid (43) led to the recovery of starting materials.

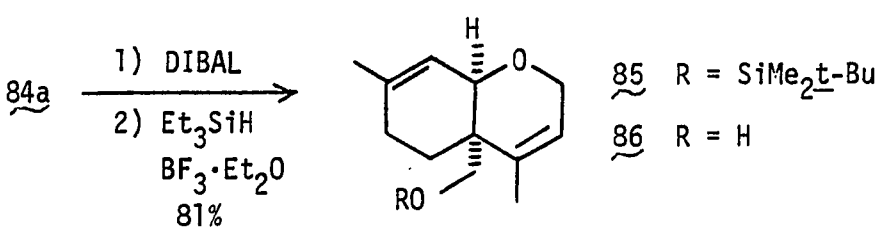
Having secured a route to our A-ring precursor, we began investigating annelation strategies for elaboration of the B and C rings. Thus, 80 was reacted with acid chlorides and pyridine, affording esters 83a,b,c in excellent yields. Ester 83a was transformed into lactone 84a by



83a X = Br
83b X = CN
83c X = CO_2Et

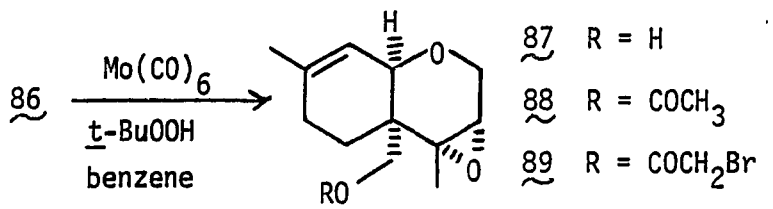
84a Y = H
84b Y = CN

reaction with neat trimethyl phosphite at 95 °C followed by cyclization with sodium hydride in THF. The overall yield from 80 to 84a was 67%. Our strategy for the conversion of 84a into the desired ketone 72 involved the reduction of the lactone to an ether, followed by the selective transformation of the olefin in ring B to a ketone. The initial phase of this plan was efficiently accomplished using a modification of a reduction procedure developed by West, et al. (44). Reduction of 83a with diisobutyl aluminum hydride (DIBAL) afforded an unstable lactol, which could be reduced to allylic ether 85 with triethyl silane and boron trifluoride etherate at -78 °C. No olefin migration was observed as evidenced by the NMR of the crude product. Removal of the alcohol protecting group with tetra-n-butyl ammonium fluoride (42) produced alcohol 86 in 88% yield.

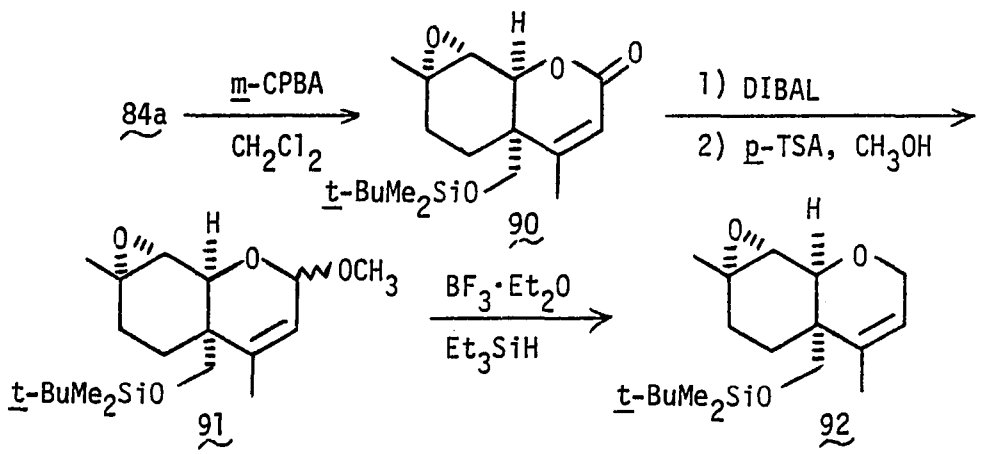


Although the conformation of 86 most consistent with the observed coupling constant (J = 3 Hz) between the C-11 (trichothecane numbering system) methine hydrogen and the vinyl proton at C-10 placed the hydroxyl group closer to the olefin in the A ring, we felt that the preference for epoxidation of homo-allylic alcohols over bis-homoallylic alcohols demonstrated by transition metal catalyzed epoxidations would be strong enough to allow for selective epoxidation of the olefin in ring B. Therefore, directed epoxidation employing the method of Sharpless and

Michaelson (45) was attempted and proved to be highly selective. The ring B epoxide (87) was the sole product by NMR and thin-layer chromatography. The yield of 87 after chromatography was 73%.



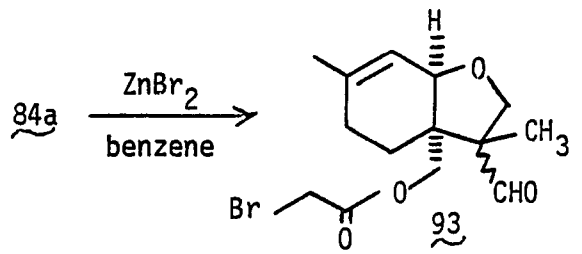
Further support for the identity of 87 was provided by the synthesis of the regioisomeric epoxide (92). This was accomplished unambiguously from 84a by a four-step sequence.



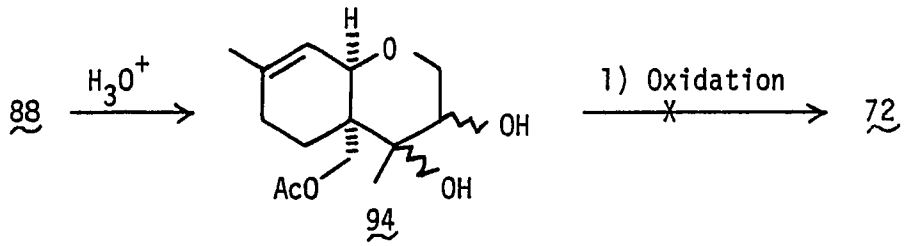
Consistent with its assigned structure, the epoxide hydrogen in 87 appeared as a doublet (J = 4 Hz). Irradiation experiments demonstrated it to be coupled to one hydrogen of an AB quartet centered at δ 4.95. The epoxide hydrogen in 92 was a singlet.

Protection of the alcohol as the acetate or bromoacetate proceeded in high yield. Unfortunately, all attempts to convert the epoxide to a

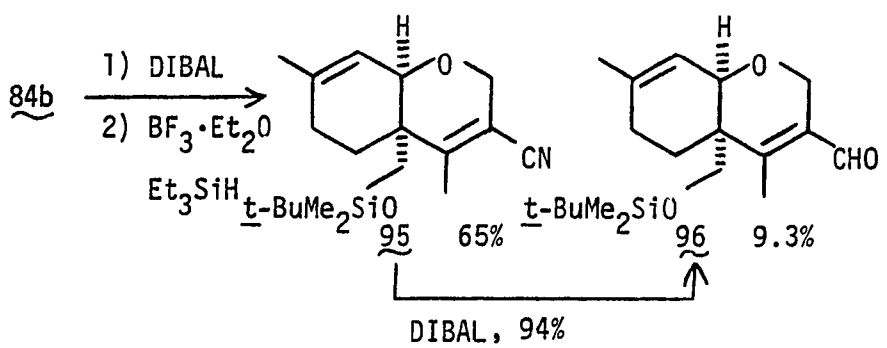
ketone failed miserably. Attempted epoxide isomerization (46) with boron trifluoride etherate in toluene (47), lithium perchlorate in refluxing benzene (48), sodium iodide in dimethylsulfoxide (49), or tin tetrachloride in toluene (50) led to either decomposition or recovery of the starting epoxide. When conditions were finally found in which migration occurred, alkyl migration occurred in preference to hydrogen migration. Thus, treatment of 89 with anhyd $ZnBr_2$ in refluxing benzene (51) furnished aldehyde 93 in high yield.



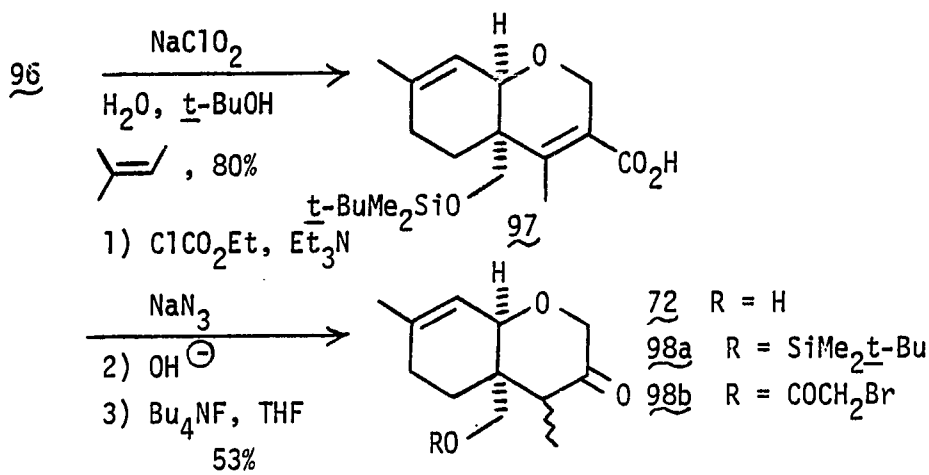
Alternatively, we felt that 72 could be approached from an α-hydroxyketone by reductive elimination. This plan would also permit the regioselective formation of an enol silyl ether. When 88 was refluxed with perchloric acid in THF-water or sulfuric acid in acetone-water, diol 94 was produced in high yield (52). Unfortunately, attempted oxidation (N-chloro-succinimide, dimethylsulfide (53); N-bromosuccinimide in aqueous dioxane (54); dimethylsulfoxide (DMSO), dicyclohexyl carbodiimide and various acids (55); DMSO, acetic anhydride (56); silver carbonate on Celite (57)) failed to yield the desired ketone. In each case, unreacted diol was recovered (58).



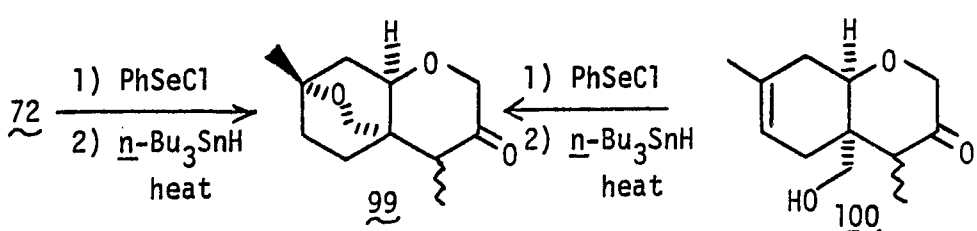
As a consequence of our failure to transform the epoxide into a ketone, an alternate route was developed. Cyano ester 83b was cyclized to bicyclic lactone 84b with 1,5-diazabicyclo[4.3.0]non-5-ene. The yield was 75% from 80. The corresponding diester 83c failed to cyclize under a variety of conditions. Treatment of 84b with DIBAL at -78 °C afforded a cyanolactol, which was further reduced to ether 95 with boron trifluoride etherate and triethylsilane. The DIBAL reduction of 95 provided aldehyde 96 in 94% yield. Aldehyde 96 was also produced as a minor product in the reduction of 84b to 95. Attempts to convert 84b directly to 96, without the intermediacy of 95 (by treatment with excess DIBAL followed by boron trifluoride etherate and triethylsilane) resulted in lower overall yields of 96.



Oxidation of aldehyde 96 with sodium chlorite in aqueous tert-butanol (59) provided the highly crystalline acid 97 in 80% yield. Acid 97 was transformed into ketone 72 by Curtius degradation (60) and desilylation (42).



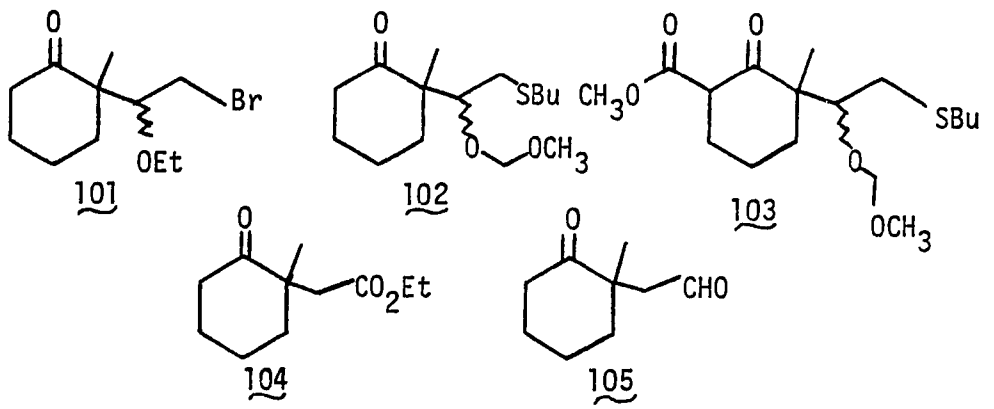
As an additional proof of structure, ketone 72 was converted into ether 99 by cyclization with phenylselenyl chloride and reductive deselenylation (61). Ether 99 was identical in all respects (IR, NMR, capillary column gas chromatography) with material prepared from isomeric ketone 100, in which the cis-ring juncture had been unambiguously defined by the synthetic approach (62).



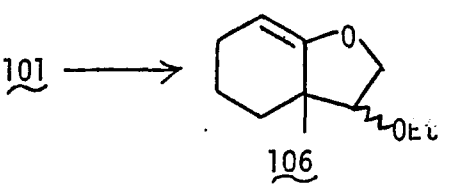
Having surmounted the obstacles presented by the synthesis of 72, we addressed the problem of introducing the C-ring. Being cognizant of

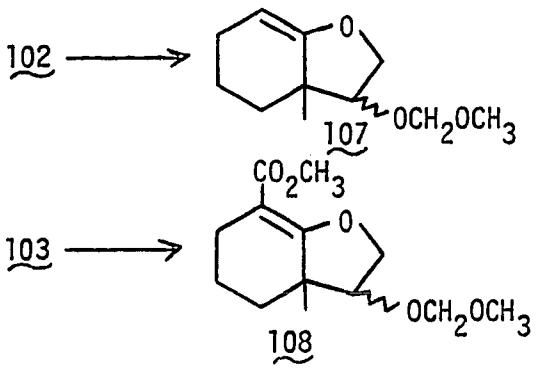
the failure of Colvin, et al. (vide supra), we set about the introduction of the quaternary center at C-5. Critical to the success of this approach were the attainment of the more highly substituted enolate and the introduction of the proper two carbon fragment with the correct relative stereochemistry.

In order to determine the best method for introducing the requisite two carbon fragment, we synthesized model systems 101-105 and submitted each to a variety of cyclization protocols. Treatment of compounds 101-



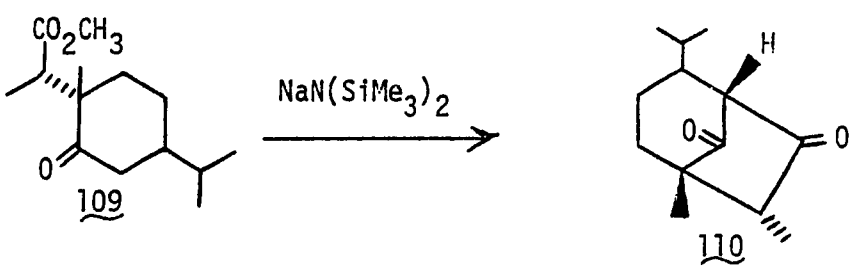
103 with numerous base-solvent pairs (101: magnesium methoxide in methanol, potassium tert-butoxide in benzene, lithium tert-butoxide in tert-butanol, Al_2O_3 in toluene; 102-3: lithium diisopropylamide in tetrahydrofuran, magnesium methoxide in methanol, potassium tert-butoxide in tetrahydrofuran) afforded solely the products derived from alkylation at the oxygen.

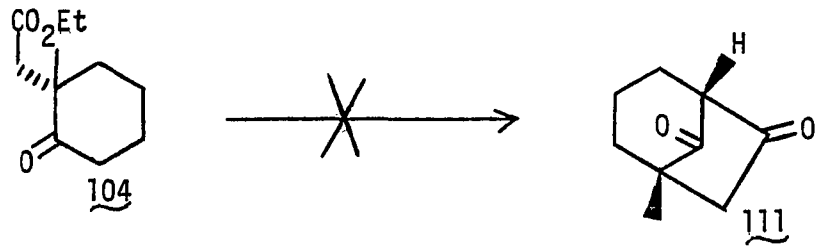




In retrospect, this result is not at all surprising. The transition state for O-alkylation should be easier to attain as the two carbon fragment is in the plane of the enolate, whereas for C-alkylation, it must be perpendicular to the enolate. Examination of molecular models indicated that the latter transition state is much less easily attained. Thus, it became obvious that the bicyclo[3.2.1]octan-8-one ring system could not be approached via the alkylative route.

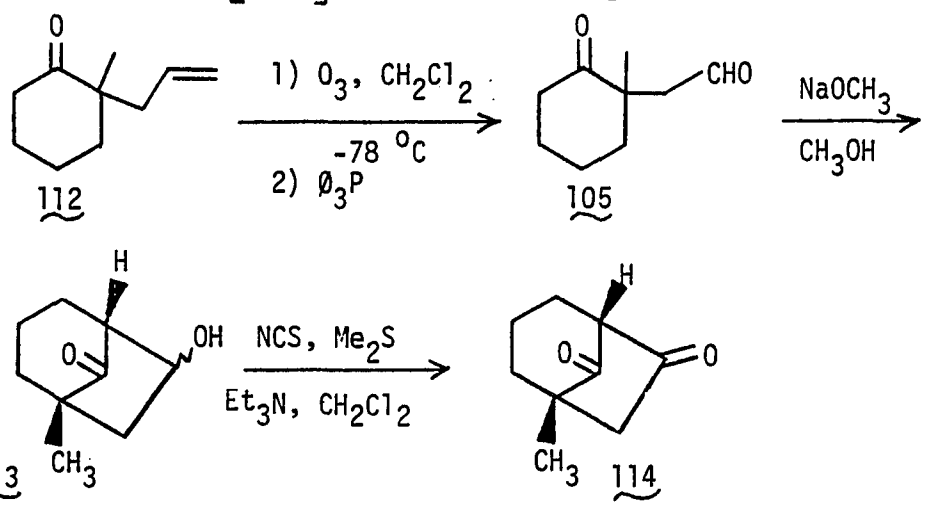
We next turned to keto ester 104. Work by Piers, et al., in which the similar keto ester 109 had been cyclized directly to diketone 110, indicated that 104 might be a precursor to the bicyclo[3.2.1]octanedione 111 (63). To our surprise, we could not duplicate the work of Piers, et al. in our system, and no conditions could be found to effect this transformation.





104 111

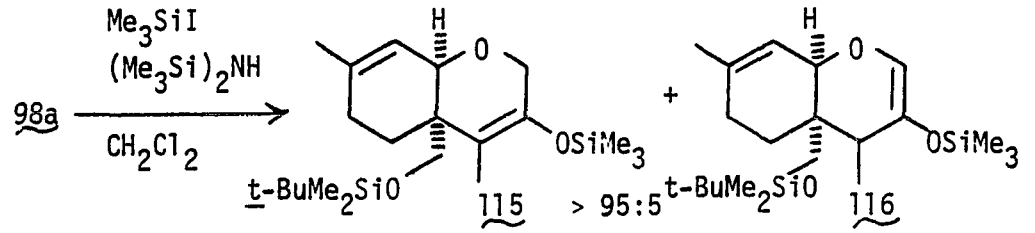
Having been thwarted by this transformation, we synthesized keto aldehyde 105 from olefin 112 (64) by either ozonolysis or osmium tetroxide catalyzed hydroxylation followed by cleavage with sodium periodate. When 105 was treated with sodium methoxide in refluxing methanol, it cyclized smoothly to ketol 113. The Corey-Kim oxidation (65) of 113 provided the bicyclo[3.2.1]octan-1,8-dione 114 in high yield.



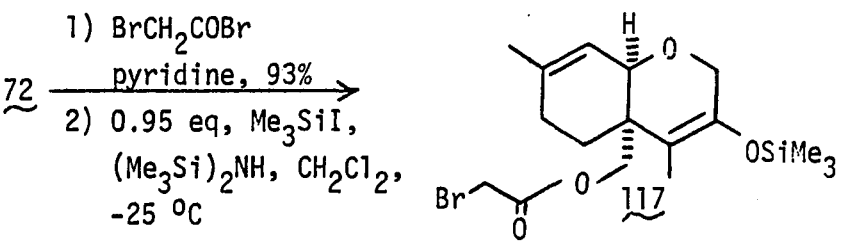
112 105 113 114

With this modest success in hand, we returned our attention to the real system. Employing the excellent procedure of Miller and McKean (66), we successfully negotiated the first obstacle toward the introduction of the quarternary center at C-5. Thus, treatment of ketone 98 with trimethylsilyl iodide and hexamethyldisilazane in methylene chloride

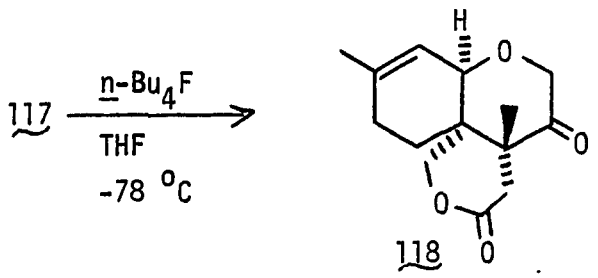
afforded the desired silyl enol ether in greater than 95% yield as determined by gas chromatography.



Buoyed by this success, we prepared the analogous silyl enol ether 117, confident that intramolecular alkylation would guarantee the stereochemistry at C-5. This strategy would avoid the mixture of epimers suffered by Fujimoto, et al. (32). Sensitive silyl enol ether 117 could



only be obtained by employing a slight deficiency of trimethylsilyl iodide (0.95 eq). When an excess was used, as is prescribed by Miller and Mckean, no recognizable products were isolated. Formation of the tetra-n-butylammonium enolate (67) at -78 °C and warming to ambient temperature furnished a 47% yield of the crystalline lactone 118. When the iodoester was employed in this reaction sequence, a slight improvement (50%) in the yield was obtained. The major by-product in each case was the acetate of 72 derived from reductive removal of the halogen (30-40%). This material could be recycled by saponification to keto alcohol 72.

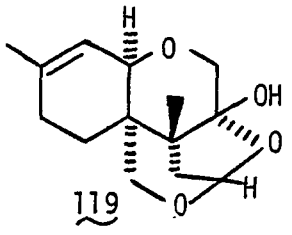


Surprisingly, attempts to alkylate the anion derived from 115 (generated by cleavage of the silyl enol ether with either methyllithium (68) or tetra-n-butylammonium fluoride) with allyl iodide or ethyl iodoacetate led to decomposition of the starting ketone. It is possible that alkylation of these anions can only be successful intramolecularly, where product formation is competitive with decomposition.

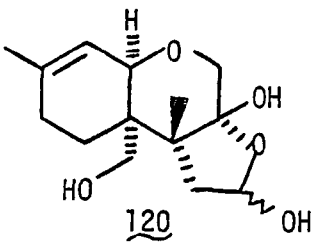
Having unambiguously established the center at carbon 5, we sought to elaborate the lactone into an aldehyde. This proved to be more difficult than expected. Attempts to differentiate the two carbonyls by protection of the ketone proved fruitless. Both attempted ketalization (69) and enol silyl ether (66) formation resulted in recovery of the starting ketone. We could produce the enol methyl ether with trimethyl orthoformate and para-toluenesulfonic acid (70), but the yield was low.

In spite of our failure to protect the ketone, we decided to attempt reduction of the lactone without protecting the ketone. Conceivably, the ketone, being adjacent to a quaternary center, would be too hindered to be reduced by a bulky hydride donor. To this end, 118 was treated with one equivalent of diisobutylaluminum hydride (DIBAL) at -78 °C. Aqueous hydrolysis afforded a single compound in which examination of the NMR

spectra revealed that reduction had occurred as predicted. This was evidenced by the upfield shift of the protons adjacent to the lactone carbonyl without any appreciable shift of those adjacent to the ketone carbonyl. Unfortunately, the infrared spectrum was devoid of absorptions in the carbonyl region. Similarly, the CMR spectrum evidenced no carbonyl resonances. Instead, it possessed two resonances (δ 99.43 and 81.09) characteristic of acetal or ketal-like structures. Two possible structures consistent with the spectral data are shown below. Fujimoto, et al. passed through an intermediate similar to 120 (32). Unlike the



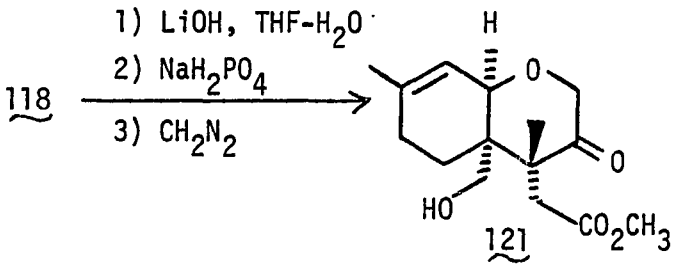
119



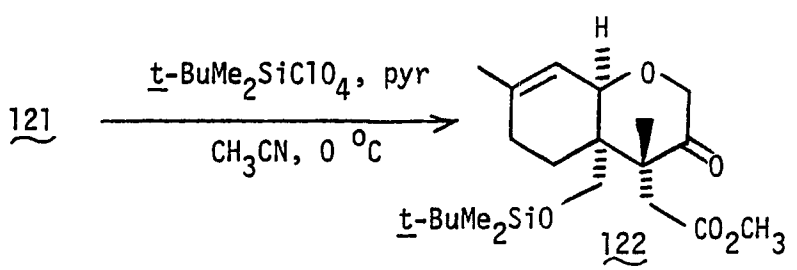
120

keto aldehyde hydrate synthesized by Fujimoto, et al., the reduction product derived from 118 did not open under basic catalysis. Attempted acetylation led to recovery of starting material, which is consistent with the internal acetal structure present in 119.

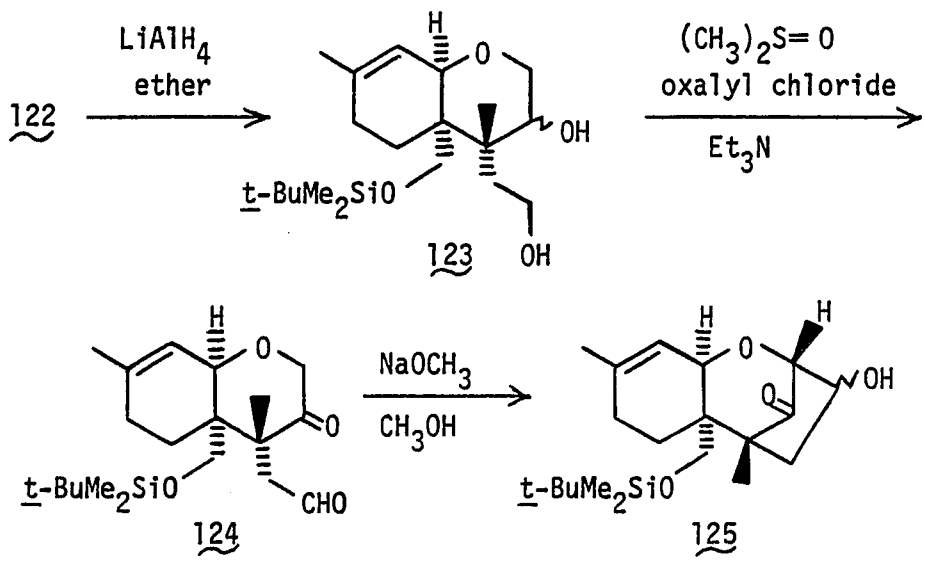
In order to avoid the dead end presented by 119, lactone 118 was opened to the hydroxy-acid and treated with diazomethane *in situ* (71).



Not surprisingly, attempts to reprotect the alcohol as the tert-butyldimethylsilyl ether employing the methods of Corey and Venkateswarlu (42) or Chaudhary and Hernandez (72) resulted in reclosure to lactone 118. The alcohol could be benzoylated (benzoyl chloride, pyridine, 0 °C) in 63% yield. The remainder of the material was lactone 118. Obviously, what we needed was a reagent which would react rapidly and quantitatively with alcohol 121 at low temperature. We found this reagent in the silyl perchlorates developed by Barton and Tully (73). Addition of 121 to an acetonitrile solution of tert-butyldimethylsilyl perchlorate and pyridine at 0 °C resulted in quantitative formation of ether 122. By employing this two step procedure, 122 was available in yields greater than 90% from keto lactone 118.



Keto ester 122 was reduced in 80% yield to diol 123 with lithium aluminum hydride. Swern oxidation (74) then furnished keto aldehyde 124, which was cyclized to tricyclic ketol 125 with sodium methoxide in refluxing methanol (32). The ease (30 min at reflux, 63% yield) with which this transformation occurs is in marked contrast to aldolization from the opposite side (vide supra).

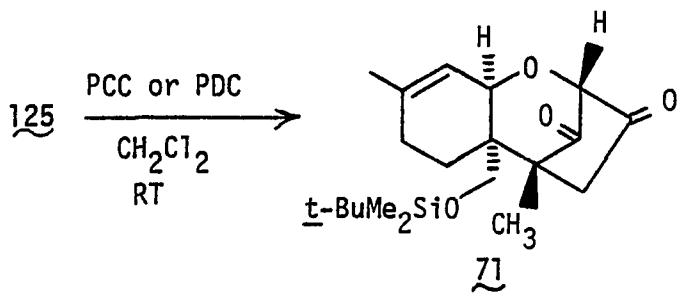


The source of these disparate actions on treatment with base must stem from the conformational preferences of the two regioisomeric aldehydes. Examination of molecular models indicated that the acetaldehyde fragment in aldehyde 124 would assume an axial orientation in order to minimize eclipsing between the quarternary methyl and carbon-7 in the A ring. This is also the conformation most favorable for intramolecular aldolization. In the regioisomeric keto aldehyde (39) no interaction of this sort exists, such that the acetaldehyde fragment rarely (if ever) adopts a position from which intramolecular cyclization can occur. Thus, Colvin, et al. found that they could not form this crucial carbon-carbon bond (29b).

Ketol 125 was formed as a mixture of C-3 epimers which was estimated to be approximately 6:1 by proton NMR. No attempt was made to ascertain which isomer predominated, but the results of Colvin, et al. would indicate

that chelation of the metal counterion in the aldol should favor the production of the exo isomer (29a).

Oxidation of 125 with either pyridinium chlorochromate (75) (PCC) or pyridinium dichromate (76) (PDC) in methylene chloride furnished tricyclic diketone 71, albeit in only 50% yield.



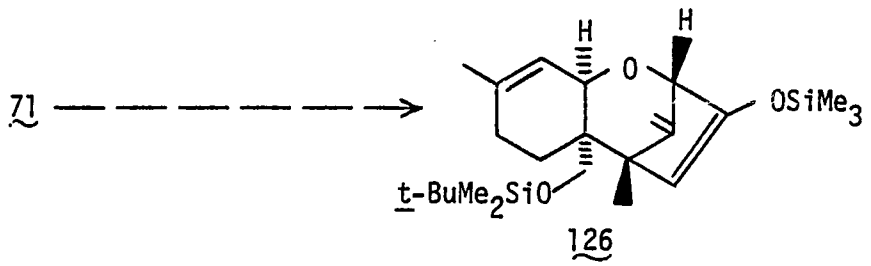
71

Strong support for the identity of diketone 71 is provided by its carbon-13 NMR, which shows the correct number of carbon atoms, two of which appear at 209.983 and 207.577.

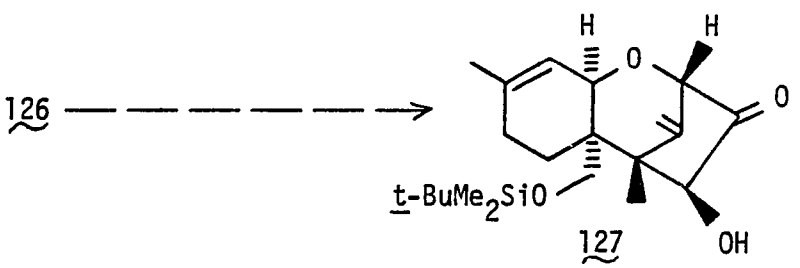
Compounds 125 and 71 possess the correct relative configuration at the four asymmetric centers present in the trichothecene skeleton and represent the first synthesis of a trichothecene possessing oxygen functionality in the C-ring and at C-15 (77, 78).

Diketone 71 should prove to be an especially valuable intermediate for the synthesis of highly oxygenated trichothecenes, in particular, diacetoxyscirpenol (4a) and calonectrin (4b).

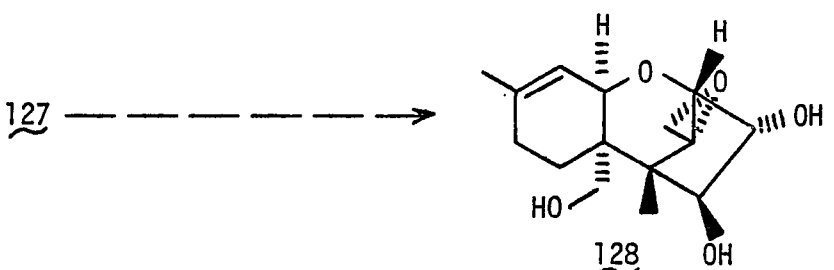
A plausible scheme for the conversion of 71 into these natural products might begin with silyl enol ether formation and olefination. This should furnish triene 126.



Epoxidation should occur selectively from the exo face of the enol ether, affording exo alcohol 127 on basic hydrolysis (79).



Reduction, epoxidation and desilylation should then afford anguidin triol, an immediate precursor to diacetoxyscirpenol. A similar scheme could be employed to synthesize the simpler calonectrin.



In summary, a synthesis of the trichothec-9-ene skeleton, in which the four asymmetric centers present are introduced unambiguously with the correct relative configuration, has been described.

EXPERIMENTAL

General

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Diethyl ether, THF, benzene and toluene were distilled from $LiAlH_4$ prior to usage. Dichloromethane was distilled from P_2O_5. All organic extracts were dried over Na_2SO_4, except where otherwise noted. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were determined on a Beckman IR-4250 spectrometer. Nuclear magnetic resonance spectra were determined on either a Hitachi Perkin-Elmer R-20B 60 MHz or Varian HA-100 instrument. Carbon-13 NMR spectra were determined on a JEOL FX-90Q Fourier Transform Spectrometer. Both proton and carbon chemical shifts are expressed in parts per million down-field from internal tetramethylsilane. High-resolution mass spectra were recorded on an AEI MS-902 high-resolution mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc.

cis-1-(1-tert-Butyldimethylsilyloxymethyl-2-hydroxy-4-methyl-3-cyclohexenyl)-1-ethanone (80)

Boron triacetate (76 g, 405 mmoles) was added in one portion to a rapidly stirred solution of 3-hydroxymethyl-3-buten-2-one (27g, 270 mmoles), 1-acetoxy-3-methyl butadiene (37.8 g, 300 mmoles) and hydroquinone (2 g) in 600 mL of dry toluene cooled to 0 °C. The resulting suspension was stored at 5 °C for two days. The now dark brown suspension

was placed in an ice bath and the catalyst destroyed by slow addition of aqueous bicarbonate with vigorous stirring. When the mixture had assumed a bright yellow-orange color, it was transferred to a separatory funnel and partitioned between water (500 mL) and ether (1 L). The organic layer was washed with water (2 x 200 mL), bicarbonate (2 x 250 mL) and brine (100 mL). The dried solution was filtered and concentrated, affording 46.2 g of a bright orange oil which was estimated to be a 3:1 mixture of compounds 74 and 75 by NMR and TLC data.

After dissolution of the crude mixture of diastereomers in dry N,N-dimethylformamide (100 mL), tert-butyldimethylchlorosilane (46.5 g, 308 mmoles) and imidazole (81.6 g, 1200 mmoles) were added. The mixture was stirred at 45 °C for 4.5 h, and then partitioned between hexanes (600 mL) and water (150 mL). The organic layer was washed with water (100 mL), brine (100 mL) and dried. Removal of the solvents yielded 68 g of silylated material.

The crude mixture of acetates was dissolved in dry methanol (500 mL) and cooled to 0 °C. Potassium carbonate (69 g, 500 mmoles) was added and the mixture was stirred vigorously. When the reaction was judged complete by TLC analysis (4-5 h), it was acidified with 6 N HCl (pH 3) and the methanol was removed under reduced pressure. The residue was taken up in ether (500 mL) and washed with water (150 mL), 1 N HCl (150 mL), bicarbonate (150 mL) and brine (100 mL). The ether layer was dried and the solvents removed. The residue was chromatographed (silica gel, 30:1 hexanes-EtOAc) to afford two major substances: the undesired diastereomer 81, R_f (3:1 hex-EtOAc) = 0.35, 8.3 g (10%): IR (film) 3450, 2960, 2860,

1715, 1255, 1105 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 0.10 (s, 6 H), 0.88 (s, 9 H), 1.68 (br s, 3 H), 1.8-2.0 (m, 4 H), 2.22 (s, 3 H), 2.60 (br s, 1 H, -OH), 3.76, 3.92 (AB quartet, J = 10 Hz, 2 H), 4.58 (m, 1 H), 5.50 (m, 1 H); 90 MHz C-13 NMR ($CDCl_3$) δ -5.72, 18.14, 22.89, 24.00, 25.82, 27.44, 27.77, 55.67, 65.17, 67.70, 123.49, 137.28 and minor isomer 80, 27.4 g (33%): R_f (3:1 hex-EtOAc) = 0.21; IR (film) 3440, 1715 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 0.10 (s, 6 H), 0.88 (s, 9 H), 1.70 (br s, 3 H), 1.97 (br s, 4 H), 2.24 (s, 3 H), 2.67 (d, J = 6 Hz, 1 H, -OH), 3.60, 3.74 (AB quartet, J = 11 Hz, 2 H), 4.16 (m, 1 H), 5.52 (m, 1 H, collapses to d, J = 5 Hz on irradiation at δ 1.70); 90 MHz C-13 NMR ($CDCl_3$) δ 18.141, 22.108, 23.020, 25.816, 27.507, 27.898, 56.250, 65.484, 68.086, 122.906, 137.733, 213.104. High-resolution mass spectrum for $C_{16}H_{30}O_3Si$ requires m/e 298.19643; found m/e 298.19645.

cis-1-(1-tert-Butyldimethylsilyloxymethyl-2-bromoacetyloxy-4-methyl-3-cyclohexenyl)-1-ethanone (83a)

To a 0 °C solution of alcohol 80 (2.25 g, 7.55 mmoles) and dry pyridine (1.45 mL, 18 mmoles) in dichloromethane (11 mL) was added a solution of bromoacetyl bromide (1.43 mL, 15.1 mmoles) in dry THF (13 mL) dropwise over a period of 10 min. The resulting suspension was stirred a further 30 min, and then poured into 200 mL of ether. The organic layer was washed with water (30 mL), 1 N HCl (2 x 20 mL), bicarbonate (2 x 20 mL) and brine (20 mL). The dried solution was filtered and concentrated, affording a quantitative yield of bromoacetate 83a: IR (film) 2980, 2960, 2870, 1740, 1715, 1275, 1105, 835,

770 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 0.10 (s, 6 H), 0.89 (s, 9 H), 1.72 (m, 3 H), 2.0-2.2 (m, 4 H), 2.17 (s, 3 H), 3.43, 3.72 (AB quartet, J = 10 Hz, 2 H), 3.73 (s, 2 H), 5.27 (br d, J = 5 Hz, 1 H), 5.60 (m, 1 H, collapses to d, J = 5 Hz on irradiation at δ 1.72). High-resolution mass spectrum for $C_{14}H_{22}O_4BrSi$ (parent ion-57) requires m/e 361.04707; found m/e 361.04603.

(±)-(4aα, 8aα)-4a-tert-Butyldimethylsilyloxymethyl-4,7-dimethyl-4a,5,6,8a-tetrahydro-2H-1-benzopyran-2-one (84a)

Bromo acetate 83a (1.694 g, 4.04 mmoles) and trimethyl phosphite (1.42 mL, 16 mL) were heated together at 90-95 °C under nitrogen for 12 h. The mixture was cooled to room temperature, and then the excess phosphite was removed under vacuum (approximately 1 mm, 10 h, room temperature), affording the crude phosphonate. High-resolution mass spectrum requires for $C_{20}H_{37}O_7PSi$ m/e 448.20463; found m/e 448.20472.

The crude phosphonate was dissolved in 16 mL of anhyd THF and added dropwise to a suspension of sodium hydride (pentane washed) in 5 mL of anhyd THF at 0 °C under nitrogen. After the completion of hydrogen evolution, the cooling bath was removed and the solution was allowed to warm to room temperature. When all starting material was judged to have been consumed by TLC analysis, the suspension was poured into ice water. The aqueous layer was extracted with ether (3 x 50 mL) and the combined ether layers were washed with water (15 mL) and brine (15 mL). Drying and removing the solvents gave an oil, which was chromatographed (silica gel, 10:1 hex-EtOAc), affording 1.604 g (67%) of a pale yellow oil:

R_f (3:1 hex-EtOAc) = 0.25; IR (film) 2980, 2970, 1725 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 0.10 (s, 6 H), 0.88 (s, 9 H), 1.71 (br s, 3 H), 1.8-1.96 (m, 4 H), 1.90 (d, J = 1.6 Hz, 3 H), 3.57, 3.68 (AB quartet, J = 9.6 Hz, 2 H), 4.94 (m, 1 H), 5.44 (m, 1 H), 5.84 (q, J = 1.6 Hz, 1 H); 90 MHz C-13 NMR δ 18.199, 18.625, 22.878, 25.224, 25.655, 27.268, 42.143, 65.533, 75.919, 119.187, 119.720, 138.800, 160.355, 163.707. High-resolution mass spectrum requires for $C_{18}H_{30}O_3Si$ m/e 322.19643; found m/e 322.19647.

(±)-(4aα, 8aα)-4a-tert-Butyldimethylsilyloxymethyl-4,7-dimethyl-4a,5,6,-8a-tetrahydro-2H-1-benzopyran (85)

Diisobutylaluminum hydride (1.0 M, hexanes) was added portion-wise to a 0.3 M toluene solution of the unsaturated lactone 84a (2.372 g, 7.37 mmoles) cooled to -78 °C (Dry Ice-CH_3OH bath) until TLC analysis judged the reaction complete. It was then poured into a rapidly stirred mixture of ice (25 g) and acetic acid (7 mL). Chloroform (50 mL) was added and the two phase system stirred vigorously for 10 min. Another 100 mL portion of chloroform was added and vigorous stirring continued until two distinct layers formed when stirring was halted (typically 30-60 min). The layers were separated and the organic layer was washed with bicarbonate (2 x 100 mL) and brine (75 mL). The dried solution was filtered and concentrated. The resultant colorless oil was used without purification.

The crude lactol and triethylsilane (1.22 g, 10.5 mmoles) in dichloromethane (25 mL) were cooled to -78 °C under nitrogen. Dropwise addition of boron trifluoride etherate (0.95 mL, 7.7 mmoles) gave a

light brown solution which was stirred a further 15 min, then quenched by addition of approximately 10 mL of aqueous bicarbonate. The cooling bath was removed and the solution was allowed to warm to room temperature with vigorous stirring. After transfer to a separatory funnel, ether (100 mL) was added and the whole washed with bicarbonate (20 mL) and brine (20 mL). Drying and removing the solvents provided a crude yellow oil which was chromatographed (silica gel, 25:1 hex-EtOAc) to yield 85 (1.83 g, 81%) as a coldrless oil: R_f (3:1 hex-EtOAc) = 0.61; IR (film) 2980, 2970, 2870, 1110 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 0.10 (s, 6 H), 0.90 (s, 9 H), 1.7-2.0 (m, 10 H), 3.50, 3.72 (AB quartet, J = 10 Hz), 4.02 (q, J = 2.5 Hz, 2 H), 4.20 (m, 1 H), 5.44 (m, 2 H); 90 MHz C-13 NMR ($CDCl_3$) δ 18.314, 23.135, 25.579, 25.898, 27.523, 41.124, 62.469, 65.511, 70.917, 121.353, 123.412, 134.517, 139.014. High-resolution mass spectrum for $C_{18}H_{32}O_2Si$ requires m/e 308.21717; found m/e 308.21645.

(±)-(4aα, 8aα)-4,7-Dimethyl-4a-hydroxymethyl-4a,5,6,8a-tetrahydro-2H-1-benzopyran (86)

Silyl ether 85 (1.68 g, 5.45 mmoles) and tetra-n-butyl ammonium fluoride (0.75 M THF, 20 mL, 15 mmoles) were combined and stirred two hours at room temperature. The light yellow solution was poured into 75 mL of bicarbonate. The aqueous layer was extracted twice with ether (100 mL) and the combined ether layers were washed with bicarbonate (25 mL) and brine (25 mL). Concentration of the dried solution afforded a light yellow oil which was chromatographed (silica gel, 5:1

hexanes-EtOAc) providing 0.93 g (88%) of alcohol 86 as a colorless oil: R_f (3:1 benzene-acetone) = 0.15; IR (film) 3450, 2980, 1675, 1450, 1115 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 1.7-2.05 (m, 10 H), 2.95 (br s, 1 H, -OH), 3.53, 3.70 (br AB quartet, J = 11 Hz, 2 H), 4.04 (m, 2 H), 4.34 (m, 1 H), 5.35 (m, 1 H), 5.62 (m, 1 H, collapses to t, J = 3 Hz on irradiation at δ 1.702, to br s on irradiation at δ 4.04); 90 MHz C-13 NMR ($CDCl_3$) 17.46, 22.914, 25.865, 26.894, 40.492, 61.837, 68.175, 74.561, 120.779, 125.058, 132.372, 139.631. High-resolution mass spectrum for $C_{12}H_{18}O_2$ requires m/e 194.13068; found m/e 194.13009.

(±)-(3α,4α,4aα,8aα)-4,7-Dimethyl-4a-hydroxymethyl-3,4,4a,5,6,8a-hexahydro-2H-1-benzopyran-3,4-epoxide (87)

tert-Butyl hydroperoxide (0.12 mL, 1.25 mmoles) in 1.25 mL of benzene was dried over sodium sulfate. The resulting clear solution was added to a 0.3 M benzene solution of alcohol 86 (0.202 g, 1.04 mmoles) and hexacarbonyl molybdenum (0.025 g). The whole was refluxed for 1.5 h. The cooled solution was filtered through silica gel (20 g, 5:1 hex-EtOAc as eluent) to provide, in order of elution, 40 mg (20%) of recovered 86 and 0.16 g (73%, 91% based on recovered 86) of epoxide 87 as a colorless oil: R_f (3:1 hex-EtOAc) = 0.10; IR (film) 3450, 1135 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 1.46 (s, 3 H), 1.72 (br s, 3 H), 1.9-2.1 (m, 4 H), 2.50 (br s, 1 H, -OH), 3.04 (d, J = 4 Hz, 1 H), 3.5-3.9 (m, 4 H), 4.14 (dd, J = 4, 13 Hz, 1 H), 5.46 (m, 1 H); 90 MHz C-13 NMR ($CDCl_3$) 19.093, 22.939, 22.048, 27.436, 39.246, 58.694, 61.891,

64.058, 64.383, 68.121, 119.532, 139.252. High-resolution mass spectrum for $C_{11}H_{15}O_2$ (P-31 = loss of CH_3O) requires m/e 179.10721; found m/e 179.10784.

(±)-(4aα, 8aα)-4a-tert-Butyldimethylsilyloxymethyl-4,7β-dimethyl-4a,-5,6,7,8,8a-hexahydro-2H-1-benzopyran-2-one-7α,8α-epoxide (90)

The olefinic lactone 84a (1.3 g, 4.1 mmoles) was dissolved in dichloromethane (10 mL) and meta-chloroperbenzoic acid (1.06 g, 4.9 mmoles of commercial 80%) was added portionwise. The slurry was stirred at ambient temperature for 3 h. It was diluted with ether (150 mL) and was washed with saturated aqueous sodium bicarbonate (10 mL), 10% aqueous sodium bisulfite (10 mL), bicarbonate (10 mL) and brine (10 mL). The dried solution was filtered and concentrated, affording 1.38 g (100%) of epoxide 90 as a colorless oil: IR (film) 2960, 2930, 2860, 1725, 1250, 1100, 830 cm^{-1}; NMR ($CDCl_3$) 0.06 (s, 6 H), 0.90 (s, 9 H), 1.32 (s, 3 H), 1.4-1.8 (m, 7 H), 1.96 (d, J = 1.5 Hz, 3 H), 3.07 (s, 1 H), 3.58 (s, 2 H), 4.67 (s, 1 H), 6.02 (q, J = 1.5 Hz, 1 H).

(±)-(4aα, 8aα)-4a-tert-Butyldimethylsilyloxymethyl-4,7β-dimethyl-2α,β-methoxy-4a,5,6,7,8,8a-hexahydro-2H-1-benzopyran-7α,8α-epoxide (91)

Diisobutylaluminum hydride (4.4 mL of a commercial 1.0 M hexanes solution) was added dropwise to a -78 °C toluene (12 mL) solution of lactone 90 (1.38 g, 4.1 mmoles) under nitrogen. When the reaction was judged complete by thin-layer chromatography (approximately 1 h),

it was poured into a rapidly stirred slurry of ice (10 g) and acetic acid (5 mL). Chloroform (50 mL) was added and the rapid stirring was continued until both layers had clarified (2 h). The layers were separated. The organic layer was washed with saturated aqueous sodium bicarbonate (3 x 10 mL) and brine (10 mL). The dried solution was filtered and concentrated. The residue was dissolved in anhyd tetrahydrofuran (10 mL). Methanol (0.6 mL) and p-toluenesulfonic acid (20 mg) were added and the solution was stirred at ambient temperature for 2 h. It was then diluted with ether (100 mL) and washed with half-saturated brine (10 mL). The dried solution was filtered and concentrated. The residue was chromatographed on silica gel (hexanes-ethyl acetate), furnishing 594 mg (42%) of 91 as a colorless oil: IR (film) 2960, 2930, 2860, 1250, 1220, 1100, 830, 770 cm^{-1}; NMR ($CDCl_3$) δ 0.06 (s, 6 H), 0.90 (s, 9 H), 1.30 (s, 3 H), 1.4-1.8 (m, 7 H), 3.23 (s, H), 3.52 (s, 3 H), 4.24 (s, 1 H), 4.85 (m, 1 H), 5.68 (m, 1 H).

(±)-(4aα, 8aα)-4a-tert-Butyldimethylsilyloxymethyl-4,7β-dimethyl-4a,5,-6,7,8,8a-hexahydro-2H-1-benzopyran-7α,8α-epoxide (92)

Boron trifluoride etherate (0.07 mL, 0.56 mmoles) was added dropwise to a -78 °C solution of acetal 91 (180 mg, 0.51 mmoles) and triethylsilane (90 mg, 0.765 mmoles) in dichloromethane (2 mL). The solution was stirred at -78 °C for 15 min, quenched by addition of saturated aqueous bicarbonate and warmed to ambient temperature. The two phase mixture was extracted with ether (2 x 50 mL) and the

combined ether layers were washed with bicarbonate (10 mL) and brine (10 mL). The dried solution was filtered and concentrated. The residue was chromatographed (silica gel, hexanes-ethyl acetate), providing 150 mg (91%) of ether 92 as a colorless oil: IR (film) 2960, 2930, 2860, 1250, 1100 cm^{-1}; 100 MHz NMR ($CDCl_3$) 0.06 (s, 6 H), 0.89 (s, 9 H), 1.28 (s, 3 H), 1.5-1.9 (m, 7 H), 2.99 (s, 1 H), 3.50 and 3.62 (AB quartet, J = 9 Hz, 2 H), 4.1 (m, 3 H), 5.58 (m, 1 H); 90 MHz C-13 NMR ($CDCl_3$) δ 18.368, 21.239, 22.268, 25.898, 26.440, 40.474, 58.622, 61.385, 61.764, 66.908, 69.725, 124.170, 132.675. High-resolution mass spectrum for $C_{14}H_{23}O_3Si$ (P-57) requires m/e 267.14165; found m/e 267.13989.

Attempted Rearrangement of Epoxide 88 with Boron Trifluoride Etherate

Boron trifluoride etherate (0.04 mL, 0.31 mmoles) was added to a solution of epoxide 88 (70 mg, 0.28 mmoles) in 1 mL of toluene cooled to -25 °C. The resulting light brown solution was stirred at -25 °C for 30 min, 0 °C for 1 h, and at ambient temperature for 1.5 h. It was then quenched by addition of saturated aqueous sodium bicarbonate solution (5 mL). Ether was added (20 mL) and the layers were separated. The organic layer was washed with bicarbonate (10 mL), water (10 mL), and brine (10 mL). The dried solution was filtered and concentrated. This afforded an intractible gum which thin-layer chromatography showed to be a mixture of many components.

Attempted Rearrangement of Epoxide 88 with Lithium Perchlorate

A solution of epoxide 88 (81 mg, 0.32 mmoles) and anhyd lithium perchlorate (38 mg, 0.35 mmoles) in 2 mL of dry benzene was refluxed for 2 h. The cooled solution was diluted with ether (50 mL) and the combined organic material was washed with water (5 mL) and brine (5 mL). The dried solution was filtered and concentrated. This furnished 80 mg of recovered 88. There was no hint of any other products by NMR or thin-layer chromatography.

Attempted Rearrangement of Epoxide 88 with Sodium Iodide

A solution of epoxide 88 (82 mg, 0.32 mmoles), ethyl iodide (0.13 mL, 1.6 mmoles), and sodium iodide (240 mg, 1.6 mmoles) in anhyd dimethylsulfoxide (5 mL) was heated at 80 ^{o}C for 3 h. The cooled solution was diluted with water (10 mL) and extracted with ether (3 x 50 mL). The combined ether layers were washed with water (2 x 10 mL) and brine (2 x 10 mL). Concentration of the dried and filtered solution afforded 75 mg of recovered 88. No other products were evidenced by NMR or thin-layer chromatography of the crude reaction product.

Attempted Rearrangement of Epoxide 89 with Tin Tetrachloride

Tin tetrachloride (0.025 mL, 0.21 mmoles) was added dropwise to a solution of the epoxide 89 (35 mg, 0.106 mmoles) in 2 mL of toluene cooled to 0 ^{o}C. Within 10 min, thin-layer chromatography evidenced several spots, such that the mixture was quenched by addition of

bicarbonate. Ether was added. The organic layer was washed with water (5 mL) and brine (5 mL). The dried solution was filtered and chromatographed. Examination of the NMR spectra of the crude product indicated that the major product was aldehyde 93. This was evidenced by the characteristic singlets at δ 1.25 (3 H) and 9.85 (1 H). No spectral peaks (IR, NMR) characteristic of the desired ketone could be found.

Rearrangement of Epoxide 89

The epoxide 89 (70 mg, 0.21 mmoles) was heated in 4 mL of anhyd toluene containing 190 mg (0.85 mmoles) of anhyd zinc bromide at a temperature of 80 ^{o}C for 3 h. The cooled solution was diluted with ether (100 mL) and washed with water (10 mL) and brine. The dried solution was filtered and concentrated. Examination of the 60 MHz NMR of the crude product demonstrated that it was almost entirely the aldehyde 93: NMR ($CDCl_3$) δ 1.25 (s, 3 H), 1.6-2.2 (m, 7 H), 3.87 (s, 2 H), 4.0-4.3 (m, 5 H), 5.55 (m, 1 H), 9.85 (s, 1 H).

(±)-(4aα, 8aα)-3,4-Dihydroxy-4,7-dimethyl-4a-acetoxymethyl-3,4,4a,5,-6,8a-hexahydro-2H-1-benzopyran (94)

The epoxide 88 (60 mg, 0.24 mmoles) was refluxed in 5 mL of 4:1 THF-water, containing 5 drops of 6 N $HClO_4$, for 4 h. The cooled solution was diluted with ether (100 mL) and then washed with water (10 mL) and brine (10 mL). The dried (Na_2SO_4) solution was filtered and concentrated. Examination of the residue proved that it consisted

entirely of diol 94: IR (film) 3450, 2970, 2940, 2850, 1720, 1280, 1130 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 1.41 (s, 3 H), 1.68 (br s, 3 H), 1.9-2.2 (m, 4 H), 2.06 (s, 3 H), 2.84 (br s, 2 H, -OH), 3.24 (m, 1 H), 3.6-4.4 (m, 6 H), 5.48 (m, 1 H).

Attempted Oxidation of Diol 94

Silver carbonate on Celite

A suspension of 1.7 g (3 mmoles) of the silver carbonate-Celite reagent and 45 mg (0.15 mmoles) of diol 94 were refluxed in toluene (10 mL) with azeotropic removal of water (Dean-Stark trap). Filtration and removal of the solvent furnished unchanged 94 after 12 h at reflux.

Dimethylsulfoxide-acetic anhydride

Acetic anhydride (0.3 mL) was added dropwise to a solution of 94 (40 mg, 0.135 mmoles) in 0.5 mL of dimethylsulfoxide. The resulting solution was stirred at ambient temperature for 12 h without showing any change by thin-layer chromatography.

N-Bromosuccinimide

N-Bromosuccinimide (27 mg, 0.15 mmoles) and diol 94 (20 mg, 0.074 mmoles) were mixed together in 2 mL of 10% aqueous dioxane at room temperature. After it had been stirred for 1 h, the solution was diluted with ether (150 mL). The organic material was washed with water (3 x 10 mL), 10% aqueous sodium bisulfite solution (10 mL), water (10 mL) and brine (10 mL). Filtration and concentration of the

dried solution afforded a light yellow oil which proved to be 1 spot by thin-layer chromatography. Examination of the NMR of the crude reaction product evidenced the loss of the C-9, C-10 olefin. A possible explanation for this would be bromohydrin formation: 100 MHz NMR ($CDCl_3$) δ 1.35 (two S, 3 H total), 1.54 (s, 3 H), 1.7-2.0 (m, 4 H), 2.16 (s, 3 H), 3.76 (s, 2 H), 3.8-4.5 (m, 5 H).

(±)-(4aα, 8aα)-4a-tert-Butyldimethylsilyloxymethyl-4,7-dimethyl-4a,5,-6,8a-tetrahydro-2H-1-benzopyran-2-one-3-carbonitrile (84b)

Cyanoacetyl chloride (15.53 g, 150 mmoles) in 50 mL of anhyd ether was added dropwise to a rapidly stirred solution of alcohol (80) (17.9 g, 60 mmoles) and pyridine (14.54 mL, 180 mmoles) in dichloromethane (120 mL) cooled to 0 ^{o}C under nitrogen. The mixture was stirred 15 min beyond the completion of addition, and then poured into 1 L of ether. The organic layer was washed consecutively with water (2 x 100 mL), 1 N HCl (2 x 100 mL), 1:1 bicarbonate-brine (2 x 100 mL) and slightly acidic brine (100 mL). The dried solution was poured through a pad of 1:1 Celite(filter aid)-silica gel (50 gm) and the solvents were then removed to afford pure cyanoester 83b (22 g, 100%).

The cyanoacetate (20.2 g, 80 mmoles) and 1,5-diazobicyclo[4.3.0]-non-5-ene (1.0 mL, 8 mmoles) were heated to reflux in benzene (150 mL) with azeotropic removal of water. After 30 min, the solution was cooled, diluted with ether (500 mL) and washed with 1 N HCl (2 x 300 mL), bicarbonate (2 x 300 mL) and slightly acidic brine (100 mL).

Filtration and concentration of the dried solution gave a crude solid which was recrystallized from 50:1 hex-EtOAc yielding 18.15 g (52.3 mmoles) of light yellow crystals (mp 145-6 ^{o}C). Chromatography (SiO_2, 10:1 hex-EtOAc) of the mother liquors afforded a further 2.81 g (7.7 mmoles) of crystals (60 mmoles total, 75%): IR (film) 2980, 2240, 1735, 840 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 0.10 (s, 6 H), 0.88 (s, 9 H), 1.74 (br s, 3 H), 1.9-2.1 (m, 4 H), 2.37 (s, 3 H), 3.68, 3.86 (AB quartet, $\underline{J}$ = 11 Hz, 2 H), 4.97 (m, 1 H), 5.43 (m, 1 H); 90 MHz C-13 NMR ($CDCl_3$) 17.948, 18.598, 22.630, 25.231, 26.857, 43.830, 65.865, 76.510, 108.081, 113.283, 118.486, 140.011, 158.48, 174.998. Anal. calcd. for $C_{19}H_{29}NO_3Si$: C, 65.71; H, 8.36. Found C, 65.79; H, 8.28.

(±)-(4aα, 8aα)-4a-<u>tert</u>-Butyldimethylsilyloxymethyl-4,7-dimethyl-4a,5,-6,8a-tetrahydro-2H-1-benzopyran-3-carbonitrile (<u>95</u>)

Diisobutyl aluminum hydride (21.7 mL of a 1.0 M hexane solution) was added dropwise to a stirred solution of lactone (6.85 g, 19.74 mmoles) <u>84b</u> in 85 mL of toluene cooled to -78 ^{o}C under nitrogen. The light brown solution was stirred a further 60 min after addition was complete, and then poured into a rapidly stirred mixture of acetic acid (25 mL) and ice (100 g). Chloroform (500 mL) was added, followed by 1 N HCl (100 mL). Stirring was continued until both layers clarified (2-3 h). The layers were separated and the organic layer was washed with 1 N HCl (100 mL), bicarbonate (2 x 100 mL), and brine (100 mL). The dried solution was filtered through a pad of 1:1 silica gel-Celite (50 g) and the solvents removed under reduced pressure.

The crude lactols were dissolved in dichloromethane (60 mL) and cooled to -78 ^{o}C under nitrogen. Triethylsilane (3.40 g, 29 mmoles) was added, followed by dropwise addition of boron trifluoride-etherate (2.64 mL, 21.5 mmoles). The reaction mixture was stirred for 15 min beyond the completion of addition, and then bicarbonate (25 mL) was added with vigorous stirring and the cooling bath was removed. On attainment of room temperature, the two phase system was poured into ether (300 mL) and the organic layer was washed with bicarbonate (50 mL) and brine (50 mL). The dried solution was filtered and concentrated. This provided a crude yellow oil, which was chromatographed (silica gel, 25:1 hex-EtOAc) to provide two major products, nitrile 95 (4.27 g, 65%); R_f (4:1 hex-EtOAc) = 0.50, mp 75-6 ^{o}C from hexanes: IR (film) 2980, 2880, 2205, 1120 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 0.10 (s, 6 H), 0.91 (s, 9 H), 1.72 (br s, 3 H), 1.8-2.0 (m, 4 H), 2.07 (t, J = 2 Hz, 3 H), 3.57, 3.70 (AB quartet, J = 10 Hz, 2 H), 4.16 (m, 3 H), 5.44 (m, 1 H). High-resolution mass spectrum for $C_{15}H_{22}O_2NSi$ (P-57 = 276) requires m/e 276.14103; found m/e 276.14199, and aldehyde 96 (0.91 g, 9.3%), R_f (4:1 hex-EtOAc) = 0.40 as a colorless oil: IR (film) 2950, 2920, 2850, 2740, 1708, 1655, 1240, 1090, 825 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 0.10 (s, 6 H), 0.90 (s, 9 H), 1.73 (br s, 3 H), 1.9 (m, 4 H), 2.23 (t, J = 1.5 Hz, 3 H), 3.63, 3.78 (AB quartet, J = 11 Hz, 2 H), 4.12 (br s, 1 H, collapses to d, J = 3 Hz on irradiation at δ 1.73), 4.27 (m, 2 H, collapses to AB quartet, 4.20, 4.36, J = 16 Hz on irradiation at δ 2.23), 5.46 (br s, 1 H, collapses to d, J = 3 H on irradiation at δ 1.73), 10.10

(s, 1 H); 90 MHz C-13 NMR ($CDCl_3$) δ -5.656, 11.901, 18.144, 23.086, 25.167, 25.752, 27.378, 42.855, 61.908, 64.835, 71.142, 120.499, 134.22, 139.293, 156.590, 189.495. High-resolution mass spectrum for $C_{19}H_{32}O_3Si$ requires m/e 336.21208; found m/e 336.21201.

(±)-(4aα, 8aα)-4a-tert-Butyldimethylsilyloxymethyl-4,7-dimethyl-4a,5,-6,8a-tetrahydro-2H-1-benzopyran-3-carboxaldehyde (96)

To a 0.3 M toluene solution of nitrile 95 (2.98 g, 8.95 mmoles) cooled to -78 °C under nitrogen was added 9.0 mL of a 1.0 M hexanes solution of diisobutyl aluminum hydride. Thirty minutes after addition was complete, the solution was poured into a rapidly stirred slurry of acetic acid (10 mL) and ice (25 g). Chloroform (200 mL) and 1 N HCl (25 mL) were added and vigorous stirring continued until both layers clarified. The layers were separated and the organic layer was washed with bicarbonate (50 mL) and brine (50 mL). Drying and removing the solvents afforded 2.82 g of aldehyde 96 as a colorless oil which was used without purification. (94% from nitrile 95, 70% overall from lactone 84b.)

(±)-(4aα, 8aα)-4a-tert-Butyldimethylsilyloxymethyl-4,7-dimethyl-4a,5,-6,8a-tetrahydro-2H-1-benzopyran-3-carboxylic acid (97)

A solution of sodium chlorite (1.41 g of commercial 85%, 12.5 mmoles) in 10 mL of NaH_2PO_4 pH 3.5 buffer was added dropwise to a rapidly stirred solution of aldehyde 96 (3.36 g, 10 mmoles) and 2-methyl-2-butene (10.6 mL, 100 mmoles) in 50 mL of tert-butanol at room

temperature. The resulting light yellow solution was stirred 8 h at ambient temperature. It was made basic with 6 N NaOH (pH 10) and the tert-butanol removed at reduced pressure. The residue was dissolved in water and was extracted twice with hexanes. The water layer was acidified (6 N HCl, pH 3) and extracted twice with ether (100 mL). The organic layer was washed with water (25 mL) and brine (25 mL). Concentration of the dried organic layer furnished a colorless solid which was recrystallized from hexanes to provide 2.5 g of colorless plates (mp 143-5 ^{o}C). Chromatography (silica gel, 5:1 hex-EtOAc) provided a further 0.35 g of crystals (2.85 g total, 80%): IR (film) 3400, 2970, 1700 cm^{-1}; 100 MHz NMR ($CDCl_3$) 0.10 (s, 6 H), 0.91 (s, 9 H), 1.72 (br s, 3 H), 1.8-2.0 (m, 4 H), 2.17 (t, J = 2 Hz, 3 H), 3.56, 3.78 (AB quartet, J = 11 Hz, 2 H), 4.22 (br s, 1 H, collapses to d, J = 4 Hz on irradiation at 1.73), 4.32 (m, 2 H), 5.46 (br s, 1 H, collapses to d, J = 4 Hz on irradiation at δ 1.73), 7.2 (br s, 1 H, -OH). Anal. calcd. for $C_{19}H_{32}O_4Si$: C, 64.77; H, 9.09. Found: C, 64.90; H, 9.20.

(±)-(4aα, 8aα)-4a-tert-Butyldimethylsilyloxymethyl-4,7-dimethyl-4a,5,-6,8a-tetrahydro-2H-1-benzopyran-3(4H)-one (98a)

Ethyl chloroformate (neat, 0.5 mL, 5.2 mmoles) was added to a 0 ^{o}C THF (10 mL) solution of acid 97 (1.3 g, 3.95 mmoles) and triethyl amine (0.66 mL, 4.75 mmoles) under nitrogen. The resulting suspension was stirred 60 min, and then sodium azide (0.51 g, 8.0 mmoles) in 3 mL of water was added dropwise. The initially homogeneous solution was

stirred 3 h at 0 °C, before being partitioned between toluene (50 mL) and water. The organic layer was washed with water (10 mL), brine (10 mL) and dried briefly over $MgSO_4$.

The filtered solution was concentrated to approximately 25 mL and heated at reflux for 30 min to effect rearrangement to the isocyanate. The toluene was removed under reduced pressure and replaced with 20 mL of THF. NaOH (5 mL of 1 N) was added and the two-phase system stirred vigorously for 2 h. After cooling to 0 °C, 6 N HCl was added to pH 3 and stirring continued a further 2 h. The inhomogeneous mixture was poured into ether (100 mL) and the organic material was washed with bicarbonate (15 mL), water (10 mL) and brine. Filtration and concentration of the organic layer afforded a crude yellow oil, which was chromatographed (silica gel, 20:1 hex-EtOAc) to provide 0.79 g (62%) of ketone 98a as a mixture of diastereomers. R_f (3:1 hex-EtOAc) minor isomer = 0.60, major = 0.55: IR (film) 2950, 2860, 1730, 1095 cm^{-1}; 100 MHz NMR ($CDCl_3$) (major isomer) δ 0.10 (s, 6 H), 0.89 (s, 9 H), 1.13 (d, J = 7 Hz, 3 H), 1.7-2.0 (m, 7 H), 2.52 (q, J = 7 Hz, 1 H), 3.34, 3.48 (AB quartet, J = 10 Hz, 2 H), 3.9-4.1 (m, 3 H), 5.55 (m, 1 H); 90 MHz C-13 NMR ($CDCl_3$) -5.787, 6.698, 18.143, 23.411, 25.752, 26.922, 28.483, 43.505, 47.277, 64.250, 73.355, 74.256, 120.697, 138.841, 211.546. High-resolution mass spectrum for $C_{14}H_{23}O_3Si$ (loss of C_4H_9) requires m/e 267.14165; found m/e 267.14106.

(±)-(4aα, 8aα)-4,7-Dimethyl-4a-hydroxymethyl-4a,5,6,8a-tetrahydro-2H-1-benzopyran-3(4H)-one (72)

The silyl ether 98a (0.56 g, 1.73 mmoles) and tetra-n-butyl ammonium fluoride (4.7 mL of an 0.75 M THF solution, 3.5 mmoles) were stirred at room temperature for 2 h. The light yellow solution was poured into ether (100 mL) and washed with bicarbonate (15 mL) and brine (10 mL). Concentration of the dried solution provided a light yellow oil which was chromatographed (silica gel, 5:1 hex-EtOAc) to provide 0.308 g (85%) of alcohol 72 as a colorless oil: R_f (3:1 benzene-acetone) = 0.27; IR (film) 3450, 1720, 1090 cm^{-1}; 100 MHz NMR ($CDCl_3$) (major isomer) δ 1.16 (d, J = 7 Hz, 3 H), 1.5-2.2 (m, 7 H), 2.60 (q, J = 7 Hz, 1 H), 3.55 (m, 2 H), 4.0 (m, 2 H), 4.26 (br s, 1 H), 5.52 (br s, 1 H). High-resolution mass spectrum for $C_{12}H_{18}O_3$ requires m/e 210.12560; found m/e 210.12605.

(±)-(4aα, 7α, 8aβ)-4,7-Dimethyl-4a,7-ethano-4a,7,8,8a-tetrahydro-2H,-5H-pyrano[4,3-b]pyran-3(4H)-one (99)

Phenylselenyl chloride (0.086 g, 0.56 mmoles) in dichloromethane (1.0 mL) was added dropwise to a solution of keto alcohol 72 in dichloromethane (2.0 mL) cooled to -78 °C under nitrogen. At the completion of addition, the cooling bath was removed and the light orange solution allowed to warm to room temperature. Removal of solvents and chromatography (silica gel, 10:1 hex-EtOAc) afforded the crude selenide which was dissolved in toluene (5 mL) and heated to reflux

with tri-n-butyltin hydride (0.22 mL, 0.82 mmoles) and a catalytic amount of azo-bis-isobutyryl nitrile. After 60 min, the solution was cooled to room temperature. Concentration and chromatography (silica gel, 10:1 hex-EtOAc) provided ether 99 as a colorless oil. R_t = 9.38 min (175 °C, isothermal, 6 ft x ¼ in, 5% SE 30 capillary column gas chromatograph): IR (film) 2960, 1725, 1150 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 0.98 (d, J = 7 Hz, 3 H), 1.14 (s, 3 H), 1.3-1.8 (m, 6 H), 2.30 (q, J = 7 Hz, 1 H), 3.60 (m, 1 H), 4.1 (m, 4 H). High-resolution mass spectrum for $C_{12}H_{18}O_3$ requires m/e 210.12560; found m/e 210.12685.

2-Methyl-2-(1-bromo-2-ethoxy-2-ethyl)-1-cyclohexanone (101)

To a solution of bromoacetaldehyde diethyl acetal (0.75 mL, 5 mmoles) and titanium tetrachloride (0.55 mL, 5 mmoles) in dichloromethane (20 mL) cooled to -78 °C under nitrogen was added 2-methyl-1-trimethylsilyloxy-1-cyclohexene 66 (920 mg) in dichloromethane (5 mL). The resulting bright red solution was stirred two hours. Water was added (1 mL), followed by 10% aqueous potassium carbonate (1 mL). After it was warmed to ambient temperature, the mixture was poured into ether (100 mL) and the organic material was washed with water (10 mL) and brine (10 mL). The dried (Na_2SO_4) solution was filtered and the solvents were removed at reduced pressure. The residue was subjected to rapid column chromatography (hexanes-ethyl acetate, silica gel), affording 608 mg (2.5 mmoles, 50%) of 101 as a colorless oil: IR (film) 2980, 2940, 2855, 1715, 1100 cm^{-1}; NMR ($CDCl_3$) δ 1.08 (s, 3 H), 1.20 (t, J = 7 Hz, 3 H), 1.7-2.5 (m, 8 H), 3.2-4.1 (m, 5 H).

3-Methyl-3-(2-methoxymethyloxy-1-thiobutyl-2-ethyl)-2-oxo-1-cyclohexane Carboxylic Acid, Methyl Ester (103)

To a -78 °C solution of lithium diisopropylamide (2.1 mmoles) in 3 mL of anhyd tetrahydrofuran (THF) was added 2-carbomethoxy-6-methylcyclohexanone (170 mg, 1.0 mmole) in 1 mL of THF. After 20 min, n-butyl thioacetaldehyde (132 mg, 1.0 mmole) was added as a 1.0 M THF solution. After 10 min, the solution was poured into NH_4Cl/NH_4OH pH 7 buffer solution (10 mL). The aqueous layer was extracted with ether (3 x 25 mL) and the combined ether layers were washed with water (10 mL) and brine (10 mL). The dried solution was filtered and the solvents were removed at reduced pressure. The residue was dissolved in anhyd dichloromethane (2 mL). Diisopropylethylamine (0.26 mL, 1.5 mmoles) and chloromethyl methyl ether (0.11 mL, 1.5 mmoles) were added. The solution was stirred for 3 h. It was poured into ether (100 mL) and the ether layer was washed with water (10 mL) and brine (10 mL). The dried (Na_2SO_4) solution was concentrated and the residue chromatographed on silica gel (hexanes-ethyl acetate), affording 270 mg (78%) of 103 as a colorless oil: IR (film) 2950, 2870, 1740, 1715, 1650, 1620, 1450, 1020 cm^{-1}; NMR ($CDCl_3$) 0.8-1.2 (m, 3 H), 1.3 (s, 3 H), 1.3-2.7 (m, 15 H), 3.35 and 3.40 (two s, 3 H total), 3.72 (s, 3 H), 4.7 (m, 3 H).

2-Methyl-2-(2-methoxymethyloxy-1-thiobutyl-2-ethyl)cyclohexan-1-one (102)

A mixture of 103 (314 mg, 0.91 mmoles) and Dabco (1,4-diazabicyclo[2.2.2]octane, 610 mg, 5.45 mmoles) were stirred together in

refluxing xylenes until thin-layer chromatography evidenced that all starting material had been consumed. Concentration and silica gel chromatography afforded 102 (130 mg, 45%) as a mixture of diastereomers: IR (film) 2950, 2860, 1715, 1050 cm^{-1}; NMR ($CDCl_3$) (major) 0.9-1.1 (m, 3 H), 1.17 (s, 3 H), 1.3-2.0 (m, 10 H), 2.4-2.9 (m, 6 H), 3.33 (s, 3 H), 4.22 (m, 1 H), 4.54 and 4.98 (AB, J = 7 Hz, 2 H).

2-(2-Methyl-cyclohexan-1-one) Acetic Acid, Ethyl Ester (104)

Methyl lithium (0.69 mL of a commercial 1.45 M ether solution) was added to a 0.5 M ether solution of 2-methyl-1-trimethylsilyloxy-1-cyclohexene (184 mg, 1.0 mmole) at room temperature under nitrogen. The resulting solution was stirred for 60 min, and then the ether was removed under vacuum. The flask was pressurized with nitrogen and dry 1,2-dimethoxyethane (2 mL) was added. The suspension was cooled to 0 ^{o}C and ethyl iodoacetate (280 mg, 1.3 mmoles) in 1.0 mL of 1,2-dimethoxyethane was added all at once. When the vigorous reaction had subsided, the suspension was poured into ice-water. The aqueous layer was extracted with ether (3 x 50 mL) and the combined ether layers were washed with water (10 mL) and brine (10 mL). The dried solution was filtered and the filtrate was concentrated. The residue was purified by bulb to bulb distillation, affording 101 mg (50%) of 104 as a colorless oil (bp 105-110 ^{o}C/1 mm Hg, lit. (68) bp 59-61 ^{o}C/0.1 mm Hg).

3-Ethoxy-3aα-methyl-2,3,3a,4,5,6-hexahydro-benzofuran (106)

Ketone 101 (205 mg, 0.83 mmoles) in benzene (1 mL) was added dropwise to a suspension of potassium tert-butoxide/tert-butanol (1:1 complex) in benzene (2 mL) at room temperature. This mixture was stirred at that temperature for 25 min, and then acidified with ice cold 1 N HCl. It was poured into ether (100 mL) and the organic layer was washed with water (10 mL) and brine (10 mL). The dried solution was filtered and concentrated, affording 106 as the sole product: IR (film) 2980, 2935, 2885, 1695, 1380, 1110, 1005 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 1.13 (s, 3 H), 1.18 (t, 3 H), 1.4-2.2 (m, 6 H), 3.4-4.2 (m, 4 H), 4.68 (m, 1 H).

3-Methoxymethyl-3aα-methyl-2,3,3a,4,5,6-hexahydro-benzofuran-7-carboxylic Acid, Methyl Ester (108)

Methyl iodide (0.065 mL, 1.0 mmole) was added to a solution of 103 (350 mg, 1 mmole) in nitromethane at room temperature. The solution was stirred at ambient temperature for 12 h and then the solvent was removed under reduced pressure. The crude sulfonium salt was dissolved in methanol and magnesium methoxide (2.6 mL of a 0.42 M solution) was added dropwise. The solution was stirred at ambient temperature for 5 h, and then it was acidified with 1 N HCl. The methanol was removed under reduced pressure and the residue was partitioned between ether (100 mL) and water (10 mL). The aqueous layer was extracted with ether (2 x 25 mL) and the combined ether layers were washed with water (10 mL) and brine (10 mL). The dried (Na_2SO_4) solution was filtered and concentrated.

The residue was chromatographed (silica gel, hexanes-ethyl acetate), providing 150 mg (59%) of enol ether 108 as a colorless oil: IR (film) 2950, 1720, 1680, 1440, 1050 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 1.20 (s, 3 H), 1.55 (dt, J = 3, 1 Hz, 1 H), 1.7-1.9 (m, 2 H), 1.97 (dt, J = 1, 3.5 Hz, 1 H), 2.33 (m, 2 H), 3.38 (s, 3 H), 3.74 (s, 3 H), 3.96 (d, J = 3 Hz, 1 H), 4.35 (d, J = 11 Hz, 1 H), 4.54 (dd, J = 11, 3 Hz, 1 H), 4.60 (d, J = 7 Hz, 1 H), 4.67 (d, J = 7 Hz, 1 H).

1-Hydroxy-3-methyl-bicyclo[3.2.1]octan-8-one (113)

Ozone was passed through a gas dispersion tube into a 0.1 M methylene chloride (CH_2Cl_2) solution of 2-allyl-2-methyl-1-cyclohexanone (400 mg, 2.63 mmoles) cooled to -78 °C. When the solution had assumed a bright blue color, the stream of ozone was replaced by a stream of nitrogen until the solution was colorless. Triphenylphosphine (690 mg, 2.63 mmoles) was added and the solution was allowed to warm to ambient temperature overnight. The solution was diluted with a large volume of hexanes and filtered. Removal of the solvents afforded the crude keto aldehyde (105), which was immediately subjected to sodium methoxide (1.3 mL of a 2.0 M solution) in refluxing methanol (5 mL). After it was refluxed for 30 min, the solution was acidified with dilute HCl and the methanol was removed at reduced pressure. The residue was partitioned between ether (100 mL) and water (10 mL). The organic layer was washed with water (5 mL) and brine (5 mL). The dried solution was filtered and concentrated. Chromatography (silica gel, hexanes-ethyl acetate) afforded 220 mg (55%) of ketol 113 as a colorless oil:

IR (film) 3450, 2980, 2870, 1760 cm^{-1}; NMR ($CDCl_3$) 1.04 and 1.08 (two s, 3 H total), 1.3-2.6 (m, 9 H), 3.3 (br s, 1 H, -OH), 4.3 (m, 1 H).

3-Methyl-bicyclo[3.2.1]octan-1,8-dione (114)

Ketol 113 (82 mg, 0.53 mmoles) in dry toluene (1 mL) was added dropwise to a suspension of N-chlorosuccinimide (107 mg, 0.8 mmoles) and dimethyl sulfide (0.08 mL, 1 mmole) in dry toluene (3 mL) cooled to -25 °C (Dry Ice-carbon tetrachloride bath). The resulting solution was stirred 2 h at that temperature and then triethyl amine (0.11 mL, 0.80 mmoles) in 0.5 mL of dry toluene was added. The cooling bath was removed and the solution was allowed to warm to ambient temperature. It was diluted with ether (150 mL) and the organic material was washed with 0.1 M HCl (5 mL), water (10 mL), and brine (10 mL). Chromatography afforded 70 mg (85%) of 114 as a colorless oil which solidified on standing: IR (film) 1760, 1740, 1200 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 1.22 (s, 3 H), 1.7-2.3 (m, 6 H), 2.38 (dd, J = 18, 1.5 Hz, 2 H, C-2 exo hydrogen), 2.70 (d, J = 18 Hz, C-2 endo hydrogen), 2.77 (m, 1H); 90 MHz C-13 NMR ($CDCl_3$) δ 18.661, 18.857, 36.742, 43.570, 50.072, 50.918, 59.372, 209.788, 216.096.

(±)-(4aα,8aα)-4a-tert-Butyldimethylsilyloxymethyl-4,7-dimethyl-3-trimethylsilyloxy-4a,5,6,8a-tetrahydro-2H-1-benzopyran (115)

Iodotrimethylsilane (0.08 mL, 0.55 mmoles) was added dropwise to a solution of hexamethyldisilazane (0.13 mL, 0.60 mmoles) and 98a (160 mg, 0.50 mmoles) in dichloromethane (CH_2Cl_2) cooled to -25 °C

under nitrogen. The resulting solution was stirred for 20 min at -25 °C and 4 h at ambient temperature. It was then partitioned between hexanes (75 mL) and aqueous sodium bicarbonate (25 mL). The organic layer was washed with saturated aqueous bicarbonate (10 mL) and brine (10 mL). The dried solution (Na_2SO_4) was filtered and concentrated, furnishing the crude mixture of silyl enol ethers. (An approximately 95:5 mixture of 115 and 116 by gas chromatography on a 30 M by 0.25 mm SEC capillary column, 175 °C): 100 MHz NMR ($CDCl_3$) δ 0.10 (s, 6 H, 0.16 (s, 9 H), 0.92 (s, 9 H), 1.58 (t, J = 2 Hz, 3 H), 1.68 (br s, 3 H), 1.7-2.0 (m, 4 H), 3.48, 3.70 (AB q, J = 10 Hz, 2 H), 3.84 (m, 2 H), 4.28 (m, 1 H), 5.36 (m, 1 H).

(±)-(4aα,8aα)-4,7-Dimethyl-4a-hydroxymethyl-4a,5,6,8a-tetrahydro-2H-1-benzopyran-3(4H)-one, Bromoacetate (98b)

Bromoacetyl bromide (0.78 mL, 9 mmoles) was added dropwise to a rapidly stirred, 0 °C solution of alcohol 72 (757 mg, 3.6 mmoles) and pyridine (1.02 mL, 12.6 mmoles) in dichloromethane (10 mL). The resulting suspension was stirred at 0 °C for 20 min and poured into ether (200 mL). The ether layer was washed with water (2 x 25 mL), 1 N HCl (25 mL), saturated aqueous sodium bicarbonate (2 x 15 mL), and brine (15 mL). The dried solution was filtered and concentrated. The residue was chromatographed (silica gel, hexanes-ethyl acetate), affording 1.01 g (85%) of 98b as a colorless oil: IR (film) 2980, 2950, 2880, 1760 (sh), 1740, 1725, 1275, 1155 cm^{-1}; 100 MHz NMR ($CDCl_3$) 1.05

(d, J = 7 Hz, 3 H), 1.6-2.1 (m, 7 H), 2.65 (q, J = 7 Hz, 1 H), 3.77 (s, 2 H), 3.8-4.3 (m, 5 H), 5.53 (m, 1 H).

(±)-(4aα,8aα)-4α-Acetic acid-4β,7-dimethyl-4a-hydroxymethyl-4a,5,6,8a-tetrahydro-2H-1-benzopyran-4(4H)-one, δ-lactone (118)

Iodotrimethylsilane (0.52 mL, 3.65 mmoles) was added dropwise to a solution of hexamethyldisilazane (1.01 mL, 4.79 mmoles) and bromoacetate 98b (1.27 g, 3.84 mmoles) in dichloromethane (40 mL) cooled to -25 °C under nitrogen. The resulting solution was stirred for 50 min at that temperature. It was then partitioned between hexanes (150 mL) and saturated aqueous sodium bicarbonate (20 mL). The organic layer was washed with bicarbonate (2 x 10 mL) and brine (20 mL). The dried solution was filtered and concentrated. The residue (consisting primarily of silyl enol ether 117) was used without purification: 100 MHz NMR ($CDCl_3$) δ 0.2 (s, 9 H), 1.61 (t, J = 1.5 Hz, 3 H), 1.68 (br s, 3 H), 1.7-1.9 (m, 4 H), 3.82 (s, 2 H), 3.87 (m, 2 H, collapses to AB q, δ 3.78, 3.94, J = 16 Hz), 4.2 (m, 3 H), 5.36 (m, 1 H); IR (film) 2960, 2900, 2840, 1740, 1695, 1685, 1250, 1110, 1090, 840 cm^{-1}.

The crude silyl enol ether 117 (3.8 mmoles) in 4 mL of anhyd tetrahydrofuran (THF) was added dropwise to a -78 °C THF (40 mL) solution of tetra-n-butylammonium fluoride (4.2 mL of a 1.0 M THF solution). The resulting solution was stirred for 15 min at -78 °C, after which the cooling bath was removed. After stirring at ambient temperature for 10 h, the solution was poured into ether (200 mL). It was washed with saturated aqueous sodium bicarbonate (2 x 25 mL) and brine (25 mL).

The dried solution was filtered and concentrated. Chromatography of the residue afforded 430 mg (47%) of lactone 118 as a colorless oil which solidified on standing. Recrystallization from ether furnished colorless crystals (mp 102-3 °C): IR (film) 2960, 2850, 1755, 1725, 1450, 1385, 1100, 735 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 1.37 (s, 3 H), 1.80 (br s, 3 H), 2.1 (m, 4 H), 2.28 and 3.14 (AB q, J = 16 Hz, 2 H), 3.55 (m, 1 H, collapses to d, J = 5 Hz on irradiation at δ 1.80), 3.84 and 3.94 (AB q, J = 12 Hz, 2 H), 4.13 and 4.43 (AB q, J = 18 Hz, 2 H), 5.51 (m, 1 H, collapses to d, J = 5 Hz on irradiation at δ 1.80); 90 MHz C-13 NMR ($CDCl_3$) δ 21.913, 22.565, 23.215, 26.597, 36.222, 40.839, 49.226, 69.516, 73.158, 74.718, 118.224, 140.530, 171.550, 211.999. High-resolution mass spectrum for $C_{14}H_{18}O_4$ requires m/e 250.12167; found m/e 250.12051.

(±)-(4aα,8aα)-4a-tert-Butyldimethylsilyloxymethyl-4α-acetic acid-4β,7-dimethyl-4a,5,6,8a-tetrahydro-2H-1-benzopyran-3(4H)-one, Methyl Ester (122)

Lithium hydroxide-monohydrate (135 mg, 3.21 mmoles) was added to a solution of keto-lactone 118 (267 mg, 1.07 mmoles) in 5 mL of 4:1 THF-water at room temperature. The two-phase system was stirred vigorously at ambient temperature for 30 min and then cooled to 0 °C. It was acidified (pH 5) with ice-cold saturated aqueous NaH_2PO_4 (pH 3.5) buffer, followed by addition of diazomethane (17.5 mL of an 0.2 M ether solution). When gas evolution had subsided, the mixture was partitioned between ether (100 mL) and water (20 mL). The layers were separated and the organic layer was washed with water (15 mL) and brine (15 mL). The

dried solution was filtered and concentrated. The crude hydroxy-ester 121 was dissolved in dry acetonitrile (3 mL) and added dropwise to a stirred solution of pyridine (0.25 mL, 3 mmoles) and tert-butyldimethylsilyl perchlorate (freshly prepared, 574 mg, 2.67 mmoles) in 3 mL of dry acetonitrile cooled to 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 1.5 h and at ambient temperature for 2 h. The solution was poured into hexanes (150 mL) and the hexanes suspension was washed with saturated aqueous sodium bicarbonate (3 x 15 mL) and brine (10 mL). The dried solution was filtered and concentrated. The residue was chromatographed (silica gel, hexanes-ethyl acetate), affording 390 mg (91%) of keto-ester 122 as a colorless oil: R_f = 0.48 (3:1 hexanes-ethyl acetate); IR (film) 2960, 2930, 2860, 1740, 1725, 1470, 1255, 1110, 840 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 0.10 (s, 6 H), 0.90 (s, 9 H), 1.37 (s, 3 H), 1.7-2.0 (m, 7 H), 2.68 and 3.26 (AB q, J = 14 Hz, 2 H), 3.54 (s, 2 H), 3.63 (s, 3 H), 4.02 (m, 1 H), 4.11 (s, 2 H), 5.45 (m, 1 H); 90 MHz C-13 NMR ($CDCl_3$) δ -5.911, 17.756, 23.220, 23.545, 25.561, 26.602, 39.218, 43.835, 51.313, 51.638, 63.343, 70.301, 71.732, 119.855, 138.974, 172.400, 211.994.

(±)-(4aα,8aα)-4a-tert-Butyldimethylsilyloxymethyl-4α-[1-(2-hydroxyethyl)]-4β,7-dimethyl-3-hydroxy-3,4,4a,5,6,8a-hexahydro-2H-1-benzopyran (123)

Keto ester 122 (125 mg, 0.315 mmoles) in ether (2 mL) was added dropwise to a suspension of lithium aluminum hydride (60 mg, 1.58 mmoles) in ether (3 mL) at ambient temperature. The mixture was stirred for 2 d at that temperature, and then water (3 drops) was added (causing

vigorous gas evolution). When the gas evolution was complete, 15% aqueous NaOH (3 drops) was added, followed by addition of 9 drops of water. The slurry was stirred vigorously until the aluminum salts solidified and separated. Ether was added (25 mL) and the mixture was filtered through Celite (filter aid). After a thorough washing of the aluminum salts with ether, the combined ether layers were dried, filtered, and concentrated. The residue crystallized on standing and was recrystallized from chloroform, furnishing 90 mg (83%) of diol 123 as colorless crystals (mp 145-7 °C): IR (Nujol) 3430, 2970, 2890, 1255, 840, 775 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 0.10 (s, 6 H), 0.94 (s, 9 H), 1.25 (s, 3 H), 1.73 (br s, 3 H), 1.8-2.2 (m, 6 H), 3.4-4.1 (m, 10 H), 5.49 (m, 1 H). High-resolution mass spectrum for $C_{16}H_{29}O_4$ (p-57) requires m/e 313.18403; found m/e 313.18352.

(±)-(4aα,8aα)-4a-tert-butyldimethylsilyloxymethyl-4α-ethanol-4β,7-dimethyl-4a,5,6,8a-tetrahydro-2H-1-benzopyran-3(4H)-one (124)

Dimethyl sulfoxide (0.10 mL, 1.36 mmoles) was added dropwise to a solution of oxalyl chloride (0.06 mL, 0.68 mmoles) in dichloromethane (2 mL) cooled to -60 °C. After 3 min, diol 123 (106 mg, 0.31 mmoles) in dichloromethane (2 mL) was added dropwise. The mixture was stirred for 16 min and then triethylamine (0.43 mL, 3.1 mmoles) in dichloromethane (0.5 mL) was added slowly. The resulting suspension was stirred for 5 min at -60 °C and 30 min at room temperature. Water (5 mL) was added with vigorous stirring and, after 1 min, the mixture was partitioned between ether (150 mL) and water (25 mL). The organic

layer was washed with water (10 mL), 1 N HCl (10 mL), and brine (10 mL). The dried solution was filtered and concentrated. Examination of the infrared and 100 MHz NMR spectra of the crude residue indicated that it was a mixture of keto-aldehyde 124 and the hydrated form: IR (film) 3430, 2960, 2930, 2860, 1730, 1715, 1255, 1080, 990, 830 cm^{-1}.

3α,β-Hydroxy-15-tert-butyldimethylsilyloxy-13-nor-trichothec-9-en-12-one (125)

Keto aldehyde 124 (110 mg, 0.32 mmoles) in 3 mL of dry methanol was refluxed with sodium methoxide (0.2 mL of a 2 M solution) for 1 h. The cooled solution was acidified (pH 5) and the solvent was removed at reduced pressure. Water (10 mL) was added and the mixture was extracted with ether (2 x 60 mL). The combined ether layers were washed with water (10 mL) and brine (10 mL). The dried solution was filtered and concentrated. The residue was chromatographed (silica gel-ethyl acetate), furnishing 70 mg (63%) of tricyclic ketol 125 as a colorless oil: IR (film) 3420, 2960, 2940, 2870, 1760, 1260, 1095, 830 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 0.10 (s, 6 H), 0.93 (s, 9 H), 1.18 (s, 3 H), 1.3-2.1 (m, 9 H), 3.2-3.7 (m, 4 H), 4.06 (d, J = 5 Hz, 1 H), 4.34 (m, 1 H), 5.50 (m, 1 H).

15-tert-Butyldimethylsilyloxy-13-nor-trichothec-9-en-3,12-dione (126)

The ketol 125 (45 mg, 0.133 mmoles) was dissolved in dichloromethane (1 mL) and added rapidly to a stirred solution of pyridinium chlorochromate (43 mg, 0.2 mmoles) in 1 mL of dichloromethane at room

temperature. After the suspension was stirred at ambient temperature for 5 h, it was diluted with ether and filtered through Florisil. Concentration of the filtrate afforded 23 mg (50%) of diketone 126 as a colorless oil: IR (film) 2975, 2930, 2860, 1777, 1743, 1460, 1255, 1090, 840, 775 cm^{-1}; 100 MHz NMR ($CDCl_3$) δ 0.06 (s, 6 H), 0.93 (s, 9 H), 1.30 (s, 3 H), 1.66 (br s, 3 H), 1.8-2.1 (m, 4 H), 2.30 (d, $\underline{J}$ = 20 Hz, 1 H), 3.54 (br s, 1 H), 3.66 (br s, 2 H), 3.86 (d, $\underline{J}$ = 20 Hz, 1 H), 4.40 (d, $\underline{J}$ = 6 Hz, 1 H), 5.51 (m, 1 H); 90 MHz C-13 NMR ($CDCl_3$) δ -5.786, 13.787, 18.076, 21.328, 23.085, 25.817, 27.898, 29.653, 50.202, 50.658, 63.273, 69.256, 77.385, 118.094, 141.570, 207.577, 209.983.

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OVERALL SUMMARY

Part I describes the successful total synthesis of the antifungal antibiotic kalafungin and a close analogue, 9-deoxykalafungin. The key step, in which all of the carbon atoms present in the target molecules were assembled, is the addition of 2-tert-butoxyfuran to either 2-acetyl-1,4-naphthoquinone or 2-acetyl-8-methoxy-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 afforded intermediate naphthydroquinone dimethyl ethers, which were oxidized to the target molecules with argentic oxide.

Part II describes the first successful total synthesis of the trichothec-9-ene skeleton containing oxygenation at both carbon-15 and in the C-ring. The four asymmetric centers present were introduced unambiguously with the correct relative configuration. The synthesis began with a Lewis acid catalyzed Diels-Alder reaction between 1-acetoxy-3-methyl butadiene and 3-hydroxymethyl-3-buten-2-one. The major product from this reaction had the desired stereochemistry at carbons 6 and 11, resulting from cis-endo addition. The thermal reaction afforded the diastereomeric acetoxyketone as the major product. The adduct from the former reaction was transformed to a bicyclic lactone by an intramolecular Knoevenagel condensation. This lactone could be converted into the desired keto-alcohol by reduction of the lactone and nitrile followed by an oxidation and Curtius degradation. Desilylation furnished an alcohol, which was reprotected as the bromoacetate. The third asymmetric center

was introduced via an intramolecular alkylation of the regiodefined silyl enol ether of the ketone with the proximate haloester. The δ-lactone produced was transformed to an aldehyde, which underwent intramolecular aldolization to introduce the final asymmetric center. Oxidation of the resulting ketol afforded 15-tert-butyldimethylsilyloxy-13-nortrichothec-9-ene-3,12-dione.

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