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REGIOSPECIFIC SYNTHESIS OF MONO- AND BICYCLIC 6-ALKOXY-2-PYRONES AND THEIR USE IN THE PREPARATION OF SUBSTITUTED AROMATICS, ANTHRAQUINONES, AND TETRACYCLIC INTERMEDIATES FOR 11-DEOXYANTHRACYCLINE SYNTHESIS

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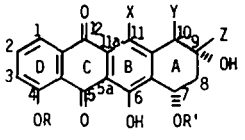
Abstract—Several mono- and bicyclic 6-methoxy-2-pyrones having substituents at C4 and C5 can be prepared regiospecifically by either of two routes: (1) regiospecific construction of a glutaconic half-ester followed by dehydrative cyclization, and (2) regiospecific Friedel–Crafts acylation of 6-methoxy-2-pyrones at C5. These pyrones undergo clean and regiospecific Diels–Alder cycloadditions with various unsymmetrical dienophiles, e.g., quinones, unsaturated esters, etc, with subsequent loss of carbon dioxide. In this manner several polycyclic aromatic natural products have been prepared such as chrysophanol, helminthosporin, pachybasin, 2-acetylemodin and the purported structure for orientalone. The utility of this approach for the synthesis of the anthracyclines is demonstrated by its use in the preparation of various tetracyclic intermediates for anthracycline synthesis.

SEVERAL anthracycline antitumor agents, e.g., adriamycin **1** and daunorubicin **2**, are extensively used today in cancer chemotherapy.[6] Their use in cancer treatment is limited by their severe cumulative cardiotoxicity.[6] In the past few years, several 11-



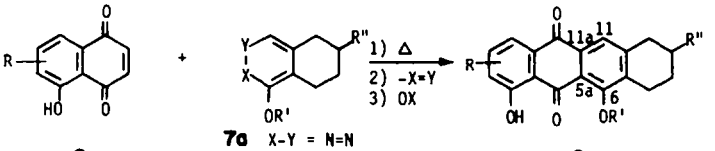
1 R = Me; X = OH; Y = H; Z = $COCH_2OH$; R' = daunosamine
2 R = Me; X = OH; Y = H; Z = $COCH_3$; R' = daunosamine
3 R = H; X = H; Y = COOMe; Z = Et;
R' = rhodosamine—2-deoxyfucose—cinerulose A
4 R = H; X = H; Y = COOMe; Z = Et; (1-OH instead of H)
R' = rhodosamine—2-deoxyfucose—2-deoxyfucose
5 R = H; X = H; Y = COOMe; Z = Et; R' = H

deoxyanthracyclines have been isolated, e.g., aclacinomycin A **3** and marcellomycin **4**, which possess good tumor-inhibitory properties and more importantly, exhibit much lower cardiotoxicity.[7] The synthesis of this group of compounds has been an active area of research for some time and five syntheses of aklavinone **5**, the aglycone of aclacinomycin A, have recently been described.[8] Several years ago we began a program aimed at developing new approaches for the synthesis of this class of molecules and their analogues. We now report the full details of this work.[9]

RESULTS AND DISCUSSION

General approach

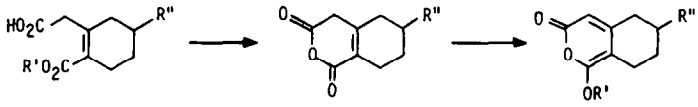
Our general strategy was to develop a convergent approach in which the C5a—C6 and C11—C11a bonds would be formed in the key molecular construction step. Thus the CD-ring precursor **6** would be any of the readily available mono- or dihydroxynaphthoquinones, all of which are known. The AB-ring synthon **7** could be any of several molecules—pyridazine **7a**, pyrones **7bc**, and dihydrobenzenes **7d**—all of which could form an aromatic B ring by thermal elimination of the X = Y fragment. Final oxidation of the hydroquinone would then give **8**. This approach would be expected to provide mainly the desired 4,6-dihydroxyanthraquinone isomer in the reaction with juglone (**6**, R = H) since regioselectivity is well known in Diels–Alder reactions with juglone.[10] Although 3-methoxy-[11a] and 3-hydroxypyrones[11b] **7b** were known to undergo Diels–Alder cycloadditions with high regioselectivity as were dihydroanisole derivatives **7d**,[11c] these were rejected as candidates for **7** because of the probable difficulty associated with preparing the bicyclic systems necessary for **7**. The inability to effect a cycloaddition between benzoquinone and 3,6-dimethoxypyridazine[12] led us to abandon **7a** as the AB



6 + **7** → **8**

7a X-Y = N=N
7b X-Y = CO-O
7c X-Y = O-CO
7d X-Y = CH_2-CH_2

component. Therefore we chose to investigate the use of 6-alkoxy-2-pyrones such as **7c** as AB ring precursors in a Diels–Alder approach to the anthracyclines. These compounds should be easily prepared by cyclization of substituted glutaconic acids or esters to the desired pyrones, perhaps via the corresponding anhydrides. We decided to examine the monocyclic system **9** as a model for the bicyclic unit **7c**.



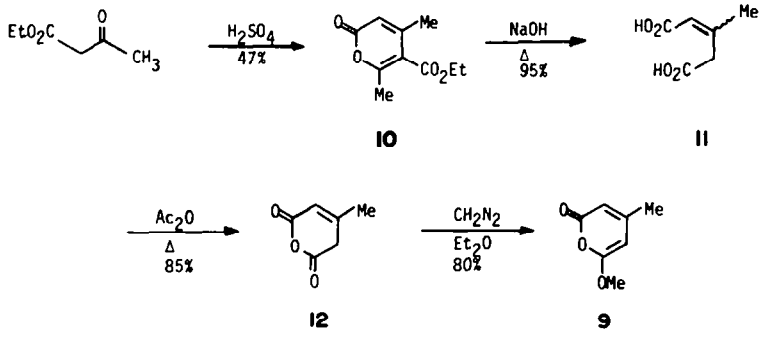
Monocyclic systems

Acid-catalyzed dimerization of ethyl acetoacetate gave in fair yield (47%) ethyl isodehydroacetate **10** which was hydrolyzed and deacetylated to give 3-methylglutaconic acid **11** in 95% yield. Dehydrative cyclization with acetyl chloride or acetic anhydride provided an 85% yield of the crystalline anhydride **12**. Since 6-hydroxy-2-pyrone is formally a tautomer of this anhydride, we attempted to carry out Diels–Alder reactions with quinones directly on **12** but these proved completely unsuccessful. Trapping of **12** in the hydroxy-pyrone form was easily effected by reaction with ethereal diazomethane to give the desired 6-methoxy-4-methyl-2-pyrone **9** in 80% yield. Thus **9** is available from ethyl acetoacetate in about 30% overall yield.

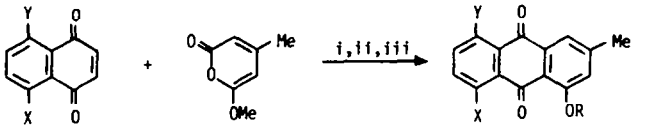
The pyrone **9** reacted readily with quinones to form several natural products. Diels–Alder addition to naphthoquinone **13c** followed by oxidation (Ag_2O—$MgSO_4$) and demethylation (48% HBr—HOAc) furnished pachybasin **14c**[13] in 64% overall yield. The regiochemical outcome of this cycloaddition approach was determined by the Diels–Alder reaction of **9** with juglone **13a** which, after oxidation and demethylation, gave a 62% overall yield of chrysophanol **14a**, identified as its diacetate by m.p.[14] and NMR spectroscopy.[15] Although regioselectivity is well known in Diels–Alder reactions of juglone,[10] the absence of the undesired isomer was significant since regiospecificity of this type is important for the synthesis of aklavinone. However, reaction of **9** with juglone acetate **13d** followed by oxidation and acetate hydrolysis (2M NaOH) furnished a *ca* 1 : 1 mixture of the two possible adducts, ziganein methyl ether **14d**[16] and chrysophanol methyl ether **14e** in low yield (13.5%). Finally, as a model for the pyrromycinone class of the anthracycline antibiotics (e.g., cinerubin) which have an additional 1-hydroxyl group, Diels–Alder reaction with naphthazarin **13b** and subsequent oxidation and demethylation afforded a 38% overall yield of helminthosporin, **14b**.[17] Thus the pyrone **9**, the monocyclic analogue of **7c**, reacts well with quinone dienophiles and, most importantly, completely regiospecifically with juglone.

Bicyclic systems

In order to apply this general method to the synthesis of 11-deoxyanthracyclines, it was now necessary to prepare a bicyclic pyrone such as **7c**. We first attempted this by a simple application of the chemistry described above. The preparation of 6-methoxy-4-methyl-2-pyrone **9** was greatly simplified by the fact that due to



10 **11** **12** **9**

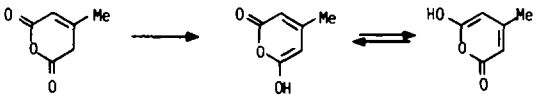


13 **9** **14**

a; X = OH, Y = H
b; X = Y = OH
c; X = Y = H
d; X = H, Y = OAc

a; X = OH, Y = H, R = H (62%)
b; X = Y = OH, R = H (38%)
c; X = Y = H, R = H (64%)
d; X = H, Y = OH, R = Me } (13.5%)
e; X = OH, Y = H, R = Me }

Reagents: i, heat ($-CO_2$); ii, Ag_2O-$MgSO_4$; iii, (for 14a-c), 48% HBr-HOAc; iii (for 14de), 2M NaOH

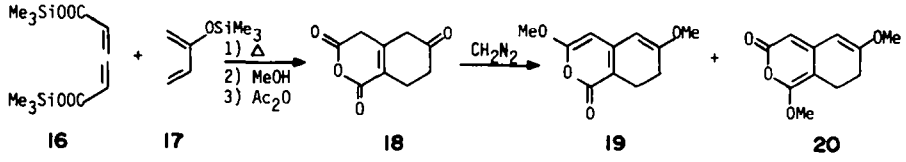


12 15

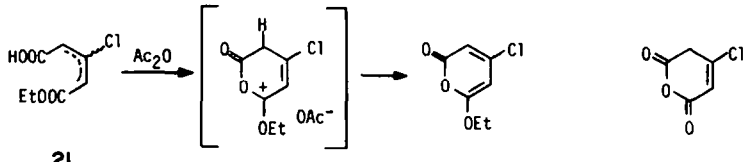
symmetry there was only one hydroxypyrone tautomer **15** of the anhydride **12**, thus producing only one possible product upon O-methylation. However, the corresponding anhydride **18**—prepared from bis(trimethylsilyl) allenedicarboxylate **16** and 2-[(trimethylsilyl)oxy]butadiene **17**[18] by cycloaddition, hydrolysis, and cyclization—no longer possesses this symmetry element and thus can and does afford two regioisomers upon O-methylation with diazomethane. Unfortunately the undesired isomer **19** is the major isomer of a 2:1 mixture, the formation of **20** being unfavorable perhaps due to increased steric hindrance in the O-methylation to produce this isomer.

deethylation which would have furnished the anhydride **24**.

Therefore the problem of the production of molecules such as **7c**, e.g. **26a,b,c**, was reduced to the problem of preparing a specific half-acid half-ester, e.g., **25a,b,c**. A fairly direct route to the ketal **25a** might begin with the readily available methyl 2,4-dihydroxybenzoate. Catalytic hydrogenation of this ester in basic methanolic solution gave a 30% yield of the diketo ester **27**[20] which was ketalized selectively to give the monoketal **28** in 48% yield. However, we were unable to add a two-carbon fragment to the ketone of **28**, e.g., carboethoxymethylenetriphenylphosphorane or the dianion of mono-*t*-butyl malonate.[21] Also the possibility of adding a two-carbon nucleophile to a β-halo or β-acetoxy α,β-unsaturated ester corresponding to **28** to give **25a** by addition-elimination was thwarted by our inability to convert the β-keto ester **28** into the necessary β-substituted α,β-unsaturated ester (using



16 17 18 19 20



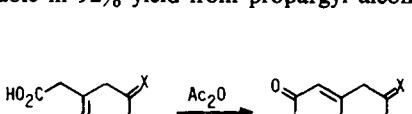
21 22 23 24

Regiospecific pyrone syntheses

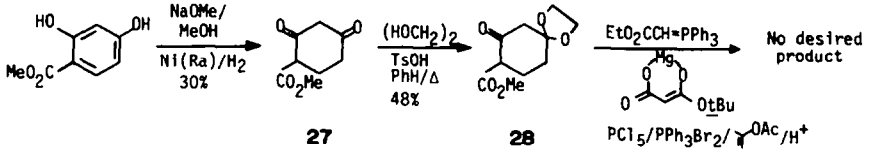
Thus we were forced to develop a new procedure for the synthesis of substituted 6-alkoxy-2-pyrones which would be regiospecific. Two potential approaches seemed promising, namely: (1) the cyclization of a specific glutaconic half-ester under dehydration conditions, and (2) the regiospecific Friedel–Crafts alkylation of a 6-alkoxy-4-alkyl-2-pyrone at only the 5-position. Both of these routes for the regiospecific synthesis of substituted 6-alkoxy-2-pyrone proved successful.

(*a*) *Glutaconic half-ester dehydration.* The general principal of the first approach, glutaconic half-ester dehydration, was tested on the isomeric mixture of β-chloroglutaconic acid monoethyl ester **21**, produced in fair yield by treating diethyl acetonedicarboxylate with PCl_5.[19] When **21** was refluxed in acetic anhydride or acetyl chloride, 4-chloro-6-ethoxy-2-pyrone **23** was produced as the predominant product. Thus, the presumed intermediate **22** (or its double-bond isomer) undergoes loss of H^+ to give **23** rather than triphenylphosphine dibromide, phosphorus pentachloride, or isopropenyl acetate and *p*-toluenesulfonic acid). Thus approaches using **28** were abandoned.

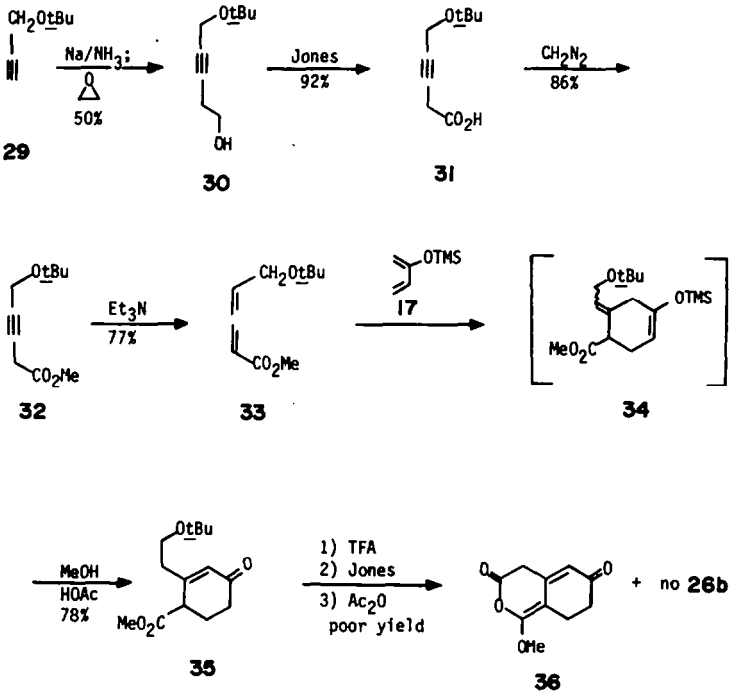
The approach which eventually proved successful involved the preparation of an unsymmetric 1,3-disubstituted allene, such as a 3-alkoxymethyl-1-carboalkoxyallene, which could be used as the dienophile in a Diels–Alder approach to the desired glutaconic half-esters **25**. We chose the ketone **25b** as our initial target, a poor choice as it turned out. Hydroxyethylation of *tert*-butyl propargyl ether **29** (available in 92% yield from propargyl alcohol and



25a X = OCH_2CH_2O **26a**
25b X = O **26b**
25c X = H, OAc **26c**

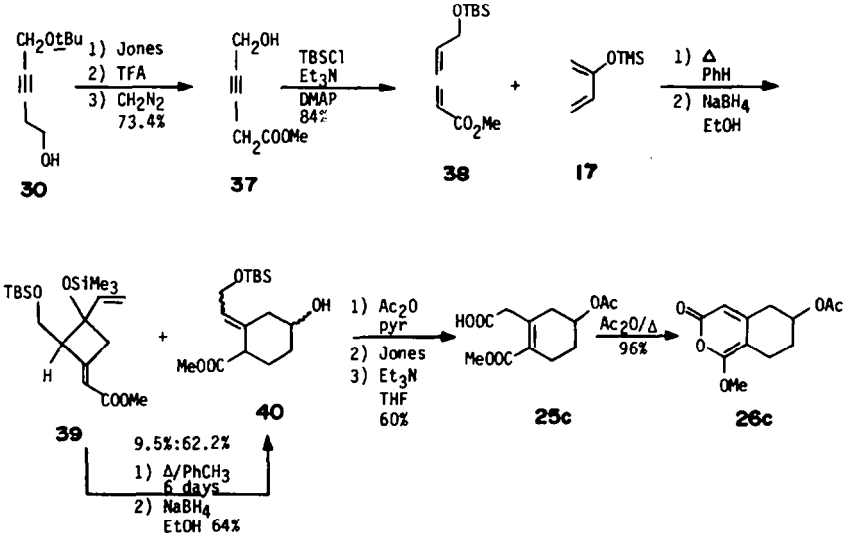


27 28



isobutylene) afforded in 50% yield the alcohol **30**. Jones oxidation of **30** produced a 92% yield of the acid **31** which was esterified with diazomethane to give the ester **32** in 86% yield. Conversion of the β,γ-acetylenic ester **32** to the allenic ester **33** was easily effected (77%) by treatment with a small amount of triethylamine. Diels–Alder cycloaddition of **33** with the silyloxydiene **17** gave an excellent yield of the cycloadduct **34** which was hydrolyzed directly to the enone **35** in 78% yield. The presence of a singlet at 5.88 δ in the ^{1}H-NMR of **35** shows clearly that the exocyclic double bond in **34** had moved into conjugation with the ketone and not with the ester as desired. However, it was still possible that this isomer might be taken onto the double bond isomer of **25b** and thence into **26b**. Thus **35** was treated sequentially with trifluoroacetic acid (to hydrolyze the *t*-butyl ether), Jones reagent (to oxidize the resultant primary alcohol), and finally acetic anhydride (to effect dehydrative cyclization). This treatment resulted in the loss of most of the material (perhaps via decarboxylation of the vinylogous β-keto acid) and produced none of the desired pyrone **26b**. A compound could be isolated in very poor yield (~5%) and has been assigned structure **36** based on its spectroscopic data. Thus it was decided to modify this route by masking the ketone functionality as an acetate, an approach which proved quite successful.

The pentynol **30** was oxidized to the acid **31** which was treated with trifluoroacetic acid to remove the *t*-butyl ether and then esterified with diazomethane to give the hydroxy ester **37** in an overall yield of 73.4%. Upon silylation of the alcohol of **37** with *tert*-butyldimethylsilyl chloride in triethylamine/methylene chloride with catalytic 4-(dimethylamino)pyridine (DMAP), the β,γ-acetylenic ester was completely converted into the allenic ester **38**. Cycloaddition of **38**

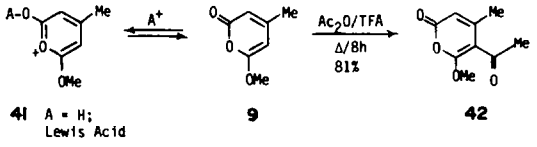


with the silyloxy diene **17** followed by direct reduction with sodium borohydride in ethanol afforded a mixture of two products with the desired cyclohexanol **40** forming the major component. The cyclobutane **39**[22] could be converted into the desired **40** by extended heating in toluene followed by reduction, thus raising the yield of **40** to over 68%. The ester **40** was converted into the desired glutaconic half-acid half-ester **25c** by initial acetylation (quantitative yield) followed by direct oxidation of the *tert*-butyldimethylsilyl ether to the acid with Jones reagent and a final treatment with base to move the double bond into the ring.[23] We were now prepared to effect the key transformation of this approach, namely the regiospecific dehydrative cyclization. Cyclization of the ester acid **25c** by the method described above for the preparation of **21**, namely, refluxing acetic anhydride for 3 hr, gave a 96% crude yield of the pyrone **26c** which could be recrystallized from ether (89%; m.p. 106–107°). Thus the specific bicyclic 6-methoxy-2-pyrone **26** is available from **30** in over 10% yield. This method of dehydrative cyclization of glutaconic half-esters is a general regiospecific route to substituted 6-alkoxy-2-pyrones.

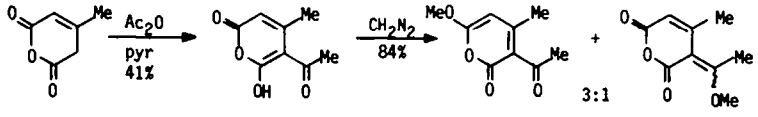
(*b*) *Friedel–Crafts acylation of 6-alkoxy-2-pyrones.* As a second method for the preparation of specific 4,5-disubstituted 6-alkoxypyrones, we decided to investigate the Friedel–Crafts acylation of pyrones such as **9**. We reasoned that substitution should occur at C5 rather than at C3 because of the much higher electron density at C5 than at C3 (see ^{13}C-NMR data in Table 1). However, it was questionable whether any Friedel–Crafts reactions of pyrones would occur since one might expect the pyrone to be transformed completely into a 2,6-dioxygenated pyrylium salt **41** in the presence of strong electrophiles or Lewis acids and thereby rendered inert to eletrophilic substitution.[24] In the event, when the crystalline pyrone **9** was treated with 1.2 eq of acetic anhydride in refluxing trifluoroacetic acid (TFA) for 8 hr, the desired 5-acetylpyrone **42** was produced in 81% yield. Presumably the protonation of the carbonyl oxygen of the pyrone **9** to give the corresponding hydroxypyrylium salt **41** (A = H) is reversible and thus some of the free pyrone is always available for substitution. It was determined that the product has structure **42**, namely that substitution had occurred at C5, rather than at the alternate electrophilic center C3 to give **43**, by both spectroscopic and chemical evidence. In the ^{13}NMR spectra (Table 1), the signal corresponding to C5 in **9** has moved downfield by 29 ppm in **42** while the signal for C3 has experienced a downfield shift of only about 9 ppm, indicating that substitution had occurred at C5. We decided to prepare the opposite 3-acetyl isomer **43** by another route for comparison. As we had shown in the bicyclic pyrone series described earlier, methylation of a glutaconic anhydride provides mainly the less-hindered 6-methoxy-2-pyrone. Thus, it was not surprising that treatment of 3-acetyl-4-methyl-2-pyrone **44**, prepared by acetylation of **12** in fair yield,[25] with diazomethane produced the 3-acetyl pyrone **43** as the major product, along with a minor byproduct assigned structure **43'**. The ^{13}C-NMR of **43** has a signal at about 87 ppm, corresponding to C5 (Table 1).

Thus, Friedel–Crafts acylations of 6-alkoxy-2-pyrones cannot only be carried out but proceed regiospecifically giving only substitution at C5. The anhydride **12** can therefore be converted regiospecifically into either the 5-acetyl **42** or 3-acetyl isomer **43** by first treating with diazomethane and then acetic anhydride or the reverse set of steps.

With the desired 4,5-disubstituted 6-alkoxy-2-pyrone **42** in hand, we decided to test its reactivity in Diels–Alder additions. Cycloaddition of **42** with methyl propiolate produced an 84% yield of a 2:1 mixture of methyl 3-acetyl-2-methoxy-4-methylbenzoate **45**, in which the two aromatic protons exhibited typical *ortho* coupling (J = 7 Hz), and the isomeric methyl 4-acetyl-3-methoxy-5-methylbenzoate **46** (aromatic protons accidentally equivalent). This reaction provides



41 A = H; Lewis Acid 9 42

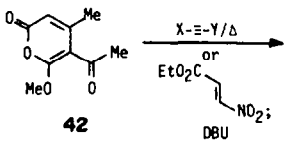


12 44 43 43'

Table 1. ^{13}C-NMR Data: Chemical shift, multiplicity, and assignment

9		42		43		59		56b	
164.28 s	C2, C4, C6	165.93 s	C2, C4, C6, $COCH_3$	197.87 s	$\underline{C}OCH_3$	169.26 s	C2, C4, C6, $\underline{C}O_2Me$	169.47 s	C2, C4, C6, $\underline{C}O_2Me$, $\underline{C}OCH_3$
160.84 s		165.01 s		165.26 s	C2, C4, C6	164.52 s		167.32 s	
160.76 s		160.54 s		164.67 s		160.44 s		165.51 s	
103.12 d	C3	154.43 s		159.21 s		155.54 s		160.04 s	
83.74 d	C5	112.90 s	C5	113.30 s	C3	104.42 d	C3	150.04 s	
55.96 q	OCH_3	111.88 d	C3	87.61 d	C5	83.21 d	C5	114.34 d	C3
22.03 q	CH_3	52.33 q	OCH_3	55.97 q	OCH_3	56.08 q	OCH_3	111.41 s	C5
		21.25 q	$CO\underline{C}H_3$	31.10 q	$CO\underline{C}H_3$	52.51 q	OCH_3	52.37 q	OMe
		19.67 q	CH_3	22.09 q	CH_3	40.83 t	CH_2	52.29 q	OMe
								40.18 t	CH_2
								20.14 q	$CO\underline{C}H_3$

chemical evidence for the correct assignment of structure for the 5-acetyl pyrone **42** since the 3-acetyl isomer **43** cannot give rise to these products **45** and **46**. Other Diels–Alder reactions of **42** with other dienophiles were also successful: dimethyl acetylenedicarboxylate produced the phthalate **47** (93%) while ethyl β-nitroacrylate gave predominantly the benzoate **48** (55%) after treatment with DBU.[26]



42

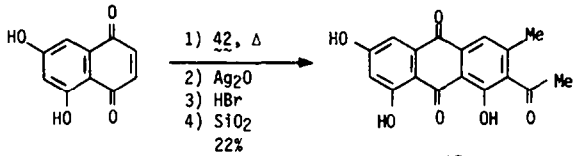
45 X = H; Y = COOMe
46 X = COOMe; Y = H
47 X = COOMe; Y = COOMe
48 X = COOEt; Y = H

We also have carried out the cycloaddition of **42** with various quinones as a model for the eventual preparation of the desired anthracyclines. Reaction of **42** with 5,7-dihydroxynaphthoquinone[27] **49** followed by oxidation and hydrolysis produced in fair yield the natural product 2-acetylemodin **50** shown to be identical with an authentic sample.[28] Reaction of **42** with methoxyquinone followed by oxidation gave in 60% yield a single product to which we have assigned structure **51**.[29] Monodemethylation (BBr_3, −78°, 10 min) afforded a monomethyl ether assigned structure **52**. This same compound is also produced by methylation (CH_2N_2, Et_2O) of the dihydroxy compound **53** produced by complete demethylation of **51** (BBr_3, 0°C, 1.5 hr). In order to assure that our structural assignment for the monomethyl ether **52** was correct, we synthesized the opposite monomethyl ether **54** by treating the adduct **51** with aqueous potassium hydroxide. Compounds **52** and **54** were completely different. Structure **52** has been assigned to the natural product orientalone based on spectroscopic studies.[30] However, the proton NMR for compound **52** (δ 7.89, 1H, s; 6.27, 1H, s) does not match that reported for orientalone (δ 7.65, 1H, s; 6.2, 1H, s). Unfortunately, it was impossible to obtain natural orientalone or its spectra for comparison purposes.[31]

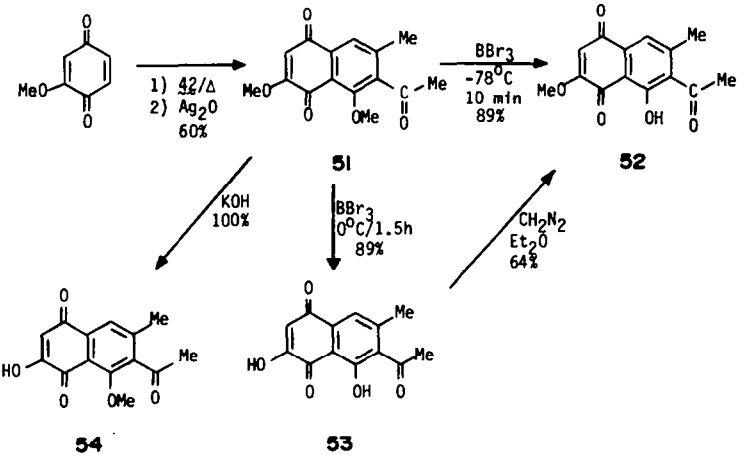
In order to test the generality of this Friedel–Crafts acylation of pyrones and to prepare more functionalized pyrones suitable for use in anthracycline synthesis, we decided to prepare 2-pyrones with functionalized substituents at both C4 and C5. Kishi[8b] has shown that methyl 1,8-dihydroxy-2-formyl-anthraquinone-3-acetate **55** can be readily converted into aklavinone **5**. Therefore an easy preparation of methyl 5-formyl-6-methoxy-2-pyrone-4-acetate **56a** coupled with its use in our Diels–Alder approach to the anthracyclines (i.e., its cycloaddition with juglone or 2-bromojuglone) would afford a new route to **55** and thence **5**. The 5-acetyl-2-pyrone-4-acetate **56b** was chosen as the model to test this general process. The known triacid **57**[19b,32] was converted into methyl 6-methoxy-2-pyrone-4-acetate **59** in 57% yield by cyclization to the acid anhydride **58** and methylation of both functions in the same step with diazomethane. This 6-alkoxy-2-pyrone **59** was also acetylated cleanly and regiospecifically at C5 with acetic anhydride in refluxing TFA giving **56b** in 62% yield. The assignment of structure **56b** to this product was against based on an analysis of the ^{13}C NMR spectra for **59** and **56b** (Table 1). The signal corresponding to C5 in **59** has moved downfield by 28 ppm in **56b** while the signal for C3 has experienced a downfield shift of only 10 ppm, indicating that acetylation had occurred at C5. An application of this route to the preparation of the formylated compound **56a** is currently under investigation.

Preparation of tetracyclic intermediates for 11-*deoxyanthracycline synthesis*

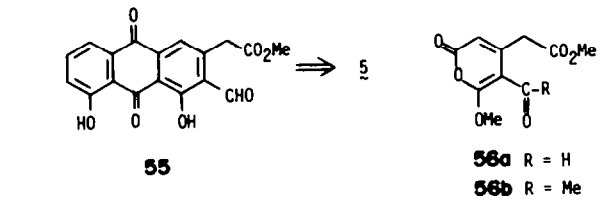
The facile regiospecific preparation of **26c** by the glutaconic half-ester dehydrative cyclization allowed



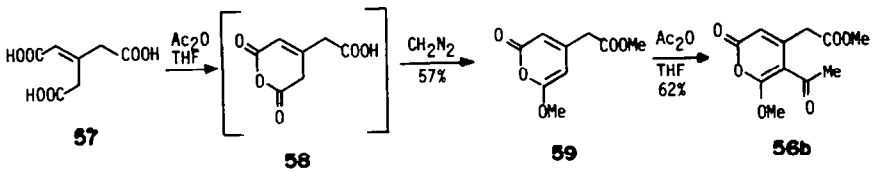
49 **50**



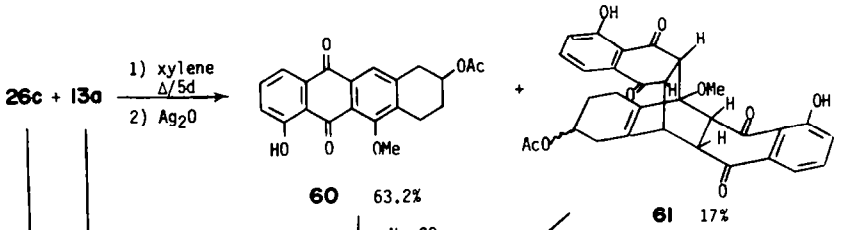
51 **52** **53** **54**



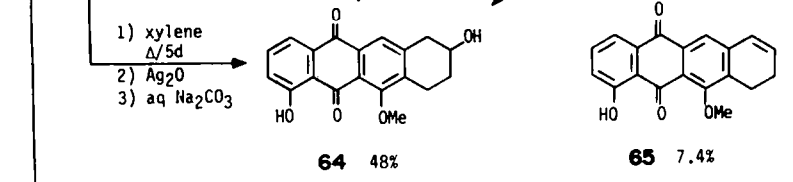
55 56a R = H 56b R = Me



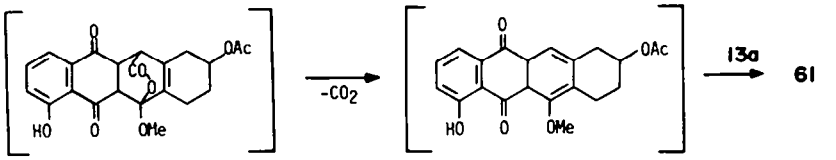
57 58 59 56b



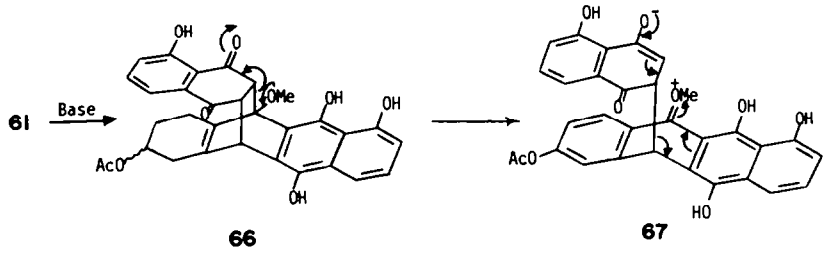
60 63.2% 61 17%



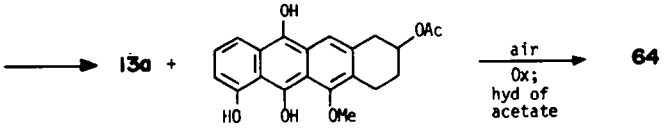
64 48% 65 7.4%



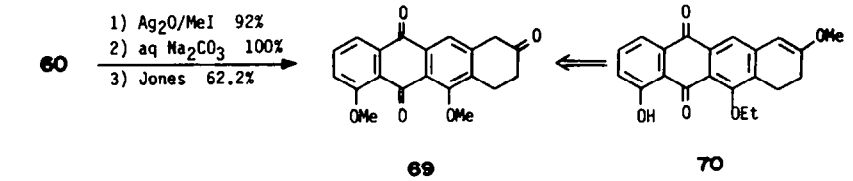
62 63



66 67



68



69 70

us to apply our Diels–Alder approach to the synthesis of tetracyclic material for anthracycline synthesis. Refluxing a solution of **26c** with juglone **13a** in xylene for 5 days followed by oxidation with silver oxide afforded a 63% yield of the desired tetracyclic acetate **60** as light yellow crystals (m.p. 164–165°). In addition, we isolated a second compound assigned structure **61** in 17% yield. This compound presumably arises by loss of CO_2 from the initial Diels–Alder adduct **62** to give the diene **63** which then can either suffer bis-enolization to give the hydroanthraquinone (leading to **60**) or undergo a second cycloaddition with another molecule of juglone **13a** to give the 2:1 adduct **61**. The acetate **60** could be hydrolyzed to the alcohol **64** in essentially quantitative yield. Surprisingly treatment of the 2:1 adduct **61** with aqueous carbonate also gave the same alcohol **64** along with some juglone. We were able to isolate a 72% yield of the alcohol **64** from **61** by this route, thus raising the yield of the alcohol **64** from **26c** and **13** to 75%. The alcohol could also be produced directly without isolation of the acetate by different treatment of the oxidation reaction mixture with base. In this manner, we obtained 48% of the pure crystalline alcohol **64** (m.p. 203–204°) along with 7% of the olefin **65**. The formation of **64** from **61** probably involves an initial base-catalyzed enolization of one of the cyclohexenedione units to a hydroquinone to give **66** followed by a facile retro-Diels–Alder process, probably via zwitterionic intermediates such as **67** to give juglone **13a** and the hydroquinone **68**. Air oxidation of **68** and hydrolysis of the acetate (clearly possible at any stage of this process) would then give **64**. The overall structure of the adducts **60** and **64** was established by the conversion of **60** to the ketone **69** in three steps (methylation, hydrolysis, and Jones oxidation) in a 57% overall yield. This same ketone was also prepared in three steps from the tetracycle **70**, made by the route of Gesson,[33] and the two samples were shown to be identical.

It is important to point out that the Diels–Alder reaction between **26c** and **13a** is regiospecific, namely **60** is the only Diels–Alder regioisomer produced in this reaction. By very careful and repeated chromatography, it was possible to isolate all of the products formed in the Diels–Alder reaction and thus to verify spectroscopically that no regioisomeric materials were produced in this reaction, indicating that the cycloaddition is regiospecific. We were unable to determine the structure of all of the byproducts but could show that they were not regioisomeric Diels–Alder adducts.

CONCLUSION

We have developed two methods for the regiospecific synthesis of 4,5-disubstituted 6-alkoxy-2-pyrones from readily available starting materials. We have demonstrated that the utility of these compounds as diene components in the Diels–Alder reaction and have prepared regiospecifically many substituted aromatics and anthraquinones, including several natural products. We have also been able to construct tetracyclic intermediates for anthracycline synthesis, again in a regiospecific manner. Further work in this area is continuing in our laboratory.

EXPERIMENTAL

General: ^{1}H-NMR were taken on a Varian T-60 or Bruker WP-200 spectrometer and are so indicated. ^{13}C-NMR were taken on a Varian CFT-20, Jeol FX90Q, or Bruker WP-200 spectrometer. All chemical shifts are reported in ppm downfield from internal TMS. IR spectra were recorded on a Perkin–Elmer model 710B or model 137 infrared spectrophotometer as a liquid film or in a soln cell with polystyrene as a standard; the abbreviations br, sh, w, refer to broad, shoulder, and weak, respectively. MS were recorded on an AEI-MS9 or an AEI-MS25 spectrometer. Data reported are the *m/e* values for the most abundant peaks and are not a complete tabulation. Silica gel for chromatography was E. Merck silica gel 60 (70–230 mesh) and for flash chromatography was EM silica gel 9385 (230–400 mesh). HPLC was performed on a Waters Prep 500 instrument using silica gel cartridges with EtOAc/hexane mixtures as eluent. Alumina for chromatography was EM neutral alumina 1077 (activity I) adjusted to the correct activity with water. All reagents and solvents were purified and distilled according to standard methods unless otherwise specified.

Ethyl isodehydroacetate, **10**

Ethyl acetoacetate (133 g, 1.02 mol) was added dropwise with stirring to ice-cooled conc H_2SO_4 (100 ml, 1.88 mol) over 1.75 hr at such a rate that the temp was maintained between 10° and 15°. The organge soln was allowed to stand at 25° for 69 hr, poured into 200 g of ice, and extracted with ether. The ether layer was washed with 10% Na_2CO_3 aq, dried with Na_2SO_4, filtered, and evaporated *in vacuo* to give an orange liquid. Distillation afforded 47 g (47%) of a yellow liquid, b.p. 85–95° (0.02 mm). Reported[34] b.p. 185–192° (35 mm).

200 MHz ^{1}H-NMR ($CDCl_3$) δ 6.01 (1H, bs), 4.39 (1H, q, J = 7 Hz), 2.39 (3H, s), 2.23 (3H, d, J = 1 Hz), 1.37 (3H, t, J = 7 Hz). IR (neat) 2955, 1730 (br), 1630, 1550, 1440, 1400, 1305, 1270, 1150, 1085, 965, 860, 780 cm^{-1}.

3-*Methylglutaconic acid*, **11**

A mixture of **10** (25.8 g, 0.141 mol) and NaOH (26.3 g, 0.657 mol) in 250 ml of water was heated to 70° for 1 hr. The mixture was cooled, extracted with ether, acidified with conc HCl, and reextracted with ether. The second organic extract was dried with Na_2SO_4, filtered, and evaporated *in vacuo* to give 18.0 g (95%) of **11** as an off-white solid, m.p. 101–105°. Reported[35] m.p. 115–116°.

5,6-*Dihydro*-4-*methyl*-2H-*pyran*-2,6-*dione*, **12**

A mixture of **11** (2.37 g, 0.0164 mol) and Ac_2O (3.0 ml, 0.032 mol) was heated at 70° for 30 min. the soln was cooled and evaporated *in vacuo*. The resulting oil was distilled (Kugelrohr) to give 1.76 g (85%) of **12** as a white, crystalline solid, b.p. 90° (0.07 mm), m.p. 79–83°. Reported [36] b.p. 210° (45 mm), m.p. 90°.

60 MHz ^{1}H-NMR ($CDCl_3$) δ 6.07 (1H, m), 3.43 (2H, m), 2.08 (3H, m). IR ($CHCl_3$) 3050, 1810, 1750, 1670, 1430, 1380, 1270, 1150, 1110, 1000, 955, 845 cm^{-1}.

6-*Methoxy*-4-*methyl*-2H-*pyran*-2-*one*, **9**

A soln of diazomethane, prepared from N-nitroso-N-methylurea (5.0 g, 0.050 mol), in 50 ml of ether was added dropwise over 20 min to an ice-cooled soln of **12** (1.26 g, 0.010 mol) in 20 ml of ether. The mixture was allowed to stand at 25° for 12 hr and evaporated *in vacuo*. The residue was chromatographed on 100 g of silica gel, using ether: benzene (5:95) as eluant, to yield 1.12 g (80%) of **9**, a pale yellow solid, m.p. 44–48°. Recrystallization gave a slightly off-white solid, m.p. 54–55°.

200 MHz ^{1}H-NMR ($CDCl_3$) δ 5.72 (1H, m), 5.33 (1H, m), 3.93 (3H, s), 2.17 (3H, bs). ^{13}C-NMR ($CDCl_3$) δ 164.28 (s), 160.84 (s), 160.76 (s), 103.12 (d), 83.74 (d), 55.96 (q), 22.03 (q). IR ($CHCl_3$) 2975, 1720 (br), 1630, 1530 (br), 1435, 1370, 1345, 1255, 1160, 1035, 1015, 950, 855, 825 cm^{-1}. Mass spectrum *m/e* 141 (6.0), 140 (M^+, 62.6), 112 (M^+—CO, 79.7), 109 (25.2), 97 (100),

69 (19.9), 53 (44.7), 44 (45.1). (Found: C, 59.89; H, 5.64. Calc for $C_7H_8O_3$: C, 59,99; H, 5.75%).

Juglone, **13a**

To a suspension of 1,5-dihydroxynaphthalene (5.0 g, 31.2 mmol) in 100 ml water was added a soln of sodium dichromate (24 g, 80.4 mmol) and 34 g conc H_2SO_4 in 240 ml water. The purple mixture was heated at 50° for 30 min, cooled to 20° and filtered. The dried ppt was extracted with hexane, and the hexane reduced in volume to induce crystal formation. The solid collected gave 200 mg (3.5%) of **13a** as orange crystals, m.p. 151–153°. Reported[37] m.p. 154°.

60 MHz ^{1}H-NMR (benzene-d_6) δ 11.9 (1H, s), 7.5–7.8 (3H, m), 6.9 (2H, s).

Naphthazarin, **13b**

An intimately ground mixture of hydroquinone (22.0 g, 0.200 mol) and maleic anhydride (20.0 g, 0.200 mol) was added to a molten mixture of 200 g $AlCl_3$ and 40 g NcCl at 180°. The purple mixture was heated to 210° for 50 min and shaken out into a mortar to cool. The residue was pulverized and boiled in water while adding conc HCl until a brown color was produced. The cooled mixture was filtered and the ppt continuously extracted with CH_2Cl_2. The resulting red soln was evaporated *in vacuo* to leave a residue which was recrystallized from heptane to give 5.0 g (13%) of fine metallic green-black needles, m.p. 220–225° (dec). Reported [38] m.p. 225–230°.

60 MHz ^{1}H-NMR ($CDCl_3$) δ 7.08 (4H, s), 12.43 (2H, s). IR (CH_2Cl_2) 1615, 1565, 1450, 1335, 1220, 1140, 1100 cm^{-1}.

Chrysophanol (1,8-*dihydroxy*-3-*methylanthraquinone*), **14a**

A soln of **9** (20 mg, 0.144 mmol) and **13a** (50 mg, 0.288 mmol) in 2 ml xylene was refluxed for 5 days, cooled, and treated with 125 mg silver oxide and 200 mg anhyd $MgSO_4$ with stirring at room temp for 12 hr. The mixture was filtered, evaporated *in vacuo*, and the residue chromatographed on preparative thick layer silica gel using CH_2Cl_2 to develop the plate to give 24 mg (62%) of 8-hydroxy-1-methoxy-3-methylanthraquinone as a yellow solid, m.p. 187–189°.

60 MHz ^{1}H-NMR ($CDCl_3$) δ 7.6 –7.8(3H, m), 7.1–7.3 (2H, m), 4.01 (3H, s), 2.48 (3H, s). IR (CH_2Cl_2) 2950, 1660, 1630, 1600, 1450, 1370, 1300, 1220, 1210, 1050, 910, 860 cm^{-1}. Mass spectrum (*m/e*) 269 (18.5), 268 (M^+, 100), 251 (17.4), 250 (M^+—CO, 5.04), 239 (25.2), 238 (12.0), 223 (17.6), 222 (60.7), 194 (10.8), 181 (12.7), 165 (11.6), 153 (10.7), 152 (11.6), 139 (10.3), 15 (10.8).

A soln of 8-hydroxy-1-methoxy-3-methylanthraquinone (24 mg, 0.089 mmol) and 1.5 ml 48% HBr in 4 ml glacial AcOH was refluxed for 5 hr. The cooled soln was diluted with water, extracted with CH_2Cl_2, and the organic phase washed with water, dried over Na_2SO_4, filtered, and evaporated *in vacuo* to give 23 mg (100%, overall yield 62%) of **14a** as a yellow orange solid, m.p. 176–179°. Reported[13] m.p. 193–194°. This solid was dissolved in 5 ml Ac_2O and one drop conc H_2SO_4, stirred at room temp for 30 min and poured into water. The aqueous phase was extracted with CH_2Cl_2, which was dried over Na_2SO_4, filtered, and evaporated *in vacuo* to give 30 mg (100%) of yellow solid, which was recrystallized from glacial AcOH to give fine yellow needles m.p. 207–208°. Reported[14] m.p. 207–208°.

60 MHz ^{1}H-NMR ($CDCl_3$) δ 8.2 (1H, m), 8.01 (2H, m), 7.7 (1H, m), 7.37 (1H, m), 7.20 (1H, m), 2.49 (3H, s), 2.43 (6H, s). Reported[15] ^{1}H-NMR ($CDCl_3$) δ 8.2, 8.0, 7.7, 7.37, 7.20, 2.50, 2.45.

Helminthosporin (1,4,8-*trihydroxy*-6-*methylanthraquinone*), **14b**

A soln of **9** (20 mg, 0.144 mmol) and **13b** (55 mg, 0.288 mmol) in 2 ml mesitylene was refluxed for 74 hr, cooled, and treated with 125 mg silver oxide and 200 mg anhyd $MgSO_4$ with stirring at room temp for 12 hr. The mixture was filtered and evaporated *in vacuo*, and the residue chromatographed on preparative thick layer silica gel using CH_2Cl_2 to develop the plate to give 18 mg (44%) of 1,4-dihydroxy-8-methoxy-6-methylanthraquinone as fine red needles, m.p. 255–258° (with sublimation).

60 MHz ^{1}H-NMR ($CDCl_3$) 7.81 (1H, m), 7.25 (2H, s), 7.15 (1H, m), 4.05 (3H, s), 2.51 (3H, s). IR (CH_2Cl_2) 3050, 1625, 1595, 1575 (sh), 1450, 1300, 1220, 1195, 1060, 875, 840 cm^{-1}. Mass spectrum (*m/e*) 285 (18.4), 284 (M^+, 100), 266 (M^+—CO, 66.2), 238 (26.3).

A soln of 1,4-dihydroxy-8-methoxy-6-methylanthraquinone (17 mg, 0.06 mmol) and 1.5 ml 48% HBr in 4 ml glacial AcOH was refluxed for 4 hr. The cooled mixture was diluted with water and extracted with CH_2Cl_2. The organic phase was washed with water, dried over $NaSO_4$, filtered, and evaporated *in vacuo* to give 14 mg (87%, overall yield 38%) of **14b** as a red solid, which was recrystallized from pyridine to give flat maroon needles, m.p. 226–227°. Reported[17] m.p. 226–227°. UV (MeOH) λ_{max} (log ε): 230 (4.64), 254 (4.31), 490 (4.08). Reported[17] UV (MeOH) λ_{max} (log ε): 230 (4.64), 254 (4.30), 490 (4.09).

Pachybasin (1-*hydroxy*-3-*methylanthraquinone*), **14c**

A soln of **9** (20 mg, 0.144 mmol) and **13c** (46 mg, 0.288 mmol) in 5 ml xylene was refluxed for 72 h, cooled and treated with 120 mg silver oxide and 200 mg $MgSO_4$ with stirring at room temp for 12 h. The mixture was filtered and evaporated *in vacuo*, and the residue chromatographed on preparative thick layer silica gel using CH_2Cl_2 to develop the plate to give 24 mg (66%) of 1-methoxy-3-methylanthraquinone as a yellow solid.

60 MHz ^{1}H-NMR ($CDCl_3$) δ 8.2 (2H, m), 7.7 (3H, m), 7.1 (1H, m), 4.02 (3H, s), 2.45 (3H, bs). Reported[39] ^{1}H-NMR δ 8.2, 7.75, 7.12, 4.02, 2.45. IR (CH_2Cl_2) 2900, 1670, 1600, 1460, 1420, 1330, 1300, 1260, 1180, 1140, 1080, 1010, 960, 900, 860 cm^{-1}. Reported[39] IR (CH_2Cl_2): identical to that given above.

A soln of 1-methoxy-3-methylanthraquinone (24 mg, 0.095 mmol) and 1.5 ml 48% HBr in 3 ml glacial AcOH was refluxed for 3.5 hr. The cooled mixture was diluted with water, extracted with CH_2Cl_2, and the organic phase washed with water, dried over $NaSO_4$ filtered, and evaporated *in vacuo*. The residue was chromatographed on preparative thick layer silica gel using CH_2Cl_2 to develop the plate to give 22 mg (97%, overall yield 64%) of **14c** as a yellow solid, which was recrystallized from acetic acid to give orange-yellow needles, m.p. 174–175°. Reported[13] m.p. 174.5–175°. IR (nujol) 3000, 1670, 1640, 1590, 1320, 1290, 1270, 1220, 1130, 990, 860 cm^{-1}. Reported[13] IR (nujol) 1670, 1640, 1590 cm^{-1}.

Ziganein methyl ether (5-*hydroxy*-1-*methoxy*-3-*methylanthraquinone*), **14d**, *and Chrysophanol methyl ether* (8-*hydroxy*-1-*methoxy*-3-*methylanthraquinone*), **14e**

A soln of **9** (17 mg, 0.122 mmol) and **13d** (55 mg, 0.244 mmol) in 2 ml xylene was refluxed for 125 hr, cooled, and treated with 125 mg silver oxide and 200 mg anhyd $MgSO_4$ with stirring at room temp for 12 hr. The mixture was filtered and evaporated *in vacuo*, and the residue chromatographed on preparative thick layer silica gel using CH_2Cl_2 to develop the plate to give 9 mg (24%) of a low melting solid. This material was dissolved in 10 ml 2N NaOH aq and heated at 100° for 1.75 hr. The soln was cooled and extracted with CH_2Cl_2, which was dried over Na_2SO_4, filtered, and evaporated *in vacuo* to give 4.5 mg (58%, overall yield 13.5%) of an orange-yellow solid, m.p. 175–187°. Reported[16] m.p. for **14d**: 197–199°. IR (CCl_4) 2950, 1650, 1630, 1600, 1450, 1370, 1290, 1260, 1220, 1210, 1100, 1050, 910 cm^{-1}. Reported[16] IR (KBr) 1656, 1631 cm^{-1}.

60 MHz ^{1}H-NMR ($CDCl_3$) δ 12.7 (1H, bs), 7.6–7.8 (3H, m), 7.1–7.3 (2H, m), 4.01 and 4.03 (3H, m), 2.48 (3H, bs). Reported[16] ^{1}H-NMR ($CDCl_3$) δ 12.42, 7.00–8.40, 4.03, 2.49.

Bistrimethylsilyl 1,3-*Allenedicarboxylate*,[40] **16**

1,3-Allenedicarboxylic acid[19b,c] (1.59 g, 12.4 mmol) was added to a 25 ml round bottom flask with a stir bar and the flask was flushed with N_2 and sealed with a rubber septum. The flask was cooled to −45° and then an equimolar mixture of trimethylsilyl chloride and hexamethyldisilazane (2.3 g, 8.5 mmol trimethylsilyl chloride, 8.5 mmol hexamethyldisilazane)

was added with stirring over a period of 3 min. The mixture was stirred at −45° for 30 min, warmed to −20° and 8 ml of dry pentane was added. After warming to 25° the mixture was stirred for 1 hr and then filtered under N_2 and the filtrate was concentrated under aspirator vacuum. Distillation (bulb to bulb, 140°, 0.8 mm) gave 2.87 g (85%) of **16** as a colorless liquid.

60 MHz ^{1}H-NMR ($CDCl_3$) δ 5.95 (2H, s), 0.32 (18H, s).

4-Carbotrimethylsilyloxy-5-(carbotrimethylsilyloxy) methylene-1-trimethylsilyloxy-1-cyclohexene

Compound **16** (0.235 g, 0.86 mmol) and **17**[18] (0.388 g, 1.6 mmol) were dissolved in 10 ml of dry benzene and the soln was refluxed for 17 hr. After cooling to 25° the volatile components were removed under high vacuum and the product was distilled (bulb to bulb, 200°, 0.25 mm) to give 0.255 g (72%) of 4-carbotrimethylsyliloxy - 5 - (carbotrimethylsilyloxy) methylene - 1 - trimethylsilyloxy - 1 - cyclohexene as a colorless liquid.

60 MHz ^{1}H-NMR ($CDCl_3$) δ 5.82 (1H, m), 4.97 (1H, m), 3.25 (2H, m), 2.0–2.5 (3H, m), 0.23 (27H, m). IR (neat) 2970, 2880, 1730–1700, 1650, 1240, 850 cm^{-1}. Mass spectrum (*m/e*) 414 (M^+), 324 (M^+—TMSOH).

7,8-Dihydro-3,6-dimethoxy-1H-2-benzopyran-1-one, **19**, *and 7,8-Dihydro-1,6-dimethoxy-3H-2-benzopyran-3-one*, **20**

Compound **16** (1.67 g, 6.1 mmol) and **17**[18] (1.8 g, 12.7 mmol) were dissolved in 7 ml of dry benzene and the soln was refluxed under N_2 for 20 hr. After cooling to 25° the volatile components were removed under high vacuum. The residue was then dissolved in 10 ml anhyd diethyl ether and 1.1 ml (27.5 mmol) of MeOH was added. After the soln was stirred for 0.5 hr at 25° the sample was concentrated under aspirator vacuum. The residue was then dissolved in 10 ml (108 mmol) of Ac_2O and the soln was refluxed under N_2 for 15 min. After cooling to 25° the sample was concentrated under high vacuum. The black residue containing the anhydride **18** was then dissolved in 10 ml CH_2Cl_2 and treated with an ethereal soln of diazomethane (generated from N-methyl-N-nitrosourea) at 25° for 1.5 hr. At this point a solid which formed was filtered off to give 0.1 g of a material which gave no NMR spectrum. The filtrate was concentrated to give 0.86 g of a red oil. The sample was then chromatographed on 150 g of silica gel eluting with 1 liter 3:7 benzene–$CHCl_3$ and 3 liters of 5:95 benzene–$CHCl_3$ and collecting 25 ml fractions. This gave 0.3 g (24%) of a red oil, from fractions 101–115, which was determined to be a slightly impure sample of a 2:1 mixture of pyrones **19** and **20** through spectral analysis.

200 MHz ^{1}H-NMR ($CDCl_3$) δ 5.35 (0.33H, s), 5.15 (0.67H, s), 5.11 (1H, s), 3.89 (1H, s), 3.79 (2H, s), 3.66 (3H, s), 2.60 (2H, t, J = 8 Hz), 2.34 (2H, t, J = 8 Hz). IR (neat) 2960, 1700–1760, 1440, 1380, 1240 cm^{-1}. Mass spectrum (*m/e*) 208 (M^+), 194 (M^+—CH_2), 180 (M^+—CO).

3-Chloroglutaconic acid monoethyl ester, **21**

Diethyl acetone-1,3-dicarboxylate (10 g, 49.5 mmol) was added dropwise to 15 g (72 mmol) PCl_5 and the mixture heated to 60° until the foaming subsided. Then more PCl_5 was added until no more foaming occurred upon addition (required about 2 g, 9.6 mmol). Then the red mixture was poured onto 100 g of crushed ice and was extracted with 3 × 125 ml of ether. The ether washes were combined and washed with 1 × 125 ml 10% $NaHCO_3$aq and the $NaHCO_3$ wash was back-washed with 2 × 100 ml of ether and then acidified with cold 10% HCl. The acidified aqueous soln was washed with 6 × 125 ml of ether and the washes were combined, dried over Na_2SO_4 and concentrated to give 3.2 g (33.6%) of **21** as an orange liquid. The product appeared to be a mixture of all four possible double bond isomers.

60 MHz ^{1}H-NMR ($CDCl_3$) δ 10.67 (1H, bs), 6.03–6.37 (1H, m), 4.17 (2H, bq, J = 6 Hz), 3.97–4.17 (1.3H, m), 3.43–3.70 (0.7H, m), 1.27 (3H, t, J = 6 Hz). IR (neat) 2400–3600 (br), 3000, 1700–1740, 1640 cm^{-1}. Mass spectrum (*m/e*) 194, 192 (M^+), 157 (M^+—Cl), 150, 148 (M^+—CO_2). (Found: C, 43.39; H, 4.80. Calc for $C_7H_9ClO_4$: C, 43.56; H, 4.72%).

4-Chloro-6-ethoxy-2H-pyran-2-one, **23**

3-Chloroglutaconic acid monoethyl ester **21** (0.552 g, 2.87 mmol) was dissolved in acetyl chloride (0.82 ml, 11.5 mmol) and the mixture was heated for 27 hr at 55–70°. The volatile components were removed under vacuum and the sample was chromatographed on 20 g of silica gel eluting with $CHCl_3$ (collecting 5 ml fractions) to give 0.253 g (50.5%) of **23** as a colorless liquid in fractions 5–15. Upon standing in the freezer (−25°) the product solidified as a white solid, m.p. 48–52°.

60 MHz ^{1}H-NMR ($CDCl_3$) δ 5.78 (1H, d, J = 2 Hz), 5.37 (1H, d, J = 2 Hz), 4.18 (2H, q, J = 7 Hz), 1.33 (3H, t, J = 7 Hz). IR (neat) 3000, 2900, 1745, 1610, 1515, 1455, 1395, 1370, 1320, 1240, 1110, 1040, 1005, 985, 945, 870, 810 cm^{-1}. Mass spectrum (*m/e*) 176, 174 (M^+), 148, 146 (M^+—CO), 139 (M^+—Cl), 120, 118.

Methyl 4,4-ethylenedioxycyclohexan-2-one-1-carboxylate, **28**

Compound **27**[20] (5 g, 29.4 mmol), ethylene glycol (1.65 ml, 29.4 mmol) and *p*-toluenesulfonic acid monohydrate (0.05 g, 0.26 mmol) were dissolved in 100 ml of dry benzene in a 200 ml round bottom flask equipped with a Dean-Stark trap and condenser with a drying tube. The soln was refluxed for 2.5 hr, cooled to 25°, washed with 10% $NaHCO_3$ aq and dried over Na_2SO_4. The solvent was removed under aspirator vacuum and the product distilled (b.p. 120–130°, 0.8–0.9 mm) to give 3 g (48%) of **28** as a colorless liquid.[41]

60 MHz ^{1}H-NMR ($CDCl_3$) δ 12.0 (1H, s), 3.9 (4H, bs), 3.65 (3H, s), 1.48–2.76 (6H, m). IR (neat) 3400, 2910, 2880, 1740, 1720, 1660, 1615, 1440, 1300, 1260, 1220, 1110, 1070, 950 cm^{-1}. Mass spectrum (*m/e*) 214 (M^+), 172, 157, 144.

t-Butyl 2-propynyl ether, **29**

To a mixture of propargyl alcohol (16 g, 286 mmol) and isobutylene (24 g, 430 mmol) in a pressure bottle cooled to −78° was added 0.5 ml conc H_2SO_4. The bottle was sealed, allowed to warm to room temp, and allowed to stir at room temp for 15 hr. The bottle was cooled to −20° and opened. Stirring at room temp for several hours removed all the unreacted isobutylene. Ether was added and the ethereal soln washed with sat $NaHCO_3$ aq and brine, dried over $MgSO_4$, filtered, and evaporated *in vacuo*. Distillation gave 29.4 g (92%), b.p. 58–59° (92 mm). Reported[42] b.p. 116–117°.

60 MHz ^{1}H-NMR ($CDCl_3$) δ 3.97 (2H, d, J = 2.5 Hz), 2.18 (1H, t, J = 2.5 Hz), 1.19 (9H, s).

5-t-Butoxy-3-pentyn-1-ol, **30**

To 1.2 liters liquid ammonia at −78° in a 3-liter three-neck flask equipped with a dry ice condenser and stirrer was added 14.1 g (0.61 mol) of Na and a catalytic amount of $FeCl_3 \cdot 5H_2O$. After stirring under reflux for 1.5 hr, t-butyl 2-propynyl ether **29** (60 g, 0.56 mol) was added at −78°. After stirring under reflux for 2.5 hr, ethylene oxide (35.6 g, 0.81 mol) was added at −78° and the mixture was stirred under reflux for 10 hr. Then the ammonia was gradually evaporated at room temp for 8 hr. The residue was taken up in 200 ml water and 80 g of ammonium chloride was added. The mixture was extracted with ether, the ether extracts were washed with brine, dried, filtered, and evaporated *in vacuo*. Distillation of the oily residue gave 42 g (50%) of **30**, b.p. 84° (0.6 mm).

200 MHz ^{1}H-NMR ($CDCl_3$) δ 4.08 (2H, t, J = 2 Hz), 3.71 (2H, t, J = 6.5 Hz). 2.50 (2H, tt, J = 2 and 7 Hz), 1.23 (9H, s). IR (neat) 3300, 2980, 2940, 2300 (w), 1395, 1370, 1200, 1060 cm^{-1}. Mass spectrum (*m/e*) 141 (M^+—CH_3), 123 (M^+—CH_2OH), 89, 83 (M^+—OtBu). High resolution mass spectrum (*m/e*) 141.0912, calc for $C_8H_{13}O_2$ 141.0916.

5-t-Butoxy-3-pentynoic acid, **31**

Compound **30** (1.04 g, 6.6 mmol) in 25 ml acetone was treated with excess Jones reagent. After stirring for 30 min at 25°, unreacted Jones reagent was destroyed by the addition of isopropanol. The mixture was then filtered and the filtrate concentrated *in vacuo*. The residue was then taken up in ether and dried over Na_2SO_4. Removal of the solvent then gave 1.03 g (92%) of **31** as a yellow liquid.

200 MHz ^{1}H-NMR ($CDCl_3$) δ 9.7 (1H, bs), 4.18 (2H, t, J = 2 Hz), 3.42 (2H, t, J = 2 Hz), 1.27 (9H, s). IR (neat) 3600–2500, 2950, 2250 (w), 1720, 1400, 1370, 1230, 1190, 1060, 1030 cm^{-1}.

Methyl 5-t-butoxy-3-pentynoate, **32**

A soln of **31** (0.5 g, 2.9 mmol) in 100 ml of ether was treated with a soln of diazomethane (generated from N-methyl-N-nitrosourea) in ether until the yellow color of the diazomethane persisted. Acetic acid was then added dropwise to destroy excess diazomethane and the reaction was dried over Na_2SO_4. After removal of the volatile components *in vacuo*, 0.46 g (86%) of **32** was obtained as an orange liquid.

60 MHz ^{1}H-NMR ($CDCl_3$) δ 3.93 (2H, t, J = 2 Hz), 3.58 (3H, s), 3.13 (2H, t, J = 2 Hz), 1.03 (9H, s). IR (neat) 2900, 2250 (w), 1730, 1430, 1380, 1360, 1250, 1180, 1060, 1020 cm^{-1}.

Methyl 5-t-Butoxy-2,3-pentadienoate, **33**

A soln of **32** (0.914 g, 4.9 mmol) in 10 ml $CHCl_3$ was treated with 4 drops of Et_3N and the soln stirred at 25° for 1 hr. After concentration *in vacuo* at 25° the product was distilled (bulb to bulb, 80°, 0.02 mm) to give 0.745 g (77%) of **33** as a colorless liquid.

60 MHz ^{1}H-NMR ($CDCl_3$) δ 5.65–5.87 (2H, m), 3.98–4.28 (2H, m), 3.73 (3H, s), 1.23 (9H, s). IR (neat) 2970, 1955, 1720, 1435, 1360, 1260, 1190, 1160, 1060, 1020 cm^{-1}. Mass spectrum (*m/e*) 184 (M^+), 183, 169 (M^+—CH_3), 128 (M^+—isobutylene), 111 (M^+—OtBu), 98.

4-Carbomethoxy-3-(2-t-butoxyethyl)-2-cyclohexen-1-one, **35**

Compound **33** (2.75 g, 14.9 mmol) and **17**[18] (3.45 g, 24.3 mmol) were dissolved in 50 ml of dry toluene and the soln was refluxed for 40 hr under N_2. The reaction was cooled to 25° and then concentrated *in vacuo* to give 4.4 g of a yellow oil which was taken up in 50 ml of MeOH containing 5 drops of AcOH and stirred at 25° for 2 hr. Again the sample was concentrated *in vacuo* and the residue was taken up in 50 ml $CHCl_3$ containing 3 drops of Et_3N and stirred at 25° for 1 hr. After removal of the solvent, the sample was chromatographed on 350 g silica gel eluting with $CHCl_3$ to give 2.97 g (78%) of **35** as a light yellow oil. Distillation of a small sample (bulb to bulb, 140°, 0.5 mm) gave a colorless liquid.

200 MHz ^{1}H-NMR ($CDCl_3$) δ 5.88 (1H, s), 3.62 (3H, s), 3.58–3.60 (1H, m), 3.39 (2H, t, J = 6.6 Hz), 2.39 (2H, t, J = 6.6 Hz), 2.05–2.40 (4H, m), 1.05 (9H, s). IR (neat) 2970, 1730, 1680, 1640, 1430, 1360, 1250, 1200, 1080 cm^{-1}. Mass spectrum (*m/e*) 254 (M^+), 198 (M^+—isobutylene), 197 (M^+—tBu), 181 (M^+—OtBu), 180, 168, 109.

7,8-Dihydro-1-methoxy-3H-2-benzopyran-3,6(4H)-dione, **36**

Compound **35** (1.02 g, 4.02 mmol) was dissolved in 8 ml anhyd trifluoroacetic acid at 25° for 20 min. The trifluoroacetic acid was then removed quickly under vacuum and the residue was taken up in MeOH and 1 g $NaHCO_3$ was added. After stirring at 25° for 0.5 hr the solvent was removed and the residue was stirred with 50 ml of $CHCl_3$ for 1 hr. The reaction was then filtered and the filtrate concentrated under vacuum to give an orange liquid. This liquid was taken up in acetone and treated with excess Jones reagent at 25° for 30 min. After excess Jones reagent was destroyed with isopropanol, the sample was filtered and the filtrate was taken up in $CHCl_3$. The $CHCl_3$ soln was washed with 10% $NaHCO_3$ aq and the $NaHCO_3$-wash was acidified with conc HCl and washed with 5 × 25 ml CH_2Cl_2. The CH_2Cl_2-washes were combined, dried over Na_2SO_4 and concentrated to give 0.141 g of an orange liquid. This liquid was dissolved in 15 ml Ac_2O and the soln was refluxed for 1.5 hr. After cooling to 25° the Ac_2O was removed under vacuum and the residue was chromatographed on 8 g silica gel. Elution with $CHCl_3$ gave 44 mg (5%) of an orange liquid, one spot on TLC (R_f = 0.7, $CHCl_3$) for which structure **36** is proposed.

60 MHz ^{1}H-NMR ($CDCl_3$) δ 5.95–6.05 (1H, m), 3.6–4.0 (2H, m), 3.8 (3H, s), 2.0–2.6 (4H, m). IR (neat) 2970, 1700–1750, 1600, 1440 cm^{-1}. Mass spectrum (*m/e*) 194 (M^+).

Methyl 5-hydroxy-3-pentynoate, **37**

To a soln of **30** (10 g, 65.8 mmol) in acetone (400 ml) was added excess Jones reagent (67 ml) with stirring at 0°. After stirring at 0° for 30 min, the mixture was stirred at room temp for 2 hr. Unreacted Jones reagent was then destroyed by the addition of isopropanol. The mixture was filtered and the filtrate concentrated under vacuum. The residue was then taken up in ether and dried over Na_2SO_4. Removal of the solvent gave the crude acid **31** (10 g, yellow liquid, crude yield 89.2%).

The crude acid **31** was dissolved in 30 ml anhyd trifluoroacetic acid (TFA) and stirred at room temp for 3 hr. The TFA was removed from the reaction mixture by high vacuum pump. The residue was dissolved in ether and a small excesss of diazomethane in ether was added. After 1 hr, the solvent was evaporated *in vacuo* to give the crude oily ester which was purified by column chromatography on silica gel to separate the hydroxy ester **37** (6.2 g, 73.4% overall yield) as a colorless oil.

200 MHz ^{1}H-NMR ($CDCl_3$) δ 4.67 (1H, s), 4.26 (2H, t, J = 2 Hz), 3.73 (3H, s), 3.33 (2H, t, J = 2 Hz). IR (neat) 3400, 2950, 1740, 1010 cm^{-1}. Mass spectrum (*m/e*) 128 (M^+, 2.7), 127 (M^+—H, 13.7), 100 (M^+—CO, 42.6), 98 (M^+—CH_2O, 100), 97 (M^+—OMe, 43.2), 96 (M^+—MeOH, 36.7), 68 (M^+—CO_2Me—H), 59 (CO_2Me^+, 70.9), 52 ($C_4H_4^+$, 99.0). High resolution mass spectrum (*m/e*) 128.0471, calc for $C_6H_8O_3$ 128.0473; 100.0525, calc for $C_5H_8O_2$ 100.0524; 98.0359, calc for $C_5H_6O_2$ 98.0368. (Found: C, 55.91; H, 6.04. Calc for $C_6H_8O_3$: C, 56.25; H, 6.25%).

Methyl 5-t-Butyldimethylsilyloxy-2,3-pentadienoate, **38**

The mixture of **37** (3.1 g, 24.2 mmol), t-butyldimethylsilyl chloride (4 g, 26.6 mmol), Et_3N (4.9 g, 48.4 mmol), and 4-dimethylaminopyridine (118 mg, 0.97 mmol) in 50 ml of CH_2Cl_2 was stirred at room temp under N_2. After stirring overnight, the mixture was diluted with ether, then washed with brine and sat NH_4Cl aq. Usual work-up gave a crude oil (5.12 g, crude yield 88.3%). Purification by chromatography over a silica gel column afforded 4.87 g (84%) of **38** as a colorless oil which is unstable to heating.

200 MHz ^{1}H-NMR ($CDCl_3$) δ 5.7 (2H, m), 4.15 (2H, t, J = 4.5 Hz), 3.72 (3H, s), 0.9 (9H, s), 0.08 (6H, s). IR (neat) 1960, 1725, 1250, 1080, 830 cm^{-1}. Mass spectrum (*m/e*) 227 (M^+—CH_3, 1.6), 186 (M^+—isobutylene, 13.6), 185 (M^+—tBu, 100), 89 ($Me_2SiHOCH_2^+$, 43.8). High resolution mass spectrum (*m/e*) 227.1084, calc for $C_{11}H_{19}O_3Si$ 227.1103; 185.0625, calc for $C_8H_{13}O_3Si$ 185.0634.

Methyl 2-(2-t-butyldimethylsilyloxyethylidene)-4-hydroxy-1-cyclohexanecarboxylate, **40**, *and Methyl 2-t-butyldimethylsilyloxymethyl-3-trimethylsilyloxy-3-vinyl-$\Delta^{1,\alpha}$-cyclobutaneacetate*, **39**

To a soln of **38** (4.87 g, 20.1 mmol) in dry toluene (25 ml) was added **17** (8.57 g, 60.35 mmol) and the soln refluxed for 24 hr under N_2. The mixture was then concentrated under high vacuum to give a residue. To a soln of the residue in MeOH (30 ml) was added $NaBH_4$ (2.3 g) at 0°C. After stirring for 3 hr, dil HCl was added and the soln extracted with CH_2Cl_2. Usual workup of the extracts gave a mixture of products which were separated by column chromatography on silica gel to afford the alcohol **40** (3.924 g, 62.2%) and the cyclobutane derivative **39** (734 mg, 9.5%) both as oils.

Compound **40**: 200 MHz ^{1}H-NMR ($CDCl_3$) δ 5.57 (1H, m), 4.25 (2H, d, J = 6 Hz), 3.48–3.8 (1H, m), 3.7 (3H, s), 1.4–2.6 (6H, m), 0.88 (9H, s), 0.06 (6H, s). IR (neat) 3400, 2960, 2940, 2860, 1720, 1260, 1100 cm^{-1}. Mass spectrum (*m/e*) 299 (M^+—CH_3), 1.1), 257 (M^+—tBu, 63.2), 197 (M^+—$tBuMe_2SiOH$—H, 29.2), 89 ($C_3H_9OSi^+$, 70.3), 75 ($C_2H_7OSi^+$, 100). High resolution mass spectrum (*m/e*) 299.1671, calc for $C_{15}H_{27}O_4Si$ 299.1678; 257.1211, calc for $C_{12}H_{21}O_4Si$ 257.1209.

Compound **39**: 200 MHz ^{1}H-NMR ($CDCl_3$) δ 5.7–6.3 (2H, m), 5.16 (1H, dd, J = 2, 16 Hz), 5.07 (1H, dd, J = 2, 12 Hz), 3.9 (2H, d, J = 6 Hz), 3.7 (3H, s), 2.8–3.4 (3H, m), 0.9 (9H, s), 0.13 (9H, s), 0.06 (6H, s). IR (neat) 1720, 1690, 1250, 840 cm^{-1}. Mass spectrum (*m/e*) 384 (M^+, 0.1), 369 (M^+—CH_3, 1.3), 327

(M^+—tBu, 20.4), 193 (M^+—OTBS—CO_2Me, 69.5), 185 (51.1), 89 ($C_3H_9OSi^+$, 100), 75 ($C_2H_7OSi^+$, 83.3). High resolution mass spectrum (*m/e*) 384.2160, calc for $C_{19}H_{36}O_4Si_2$ 384.2152; 327.1460, calc for $C_{15}H_{27}O_4Si_2$ 327.1448.

Conversion of **39** *into* **40**. A soln of derivative **39** (500 mg) in dry toluene (10 ml) was heated at 130° for 6 days in a sealed tube. The reaction mixture was evaporated *in vacuo* to give a residue. The residue was treated by the same procedure as described above, namely sodium borohydride reduction, to afford the alcohol **40** (261 mg, 63.8%).

Methyl 4-acetoxy-2-(2-t-butyldimethylsilyloxyethylidene)-1-cyclohexane-carboxylate, acetate of **40**

To a soln of **40** (148 mg) in pyridine (1.5 ml) was added Ac_2O (1.5 ml). After stirring for 6 hr at room temp, MeOH was added to the mixture and the solvent was then evaporated *in vacuo*. The residue was chromatographed on silica gel to give the acetate of **40** (164 mg, 97.7%) as an oil.

200 MHz ^{1}H-NMR ($CDCl_3$) δ 5.56 (1H, bt, J = 6 Hz), 4.66 (1H, m), 4.22 (2H, d, J = 6 Hz), 3.65 (3H, s), 3.5–3.7 (1H, m), 2.0 (3H, s), 1.2–2.6 (6H, m), 0.88 (9H, s), 0.04 (6H, s). IR ($CHCl_3$) 1705, 1260, 850 cm^{-1}. Mass spectrum (*m/e*) 341 (M^+—CH_3, 1.2), 299 (M^+—tBu, 58.7), 239 (M^+—tBu—AcOH, 38), 117 ($C_4H_9O_2Si^+$, 100). High resolution mass spectrum (*m/e*) 341.1779, calc for $C_{17}H_{29}O_5Si$ 341.1785; 299.1281, calc for $C_{14}H_{23}O_3Si$ 299.1314; 239.1126, calc for $C_{12}H_{19}O_3Si$ 239.1104.

5-Acetoxy-2-carbomethoxycyclohex-1-eneacetic acid, **25c**

To soln of **40** (1.95 g) in acetone (100 ml) was added Jones reagent (15 ml) at 0°. After stirring for 1 hr at 0° and 0.5 hr at room temp, the mixture was filtered and the filtrate was concentrated *in vacuo*. The concentrate was extracted with CH_2Cl_2 and the extract treated as usual to give a residue (1.6 g). To a soln of the residue in dry THF (20 ml) was added Et_3N (6 ml), and the mixture was refluxed for 6 hr. After evaporation of the solvent, the residue was washed successively with HCl and brine. Normal workup gave the crude product which was chromatographed to afford the acidic residue (840 mg, overall yield 60%) as an oil. The acidic residue was observed by NMR spectroscopy to contain a small amount (< 10%) of the double bond isomer in addition to the acid **25c**.

200 MHz ^{1}H-NMR ($CDCl_3$) δ 5.03 (1H, bt, J = 6 Hz), 3.76 (3H, s), 3.48 (2H, s), 2.5 (4H, m), 2.06 (3H, s), 1.6–2.2 (2H, m). IR ($CHCl_3$) 3500–2400, 1730–1710, 1650, 1255, 1028 cm^{-1}. Mass spectrum (*m/e*) 238 (M^+—H_2O, 1.2), 196 (M^+—AcOH, 20.2), 178 (M^+—AcOH—H_2O, 38.8), 164 (M^+—AcOH—MeOH, 100), 152 (M^+—AcOH—CO_2, 75.4). High resolution mass spectrum (*m/e*) 238.0847, calc for $C_{12}H_{14}O_5$ 238.0841; 196.0735, calc for $C_{10}H_{12}O_4$ 194.0735; 178.0602, calc for $C_{10}H_{10}O_3$ 178.0630. (Found: C, 56.00; H, 6.38. Calc for $C_{12}H_{16}O_6$: C, 56.25; H, 6.29%).

6-Acetoxy-1-methoxy-5,6,7,8-tetrahydro-3H-2-benzopyran-3-one, **26c**

The acid **25c** (132 mg, 0.51 mmol) in Ac_2O (3 ml) was refluxed for 3 hr under N_2. After cooling to room temp, the solvent was removed under high vacuum to give a crystalline product which was chromatographed on silica gel eluting with 4:1 $CHCl_3$:ligroine to afford the pyrone **26c** (118 mg, 96%) as crystals. Recrystallization from ether gave 109 mg (89%) of colorless crystals, m.p. 106–107°.

200 MHz ^{1}H-NMR ($CDCl_3$) δ 5.1 (1H, q, J = 5 Hz), 5.05 (1H, s), 2.8 (3H, s), 2.4–2.8 (4H, m), 2.0 (3H, s), 1.7–2.2 (2H, m). IR (nujol) 1725, 1650, 1580, 1235 cm^{-1}. Mass spectrum (*m/e*) 238 (M^+, 44.1), 178 (M^+—AcOH, 87.7), 150 (M^+—AcOH—CO, 100). High resolution mass spectrum (*m/e*) 238.0840, calc for $C_{12}H_{14}O_5$ 238.0841. (Found: C, 60.40; H, 5.84. Calc for $C_{12}H_{14}O_5$: C, 60.48; H, 5.93%).

5-Acetyl-6-methoxy-4-methyl-2H-pyran-2-one, **42**

A soln of **9** (0.455 g, 3.18 mmol) and Ac_2O (0.35 ml, 3.72 mmol) in 4 ml of trifluoroacetic acid was refluxed under a N_2 for 8 hr. The dark soln was cooled and evaporated *in vacuo* to yield a brown solid. Sublimation (45° at 0.02 mm) afforded 0.469 g (81%) of **42** as a white crystalline solid, m.p. 62–64°.

200 MHz ^{1}H-NMR ($CDCl_3$) δ 6.02 (1H, bs), 3.88 (3H, s), 2.40 (3H, s), 2.22 (3H, d, J = 0.4 Hz). ^{13}C-NMR ($CDCl_3$) δ 165.93 (s), 165.01 (s), 160.54 (s), 154.53 (s), 112.90 (s), 111.88 (d), 52.33 (q), 21.25 (q), 19.67 (q). IR ($CHCl_3$) 2970, 2930, 1735 (sh), 1710 (br), 1625, 1540, 1440, 1395, 1375, 1305, 1290 (br), 1150, 1085, 965, 865, 850 cm^{-1}. Mass spectrum (*m/e*) 182 (M^+, 25.9), 154 (M^+—CO, 43.2), 151 (M^+—OMe, 20.0), 139 (M^+—CH_3CO, 21.0), 123 (22.4), 122 (23.6), 109 (12.7), 53 (14.7), 52 (11.0), 43 (100). (Found: C, 59.37; H, 5.42. Calc for $C_9H_{10}O_4$: C, 59.34; H, 5.53.

3-Acetyl-6-hydroxy-4-methyl-2H-pyran-2-one, **44**

A mixture of Ac_2O (0.20 ml, 2.2 mmol) and 0.5 ml of pyridine was added dropwise to **12** (0.238 g, 1.89 mmol). The reaction was moderated by cooling in a water bath. When the reaction had subsided, it was allowed to stand at 25° for 1 hr. After decomposition with 1 ml of HCl and 5 g of ice, the mixture was cooled and filtered. The dark residue was washed with cold, dil HCl and suspended in water. Solid $NaHCO_3$ was added carefully until soln was complete and charcoal was added. After filtration, the filtrate was acidified with an excess of conc HCl with cooling in an ice bath. The ppt was filtered and washed with dil HCl to give 0.129 g (41%) of a white crystalline solid, m.p. 135–137°. Reported[25] m.p. 131–132°.

60 MHz ^{1}H-NMR ($CDCl_3$) δ 5.81 (1H, bs), 2.60 (3H, s), 2.39 (3H, bs). IR ($CHCl_3$) 1750, 1650, 1600, 1550, 1400, 1380, 1130, 980 cm^{-1}.

3-Acetyl-6-methoxy-4-methyl-2H-pyran-2-one, **43**, *and 5-(1-Methoxyethylidene)-4-methyl-2H-pyran-2,6(5H)-dione*, **43'**

A soln of diazomethane, prepared from N-nitroso-N-methylurea (0.20 g, 2.0 mmol), in 10 ml of ether was added to a suspension of **44** (0.215 g, 1.28 mmol) in 20 ml of ether at 0° over 5 min. The resulting soln was stirred for 15 min at 0° and then evaporated *in vacuo*. Sublimination (75° at 0.02 mm) of the residue yielded 0.195 g (84%) of a white solid, m.p. 58–65°. Based on ^{1}H-NMR integration, this solid is an inseparable 3:1 mixture of **43** and a compound tentatively assigned structure **43'**.

Compound **43**: 200 MHz ^{1}H-NMR ($CDCl_3$) δ 5.41 (1H, s), 4.01 (3H, s), 2.54 (3H, s), 2.40 (3H, s). ^{13}C-NMR ($CDCl_3$) δ 197.87 (s), 165.26 (s), 164.67 (s), 159.21 (s), 113.30 (s), 87.61 (d), 55.97 (q), 31.10 (q), 22.09 (q). IR of mixture ($CHCl_3$) 1745, 1650, 1595, 1555, 1400, 1380, 1130, 975 cm^{-1}. (Found: C, 59.23; H, 5.45. Calc for $C_9H_{10}O_4$: C, 59.34; H, 5.49%).

Compound **43'**: 200 MHz ^{1}H-NMR ($CDCl_3$) δ 5.69 (1H, m), 4.16 (3H, s), 2.45 (3H, s), 2.32 (3H, d, J = 0.4 Hz).

Methyl 3-acetyl-2-methoxy-4-methylbenzoate, **45**, *and Methyl 4-acetyl-3-methoxy-5-methylbenzoate*, **46**

A mixture of **42** (0.0471 g, 0.259 mmol) and methyl propiolate (0.50 g, 6.0 mmol) was heated in a sealed tube at 150° for 72 hr. The soln was then cooled and concentrated *in vacuo*. The residue was chromatographed on preparative thick layer silica gel with benzene as eluent to give 0.0484 g (84%) of a pale yellow oil. The oil was determined to be an approximately 2:1 mixture of **45** and **46** by integration of the ^{1}H-NMR spectrum.

Compoind **45**: 200 MHz ^{1}H-NMR ($CDCl_3$) δ 7.81 (1H, d, J = 7 Hz), 7.09 (1H, d, J = 7 Hz), 3.93 (3H, s), 3.88 (3H, s), 2.50 (3H, s), 2.32 (3H, s). ^{13}C-NMR ($CDCl_3$) δ 170.14 (s), 167.65 (s), 138.78 (s), 136.37 (s), 134.59 (s), 131.27 (d), 128.64 (d), 128.09 (s), 52.16 (q), 51.93 (q), 19.76 (q), 19.56 (q). IR of mixture (neat) 2940, 1715 (br), 1595, 1435, 1260 (br), 1155, 1115, 1075, 1030, 800, 760 cm^{-1}. Mass spectrum (*m/e*) 222 (M^+, 29.1), 207 (M^+—CH_3, 38.4), 191 (M^+—OMe, 100.0), 190 (M^+—MeOH, 51.0), 175 (13.6), 163 (27.1), 162 (37.9), 159 (10.5), 133 (12.6), 132 (12.0), 131 (15.7), 105 (14.8), 104 (14.5), 103 (20.2), 91 (12.2), 77 (21.2), 51 (17.4), 44 (31.6), 43 (21.2). (Found: C, 64.89; H, 4.35. Calc for $C_{12}H_{14}O_4$: C, 64.86; H, 6.35%).

Compound **46**: 200 MHz ^{1}H-NMR ($CDCl_3$) δ 7.71 (2H, bs), 3.93 (3H, s), 3.91 (3H, s), 2.34 (6H, s).

Dimethyl 4-acetyl-3-methoxy-5-methylphthalate, **47**

A soln of **42** (0.048 g, 0.26 mmol) and dimethyl acetylenedicarboxylate (1.0 ml, 8.1 mmol) in 1 ml dry toluene was heated in a sealed tube at 140° for 60 hr. The mixture was cooled and evaporated *in vacuo*. The oily residue was chromatographed on 20 g of silica gel using first benzene and then CH_2Cl_2 as eluents to give 0.069 g (93%) of **47** as an oil.

200 MHz ^{1}H-NMR ($CDCl_3$) δ 7.70 (1H, s), 3.93 (6H, s), 3.89 (3H, s), 2.34 (3H, s), 2.26 (3H, s). ^{13}C-NMR ($CDCl_3$) δ 169.28 (s), 169.09 (s), 165.76 (s), 138.71 (s), 135.99 (s), 133.69 (s), 132.51 (s), 129.10 (d), 128.26 (s), 52.88 (q), 52.59 (q), 52.33 (q), 19.49 (q), 16.65 (q). IR (neat) 2930, 1715 (br), 1625, 1600, 1440, 1260 (br), 1170, 1115, 1035, 840, 800 cm^{-1}. Mass spectrum (*m/e*) 191 (M^+—CO_2Me—OCH_2, 22.8), 185 (11.0), 171 (100.0), 157 (37.4), 143 (30.3), 129 (11.1), 127 (21.5), 115 (36.0), 113 (38.6), 69 (37.3), 59 (52.6), 53 (29.8), 47 (15.3), 44 (11.2), 43 (44.3). Found: C, 60.03; H, 5.73; Calc for $C_{14}H_{16}O_6$: C, 60.00; H, 5.75%).

Ethyl 3-nitropropenoate

Dinitrogen tetroxide (10 ml, 0.175 mol) was added *via* syringe to mixture of ethyl acrylate (45 ml, 0.41 mol) and I_2 (31.0 g, 0.122 mol) in 400 ml of anhyd ether cooled to 0°. The mixture was stirred for 1 hr, allowed to warm to 25°, and stirred for 4 hr. The soln was washed with sat $Na_2SO_2O_3$ aq soln, sat $NaHCO_3$ aq, sat NaCl aq, dried with Na_2SO_4, and concentrated *in vacuo*. The crude ethyl 2-iodo-3-nitropropionate was dissolved in 400 ml of anhyd ether, treated with powdered anhyd NaOAc (30 g, 0.37 mol), and refluxed for 3 hr. The cooled soln was decanted, washed with sat $Na_2S_2O_3$ aq, sat $NaHCO_3$ aq, sat NaCl aq, dried with Na_2SO_4, filtered through neutral alumina, and evaporated *in vacuo*. Recrystallization from pentane gave 6.6 g (19%) of a yellow solid, m.p. 25.5–26.5°. Reported[43] m.p. 26–26.5°.

60 MHz ^{1}H-NMR ($CDCl_3$) δ 7.77 (1H, d, J = 14 Hz), 7.13 (1H, d, J = 14 Hz), 4.37 (1H, q, J = 7 Hz), 1.34 (3H, t, J = 7 Hz). IR (neat) 3075, 2950, 1720 (br), 1640, 1530 (br), 1465, 1360, 1275 (br), 1170, 1095, 1025, 945, 855, 760, 670 cm^{-1}.

Ethyl 4-acetyl-3-methoxy-5-methylbenzoate, **48**

A soln of **42** (0.0461 g, 0.253 mmol) and ethyl 3-nitropropenoate (0.148 g, 1.02 mmol) in 1 ml of dry toluene was heated in a sealed tube at 135° for 48 hr. The mixture was cooled and evaporated *in vacuo*. To a soln of the crude adduct in 10 ml of anhyd tetrahydrofuran, cooled to 0°, was added dropwise a soln of 1,8-diazabicyclo[5.4.0]undec-7-ene (0.200 g, 1.32 mmol) in 5 ml of anhyd tetrahydrofuran. After stirring for 6 hr, the mixture was poured into water, extracted with CH_2Cl_2, dried with Na_2SO_4, and evaporated *in vacuo*. The residue was chromatographed on preparative thick layer silica gel using benzene as eluent to yield 0.033 g (55%) of **48** as an oil which solidified on standing.

90 MHz ^{1}H-NMR ($CDCl_3$) δ 7.68 (2H, bs), 4.35 (2H, q, J = 5 Hz), 3.89 (3H, s), 2.30 (6H, s), 1.37 (3H, t, J = 5 Hz). ^{13}C-NMR ($CDCl_3$) δ 169.82 (s), 166.16 (s), 137.89 (s), 135.21 (s), 131.04 (s), 128.57 (d), 128.35 (s), 61.13 (t), 52.09 (q), 19.55 (q), 14.31 (q) [2 carbons are not resolved]. IR ($CHCl_3$) 2955, 2920, 1715, 1435, 1310, 1270, 1125, 1080 cm^{-1}. Mass spectrum (*m/e*) 236 (M^+, 14.4), 205 (M^+—OMe, 19.7), 204 (M^+—MeOH, 25.6), 191 (M^+—OEt, 30.8), 105 (14.4), 91 (28.5), 77 (11.0), 43 (33.3), 28 (100.0). (Found: C, 65.91; H, 6.88. Calc for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83%).

5,7-Dihydroxynaphthoquinone, **49**[27]

Freshly recrystallized lead tetraacetate (6.5 g, 0.0147 mol) was added over 10 min to a soln of **13b** (2.5 g, 0.13 mol) in 40 ml of glacial AcOH. The dark mixture was stirred for 2 hr and filtered. The dark purple crystals were added to a mixture of Ac_2O (15 ml, 0.15 mol) and 15 drops of conc H_2SO_4 and stirred for 8 hr. The mixture was poured onto ice and filtered to give a residue which was recrystallized from EtOH (charcoal) to obtain 2.87 g (65%) of an orange solid, m.p. 160–161°. Reported[27b] m.p. 160°.

60 MHz ^{1}H-NMR ($CDCl_3$) δ 7.36 (2H, s), 6.59 (1H, s), 2.40 (6H, s), 2.32 (3H, s). IR ($CHCl_3$) 1775, 1666, 1370, 1180, 1130, 1010 cm^{-1}.

A hot soln of $SnCl_2$ (2.4 g, 0.013 mol) in 5 ml of conc HCl was added to a soln of NaOH (7.5 g, 0.198 mol) in 15 ml of water. The resulting soln was cooled, Celite added, and the soln filtered. The filtrate was added to 2,5,8-triacetoxynaphthoquinone from above (0.50 g, 1.5 mmol) and refluxed for 5 hr. The cooled mixture was poured slowly into a mixture of 25 ml of conc HCl and cooled in a Dry-Ice acetone slush bath, maintaining the temp below 0°. The soln was extracted rapidly with cold ether, washed with cold phosphate buffer soln (pH 7), sat NaCl aq containing a small amount of sodium dithionate, poured onto silver oxide (3.0 g, 0.013 mol) and Na_2SO_4 (10 g, 0.070 mol) and stirred for 1 hr under a N_2 atm. The orange soln was filtered and evaporated *in vacuo* to yield 0.25 g (88%) of **49** as an orange solid, m.p. 162–165°. Reported[27b] m.p. 165–170° (dec).

60 MHz ^{1}H-NMR (acetone-d_6) δ 7.08 (1H, d, J = 2 Hz), 6.98 (2H, s), 6.66 (1H, d, J = 2 Hz).

2-Acetyl-3-methyl-1,6,8-trihydroxyanthraquinone 2(-acetylemodin), **50**

A soln of **49** (0.214 g, 1.13 mmol) and **42** (0.103 g, 0.566 mmol) in 4 ml of dry *o*-xylene was heated in a sealed tube at 140° for 5 days. The black mixture was cooled and stirred with a mixture of silver oxide (1.0 g, 4.43 mmol) and $MgSO_4$ (2.0 g, 0.17 mol) in 25 ml of dry benzene for 16 hr. The mixture was filtered through Celite and evaporated *in vacuo*. The residue was dissolved in a mixture of conc HBr (1.5 ml, 0.013 mol) and 3.5 ml of glacial AcOH and refluxed for 3.5 hr. The cooled soln was diluted with water, extracted with CH_2Cl_2, washed with sat NaCl aq, dried with Na_2SO_4, and evaporated *in vacuo*. The crude product was chromatographed on preparative thick layer silica gel containing 2% oxalic acid with EtOAc: MeOH (19: 1) as eluent to give 0.063 g of **42** and 0.015 g (22%, based on recovered starting material) of **50** as an orange solid, m.p. 289–290°, reported[28] m.p. 295–296°, identical with an authentic sample[28] by 200 MHz ^{1}H-NMR and TLC.

200 MHz ^{1}H-NMR (DMSO-d_6) δ 7.53 (1H, s), 7.10 (1H, d, J = 2 Hz), 6.56 (1H, d, J = 2 Hz), 2.31 (3H, s).

Methoxybenzoquinone

A mixture of 2-methoxyhydroquinone (0.357 g, 2.55 mmol) and silver carbonate on Celite (2.9 g, 5.0 mmol) in 40 ml of dry benzene was refluxed under a N_2 atm for 1 hr. The cooled soln was dried with Na_2SO_4, and evaporated *in vacuo* to afford 0.35 g (100%) of methoxybenzoquinone as a bright yellow solid, m.p. 141–143°. Reported[44] m.p. 142°.

60 MHz ^{1}H-NMR ($CDCl_3$) δ 6.79 (2H, d, J = 2 Hz), 6.03 (1H, bs), 3.88 (3H, s). IR ($CDCl_3$) 2990, 1680, 1655 (br), 1595, 1460, 1375, 1355, 1220 (br), 1175, 1105, 1000, 870 cm^{-1}.

6-Acetyl-3,5-dimethoxy-7-methylnaphthoquinone, **51**

A soln of **42** (0.135 g, 0.740 mmol) and methoxybenzoquinone (0.380 g, 2.75 mmol) in 4 ml of dry *o*-xylene was heated in a sealed tube at 160° for 7 days. The black mixture was cooled and stirred with a mixture of silver oxide (1.0 g, 4.3 mmol) and $MgSO_4$ (2.0 g, 0.017 mmol) in 25 ml of dry benzene for 16 hr. The mixture was filtered through Celite and evaporated *in vacuo*. The crude solid was chromatographed on 100 g of silica gel using an EtOAc: hexane gradient as eluent to give 0.122 g (60%) of **51** as a yellow solid, m.p. 182–184°.

200 MHz ^{1}H-NMR ($CDCl_3$) δ 7.89 (1H, s), 6.13 (1H, s), 3.97 (3H, s), 3.90 (3H, s), 2.66 (3H, s), 2.41 (3H, s). ^{13}C-NMR ($CDCl_3$) δ 184.34 (s), 180.79 (s), 169.25 (s), 161.19 (s), 141.16 (s), 140.99 (d), 138.36 (s), 133.48 (s), 126.83 (s), 126.39 (s), 108.26 (d), 56.52 (q), 52.45 (q), 20.07 (q), 19.11 (q). IR ($CHCl_3$) 2915, 1725, 1675, 1643, 1618, 1585, 1435, 1333, 1278, 1160, 1102, 1080, 1020, 855 cm^{-1}. Mass spectrum (*m/e*) 275 (15.2), 274 (M^+, 100), 259 (M^+—CH_3, 55.7), 243 (M^+—MeO, 40.3), 242 (M^+—MeOH, 17.3), 214 (33.6), 175 (11.1). Found: C, 65.54; H, 5.03. Calc for $C_{15}H_{14}O_5$: C, 65.69; H, 5.14.

6-Acetyl-5-hydroxy-3-methoxy-7-methylnaphthoquinone, **52**

Method A: BBr_3 (0.50 ml, 5.3 mmol) was added slowly *via* syringe to a soln of adduct **51** (0.067 g, 0.24 mmol) in 20 ml of dry CH_2Cl_2 cooled to −78°. After stirring at this temp for 10 min, the mixture was diluted with 25 ml of water. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with brine, dried with Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was recrystallized from benzene-petroleum ether to afford 0.057 g (89%) of **52** as yellow-orange crystals, m.p. 191–192°.

Method B: A soln of diazomethane, prepared from N-nitroso-N-methylurea (0.10 g, 1.0 mmol), in 5 ml of ether was added to a soln of **53** (0.041 g, 1.68 mmol) in 5 ml of MeOH and 5 ml of ether at 0°. After stirring for 10 min at 0°, the soln was evaporated *in vacuo*. Sublimation of the residue at 140° (0.01 mm) gave 0.028 g (64%) of **52** as a yellow-orange solid, m.p. 191–192°. 200 MHz ^{1}H-NMR ($CDCl_3$) δ 12.06 (1H, bs), 7.89 (1H, s), 6.27 (1H, s), 3.98 (3H, s), 2.66 (3H, s), 2.40 (3H, s). ^{13}C-NMR ($CDCl_3$) δ 184.08 (s), 180.65 (s), 168.21 (s), 160.94 (s), 141.87 (s), 141.04 (d), 138.51 (s), 133.75 (s), 128.17 (s), 127.09 (s), 108.33 (d), 56.46 (q), 20.61 (q), 19.18 (q). IR ($CHCl_3$) 3425, 2920, 1710, 1660, 1630, 1585, 1375, 1340, 1265, 1160, 1100, 1070, 880 cm^{-1}. Mass spectrum (*m/e*) 260 (M^+, 67.8), 245 (M^+—CH_3, 100.0), 229 (M^+—MeO, 24.1), 228 (M^+—MeOH, 13.4), 203 (18.0), 202 (12.8), 161 (30.5).

6-Acetyl-3,5-dihydroxy-7-methylnaphthoquinone, **53**

BBr_3 (0.50 ml, 5.2 mmol) was added *via* syringe to an ice-cooled soln of adduct **51** (0.103 g, 0.376 mmol) in 15 ml of dry CH_2Cl_2. The resulting dark soln was stirred at 0° for 1.5 hr, allowed to warm to 25°, and poured into 50 ml of water. The organic layer was separated, the aqueous layer was extracted with ether and then extracted with 5% KOH aq. The basic soln was acidified with conc HCl and extracted with ether. The organic extracts were dried with Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was recrystallized from EtOAc-hexanes to afford 0.063 g (68%) of **53** as a yellow solid, m.p. 206–209° (dec).

200 MHz ^{1}H-NMR (acetone-d_6) δ 7.84 (1H, s), 6.18 (1H, s), 2.70 (3H, s), 2.47 (3H, s). IR (KBr) 3100 (br), 1708, 1630 (br), 1575, 1335, 1190, 860 cm^{-1}. Mass spectrum (*m/e*) 246 (M^+, 100.0), 201 (12.6), 200 (72.7), 172 (14.8), 115 (11.8), 77 (11.5), 51 (11.0).

6-Acetyl-3-hydroxy-5-methoxy-7-methylnaphthoquinone, **54**

A mixture of adduct **51** (0.028 g, 0.102 mmol) and KOH (0.040 g, 1.02 mmol) in 40 ml of water was stirred at 25° under a N_2 atm for 24 hr until the adduct had dissolved. The soln was washed with ether and acidified with dil HCl aq. The acidic soln was extracted with $CHCl_3$, dried with Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was sublimed at 130° (0.02 mm) to give 0.027 g (100%) of **54** as a yellow solid, m.p. 173–177° (dec).

200 MHz ^{1}H-NMR ($CDCl_3$) δ 7.91 (1H, s), 6.31 (1H, s), 3.98 (3H, s), 2.68 (3H, s), 2.41 (3H, s). ^{13}C-NMR ($CDCl_3$) δ 184.48 (s), 182.42 (s), 168.99 (s), 157.01 (s), 142.53 (s), 140.88 (d), 138.80 (s), 134.48 (s), 127.06 (s), 126.95 (s), 108.94 (d), 52.52 (q), 20.32 (q), 19.13 (q). IR ($CHCl_3$) 3330, 2925, 1720, 1655, 1582, 1380, 1340, 1270, 1205, 1160, 1075 cm^{-1}. Mass spectrum (*m/e*) 261 (15.5), 260 (M^+, 100.0), 245 (M^+—CH_3, 16.3), 229 (M^+—MeO, 37.5), 228 (M^+—MeOH, 17.7), 201 (13.9), 200 (66.3), 83 (10.2), 69 (11.2).

Diethyl 3-chloroglutaconate

Diethyl 3-oxoglutarate (47.0 g, 0.232 mol) was added dropwise with stirring over 10 min to PCl_5 (85.0 g, 0.408 mol) and then heated to 65° for 10 min. More PCl_5 (5.0 g, 0.024 mol) was added and heating continued for an additional 20 min. The red soln was poured onto 300 g of ice and stirred for 30 min. The mixture was extracted with ether, dried with Na_2SO_2, and concentrated *in vacuo* to give an orange oil. The oil was diluted with 150 ml of abs EtOH containing 15 ml of conc H_2SO_4. The resulting soln was heated to boiling, and, while periodically adding more EtOH, 700 ml of EtOH was distilled. The soln was cooled, poured into 250 ml of water, saturated with solid NaCl, and extracted with ether. The combined extracts were washed with 10% Na_2CO_3 aq, dried with Na_2SO_4, and concentrated *in vacuo* to give a yellow oil. Distillation yielded 34.3 g (67%) of a clear liquid, b.p. 95–105° (1 mm). Reported[45] b.p. 134–139° (9.5 mm).

60 MHz ^{1}H-NMR ($CDCl_3$) δ 6.27 and 6.20 (1H, s), 4.22 (4H, q, J = 7 Hz), 4.08 and 3.45 (2H, s), 1.58 (6H, t, J = 7 Hz). IR (neat) 2950, 1720 (br), 1630, 1360, 1305, 1170 (br), 1025 cm^{-1}.

Ethyl 4-carboethoxymethyl-6-methyl-2-oxo-2H-pyran-4-carboxylate

Freshly distilled ethyl acetoacetate (17.0 g, 0.131 mol) was added dropwise over 10 min to a suspension of sodium hydride (2.5 g, 0.104 mol) in 500 ml of dry benzene under a N_2 atm, and the resulting mixture refluxed for 30 min. After cooling to 50°, diethyl 3-chloroglutaconate (22.0 g, 0.100 mol) was added dropwise over 10 min. The yellow soln was refluxed for 2 hr, cooled, and decomposed with 50 ml of 2N H_2SO_4. The organic layer was separated and the aqueous layer extracted with benzene. The combined extracts were washed with water, dried with $MgSO_4$, filtered, and concentrated *in vacuo* to afford a yellow oil which was distilled to give 21.4 g (75%) of the pyrone as a pale yellow liquid, b.p. 145–155° (0.01 mm). Reported[32] b.p. 172–174° (1 mm).

60 MHz ^{1}H-NMR ($CDCl_3$) δ 6.09 (1H, s), 4.31 (2H, q, J = 7 Hz), 4.17 (2H, q, J = 7 Hz), 3.70 (2H, s), 2.49 (3H, s), 1.38 (3H, t, J = 7 Hz), 1.26 (3H, t, J = 7 Hz). IR (neat) 2950, 1725 (br), 1625, 1540, 1400, 1305, 1265, 1180, 1085, 1030, 980, 865 cm^{-1}.

3-Carboxymethylglutaconic acid, **57**

A mixture of **35** (14.8 g, 0.052 mol) and NaOH (10.3 g, 0.258 mol) in 100 ml of water was heated at 70° for 1 hr. The soln was cooled to 25°, extracted with ether, and acidified with conc HCl. The acidified soln was extracted with ether, dried with Na_2SO_4, filtered, and evaporated *in vacuo*. The resulting solid was taken up in acetone, filtered while hot, and evaporated *in vacuo*. Recrystallization from $CHCl_3$ yielded 6.59 g (68%) of **57** as an off-white solid, m.p. 131–132.5°. Reported[32] m.p. 136–137°.

60 MHz ^{1}H-NMR (acetone-d_6) δ 6.01 (1H, s), 4.80 (3H, bs), 3.85 (2H, s), 3.32 (2H, bs).

Methyl 6-methoxy-2-oxo-2H-pyran-4-acetate, **59**

A soln of **57** (0.50 g, 2.66 mmol) and Ac_2O (0.50 ml, 5.4 mmol) in 20 ml of anhyd tetrahydrofuran was refluxed for 30 min under a N_2 atm. The soln was cooled to 0° and a soln of diazomethane, prepared from N-nitroso-N-methylurea (5.0 g, 0.050 mol), in 50 ml of ether was added over 10 min. After stirring at 0° for 30 min, the soln was evaporated *in vacuo*. Flash chromatography of the residue using ether : benzene (1 : 9) as eluent yielded 0.301 g (57%) of **59** as a clear oil.

200 MHz ^{1}H-NMR ($CDCl_3$) δ 5.80 (1H, bs), 5.40 (1H, bs), 3.93 (3H, s), 3.74 (3H, s), 3.43 (2H, s). ^{13}C-NMR ($CDCl_3$) δ 169.26 (s), 164.52 (s), 160.44 (s), 155.54 (s), 104.42 (d), 83.21 (d), 56.08 (q), 52.51 (q), 40.83 (t). IR ($CHCl_3$) 2925, 1710 (br), 1625, 1525 (br), 1440, 1330, 1260, 1160, 1010, 848 cm^{-1}. Mass spectrum (*m/e*) 198 (M^+, 55.8), 170 (M^+—CO, 100.0), 167 M^+—MeO, 28.3), 155 (17.3), 139 (M^+—CO_2Me, 20.7), 138 (23.7), 135 (18.9), 127 (16.3), 123 (27.9), 112 (19.1), 111 (28.7), 95 (12.5), 79 (13.2), 69 (12.6), 68 (11.7), 59 (59.3), 55 (11.6), 53 (13.2), 52 (21.4), 51 (16.9), 44 (16.8), 43 (11.1), 41 (10.3).

Methyl 5-acetyl-6-methoxy-2-oxo-2H-pyran-4-acetate, **56b**

A soln of **59** (0.250 g, 1.26 mmol) and Ac_2O (0.20 ml, 2.2 mmol) in 4 ml of dry trifluoroacetic acid was refluxed for 4 hr under N_2. The dark soln was cooled and evaporated *in vacuo*. Flash chromatography of the residue using EtOAc : hexanes (1 : 1) as eluent gave 0.178 g (62%) of a yellow oil.

200 MHz ^{1}H-NMR ($CDCl_3$) δ 6.09 (1H, s), 3.83 (3H, s), 3.71 (3H, s), 3.70 (2H, s), 2.50 (3H, s). ^{13}C-NMR ($CDCl_3$) δ 169.47 (s), 167.32 (s), 165.51 (s), 160.04 (s), 150.04 (s), 114.34 (d), 111.41 (s), 52.37 (q), 52.29 (q), 40.18 (t), 20.14 (q). IR (neat) 2950, 1780 (sh), 1725 (br), 1620, 1540, 1435, 1260, 1175 (br), 865, 735 cm^{-1}.

Mass spectrum (*m/e*) 240 (M^+, 13.4), 209 (M^+—MeO, 18.3), 208 (M^+—MeOH, 14.4), 180 (23.0), 152 (14.1), 59 (13.5), 43 (100.0).

8-Acetyloxy-1-hydroxy-11-methoxy-7,8,9,10-tetrahydronaphthacene-5,12-dione, **60**, *and the bis-adduct*, **61**

A soln of the pyrone **26c** (127 mg, 0.53 mmol) and juglone **13a** (139 mg, 0.8 mmol) in 5 ml of xylene was refluxed for 5.5 days, cooled, and treated with 550 mg silver oxide and 550 mg anhyd $MgSO_4$ with stirring at 25° for 12 hr. The mixture was filtered, evaporated *in vacuo*, and the residue chromatographed on silica gel eluting with $CHCl_3$: ligroine (1 : 1) to give 124 mg (63.2%) of **60** as a yellow solid and 48 mg (16.6%) of **61**. Recrystallization of **60** from diethyl ether gave yellow crystals, *m.p. 164–165°*.

Compound **60**: 200 MHz ^{1}H-NMR ($CDCl_3$) δ 13.0 (1H, s), 7.88 (1H, s), 7.78 (1H, dd, J = 8, 1 Hz), 7.65 (1H, dd, J = 8, 8 Hz), 7.29 (1H, dd, J = 8, 1 Hz), 5.26 (1H, quintet, J = 5 Hz), 3.94 (3H, s), 3.24 (1H, dd, J = 5, 8 Hz), 3.1–3.0 (3H, m), 2.06 (3H, s), 2.2–2.0 (2H, m). ^{13}C-NMR ($CDCl_3$) δ 188.5, 182.3, 170.5, 162.6, 159.2, 143.3, 138.9, 136.0, 132.8, 124.6 (2 peaks), 123.0, 122.6, 118.8, 116.9, 68.0, 63.1, 35.1, 26.5, 23.4, 20.8. IR (Nujol) 1735, 1675, 1635, 1585, 1255 cm^{-1}. Mass spectrum (*m/e*) 366 (M^+, 4.6), 306 (M^+—AcOH, 100), 291 (M^+AcOH—CH_3, 65.6). High resolution mass spectrum (*m/e*) 366.1100, calc for $C_{21}H_{18}O_6$ 366.1103; 306.0885, calc for $C_{19}H_{14}O_4$ 306.0892. (Found: C, 68.54; H, 5.10. Calc for $C_{21}H_{18}O_6$: C, 68.83; H, 4.96%).

Compound **61**: 60 MHz ^{1}H-NMR ($CDCl_3$) δ 11.9–11.5 (2H, m), 7.75–7.15 (6H, m), 3.88 (3H, s), 3.9–3.3 (9H, m), 1.75 (3H, s), 1.8–1.5 (3H, m). IR ($CHCl_3$) 1735, 1695, 1655, 1600, 1573, 1450, 1260 cm^{-1}. Mass spectrum (*m/e*) 482 (M^+—AcOH, 0.8), 368 (dihydro **60**, 39.6), 308 (dihydro **60**—AcOH, 100), 276 (dihydro **60**—AcOH—CO, 61.2), 174 (1,4,5-trihydroxynaphthalene$^+$, 76.2). (Found: C, 68, 46; H, 4.86. Calc for $C_{31}H_{26}O_9$: C, 68.63; H, 4.83%).

1,8-Dihydroxy-11-methoxy-7,8,9,10-tetrahydronaphthacene-5,12-dione, **64**

Method A: To a soln of **60** (34 mg, 0.093 mmol) in 1 ml of $CHCl_3$ was added 50 mg Na_2CO_3 in 5 mal of aqueous MeOH and the soln was stirred at 25° for 6 hr. Normal workup gave a residue which was chromatographed on silica gel eluting with $CHCl_3$ to give 30 mg (100%) of **64**. Recrystallization from benzene/diethyl ether gave slightly yellow crystals, m.p. 203–204°. 60 MHz ^{1}H-NMR ($CDCl_3$) δ 13.0 (1H, s), 7.77 (1H, bd, J = 8 Hz), 7.70 (1H, bt, J = 8 Hz), 7.24 (1H, bd, J = 8 Hz), 7.23 (1H, s), 4.27 (1H, bm), 3.92 (3H, s), 2.9–3.2 (4H, m), 1.9–2.2 (2H, m), 1.8 (1H, bs). IR ($CHCl_3$) 1665, 1630, 1590, 1465, 1365, 1295, 1270 cm^{-1}. Mass spectrum (*m/e*) 325 (M + 1, 19), 324 (M^+, 100), 309 (M^+—CH_3, 44.6), 307 (M^+—OH, 22.4), 306 (M^+—H_2O, 72.9), 291 (M^+—H_2O—CH_3, 50.6).

Method B: A mixture of the pyrone **26c** (356 mg, 1.49 mmol) and juglone **13a** (384 mg, 2.20 mmol) was reacted under the identical conditions given above for the Diels–Alder reaction and silver oxide oxidation to give a residue. To a solution of this residue in 30 ml of MeOH : CH_2Cl_2 : water (10 : 3 : 2) was added 1.6 g of Na_2CO_3. After stirring for 1 day at 25° and refluxing for 1 hr, the mixture was acidified with dil HCl and extracted with CH_2Cl_2. Normal workup gave a crude mixture which was chromatographed on silica gel eluting first with $CHCl_3$: ligroine (2 : 1) to give 34 mg (7.4%) of **65** as an oil. Further elution with $CHCl_3$ gave 230 mg (47.5%) of **64** as yellow crystals. *Compound* **65**: 60 MHz ^{1}H-NMR ($CDCl_3$) δ 11.4 (1H, s), 7.1–7.8 (4H, m), 6.58 (1H, bd, J = 9 Hz), 6.27 (1H, dt, J = 8, 4 Hz), 3.89 (3H, s), 2.99 (2H, bt, J = 8 Hz), 2.3–2.6 (2H, bm). IR ($CHCl_3$) 1665, 1635, 1580, 1450, 1345, 1310, 1285, 1255 cm^{-1}. Mass spectrum (*m/e*) 306 (M^+). (Found: C, 73.60; H, 4.89. Calc for $C_{19}H_{14}O_4$: C, 74.50; H, 4.61%).

Method C: the bis-adduct **61** (14 mg, 0.026 mmol) dissolved in 2.5 ml of methanol containing 20 mg of sodium carbonate was stirred at 25° for 7 hr. Normal workup gave a residue which was chromatographed on silica gel eluting with chloroform to give 6 mg (72%) of the alcohol **64** as yellow crystals. A trace of the acetate **60** was also isolated from the column.

9,10-Dihydro-1,11-dimethoxynaphthacene-5,8(7H),12-trione, **69**

Method A: To a soln of the acetate **60** (23 mg, 0.06 mmol) in ml of dry $CHCl_3$ were added silver oxide (29 mg) and MeI (0.4 ml) and stirred at room temp. Three additional portions of silver oxide (20 mg) and MeI (0.4 ml) were added during the reaction. After stirring for 3 days, the mixture was filtered, and the inorganic part was washed with hot $CHCl_3$. The $CHCl_3$ filtrates were evaporated *in vacuo* to give a crude product which was chromatographed on silica gel column eluting with $CHCl_3$: ligroine (1 : 1) to give 22 mg (92%) of the 1,11-dimethoxy 8-acetate. 60 MHz ^{1}H-NMR ($CDCl_3$) δ 7.2–7.85 (4H, m), 5.26 (1H, quintet, J = 5 Hz), 4.03 (3H, s), 3.96 (3H, s), 2.9–3.2 (4H, m), 2.05 (3H, s), 1.95–2.15 (2H, m).

To a soln of the dimethoxyacetate (20 mg, 0.052 mmol) in 5.5 ml of MeOH : $CHCl_3$: water (4 : 1 : 0.5) was added Na_2CO_3 (45 mg) and the soln stirred at room temp for 12 hr. After acidification with dil HCl, the mixture was extracted with CH_2Cl_2. Usual workup of the extracts afforded 20 mg (100%) of the dimethoxy alcohol. 60 MHz ^{1}H-NMR ($CDCl_3$) δ 7.2–7.85 (4H, m), 4.2 (1H, bm), 4.03 (3H, s), 3.95 (3H, s), 2.9–3.2 (4H, m), 1.9–2.2 (3H, m). IR ($CHCl_3$) 3300, 1665, 1630, 1585, 1455, 1355, 1285, 1255 cm^{-1}.

To a soln of the crude alcohol (20 mg) in acetone (5 ml) was added cooled Jones reagent (8 drops) at 0°. After stirring for 20 min, isopropanol was added to the mixture which was extracted with CH_2Cl_2. Usual workup of the extracts gave a residue (22 mg) which was chromatographed on silica gel eluting with $CHCl_3$: ligroine (1 : 1) to give 11 mg of **69** (62.2% overall yield from the dimethoxy acetate). This ketone decomposed gradually at room temp. Rechromatography on silica gel gave 7 mg of crystals, m.p. 215°. 60 MHz ^{1}H-NMR ($CDCl_3$) δ 7.2–7.8 (4H, m), 4.05 (3H, s), 4.0 (3H, s), 3.71 (2H, s), 3.28 (2H, t, J = 7 Hz), 2.57 (2H, t, J = 7 Hz). IR ($CHCl_3$) 1720, 1670, 1585, 1340, 1290, 1260, 1010 cm^{-1}. (Found: C, 71.23; H, 4.70. Calc for $C_{20}H_{16}O_5$: C, 71.42; H, 4.79%).

Method B: To a soln of **70**[33] (97 mg, 0.28 mmol) in dry CH_2Cl_2 (30 ml) was added $AcCl_3$ (250 mg, 1.88 mmol) and the mixture was stirred at room temp under N_2. After stirring for 4 days, dil HCl was added and then the mixture was extracted with a large amount of CH_2Cl_2. Usual workup of the extracts gave a residue (104 mg). To a soln of this residue in dry acetone (20 ml) was added anhyd K_2CO_3 (500 mg) and Me_2SO_4 (1 ml). After stirring under reflux for 4 hr, the mixture was concentrated *in vacuo*, poured onto water, and extracted with CH_2Cl_2. Normal workup gave a residue which was treated with 1 ml of 3.5% HCl in 10 ml of acetone and refluxed for 30 min. Water was added and the soln extracted with CH_2Cl_2. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a residue which was chromatographed on silica gel eluting with $CHCl_3$ containing a trace of acetone to give 86 mg of the ketone **69**. Recrystallization gave crystals, m.p. 215°. ^{1}H-NMR and IR identical to that prepared by Method A.

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