# APPROACHES TO THE SYNTHESIS OF XANTHONE ANALOGS OF THE ANTHRACYCLINE CLASS OF ANTICANCER AGENTS

A Thesis

by

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*To my parents, who helped me find the path*

*To my wife, who accompanies me along this path*

## ABSTRACT

Several strategies outlining approaches to the synthesis of the heteroanthracyclinones 4-demethoxyxanthodaunomycinone and 4-demethoxy*iso*xanthodaunomycinone (7,8,9,10-tetrahydrobenzo(*b*)-6,7,9,11-tetrahydroxy-9-acetylxanthen-12 and 5-one) are described.

The condensation of tetralin 2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol with *o*-methoxybenzoic acid was investigated and useful large-scale syntheses of important 1,4-dimethoxy-substituted xanthone intermediates were developed.

Diels-Alder cycloaddition reaction between a xanthone-derived *o*-quinodimethane intermediate and an olefin afforded a low yield of adduct. On the other hand, excellent yields of isolable but labile adducts were obtained in the cycloaddition reaction between xanthoquinone (and also thioxanthoquinone) and Danishefsky's dienes. The formation of linear *vs* internal adducts was rationalized on the grounds of resonance and FMO theory. Efforts to induce unactivated dienes to cycloadd using catalysts as well as annulation studies on model compounds using the novel reagent (E)-N-vinylpyrrolidine-β-(2-lithio-1,3-dithian-2-yl) (as a synthon of the α,β-dianion of acetaldehyde) are discussed.

The synthesis of daunomycin and xanthodaunomycin analogs carrying a carbon substituent at position 7 were not accessible using the Diels-Alder cycloaddition reaction as diene 1-carbomethoxy-3-triethylsilyloxy-1,3-butadiene failed to react with either quinizarinquinone or xanthoquinone even at elevated temperatures.

The compound 4-hydroxy-1-[[2-[(2-hydroxyethyl)amino]ethyl]amino]xanthone and the 4-methoxy derivative were prepared and found to be *inactive* in the *in vivo* P-388 mouse leukemia model system.

## RESUME

On décrit plusieurs stratégies pour la synthèse des hétéroanthracyclinones déméthoxy-4-xanthodaunomycinone et déméthoxy-4-*iso*xanthodaunomycinone (tétrahydrobenzo(*b*)-7,8,9,10 tétrahydroxy-6,7,9,11 acétyl-9 xanthen-12 et -5-one).

On a étudié la condensation de l'acétyl-2 diméthoxy-5,8-tétrahydro-1,2,3,4 naphthol-2 sur l'acide *o*-méthoxy-benzoique et on a développé des synthèses qui nous ont permis de préparer en grande quantité des diméthoxy-1,4 xanthones.

Une addition de Diels-Alder d'un *o*-quinodiméthane (généré à partir de xanthone) sur une oléfine a conduit à un adduit avec de faibles rendements. Par contre, les adduits de la cycloaddition de xanthoquinone (et aussi de thioxanthoquinone) sur les diènes de Danishefsky ont été obtenus avec d'excellents rendements. La formation d'adduits linéaires en fonction d'adduits internes peut être expliqué par la théorie de résonance et la théorie d'orbitales moléculaires frontières. Plusieurs essais afin de faire réagir les diènes non-activés en présence de catalyseur dans les réactions de cycloaddition sont rapportés. D'autres essais ont porté sur la réaction d'annulation de produits modèles utilisant un nouveau réactif (E)-N-vinylpyrrolidine-β-(lithio-2 dithian-1,3 yl-2) comme synthon du dicarbanion α,β du acétaldehyde.

La synthèse d'analogues de daunomycinone et xantho-daunomycine avec un substituant carboné à la position 7 n'a pu être réalisée par la réaction Diels-Alder parce que le diène carbométhoxy-1 triéthylsilyloxy butadiène-1,3 ne réagit ni avec le quinizarinquinone ni avec le xanthoquinone même à des températures élevées.

Le composé [[hydroxy-2 éthyl amino]-2 éthyl amino]-1 hydroxy-4 xanthone et l'analogue méthoxy-4 ont été préparés mais ceux-ci n'ont démontré aucune activité antitumorale *in vivo* vis-à-vis les céllules leucémiques P-388.

## ACKNOWLEDGEMENTS

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## LIST OF ABBREVIATIONS AND SYMBOLS

| | |
|---|---|
| A | adenine |
| Å | angstrom |
| Ac | acetyl |
| AD-32 | N-trifluoroacetyladriamycin-14-valerate |
| AIBN | azo*bis*isobutyronitrile |
| amu | atomic mass unit |
| Ar | aryl |
| ATP | adenosine triphosphate |
| bp | boiling point |
| br | broad |
| Bu | butyl |
| *t*-Bu | *tert*-butyl |
| C | cytosine |
| *ca.* | *circa* |
| CAN | ceric ammonium nitrate (ammonium cerium(IV) nitrate) |
| *m*-CPBA | *meta*-chloroperoxybenzoic acid |
| cat. | catalyst, catalytic |
| $cm^{-1}$ | reciprocal centimeters (wavenumber) |
| $^{13}C$.m.r. | carbon magnetic resonance |
| conc. | concentrated |
| $CoQ_{10}$ | coenzyme $Q_{10}$ |
| d | doublet |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| dec. | decomposes |
| DHP | dihydropyran |

| | |
|---|---|
| DMA | N,N-dimethylacetamide |
| DMAP | 4-dimethylaminopyridine |
| DME | 1,2-dimethoxyethane |
| DMF | N,N-dimethylformamide |
| DMSO | dimethyl sulfoxide |
| DNA | deoxyribonucleic acid |
| $E^+$ | electrophile |
| EI | electron impact |
| epr | electron paramagnetic resonance |
| eq | equivalent |
| esr | electron spin resonance |
| Et | ethyl |
| $Eu(thd)_3$ | *tris*(2,2,6,6-tetramethyl-3,5-heptane-dionato)-europium(III) |
| eV | electron volt |
| FMO | frontier molecular orbital |
| $FP_{oxid}$ | flavoprotein (oxidized) |
| $FP_{red}$ | flavoprotein (reduced) |
| FT | Fourier transform |
| G | guanine |
| g | gram |
| gc | gas chromatography |
| gc/ms | gas chromatography-mass spectrometry |
| GSH | glutathione reduced |
| GSSH | glutathione oxidized |
| h | hour(s) |

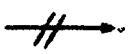
| | |
|---|---|
| HMPA | hexamethylphosphoramide (hexamethylphosphoric triamide) |
| $^1$H.m.r. | proton magnetic resonance |
| HOMO | highest occupied molecular orbital |
| HPLC | high pressure liquid chromatography |
| Hz | hertz |
| IR (ir) | infrared |
| J | coupling constant (three bonds) |
| $^n$J | coupling constant (n bonds) |
| k | kilo |
| kcal | kilocalories |
| LAH | lithium aluminium hydride |
| LDA | lithium diisopropylamide |
| LiTMP | lithium 2,2,6,6-tetramethylpiperidide |
| L-Selectride | lithium tri-*sec*butylborohydride |
| LUMO | lowest unoccupied molecular orbital |
| M | molar |
| m | multiplet |
| *m* | *meta* |
| Me | methyl |
| MEM | β-methoxyethoxy methyl |
| mg | milligram(s) |
| MHz | megahertz |
| min | minute(s) |
| mL | milliliter(s) |
| mmol | millimole(s) |

| | |
|---|---|
| MOM | methoxymethyl |
| MOP | 2-methoxypyridine |
| mp | melting point |
| Ms | methanesulfonyl (mesyl) |
| ms | mass spectrum |
| N | Normal |
| n | normal |
| NADH | nicotinamide adenine dinucleotide-reduced |
| NADP | nicotinamide adenine dinucleotide phosphate-oxidized |
| NADPH | nicotinamide adenine dinucleotide phosphate-reduced |
| NBS | N-bromosuccinimide |
| nmr | nuclear magnetic resonance |
| Nu | nucleophile(ic) |
| *o* | *ortho* |
| $O_2^{\cdot-}$ | superoxide |
| Ox | oxidation |
| *p* | *para* |
| PCC | pyridinium chlorochromate |
| PDC | pyridinium dichromate |
| PG | protecting group |
| Ph | phenyl |
| pmr | proton magnetic resonance |
| PPA | polyphosphoric acid |
| ppm | parts per million |
| q | quartet |
| Red-Al | sodium *bis*-(2-methoxyethoxy)aluminium hydride (Vitride) |

| | |
|---|---|
| RNA | ribonucleic acid |
| rt. | room temperature |
| s | singlet |
| *sec* | secondary |
| SOD | superoxide dismutase |
| T | temperature |
| T | thymine |
| t | triplet |
| TBAF | tetrabutylammonium fluoride |
| TCNE | tetracyanoethylene |
| *tert* | tertiary |
| TES | triethylsilyl |
| TFA | trifluoroacetic acid |
| TFAA | trifluoroacetic anhydride |
| THF | tetrahydrofuran |
| THP | tetrahydropyran |
| Triton B | N-benzyltrimethylammonium hydroxide |
| tlc | thin layer chromatography |
| TMEDA | N,N,N',N'-tetramethylethylenediamine |
| TMP | 2,2,6,6-tetramethylpiperidine |
| TMS | trimethylsilyl |
| TMS-Cl | trimethylsilyl chloride |
| TMS-I | trimethylsilyl iodide |
| *p*-TsOH | *para*-toluenesulfonic acid |
| μ | micron |
| u.v. | ultraviolet |
| v | volume |

| | |
|---|---|
| w | weight |
| z | electron-charge |
| Zn* | Zinc (activated) |

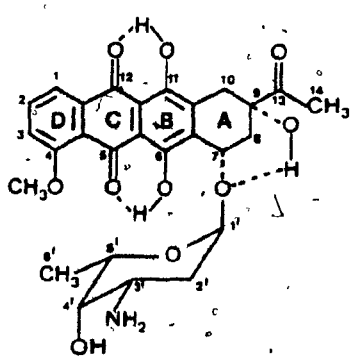
## SYMBOLS

| | |
|---|---|
|  | ultrasound |
|  | 1-electron transfer |
|  | 2-electron transfer |
| Δ | heat |
|  | reaction does not occur |
|  | a series of reactions are involved |
| [O] | oxidation |

# INTRODUCTION

## A. THE ANTHRACYCLINES

Daunomycin* (1) and adriamycin* (2) are naturally occurring antibiotic antitumor agents and are members of an important class of antibiotics known as the anthracyclines.

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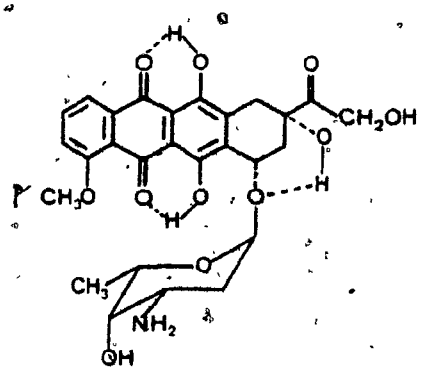


2

The anthracyclines are produced by various species of *Streptomyces* and occur both as aglycones termed anthracyclinones, and as glycosides.

The aglycones, characterized by a tetrahydronaphthacene quinone moiety, show some differences in ring A substituents as well as in the degree and pattern of hydroxylation (Figure 1).

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*Daunomycin and adriamycin are trivial names, the international non-proprietary names are daunorubicin and doxorubicin respectively. We will adhere to common practice and use the trivial names throughout the thesis.

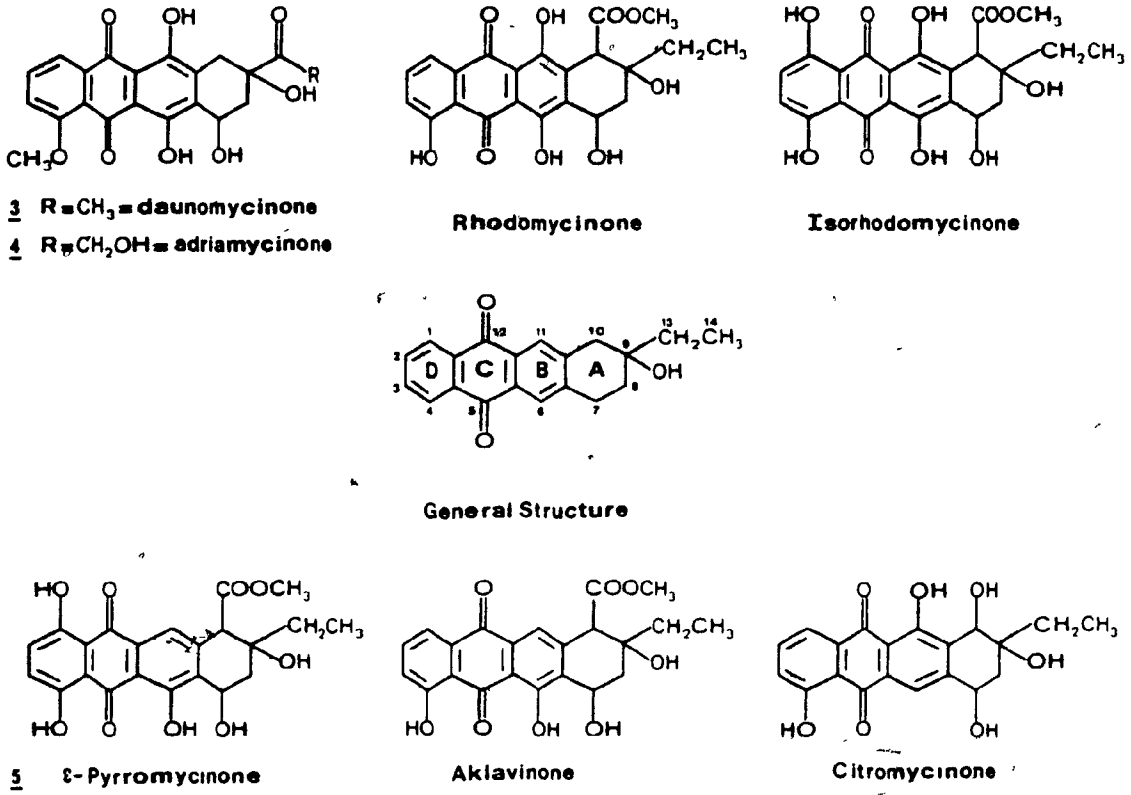



Figure 1: General Structures of the Major Naturally Occurring Anthracycline Aglycones.

These differences can be readily accounted for on the basis of their biogenesis which starts from a common polyketide precursor as both daunomycinone (3)[1] (adriamycinone (4)) and ε-pyrromycinone (5)[2,3] were found to be derived from the hypothetical product of the "head to tail" formal condensation of nine acetate units and one propionate unit (Figure 2). An interesting feature of daunomycin (and adriamycin) is that, unlike the other mycinones, the ethyl group is oxidized and the OH group at the 4-position is methylated.

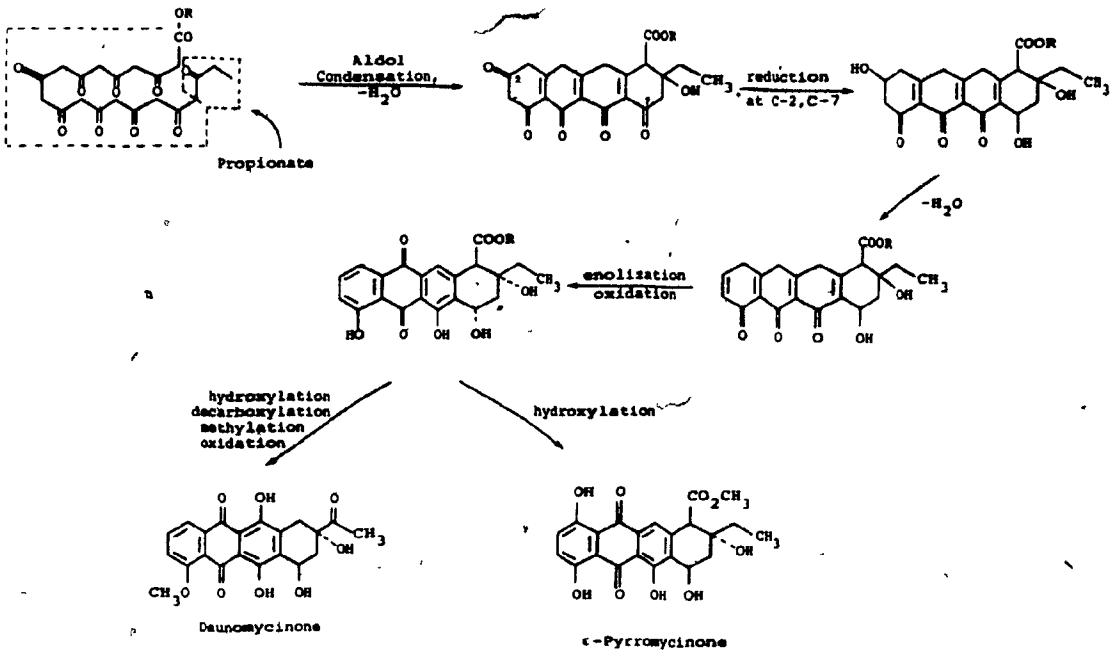



Figure 2: Proposed Biosynthetic Pathway of the Anthracyclinones.

Many anthracyclines, especially those with important antibacterial and antitumor activity, occur naturally as glycosides. The glycosidic linkage generally involves the 7-OH group (and/or sometimes the 10-OH group) of the anthracyclinone part and the α-anomer of a sugar with the L-configuration (Figure 3). Sometimes di- and trisaccharide chains are found. When these latter sugars (shown in Figure 3) are linked to ε-pyrromycinone, they give rise to musettamycin and marcellomycin respectively.

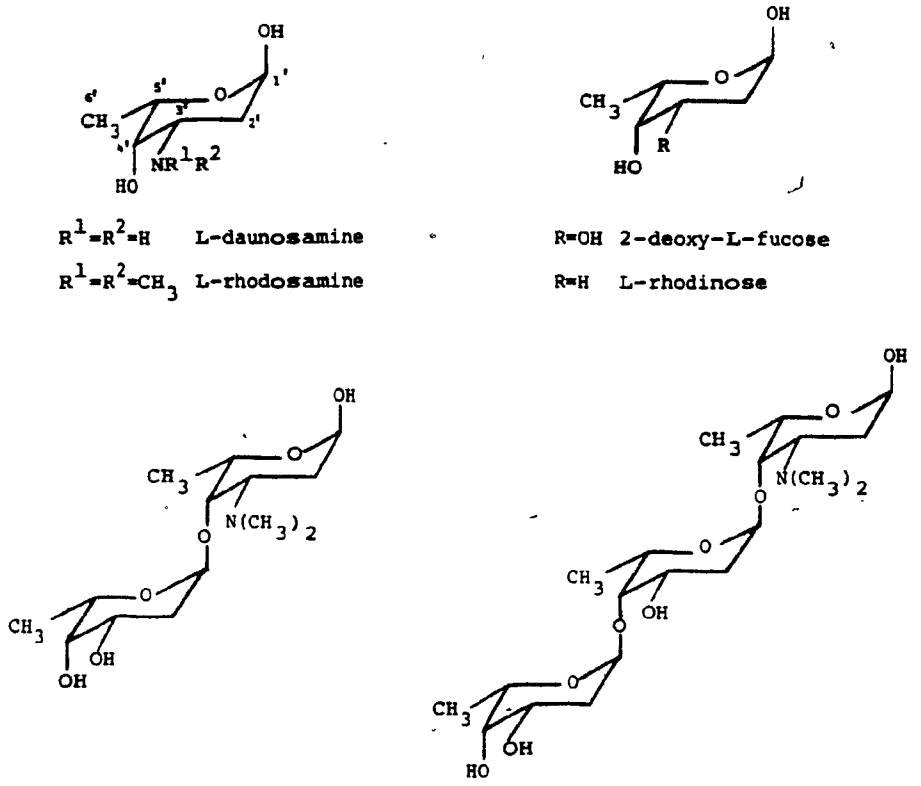



Figure 3: Representative Sugars Found with the Anthracyclines[4,5].

## B. USE AND TOXICITY OF DAUNOMYCIN AND ADRIAMYCIN

The earliest known anthracycline was isolated in 1950* by Brockmann and Bauer[7] and showed potent antibacterial activity *in vitro*. Unfortunately, β-rhodomycin I turned out to be highly toxic and no use could be made of it[8]. However, this stimulated the search for new, different anthracyclines. The isolation of two other anthracycline antibiotics, cinerubins A

*The anthracyclines were discovered as early as 1939[6] but it was only later (in the 1960's) that a mixture of rhodomycinones and isorhodomycinones were isolated. But by then these were known because of Brockmann's work.

and B, in 1959 generated some excitement because they inhibited various murine sarcomas and carcinomas but their high toxicity again prevented their further development as antitumor agents[9]. It was not until 1963 that the first useful anthracycline, daunomycin was simultaneously isolated from cultures of *Streptomyces peucetius* by Farmitalia in Italy[10,11] and from *Streptomyces coeruleorubidus* by Rhône-Poulenc in France[12,13]. Although weakly active against some microorganisms, it exhibited sufficiently high cytotoxic activity against normal and neoplastic cells[14,15] to warrant clinical studies and was quickly shown to be effective in the treatment of acute leukemias[16-19] including childhood and adult acute lymphocytic leukemia, acute nonlymphocytic leukemia and acute myelogenous leukemia.

The search for new biosynthetic analogs from cultures of daunomycin-producing microorganisms* led to the isolation of adriamycin in 1969[20]. Adriamycin has quickly established itself as an outstanding antitumor agent showing a broad spectrum of antitumor activity including soft tissue tumors and bone sarcomas, neoplasms that are known to be relatively insensitive to other chemotherapeutic agents (Table 1)[17,21-26]. Its use in combination with other drugs has allowed both an increase in response rates and a lower incidence of toxic side effects[27].

---

*Adriamycin was obtained from *S. peucetius* var. *caesius*, a mutant strain of *S. peucetius*.

Table 1: Tumor Activity Spectrum of Adriamycin/Tumor Responsiveness.

| Established activity | Possible activity | Unresponsive |
|---|---|---|
| Breast adenocarcinoma | Stomach adenocarcinoma | Large bowel adenocarcinoma |
| Soft tissue and bone sarcomas | Ovarian adenocarcinoma | Malignant melanoma |
| Bladder adenocarcinoma | Prostate adenocarcinoma | Renal cancer |
| Bronchogenic carcinoma | Squamous cell carcinoma, cervix | Chronic leukemias |
| Testicular carcinoma | Squamous cell carcinoma, head and neck | |
| Thyroid carcinoma | Hepatoma | |
| Pediatric solid tumors | Multiple myeloma | |
| Malignant lymphomas | Pancreatic adenocarcinoma | |
| Acute leukemias | Endometrial adenocarcinoma | |
| | Brain tumors | |

However, daunomycin and adriamycin display a number of important side effects some of which are common to other antitumor agents[24-26,28]. Myelosuppression, manifested primarily as leukopenia, is a dose-limiting toxicity which reduces the utility of anthracyclines and which is considered in some quarters[29] sufficiently important so as to justify reduction of myelosuppression as a priority over the development of anthracyclines displaying reduced cardiotoxicity. Thrombocytopenia and anemia may also accompany leukopenia but

these effects tend to be less severe in contrast to stomatitis which occurs frequently in severe form. Gastrointestinal toxicities, as reflected in nausea and vomiting, occur frequently and are accompanied by anorexia and diarrhea. Alopecia (loss of scalp, axillary and pubic hair) occurs in virtually all patients but growth resumes upon cessation of chemotherapy. Hypersensitivity including fever, urticaria and anaphylaxis as well as hyperpigmentation have also been observed[26]. The effects of radiation therapy are potentiated by adriamycin[30]. Both daunomycin and adriamycin (and the anthracyclines in general) are immunosuppressive[31] as well as mutagenic[32] and carcinogenic[33-35]. Severe irritation of tissues at the site of injection can be a very serious complication if care is not taken to avoid extravasation[36]. Although these reactions may be severe, they are dose-related, reasonably predictable and reversible. The most dangerous side effect is cardiotoxicity*[37-39] characterized by: (i) transient electrocardiographic changes returning to normal when therapy is withheld and (ii) a delayed progressive cardiomyopathy with high risk of conjestive heart failure when a cumulative dose of 500 mg $m^{-2}$ is exceeded[24,39]. Cardiotoxicity emerges as the most limiting side effect because treatment must be stopped while the tumor is still responding to the drug. The incidence of some of these toxic effects is summarized in Table 2[24,25,28,41].

*A number of other drugs (cyclophosphamide, 5-fluorouracil, actinomycin D, mithramycin, *cis*-platinum among others) have been reported[40] to induce cardiomyopathy. However, cardiotoxicity occurs only rarely with these agents and is clearly not the dose-limiting toxicity.

Table 2: Incidence of Toxic Effects of Adriamycin in Patients.

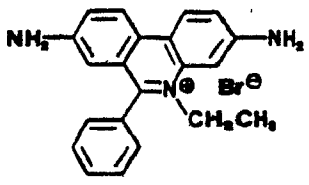
| Side effect | (percent) |
|---|---|
| Alopecia | 100 |
| Myelosuppression | 60-80 |
| Stomatitis | 80 |
| Nausea and Vomiting | 20-55 |
| ECG abnormalities | 2-30 |
| Cardiomyopathy | 1-2 |

The outstanding clinical effectiveness of adriamycin as an anticancer drug and an awareness of its side-effects prompted the search for new anthracyclines and stimulated intense efforts aimed at developing synthetic analogs. As a result, well over 500 new related compounds are now known and this number may be expected to increase in the future. In spite of these efforts, little improvement has been reported as yet in the separation of antitumor activity from cardiotoxicity (except in a few noteworthy cases). It is hoped that a more detailed knowledge of the biochemical properties of the anthracyclines (which has been made possible by the numerous structure-activity relationship studies) will lead to the design of drugs with markedly improved therapeutic/toxic ratios. A review of the literature will make apparent the enormous effort which has been expended in the search for some

integrated understanding of how these drugs exert their effect(s). However, such an integration is as yet very difficult and will require more time before a clearer and more complete picture can emerge.

## C. MECHANISM OF ACTION

Historically, DNA has been considered as the primary target in the cytotoxic action of the anthracyclines. There is a large body of biophysical and biochemical data (some of which are not as scientifically rigorous as initially thought) indicating that the antibiotics bind by an intercalation mechanism so that the resulting distortion in the macromolecular structure would alter the function of DNA and ultimately leads to cell death. However, intercalation alone may not account for the antitumor effect of the anthracyclines. Two classical intercalators, ethidium bromide (6) and 9-aminoacridine (7) are not effective as anticancer drugs*. Moreover, in view of

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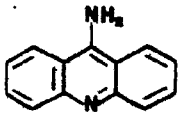


7

*To explain the exceptionally high antitumor activity of adriamycin in comparison to compounds 6 and 7, it has been proposed that an irreversible-template binding (possibly because of the amino sugar) at relatively low drug to DNA ratios (obtained at therapeutically administered drug levels) is involved[42].

their multifunctional chemistry, it is not surprising that the *in vivo* mechanism of the anthracyclines may be complex. Indeed, considerable evidence has emerged over the years indicating that *in vivo* the anthracyclines can act by mechanisms unrelated to intercalation.

The main biochemical effects of adriamycin which have been studied in some detail can be dissected into different broad classes. These include:

(1) Interaction with DNA involving both intercalation and non-covalent binding;

(2) Direct Membrane Binding. For instance, adriamycin is known to bind to cell membranes and to directly alter membrane function;

(3) Generation of Reactive Intermediates. This includes formation of (i) free radicals and (ii) alkylating species.

Interestingly, each of these biochemical effects can account in varying degrees for the slight selectivity of the anthracyclines toward cancer cells as well as their cardiotoxicity.

## C.1 Interaction with DNA

When daunomycin and adriamycin are added to cell cultures, they concentrate in the nuclei and bind avidly to DNA[15,43]. As a consequence of these observations, the interaction of daunomycin and adriamycin with DNA was extensively

analyzed and strong evidence was produced indicating that this binding plays a role in their antitumor activity[44,45]. The formation of an anthracycline-DNA complex can be envisaged as resulting from either an intercalation process* where the drug inserts itself between adjacent base pairs or binding to the outside part of the helix[48]. These mechanisms can be readily differentiated through the resulting changes in the physico-chemical properties of both the antibiotics and DNA[43,49].

C.1.1 Physical-chemistry of antibiotic binding onto DNA

(i) Physico-chemical changes in the anthracycline properties:

Upon binding to DNA, both drugs do not suffer the typical bathochromic† shift associated with exposure to bases[43,49] (which favor the formation of the better electron donor properties of the phenolic groups $O^-$) and the characteristic polarographic wave associated with quinone reduction is inhibited[49] as is the appearance of the semiquinone ESR signal[50]. These effects show that the anthracycline chromophore is extracted from the solvent and transferred to a less polar environment, thus making the hydroxyl and quinone functions of rings B and C unavailable for reaction.

---

*This type of molecular association was originally postulated by Lerman[46] for acridine dyes and DNA, and then widely accepted as the mode of interaction of different drugs with DNA[47].

†Bathochromic shift is sometimes referred to as the red shift.

While these findings are consistent with the intercalation binding mode, the validity of two other widely used techniques, namely, visible absorption and fluorescence quenching spectroscopy, has been questioned because they led to ambiguous results concerning the nature of the interaction between these drugs and DNA. The main objection here was that these methods monitor spectral changes that are not unique to the anthracyline association with double stranded DNA and even if they were so the changes cannot be unequivocally ascribed to intercalation. (This criticism is of particular concern in light of the emerging evidence that other unrelated mechanisms of action might be primary ones). The decrease of absorption (hypochromicity) and bathochromic shift in the visible spectra of daunomycin and adriamycin after complexation with DNA can be associated with an intermolecular charge transfer between purine-pyrimidine bases and the quinone chromophore*[49,51]. On the other hand, similar albeit not fully resolved changes in the absorption spectrum of the bound species may originate from a completely different interaction mechanism. One such mechanism is chelation of metal ions since both daunomycin and adriamycin are known to form stable complexes[49] with metals. Recently, some evidence has appeared suggesting that Cu(II) might be involved in adriamycin binding to DNA[53-55]. Another interaction deserving consideration is self association[56].

*The reasonable assumption that the removal of the hydroxyl proton on the chromophore is at the origin of the observed-shift in the spectrum is not supported by evidence from the model daunomycin-DNA complex that indicates no disruption of intramolecular bonding[52].

Although adriamycin does not dimerize very readily at the concentrations expected inside the cell after a therapeutic dose, in *in vitro* binding studies much higher drug concentrations as well as high ionic strengths are usually employed which facilitate ligand dimerization. In fact, the ionic conditions used not only can alter some relevant physico-chemical properties of the drugs but they can also minimize non-intercalative forms of binding to DNA[57-59].

Spectrofluorimetric analysis of binding which is based on the observation that the typical fluorescence of daunomycin or adriamycin is dramatically quenched following intercalation[49], similarly cannot reflect specific interactions as it can simply result from any process where the drug chromophore engages in the formation of a charge transfer complex. For the same reason, the bathochromic shift observed upon binding in the ultraviolet spectrum of the drugs[49,56] must be interpreted with caution since multiple interactions with a variety of other components may account for the observed effects.

(ii) Physico-chemical changes in DNA properties:

The typical elongation and stiffening of the double helix associated with the drug intercalation process is revealed by the reduction of the sedimentation coefficient and the buoyant density in CsCl as well as by the increased viscosity of DNA solutions in the presence of anthracyclines[43,49,60]. The stabilization of the helix due to a lowering of the repulsions between the phosphate groups of the backbone is

evidenced by the drug-induced increase in the melting temperature ($T_m$) of DNA[61]. In addition, daunomycin and adriamycin cause uncoiling of circular supercoiled DNA, a phenomenon consistent with a local untwisting of the macromolecules due to ligand insertion between base pairs*[61,62].

### C.1.2 Intercalation models of anthracycline-DNA complex

Further evidence of intercalation has come from X-ray diffraction measurements of a daunomycin-DNA complex[64]. The results suggest that the complex has a conformation similar to that of B-DNA and indicate that the antibiotic has its chromophore inserted between adjacent base pairs with extensive reciprocal overlap (with the base pairs lying immediately above and below in close Van der Waals contact) providing a weak driving force for intercalation. The amino sugar sits in the major groove of the double helix with the charged amino group interacting ionically with a phosphate anion one base pair away from the intercalation site. The importance of hydrogen bonding interactions between the hydroxyls of the anthracycline and the phosphates of DNA depends on the model adopted.

The fine details of the proposed three distinct models depend on the conformation assumed by the A ring of the drug. Pigram *et al.*[64] proposed a hydrogen bond between the

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* A word of caution is necessary because a steroid, which clearly does not possess the geometrical requirements for intercalation unwinds supercoiled DNA[63].

C-9 hydroxyl group and the first phosphate from the intercalation site. Henry[65] proposed that upon intercalation the configuration changes so drastically that the amino group of the sugar will bind to the first phosphate away from the intercalation site and that in turn this will permit hydrogen bond formation between the C-4' hydroxyl group and the second phosphate from the site as well as between the C-9 hydroxyl group and the phosphate at the intercalation site. However, the affinity of the 4'-epianalogs of adriamycin[66] and the observation that the 4'-deoxy analogs of both daunomycin and adriamycin have binding constants of the same order of magnitude as the parent compounds[67,68] does not support the involvement of the 4'-hydroxyl group in hydrogen bonding as visualized*. Neidle and Taylor[70] proposed a hydrogen bond between the C-7 oxygen and the C-9 hydroxyl group. This latter drug-DNA model correctly predicted the low unwinding angle induced by the anthracyclines in DNA[62,71] and this predominating angle is preferred in solution as was shown by PMR studies[72]. It is now the generally accepted working model[73] (Figure 4) for anthracycline-DNA interactions.

Recently, the "classical" interaction of the amino sugar with the phosphate backbone in the major groove of DNA as deduced from the above studies has been challenged by other X-ray analyses and by NMR studies of the complex in solution. Apparently, most intercalating drugs with bulky non-intercalating

*In a recent report[69], the evidence provided indicated that the 4'-hydroxyl group is involved in hydrogen bonding thus lending support to the model proposed by Henry[65].

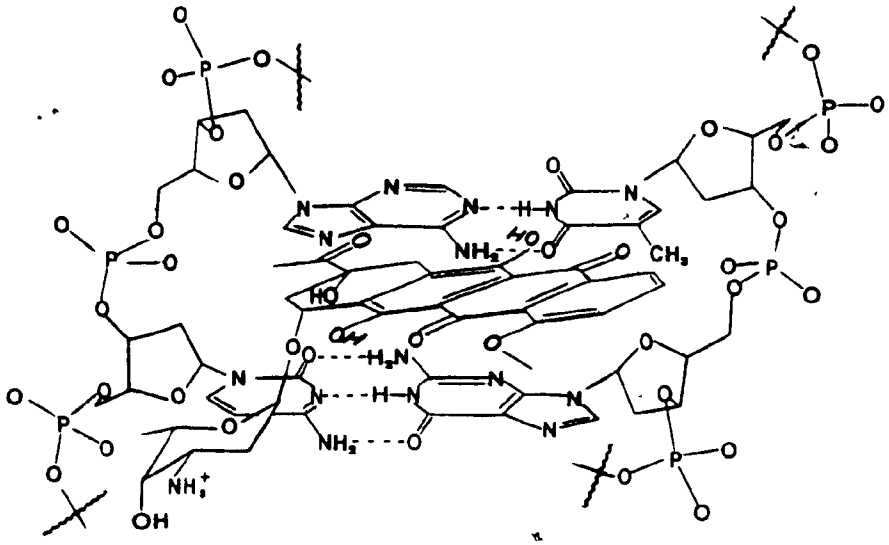

Figure 4 : A Simplified Representation of the Daunomycin-DNA Binding Model.

substituents favor a close contact of such substituents with the minor groove[74,75]. Evidence regarding the minor groove location of the daunosamine part has also been obtained from PMR studies[76,77] and from X-ray analysis[52] of complexes involving short synthetic polynucleotide sequences. The classical and the minor groove models of intercalation differ mainly in the respective orientation of the chromophore relative to the hydrogen bonds of the base pairs (almost parallel in the former, perpendicular in the latter)[52,75-77] and in the extent of the interaction between the charged amino sugar and

the phosphate backbone of DNA. Stabilization of the chromophore-oligonucleotide complex is provided mainly by hydrogen bonding.

However, these results are not surprisingly* in disagreement with those obtained from solution studies which have convincingly shown that the amino group of daunosamine plays an essential part in the stabilization of the anthracycline-DNA complex[43,63,65,81]. This is evidenced by the observation that adriamycin binds to heat-denatured DNA, (presumably single stranded) with a large affinity constant ($K_a$ = 1.5 x $10^5$ $M^{-1}$)[82] which the ring-ring stacking forces cannot account for. The importance of both the charge of the sugar moiety and its position is indicated by comparing the behaviour of analogs such as N-acetyl-daunomycin and 2-amino-2-deoxyfucosyldaunomycinone (amino group in position 2'; see Figure 3) which show substantially reduced affinity for DNA relative to the parent compound.

The association of the anthracycline amino sugar to the major or the minor groove during intercalation can play a role in the determination of the mode of binding to different configurations of DNA that may be relevant to the *in vivo* effects. The A, B and Z-configurations of DNA have different widths and depths relative to the helical groove and these could restrain or facilitate intercalation. It is

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* Short synthetic polynucleotides might exhibit "fraying" at the end which may affect the results obtained while the details of the binding do not consider other possible sequences present in the chromatin organization of mammalian DNA, nor do they take into account that not only B, but also A and Z configurations of DNA might occur *in vivo*[78-80].

known for example, that daunomycin and adriamycin do not intercalate with nucleic acids in the A conformation (as in double stranded RNA[83-85]) but bind externally to this form, possibly through electrostatic association between the amino sugar and the phosphate residues[48,49,69].

C.1.3 Base pair specificity of the anthracyclines

Selective affinity for specific sequences in DNA may be of particular importance in the biological effectiveness of the anthracyclines (and drugs in general), because, depending upon their sequence specificity in binding, they could affect the activity of certain genes. Furthermore, specific sequences are known to have a profound influence on DNA conformation[78,86,87] whose stability depends on the different stacking interactions between neighbouring base pairs. These variable DNA conformations can affect drug binding[88], both of the intercalative and non-intercalative types (at least in the case of the anthracyclines). While the question of preference* of the anthracyclines for G-C over A-T base pairs has been the subject of a number of studies, no definite conclusion can as yet be drawn (*cf.* ref. 43, 90-97). These studies have however raised the question of whether the overall DNA conformation rather than the base sequences *per se* can dictate the binding specificity of the antibiotics *in vivo*. For example, alternating

*One simple view of why preference should exist is that the G-C base pair is more polar than the A-T base pair, and should therefore interact more favorably with an easily polarized ring system[89].

G-C polymers maintain the B conformation as do methylated G-C pairs at physiological salt concentrations as judged by PMR spectroscopy[98]. However, methylated G-C pairs assume the Z-conformation at concentrations of NaCl much lower than those necessary for the B to Z transition of non-methylated G-C pairs. The B-Z transition for methylated G-C pairs is also sensitive to $MgCl_2$ and occurs at concentrations of this salt in the physiological range[98]. These effects may be relevant in light of the fact that adriamycin appears to intercalate preferentially with the B-form presumably due to steric factors (the Z-form having a smaller radius)[99].

It is clear that a better understanding of the mode of action of the anthracyclines at the molecular level may be derived from the base pair specificity studies but this must await a better understanding of interaction mechanisms with the various conformations of DNA.

### C.1.4 External binding to DNA

It has become apparent from the variability in the association constant of adriamycin (or daunomycin) with DNA that the early assumption of the existence of a single homogeneous class of binding sites is not valid. As a whole the results are more consistent with a two site model[48,100]. Upon saturation of the intercalation sites (saturation involving about 2 drug molecules per 5 base pairs[101]) additional drug molecules can bind to the exterior of the helix, presumably

through electrostatic interaction with the phosphate groups*. This effect of external binding may in fact prove to be very important because a potentially reactive chromophore remains available for redox reactions of the quinone part[104], for metal ion binding or for bridging other DNA related structures in the chromatin organization[105]. This type of binding does not occur only in cases where intercalation is not permitted. As will be seen later, this type of binding can also lead to moderate inhibition of protein synthesis (the drug binding weakly to RNA) and thus play a potentially critical role in the overall mechanism of action and eventual inhibition of the polymerase.

C.1.5 Effects on cellular processes

Consistent with the DNA complexing properties of these antibiotics are the findings that both drugs inhibit the synthesis of DNA[106-112] and RNA[90,93,109-117] *in vitro* (intact cells) and *in vivo* as well as in cell-free systems. Studies with various isolated polymerase systems (mammalian[111], bacterial[106], viral[111,113]) have shown that the inhibitions are not due to drug-polymerase interactions but can be accounted for by drug/template DNA complex formation. This results in the impairment of DNA in its function as a template in the processes

* The fact that daunomycin and adriamycin have a total number of potential binding sites of one every three to six base pairs led to the hypothesis that anthracyclines may bind through a neighbouring site exclusion process, whereby the bound ligand alters the conformation of adjacent binding sites[102,103]. This "negative cooperativity" mode can explain the reduced total number of binding sites in respect to the potential intercalation sites.

of nucleic acid expression and synthesis, thus leading to a diminution (or even complete cessation) of cell growth and eventual cell death in some cases. Both daunomycin and adriamycin inhibit the reverse transcriptase activity of RNA tumor viruses[43,92,113,118-120]. Protein synthesis appears to be much less sensitive than other metabolic processes to the action of anthracyclines[5,121-123] and in general is not inhibited* except at high drug concentration and after long exposure times[121,124].

The precise mechanism by which the drug-DNA interaction inhibits template activity is not clear. The prevention of separation of the DNA strands or hindrance to the attachment of the polymerase due to distortion of the DNA structure have been proposed as possible causes[43]. Goodman *et al.*[42] have suggested the presence of two modes of template-mediated inhibition, one for low drug:DNA ratios and the other for a ratio greater than 1:15. The first mode (low drug ratios) is thought to involve binding of the enzyme to template DNA with initiation of DNA synthesis but at a reduced rate owing to an irreversible block of the enzyme (possibly because of binding to the amino sugar) at the drug intercalation sites. (Similarly, DNAse II binds to DNA in the presence of drug but is unable to function†[125]). The second mode suggests that the

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*In the cell-free system adriamycin is capable of binding to some of the RNA molecules involved in protein synthesis[121,124].

†The inhibition of DNAse I is considered further evidence of direct template binding because inhibition was observed with only those drugs which formed a complex with DNA[126]. However, no mention was made with regards to the drug concentration used providing no information on the specific mode of the inhibition.

polymerase is prevented from binding to the template because of externally bound drug. The inhibition in this case can be reversed by the addition of template DNA because the free enzyme retains the ability to initiate nucleic acid synthesis.

The observation that binding to a DNA template affects viral polymerases more effectively than those of normal cells, has been related to a special selectivity of the drugs[127]. The preferential inhibition of DNA polymerase α (the enzyme presumably catalyzing the DNA replicative process) over DNA polymerase β (the presumed repair enzyme) is at the origin of the classification of the antitumor anthracyclines as "cell specific" cytotoxic agents, *i.e.*, compounds acting selectively on cells endowed with high levels of mitotic activity*[128].

The cardiotoxicity of the anthracyclines has been related to the inhibition of myocardial DNA metabolism, in particular DNA-replication and DNA-repair mechanisms[131-133] as well as DNA-directed RNA synthesis (and therefore inhibition of synthesis of the proteins necessary for myocardial function and integrity)[134,135]. Because of the special nature of the heart tissue (the ventricular adult tissue is unable to regenerate) these inhibitory effects are particularly damaging[136].

The possibility that daunomycin and adriamycin may

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*When cells enter the replicative cycle, their content of α polymerase rises substantially, while their content of β polymerase remains unchanged[129,130]. Under these conditions, cells involved in the mitotic cycle would be more susceptible to an agent which preferentially inhibits the α polymerase.

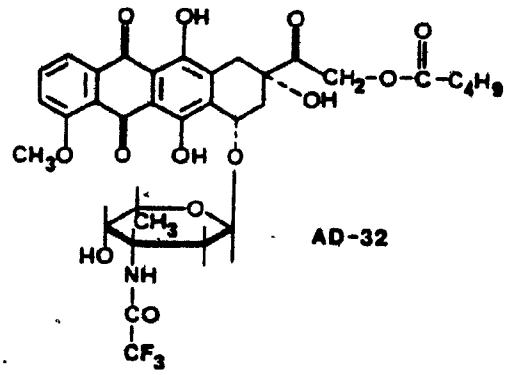
inhibit nucleic acid synthesis by a mechanism other than DNA intercalation has been suggested recently. It would appear that for some eukaryotic DNA[137] and RNA-polymerases[138] binding of anthracyclines to the enzymes could be an important determining factor of the inhibition. However, while these results provide yet another possibility regarding the mechanism of action of daunomycin and adriamycin, it remains to be determined which mechanism is primarily responsible for their antitumor activity.

C.2. Membrane Binding

There are reasons to question the importance of intercalation into DNA as the primary or sole mode of action responsible for the cytotoxicity of the anthracyclines. The most notable discrepancy is supplied by synthetic analogs generated during the course of structure-activity relationship studies and, in general, the results tend to indicate that there exists no obvious correlation between cytotoxicity and DNA binding ability. A striking example is N-trifluoroacetyl-adriamycin-14-valerate (AD-32)[139-140] (8) which is an effective antineoplastic agent in spite of its apparent inability to enter the cell nucleus[141] or to bind onto isolated DNA[142]. Accordingly, its cytotoxicity must rely on a different mechanism*[126,143,146].

The anthracyclines bind with high affinity to cell

* Although the cytotoxicity of AD-32 has been related to its effect on cell membranes[143], the mechanism of action is far from having been elucidated[144,145].

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membranes and there is an increasing amount of experimental evidence that membrane properties as controlled by interactions with lectins[147], phospholipid structure and organization[148], fluidity[148,149] and transport of small molecules and ions[150] among others may be involved in the cytotoxic action of these drugs.

This does not necessarily imply that the plasma membrane is the primary target but regardless of the nature of the ultimate target, the drug must initially interact with the cell membrane and it is thus most reasonable to assume that this first encounter may be an important determinant of the final biological effect.

Increased agglutination of cells by concanavalin A upon treatment with adriamycin is evidence that membrane

integrity is affected[147]. It is suggested that this increased agglutination arises from an enhanced clustering of membrane receptors occupied by concanavalin A, an effect conditioning the agglutination process. The enhanced clustering by adriamycin requires that it interacts with some membrane constituent and it is known to bind onto phospholipids *in vitro*[151].

No complexation with neutral phospholipids has been observed[152] but adriamycin binds to the negatively charged phospholipids cardiolipin and phosphatidylserine quite strongly*. It has been proposed[152b] that anthracyclines bearing a daunosamine residue are capable of binding to the negatively charged phospholipids *via* the protonated sugar amino group. There is little reason to expect any selective interaction with cell membrane components based solely on the properties of daunosamine as there are many other constituents (N-acetyl derivative of neuraminic acid, sulfated polysaccharides, sulfated mucopolysaccharides[153], uronic acid polysaccharides and proteins with an excess of acid over basic groups) to which adriamycin can bind. Nevertheless, because of the large affinity for adriamycin for cardiolipin and the importance of the latter in membranes, interaction phenomena

*The binding of adriamycin to cardiolipin is much stronger than it is to phosphatidylserine. The association constant $K_a$ is $1.6 \times 10^6$ and $1.8 \times 10^4$ $M^{-1}$ respectively (*cf.* $K_a$ for adriamycin-DNA is $2.4 \times 10^6$ $M^{-1}$). It has been suggested that the greater affinity for cardiolipin *vs* phosphatidylserine arises because the two adriamycin molecules bound to cardiolipin interact *via* ring stacking and this provides more free energy of association[152b]. It is clear from the association constant that cardiolipin could be a competitive target for adriamycin[152a].

with this lipid has been given special attention.

Cardiolipin is a major component of the inner leaflet of the mitochondrial membrane and its presence has been shown to be important for mitochondrial function[154]. As the name implies, this lipid can be isolated in quantity from cardiac mitochondria. Binding of adriamycin to cardiolipin thus may serve to localize the drug at the level of cardiac mitochondria and the resulting alterations in mitochondrial membrane function could result in altered ATP generation and calcium handling by the mitochondria with devastating consequences for cardiac function. This simple hypothesis may provide a molecular basis for the cardiac toxicity of the anthracycline antibiotics[148,152b].

However, no definite evidence has appeared as yet which allows a quantitative estimation of such binding in relation to the effects observed on mitochondrial function or to the pathogenic effects leading to eventual cardiomyopathy. It has been suggested[152a,155] that the adriamycin-induced inhibition[156] of the synthesis of the membrane enzymes cytochromes a and $a_3$ may be related to binding onto cardiolipin. Other important effects on mitochondrial function such as perturbation of electron transport[157-159] and superoxide generation[160] may be connected with lipid peroxidation and will be dealt with later.

It has been suggested[148,152b] that the binding of adriamycin to cardiolipin may also play an important role in

determining the susceptibility of neoplastic cells to the anthracycline antibiotics. Although cardiolipin is normally restricted to mitochondrial membranes, it is actually found in all cellular membranes upon malignant transformation[161]. This could mean that a tumor cell may present a modified surface to an approaching drug molecule and behave differently from one which lacks cardiolipin on the surface of its membrane.

The most provocative suggestion that the cell membrane may act as a key target as opposed to DNA-dependent systems is based on the observation[162-164] that adriamycin covalently linked to polymer beads* retains potent cytotoxic properties. Indeed, Tritton[162,163] and Tolkes[164] prepared microspheres to which adriamycin was covalently attached through the sugar amine group to reactive functions on the polymer (Figure 5), thus making adriamycin effectively inaccessible to the cell interior. Since the drug conjugate was cytotoxic and drug release by the spheres ruled out on the basis of adequate control experiments, it was concluded that adriamycin must exert its effect at the cell membrane level. This type of drug conjugation to a support may in fact prove to be quite advantageous as the drug may no longer be available to those compartments involved in its metabolic breakdown, thus permitting the continuous perturbation of the

*Tritton used 6% cross-linked agarose beads (40 to 210 μm in diameter) derivatized with 1,1'-carbonyldiimidazole, which can react with free amino groups. Tolkes used polyglutaraldehyde microspheres (0.20 to 0.45 μm in diameter). The aldehyde function at the surface of the microspheres forms a Schiff base with free amino groups.

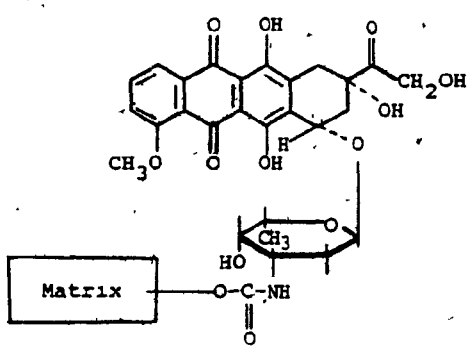


Figure 5: Structure of Adriamycin Linked to a Polymeric Matrix Used by Tritton.

cell. Since such preparations do not affect the chromophore, it remains free to bind metal ions and to undergo those redox reactions which may be responsible for the observed cytotoxic effect.

However, although interesting, these results raise a number of questions. First, in these studies the attachment of the drug to the polymer beads is through the amino group. This means that the amine is unavailable for interaction with the cell membrane and this is inconsistent with a previous conclusion that the amino sugar part is critical for drug binding to the membrane. It remains possible that the amine group may not be essential for binding (although in one case, the $NH_2$ is in the form of a basic Schiff base) but this is not consistent with the numerous studies that have demonstrated

the apparent importance of the amino function for biological activity. Moreover, the beads offer adriamycin to the cell surface in a manner not encountered under normal physiological conditions, *i.e.*, the drug molecules are arranged in an ordered fashion "like a picket fence along the bead surface" (Figure 6). Under these circumstances the interactions involved

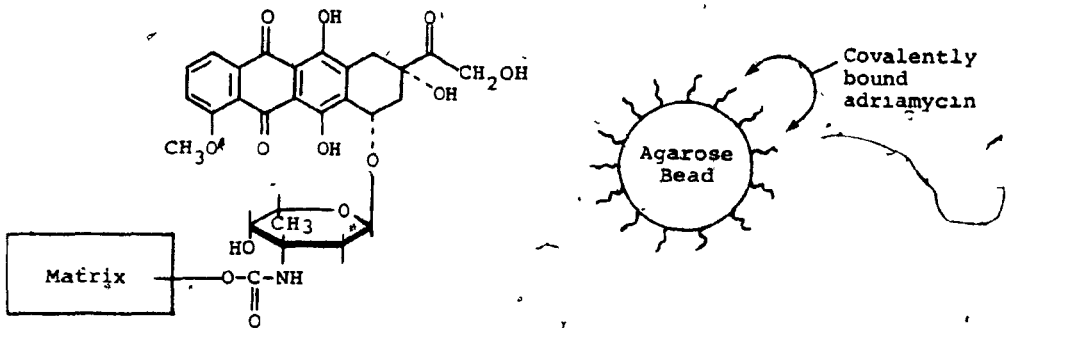


Figure 6: Representation of Adriamycin Covalently Bound to Agarose Bead.

may bear little or no relationship to those of the free drug in solution.

Still, these experiments do not rule out the possibility that free adriamycin can affect cell viability through DNA intercalation but they show nevertheless that under special circumstances, cytotoxicity can be achieved without interaction of the drug with DNA or other intracellular organelles. These observations have stimulated much work, the results of which point to significant membrane effects induced by the anthracyclines.

## C.3 Generation of Reactive Species

### C.3.1 Free radical formation

The most rapidly evolving area in anthracycline research centers on the involvement of free radicals. Adriamycin can undergo one electron reduction to the semiquinone or a two electron reduction to the dihydroquinone provided it is not intercalated[50,165-167] with DNA. Each of these species has its own chemistry and an associated but conjectural role in the action of anthracyclines.

The one electron reduction of adriamycin (and other anthracyclines) has been shown to be catalyzed by various flavin-centered oxido-reductases including cytochrome P-450 and xanthine oxidase[168-170] at the mitochondrial[160], microsomal[171,172] and nuclear[173] level. (This reduction also occurs spontaneously, to some extent, at neutral pH[174]). In the presence of oxygen, this process leads to the regeneration of the parent anthracycline and the formation of the superoxide anion followed by the appearance of the hydroxyl radical[160,168,171,175-177].

Superoxide, which by itself is not very reactive[178], can undergo a series of reactions leading to the generation of such species as hydrogen peroxide and a highly reactive hydroxyl radical[178,179]. It can also yield hydrogen peroxide directly *via* spontaneous disproportionation but the reaction is markedly accelerated by the ubiquitous enzyme superoxide

dismutase (SOD)[180] (Eqn. 1).

$$2\ O_2^{\cdot-} + 2\ H^+ \xrightarrow{SOD} O_2 + H_2O_2 \qquad (1)$$

The hydrogen peroxide formed by this reaction and by flavin-linked oxidases is decomposed by the heme enzyme catalase[181] to innocuous products (Eqn. 2) thus insuring protection of the cells against peroxide.

$$2\ H_2O_2 \longrightarrow 2\ H_2O + O_2 \qquad (2)$$

The hydroxyl radical may be formed through reductive lysis of hydrogen peroxide by the superoxide radical (Eqn. 3)[182] and exert its damaging effects especially in those organs which are deficient in those enzymes (*e.g.* superoxide dismutase,

$$O_2^{\cdot-} + H_2O_2 \longrightarrow O_2 + OH^- + OH^{\cdot} \qquad (3)$$

and catalase) that normally inhibit its formation. However, this latter process, the so-called Haber-Weiss reaction[183], is kinetically too slow to be of significant* biological importance unless it is catalyzed[185-188]. The *in vitro* observations[179,189] that chelated oxidized iron can exert

*This has led to a bitter controversy where the significance and role of superoxide dismutase has been questioned[184,185].

such a catalytic effect led to the proposal that cellular iron, presumably chelated as in the ATP-$Fe^{3+}$ complex could catalyse the formation of hydroxyl radicals *in vivo*[190,191]. (A summary of the proposed redox processes leading to hydroxyl radical formation is shown in Figure 7).

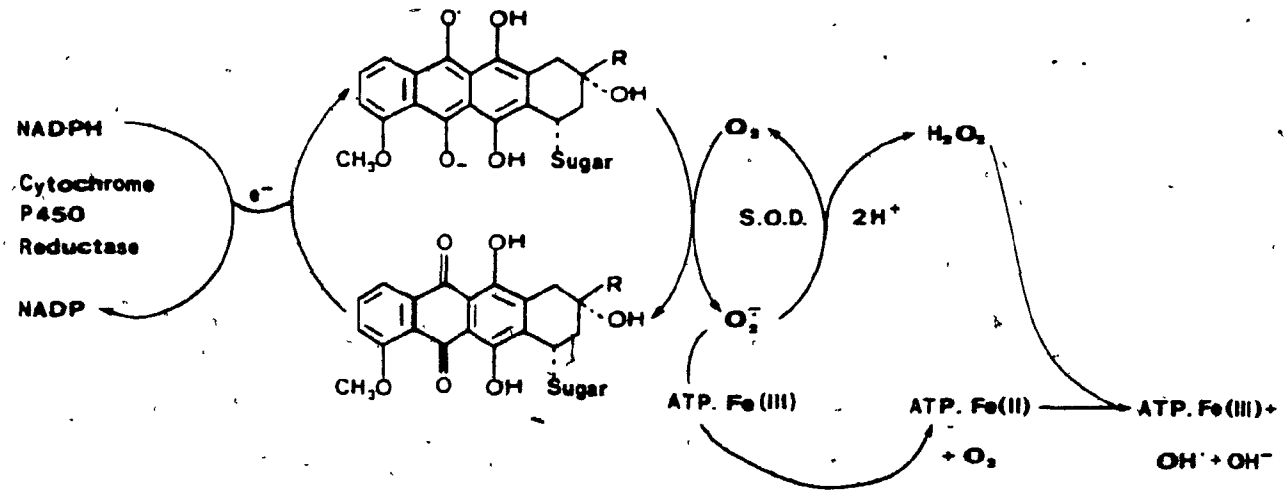


Figure 7: Schematic representation of the proposed mechanism of anthracycline interaction with microsomal cytochrome P-450-mediated redox cycle leading to superoxide and, through the intervention of complexed iron, to the hydroxyl radical.

The *in vivo* intracellular concentration of iron is low and it may be expected that upon addition of adriamycin it is likely that any available Fe(III) will suffer chelation in view of the affinity of adriamycin for Fe(III)[192]. However, this may be of little consequence as there is evidence that the adriamycin-Fe(III) complex will mediate a $H_2O_2$-dependent

hydroxyl radical formation[193]. In addition, it was recently observed that the hydroxyl radical (or a species with very similar properties) was formed simply by mixing the adriamycin semiquinone with hydrogen peroxide in the absence of iron[194].

The toxicity of the hydroxyl radical derives (in part) from its ability to cause peroxidation of membrane lipids and to degrade DNA*.

C.3.1.1 Peroxidation of membrane lipids

Although the precise mechanism of membrane damage is not known, the reactive species† derived from the superoxide radical (such as hydroxyl and peroxy radicals) can initiate free radical-mediated chain reactions that result in peroxidation of unsaturated fatty acids (Figure 8).

The biochemical consequences of lipid peroxidation at the membrane level are exceedingly complex and involve not only the unsaturated lipids but also the many different proteins and enzymes that form an integral part of membranes[198-201]. The sulfhydryl enzymes are particularly susceptible[201] and easily inactivated as a result of membrane structure perturbation or by cross-linking reactions (which may occur between proteins

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*Depending upon the proximity of the particular antibiotic to a cellular macromolecule, this can give rise to membrane lipid peroxidation and/or DNA damage[195].

†There are different opinions regarding the reactive species involved in the initiation of lipid peroxidation. Superoxide itself is not considered to initiate peroxidation directly but several reactions have been proposed in which $O_2^-$ reacts with $H_2O_2$ and/or ATP-$Fe^{3+}$ producing $^1O_2$, $OH^\cdot$ or an ATP-perferryl ion (ATP-$Fe^{2+}$-$O_2$ $\leftrightarrow$ ATP-$Fe^{3+}$-$O_2^-$) complex. All three of these products may initiate lipid peroxidation[196,197].

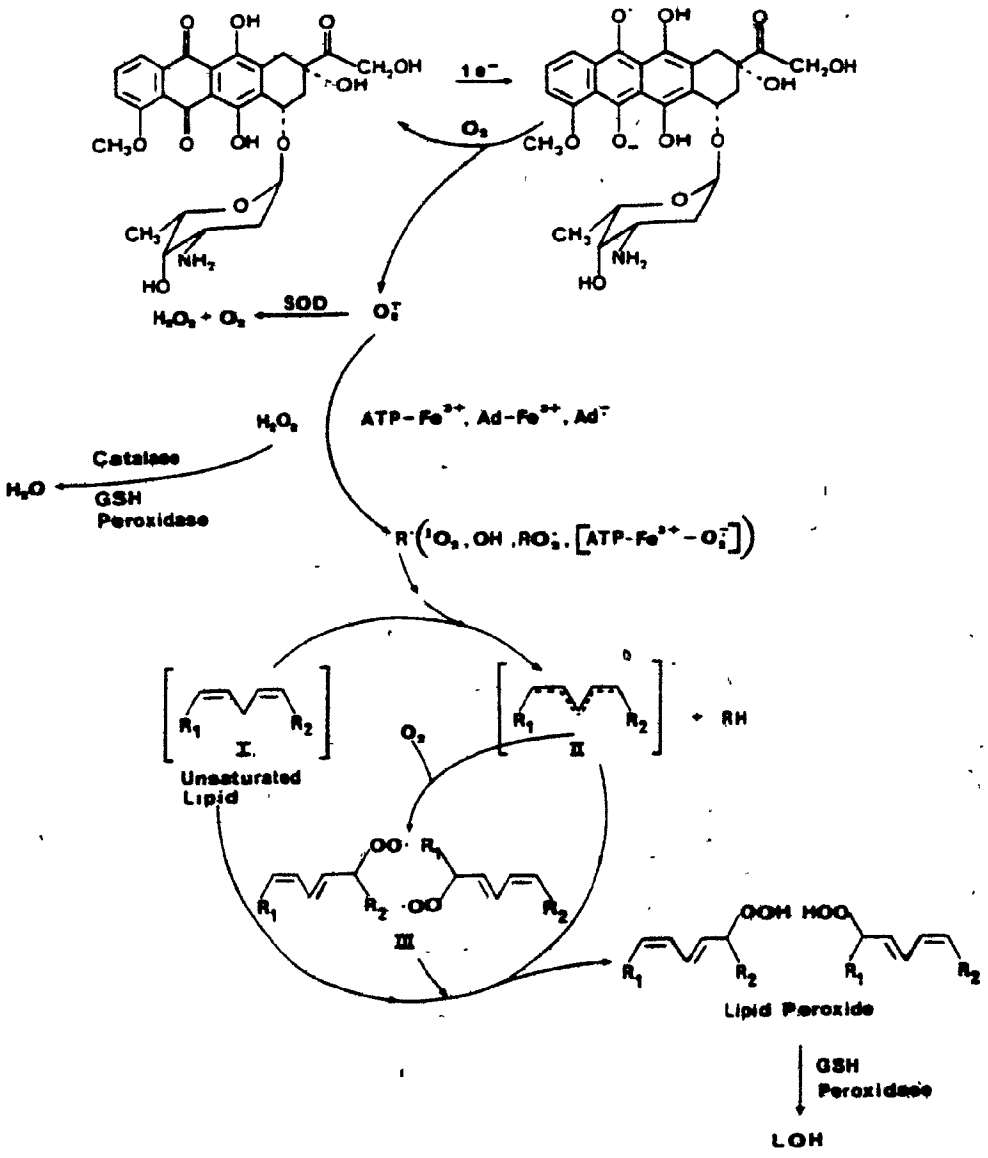


Figure 8: A schematic representation for the mechanism of adriamycin-induced lipid peroxidation. After enzymatic reduction, the quinone moiety of adriamycin is regenerated autocatalytically with the production of superoxide anion ($O_2^-$). The reactive species derived from it ($R^\cdot$), such as singlet oxygen, hydroxyl radicals, peroxy radicals and ATP-perferry ion complex can remove hydrogen from unsaturated fatty acid (I) to yield the fatty acid free radical (II), which reacts with oxygen to produce a fatty acid peroxy radical (III). A cycle is set up in which (III) can abstract a proton from another molecule of (I) to yield an unsaturated fatty acid hydroperoxide (lipid peroxide) and another molecule of (II), which can continue the autocatalytic chain reaction of lipid peroxidation. The biological defense mechanisms, superoxide dismutase (SOD), catalase and glutathione peroxidase are shown at the sites at which these may act to prevent detrimental consequences.

or lipids and proteins) initiated by lipid peroxidation. The mitochondrial membranes and the endoplasmic reticulum contain a high proportion of unsaturated fatty acids[202] and consequently, these membranes are also highly susceptible to lipid peroxidative damage.

The possible link between anthracycline-mediated free radical generation and cardiac toxicity was first proposed by Myers *et al.*[203] on the basis of the detection of malondialdehyde* (a known product of unsaturated fatty acid peroxide degradation) in cardiac muscle after treating mice with adriamycin. Coupled to this finding was the observation that tocopherol reduced lipid peroxidation and concomitantly lessened the cardiac toxicity without compromising the antitumor activity of adriamycin. Subsequently, a number of groups[160,206,207] have shown that both cardiac mitochondria and cardiac sarcosomes generate the superoxide anion in the presence of adriamycin or daunomycin. Since these targets are prominent sites of injury, these observations are of considerable interest. In addition, these intracellular sites of action regulate the availability of intracellular calcium to the contractile proteins and abnormalities in calcium handling are characteristic of cardiomyopathy. Evidence has been obtained[208,209] that a specific defect occurs in mitochondrial calcium transport after anthracycline administration. Alterations in the activity of NADH-oxidase and the succino-

*Interestingly, malondialdehyde is carcinogenic[204] as well as mutagenic[205].

oxidase system, which constitute the respiratory chain enzymes requiring coenzyme $Q_{10}$ ($CoQ_{10}$) as cofactor[210], have been associated with lipid peroxidation damage*[211]. Thus, it is suggested that the formation of free radicals in the heart may destroy the function of key cellular components through oxidation and as a result, cardiotoxic effects are observed.

The particular sensitivity of the heart to the effects of free-radicals may be accounted for by a deficiency in the protective enzymes superoxide dismutase and catalase[171,215,216] relative to an organ such as the liver which normally generates free radicals during the catabolism of drugs and endogenous compounds. Cardiac tissue possesses less than 10% of the catalase activity and less than 25% of the superoxide dismutase activity found in the liver[217]. The protective enzyme glutathione peroxidase†, whose proposed role is to detoxify lipid peroxides by reducing them to stable lipid alcohols[220,221] and destroy hydrogen peroxide by reducing it to water[222-224] (Figure 9), has the same level of activity in both organs. However, adriamycin depresses the activity of glutathione peroxidase in cardiac tissue[160,225,226].

Cardiac glutathione peroxidase levels reached a nadir at 24 hours following adriamycin treatment and remained

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*Alternatively, it has been proposed[157,210,212] that adriamycin competes with ubiquinone ($CoQ_{10}$) for several ubiquinone dependent oxidoreductases. It is pointed out that ubiquinone can act as a radical scavenger[210,213] and its use in "rescue" therapy for cardiotoxicity was suggested[214].

†Glutathione peroxidase, which requires selenium as a cofactor[218], is a cytosolic enzyme with its function directed towards the removal of hydrogen peroxide in the cytosol as it may not have access to lipid peroxides formed within cell membranes[219].

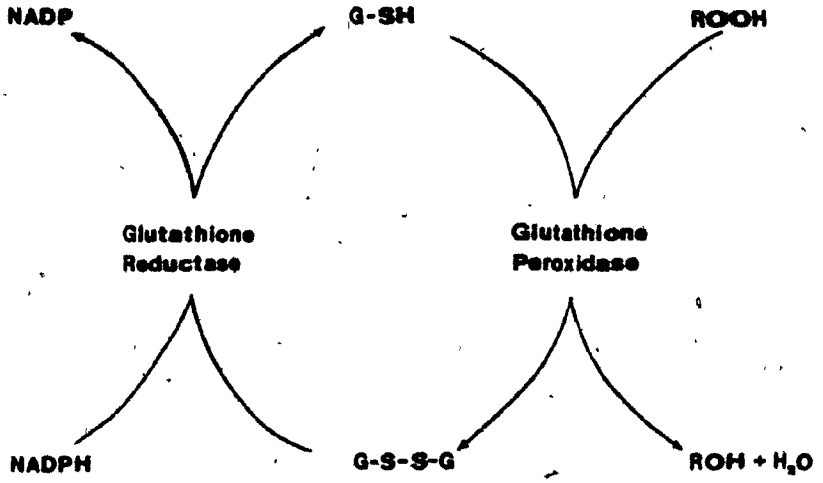


Figure 9: Reduced glutathione (G-SH) converts peroxides (ROOH) to alcohols (or water in the case of $H_2O_2$) in the presence of glutathione peroxidase and in the process is itself oxidized (G-S-S-G). Oxidized glutathione is reduced to G-SH in the presence of glutathione reductase and NADPH.

depressed over a period of between 4 and 5 days. During this period of enzyme depression, two major intracellular paths for peroxide removal are unavailable to cardiac tissue. Thus, adriamycin is able to catalyze the formation of hydrogen peroxide at the same time that it attenuates one of the key mechanisms for hydrogen peroxide removal.

C.3.1.2 DNA nicking

The ability of daunomycin and adriamycin to damage DNA in mammalian cells is well documented. These drugs are known to cause single strand breaks[227-229] which may be responsible for chromosomal rearrangement including the increased

frequency of sister chromatid exchanges[230,231] and mutational events[32]. In addition, these compounds are very effective carcinogens in rats[33-35].

Lown *et al.*[176,177,232-236] have shown that the cleavage* of DNA depends on the induction of hydroxyl radical formation by adriamycin as a result of its redox properties (summarized in Figure 7). This is consistent with a previous study in which the ability of the hydroxyl radical to cause DNA strand scission was demonstrated[239]. Coupled with the fact that the nucleus contains the enzyme NADPH cytochrome P-450 reductase which can catalyze the reduction[173] of adriamycin, and the fact that there exists a correlation between DNA strand breakage and cytotoxicity[240], the drug-induced free-radical formation constitutes a plausible mechanism for single strand breakage. (It may also provide a mechanism for the mutagenicity and carcinogenicity of these drugs). Unfortunately, there are no published studies which have addressed the question of the actual mechanism of single strand breakage in a living cell.

The premise that the cardiotoxicity of the anthracyclines is related to the documented free-radical cascade is supported by the observation that the analog 5-iminodaunomycin

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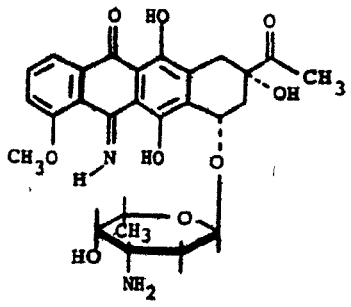
* Some strand breaks result from the action of topoisomerase[201] releasing the torsion placed in the double helix by drug intercalation but this is not the cause of cytotoxicity[237]. However, recently it was found, in contrast to a previous report[235], that the binding of the drug to DNA must cause considerably more single strand breakage than originally thought, as the anthracycline, 5-iminodaunomycin, which has a negligible capacity to form semiquinone radicals *in vitro* causes extensive single strand breakage[238].

(9) is less cardiotoxic than daunomycin[241]. This quinone-modified analog displays a slower rate of reduction and a slower rate of reoxidation of the reduced form relative to daunomycin[235,242] which in turn, makes it a less efficient



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substrate in the redox cycle shown in Figure 7. As only a small decrease in antitumor activity is observed with 5-iminodaunomycin (with 5-iminoadriamycin, antitumor efficacy* was significantly increased, although potency* was decreased[243]), this result suggests for the first time that it may be possible to separate cardiotoxicity from antitumor activity†[236].

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*Compounds have antitumor efficacy if %T/C or survival time of treated mice relative to controls is ≥ 120. Potency compares the dose of analog and dose of parent drug required to give the same effect.

†However, this may have to wait further *in vivo* evaluation because the selective cytotoxicity displayed by the anthracyclines may be due to the same factor believed to be responsible for cardiotoxicity, *i.e.*, the significantly deficient levels of the protective enzymes, superoxide dismutase, catalase and glutathione peroxidase[195,215,216,244,245].

### C.3.2 Anthracyclines as alkylating agents

Reduction of daunomycin or adriamycin under anaerobic conditions leads to glycosidic bond cleavage and isolation of the 7-deoxyaglycone* and daunosamine[168,170,207,248-252]. The mechanism of glycosidic bond cleavage involving either one or two electron reduction (depending on the reducing agent[170,253]), has been intensely investigated and debated because of the potential role that the reactive intermediates might play in the covalent binding of the drugs to biological macromolecules including DNA.

#### C.3.2.1 One-electron reduction

The one-electron reduction of the quinone part provides a semiquinone (which is in all likelihood protonated at physiological pH)[254] that heterolytically eliminates the glycoside residue to yield a semiquinone methide which undergoes a "rearrangement" in which the unpaired electron migrates to the C-7 position (Figure 10). The radical thus formed can abstract hydrogen (and initiate lipid peroxidation) or it can reduce molecular oxygen (initiating an oxygen-dependent lipid peroxidation and DNA degradation) but it is believed to be the alkylating species responsible for covalent binding to DNA[170,172,255-260]. The C-7 radical might also be expected to react with itself to yield an alygcone dimer.

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*Reductive deglycosidation to the inactive 7-deoxy aglycones is one of the important clinical disadvantages associated with the anthracyclines[45,246,247].

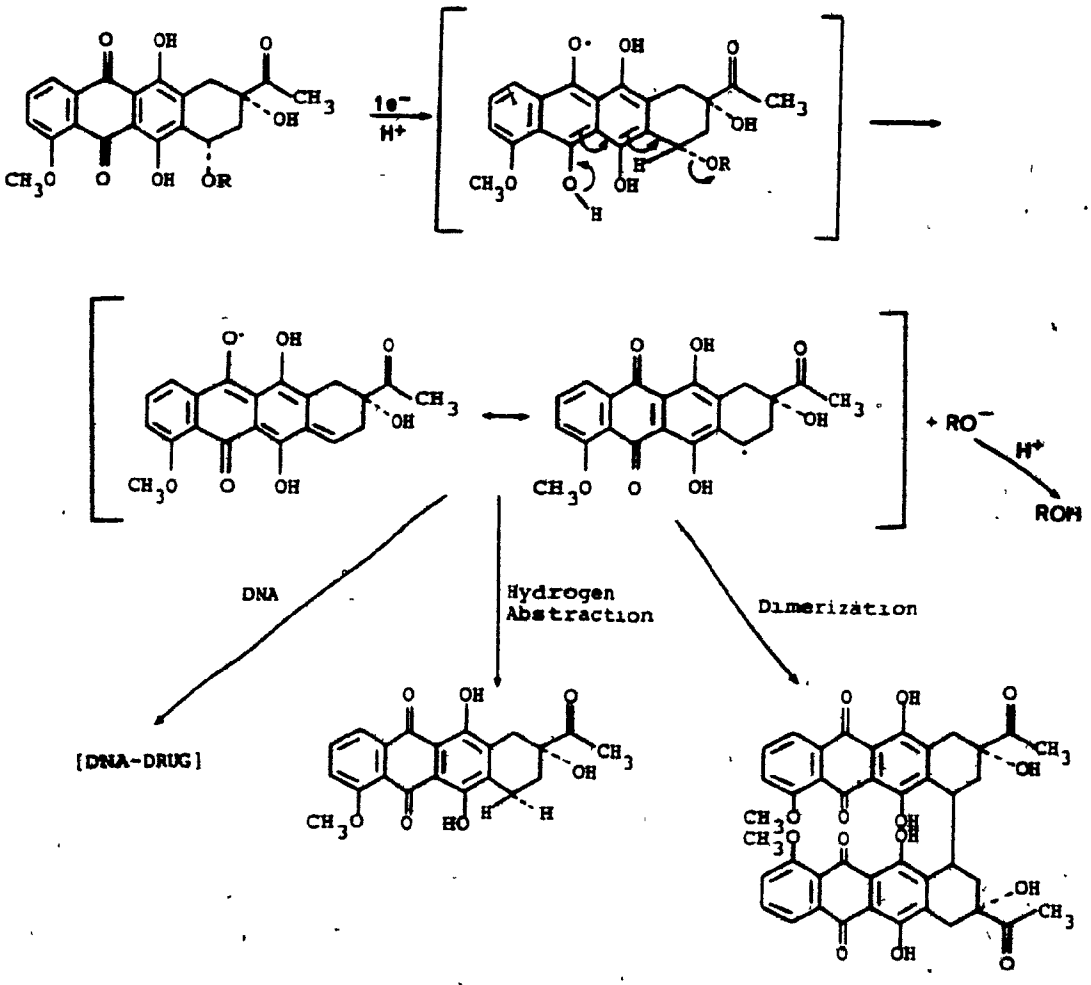
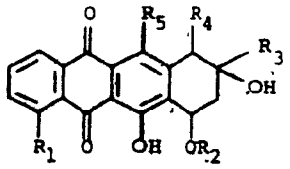
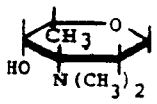
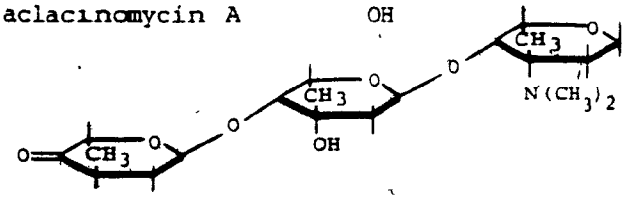



Figure 10: Proposed mechanism for DNA alkylation and formation of deoxyaglycone and deoxyaglycone dimer from a carbon-centered free-radical intermediate derived from the anthracycline semiquinone intermediates.

While the formation of such a dimer has not been described for daunomycin (or adriamycin), it has been identified in the case of the one-electron reduction of 1-deoxypyrromycin (10), aclacinomycin A (11) and aklavinone (12)[261-263]. The isolation of these dimers was, in fact,

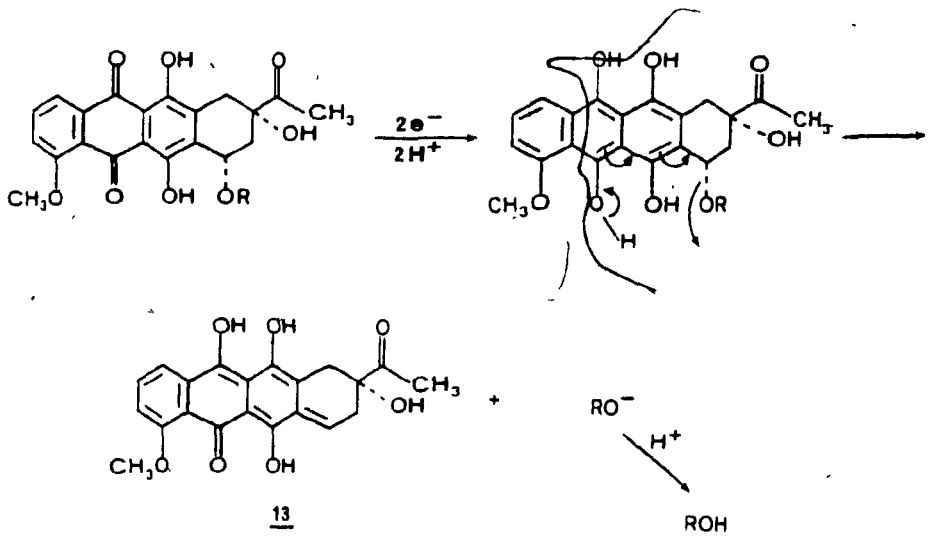


| | | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ |
|---|---|---|---|---|---|---|
| 10 | 1-deoxypyrromycin | OH |  | $CH_2CH_3$ | $CO_2CH_3$ | H |
| 11 | aclacinomycin A | OH |  | $CH_2CH_3$ | $CO_2CH_3$ | H |
| 12 | aklavinone | OH | H | $CH_2CH_3$ | $CO_2CH_3$ | H |

considered as constituting evidence for the proposed mechanism underlying the one electron-induced reactivity of the anthracyclines..

C.3.2.2 Two-electron reduction

The two-electron reduction of the quinone part leads to the corresponding hydroquinone which subsequently undergoes heterolytic glycoside bond cleavage to yield a methide intermediate. This quinone methide 13 is potentially electrophilic[264-267] as well as nucleophilic[268] and thus provides an attractive intermediate for covalent binding onto macro-



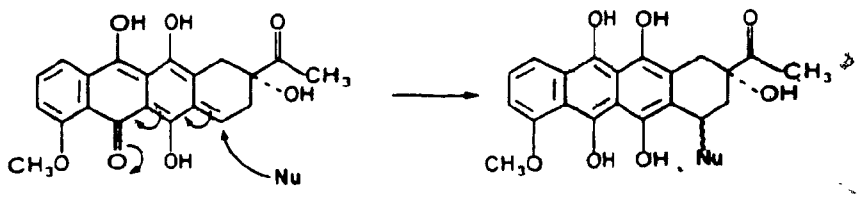
13

Quinone Methide

molecules[104,255,256,264-268].

In the first path of reactivity, the quinone methide serves as an electrophile (Michael acceptor) capable of reacting with the nucleophilic sites of macromolecules*. This mode of induced reactivity is an illustration of the phenomenon of bioreductive activation extensively discussed by Moore[264,265]. While the trapping of electrophilic intermediates presumably generated by reductive cleavage of daunomycin has been unsuccessful[253-268a], such trapping of 7,11-dideoxyanthracyclinone quinone methide by thiolate nucleophiles was recently reported[267]. The initial product, hydroquinone 14a, undergoes disproportionation so that quinone methide formation becomes autocatalytic. The isolated adducts are converted anaerobically

*Some principal nucleophilic sites in DNA are the N-7 position of guanine, the N-3 position of adenine and the exocyclic O-6 position of guanine[269].



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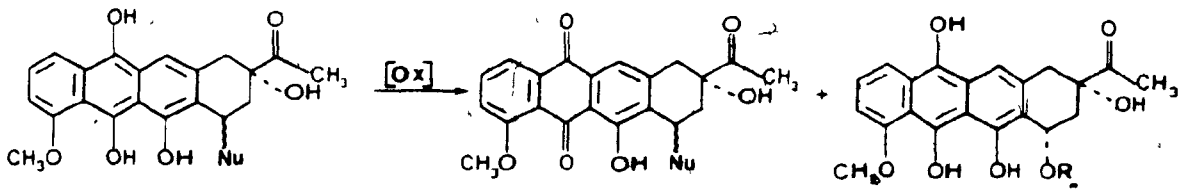
in the absence of nucleophiles to 7-deoxyanthracyclines which explains why it has been so difficult in the past to obtain



14a

positive results in trapping experiments[253]. The failure to observe nucleophilic addition to daunomycin suggests that the quinone methide is either unreactive or is more readily protonated and susceptible to faster tautomerization because of the C-11 hydroxyl group[253]. Alternatively, the adduct may be more poorly capturable by disproportionation.

In the second path of reactivity, the quinone methide now serves as a nucleophile capable of reacting with the electrophilic sites of macromolecules*. Reaction of quinone

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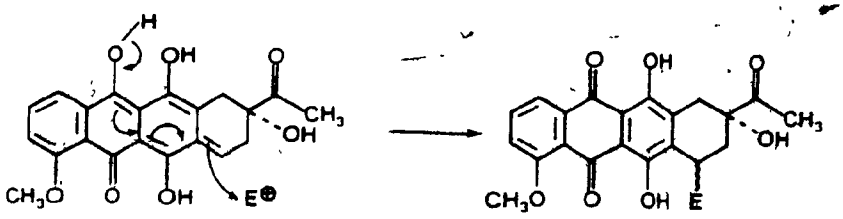
* Covalent bond formation can be expected with electrophilic sites in DNA such as the 2- or 4-position of a pyrimidine base or the 2- or 6-position of a purine base. In addition, guanine is expected to be more reactive than adenine and cytosine more reactive than thymine[270,271].

methide 13 with an electrophile regenerates the quinone but subsequent reduction of the adduct would not be expected to



13

promote cleavage of the new bond at the 7-position (because electrophiles are usually poor leaving groups). The simplest example of the reaction of quinone methide 13 with an electrophile is, of course, proton capture to give 7-deoxydaunomycinone. An interesting illustration of the proposed nucleophilic reactivity of the quinone methide towards a relevant substrate was obtained in trapping experiments using benzaldehyde as the electrophile[268].

Recently, however, it was reported[170] that there is little evidence that the anthracyclines can undergo two electron reductions *in vivo*. Bachur *et al.* found that adriamycin underwent reduction with flavin oxidoreductases, capable of single-electron transfer but was a poor substrate for the flavoproteins capable of two-electron transfers. On the

other hand, Sinha and Gregory[256] found that α-tocopherol (a presumed free-radical scavenger) had no effect on the covalent binding of adriamycin to DNA. However, glutathione interfered with binding, an indication that the quinone methide was formed. Some doubt has also been cast on the evidence purporting to show that adriamycin binds covalently to DNA. This evidence was based mainly on the finding that binding of the drug to DNA persisted after repeated extractions and washings under conditions known to liberate intercalated drugs[255,257,258]. That covalent binding may indeed occur was reported by Ghezzi *et al.*[272], who showed that $^{14}$C-labeled adriamycin binds covalently to microsomal proteins in NADPH-dependent reactions. It is clear that more of this type of direct proof of covalent binding should be adduced before confidence in the alkylation mechanism (either as a result of one-electron or two-electron reduction) can be sustained.

Both the C-7 radical (resulting from a semiquinone rearrangement) and the quinone methide pathways may be more important mechanisms in *in vivo* situations for the induction of DNA damage or breakage[163,258]. For example, while it is observed that the binding of anthracyclines to isolated DNA causes molecular distortions but never damage or breakage of the DNA strands, intact living cells treated with the drugs rapidly show DNA damage[15,228,229,273]. This suggests that *cellular* activation to one or the other of the alkylating species (or hydroxyl radical formation) probably occurs, a

process facilitated by the integrity of living cells[172,258]. In addition, the ability of adriamcyin to kill tumor cells under hypoxic* conditions supports the theory of its bio-reductive activation[275,276].

A summary of the hypothetical process undergone by the anthracyclines in the cell (adapted and modified from Bachur *et al.*[173]) is shown in Figure 11.

Once across the cell membrane, the drug may follow two paths. It may go directly to the nucleus to suffer reduction by flavo proteins located in the nuclear stroma. This would result in the formation of the semiquinone free radical† intermediate which can react directly with DNA or to the drug free-radical which can react with oxygen to form superoxide free-radicals and subsequently hydrogen peroxide and hydroxyl radicals. The hydroxyl radicals would damage DNA and other nuclear structures. The regenerated quinone group becomes available again for single-electron reduction by a recycling process. The drug may also bind covalently to DNA or other nuclear structures and because the quinone group would be free, it could participate in the single-electron reduction process. However, an intercalated drug can no longer be available for free radical formation. In the

*Hypoxic cells are resistant to chemotherapeutic agents directed against proliferating cells. It is hypothesized that hypoxic cells remote from the vascular supply of a tumor mass might have a greater capacity for reductive reactions than their normal well-oxygenated counterparts[274].

†The 2-electron reduction process is not discussed here because it is not considered likely by Bachur who proposed the reaction pathway in question.

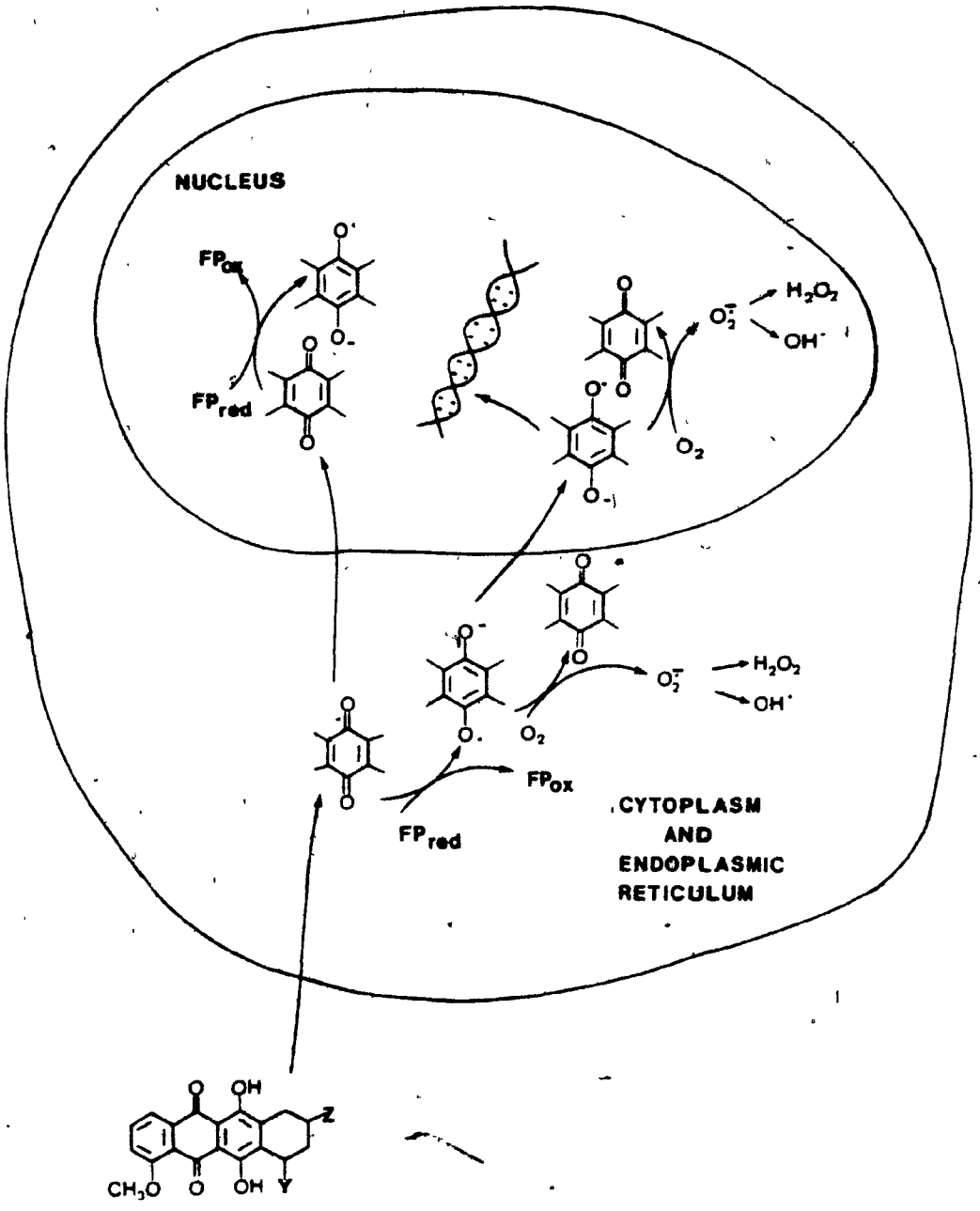



Figure 11: Possible reaction pathways of quinone-type drugs in the cell. $FP_{red}$, reduced flavoprotein; $FP_{ox}$, oxidized flavoprotein.

cytoplasm, the endoplasmic reticulum flavo proteins or the mitochondrial enzymes also catalyze the formation of drug

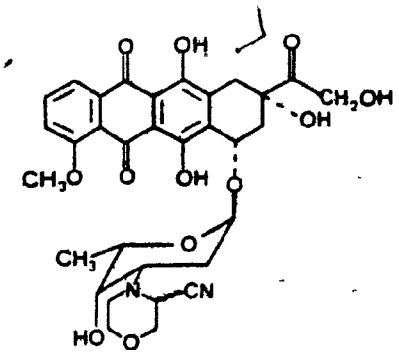
free-radicals which may react with cellular components such as cell membranes or may generate hydroxyl radicals inflicting damage on various cellular components (*via* oxygen mediated lipid peroxidation). It is possible that semiquinone free-radicals produced at the endoplasmic reticulum level may travel to and penetrate the nucleus where they can cause damage as discussed above.

The scheme is greatly over-simplified because the rate of adriamycin semiquinone reaction with $O_2$ is so high that the reduced form could only survive to be captured by DNA if the cell's internal $O_2$ concentration were very low. Moreover, under such circumstances, formation of oxygen radicals by reduced drug would not be possible either[166].

## D. CONCLUSION

The anthracyclines are structurally complex agents which give rise to multiple biochemical effects. How these antibiotics elicit these effects is a question that can be divided into two main parts. Adriamycin can be looked upon as a passive molecule that binds to DNA and, by distorting the latter's geometry, alters its function. Alternatively, the chemical reactivity (basicity of the amino group, the redox potential of the chromophore) of the antibiotic can serve as a basis to explain its biological effects. As we have seen, there is no persuasive evidence favoring one view or the other. Both rationales can "explain" the selective cytotoxicity

of these antibiotics towards cancer cells relative to normal cells and both views also offer "acceptable" explanations for their cardiotoxicity. However, besides the fact that these proposed mechanisms cannot explain why adriamycin is cytotoxic at a concentration inferior to that required to inhibit DNA synthesis[277] or why the new analog of adriamycin, 3'-(3-cyano-4-morpholinyl)-3'-deaminoadriamycin (15) is not only an intensely potent antitumor agent but also lacks



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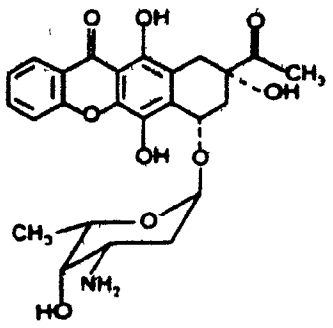
cardiotoxicity[278,279], these mechanisms, by themselves, do not tell a complete story. For example, these rationalizations cannot account for the wider spectrum of activity of adriamycin relative to daunomycin even though the two drugs are virtually identical from the structural and reactivity point of views as we have noted and emphasized in this presentation.

The superior activity of adriamycin over daunomycin is perhaps best explained by taking into account their respective

effects on the immune system. Daunomycin is apparently more immunosuppressive than adriamycin[280-282]. In addition, although the chemistry of the two antibiotics may not be significantly different (differing only at the C-14 position) their transport and rate of metabolism *in vivo* are certainly not the same[109,117,283,284]. The complexities inherent to intact living systems can be appreciated further. A very important point (which is very often neglected by most researchers in this field) is that cancers are not homogeneous. They tend to preserve, in varying degrees, the metabolic characteristics of their tissue of origin. There is biochemical heterogeneity even within a tumor class[285]. They also differ in their ability to repair DNA[286], in their content of superoxide dismutase, catalase and glutathione peroxidase[195,215,216,244] as well as in their ability to take up certain trace metals[287,288]. Since these parameters cannot be easily identified, our chances of success are similarly uncertain but our awareness of them will ultimately help us understand the very complex nature of the interactions between drugs and their target organisms.

## E. THE GOAL OF THE PROJECT

The aim of our project was to develop useful synthetic strategies of the synthesis of the chromophore unit of 4-demethoxyxanthodaunomycin (16) and its regioisomer 4-demethoxy*iso*xanthodaunomycin (17). The reason for synthesizing



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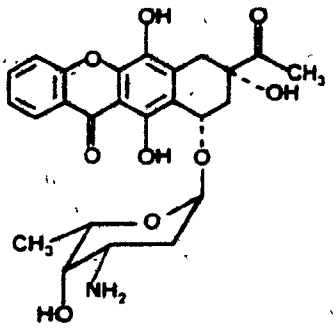
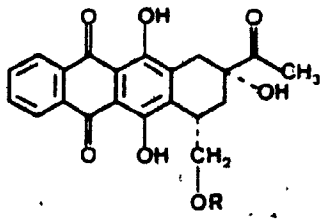


17

such compounds carrying a modified chromophore was to evaluate the hypothesis that daunomycin-mediated formation of free radical species may be a cause of cardiotoxicity. Testing of this hypothesis may be possible with compounds such as 16 and 17 because the "xanthone" unit is not as efficient an electron-acceptor as the quinone unit of daunomycin and as a result these analogs would be expected to display a lower rate of reduction relative to 1. (We have already seen that 5-iminodaunomycin, which was disclosed while our own work was in progress, exhibits a lower rate of reduction than 1 and shows significantly less cardiotoxicity). Extensive structure-activity relationship studies have been useful in identifying the chemical features which are not critical for activity. However, we were reluctant to introduce too many modifications, some of which might mask the primary effect that we are seeking while others might cause alterations in transport, metabolism and response of the immune system.

Consequently, the only additional feature which we decided to alter involved removal of the substituent at the C-4 position. This choice not only simplified the synthetic strategy but a potentially more useful compound may be obtained because it is known that a 10-fold increase in *in vivo* potency is associated with the removal of the 4-methoxy substituent of daunomycin and adriamycin.

In addition, we planned to synthesize the 4-demethoxy-daunomycin analog 18 and 4-demethoxyxanthodaunomycin analogs 19 and 20. Since the anthracyclines suffer *in vivo* deactivation through



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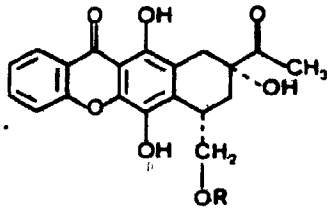

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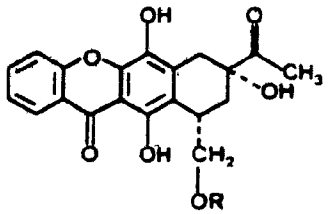

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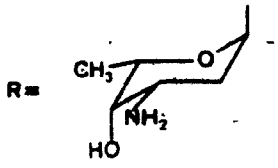
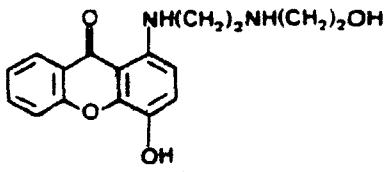


conversion to the corresponding 7-deoxyaglycone, it would be interesting to see what effect replacement by a "stabilized" substituent might have. At the same time, the bioactivation hypothesis requiring a 1-electron or 2-electron reduction of anthracyclines prior to the generation of alkylating species at

C-7 would become verifiable because such analogs as 18, 19 and 20 cannot eliminate their C-7 carbon substituent.

In a parallel vein, some aminoanthraquinones have generated a considerable amount of interest because while they incorporate only a few features of the anthracyclines, they show significant antitumor activity. However, like the anthracyclines they are cardiotoxic. As we felt that these compounds might also be involved in the generation of free-radical species, we decided to attempt the synthesis of compound 21 because its redox potential is expected to be altered relative to the parent anthraquinones. The information obtained should prove extremely useful regardless of the results because research work on the aminoanthraquinones is not yet as extensive as on the anthracyclines and relatively little is known also about their mechanism and site of action.

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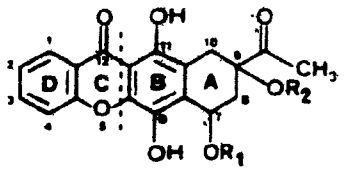
# CHAPTER 1

## SYNTHESIS OF THE HETEROANTHRACYCLINES AND *iso*-HETEROANTHRACYCLINES *via* C-RING FORMATION

### 1.1 DISCUSSION OF THE SYNTHETIC STRATEGY

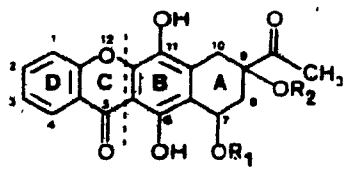
A simple retrosynthetic analysis of the heteroanthracycline ring system 22 and its isomer 23 would involve among other possibilities the bond disconnections shown below, an operation suggesting a strategy based on the creation of the DC rings from an appropriate AB fragment. This strategy




22

16 $R_1$ = daunosaminyl, $R_2$ = H

24 $R_1$ = $R_2$ = H




23

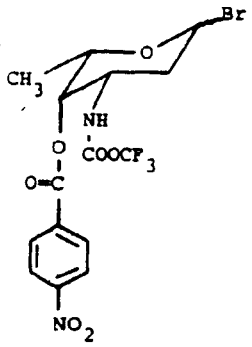
17 $R_1$ = daunosaminyl, $R_2$ = H

25 $R_1$ = $R_2$ = H

requires in principle, the condensation of an appropriately protected *o*-phenolic acid derivative of the D-ring part with either a fully functionalized AB-ring intermediate or a suitable AB-ring precursor which can be further functionalized

after the formation of ring C.

The glycosidic bond between the aglycone (24 and 25) and the amino sugar 4-O-*p*-nitrobenzoyl-3-N-trifluoroacetyl-daunosaminyl bromide (26) (readily prepared from N-trifluoro-acetyldaunosamine (27) which was made available to us by Bristol Laboratories, Syracuse) carried out under Koenigs-Knorr conditions*[289] completes the synthesis of heteroanthracyclines 16 and 17.

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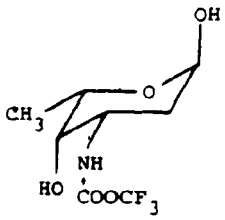


27

Goodman *et al.*[291] were the first to demonstrate the feasibility of such a strategy where position 7 was functionalized after a C-ring formation reaction ultimately led to the simple anthracyclinone 28. This pattern was exploited by Wong *et al.* who reported the successful synthesis of 4-demethoxy-7-O-methyldaunomycinone (29)[292] and later of daunomycinone (3)[293] (Scheme 1.1), using the appropriate phthalic acid derivatives and the partially substituted tetralin,

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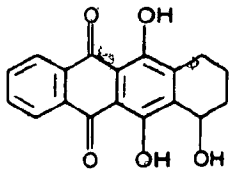
*Recently, trimethylsilyl trifluoromethanesulfonate has been reported to be an excellent glycosidation reagent for anthracycline synthesis[290].



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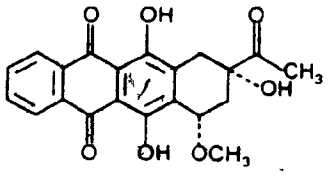
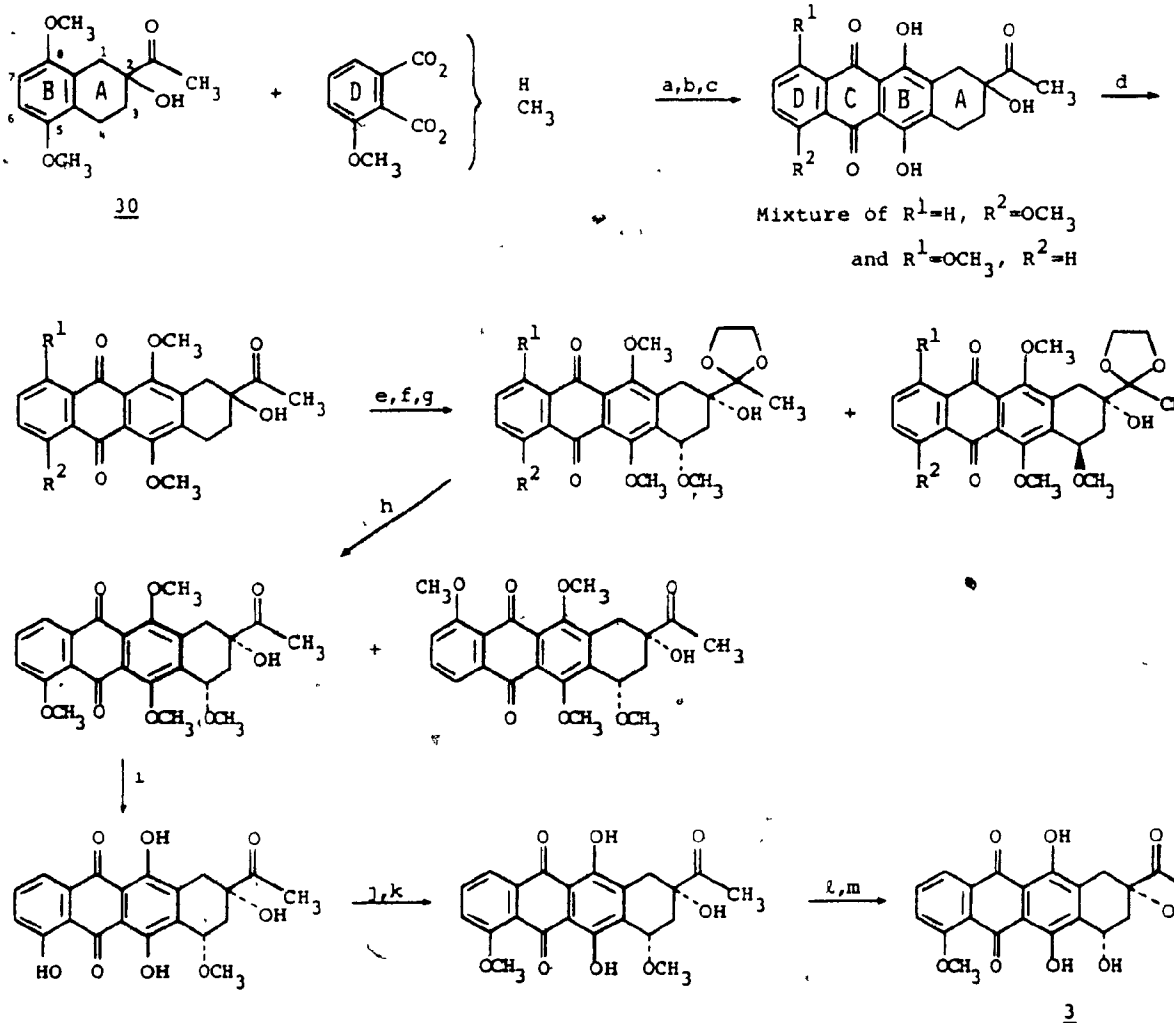


29

Scheme 1.1



30

Mixture of $R^1$=H, $R^2$=$OCH_3$ and $R^1$=$OCH_3$, $R^2$=H

3

a) $(CF_3CO)_2O$; b) NaOH; c) HF; d) $(CH_3)_2SO_4$, $K_2CO_3$; e) $HOCH_2CH_2OH$, TsOH; f) NBS; g) $CH_3OH$; h) HCl, aq THF; i) $AlCl_3$; j) $Pb(OAc)_4$; k) $(CH_3)_2SO_4$, $K_2CO_3$; ℓ) $CF_3CO_2H$; m) $NH_4OH$.

(±)-2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (30) itself prepared in seven[292] or nine steps[293] from 2,5-dimethoxybenzaldehyde. Although this work suggests that a fully functionalized AB-ring is not initially required to achieve success, there have been some reports[289,294] that only low yields of daunomycinone could be obtained when Wong's methodology for the functionalization of position 7 was followed. These observations have without doubt encouraged the application of strategies where tetralins already incorporating an oxygen function at position 7 were used as key intermediates.

Since the tetralins 31-33 are readily accessible from an intermediate* (tetralone 46) previously produced in the synthesis of tetralin 30 (*vide infra*), they were adopted as prototypes in attempted syntheses of the anthracyclines. (Although the 2-position of these tetralins is not hydroxylated, this operation is not considered as posing a problem). It was found, perhaps not surprisingly, that the conditions associated with the Friedel-Crafts acylation reaction were not tolerated very well by the tetralin substrates 31[298], 32a[299] and 32b[295,299] which led to low yields of condensation product. In the case of the masked quinone 33 the acylation conditions proved incompatible with the substrate, decomposition products being observed[295].

This unsuccessful attempt to use tetralins 31-33 as intermediates discouraged further work along these lines.

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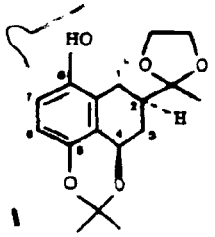
*Tetralin 33 was prepared from the brominated analog of tetralone 46[295-297].



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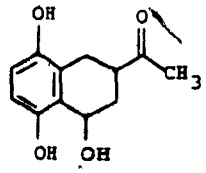
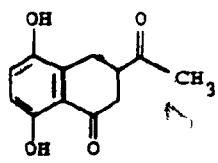


32a



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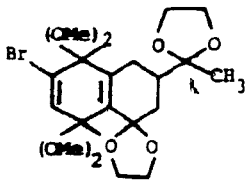

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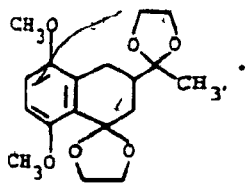

34*

However, this information helped in the formulation of our approaches to the synthesis of the heteroanthracyclines.

In our plan to construct ring C through a Friedel-Crafts acylation, it was immediately apparent that tetralins 31, 32 and 34 would be unsuitable which left us with tetralin 30 as the only alternative. It was anticipated that formation of the ether linkage would not be easy. We felt that one way to achieve this was by oxidizing ring B of either tetralin 30 or hydroxybenzophenone 35 to quinones 36 and 37 respectively followed by 1,4-addition of the appropriate phenol, the adduct subsequently suffering aromatization through tautomerization (Scheme 1.2). We were encouraged to pursue this approach by the report[300,301] that tetralin 30 undergoes oxidative-demethylation to quinone 36 in 98% yield, thus showing that ring A is stable to these oxidizing conditions.

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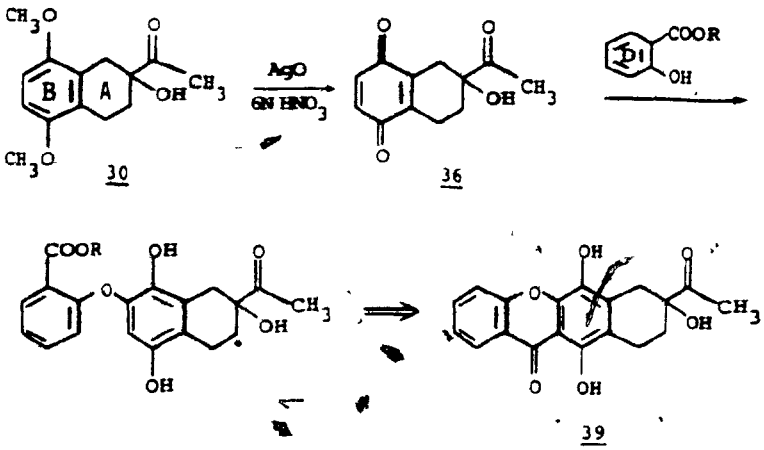
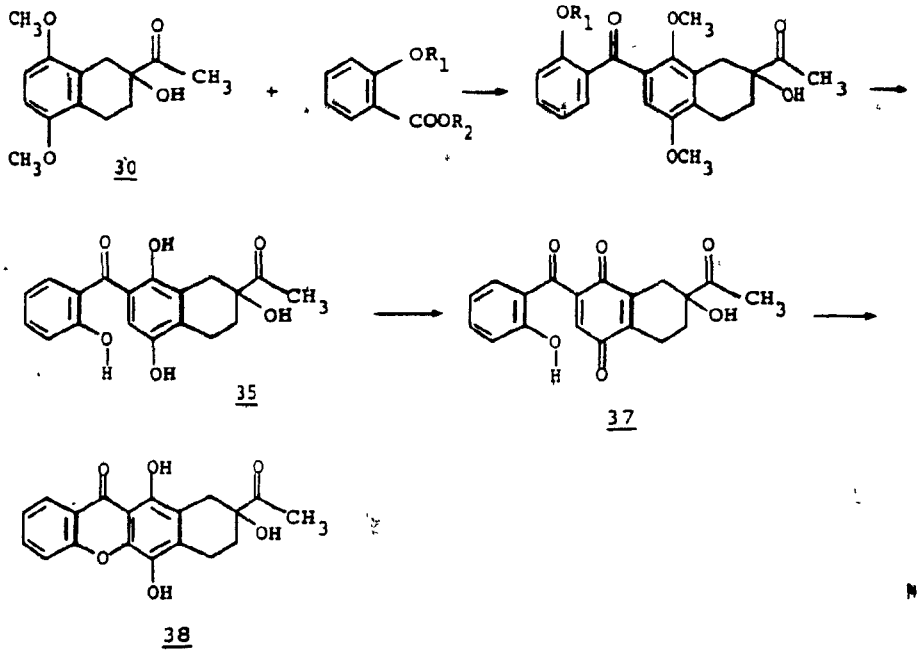
*Tetralin 34 can be easily prepared from tetralone 46 using conditions used to prepare tetralin 33[295-297].

Scheme 1.2*

Route 1




Route 2




*The regioisomers are not shown.

However, in parallel studies on xanthone synthesis*, it was observed that phenolic-OH addition (of the Michael type, as in Route 1) to quinones is generally difficult. On the other hand, addition to an *activated quinone* such as 37 can occur readily even in the absence of the catalyst 4-dimethylamino-pyridine (DMAP)[302-304]. Alternatively, cyclization of an *o*-hydroxybenzophenone such as 35 (Route 2) may be induced by oxidation to 37 with DDQ (2,3-dichloro-5,6-dicyano-*p*-benzo-quinone)[305] to yield 38 by way of a 1,4-addition and tautomer-ization process.

On the basis of these considerations, it appeared that Route 2, where an intermolecular Friedel-Crafts acylation reaction is carried out in a first step, was more likely to succeed. Accordingly, we proceeded with the synthesis of tetralin 30.

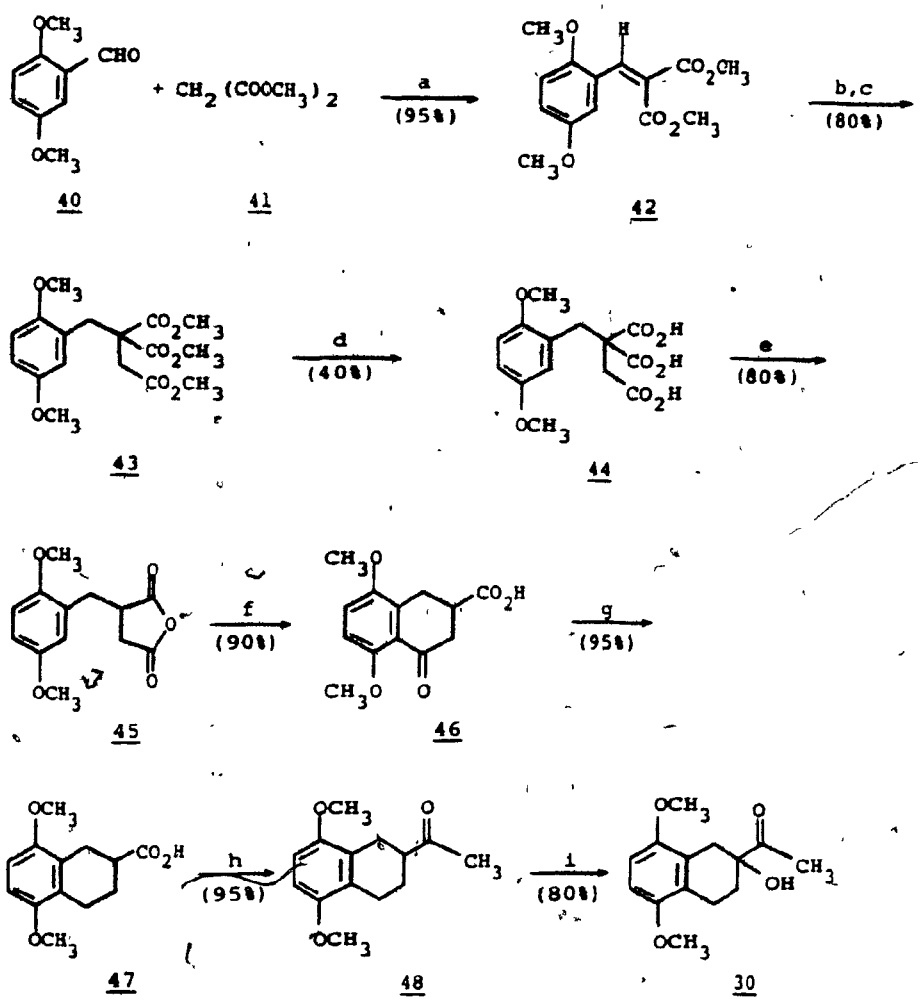
## 1.2 SYNTHESIS OF (±)-2-ACETYL-5,8-DIMETHOXY-1,2,3,4-TETRAHYDRO-2-NAPHTHOL

We modeled the synthesis of tetralin 30 (Scheme 1.3) after Wong's[293] but modified certain key steps according to methods reported elsewhere[295-297,306-311].

A crystalline Knoevenagel product 42 was obtained in excellent yield by the reaction of commercially available 2,5-dimethoxybenzaldehyde (40) and dimethyl malonate (41). Reduction of the unsaturated diester 42 with lithium tri-*sec*-

*A more extensive discussion is given in Chapter 2.

Scheme 1.3




a) $C_5H_{11}N$, HOAc; b) Li(*sec*-$Bu_3BH$); c) $BrCH_2COOCH_3$; d) KOH, $H_2O$; e) $Ac_2O$; f) TFA–TFAA; g) $(CH_3CH_2)_3SiH$, TFA; h) $CH_3Li$; i) t-BuOK, $O_2$, $P(OCH_3)_3$.

butylborohydride followed by *in situ* alkylation of the carbanion[311] with ethyl bromoacetate gave triester 43. The reduction reaction, followed by pmr, was complete within 30 min

as evidenced by the disappearance of the olefinic signal at 7.90 ppm. The alkylation reaction, monitored by the appearance of the methylene signal at 2.76 ppm, was complete only after refluxing for 3 h. This preparation of the triester constitutes an improvement over another method[307,312] which we had initially used and which involved the alkylation of diethyl 2-carbethoxysuccinate with dimethoxybenzyl chloride (the ethyl analog of triester 43 being obtained). Triester 43 was hydrolyzed under alkaline conditions to the triacid 44 which was obtained in only a 40% yield owing to difficulties in isolation. Decarboxylation with concomitant formation of anhydride 45 was accomplished in boiling acetic anhydride. Cyclization of 45* to tetralone 46 was conveniently and cleanly performed using a mixture of trifluoroacetic anhydride (TFAA) and trifluoroacetic acid (TFA). Reduction of tetralone 46 to tetralin 47 was achieved in nearly quantitative yield using triethylsilane in TFA[313]. This method constitutes an excellent alternative to catalytic hydrogenation and other conventional methods for the reduction of aryl ketones in the presence of other functional groups. Addition of methyllithium to acid 47 followed by careful hydrolysis[309,310] gave ketone 48 which was α-hydroxylated by the standard method[292,306-308] involving treatment of the methyl ketone with potassium t-butoxide, oxygen and trimethyl phosphite in dimethylformamide (DMF).

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* It is not necessary to use an anhydride for the cyclization reaction[307,308]. In a separate experiment, the precursor (diacid) was cyclized without difficulty.

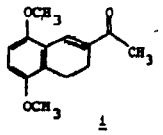
The overall isolated yield of hydroxyketone by this long sequence, was 16% but the approach is nevertheless valuable as it gives access to the potentially useful tetralone 46 and tetralin 48*. However, the established importance and versatility[300,301,317] of tetralin 30 in the synthesis of natural anthracyclines and related analogs, has stimulated numerous efforts to achieve its preparation more efficiently and in a more direct fashion[289b,300,301,318-327]. These efforts have been generally successful although discrepancies between some of the claims concerning methodology have appeared (*cf.* refs. 289b with 300, 301 and 319), which casts doubts on the general usefulness of the published strategies. Literature reports are also concerned with improvements in the synthesis of intermediates[136,318,327-329] for the preparation of tetralin 30 and a considerable effort has been made to generate easily optically active material[322-325,330-335a,b].

## 1.3 ATTACHMENT OF RING D TO RING AB

The condensation of tetralin 30 with *o*-methoxybenzoic acid (49) was attempted using a mixture of TFAA-TFA as the catalyst. Since tetralin 30 incorporates a potentially reactive *tert*-OH group†, care was taken to use only a small

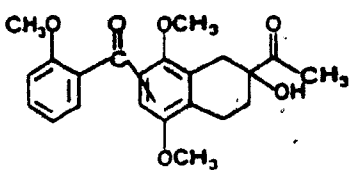
*Wong *et al.* have recently reported[315] the use of tetralin 48[316] in the synthesis of the heteroanthracylines.

†Dehydration of tetralin 30 to i was an expectable possibility. However, the conditions required for this are quite drastic and involve the use of 96% sulfuric acid for 10 min at room temperature[336].

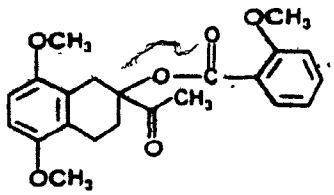



i

excess of acid reactant 49. After refluxing for a period of about 16 h, a quantitative yield of a crystalline product (transparent prisms) was obtained. The spectral and chemical properties of this material established that the ester 52 had formed rather than the expected benzophenone 50 and 51.



50 and 51



52

In its pmr spectrum, the compound showed no exchangeable proton ($D_2O$) and there was also no change in either the chemical shift or the intensity of the signal at 6.63 (H-6, H-7 of tetralin 30). The absence of a hydroxyl group was confirmed by infrared spectroscopy which also revealed the absence of absorption for a diaryl carbonyl group. In its mass spectrum, a metastable peak at 140.16 amu indicated that the fragment ion with m/z 232 (base peak) originated from the molecular ion of m/z 384. This is easily accounted for by a fragmentation pattern involving a McLafferty rearrangement of the ionized ester 52 as shown in Figure 12. It is difficult to find a likely fragmentation pattern yielding an ion of m/z 232 using benzophenone 50 and 51 as the structure. Finally, alkaline hydrolysis of the crystalline product gave only

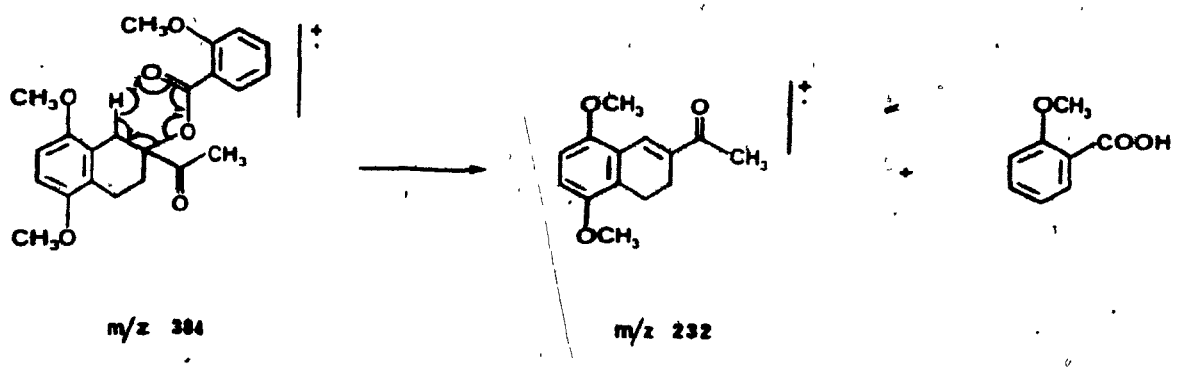


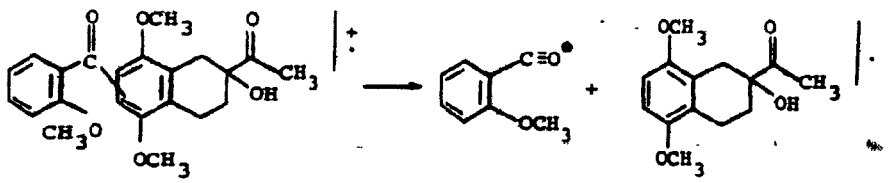

Figure 12: A McLafferty rearrangement of ester 52 with the formation of an energetically stable conjugated ion and neutral fragment.

tetralin 30 and *o*-methoxybenzoic acid in quantiative yield, providing unequivocal proof that only ester 52 had been formed in the condensation reaction.

The reaction was then repeated under different conditions. Using a large excess of *o*-methoxybenzoic acid and more vigorous conditions, a mixture of ester 52 plus another compound conceivably corresponding to diketo-ester 53 and 54 was obtained as judged on the basis of chromatographic behavior (tlc) and spectral analysis. Alkaline hydrolysis of this material and purification of the product by flash chromatography[337] gave tetralin 30 and the desired benzophenone compound in 25% and 60% yield, respectively. The benzophenone was obtained as an oil consisting of a mixture of the expected regioisomers 50 and 51 but these could not be differentiated by low field (60 MHz) pmr spectroscopy.

The spectral data for compounds 50 and 51 were

consistent with the expected pattern: a downfield shift in the H-6 or H-7 proton of about 0.23 ppm (relative to tetralin 30) was observed and the OH group absorbed at 3480 $cm^{-1}$ in the infrared while the diaryl carbonyl absorbed at 1660 $cm^{-1}$. A sharp intense band at 1705 $cm^{-1}$ was assigned to the aliphatic carbonyl group, a stretching mode which was obscured in ester 52. The mass spectrum showed an ion at m/z 135, which is the base peak corresponding to the highly stabilized fragment 55 (shown here in only one of its many possible resonance forms).



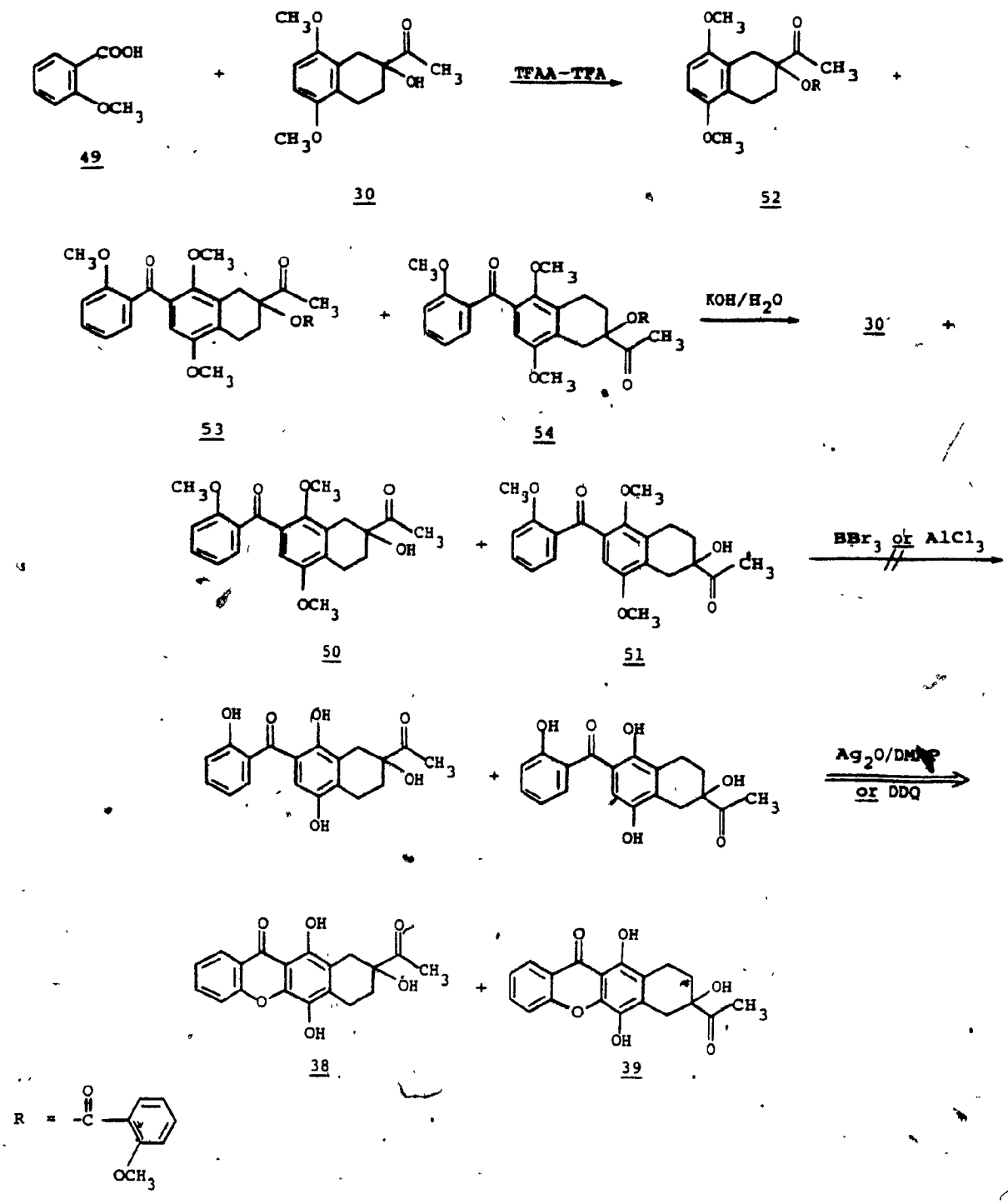
50 and 51 — m/z 384 → 55 — m/z 135

These spectral data for benzophenone 50 and 51 are in total agreement with those recently reported by Lown *et al.*[327] for the same material.

## 1.4 ATTEMPTS TO DEMETHYLATE BENZOPHENONE (50 and 51)

Selective oxidative-demethylation of ring B of the benzophenone appeared impractical because demethylation of the D-ring would still have to be accomplished. Accordingly, complete demethylation was attempted using a mixture of hydro-

bromic acid-acetic acid-water heated to 50°C for 24 h[338]. The pmr spectrum of the solution indicated that demethylation was incomplete under these conditions. Longer reaction times led to extensive decomposition. Similarly, reaction with hydroiodic acid in acetic acid at room temperature or exposure to boron tribromide ($BBr_3$)[339] at -78°C followed by warming to room temperature also resulted in extensive decomposition. Milder conditions, such as quenching of the $BBr_3$-containing mixture with methanol at -78°C gave rise to incomplete demethylation and longer reaction times again favored decomposition (as judged by tlc and pmr analysis). The claim[340] that trimethylsilyl iodide (TMS-I) is milder as a demethylating reagent encouraged us to compare it with $BBr_3$, but here again extensive decomposition occurred regardless of whether the reagent was generated *in situ* (TMS-Cl, NaI, acetonitrile[341]) or added as such. Finally, we attempted to demethylate with aluminium trichloride in benzene at room temperature over a period of 30 h. This led to a complex mixture of partially demethylated products as well as decomposed material. The crude mixture thus obtained was submitted to coupling conditions for ring C formation by treatment with silver(I) oxide in the presence of a catalytic amount of DMAP, or by treatment with DDQ[342]. However, no evidence was obtained that any 4-demethoxy-7-deoxyxanthodaunomycinone 38 (or its isomer 39) had formed. Discouraged by these results, attempts to demethylate benzophenone 50 and 51 were abandoned.




49 30 52 53 54 30 50 51 38 39

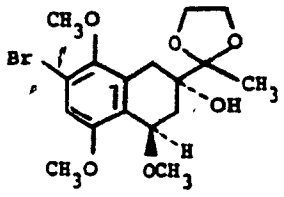
## 1.5 CONCLUSION

The above strategy was set aside for the following reasons: the difficulties encountered with the demethylation process as well as the overall inefficiency of the chemical approach even at the exploratory level, let alone the preparative aspects of tetralin 30, contributed to our negative decision. It may be, however, that if more time had been available these obstacles could be overcome. A different but equally valid reason for abandoning this approach lay in the disclosure by Wong *et al.*[315a] at a National conference that they had been exploring a very similar approach to the synthesis of heteroanthracyclines. On that occasion, Wong reported that work carried out in collaboration with the Italian pharmaceutical company Farmitalia allowed ready access to large quantities of tetralin 48, an advantage which apparently allowed his group to be on the verge of a breakthrough in the synthesis of the heteroanthracyclines. Subsequent to this communication by Wong[315a], Lown *et al.*[327] have published the synthesis of the same heteroanthracyclines by applying the same convergent strategy but differing from our own work and that of Wong only in certain details. Very recently, Wong *et al.*[315b] published a detailed account of their previously announced but as yet incomplete work.

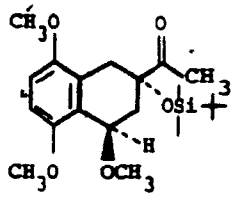
The synthesis based on ring C formation from an AB and D-ring precursor now appears to have greater potential than when we first began our study owing to subsequent

improvements in the synthesis of both racemic and optically active tetralin 30. However, what has also become strikingly clear from the published work of both Wong and Lown is that a very important handicap remains, namely functionalization of the benzylic position at 7, an operation which is so inefficient that attainment of the final goal can be considered at best as only partially successful. This functionalization problem has been hinted at before in connection with the synthesis of anthracyclines and it is even more serious where heteroanthracyclines are concerned*. The great difficulty at functionalizing cleanly the 7-position emphasizes the need for a fully functionalized AB-ring fragment before attempting any coupling reaction. The problem nevertheless remains that the generation of usable, fully functionalized tetralins is not an easy task. It is only recently that some appropriately fully functionalized tetralins such as 56-59 were described. These turned out to be viable intermediates in the synthesis of anthracyclines but required major efforts[335,344-347] where ingenious avoidance of Friedel-Crafts acylation conditions was a key to success. Although one can only speculate on the tolerance of these relevant tetralins to Fridel-Crafts conditions, the reported enormous efforts to avoid Fridel-Crafts acylation conditions are understandable and casts doubt as to

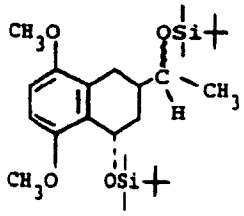
*It is not known whether the use of 1,3-dibromo-5,5-dimethylhydantoin as a brominating agent recently reported by Cava *et al.*[343] will be helpful in this regard. It is anticipated that in the *iso*-heteroanthracycline derivative (substituent at position 7 is *para* to the heteroatom) a very labile bromo-derivative may result. Some indication of this was given by Wong's recent disclosure that only one isomer, *i.e.* 22 which places the heteroatom of the same side as the 7-position, could be obtained using his own methodology.



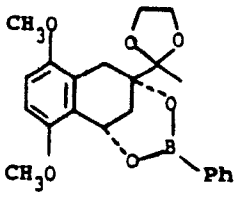
56[344]



57[345]



58[346]



59[335,347]

their usefulness in the type of strategy initially adopted by us and also by Wong and Lown.

Although no easy solution is yet in sight, it would appear that a viable strategy patterned on that of Wong or Lown should center on the discovery of coupling conditions compatible with the properties of the relevant tetralin intermediates. Perhaps, tetralins carrying different functionalities but compatible with Friedel-Crafts acylation conditions and stable to oxidizing media should be constructed in order to re-establish the viability of the initial strategy for the generation of heteroanthracyclines. Presently, however, it appeared best to focus our efforts on alternative strategies which had been concurrently conceived and explored in order to improve the prospects described above.

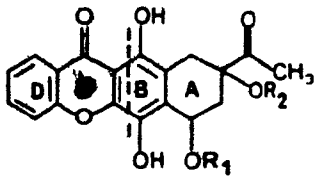
# CHAPTER 2

# SYNTHESIS OF 1,4-DIMETHOXYXANTHONE AS A KEY INTERMEDIATE IN THE SYNTHESIS OF HETEROANTHRACYCLINES

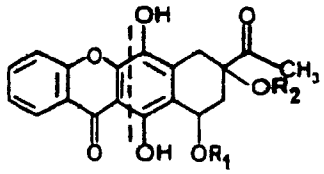
## 2.1 ANALYSIS OF SOME POSSIBLE SYNTHETIC STRATEGIES FOR THE SYNTHESIS OF HETEROANTHRACYCLINES

### 2.1.1 Synthesis *via* B-Ring Formation from A and DC Ring Intermediates

An alternative approach to the synthesis of heteroanthracyclines 22 and 23 would consist in forming the B-ring part from appropriate precursors as shown below. In principle,



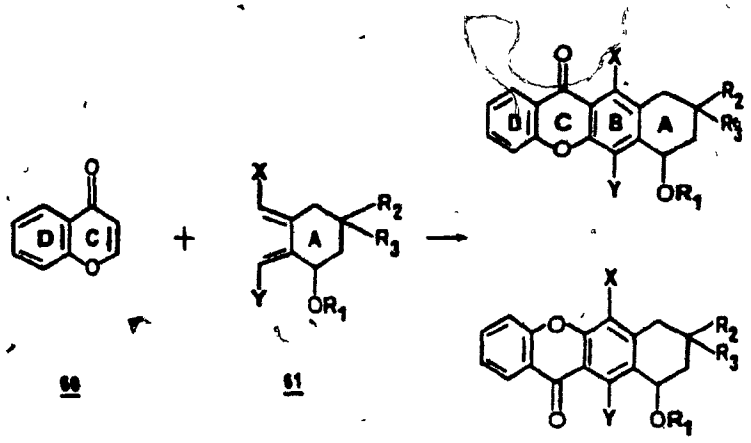

22




23

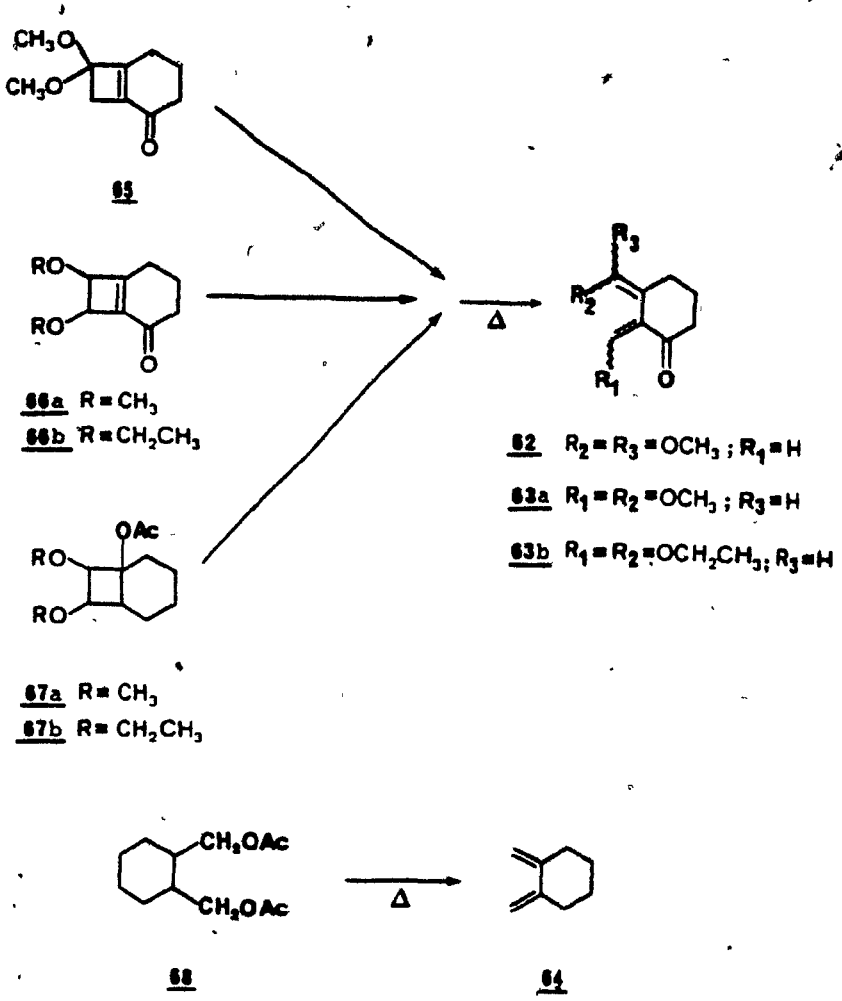
this might be achieved through a Diels-Alder reaction between the commercially available chromone, benzo-4H-pyran-4-one (60) and a diene such as 61 as shown in Equation (1).

At the time that we first considered this approach, the only related dienes available were 62-64 as they can be

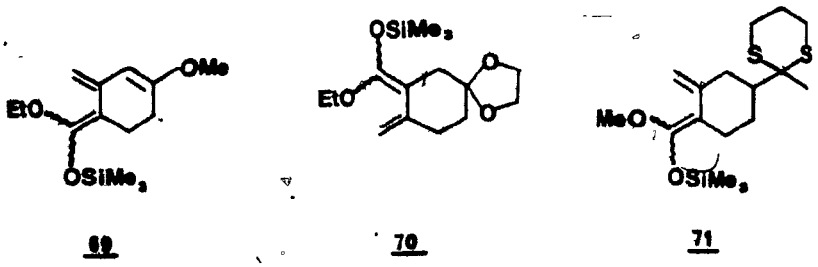


(1)

generated *in situ* by thermolysis of the precursor cyclobutenes[348] 65, 66, acetate[348] 67 and diacetate[349] 68. The absence in these dienes of relevant functionalities as present in the A-ring of 22 (or 23) made them inappropriate for our immediate purposes. Although they can certainly be useful in the synthesis of analogs lacking substituents for the general purpose of delineating structure-activity relationships, such studies were assigned a lower priority. Recently, there appeared a number of reports[350,351] where this approach to the synthesis of anthracyclines was exploited. This was made possible through the development of new and more highly substituted dienes of general formula 61. For instance, Gesson *et al.* described the preparation and use of dienes 69[350a,b], 70[350c] and 71[350d]. As one might have expected, considerable efforts were necessary in order to make these dienes accessible. The main drawback here is that these diene intermediates do not provide for the concomitant introduction of a suitable functional group at position 7 of ring A. In



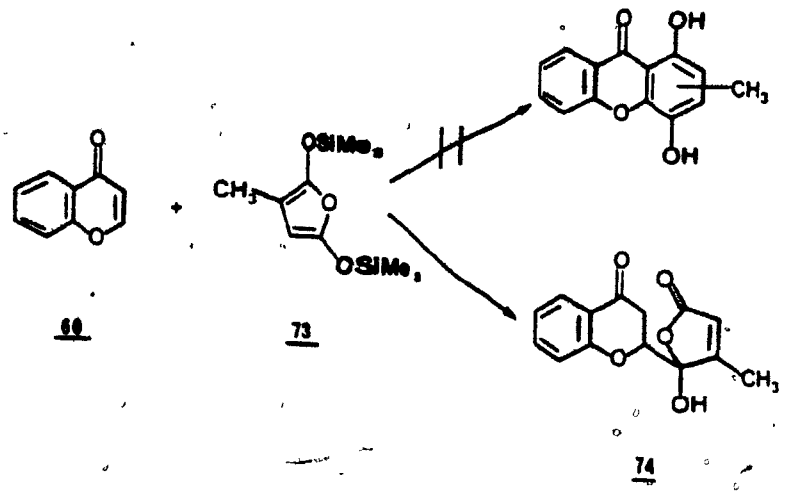

an extension of their earlier work[348], Boeckman *et al.* managed to incorporate an oxygen function at that ring A position by using a cyclobutene such as 72[351], thus avoiding at the later stages the problems associated with functionalization of the



benzylic carbon at position 7. In this manner, they were successful at synthesizing adriamycin, daunomycin and their 6-deoxy analogs. In light of these excellent results, due to the accessibility of cyclobutene 72, we decided to evaluate the potential of the approach outlined in Equation 1.


72

Unfortunately, after an extensive literature search, we were unable to find any evidence that chromone 60 can participate as a dienophile in Diels-Alder reactions. However, it displays the reactivity typical of α,β-unsaturated carbonyl compounds, with the β-position (C-2) being susceptible to nucleophilic addition[352]. A most revealing observation by Chan and Brownbridge[353a,b] is the behavior of chromone 60 towards diene 73, a reaction that led only to the product of Michael addition 74. On the other hand, diene 73 was shown[353b] to be sufficiently reactive to yield Diels-Alder adducts with ethyl acrylate and dimethyl acetylenedicarboxylate. Accordingly, failure of chromone 60 to react as a dienophile can be ascribed to electronic deactivation and not because diene 73 is insufficiently electron rich.

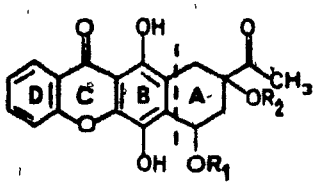



60 73 74

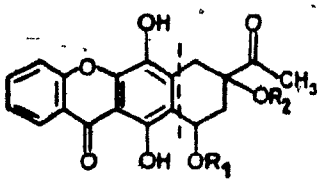
This documented evidence left little doubt that the approach based on a Diels-Alder reaction of chromone 60 with dienes as a route to heteroanthracyclines 22 and 23 was not viable.

### 2.1.2 Synthesis *via* A-Ring Formation from DCB-Tricyclic Precursors

A potentially more versatile approach to structures such as 22 and 23 would involve formation of ring A as illustrated by the bond disconnections shown below. Obviously, this strategy implies the use of an appropriate DCB-tricylic intermediate recognizable as a xanthone derivative. Such a scheme lends itself to many variations in the construction of ring A, as is known to be the case for the assemblage of the naturally occurring anthracyclines, a topic to be dealt with in some detail in the following sections. However, before implementing

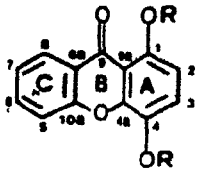


22



23

this strategy, it was necessary at first to develop a practical synthesis of the requisite 1,4-disubstituted xanthone 75 or 76. This problem will presently be dealt with.



75 R = H
76 R = $CH_3$

## 2.2 SYNTHESIS OF 1,4-DISUBSTITUTED XANTHONE

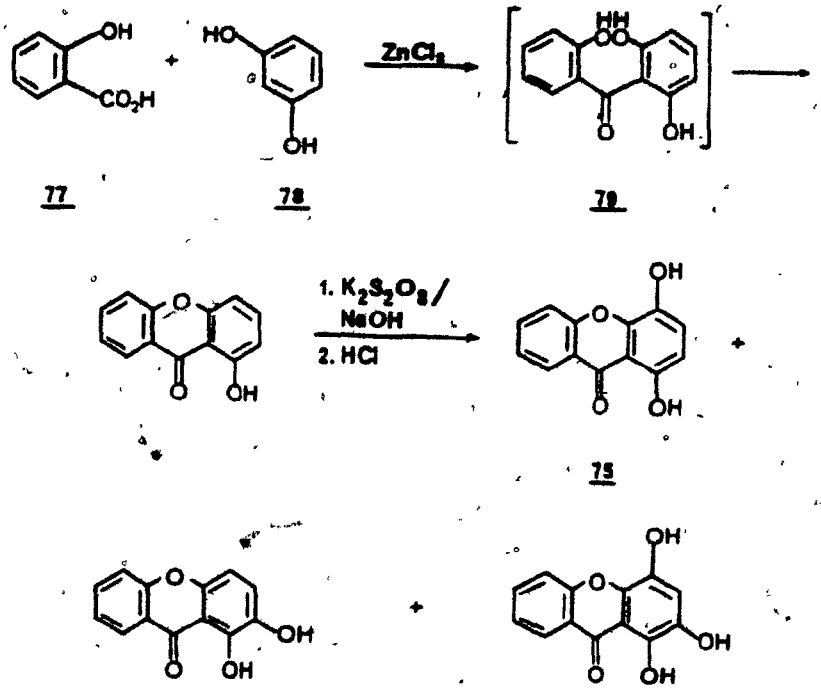
Xanthones, by themselves, form an interesting class of compounds. Many are naturally occurring in plants, fungi and lichen[354,355] and have been known and studied for a long time. In fact, the synthesis of hydroxy-xanthones was reported as early as 1883 and the methodology consisted basically of heating a phenolic acid and a phenol with or without a dehy-

drating agent. Although this early method has been described 'as not being easily reproducible', it, together with modified versions, remained until recently[356-358] the process most often used for the generation of xanthones. Because of a growing interest in them owing to their potentialities as antischistosomal agents[356], central nervous system stimulants[359], antiviral[360], antiallergic[357,358,361] and antitumor agents[356], a few alternative[362-364] but less general synthetic methods have been developed for this ring system.

### 2.2.1 Attempted Xanthone Synthesis Using the Modified Nencki Reaction

We found in the literature that the desired 1,4-dihydroxyxanthone could be prepared[365,366] by reacting salicylic acid (*o*-hydroxybenzoic acid) (77) with resorcinol (78) in the presence of fused zinc chloride (Nencki reaction) followed by Elbs persulfate oxidation of the phenolic intermediate (Scheme 2.1). However, the experimental conditions in the first step are very harsh with the result that extensive decomposition occurs and is accompanied by the formation of resinous material. This, coupled with the fact that the Elbs oxidation reaction leads to a mixture of at least three compounds, the desired one being produced in a 10% yield at best, discouraged the adoption of this methodology for large scale operations. Attempts at improving the process as well

Scheme 2.1




as the approach were reported. Thus, Grover *et al.*[367] observed that the addition of phosphorus oxychloride to the fused zinc chloride improved the yield of the Nencki reaction. They also noted that the intermediate 2,6-dihydroxy compound such as 79 cyclizes to the xanthone spontaneously. However, for other types of hydroxybenzophenone intermediates a separate cyclization step is required and involves dehydration by heating under pressure in an autoclave[366,367]. A number of other methods* and reagents have also been described and

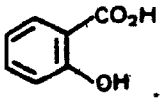
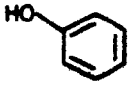
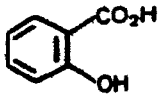
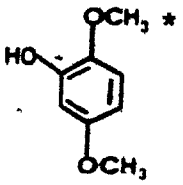
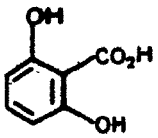
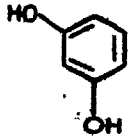
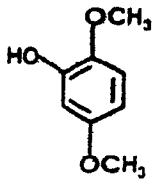
*The methods are not general. The results are not always reproducible and their success depends on the benzophenone derivative. Recently, the oxidative coupling using DDQ[327] and lead tetraacetate[315b] was successfully applied to the synthesis of the heteroanthracyclines.

include in part the following: (i) oxidative coupling either photochemically[339] or chemically with (DDQ)[327,339,368,369], manganese dioxide[339], manganese *tris*(acetylacetonate)[339], alkaline potassium ferricyanate[370,371], and recently lead tetraacetate[315b]; (ii) a base-catalyzed process[338]. It was also mentioned[366] that the use of partially hydrolyzed phosphorus oxychloride is a more efficient reagent than the phosphorus oxychloride-zinc chloride mixture. However, in our hands these various modifications of reaction conditions using the reagents listed in Table 3 failed to give the desired xanthone or benzophenone products. Only intractable tars were obtained. These disappointing results forced us to design a new approach to the synthesis of relevant xanthones.

### 2.2.2 Attempted Xanthone Synthesis *via* O-Alkylation of 2-Carbomethoxy-1,4-benzoquinone

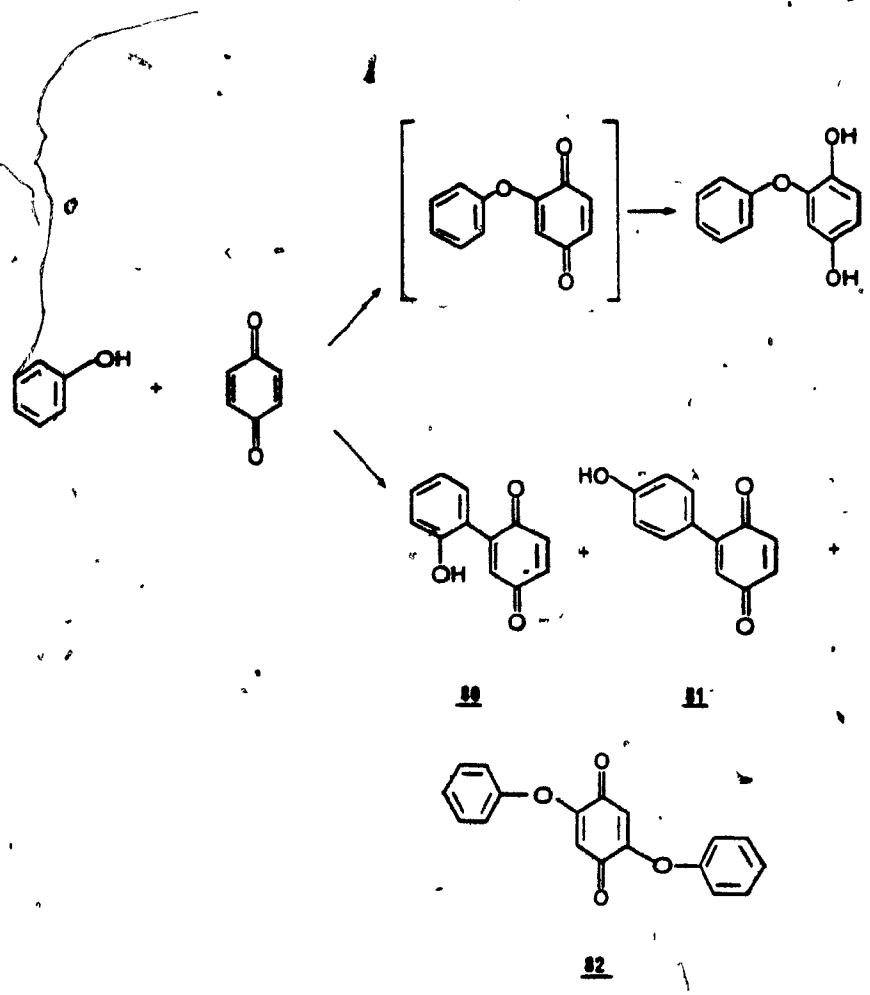
As an alternative strategy, we speculated that 1,4-benzoquinone may be coaxed into a Michael addition reaction with phenol (Scheme 2.2) by analogy with its behavior toward thiophenol[372]. It is well-known[373], however, that the reaction of phenol with benzoquinone gives mainly polymers but under controlled conditions it has been possible to isolate in low yields the products of C-substitution 80 and 81 (*o*- and *p*-hydroxyphenylbenzoquinones) and O-substitution 82 (phenoxyquinone). Indeed, there are very few known examples[373-375]

Table 3: Reactants Used in the Modified Nencki Reaction.

| Entry | Phenolic Acid | Phenol | Reagent |
|---|---|---|---|
| 1 |  |  | $ZnCl_2$, $POCl_3$ |
| 2 | " | " | $POCl_3$, $H_2O$ |
| 3 |  |  * | $ZnCl_2$, $POCl_3$ |
| 4 | " | " | $POCl_3$, $H_2O$ |
| 5 |  |  | $ZnCl_2$, $POCl_3$ |
| 6 | " |  | $ZnCl_2$, $POCl_3$ |

* The reactant 2,5-dimethoxyphenol (98) was used instead of 1,2,4-trihydroxybenzene. While neither compound is sold commercially, compound 98 was available because it had been prepared for use in another reaction (*vide infra*).

Scheme 2.2



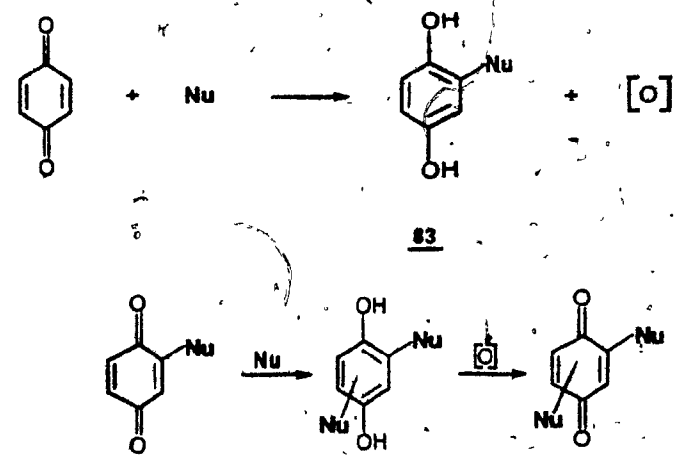

80 81

82

of O-addition reactions with benzoquinones and most are not synthetically useful and all involve the addition of simple alcohols under acid-catalyzed conditions. Presumably, the weak nucleophilicity of alcohols and phenols does not favor 1,4-addition across the double bonds of benzoquinone. For instance, when zinc chloride was used as catalyst for the addition of salicylic acid to benzoquinone only polymeric material was obtained.

A complicating feature of this kind of chemistry is the formation of the hydroquinone product 83, an intermediate strongly susceptible to air oxidation and to attack by unreacted quinone, side reactions which promote further addition reactions and polymerization as shown in Scheme 2.3. It is probable side reactions of this kind which are at the origin of the phenoxyquinone 82.

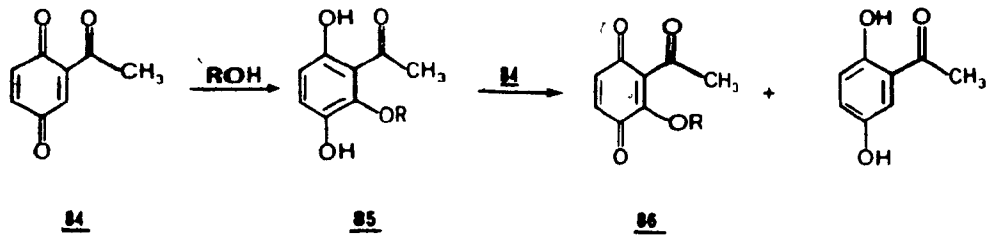
Scheme 2.3




These prohibitive difficulties in causing benzoquinone to give O-substituted products can be effectively circumvented by using "activated" benzoquinones[303,376]. For example, 2-acetyl-1,4-benzoquinone (84) undergoes Michael addition with alcohols under very mild conditions. However, as can be expected, oxidation by starting material of the

hydroquinone 85 initially produced occurs with the consequence that the yield of desired product 86 is reduced to a maximum of 50% (Scheme 2.4). As a result, we were not encouraged to adopt this approach until Müller *et al.*[304] introduced a modification which allowed them to synthesize xanthones*.

Scheme 2.4




In spite of their reported low overall yield† (15%) of xanthone product, we nevertheless attempted the same reaction but with phenol instead of *p*-cresol as the substrate with the hope of generating the desired 1,4-dimethoxyxanthone (76). The reaction sequence is summarized in Scheme 2.5 and consists of a Michael addition of phenol to the activated quinone 87 (2-carbomethoxy-1,4-benzoquinone)§ as catalyzed by the nucleo-

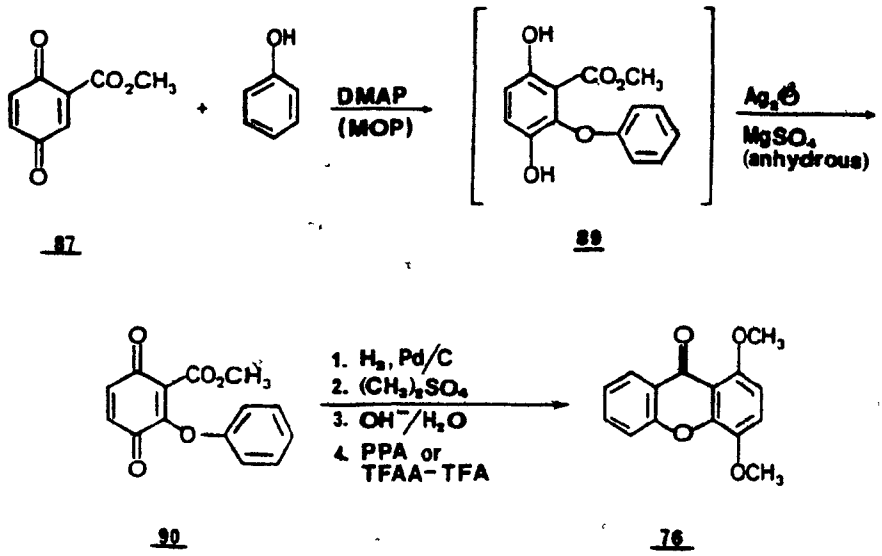
---

*The method was described as being applicable also to the synthesis of thioxanthones and acridones.

†The yield is incorrectly reported in ref. 377.

§Prepared by oxidation with silver(II) oxide of methyl 2,5-dihydroxybenzoate (88). Details are provided in the Experimental Section because the published method[378] was modified.

Scheme 2.5




philic bases DMAP or 2-methoxypyridine (MOP). The expected addition product 89 was not isolated but immediately oxidized with silver(I) oxide to the quinone 90. Catalytic hydrogenation of the latter followed by methylation, ester hydrolysis and finally treatment with polyphosphoric acid was expected to afford the desired key intermediate 76.

However, this experimental protocol, which included extreme precautions (inert atmosphere, absence of light, temperature control, reaction time), led only to the formation of black resinous material. Moreover, the omission of silver(I) oxide was of no avail although less polymeric material was formed. We have no clear explanation for this total failure in achieving control of the reaction with 87. Such a result simply reflects the typical behavior of reactive quinones.

### 2.2.3 Attempted Xanthone Synthesis *via* C-Alkylation of Benzoquinone Monoketal

We next considered a process where a benzophenone intermediate would be generated through addition to benzoquinone of the carbanion of a salicylate equivalent followed by ring closure with the *o*-phenolic group rather than *vice versa* as above. However, it is well-documented that Michael addition of organometallic reagents to benzoquinones is not generally useful. Intractable tars are often obtained[374,379]. Furthermore, quinones are susceptible to electron-transfer reduction processes and thus cause Grignard reagents to undergo oxidative dimerization[375] and suppress the general ability of organocuprates to enter into 1,4-addition reactions[380,381]. This, coupled with the ever present possibility of oxidation of the initial alkylation product by unreacted quinone, suggests that a suitably protected but reactive benzoquinone should be used in order to eliminate these difficulties.

The benzoquinone monoketal, 4,4-dimethoxycyclohexa-2,5-dienone (91), described by Durckheimer and Cohen[382] appeared to fulfill the necessary requirements for our purposes. In fact, monoketal 91 undergoes Michael additions[383-385] to give adducts stable to oxidation and is much less susceptible to electron-transfer reduction processes than benzoquinones. In most cases*, the monoketal behaved predictably towards

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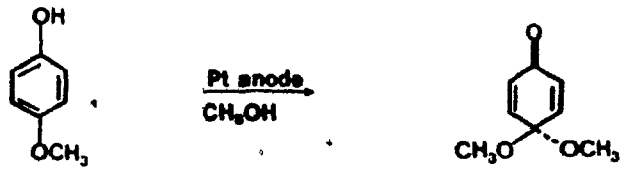
* Organocuprates and *tert*-butyl Grignard reagents gave reduction of the monoketal, *i.e.* *p*-methoxyphenol starting material.

organometallic reagents[380,381,386]. It is easily prepared* electrochemically[380] in high yield (85%) by anodic oxidation of *p*-methoxyphenol (92) in the presence of methanol.




92 91

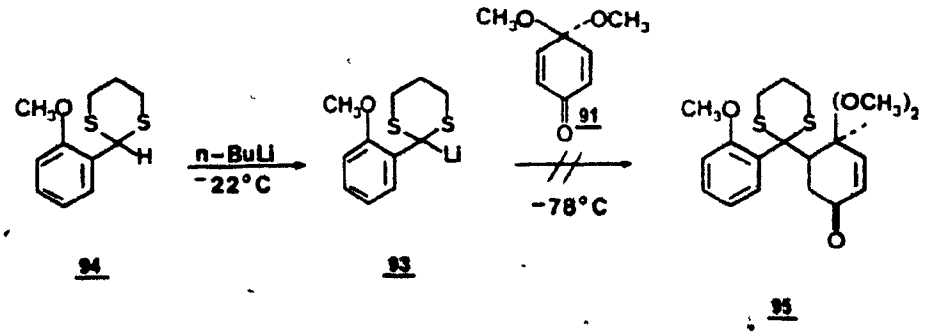
Alternatively, it can be economically prepared by the anodic oxidation of the commercially more readily available 1,4-dimethoxybenzene to the benzoquinone *bis*ketal (first described by Belleau and Weinberg[387]) followed by partial mono-hydrolysis[386]. The product is of course acid labile but is sufficiently stable for use with a minimum of special precautions†.

The carbanion of the salicylate equivalent selected for reaction with the monoketal 91 was the dithianide 93. The starting material 1-(*o*-methoxy)phenyl-1,3-dithiane (94) was conveniently prepared in excellent yield (90%) from *o*-methoxybenzaldehyde and 1,3-propanedithiol by the method of Chan and Ong[388]. The corresponding carbanion 93 generated by

*For less convenient preparations by standard oxidation methods see ref. 386.

†It is best that the glassware be rinsed with methanolic sodium hydroxide and oven-dried before use with the ketals. For chromatography, the silica gel should be treated with aqueous ammonium hydroxide in order to minimize catalyzed hydrolysis (see Experimental for details).

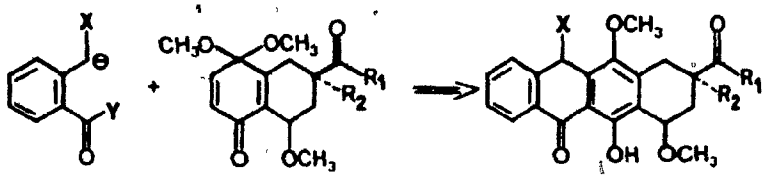
treatment of 94 with n-BuLi was added at -78°C to a solution of the monoketal 91 in THF. An intense blue color immediately appeared and the mixture was allowed to warm to room temperature before quenching with water. Thin-layer chromatography indicated the presence of several products but no evidence could be obtained that the desired adduct 95 had formed. Also unsuccessful were variations in experimental conditions:




different temperatures or quenching of the reaction at low temperature with methanol were of no avail. Although no *p*-methoxyphenol could be recovered from the reaction mixture, the possibility remains that electron-transfer may have occurred to give a phenoxy radical (after elimination of LiOMe) capable of coupling reactions. The intense color observed upon mixing the reagents supports the suggestion that an anion-radical intermediate may be formed[380,389]. It has also been observed that the course of the reaction of organometallics with benzoquinone monoketals may be strongly dependent on the nature of the reagent[386,389b].

No attempt was made to react phenol in a Michael fashion with monoketal 91, although such additions do occur with methanol, certain thiols, amines and some carbanions[382-386,390,391]. Interestingly, the strategy has been extended to highly functionalized monoketals such as 96 and has allowed the synthesis of anthracyclinones[382,383,386,391] as shown in Scheme 2.6.

Scheme 2.6



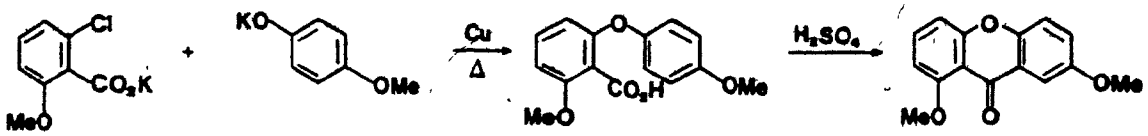
96

In summary, the above tactical failures in achieving the synthesis of a key xanthone can be ascribed to some inherent undesirable properties of the quinone substrates. It should be noted though that previous successes with such quinones in the natural product area turned out not to guarantee a similar outcome in the heteroanthracycline series. The fact that our benzoquinone substrates could not even be used to achieve O-alkylation of phenols discouraged further efforts to involve benzoquinones as intermediates and justified a search for alternative approaches.

## 2.2.4 Xanthone Synthesis *via* the Modified Ullmann Reaction

Ullmann and Panchaud[355,360] reported the synthesis of a xanthone using a strategy where the diaryl ether linkage* is formed in the first step through an aromatic substitution reaction. The xanthone ring system is subsequently formed by an intramolecular Friedel-Crafts acylation (Scheme 2.7).

Scheme 2.7




The ether forming step requires vigorous reaction conditions (T > 200°C) and although yields (> 70%) were reported for many reactants, the yields for methoxy-substituted phenols were much lower and even negligible when the reactants carried substituents like alkoxy carbonyls. Nevertheless, the process appeared general enough to deserve consideration as a solution to our problem, provided milder reaction conditions can be successfully applied.

Fortunately, this reaction of Ullmann became more attractive when it was found[392,393] that copper(I) oxide will catalyze the reaction at lower temperatures in DMA as the

*The Ullmann ether synthesis should not be confused with the Ullmann coupling reaction which is used to form biaryls from aromatic halides.

solvent and allow good yields (> 60%) of diaryl ether products. (The fact that phenols as such can be used in place of phenoxide anions also constitutes a notable departure from the traditional Ullmann procedure). The important observation was made that iodoaryl compounds were more reactive in this reaction than other halogen-substituted aromatics*. These precedents encouraged us to adopt the Ullmann process to the synthesis of the requisite xanthones. One of the substrates was the commercially available *o*-iodobenzoic acid which was converted to its methyl ester 97[394] in order to suppress the side reaction of decarboxylation during condensation.

Esterification on a modest scale was carried out cleanly and quantitatively using diazomethane (prepared[395] from Diazald). Large quantities of the ester were prepared by other methods, the preferred one[396] consisting in boiling the iodoacid in methylene chloride in the presence of methanol and sulfuric acid as the catalyst and dehydrating agent. After 3 days, two layers had formed and the top aqueous one simply siphoned off. One mole quantities of the ester could be easily prepared in 90% yields by this procedure. Subsequently, an even more convenient method was adopted for the preparation of the ester. It is based on the use of chlorotrimethylsilane and methanol as reported[397]. The advantage with this new procedure for large scale preparations

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* This important feature was made use of in the synthesis of lucanthone analogs[356].

is the short reaction times required and the improved yields (> 95%) obtained. The by-product hexamethyldisiloxane is easily separated by distillation.

The other substrate for the modified Ullmann process as applied to the generation of dimethoxyxanthone is 2,5-dimethoxyphenol (98), an intermediate not commercially available. It was easily prepared* in two steps from 2,5-dimethoxybenzaldehyde (40), the first one involving a Baeyer-Villiger oxidation[399,400] with *m*-chloroperoxybenzoic acid (*m*-CPBA) in refluxing methylene chloride to give almost exclusively formate 99 in excellent yield[401]. Only a small amount (< 5%) of 2,5-dimethoxybenzoic acid (100) was produced (Scheme 2.8). The oxidation was carried out in the presence of a small amount of the free radical inhibitor† 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide (101)[402] in order to prevent decomposition[399,403] of the peroxy acid. The resulting formate (easily isolable) was easily hydrolyzed quantitatively under alkaline conditions.

A number of experimental tests were performed in order to optimize the conditions for diaryl ether formation by the modified Ullmann method. Although long reaction times (as long as 72 h) and high temperatures have been commonly

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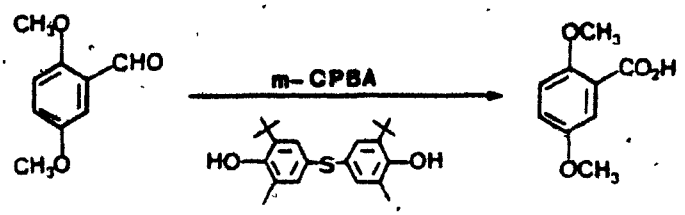
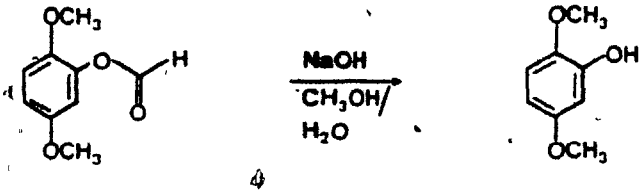
*Compound 98 has been prepared by a number of other less expedient routes[398] including: (i) Baeyer-Villiger oxidation of 2,5-dimethoxyacetophenone, (ii) from dimethoxyphenylmagnesium bromide and (iii) by diazotization of 2,5-dimethoxyaniline.

†The free radical inhibitor 2,4,6-tri-*tert*-butylphenol gave comparable results.

Scheme 2.8

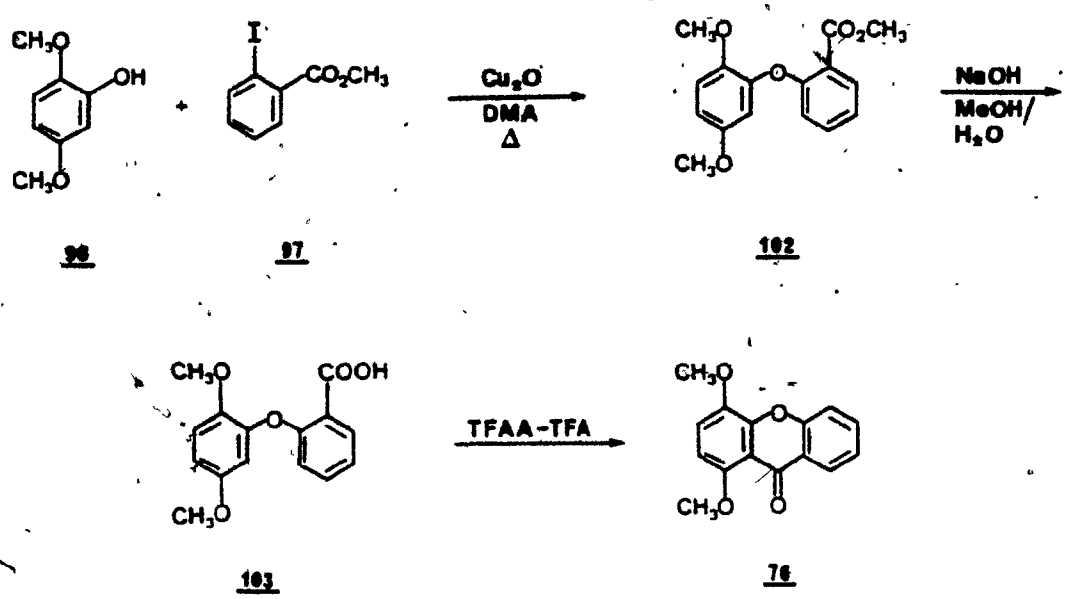



40 101 100




99 98

used, we found that in the case of our substrates, a reflux time exceeding 24 h was detrimental and inferior yields were obtained owing to the formation of tarry by-products. It was best to shorten the reaction time which favored formation of the diaryl ether 102 in a form sufficiently pure for use in the subsequent step without purification. Hydrolysis of the ester function was easily followed by pmr spectroscopy and the corresponding acid 103 was produced in a quantitative yield. Cyclization of the latter to the xanthone was initially carried out using polyphosphoric acid (PPA) with sulfolane (tetramethylene sulfone) as solvent. These conditions proved inconvenient however because of mechanical parameters and work-up problems associated with the solubility




of the solvent in water. The yield of xanthone was poor and the product accompanied by relatively large quantities (*ca.* 20%) of a by-product. Efforts to improve the yield by using a smaller amount* of PPA were not significantly successful. It was gratifying however that the use of a mixture of TFAA and TFA finally gave excellent yields of xanthone. The 200 MHz $^1$H.m.r. spectrum of 1,4-dimethoxyxanthone (76), including the expanded aromatic region, is shown in Figure 13. By-product formation could be minimized (less than 5% of the total amount of xanthone) by slowly adding the organic substrate as a dilute solution in methylene chloride to a stirred mixture of TFAA-TFA. The by-product is presumed to be the "dimeric" compound 104 which would be the result of an efficient

*It is reported[404] that a large excess of PPA is not necessary and may lead to lower yields.

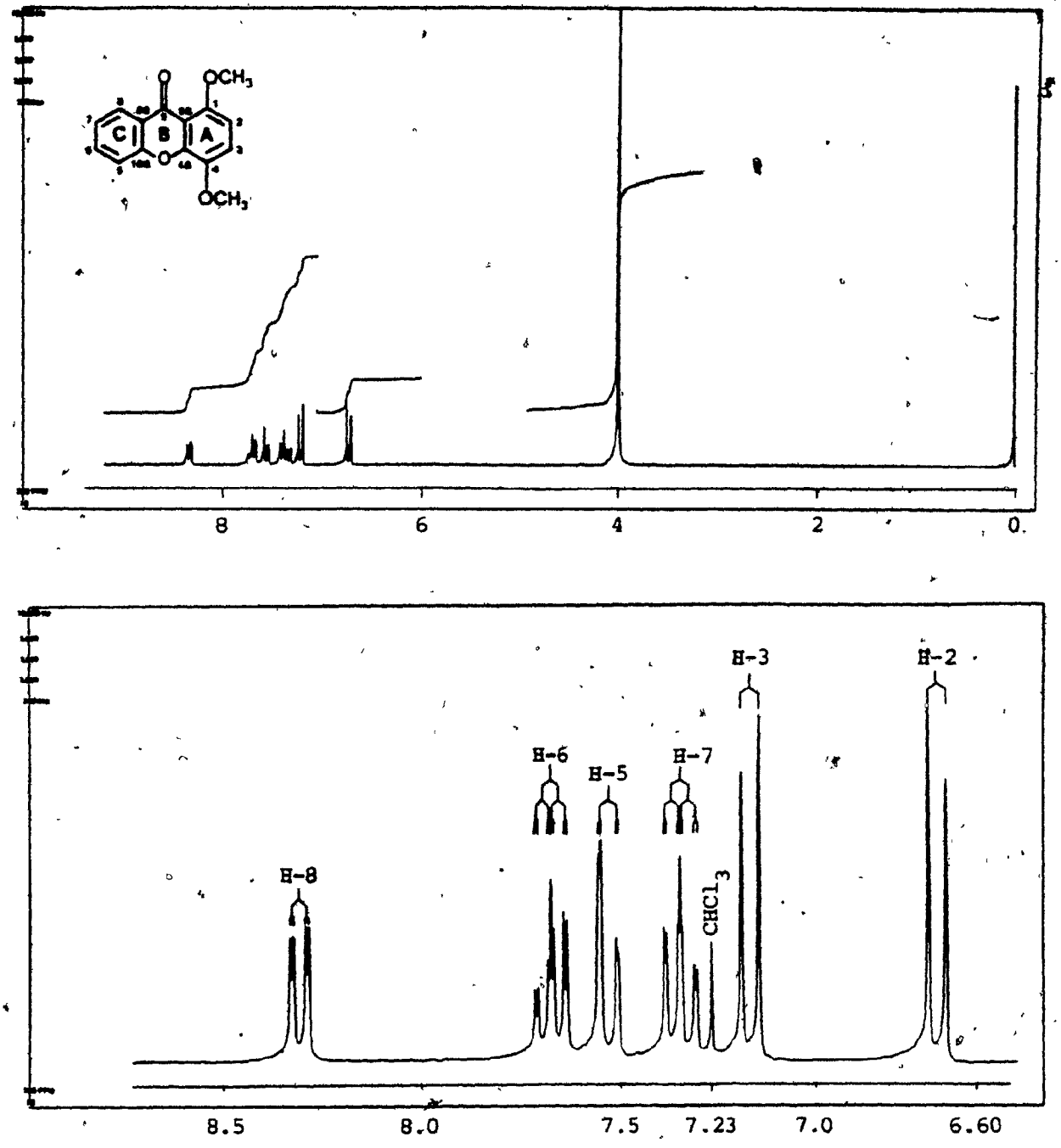
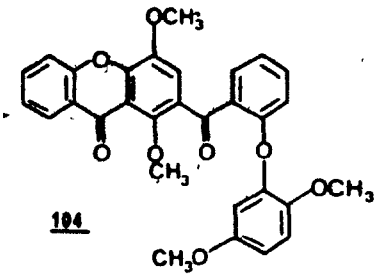



Figure 13: The 200 MHz $^1$H.m.r. Spectrum of 1,4-Dimethoxyxanthone, Including the Expanded Aromatic Region, in $CDCl_3$.



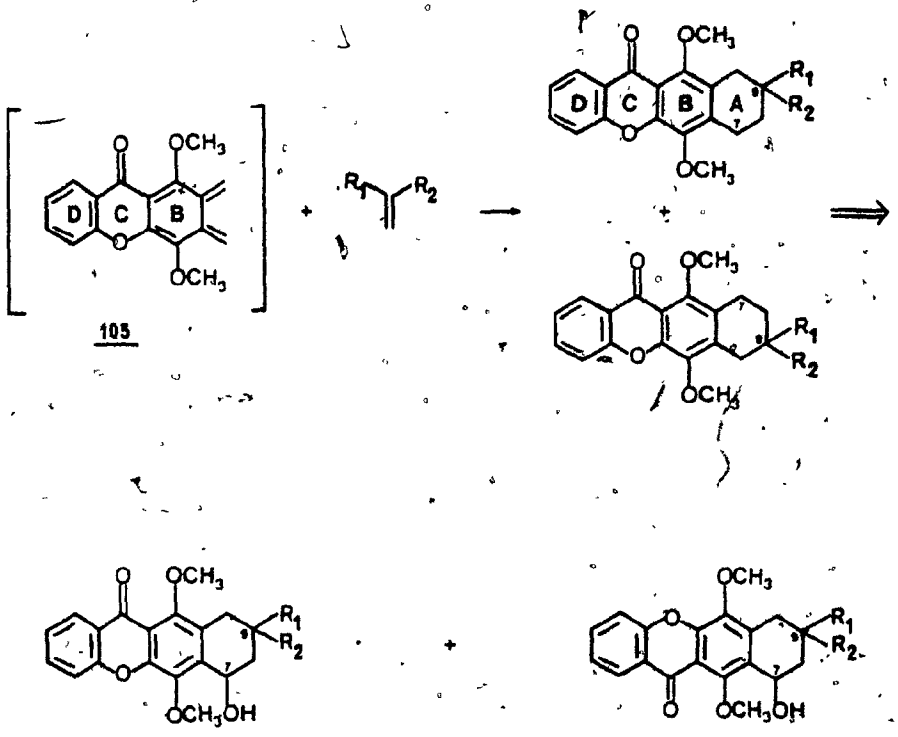
104

competition between the intramolecular and intermolecular acylation pathways. The structure was assigned on the basis of pmr, ir and mass spectral data. The pmr spectrum of this product indicated the presence of two different kinds of methoxy groups. The chemical shifts amounting to 4.0 and 3.7 ppm for these groups correspond to the chemical shifts observed for the methoxy group of xanthone 76 and that of the diaryl ether 102 respectively. The AB quartet arising from coupling between protons H-2 and H-3 of xanthone 76 was noticeably absent from the spectrum of compound 104 indicating that intermolecular acylation involved position C-2 or C-3 (C-2 being more likely). The proton ratios were exactly as expected for the assigned structure, whereas the infrared spectrum of the product confirmed the presence of the xanthone carbonyl at 1670 $cm^{-1}$ which probably overlapped the diaryl carbonyl band (1665 $cm^{-1}$). Finally, convincing evidence that 104 has indeed a dimeric structure such as shown was provided by the mass spectrum which displayed a molecular ion of m/z 512 corresponding to that expected for the assigned formula.

# CHAPTER 3

## A-RING FORMATION *via* CYCLOADDITION AND ANNULATION METHODS

Among the many different approaches available to construct the A-ring the first that we considered had already been applied to the synthesis of anthracyclines[405,406]. Our strategy centered on the Diels-Alder reaction of a xanthone-derived *o*-quinodimethane intermediate 105 with an appropriately substituted dienophile, a process conducive in principle to formation of both regioisomers as shown in Equation 2*.



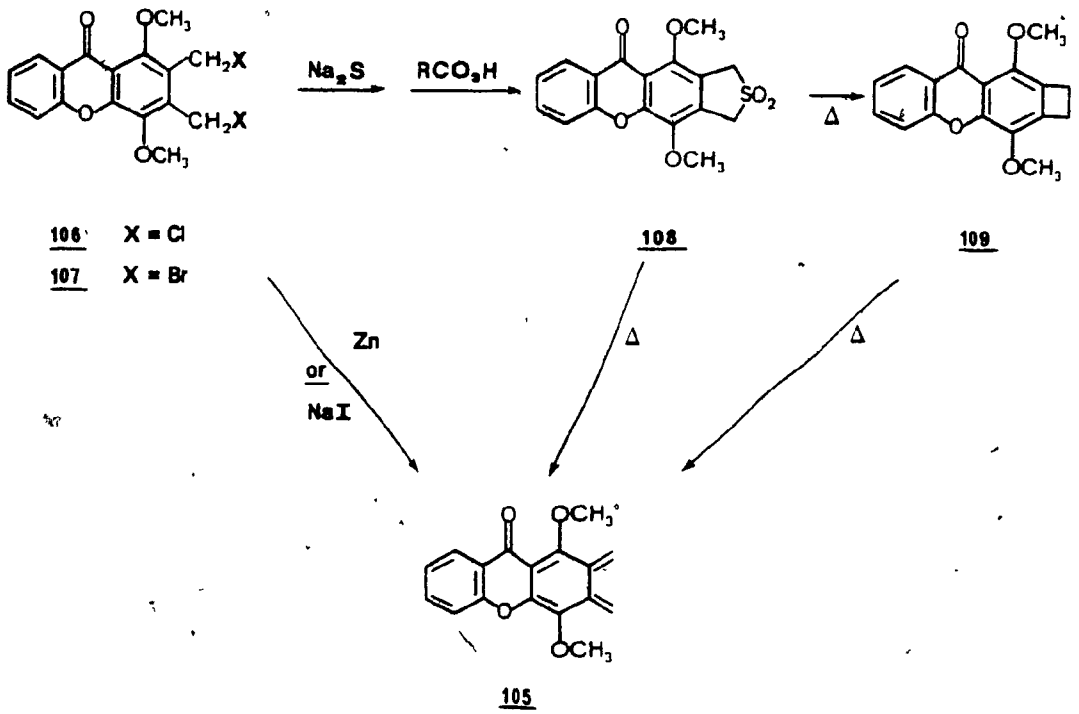
(2)

*Functionalization of position 7 would be conducted as previously described (Ch. 1) while the extent of elaboration required at position 9 would depend on the dienophile used.

Despite this apparent drawback regarding the lack of control over the regiochemistry, the fact that both isomers were of interest to us made this approach acceptable nonetheless.

Some possible precursors of diene 105 may be identified as the dihalides 106 and 107, the sulfone 108, or the benzocyclobutene 109[405b,407]. Presuming that cyclobutene 109 can be obtained from sulfone 108 which in turn may be derivable from dihalide 106 or 107 (Scheme 3.1), it appeared worthwhile to initiate that study by developing a synthesis of the requisite dihalide intermediate. Since the generation of *o*-quinodimethane from such dihalides is normally achieved at room temperature or with low heating, this tactic

Scheme 3.1



was preferred over the use of a sulfone intermediate because of the higher temperature (≥ 200°C) required for diene formation by $SO_2$ extrusion[407,408].

## 3.1 SYNTHESIS OF 2,3-DISUBSTITUTED-1,4-DIMETHOXYXANTHONE

### 3.1.1 Attempted Synthesis of 2,3-*bis*(Chloromethyl)-1,4-Dimethoxyxanthone

Although benzylic dibromides have been generally used as *o*-quinodimethane precursors, a dichloride analog appeared more convenient because of its formal accessibility by chloromethylation of 1,4-dimethoxyxanthone (76)*. Similar dichloro derivatives react easily and cleanly with either sodium iodide[409] or metals[409,410] (zinc being the most commonly used) to generate *o*-quinodimethanes although their reactivity is inferior to that of the dibromide analogs.

The chloromethylation reaction was initially attempted using standard literature procedures[411]. Thus, hydrogen chloride was bubbled vigorously into a gently heated (35°C) mixture of 1,4-dimethoxyxanthone (76), formalin (40% aqueous formaldehyde)†, concentrated hydrochloric acid and acetic acid. The reaction was monitored by tlc and quenched after *ca.* 9 h.

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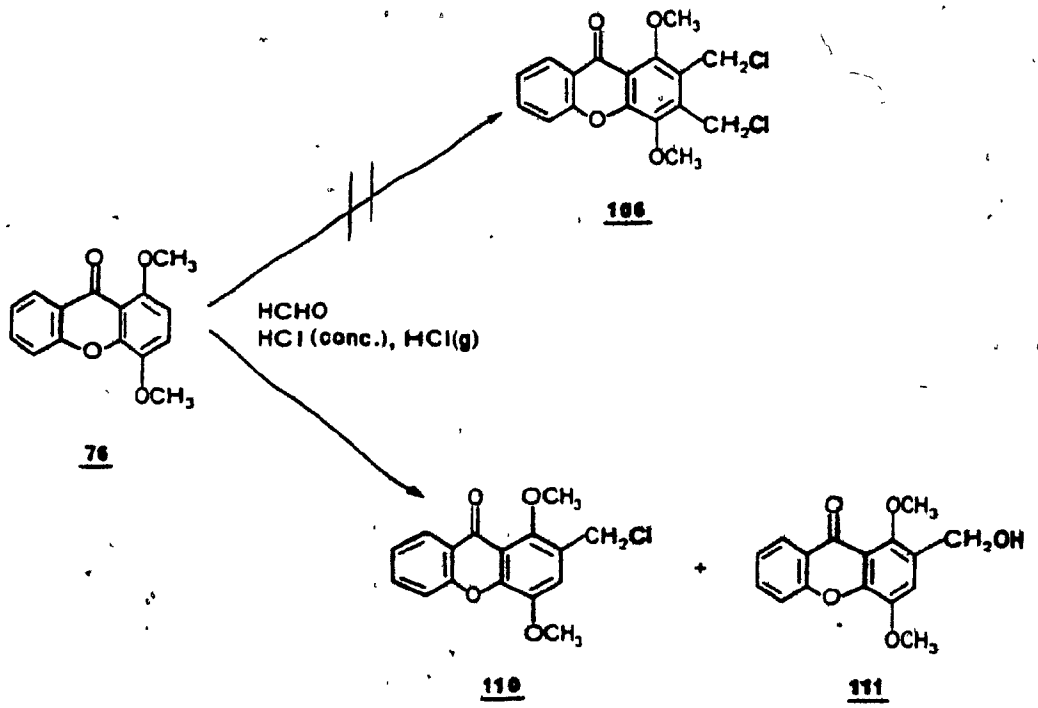
*Bromomethylation is problematical and when bromomethyl methyl ether is used with a catalytic amount of concentrated $H_2SO_4$, bromination of 1,4-dimethoxyxanthone occurs.

†The use of paraformaldehyde, freshly fused zinc chloride as catalyst[411,412] and hydrogen chloride was disappointing. Mechanical difficulties led to a low yield (*ca.* 20%) of monochloromethylated xanthone 110 along with unreacted xanthone 76.

Two major components were obtained after purification by flash chromatography. The less polar compound, (*ca.* 60% based on compound 76) was identified as the monochloromethylated compound 110 on the basis of its pmr and mass spectral characteristics. At high field (200 MHz) its pmr spectrum clearly indicated that substitution had occurred in the A-ring as evidenced by the collapse of the AB-quartet (due to H2-H3 coupling) to a single peak shifted downfield by *ca.* 0.15 ppm. There was no alteration of the C-ring splitting pattern (or in the peak intensities) thus showing that no substitution had occurred there. The signal at 4.81 ppm was assigned to the benzylic protons whereas the methoxy groups appeared as a broad singlet (in $CD_2Cl_2$) and were not significantly shifted downfield relative to the parent compound. The relative peak intensities were consistent with the assigned structure 110. The substitution was assumed* to have occurred at the C-2 position on the basis that the oxygen heteroatom should preferentially activate that position towards aromatic electrophilic substitution. The mass spectrum of the compound displayed a molecular ion of m/z 304 in agreement with the expected molecular weight. The isotope peak ratio (M+2)/M, (31.9%), was essentially identical to the value predicted[413] (32.6%) for molecules containing one chlorine atom, thus confirming that only monochloromethylation had occurred.

*The structure was proven to be correct by the unequivocal synthesis of related compounds. This is discussed in Appendix 1.

The more polar material (*ca.* 20% based on compound 76) was identified as 2-hydroxymethyl-1,4-dimethoxyxanthone (111). Its pmr spectrum was essentially identical to that of compound 110 except for the presence of an exchangeable proton ($D_2O$). The infrared spectrum of the product confirmed the presence of the hydroxyl function whose stretching




frequency occurred at 3480 $cm^{-1}$. The mass spectrum of the product included the molecular ion of m/z 286 which is the value corresponding to the expected molecular weight.

A small amount of more polar material was also eluted with methanol but it was not characterized.

The formation of benzyl alcohol 111 is not surprising.

While some part undoubtedly arises from hydrolysis of the chloromethylxanthone 110 (during work-up and chromatography), it may also act as an intermediate in the chloromethylation reaction and is accounted for by way of the following mechanism[411,414-416]:

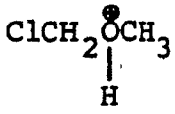
$$CH_2O + H^{\oplus} \rightleftarrows {}^{\oplus}CH_2OH \leftrightarrow CH_2={}^{\oplus}OH$$

$$ArH + {}^{\oplus}CH_2OH \rightarrow ArCH_2OH + H^{\oplus}$$

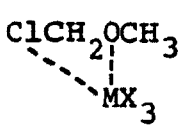
(I)

$$ArCH_2OH + HCl \rightleftarrows ArCH_2Cl + H_2O$$

The fact that no *bis*(chloromethylated)xanthone 106 was formed suggested that its generation would require more vigorous reaction conditions. It also appeared desirable to apply conditions unfavorable to the formation of the corresponding benzylic alcohols. To this end, we considered the use of the commercially available chloromethyl methyl ether, since its chloromethylating properties are well established[359,411,412,415-423]. In the presence of protons or a Lewis acid, the alkylating species are thought to have structures II and III respectively[415,416,419].



II



III

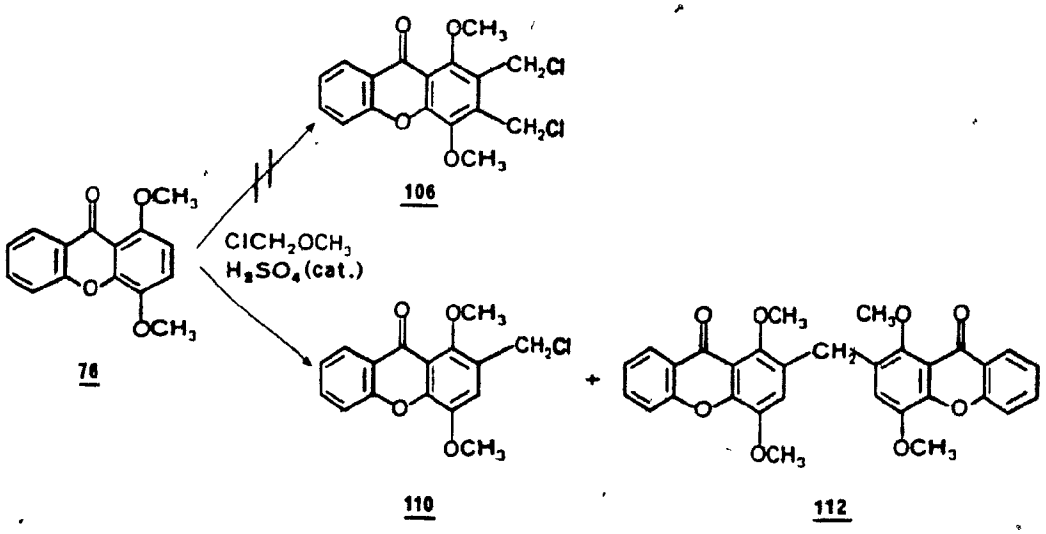
M = metal
X = halide

In principle it is possible to achieve methoxymethylation (especially in the presence of Lewis acids), but in practice, chloromethylation dominates to the extent that ether formation has only been rarely observed[411,422].

It was reported[423] that a complex of tin(IV) chloride-chloromethyl methyl ether was effective in forming *bis*-chloromethylated products from various aromatic compounds that even carry deactivating groups. However, reaction of 1,4-dimethoxyxanthone (76) with a large excess of this tin complex resulted in only a 30% yield of monochloromethylated compound 110 with no trace of any *bis*-chloromethylated compound being detectable even after refluxing for 96 h in chloroform. A similar result was obtained with a zinc chloride-chloromethyl methyl ether complex. Catalytic amounts of Lewis acids such as $SnCl_4$, $TiCl_4$, $AlCl_3$ as well as catalytic amounts of strong acids like *p*-TsOH, TFA with chloromethyl methyl ether gave unrewarding results as only monochloromethylated compound 110 was obtained and in yields never exceeding *ca.* 30% even after long reaction times.

The use of 30% fuming sulfuric acid[417] led to the formation of intractable tars as well as a small amount of what was later identified as the diarylmethane compound 112

(*vide infra*). A catalytic amount of concentrated sulfuric acid and gentle heating (< 35°)[424] led, after 4 h, to a mixture of three components which after separation by flash chromatography were identified as unreacted starting material (*ca.* 10%), a fraction of low polarity (*ca.* 70% based on xanthone 76) which consisted of the monochloromethylated compound 110 and a more polar fraction obtained as an uncrystallizable oil identified by pmr and mass spectrometry as the diarylmethane compound 112. The pmr spectrum of this



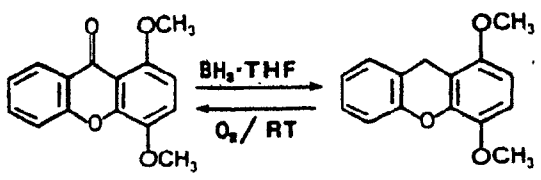

latter material showed no significant differences in the C-ring splitting pattern of the protons relative to the parent compound. However, the singlet arising from the proton at position 3 was shifted upfield by *ca.* 0.17 ppm Hz relative to chloromethyl compound 110. An upfield shift of *ca.* 0.63 ppm was also observed for the benzylic protons. This latter shift

is in the range expected for the replacement of a benzylic chlorine by an aromatic substituent. The mass spectrum of the product indicated that it contained no chlorine atom but included a molecular ion of m/z 524 which corresponds to the molecular weight of the diarylmethane 112. The reaction was repeated but at different temperatures over various time periods but this led only to variations in the ratio of the same three components, no trace of *bis*-(chloromethylated) compound 106 being detectable.

It became apparent therefore that the carbonyl group of 1,4-dimethoxyxanthone (76) is too strongly deactivating to permit electrophilic attack by the reagent at position 3. If this conclusion were correct, removal of the xanthone carbonyl should allow introduction of the desired second chloromethyl group.

### 3.1.2 Reduction of 1,4-Dimethoxyxanthone to 1,4-Dimethoxyxanthene

The reduction of 1,4-dimethoxyxanthone (76) to the corresponding xanthene 113 was carried out cleanly in one step and in quantitative yield using the borane-THF complex as




76 113

reagent. A reaction time of 4 h at room temperature using dry THF or methylene chloride as solvents served our purpose. Interestingly, reduction of xanthone itself was much faster under the same conditions[425]. This difference in reactivity may be attributed to the steric hindrance provided by the methoxy group as well as to the lower solubility of our substrate which required the use of more dilute solutions. The xanthene 113 was stored under an inert atmosphere as it is susceptible to air oxidation, slowly reverting to the 1,4-dimethoxyxanthone at room temperature*. Its 60 MHz pmr spectrum consisted of an AB-quartet (shifted upfield relative to xanthone 76), the H-3 proton resonating at 6.66 ppm and the H-2 proton at 6.35 ppm; the methylene group appeared at 3.90 ppm and the ring C protons gave a broad poorly resolved multiplet. Its infrared spectrum confirmed the absence of a carbonyl group.

### 3.1.3 Attempted *bis*-Chloromethylation of 1,4-Dimethoxyxanthene

Chloromethylation of the 1,4-dimethoxyxanthene (113) was attempted using chloromethyl methyl ether in $CHCl_3$ at 35°C and concentrated sulfuric acid as the catalyst. After 2 h, the reaction was complete and the mixture purified to yield two fractions in about equal quantity (*ca.* 30%). The least

*The oxidation of xanthene using oxygen in aqueous NaOH in the presence of phase-transfer catalyst is known[426].

polar compound was identified by pmr and mass spectroscopy as 2-chloromethyl-1,4-dimethoxyxanthene (114)*. The latter's pmr spectrum indicated that substitution occurred on the A-ring on the basis that the AB-quartet of the starting material now appeared as a singlet. No change in the peak intensities of the ring-C protons occurred. The mass spectrum of the product included a molecular ion of m/z 290 corresponding to the expected molecular weight of 114 and the intensity of the isotope peak ratio (M+2)/M indicated that only one chlorine atom was present in the molecule. The more polar compound turned out to have an pmr spectrum similar to that of compound 112, the upfield shifts of *ca.* 0.25 ppm and 0.53 ppm in the resonance frequencies of the H3-proton and the benzylic protons being accounted for by the diarylmethane structure 115. The mass spectrum of this material showed a molecular ion of m/z 496 (base peak) which coincides with the molecular weight of 115. Unfortunately, no indication of the presence of any *bis*-chloromethylated product in the mixture was obtained.

The reaction was repeated under similar conditions except that acetic acid was used as cosolvent and catalyst. The reaction took much longer to reach completion and after 12 h, analysis by tlc indicated that only monochloromethylated compound 114 had formed. No evidence that the *bis*-chloromethylated compound 116 or the diarylmethane 115 were generated

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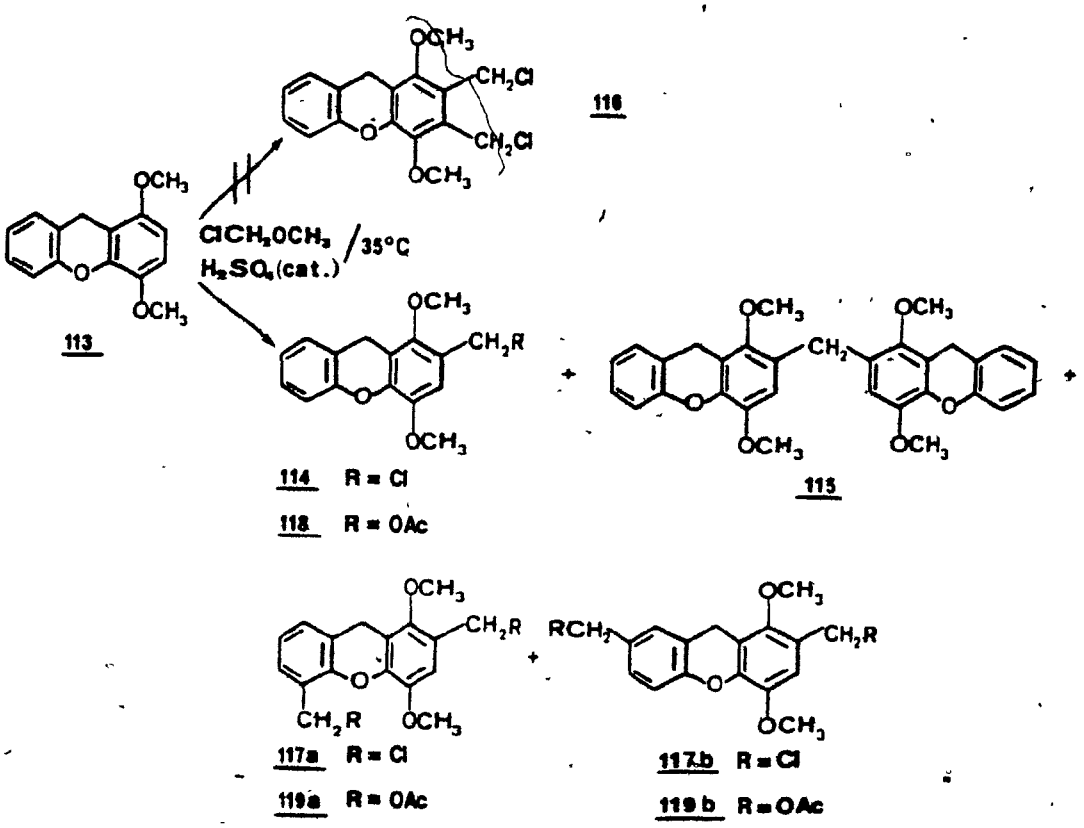
*In order to obtain excellent quantities of pure 114, it is best to reduce 2-chloromethyl-1,4-dimethoxyxanthone using $BH_3$·THF. (Details are given in the Experimental).

was obtained. The reaction was then allowed to continue for an additional 72 h. Analysis by tlc indicated the presence of three compounds which included a small amount (*ca.* 10%) of 115. Purification by flash chromatography was difficult (and only partially successful) because the components had similar $R_f$ values. The main fraction (*ca.* 50% based on 113) which contained two components gave a mass spectrum clearly indicative of the presence of the *bis*-chloromethylated derivative. In fact, a molecular ion of m/z 338 corresponding to the molecular weight of compound 116 was observed and the ratio for the isotope peaks (M+2)/M (65%) and (M+4)/M (10%) corresponded exactly to those expected for a molecule containing two chlorine atoms. The pmr spectrum of this material showed two benzylic type of proton signals, an observation consistent with the presence of the *bis*-chloromethylated compound. However, the signal at *ca.* 6.73 ppm which was previously attributed to the H-3 proton was still visible. Furthermore, the peak intensities of the ring-C protons showed that there were only 3 protons on the ring, an indication that substitution of ring C had occurred. Accordingly, the *bis*-chloromethylated compound can be represented most reasonably by structures 117a and 117b. The mass spectrum of the crude reaction products also revealed that some reaction with the cosolvent acetic acid had occurred. The yield of acetoxymethylated compounds 118 and 119 was estimated by pmr spectroscopy to be less than 10%, the result of a minor side

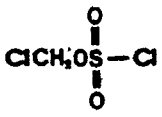



reaction which has been rarely mentioned in the literature[411].

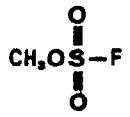
It is clear that in spite of the removal of the deactivating carbonyl group of the xanthone, it remained impossible in our hands to prepare the 2,3-*bis*-chloromethylated xanthene 116 although a second substitution, but at the C-ring level, occurred readily. While alternative approaches to the synthesis of 116 were being contemplated, an intriguing unique reagent potentially useful as a chloromethylating agent (the chloromethyl chlorosulfonate (120)) was brought to our attention[427,428]. We were thus encouraged to make one more attempt at the preparation of the 2,3-*bis*-chloromethylated xanthone derivative through the use of the special reagent 120.

### 3.1.4 Attempted Chloromethylation with Chloromethyl Chlorosulfonate

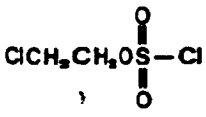
Although chloromethyl chlorosulfonate (120) was first prepared[428a] in the early 1930's, the only reference to its use can be found in the old patent literature[428b]. Structurally, it resembles the powerful methylating agent methyl fluorosulfonate (121) (Magic methyl) and being the homolog of β-chloroethyl chlorosulfonate (122), a known



120



121



122

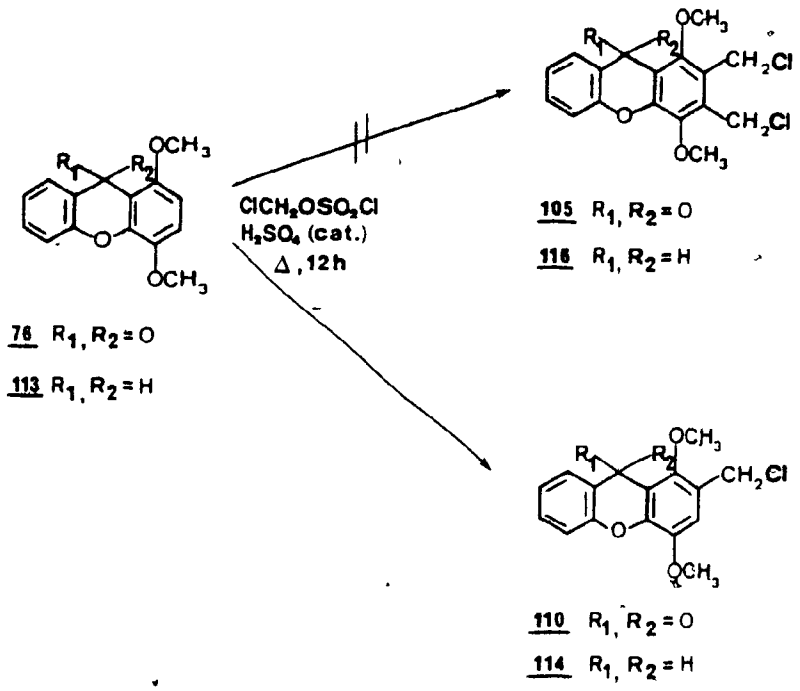
chloroethylating agent[411], we were hopeful that analog 120 would behave as an alkylating agent powerful enough to achieve *bis*-chloromethylation of our substrate(s) in the desired manner.

Chloromethyl chlorosulfonate 120 was obtained as a clear free-flowing liquid after relatively long and tedious operations consisting basically of the addition of paraformaldehyde to neat chlorosulfonic acid followed by a number of distillations. The reagent was characterized by its physical properties as well as by pmr spectroscopy and gc/ms (in order to ascertain its purity). All the data were consistent with those expected for structure 120.

Unfortunately, its reaction with 1,4-dimethoxyxanthone (76) gave disappointing results. There was no sign of reaction after stirring for several days at room temperature even after catalytic amounts of concentrated sulfuric acid had been added. The monochloromethylated compound 110 was obtained in a small yield (< 10%) after addition of catalytic amounts of concentrated sulfuric acid and a reaction time of 12 h in boiling methylene chloride.

When a catalytic amount of aluminium chloride was added[411] instead and the mixture refluxed for 75 h, the yield of 110 reached about 20%. Changing the substrate to 1,4-dimethoxyxanthene (113) gave no better results than with xanthone 76 under similar conditions. Only a small yield (< 20%) of monochloromethylated xanthene 114 was obtained and was accompanied by increased amounts of resinous material.

These results brought to an end our efforts to achieve the desired *bis*-chloromethylation of either the xanthone or xanthene substrates. The development of another approach involving the synthesis of a different xanthone substrate became necessary. However, we thought it worthwhile at that stage to explore the potential of chloromethyl chlorosulfonate (120) as a chloromethylating agent but for more conventional substrates.

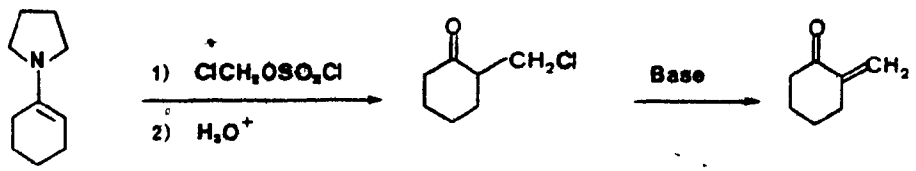



Potential Usefulness of Chloromethyl Chlorosulfonate

Even though the chloromethyl chlorosulfonate (120) failed to chloromethylate our xanthone or xanthene substrates in a satisfactory manner, it was felt nevertheless that better nucleophiles may be more likely to give valuable results. At first then we considered reacting it with an enamine because one may expect the reagent to yield α-chloromethylketones directly, a class of substances of considerable synthetic utility by virtue of their ready convertibility to α-methylene ketones (such as 123), an arrangement found in many naturally occurring sesquiterpenes and antibiotics[429-431].

When this reaction was attempted with the pyrrolidine

enamine of cyclohexanone[432] (124) under a variety of conditions, only black resinous material was obtained. The use of low temperature and high dilution led to a complex mixture of compounds which could not be identified by gc/ms or pmr spectroscopy.



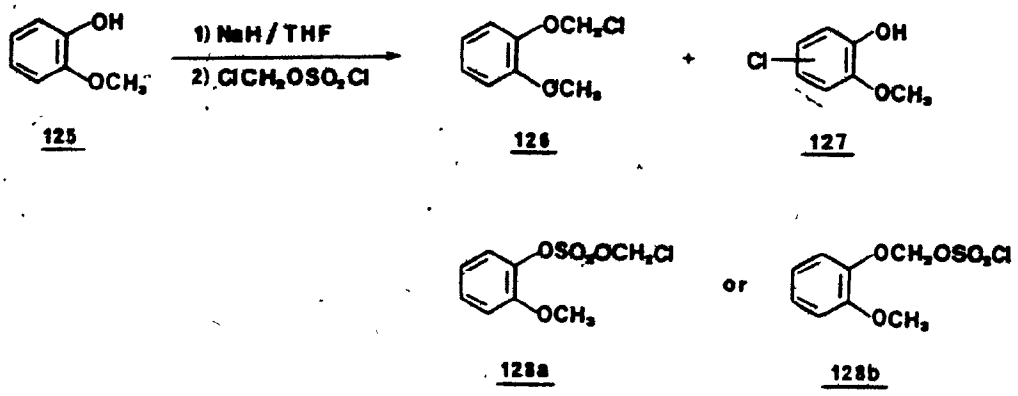

124 123

In another attempt at discovering a useful application for the reagent, guaiacol (125) was used as a substrate. The desired product guaiacyl-O-methyl chloride (126) is used as an alcohol protecting group and appears more convenient than β-methoxyethoxymethyl chloride (MEM-Cl) because it is less troublesome to remove[433]. However, there exist only two methods available for the preparation of this reagent 126 and only one of them is practical. Reaction of chloromethyl chlorosulfonate 120 with guaiacol might lead to 126 in one step, which motivated us to explore this possibility.

Accordingly, the sodium salt of guaiacol was generated with sodium hydride in THF and the mixture added in small portions over a long period of time under an inert

atmosphere to a vigorously stirred excess solution of very dilute chloromethyl chlorosulfonate. The reaction was vigorous and complete after some minutes. Analysis by gc/ms indicated the presence of three components one of which was dominant.

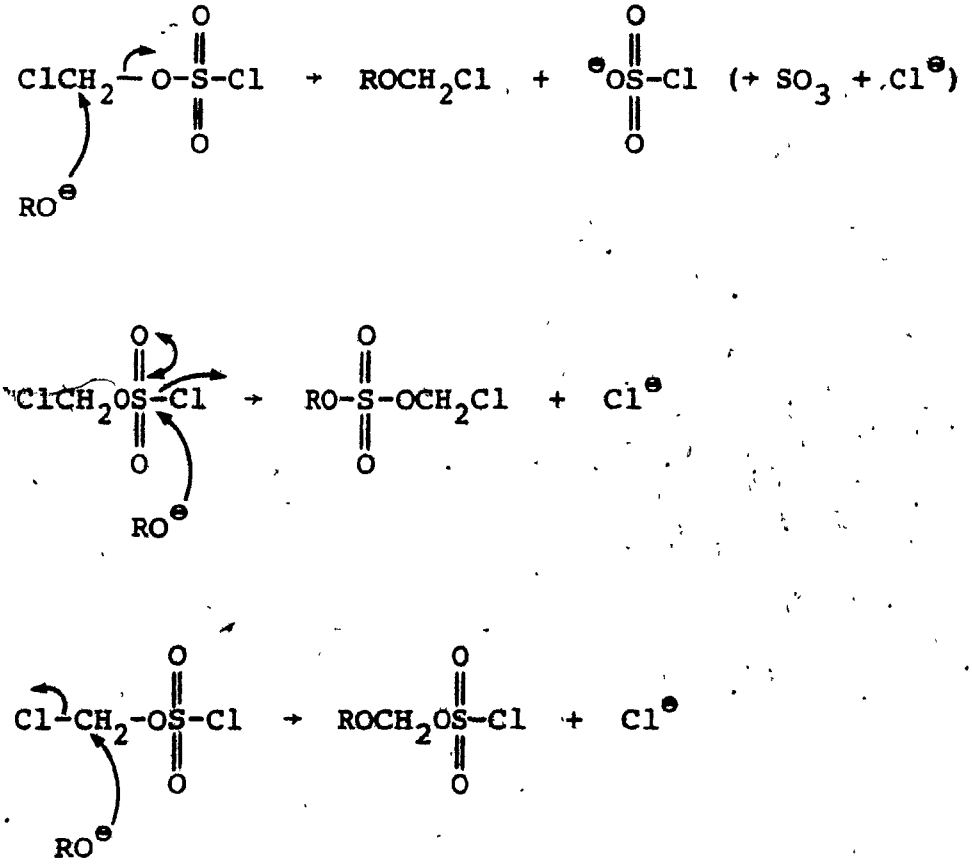
The first compound (*ca.* 10%) to elute from the gc column was assigned structure 127 primarily on the basis of mass spectral evidence. Its formation is surprising because chloromethyl chlorosulfonate may not be expected to act as a source of electrophilic chlorine atoms. The next component (*ca.* 60%) was characterized as guaiacyl-O-methyl chloride (126) on the basis of its mass and pmr spectra which agreed with the literature values[433]. The last component from the column (*ca.* 30%) was assigned either structure 128a or 128b




as judged from its mass spectrum. Its pmr spectrum was not very informative since for both structures, the methylene protons may be expected to display similar chemical shifts.

However, regardless of the exact identity of this third component, it is clear that under our reaction conditions, chloromethyl chlorosulfonate 120 is capable of reacting by different modes (Scheme 3.2).

Scheme 3.2




Although these results are far from being exhaustive it is obvious that more work would be required in order to ascertain the potential usefulness of chloromethyl chlorosulfonate 120 as a reagent in organic synthesis.

Unfortunately, time was not available to explore further the chemistry of this unusual reagent and a return to our main concern took precedence.

### 3.1.5 Synthesis of 2,3-*bis*(Bromomethyl)-1,4-dimethoxyxanthone

Our failed attempt at the preparation of *bis*-chloromethylxanthone led us to consider an alternative approach involving 2,3-dimethyl-1,4-dimethoxyxanthone (129) as an intermediate susceptible to benzylic halogenation[405,406]. No difficulty was encountered in the synthesis of the desired xanthone 129 using our previously described method as applied to the problem at hand.

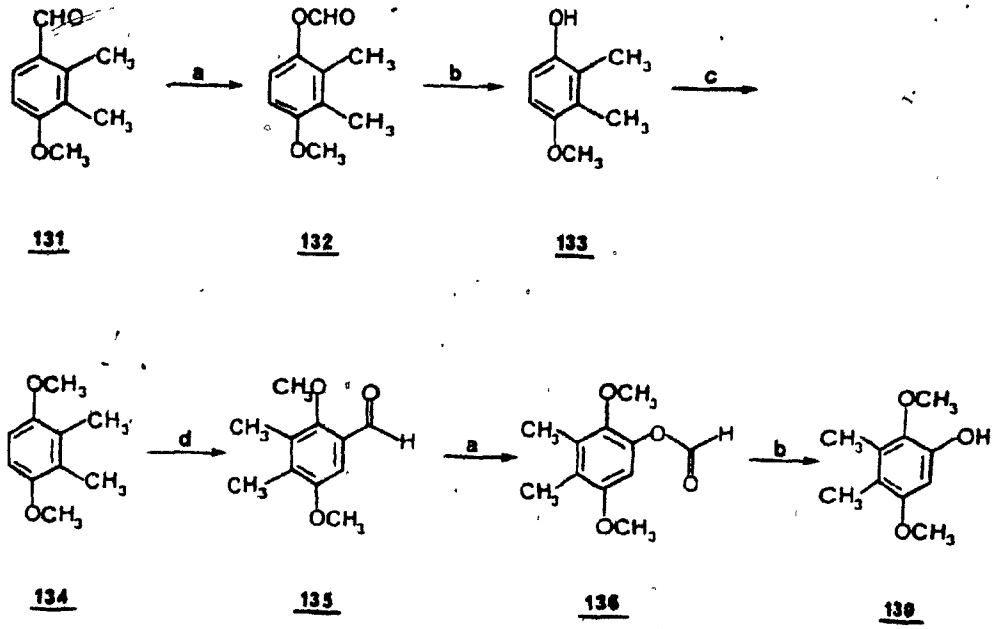
Access to dimethylxanthone 129 depended on the availability of 3,4-dimethyl-2,5-dimethoxyphenol (130) which fortunately could be easily prepared in 6 steps in 72% overall isolated yield (not optimized) from commercially available 2,3-dimethyl-4-methoxybenzaldehyde (131).

Unlike the Baeyer-Villiger oxidation of 2,5-dimethoxybenzaldehyde (Scheme 2.8) which required heating in a solvent with *m*-CPBA, the aldehyde 131 underwent quantitative oxidation to formate 132 within 45 min at 0°C in the presence of the free-radical inhibitor 101*. In this case, the lower reaction temperature prevented subsequent oxidation of the aldehyde to the acid. Careful alkaline hydrolysis of the formate

---

* The free-radical inhibitor underwent oxidation to the sulfone (mp 239-240°C) which crystallized in the reaction solvent.

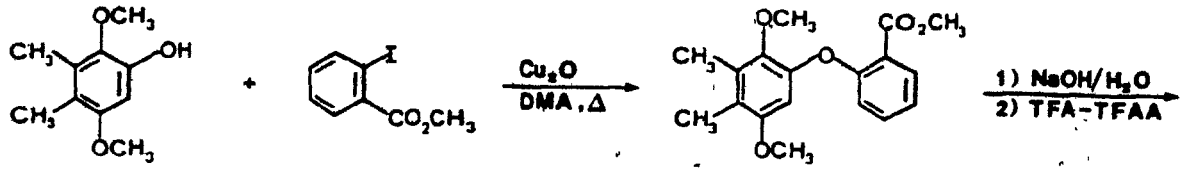
at 0°C gave a quantitative yield of phenol 133 as a white crystalline solid. Methylation of the latter with excess dimethyl sulfate in refluxing acetone in the presence of potassium carbonate powder gave a 96% yield of dimethoxy compound 134 which crystallized in the form of transparent plates[434]. The next step involved ring formylation of 134 using α,α'-dichloromethyl methyl ether and titanium(IV) chloride at 0°C[435,436]. A reaction time of 1 h was sufficient to generate an excellent yield (98%) of aldehyde 135 which crystallized as off-white needles. The latter was then submitted to Baeyer-Villiger oxidation which proceeded vigorously at 0°C to give formate 136. The transformation



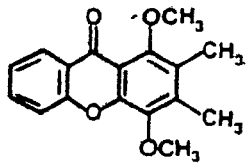

a) *m*-CPBA, free radical inhibitor 101, 0°C; b) $NaOH/H_2O$, 0°C; c) $(CH_3)_2SO_4$, $K_2CO_3$, reflux; d) $Cl_2CHOCH_3$, $TiCl_4$, 0°C.

was complete within 1 h but some oxidation (*ca.* 10%) to the corresponding acid also occurred. Alkaline hydrolysis of the crude mixture gave a good yield (83%) of the desired phenol 130, which crystallized as transparent needles. In spite of the fact that this strategy lacks expeditiousness and is perhaps tedious, it nevertheless represents an improvement over other schemes[437-439] for the preparation of 134, the advantage lying in the unnecessary purification of the intermediates and the excellent overall yield of product.

Reaction between phenol 130 and methyl-*o*-iodobenzoate (97) in refluxing DMA for 24 h gave after alkaline hydrolysis, followed by cyclization with TFA-TFAA and purification by flash chromatography, a 52% yield of pure 2,3-dimethyl-1,4-dimethoxyxanthone (129).



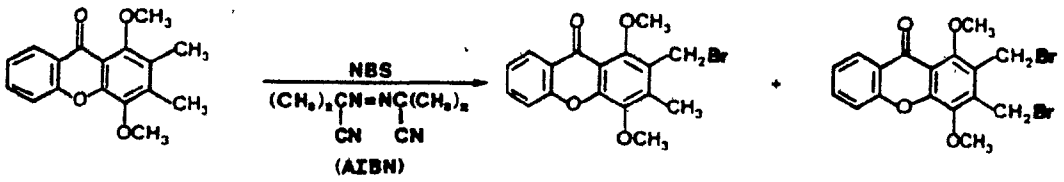

130 97



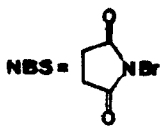

129

The pmr spectrum had resonances at 2.33 and 2.26 ppm which were assigned to the ring methyl groups. The ring C protons showed the typical splitting pattern of xanthone itself. The mass spectrum showed the molecular ion of m/z 284 in agreement with the expected molecular weight. The infrared spectrum of the product was not significantly different from that of 1,4-dimethoxyxanthone (76).

Benzylic bromination was easily and conveniently carried out using N-bromosuccinimide (NBS) in the presence of a small amount of the free-radical initiator azo*bis*isobutyronitrile (AIBN)[440]. Due to the low solubility of xanthone 129 in $CCl_4$, a large volume of solvent was required and consequently it was necessary to heat under reflux for a long period of time (*ca.* 26 h). Purification of the product by flash chromatography gave a small amount (*ca.* 5% based on 129) of a monobrominated compound 137 which was characterized by its pmr and mass spectra. Structure 137 was assigned on the basis of the rationale that the benzylic position *para* to the heteroatom should be more highly activated towards free-radical bromination. Pure *bis*-brominated xanthone 138 (*ca.* 80% based on 129) was obtained as a white crystalline compound. Its low field (60 MHz) pmr spectrum showed the benzylic protons as a broad singlet at 4.83 ppm. Its mass spectrum included the molecular ion of m/z 440 corresponding to the expected molecular weight and also showed (M+2)/M and (M+4)/M isotope peak ratios as expected for a compound carrying




129 137 138




two bromine atoms.

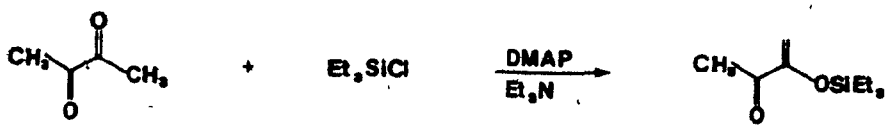
Having thus obtained 2,3-*bis*(bromomethyl)-1,4-dimethoxyxanthone we were now ready to proceed with our strategy involving a Diels-Alder reaction between the relevant *o*-quinodimethane intermediate and a dienophile as shown in Equation 2 (page 98).

## 3.2 DIELS-ALDER CYCLOADDITION WITH AN *o*-QUINODIMETHANE INTERMEDIATE

### 3.2.1 Generation of *o*-Quinodimethane 105 *via* Dibromide 138

The use of 3-(trimethylsilyl)oxy-3-buten-2-one (139) as a dienophile capable of trapping an anthraquinone-derived *o*-quinodimethane intermediate was recently reported[441]. However, a low yield of adduct was obtained, a result which we believe is a manifestation of the labile nature of the

olefin. In order to enhance its stability[442] under the reaction conditions, the triethylsilyl analog 140 was prepared by a modification of the literature procedure[443] for the

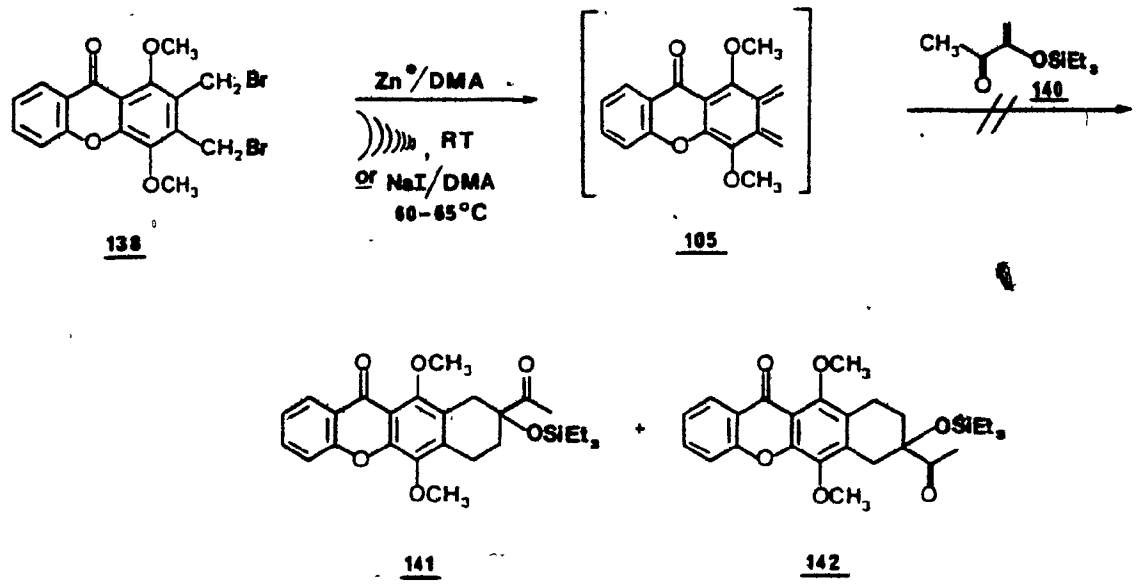



140

generation of olefin 139. Reaction between excess olefin 140 and the dibromide 138 in the presence of activated zinc (Zn*)[441,444] in dry DMA failed to produce any adduct. Repeated attempts involving the use of Zn* and ultrasound[445,446], or sodium iodide† in DMA, yielded only unreacted olefin and an insoluble high molecular weight material. There was no trace of any desired adduct 141 or 142. Analysis by tlc indicated that a very small amount of compound with an $R_f$ corresponding to that of dimer 143 was produced.

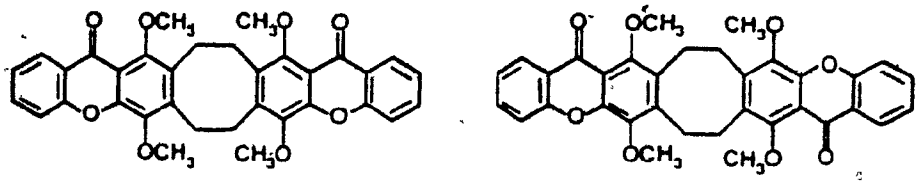
This cyclooctadiene 143 was deliberately prepared for comparison purposes by ultrasonic irradiation of dibromide 138 with Zn* in the absence of a dienophile trap. Under these conditions, 138 was all consumed and polymeric material was mostly produced. Nevertheless, a small amount (*ca.* 10%)

† Sodium iodide was used in place of zinc to alleviate some of the problems usually associated with using metals. These problems include: poor reproducibility due to the variation in activity from one batch to another of the metal and to the heterogeneous reaction conditions; and, causing reductions of susceptible functional groups.




138 105 141 142

of dimer 143 (presumably obtained as a mixture of two isomers) was formed which was characterized by its mass spectrum and behaviour on tlc.




143a 143b

Unfortunately, while we were able to improve the stability of 139 by adopting olefin 140 instead, the greater steric bulk of the latter seemingly precluded reaction with the diene. Accordingly another type of olefinic trap was sought. Although 3-acetoxy-3-buten-2-one (144) was reported[441,447] to

be useful in Diels-Alder reactions, difficulties in preparing it in good yields have hindered its widespread use. However, we found that a substantial improvement over existing procedures[439,441b,447] could be made by a simple modification involving the use of freshly distilled reagents together with the addition of a small amount of DMAP. We then attempted the reaction of dibromide 138 with excess olefin 144 using sodium iodide in anhydrous DMA and indeed, an excellent yield (*ca.* 80%), but of the unexpected diacetoxy compound 145, was obtained. A simple and plausible explanation for this result might be that the olefin was initially contaminated with acetic acid or that the olefin was undergoing some hydrolysis. Only after rigorous purification procedures* the formation of diacetoxy 145 was completely suppressed. Such precautions were not productive because adduct 146 (or its isomer 147) was not generated. Insoluble, high molecular weight materials were again obtained as well as unreacted olefin and unidentified polar material. Analysis by tlc indicated that a small amount of dimer 143 was again formed.

Initially, we selected olefins 140 and 144 as reactants primarily because their reaction as envisaged would create an adduct with a highly functionalized A-ring.

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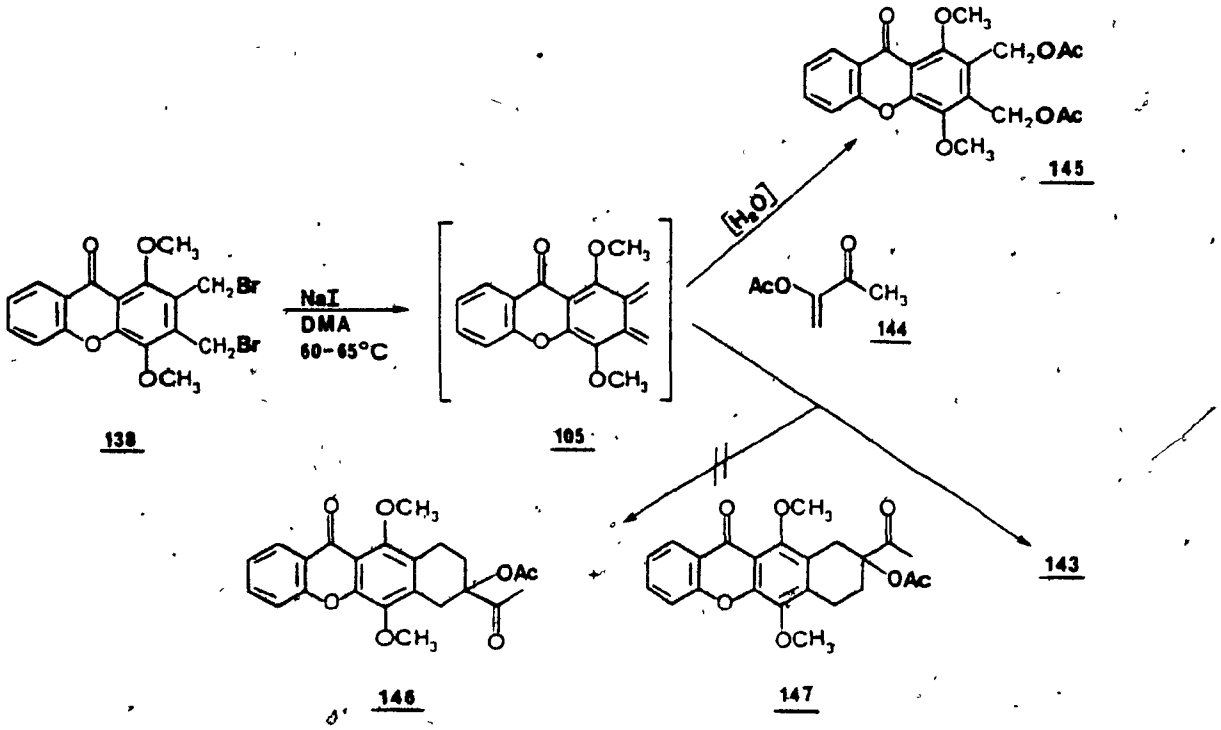
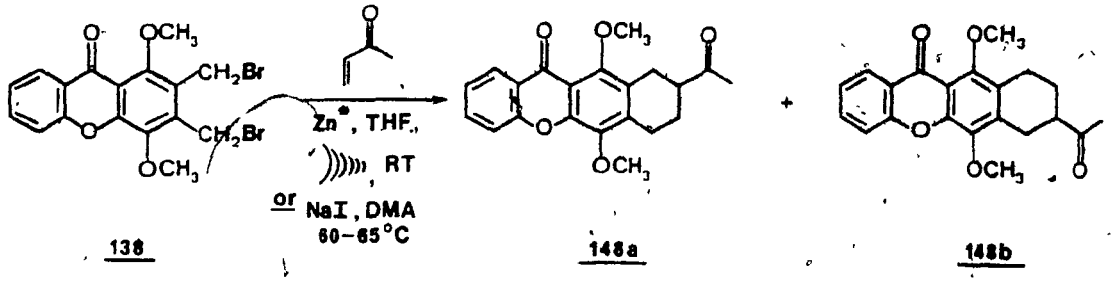
*Bicarbonate wash of the olefin did not help as diacetoxy 145 was obtained again in excellent yield when the reaction was repeated. Water was then scrupulously removed from all the reactants. DMA was dried over 3Å molecular sieves for 60 h and distilled from $CaH_2$ into the reaction vessel which had been flame dried. The sodium iodide was dried under vacuum over $P_2O_5$ for 60 h while the olefin was redistilled and only the middle fraction boiling within a range of 1.5°C was collected.




However, because of their low dienophilic activity they turned out to be poor choices. It thus became apparent that it would be necessary to use a more reactive dienophile in order to trap effectively the reactive *o*-quinodimethane intermediate 105. Accordingly, we explored the use of the more reactive methyl vinyl ketone.

When a mixture of dibromide 138 and excess methyl vinyl ketone was treated with Zn* in THF† while irradiating with ultrasound or when treated with sodium iodide in DMA, numerous compounds were formed (tlc) including insoluble polymeric material and a small amount of dimer 143. After extensive chromatography, an impure adduct 148 (*ca.* 10%) was

†Reactions in dry DMA, DMF and dioxane[445] gave the same results. We adopted THF because of its greater convenience.

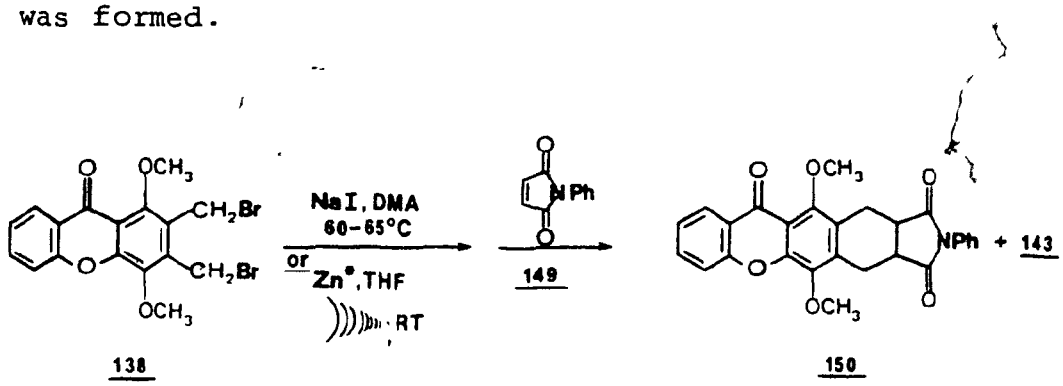



138 148a 148b

isolated. It probably† consisted of a mixture of both possible isomers but we were unable to clearly confirm this expectation from the appearance of its pmr spectrum. Efforts to improve the yield of adduct 148 by lowering the temperature to 0°C, or by using more dilute solutions of dibromide 138 in the presence of larger excesses of olefin were of no avail. These discouraging results raised some fundamental questions. The fact that dibromide 138 was completely consumed (under all reaction conditions) led us to question whether methyl vinyl ketone is indeed sufficiently reactive to effectively trap the intermediate *o*-quinodimethane 105. Would an olefin of still greater reactivity cycloadd efficiently? In order to answer this question we decided to use N-phenylmaleimide (149) a well-known highly reactive dienophile[448-451] of unquestionable ability to trap *o*-quinodimethane 105. When the reaction between dibromide 138 and excess N-phenylmaleimide 149 was carried out using either NaI in DMA or Zn* in THF under ultrasonic radiation, a surprisingly low yield (*ca.* 20%) of

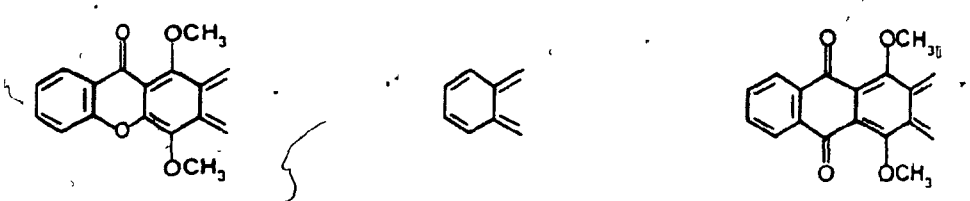
† The heteroatom and the carbonyl polarize the coefficients of the highest occupied molecular orbital (HOMO) to a different degree. The ratio of one regioisomer to the other will depend on how large this net polarization may be. In principle, adduct 148a is expected to predominate. (This is discussed in greater detail later in the chapter).

the expected adduct 150 was obtained. The reaction mixture also included insoluble high molecular weight material and tlc analysis indicated that only a very small amount of dimer 143 was formed.




138 149 150

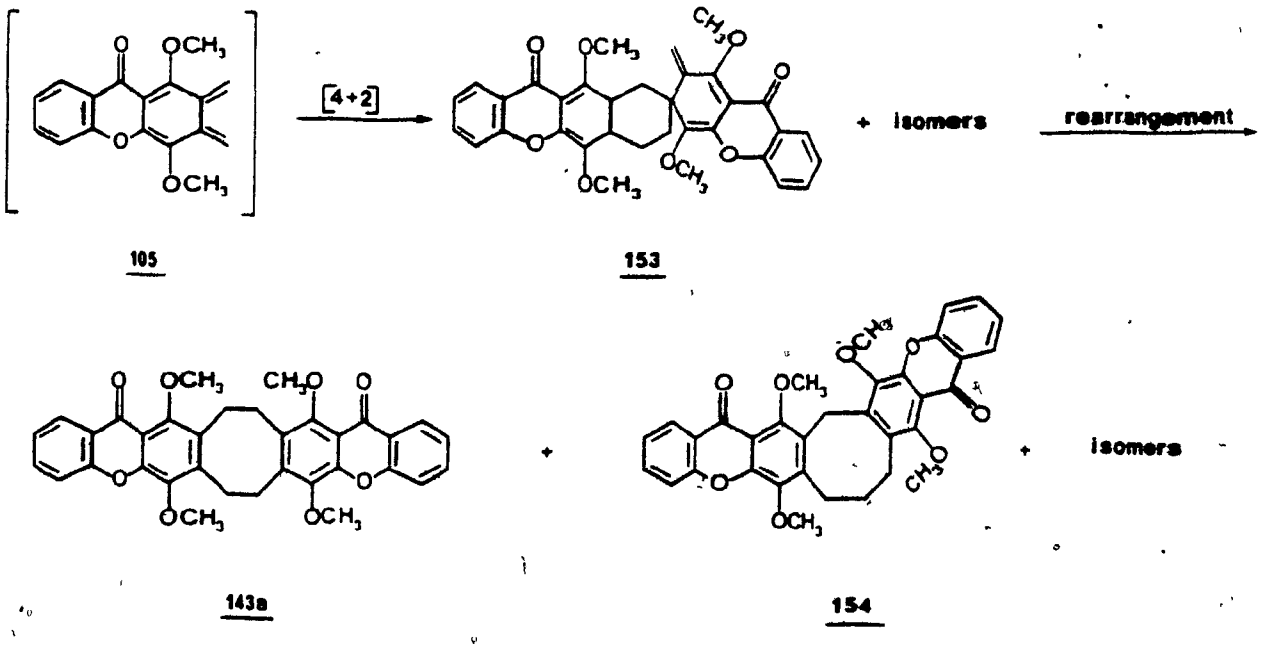
Theoretical calculations[452] show that the HOMO-LUMO separation of *o*-xylylene 151 (and derivatives) is small which accounts for their high reactivity and propensity to dimerize. In the case of xanthone-derived *o*-quinodimethane intermediate 105, the reactivity of the "diene" should be certainly increased[453] as a result of the electron-donating ability of the heteroatom (*vide infra*). On the other hand, in the anthraquinone-derived *o*-quinodimethane 152, the carbonyl moiety by virtue of its electron-withdrawing ability, serves to moderate the reactivity of the diene, thus increasing its stability. Therefore, failure of N-phenylmaleimide to




105 151 152

efficiently trap *o*-quinodimethane 105 may be the result, in part, of the detrimental short life of the latter.

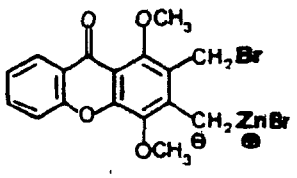
The formation of dimer 143, which was uniformly isolated in small quantities, deserves comment. Its formation may be accounted for by the rearrangement[448] of a spiro dimer such as 153 derived by a concerted, thermally allowed [2+4] cycloaddition of intermediate 105 with the formation of isomeric structure 154 being equally probable. However, there may be



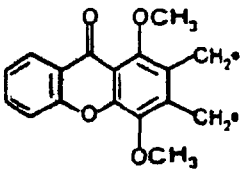

105 153 143a 154

other mechanisms, such as a non-concerted [4+4] cycloaddition of 105 that may be operative or possibly one where ionic intermediate* 155 or diradical intermediate 156 may be involved. Until we can show unequivocally that 105 is the intermediate

* The structure shown is of the more stable of the two isomeric intermediates possible.



155



156

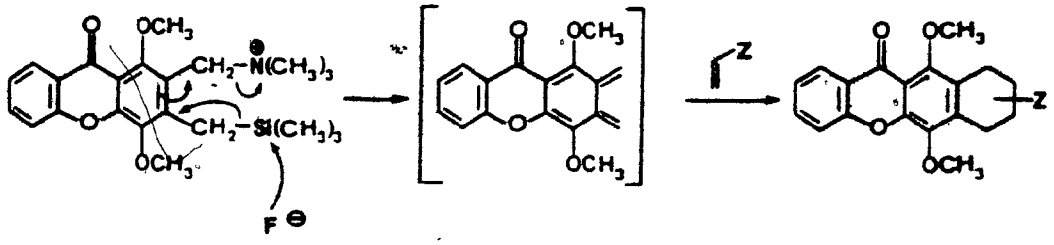
which is indeed generated, it is safer to conclude that under the reaction conditions used, intermediates 155 and 156 are equally plausible intermediates that can account for our observations.

The difficulties that we experienced with the use of *o*-quinodimethane 105 are not unique and differ only in detail with those encountered by others[405,406,441] in attempts at generating *o*-quinodimethane 152 through the action of zinc or sodium iodide on anthraquinone precursors. Low yields, extensive side-reactions and generally poor control of the conditions suggest the operation of a complex relationship between solvent, temperature, concentration and nature of the substrate. It might be extremely useful if one could study the chemistry of *o*-quinodimethane 105 as generated under conditions not conducive to such a complex interplay of variables. Attempts at developing a relevant strategy were considered next.

Two other methods for generating intermediate 105 were envisaged. The first attractive one involves the fluoride ion-induced 1,4-elimination of an *o*-(α-trimethylsilylalkyl)benzyltrimethylammonium halide as recommended by Saegusa

*et al.*[454] (Scheme 3.3). Although this method may not be ideal because of the polar nature of the reactant which dictates the use of experimental conditions similar to those already applied, we were nonetheless attracted to it. As it turned out, the synthesis of precursor 157 proved to be too difficult in the xanthone series of analogs and we were forced to abandon this approach for practical reasons.

Scheme 3.3



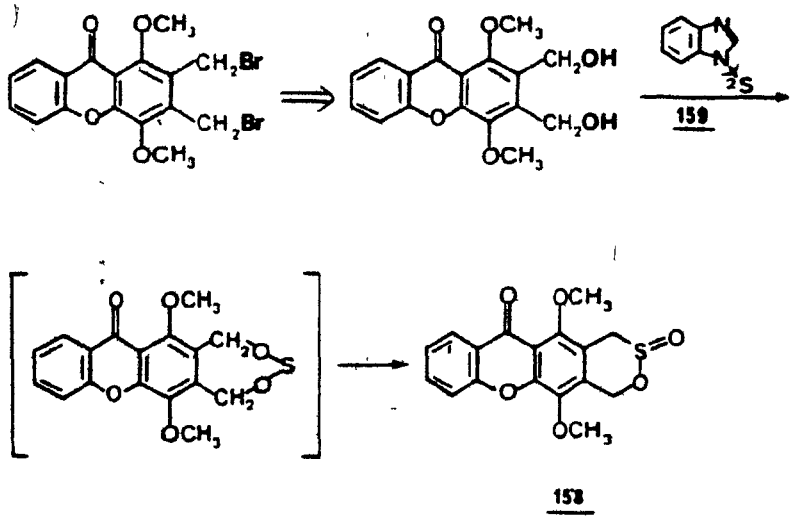

157 105

A more attractive alternative where reaction conditions would intervene minimally in the generation of *o*-quinodimethane 105 involves thermolysis of appropriate precursors as will be discussed next.

### 3.2.2 Thermal Generation of *o*-Quinodimethane 105

The high temperature (≥ 200°C) necessary to generate *o*-quinodimethane from either sulfone 108 or benzocyclobutene 109

requires the use of special apparatus[407], techniques that are impractical for our purposes and for large scale preparations. A more attractive precursor is β-sultine 158 as it is expected to extrude sulfur dioxide at a lower temperature (*ca.* 80°C)[455] and is obtainable[456], in principle, by reaction with a readily available diol and the sulfur transfer reagent benzimidazole 159. However, previous experience with this reagent in our laboratories using related diols as substrates was not encouraging, which led us to seek an alternative source of *o*-quinodimethane.



158

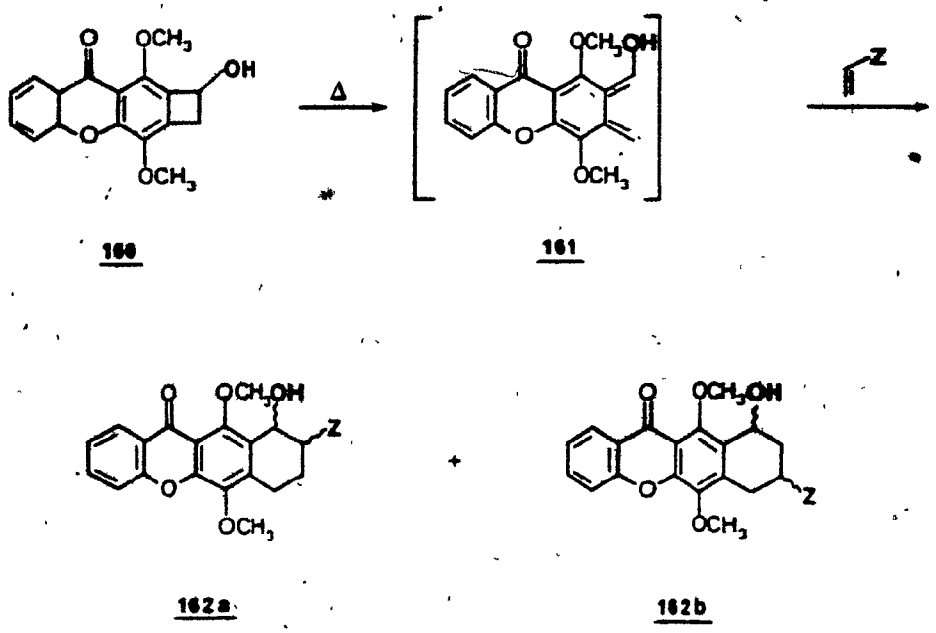
The observations[457-459] that the introduction of a certain substituent such as hydroxyl on the cyclobutene ring of benzocyclobutene reduces by as much as 120°C* the temperature

*The increase in ease of electrocyclic ring opening has been explained by frontier molecular orbital (FMO) theory[460,461] in a more adequate fashion than a previous suggestion[457] which related the process with the $^{13}C$ nmr chemical shifts.

required for electrocyclic ring opening incited us to consider the use of the hydroxybenzocyclobutene derivative 160. However, for ring opening of the latter, either a higher temperature or a longer reaction time may be needed (compared to unsubstituted benzocyclobutenol) because *peri*-substituents ($OCH_3$, OH) would sterically interfere with the outward conrotatory motion imposed by the hydroxyl group[458,459,461-464] upon diene generation. This disadvantage is offset by the fact that a benzocyclobutenol derivative would yield an adduct carrying a key hydroxyl function at position 7. On the other hand, a mixture of regioisomers may be expected although in unequal amounts because of the polarization of the diene. The predominating isomer may be anticipated on the basis of FMO calculations.

According to this theory, the cycloaddition reaction is dominated by the interaction between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of the reactants. The carbonyl group and the oxygen heteroatom will certainly affect these orbitals because they are vinylogous to the diene. However, the overwhelming dominating effect should be exerted by the hydroxyl group*. Thus the predicted behaviour of *o*-quinodimethane 161 should simply mimick that of an electron rich diene. If we were to

*Functional groups attached to the inner carbons of 1,3-dienes affect the FMO energy less than functional groups attached at the terminals. This is due to the fact that the MO coefficients are smaller at the inner positions and the perturbation of the orbital energies is proportional to the square of the orbital coefficient in the MO's[465-467].



160 161

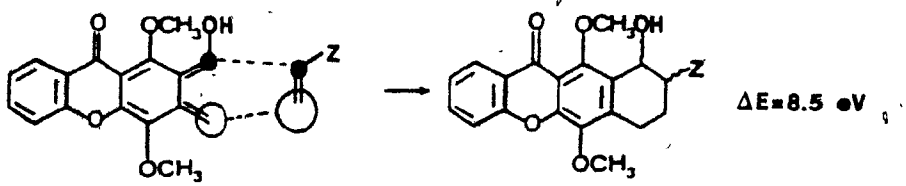
162a 162b

chose a dienophile where Z is an electron-withdrawing group, the more energetically favorable interaction will be that of the HOMO(diene)-LUMO(dienophile) where an estimated energy-gap of 8.5 eV would exist instead of a gap of 13.4 eV for a HOMO(dienophile)-LUMO(diene) interaction*.

To predict the regioisomer it is necessary to match the largest coefficient of the terminal MO for the controlling pair of FMO's[468-470]. For a 1-substituted diene, the hydroxyl group increases the magnitude of the coefficient of the HOMO on the opposite terminal (the opposite is true for the LUMO). Similarly for the LUMO, an electron-withdrawing group will increase the magnitude of the coefficient on the opposite

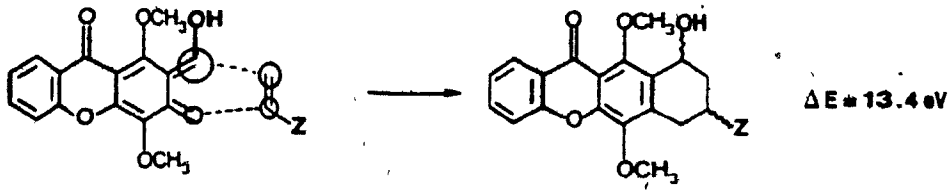
*For illustrative purposes it was *assumed* that the energy of the HOMO and LUMO of diene 161 would be similar to that of a typical diene (see Appendix 2). Based on the arguments presented, we feel that this is justifiable, however, the energy values quoted should not be given *per se* any significance.

terminal (the same is true for the HOMO). The result of matching of the orbitals leads to the prediction that regioisomer 162a* should be formed preferentially. The difference




HOMO (−8.5 eV) LUMO (0 eV) 162a

in ΔE's (4.9 eV) between the two possible interactions is large enough† to neglect the importance of the LUMO(diene)-HOMO(dienophile) interaction which would otherwise lead to the prediction that the desired isomer 162b would be generated.




LUMO (2.5 eV) HOMO (−10.9 eV) 162b

*The stereochemistry of the adduct would normally be expected to place the hydroxyl and Z-substituent *cis* to each other as a result of an *endo*-approach by the reactants. However, Kametani *et al.*[471] and more recently Wallace *et al.*[462] found that for similar reactants (under thermal conditions) stereoisomers were formed which led them to speculate that the reaction proceeded either by a stepwise mechanism *via* diradical or ionic intermediates[471] or that steric requirements force an *exo*-approach by the reactants[462].

†With a difference greater than 1.7 eV (*i.e.* > 39 kcals) it is usually safe to ignore the higher energy pair[472].

On the other hand, one can choose to use an electron-rich dienophile as the reactant. In this case, both combinations of interactions, [HOMO(diene)-LUMO(dienophile) and HOMO(dienophile)-LUMO(diene)] have the same energy-gap (estimated at 11.5 eV) so that both possible pairings must be considered when the coefficients of the molecular orbitals are matched. The molecular orbitals are polarized[470] in the fashion shown in Figure 14 and for both interactions the prediction is that isomer 162c should be formed preferentially*.

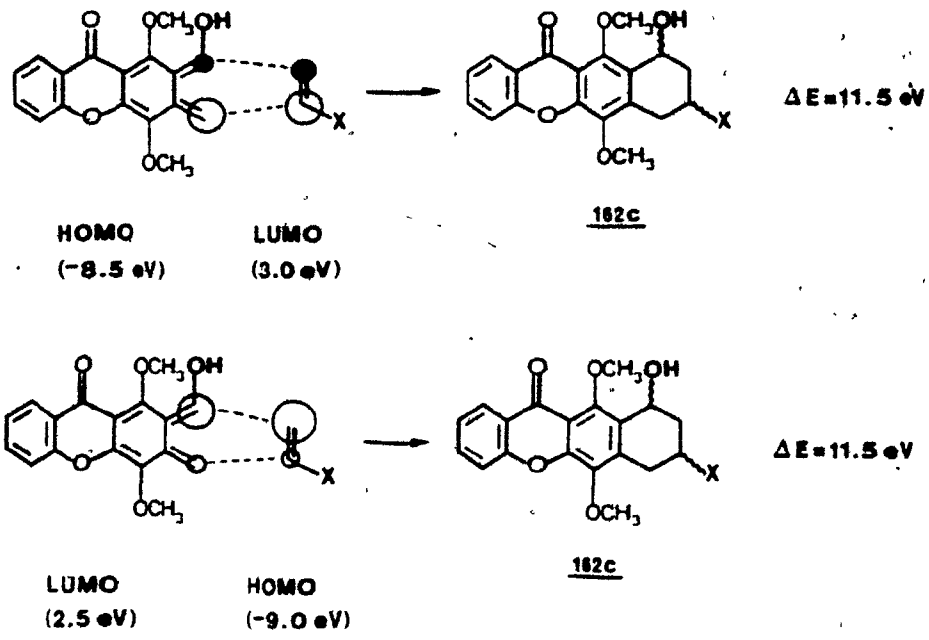



Figure 14: Both combinations of orbitals favor formation of the "meta" adduct.

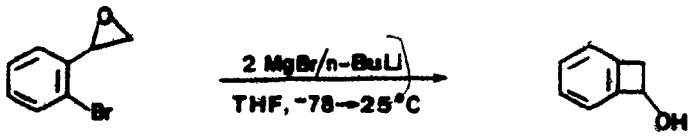
*According to Houk[473] when a diene and alkene are both substituted by electron-releasing groups, interactions of the non-frontier π orbitals of the diene with the alkene MO's can occur in the unsymmetrical transition state, and such interactions could conceivably alter regiochemical predictions.

The higher energy gap of 11.5 eV resulting from the use of an electron-rich dienophile compared with the energy-gap of 8.5 eV when an electron-poor dienophile is used, should be reflected in a slower reaction rate and it is for this reason that in general, dienophiles with electron-withdrawing groups are better substrates than electron-rich dienophiles in Diels-Alder reactions.

There is little doubt that the FMO theory is useful for predicting the outcome of the reactions and in the case of simple reactions of *o*-quinodimethane with electron poor dienophiles, the theory led to correct predictions[462,464,471]. But because there is no precedent in the literature concerning the predictable behaviour of 161, it is imperative that the course of its reaction be tested experimentally. While our main goal remained a practical one conceived to produce a usable regioisomer, the experimental outcome would serve at least to test the validity of the theoretical treatments.

### 3.2.2.1 Attempted synthesis of a benzocyclobutenol derivative

Benzocyclobutenols are not readily accessible as they involve multi-step syntheses[462,474,475]. Recently, however, Durst *et al.*[476] introduced a simple and efficient synthesis of benzocyclobutenol (163) from epoxide 164 which appeared suitable as a method for the generation of the desired benzocyclobutenol derivative 160.



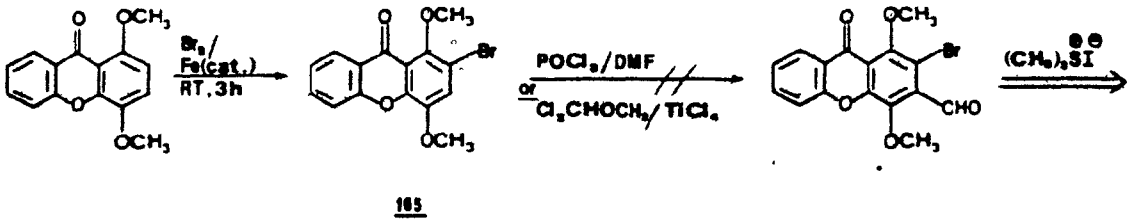

164 163

On the basis of our previous experience with the chloromethylation of 1,4-dimethoxyxanthone, regioselective bromination at the 2-position should be easily achieved. As expected, reaction of 1,4-dimethoxyxanthone with molecular bromine* in the presence of a catalytic amount of iron filings (unactivated) gave after 3 h at room temperature an excellent isolated yield (> 90%) of 2-bromo-1,4-dimethoxyxanthone (165). The high field (200 MHz) pmr spectrum of the product indicated that no ring C substitution had occurred and the $^{13}C$ nmr spectrum provided unequivocal evidence that substitution had occurred at the C-2 position. The mass spectrum included a molecular ion of m/z 334 (base peak) corresponding to the molecular weight of the expected compound and also showed a peak of (M+2)/M in confirmation of the presence of one bromine atom in the molecule.

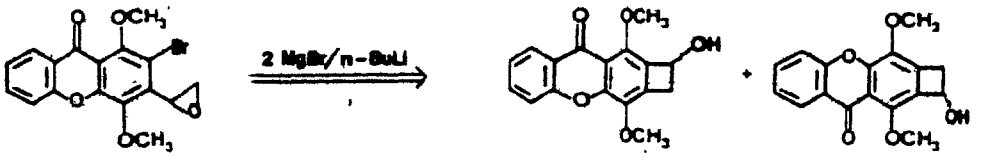
It was anticipated that formylation of this 2-bromo-1,4-dimethoxyxanthone (165) might be difficult because the C-3 position is deactivated towards electrophilic aromatic substitution. Furthermore, the small, but nevertheless

*Large excesses of bromine or longer reaction times should be avoided because mass spectroscopy indicated that a small amount of *bis*-brominated compound also formed.

deactivating effect of the *o*-bromo substituent as well as its steric bulk may not favor the formylation reaction. The use of the Vilsmeier complex between phosphoryl chloride and DMF or the excellent formylating agent α,α'-dichloromethyl methyl ether - titanium(IV) chloride under a variety of conditions including temperature effects (room temperature or gently refluxed in methylene chloride) were totally unsuccessful.

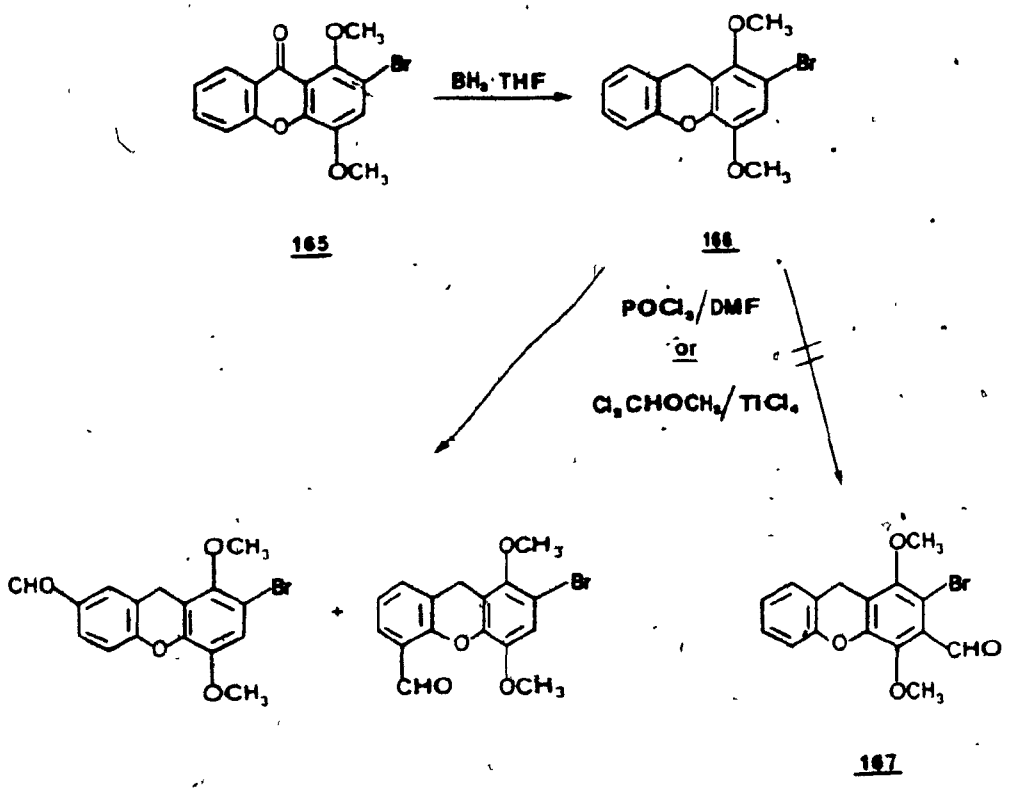



165




166a 166b

We then attempted to formylate 2-bromo-1,4-dimethoxyxanthene (166) (obtainable in quantitative yield by diborane reduction of xanthone 165), using the same reagents under similarly varied conditions, but starting material was again largely recovered along with a small amount (< 10%) of material carrying a formyl group on ring C, as evidenced by 200 MHz pmr spectroscopy with no indication that any




compound 167 was formed.

These results showed quite conclusively that formylation, like chloromethylation, at the 3-position of the ring system was not feasible despite the greater inherent reactivity of the formylating agents relative to the conventional chloromethylating agents*. Clearly, a different approach was needed in order to synthesize the benzocyclobutenol intermediate 160.

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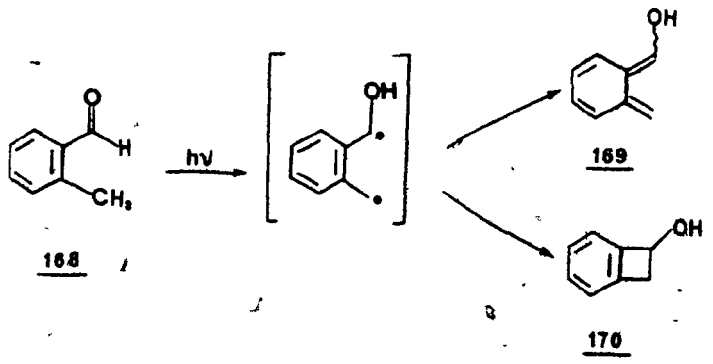
* We have evidence demonstrating that formylation of 1,4-dimethoxyxanthene occurs within one-half hour while under similar conditions chloromethylation requires several hours.

### 3.2.2.2 Attempted synthesis of 2-formyl-3-methyl-1,4-dimethoxyxanthene

The observation that *o*-methylbenzaldehyde (168) undergoes photoenolization[477,478] to yield either hydroxyquinodimethane 169 or benzocyclobutenol 170 led us to briefly consider the synthesis of 2-formyl-3-methyl-1,4-dimethoxyxanthene (171)* as a precursor of the corresponding quinodimethane or cyclobutenol.




168 169 170

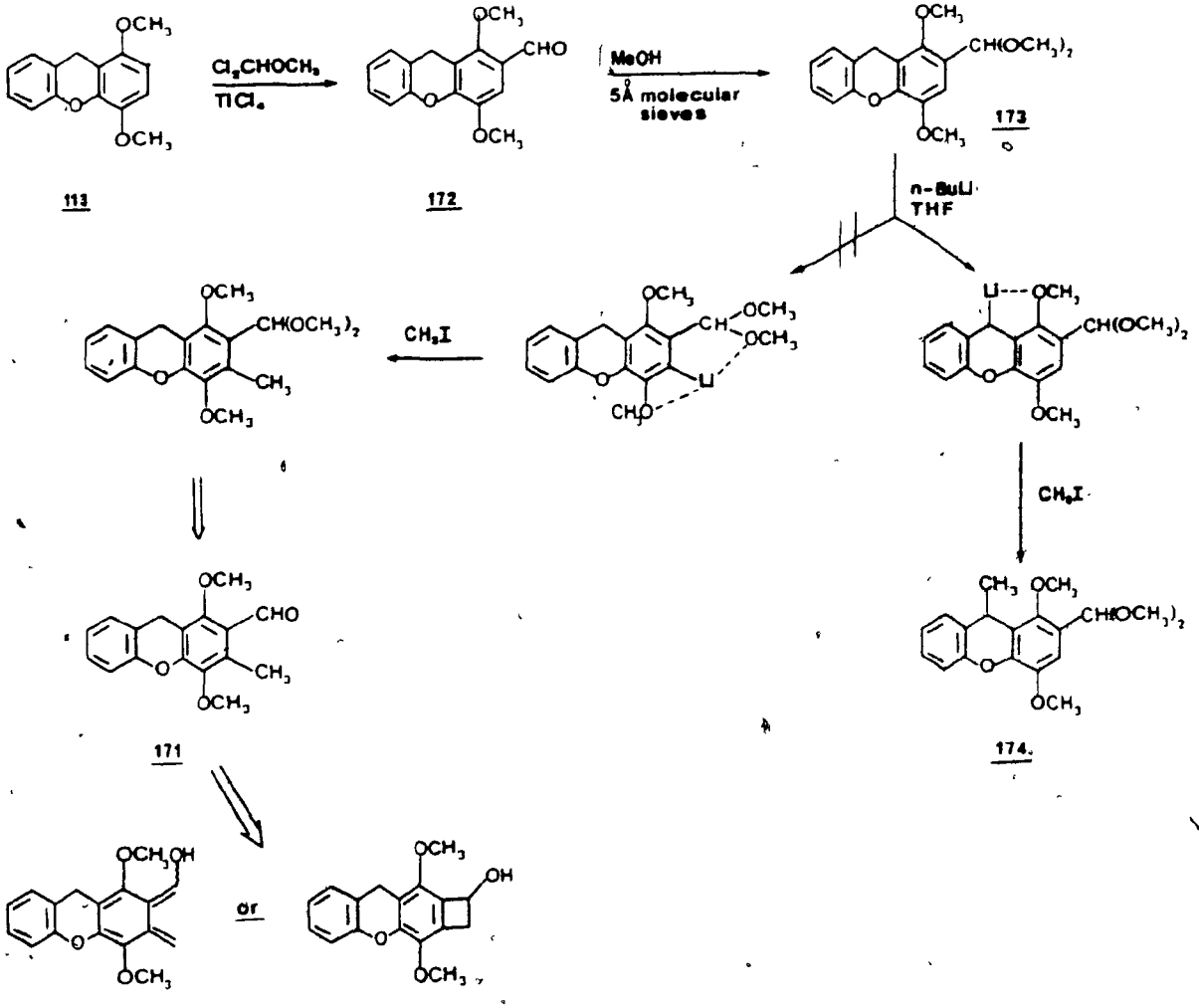
While 1,4-dimethoxyxanthene (113) underwent $TiCl_4$-catalyzed formylation at the C-2 position† with α,α'-dichloromethyl methyl ether to afford 172 followed by ready acetal formation in the presence of methanol and 5Å molecular sieves or *p*-TsOH[479], lithiation of 173 at the C-3 position did not

*The C-9 carbonyl was removed to avoid interference with either the photochemistry or the organometallic reactions.

†This was proven by comparing the $^{13}C$ nmr and $^{1}H$mr spectra of unequivocally synthesized 2-methyl-1,4-dimethoxyxanthene with that of compound 172 after reduction of the aldehyde functional group to a methyl group using $Et_3SiH$-TFA[313]. (See Appendix 1).

prove possible in spite of the *ortho*-directing effect of the methoxy groups. Instead, n-BuLi caused deprotonation of the more acidic C-9 xanthene protons ($pK_a \sim 30$)[480,481] since methylation of the anion afforded only compound 174 (Scheme 3.4). Nevertheless, the fact that 1,4-dimethoxyxanthene undergoes regioselective formylation may prove to be very useful in other respects (see Appendix 3).

Scheme 3.4



### 3.2.2.3 Attempted synthesis of benzocyclobutenol 160 *via* a benzyne intermediate through a [2+2] cycloaddition

From a preparative point of view, the synthesis of benzocyclobutenes *via* the [2+2] cycloaddition of olefins to benzynes has not been used extensively. This can be attributed in part to the fact that only modest yields (< 50%) are usually obtained[482]. The growing interest in benzocyclobutenes (because of their emergence as useful synthetic intermediates[458,463,464,471,475,483-485]) has done much to simulate interest in studies[486,487] directed at improving the methodology. Recent *ab initio* calculations by Houk *et al.*[487] revealed that the inherent electrophilicity of benzyne is the result of a lowering in the energy of the LUMO orbital thus demonstrating that the rate of reaction between benzyne and an olefin increases as the latter becomes more electron-rich (increasingly nucleophilic). At least one successful illustration of this hypothesis was given in the area of synthesis[486]. Various methods to generate benzyne have been improved which minimize the side reactions[488-490] associated with the use of organometallic reagents or with reaction conditions favoring metal-halogen exchange as well as direct nucleophilic substitution. Reports[491,492] that benzyne can be readily generated from 2-bromo-1,4-dimethoxybenzene when treated at low temperature with LDA[492] were very encouraging and led us to consider the possibility of using 2-bromo-1,4-

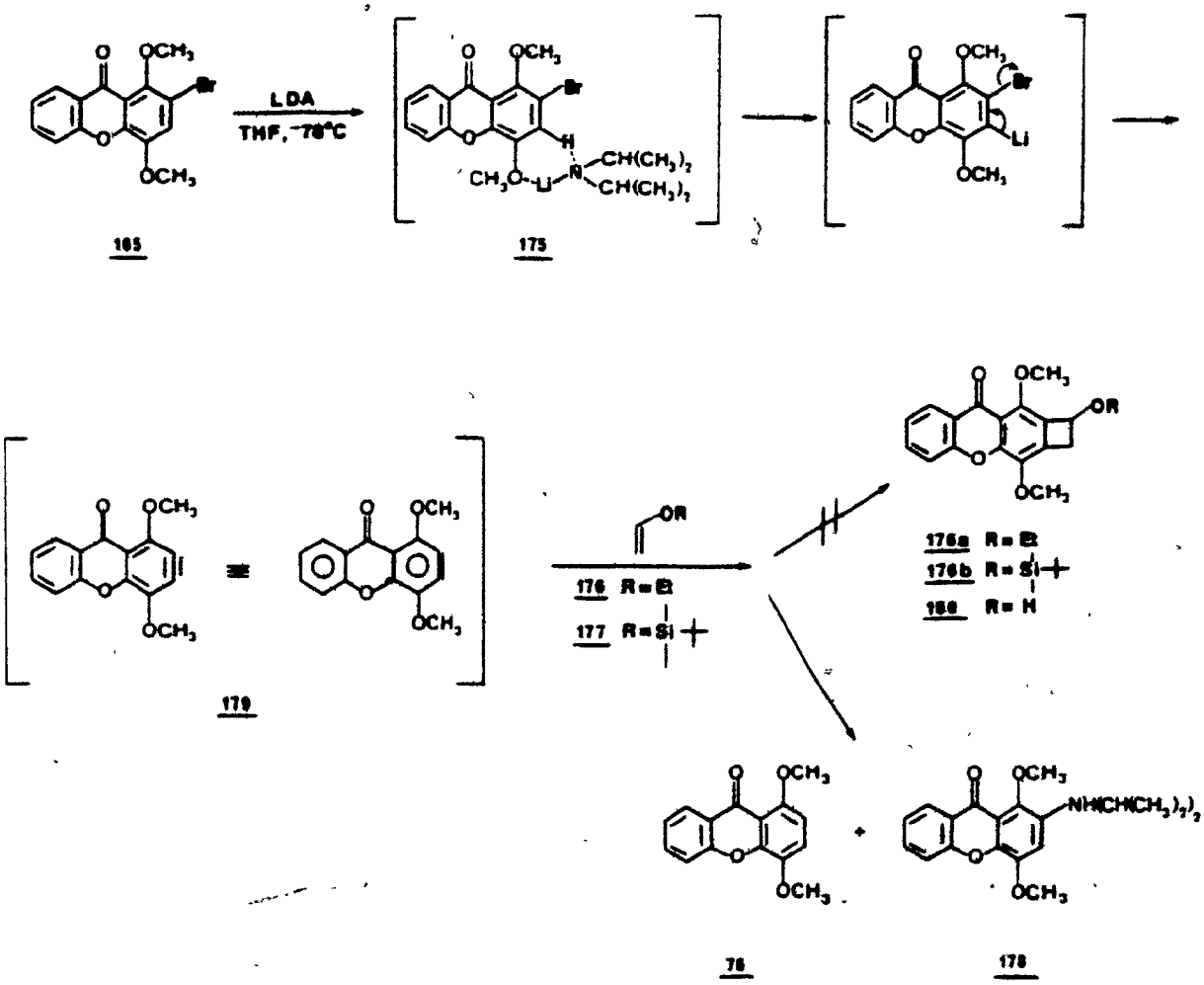
dimethoxyxanthone (165) as a potential source of benzyne. Because electronic effects on arynes are largely inductive in origin[485,490,493], the methoxy groups should increase their electrophilicity and thus promote the reaction in a productive manner. Furthermore, the methoxy group should help direct the organometallic reagent toward the *ortho*-position through formation of a complex such as 175, a possibility that should facilitate metalation of the substrate.

For our initial studies we decided to use the readily available ethyl vinyl ether (176) as the reactant because it was shown to act as a good trapping agent for benzyne[487,494]. Obviously, the silylated olefin 177[495,496] would be more useful eventually because subsequent deprotection to alcohol 160 would pose no difficulty.

The reaction was carried out by adding a small excess of LDA at -78°C to a large excess of ethyl vinyl ether to which was added a THF solution of 2-bromo-1,4-dimethoxyxanthone (165) followed by stirring for 3 h. After allowing the reaction mixture to warm up to room temperature over a period of 2 h, the mixture (comprising of several components as judged by tlc) was purified by flash chromatography. The main fraction (*ca.* 60%) was identified as 1,4-dimethoxyxanthone (76), product resulting from the reduction of aryl halide 165. A plausible mechanism for this reduction involves the transfer of a β-hydrogen of LDA as a hydride equivalent[490,497-499] (Scheme 3.5). No product of carbonyl reduction

as a result of a hydride* transfer was isolated.

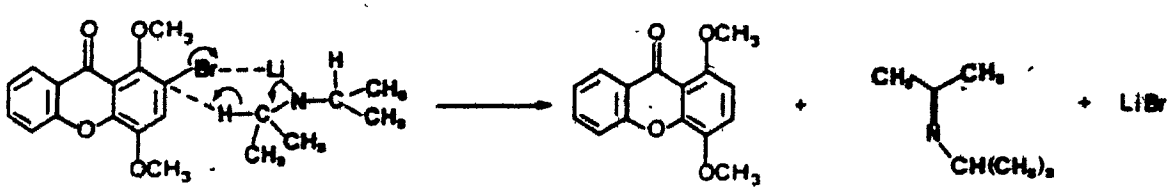
The mass spectrum of the more polar fraction (*ca.* 5%) included a molecular ion of m/z 355, value consistent with the molecular weight corresponding to compound 178 and whose




formation would be the result of the addition of LDA to benzyne 179 (this in spite of the low nucleophilicity of LDA).

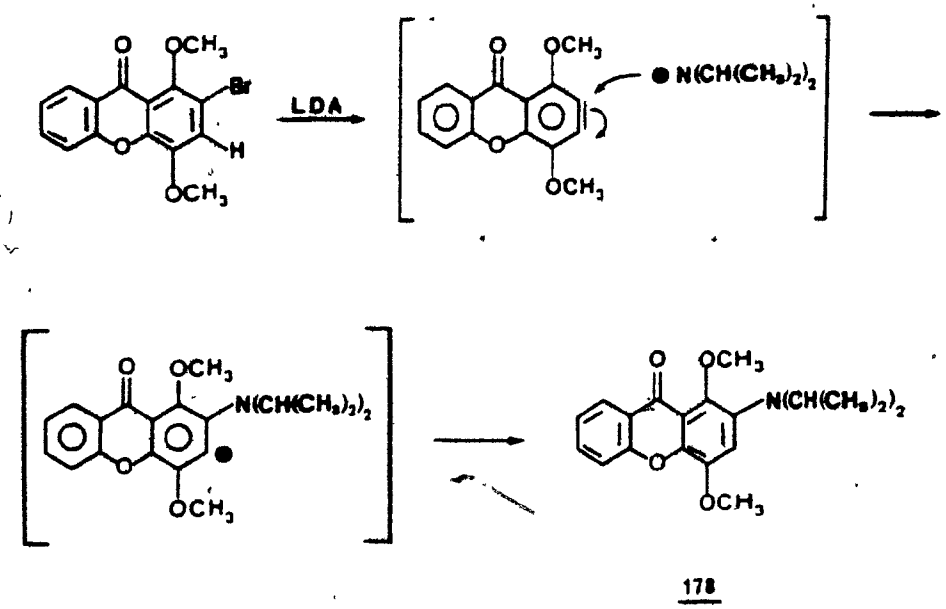
*Recent evidence[499] rejects the idea that carbonyl reduction occurs as a result of single electron transfer[500].

Scheme 3.5



76

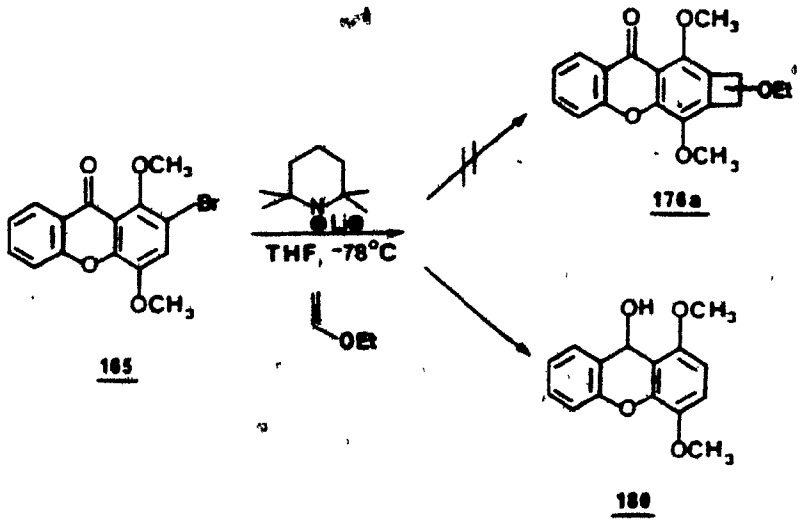
Although some polar material could not be identified clearly, its spectroscopic properties did not correspond to those expected for the adduct 176a.



178

In order to suppress the reduction process[498] leading to 76 we substituted LDA by lithium 2,2,6,6-tetramethylpiperidide (LiTMP) which does not carry β-hydrogens while being effective in the generation of benzyne[497,501]. Moreover,

this base (LiTMP) is non-nucleophilic and being more hindered than LDA, addition to benzyne should be prevented. Under the conditions for aryne generation from 165 by LDA, the base LiTMP in an excess of ethyl vinyl ether at -78°C again led to a complex mixture which after arduous purification procedures was found to contain none of the desired benzocyclobutene 176a. However, a small amount (< 10%) of a compound identified by pmr and infrared spectroscopy as 1,4-dimethoxyxanthhydrol (180) was isolated. Its formation is not easily




accounted for although electron transfer[502] followed by hydrogen transfer from the solvent is a possibility. The other components of the mixture could not be identified.

These difficulties in the generation of the desired benzocyclobutenol intermediate led us to abandon this strategy. This was a major setback because it eliminated the possibility

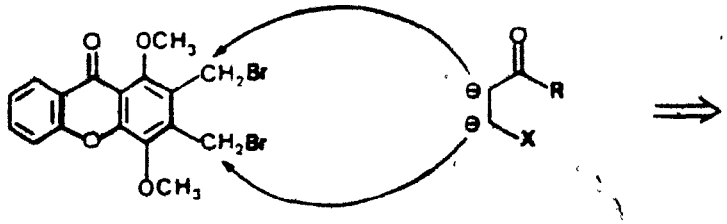
of producing the *o*-quinodimethane intermediate under thermal conditions and so prevented us from verifying concomitantly the predictions of the FMO theory regarding the preferential formation of regioisomers. Moreover, the possibility of generating a useful key intermediate functionalized at position 7 was also denied.

We then turned our attention to the synthesis of the desired tetracyclic ring system using an approach based on the *bis*-alkylating properties of dibromide 138.

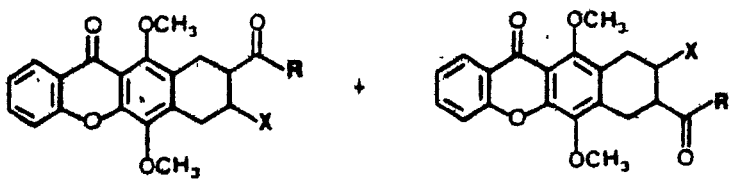
## 3.3 ANNULATION REACTION INVOLVING *bis*-ALKYLATION IN A SINGLE OPERATION

### 3.3.1 Discussion of Strategy

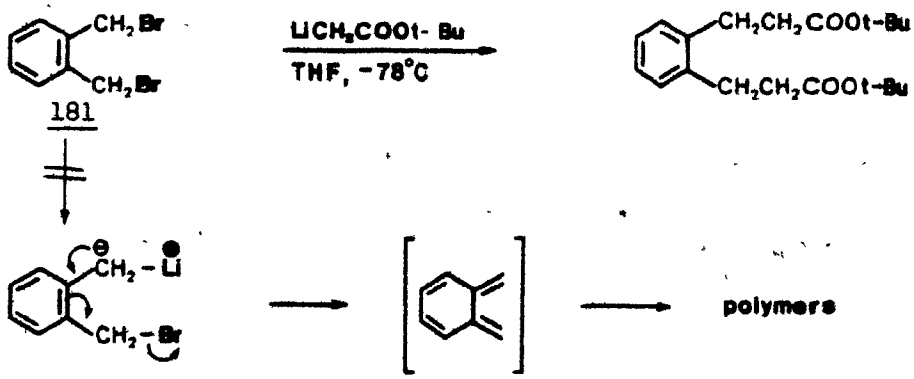
In order to exploit the dialkylating ability of dibromide 138, it appeared possible to develop a dianion equivalent (synthon) such that an annulation reaction of the type shown in Equation 3 could be carried out. One concern




138 (3)

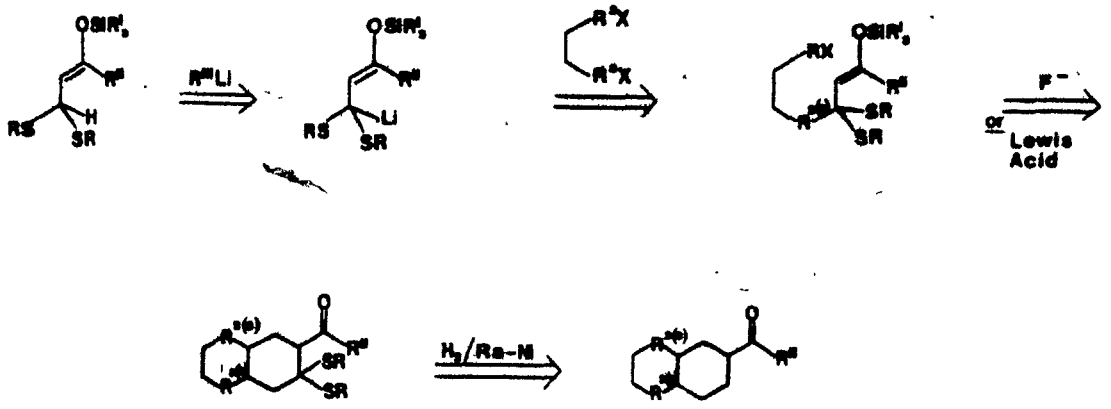


with such an approach is the possibility of a halogen-metal exchange process conducive to the collapse of the dibromide to the *o*-quinodimethane 105. However, a report by Ewing and Paquette[503] indicating that α,α'-dibromo-*o*-xylene (181) could be used as a *bis*-alkylating species at low temperature encouraged us to test this approach (Equation 3).




We required a reagent that fulfills the following criteria: a) it should possess two vicinal nucleophilic sites capable of being *activated* independently of each other; b) the masked carbonyl group should be easily *regeneratable* and c) function X (Equation 3) should be easily *removable* or *transformable* after annulation. A structure which fulfills these requirements is the dithio-silyl enol ether. The dithio-group serves to activate the allylic proton making it considerably more acidic so that allylic carbanion generation

with an alkyllithium base should proceed readily and allow smooth substitution of the dibromide. Subsequently, intramolecular alkylation of the silyl enol ether β-carbon should be induced by fluoride ion[504-511] or Lewis acids[510-516]. As a




consequence of this ring closure, the carbonyl group would be automatically regenerated while the dithio group would subsequently be eliminated by hydrogenolysis* to yield the desired compound.

### 3.3.2 Preparation of Dithio-Silyl Enol Ether 182

Evans *et al.*[518] showed that reaction between α,β-unsaturated ketones and thiosilanes, in the presence of an initiator, results exclusively in 1,4-addition. We foresaw no difficulty in promoting a similar addition of an appropriate thiosilane to a 4-thio-substituted-α,β-enone to give the

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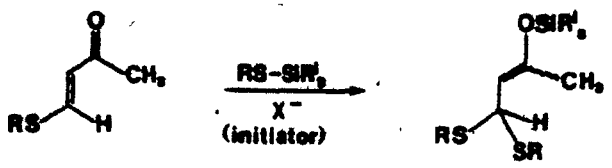
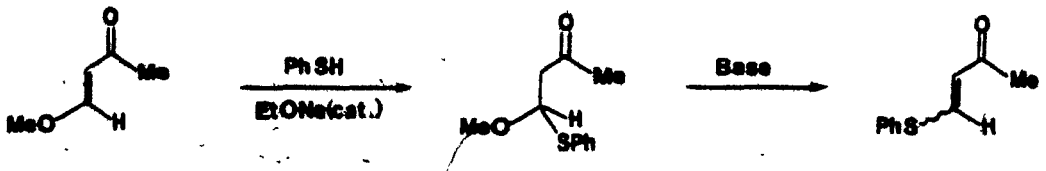
*To prevent reduction of the carbonyl group during hydrogenolysis, it could be protected as the dimethyl ketal (acetal)[517].

desired reagent 182. We chose to prepare 4-phenylthio-3-buten-2-one (183) through the base-catalyzed[519] addition of thiophenol




182

to E-4-methoxy-3-buten-2-one (184) and as expected, the process gave excellent results[520]. However, the base-catalyzed elimination of methanol did not work well, probably as a consequence of competing aldol condensation. Accordingly, a more efficient method was sought.

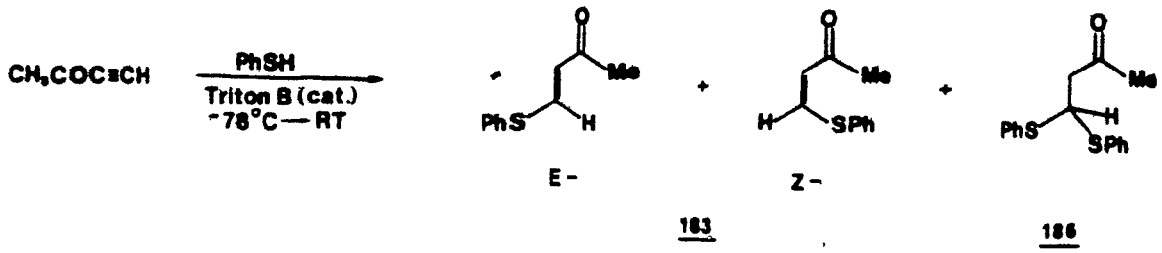



184 183

As the Michael addition of thiols to alkynes is well-known[521,522], we proceeded with the addition of thiophenol to 3-butyn-2-one (185)* at low temperature using a catalytic amount of N-benzyltrimethylammonium hydroxide

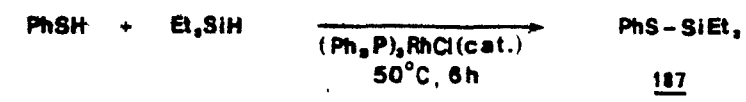
*Commercially available 3-butyn-2-one is very expensive and very difficult to obtain.

(Triton B). An optimized yield of 93% (based on 185) of thio-enone 183 was thus obtained as well as a small amount (< 7%) of *bis*-addition product 186. Thio-enone 183 consisted of a mixture of geometrical isomers [E-(J ≅ 15 Hz) and Z-(J ≅ 10 Hz)] in a ratio of 7:2. The next step called for

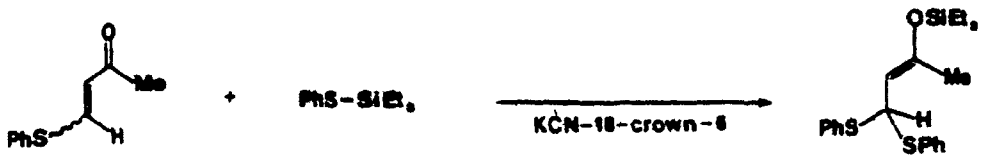



the use of thiotrimethylsilane according to Evans *et al.*[518] but we were apprehensive about its sensitivity to hydrolysis and its ability to participate in rearrangements.

We therefore developed a modification of a literature procedure[523] which allowed instead a practical preparation of phenylthiotriethylsilane (187). This reagent was obtained simply by heating thiophenol and triethylsilane in the presence of Wilkinson's catalyst [*tris*(triphenylphosphine)rhodium(I) chloride] for 6 h. Distillation gave an excellent yield (*ca.* 95%) of thiosilane 187 as a high boiling viscous oil. The reaction at room temperature between thio-



enone 183 and thiosilane 187 in the presence of a catalytic amount of initiator, KCN-18-crown-6 complex[518] was stopped after 22 h. The pmr spectrum of the crude reaction mixture indicated that the desired addition compound 188, presumably




183 187 188

the more stable* E-isomer, was formed in excellent yield (*ca.* 95% based on 183). The infrared spectrum confirmed that there was no unreacted thio-enone 183 and showed a double-bond silyl enol ether stretch at 1660 $cm^{-1}$.

## Attempted Model Alkylation of Dithio-Silyl Enol Ether 182

Metalation of 188 was attempted using n-BuLi in the presence of 1 eq of tetramethylethylenediamine (TMEDA)[524]. Despite the expected increase in acidity of the allylic hydrogen, no deprotonation occurred even after 2 h at -78°C because attempted trapping of the anion with methyl iodide

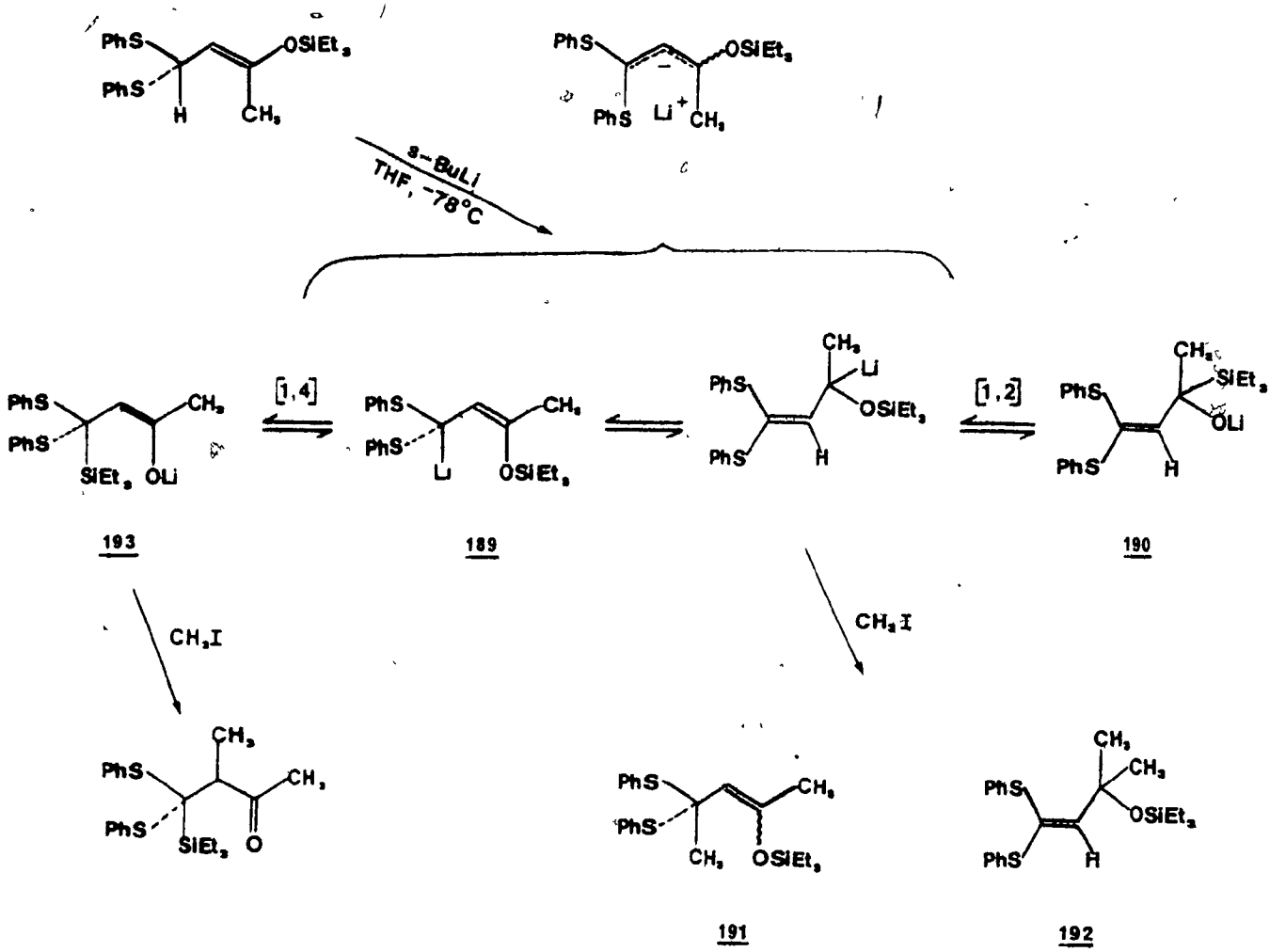
*Although stable enough to work without special precautions in air at room temperature for short periods of time, silyl enol ether 188 was remarkably unstable toward silica gel. Quantitative conversion to the ketone was obtained during purification by flash chromatography. Because of this, we never used an excess of thiosilane 187 but allowed the reaction to progress for a longer period of time instead.

gave only starting material. The use of n-BuLi at a higher temperature (-40°C) led to the rapid formation of a dark brown solution which quickly deteriorated. Reaction of 188 with *sec*-BuLi[525] in the presence of 0.5 eq of hexamethylphosphoramide (HMPA)* or in its absence at -78°C for 0.5 h followed by addition of methyl iodide at -78°C gave rise to a complex mixture of products. One may expect that deprotonation of 188 might lead to an equilibrium mixture consisting of the lithiated species 189 and 190 which will react with methyl iodide to give a mixture of γ-alkylated compound 191 and the α-alkylated isomer 192[529,530]. Furthermore, anion 189 may also suffer a [1,4] sigmatropic rearrangement[530†] to give enolate 193 although we felt that the use of the bulky triethylsilyl protecting group would discourage this rearrangement[529,531]. Efforts to identify any one of the resulting compounds were not successful, the difficulties being compounded by the tendency of some consistuents to decompose during chromatographic processing. Attempted purification by low pressure distillation was not feasible. This disappointing result may be a reflection of the anion instability under the

---

*Extreme caution should be used when handling HMPA which has come under close scrutiny because of its carcinogenic activity[526,527]. The use of a cyclic urea, 1,3-dimethyl-2-oxo-hexahydropyrimidine, has been proposed as a possible alternative to HMPA[528].

†It is known that trialkylsilyl groups (especially trimethylsilyl) have a propensity to participate in sigmatropic rearrangements[531]. Recent work by Evans *et al.*[529] has shown that these rearrangements appear to be subject to steric constraints at silicon and that the use of sterically hindered silyl groups might be helpful in slowing down, but not necessarily eliminating these rearrangements.

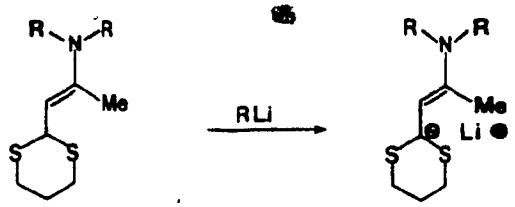



the reaction conditions and may account for the complex mixture of products that is generated. Coupled with the fact that arduous purification procedures of the mixture could not be avoided and were unlikely to succeed in any event, we were forced to conceive and develop a more reliable (it was hoped) reagent for the annulation strategy as discussed above.

### 3.3.3 Use of Dithiane-Enamine as a Potential Reagent

An interesting variation on the theme represented

by 188 would consist in replacing the silyl enol ether part by an enamine function which should be endowed with excellent nucleophilic properties as is well-known. Being stable towards strong alkyllithium bases[532], the acidic allylic proton of the dithiane ring part should be easy to abstract with an appropriate base as shown in the following equation.




194

3.3.3.1 Synthesis of dithiane-enamine 194

Reaction between (E)-4-methoxy-3-buten-2-one (184) and 1,3-propanedithiol in the presence of a catalytic amount of $BF_3 \cdot Et_2O$ for 3 h at 0°C gave essentially a quantitative yield of pure, crystalline kéto-dithiane 195.

Although enamines derived from acyclic ketones are generally regarded as being unstable and prone to self-condensation[533,534], the use of titanium(IV) chloride both as a water scavenger and a catalyst has facilitated their preparation. However, it appears that with unsymmetrical ketones such as 195 which can yield in principle two regio-

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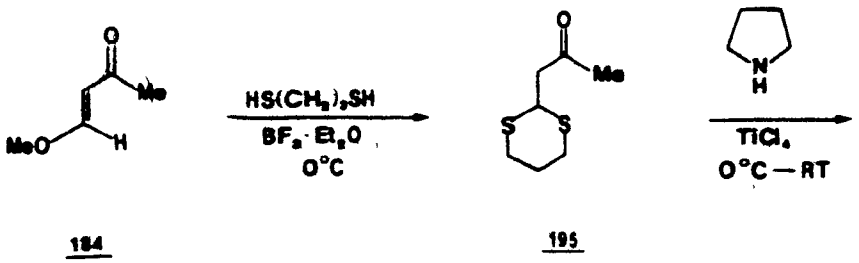
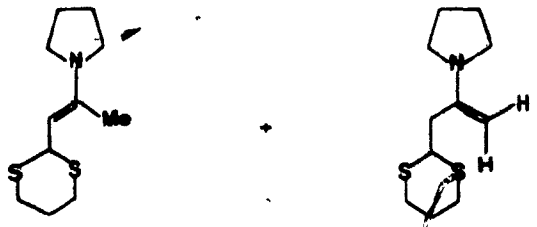
* Enamine prepared using Dean-Stark water separator and *p*-TsOH (cat.) gave condensation products.

isomeric enamines[534-538], the predominant product is the one where the double bond is least substituted presumably as a consequence of a kinetic control of the process[533,535,536]. Since we required the other isomer 194 where the double bond is more highly substituted, the recommended method for enamine preparation made us apprehensive. Nevertheless, the reaction between keto dithiane 195, pyrrolidine and titanium(IV) chloride at 0°C was attempted and found to give a substantial amount of the more substituted enamine 196. However, it was not possible to determine from the pmr spectrum of the products the relative amount of the less substituted enamine 197 because the resonance signal in the region around 4.0 ppm where the vinyl protons should appear[539] was ill-defined. The pmr data also indicated the presence of unreacted ketone, occluded pyrrolidine as well as unidentified material. Although the product(s) were very labile, it was nevertheless possible to efficiently remove the titanium salts by filtration through Celite under an inert atmosphere with negligible hydrolysis. Attempted purification by low pressure distillation resulted in extensive decomposition while chromatography ($SiO_2$ or $Al_2O_3$) led to hydrolysis to the starting ketone. Since the use of a mixture of enamines (196 and 197) in our projected reaction with the *bis*-alkylating model substrate 181 would further compound the problem of purification and access to workable quantities of properly annulated material, we decided to attempt the

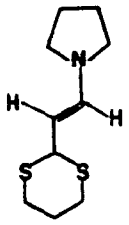



184 195



196 197

preparation of enamine 198 instead because it can exist in only one regioisomeric form possessing the desired stereoelectronic features.



198

### 3.3.3.2 Synthesis of enamine 198

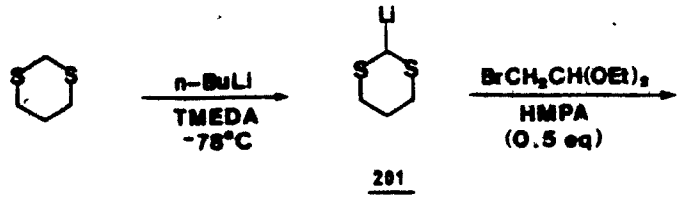
A literature search showed that aldehyde 199 had been

prepared[540,541] by reacting bromoacetaldehyde diethyl acetal (200) and 2-lithio-1,3-dithiane (201). In attempting to reproduce this work, considerable difficulties were encountered. Several precautions were taken such as recrystallizing and storing the very hydroscopic 1,3-dithiane over $P_2O_5$ and carefully distilling the diethyl acetal 200. Our meticulousness was of no avail, the reported yield of product being unreproducible under the prescribed conditions or non-existent. Although this negative result was previously noted by others[542] no effective solution to the problem was offered. We also observed that the use of the more reactive iodoacetaldehyde diethyl acetal (202)* failed to improve the yield. Finally, attention was paid to the well-documented fact that HMPA can promote alkylation reactions even at low temperature[544-548]. We were pleasantly surprised to observe that by adding 0.5 eq of HMPA to the reaction medium, alkylation of the lithio-dithiane by the bromoacetal proceeded in almost quantitative yield even at -78°C†. We subsequently modified the experimental conditions for the generation of lithio-dithiane 201 in such a manner that the whole process could be

---

*Reacting NaI with $BrCH_2CH(OEt)_2$ in refluxing acetone did not result in any exchange to give the iodoacetal. Apparently, heating in a sealed tube at high temperature is necessary for this Finkelstein-like[543] reaction to occur. The iodoacetal was best prepared by treating vinyl acetate in ethanol with iodine monochloride[543].

†The effect of HMPA is truly dramatic. Seeback and Corey[540c] report that the same reaction (without HMPA) requires 46 h at 0°C. We found that reaction with HMPA was complete when stirred at -78°C for 5 h followed by a slow warming up to room temperature over a period of 8 h. However, in our hands, if the alkylating agent is added at -78°C without HMPA and kept there for 5 h (or less) before warming the solution, the yields are diasterously low.

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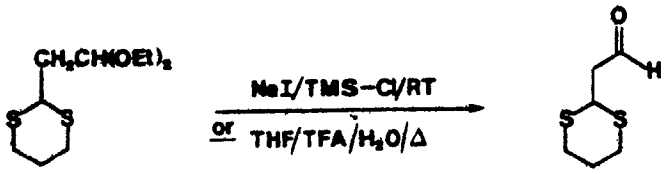


202 199

conveniently carried out at -78°C, thus insuring that decomposition of the alkylating agent through elimination reactions was negligible. The next step involved hydrolysis of acetal 202 a simple process which proved to be quite troublesome*. Unsatisfactory results were obtained with perchloric acid[541], acetic acid[542] and concentrated HCl-dioxane[550] as catalysts. However, at 45°C, a mixture of 10% TFA in THF-$H_2O$ (1:1) gave satisfactory results after 3 h but TMS-I[551-553], generated *in situ*[341], was found to give high yields of aldehyde consistently within 30 min at RT†. We then reacted aldehyde 199 with pyrrolidine and titanium(IV) chloride to obtain an excellent yield of enamine 198, presumably

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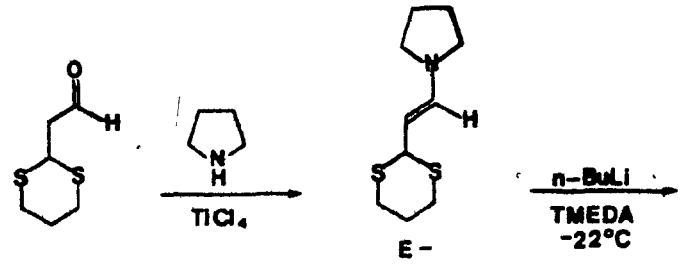
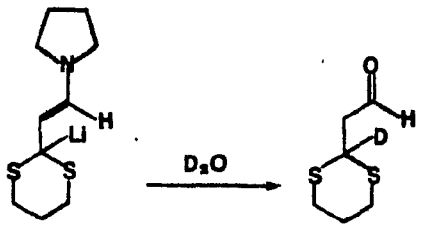
*The ethylene glycol acetal (1,3-dioxolane) is apparently more easily hydrolyzed[549].

†Stirring for longer periods than 30 min resulted in decomposition and there was no evidence that trimethylsilyl iodide added to the aldehyde, reversibly, as has been suggested by Jung *et al.*[554].

as the more stable E-isomer. Its pmr spectrum showed no evidence that any starting material was left unreacted. After careful filtration through a pad of Celite under an inert atmosphere, a relatively pure (by pmr) crystalline enamine, free of titanium salts was obtained with no evidence that extraneous products were present. Reaction of enamine 198 with n-BuLi in the presence of 1 eq TMEDA gave a complex stable at -22°C which after 1.5 h was decomposed with $D_2O$ to give hydrolyzed material in which the allylic acidic proton was completely exchanged. We were accordingly ready to attempt alkylation of 198 with *o*-xylene dibromide (181) as a model substrate. After generating the lithium complex 203 at -22°C, it was transferred under an inert atmosphere to a dilute THF

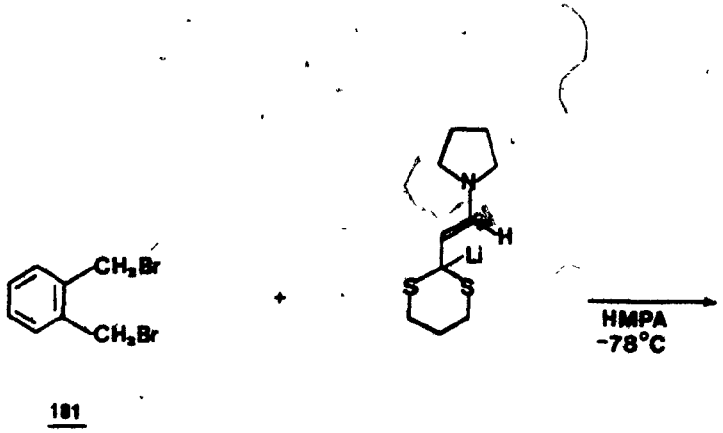



199 198




203

solution of *o*-xylene dibromide (181) containing 0.5 eq of HMPA at -78°C and the mixture stirred for 2 h. The mixture was allowed to warm slowly to room temperature but the pmr spectrum of an aliquot gave evidence that ring closure had not yet occurred. The mixture was then heated under reflux for 2 h and although mostly resinous material had formed, extensive purification of the residual mass by flash chromatography yielded a small amount (*ca.* 15% of the total) of adduct 204. Its pmr spectrum showed a doublet (J = 1.5 Hz)

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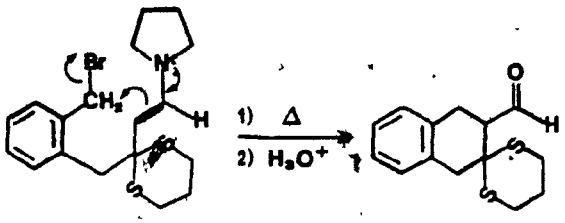
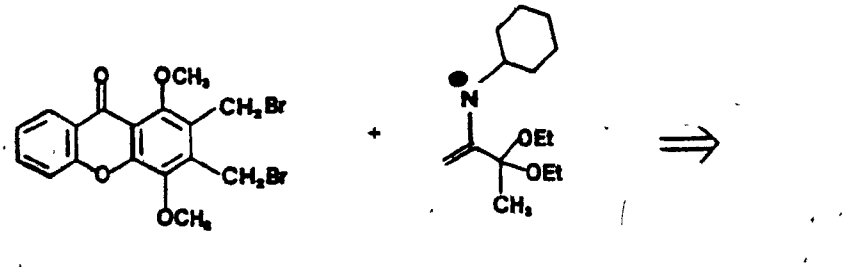



204

originating from the aldehyde function and its mass spectrum included a molecular ion of m/z 264 corresponding to the molecular weight of 204.

### 3.3.4 Conclusion

Although the latter strategy proved to be workable, extensive development work would be needed in order to improve the yield. As it stands, the scheme is not practical for our purposes. We were not encouraged to develop this approach not only because of the problems that beset the preparation of reagents 188, 196 and 198, but because a growing number of reports (*viz.* Refs. 315 and 316) clearly suggest that *early* functionalization of position 7 appears to determine the practical success of anthracycline syntheses. In fact, one of the main reasons for not using synthon 205 as previously developed in our laboratories[321], centers on the fact that in the xanthone series of analogs it would lead to intermediate 206

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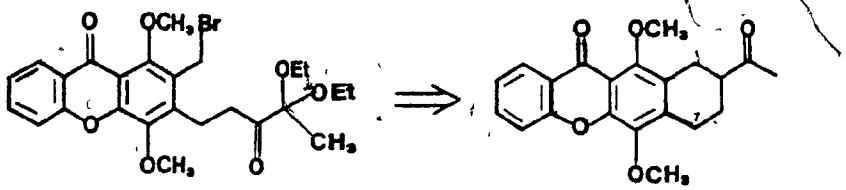



206

(only one isomer is shown)

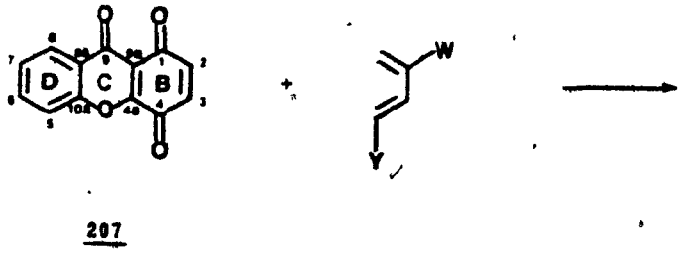
which calls for the *late* introduction of a functionality at position 7, a problem of considerable magnitude[315,316]. This value judgement is of course of a retrospective nature.

# CHAPTER 4

## A-RING FORMATION USING XANTHOQUINONE AND QUINIZARINQUINONE AS DIENOPHILES IN THE DIELS-ALDER CYCLOADDITION REACTION

### 4.1 STRATEGY

Of the strategies attempted so far for the construction of ring A, none were more appealing than the Diels-Alder cycloaddition involving xanthoquinone 207 (Equation 4). In principle, this strategy readily gives access to both linear regioisomers 208 and 209 with the likelihood that one isomer will predominate.

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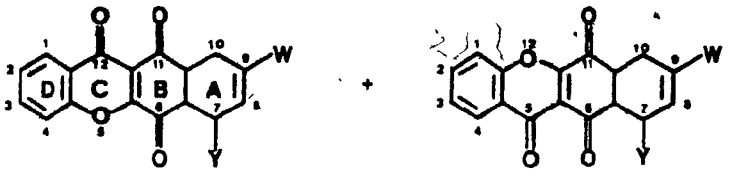
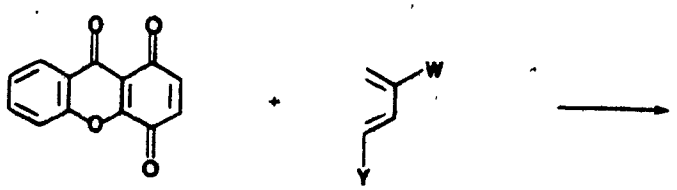



208 209 (4)

A possible drawback of this strategy is the possibility that isomers 210 and 211 might also be formed as a result of a competing diene addition to the internal double bond (Δ-4a,9a)[555]

(Equation 5).

In order to answer this question we initially sought theoretical reasons for chosing between these two different modes of cycloaddition.



207

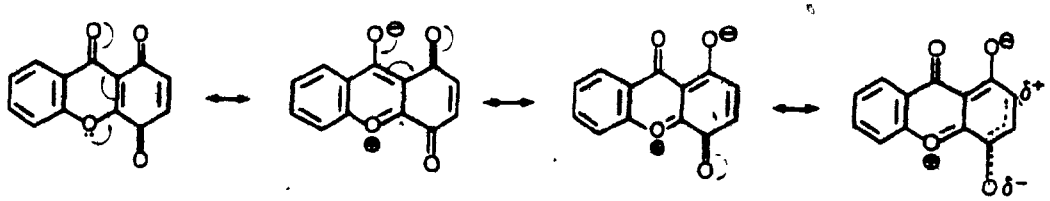
(5)

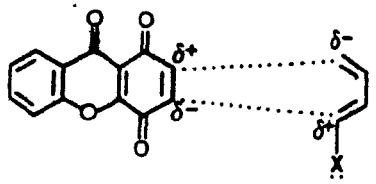
210 211

## 4.2 PREDICTION OF THE REACTIVITY OF XANTHOQUINONE USING RESONANCE AND FMO THEORIES

There is ample evidence[556-559] indicating that electron-donating substituents deactivate quinone substrates while electron-withdrawing substituents activate the double bond towards Diels-Alder cycloaddition reactions. For simple quinones, this effect can be easily rationalized using resonance theory arguments. If we apply the same simple rationale to xanthoquinone 207 one may predict that the external double bond (Δ2,3) should be the more reactive one because

the π-electrons are not as delocalized as those of the internal double bond. By the same token, the C-4 carbonyl should be more electron-withdrawing than the C-1 carbonyl and hence should act as the principal regiochemical director.






X = electron-donating group

Unfortunately, resonance theory does not make provisions for the influence of the acceptor substituent at C-9a on the external double bond. Nor does it adequately take into account the influence of donors at the substituted double bond, thus providing no explanation for the failure of the most nucleophilic terminus of a diene to react with the C-4a position.

On the other hand, treatment of quinones by FMO theory has the advantage that all the carbons of the quinone are taken into account simultaneously[560]. As the necessary calculations for xanthoquinone were not available, an extension

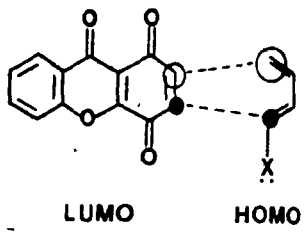
of FMO treatments of substituted quinones was used*.

The activating or deactivating effect towards cycloaddition caused by electron-withdrawing or electron-donating substituents respectively can be explained on the basis of the HOMO(diene)-LUMO(dienophile) interaction: Electron-withdrawing substituents lower the energy of the LUMO making the HOMO-LUMO energy gap smaller, while electron-donating substituents raise the energy of the LUMO resulting in a greater energy gap. Calculations on 2-substituted benzoquinones[560] indicate that with electron-donating groups an increase in the size of the coefficient of the LUMO occurs at the unsubstituted double bond with the largest increase occurring at the *para*-carbon; with electron-withdrawing groups the size of the coefficient of the LUMO increases at the substituted double bond with the largest coefficient on the β-carbon. As xanthoquinone combines both these effects simultaneously, the net effect will be determined by the relative electron-donating or electron-withdrawing ability of the functional groups. Recently, Burnier and Jorgensen[465] developed a system whereby the relative electron-donating or -withdrawing ability of functional groups is assigned a numerical value based on quantum calculations and other empirical data. This approach has thus far proven very

*Valenta[561], among others[562,563], found that the regioselectivity of methyl substituted benzoquinone in Diels-Alder reactions could not be understood on the basis of FMO theory. However, this "anomalous" behaviour is a specific case, which was recently dealt with and explained by Houk[564], and in no way negates the validity of FMO treatment of benzoquinone.

successful and encouraged us to extend it to our system. Not surprisingly, the heteroatom can be predicted to exert a greater effect than the carbonyl group and consequently it should influence both the reactivity and the regiochemistry of the reaction.

On the basis of these arguments, we can expect that the internal double bond will be deactivated (since it has a LUMO of higher energy) relative to the external double bond and that the coefficients of the LUMO will be larger at the external double bond where the largest coefficient appears at C-2. The result of this polarization is that the most nucleophilic terminus (the terminal with the largest HOMO coefficient) of the diene, will become attached to C-2 and thus will determine the regiochemistry.

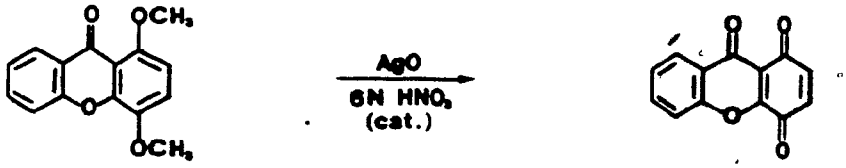



X = electron-donating group

While a number of simplifications have been made in the application of the FMO theory, they are all well within the limits set by similar analyses[465,560] that were substantiated by experimental evidence. In this respect, our prediction that the desired linear adduct should be formed with the regiochemistry shown, appeared meaningful and encouraging.

## 4.3 PREPARATION OF XANTHOQUINONE

The first step towards achieving our goal consisted of preparing xanthoquinone 207. It was prepared easily and in excellent yield (91%) by oxidative-demethylation[565] of 1,4-dimethoxyxanthone (76). The reaction was conducted in acetone at room temperature using a four-fold excess of *freshly prepared* silver(II) oxide*. After addition of the substrate, the mixture was briefly sonicated (to disperse




76 207

the oxidant) before the reaction was initiated by the addition of a catalytic amount of 6N nitric acid. A short reaction time of 6 min was optimum after which decomposition became an important side reaction. The crude product proved to be sufficiently pure and simple filtration through a pad of dry Celite afforded the xanthoquinone in a state of purity exceeding 98%. The use of cerium(IV) ammonium nitrate (CAN)[567] (an oxidizing agent much less expensive than AgO) was found to be inadequate because it gave a much lower yield of product

* Commercial AgO can be used but it is important to activate it by sonication for 1 h before using it[566].

and in an inferior state of purity.

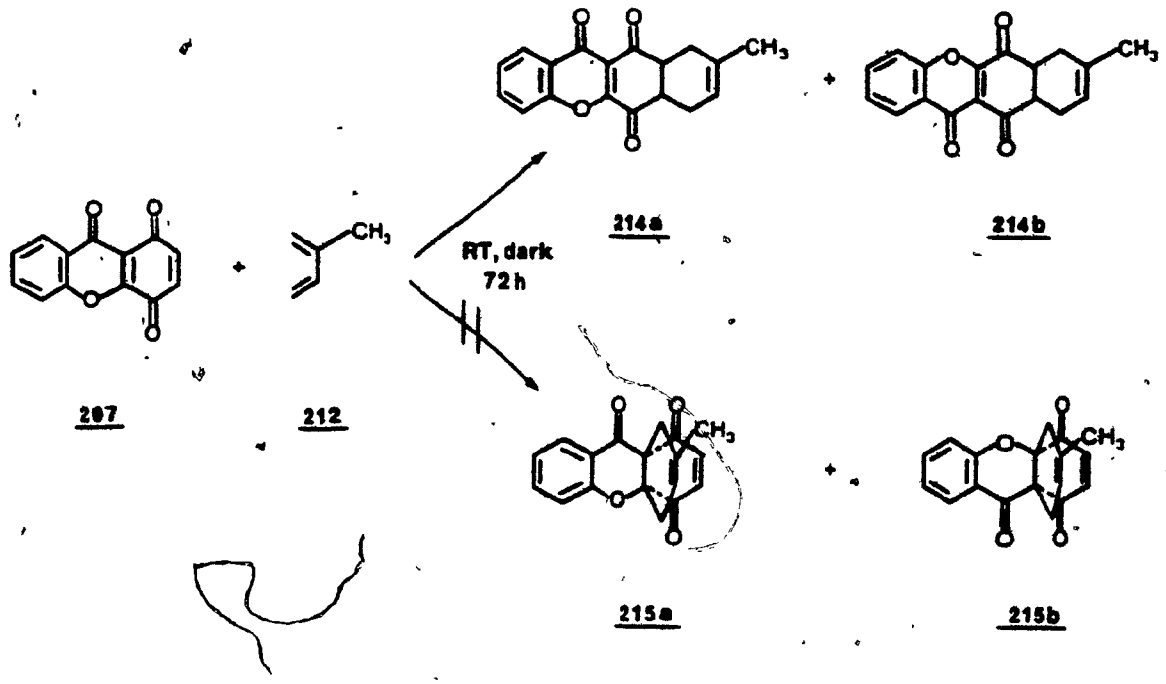
The 200 MHz pmr spectrum of the desired quinone 207 showed a rough AB quartet for the protons on ring A with chemical shifts centered at 7.08 and 6.90 ppm with a coupling constant J = 10 Hz. The infrared spectrum showed a single strong carbonyl stretch at 1693 $cm^{-1}$. The mass spectrum included the molecular ion of m/z 226 (base peak) as well as a prominent $[M+2]^{+\cdot}$ peak due to the $MH_2^{+\cdot}$ ion originating from the reduction of the xanthoquinone by residual moisture in the inlet system and in the ionization chamber of the mass spectrometer[568,569].

## 4.4 CYCLOADDITION REACTIONS BETWEEN XANTHOQUINONE AND 2-SUBSTITUTED- AND 2,4-DISUBSTITUTED-1,3-DIENES

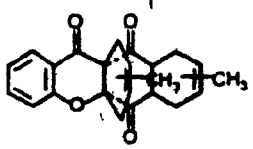
### 4.4.1 Reaction Between Xanthoquinone and 2-Methyl-1,3-butadiene

An easy way to verify the prediction that the linear adduct should be formed in preference to the internal adduct involves testing the behaviour of the quinone towards commercially available 2-methyl-1,3-butadiene (isoprene) (212). While the latter is not representative of dienes in general and affords an adduct of little value for our specific purposes, it can nevertheless be very useful as it provided an example of a diene that adds to the internal double bond of the diquinone quinizarinquinone (213)[570].

The xanthoquinone substrate proved to be a reasonably good dienophile as reaction with a small excess* of isoprene at room temperature in the dark afforded a quantitative yield of a reddish-brown compound identified by the usual spectroscopic methods as the linear adduct 214. The pmr spectrum clearly showed the absence of the AB-quartet originating from the vinyl quinone protons of 207, signals which would obviously be present in adduct 215. A broad singlet at 5.4 ppm was the only vinylic resonance observed. The fact




*A large excess of isoprene was avoided in order to prevent the formation of diadduct i. However, if such an adduct is formed, the terminal double bond must react first as the internal Diels-Alder adduct will most likely not undergo further addition because its bent structure will cause severe steric hindrance to the approach of a second diene molecule[571].



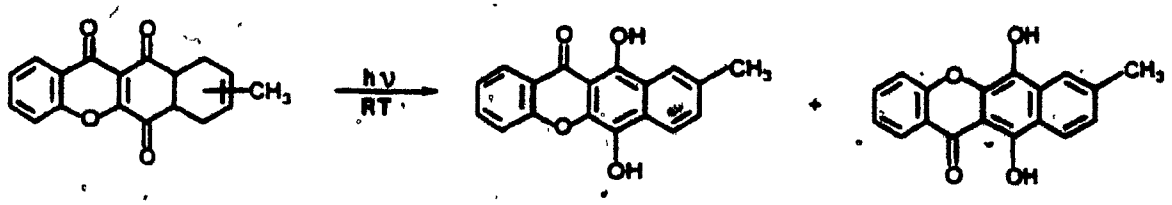
that the orbitals of isoprene are only slightly polarized[466,572] means that the primary interactions of the cycloaddition process can hardly favor the formation of a single regioisomer[564,573]. Nevertheless secondary orbital interactions[466,564,573-577] may be expected to have some influence on the regioselectivity of such cylcoadditions. However, it was not possible to determine unequivocally* by pmr spectroscopy whether regioisomers were formed in equal amounts or if one regioisomer was indeed formed preferentially, (albeit not necessarily exclusively). The results of proton decoupling experiments were also ambiguous. The infrared spectrum showed the olefin stretch at 1678 $cm^{-1}$ but it overlapped with the carbonyl stretching band. The mass spectrum showed the molecular ion of m/z 294 (base peak) corresponding to the expected molecular weight of 214, as well as a distinctive $[M^{+} - CH_3]$ fragment. No retro-Diels-Alder process was observed, thus confirming that the linear adduct was formed[581]. Adduct 214 was very sensitive to light and underwent aromatization to form the highly insoluble compound 216 whose pmr spectrum showed the methyl group had shifted downfield to 2.2 ppm.

As an alternative process, adduct 214 could be obtained by oxidizing 1,4-dihydroxyxanthone (75)† with silver(I) oxide and trapping *in situ* the generated xanthoquinone with

---

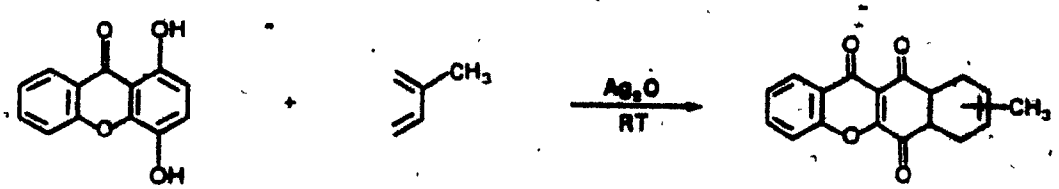
*The interpretation of the spectrum was made difficult because long range coupling resulting in a broadening of the methyl signal has been observed[578-580] for similar molecules but where regioisomers are not possible.

†Prepared in quantitative yield by the demethylation of 1,4-dimethoxyxanthone with $BBr_3$[582].



214 216a 216b

isoprene. This technique[583] specially developed for quinones too unstable to isolate, gave results identical in every respect to those already obtained as described above. Even though $Ag^+$ can behave as a Lewis acid catalyst[584,585], it exerted no catalytic effect under our conditions. This method



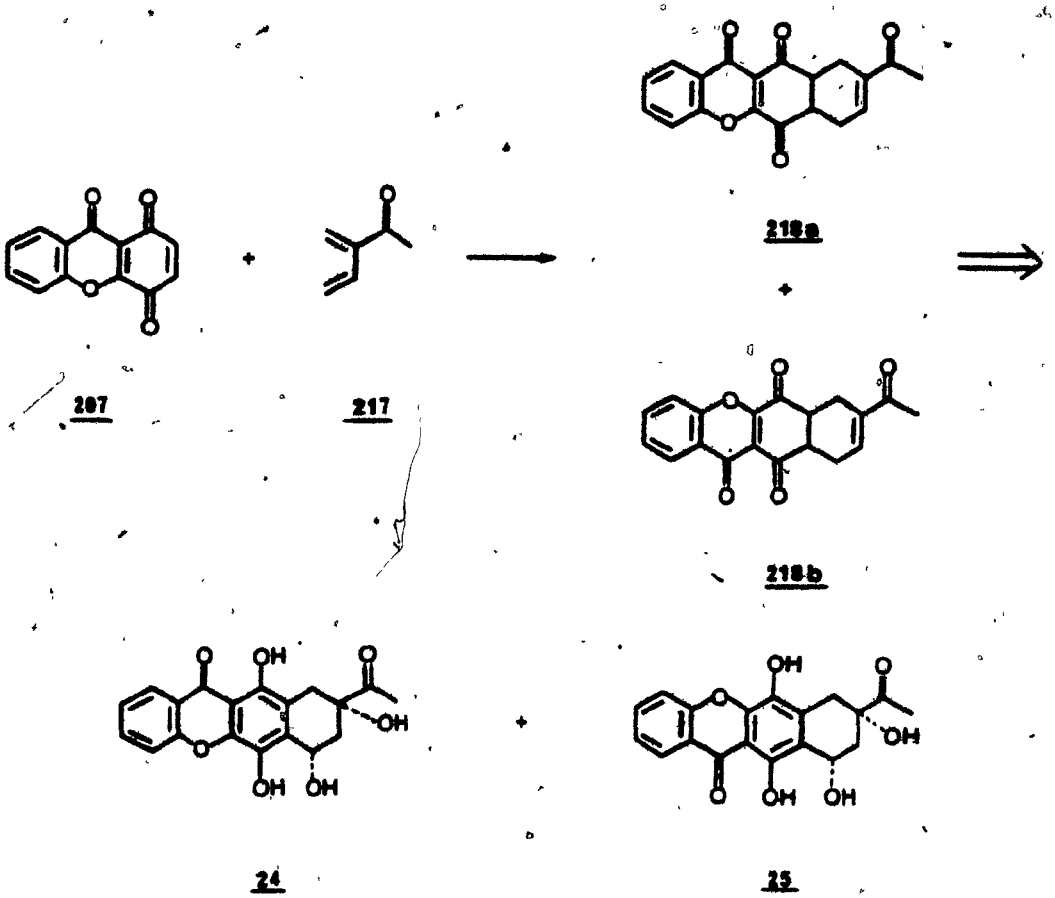
75 212 214

of *in situ* trapping appeared convenient primarily from a technical point of view but it eventually became an important factor in a successful cycloaddition reaction involving a quinone substrate which was reported[439] as unutilizable in a Diels-Alder reaction.

Encouraged by these results on the reactivity of xanthoquinone, we then directed our efforts towards the use of dienes potentially useful in the attainment of our synthetic goal.

### 4.4.2 Reaction Between Xanthoquinone and 2-(2-Methyl-1,3 dithian-2-yl)-1,3-butadiene (222)

Initially, we envisaged a cycloaddition reaction between xanthoquinone and the diene 2-acetyl-1,3-butadiene (217) with the hope of generating adduct 218 which could then

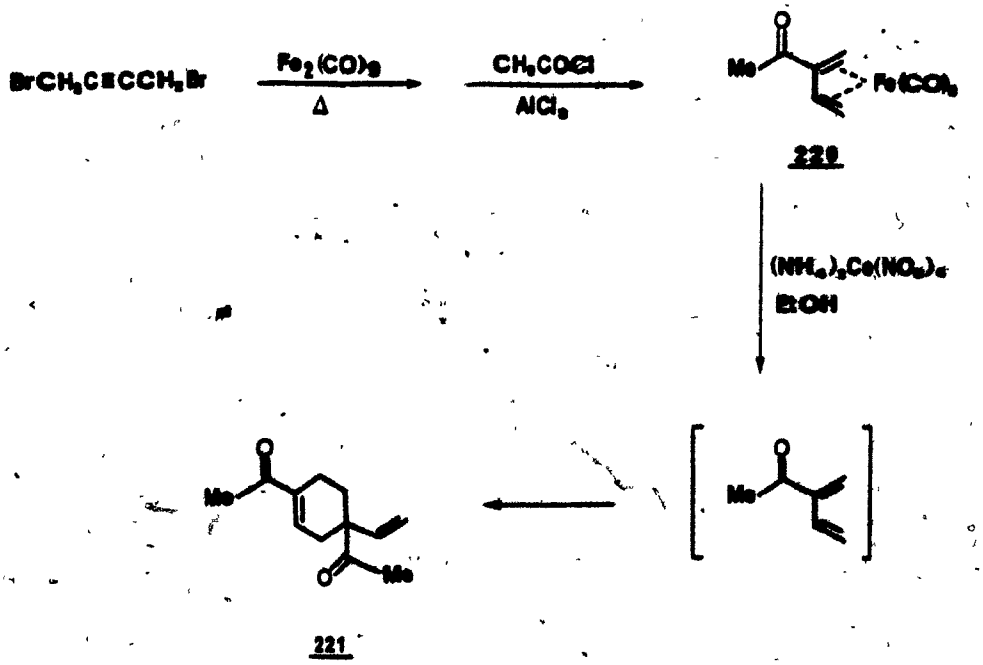



207 217 218a + 218b

24 25

be elaborated into the desired aglycones 24 and 25. Although the synthesis of diene 217 can in principle be achieved in a straightforward manner through the addition of vinylmagnesium

bromide to biacetyl (219)* followed by dehydration of the adduct, such an approach is unproductive because of the propensity of 2-substituted dienes carrying electron-withdrawing groups to polymerize[588,589]. Recently, Brion *et al.*[589,590] found that diene 217 could be prepared as a stable organometallic complex 220, but unfortunately, attempts at decomplexation (with CAN in ethanol) and *in situ* trapping of the generated diene with various dienophiles resulted mainly in the formation of dimer 221 through self-condensation.

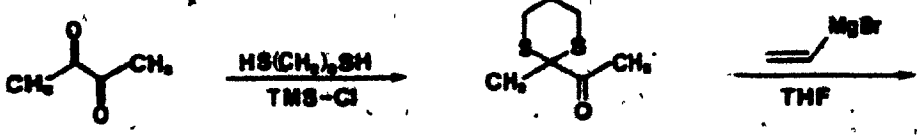



Consequently, we chose to prepare the protected diene 222 instead.

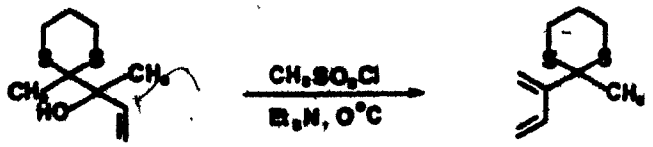
Addition of 1,3-propanedithiol to biacetyl[388] gave an almost quantitative yield of dithiane 223. Reaction with

*Monoaddition of Grignard reagents to biacetyl is known[586,587].

excess vinylmagnesium bromide gave, after work-up with ethylenediaminetetraacetic acid tetrasodium salt[591,592], alcohol 224 in *ca.* 80% yield. Even under the very mild conditions provided by 5Å molecular sieves[593], it was not possible to effect direct dehydration of 224, but this was readily accomplished by reacting it with mesyl chloride and excess triethylamine[594]. Low pressure fractional distillation led




223

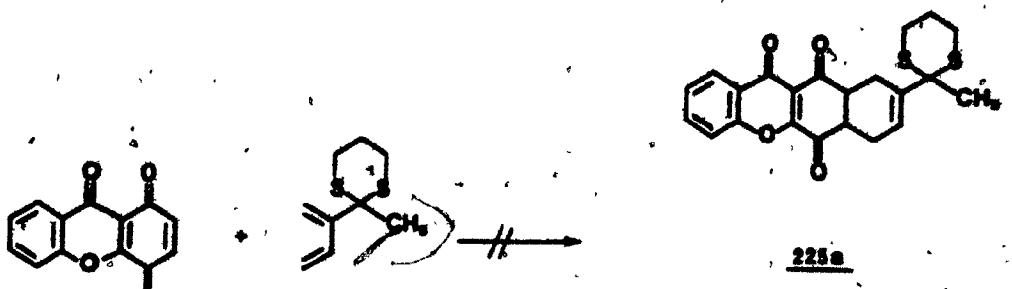



224 222

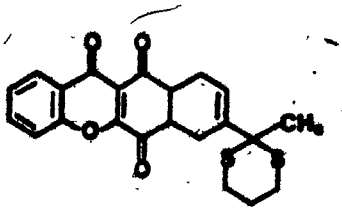
to the isolation of diene 222, a yellowish viscous oil, in *ca.* 60% yield. Its pmr spectrum exhibited a complex splitting in the region between 5-6 ppm where the dienic protons are expected to resonate. The infrared spectrum confirmed the presence of a diene which gave rise to an intense band at 1610 $cm^{-1}$ overlapping with another band at 1650 $cm^{-1}$.

The reaction between diene 222 and xanthoquinone did

not yield any adduct 225 even after long reaction times, starting material being recovered. This result was puzzling until we noted that 222 also failed to react with 1,4-benzoquinone and 1,4-naphthoquinone as recently reported[595]. There is, however, no obvious reason for the apparent lack of



207 222 225a



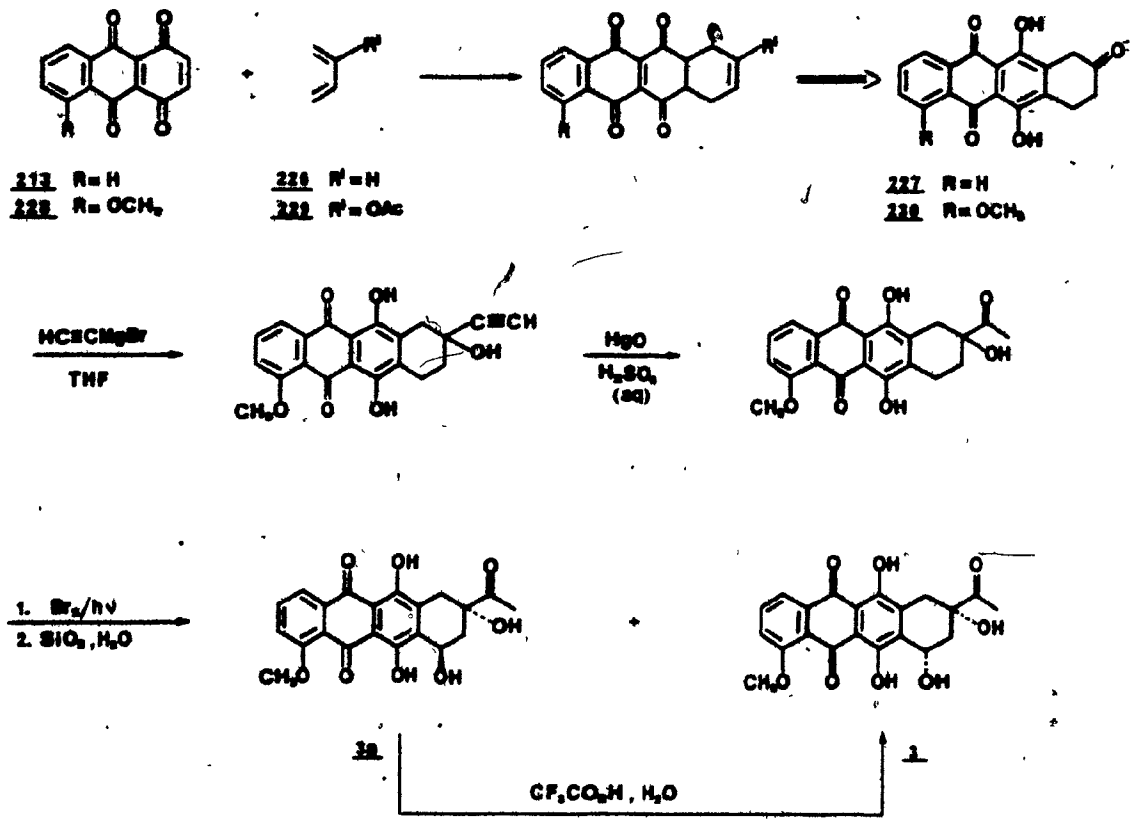
225b

reactivity of diene 222. This disappointing result led us to consider the use of some simple dienes which have been used successfully in the synthesis of anthracyclines and depending on the results, some other suitable diene would then be tailored to our needs.

### 4.4.3 Reaction Between Xanthoquinone and *More* Simple 2-Substituted Dienes

In an extension of Inhoffen's work[555], Lee *et al.*[581] used the Diels-Alder cycloaddition reaction between quinizarin-quinone (213) and 1,3-butadiene (226) to generate compound 227 which possesses the basic skeleton of the anthracyclines (Scheme 4.1). Using the same approach but slightly different substrates (228, R=$OCH_3$; 229, R'=OAc) Kende *et al.*[596] arrived

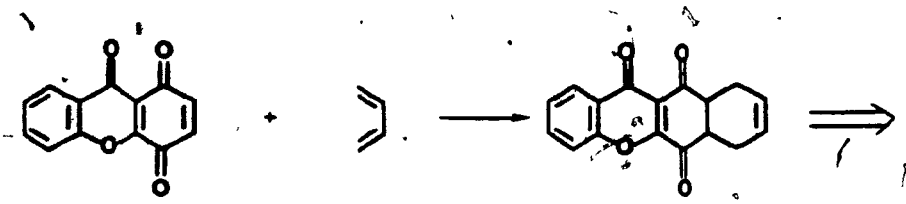
Scheme 4.1



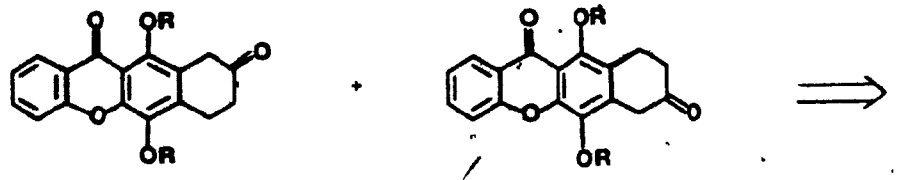
at an analogous ketonic intermediate which was transformed into daunomycinone (3) in 4 steps. The introduction* of the side-chain on ketone 230 involves a two-carbon homologation through reaction with ethynylmagnesium bromide followed by treatment of the resultant ethynyl carbinol with yellow mercuric oxide in dilute sulfuric acid. The C-7 position was then functionalized selectively *via* free-radical bromination to give a very labile compound which after solvolysis on moist silica gel afforded daunomycinone (3) and its 7-epimer (3a). The latter could be subsequently epimerized to the relevant isomer by treatment with trifluoroacetic acid followed by hydrolysis.

On that basis, we felt that if the use of simple dienes could lead to an analogous ketone such as 231, it might become possible to apply Kende's methodology and achieve the synthesis of xanthodaunomycinone. Accordingly, the reaction between xanthoquinone and butadiene 226 was attempted. The results were disappointing as the reaction was sluggish at room temperature and unproductive as regards adduct formation. At a higher temperature (110°C), reaction with butadiene sulfone 232 (a convenient source of butadiene)[577,598] in a sealed bomb, gave products of disproportionation[581,599,600] (233 and 75) as well as the fully aromatized[601] compound 234 as evidenced by the pmr spectrum of the mixture. There was no indication that these conditions led to any of the desired

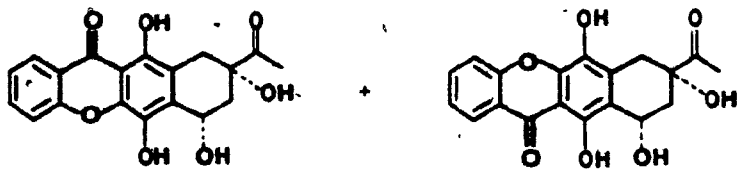
*Many different ways to manipulate the C-9 position are now available mainly due to the efforts made to synthesize tetralin 30 (Chapter 1).



207 226

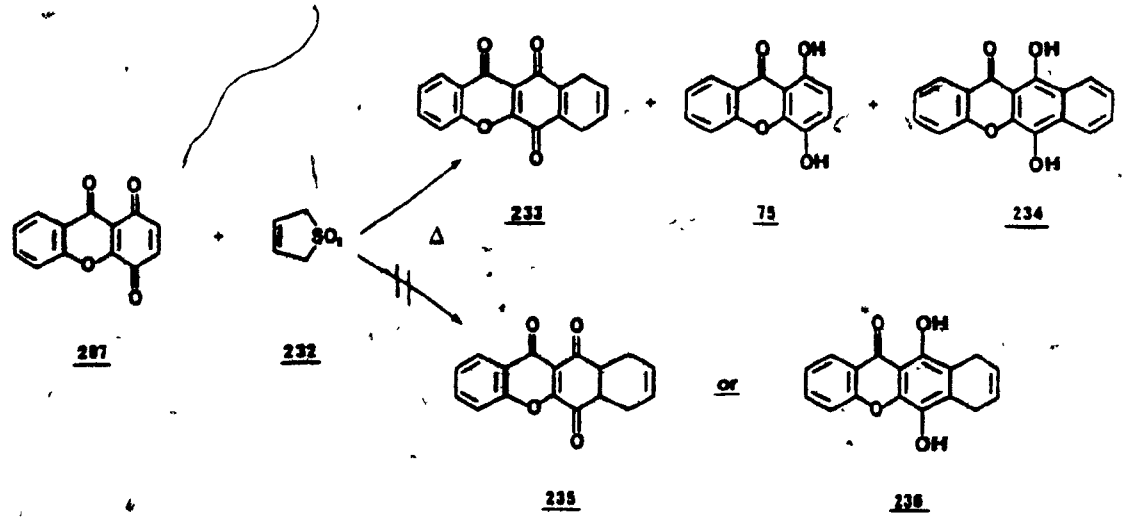


231a 231b



24 25

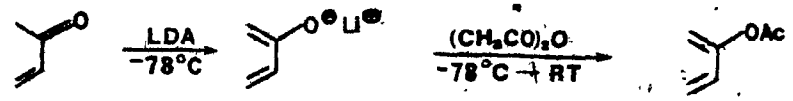
adduct 235 (or 236 as the tautomer is sometimes isolated instead).




207 232 233 75 234 235 236

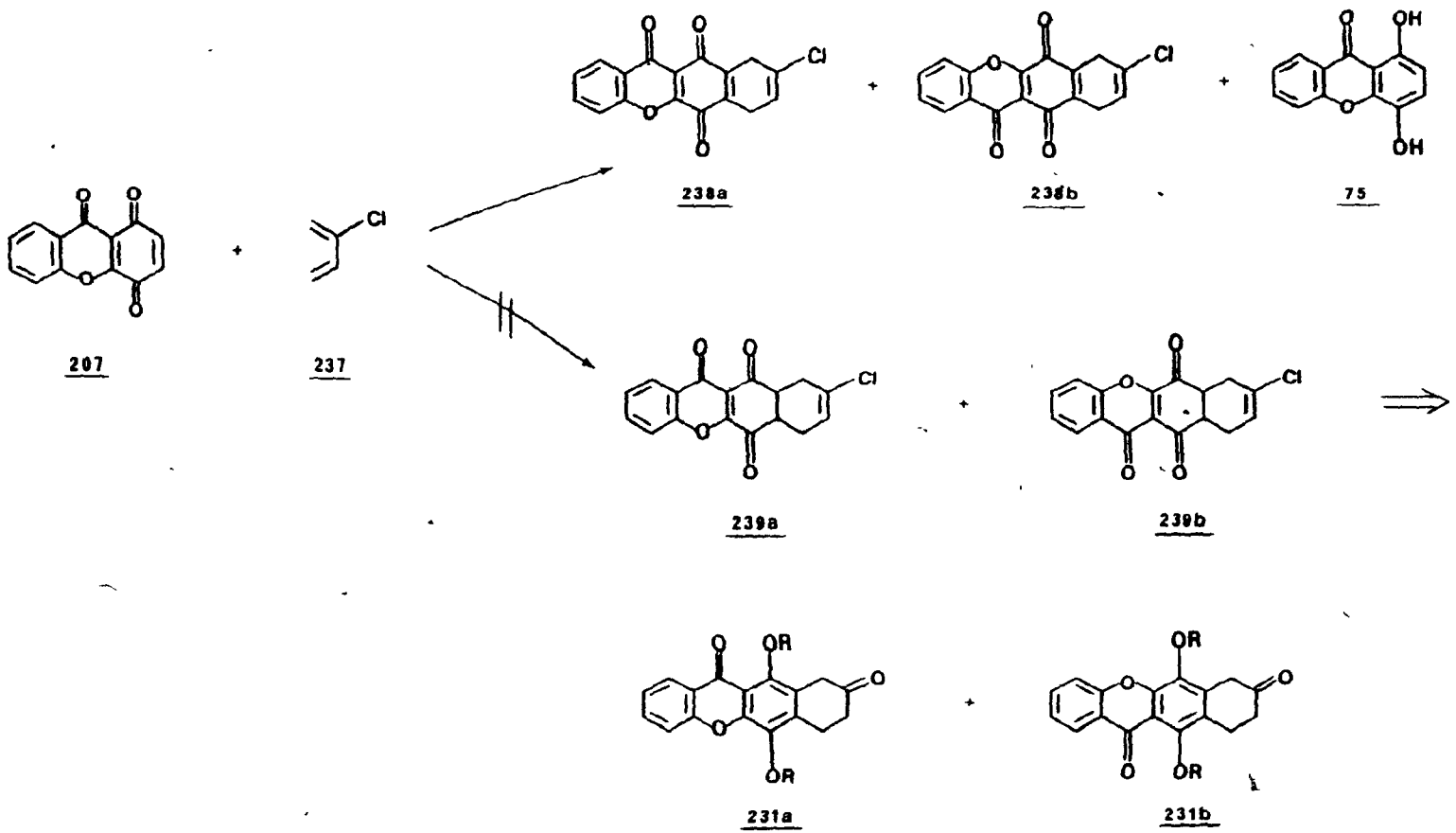
The use of 2-chloro-1,3-butadiene (chloroprene) (237), a potential precursor of intermediate 231, was also unsuccessful, no reaction being observed at room temperature in spite of its higher reactivity[564,602] relative to 226. Heating in a sealed tube again led to disproportionation products 238 and 75. The presence of 239 was detectable only by mass spectrometry.

We also attempted the cycloaddition of 2-acetoxy-1,3-butadiene (229) with the xanthoquinone. Our efforts were initially hampered by difficulties in the preparation of this diene starting from methyl vinyl ketone, isopropenyl acetate and an acid catalyst according to a literature procedure[603]. Eventually, excellent results were obtained when the enolate of methyl vinyl ketone (obtained by treatment with LDA at -78°C) was acetylated with acetic anhydride on a small scale.




229

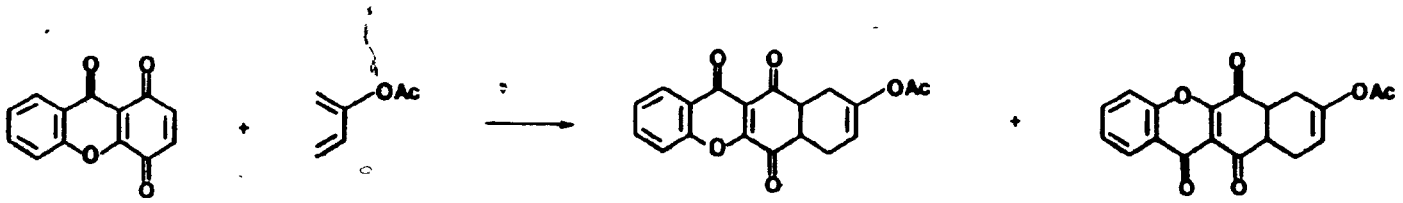
The cycloaddition reaction was attempted under a variety of conditions including those described by Kende[596]. In spite of these efforts, only mass spectral evidence was produced that adduct 240 (or the tautomer 241) may have formed as part of a mixture consisting of at least several compounds (according to


207
237
238a
238b
75
239a
239b
231a
231b

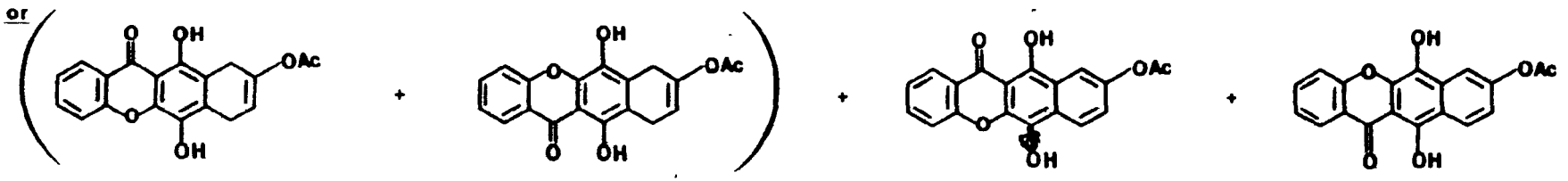
tlc) including the fully aromatized product 242 as detected by mass spectroscopy.

These results did little to encourage further work with 2-substituted dienes as a general strategy. However, considerable success has been reported[604-606] using 2-trimethylsilyloxy-1,3-butadiene (243) as a reactant in certain cycloaddition reactions and the fact that silyloxy dienes are at least as reactive as alkoxydienes[604,607] was encouraging to us.

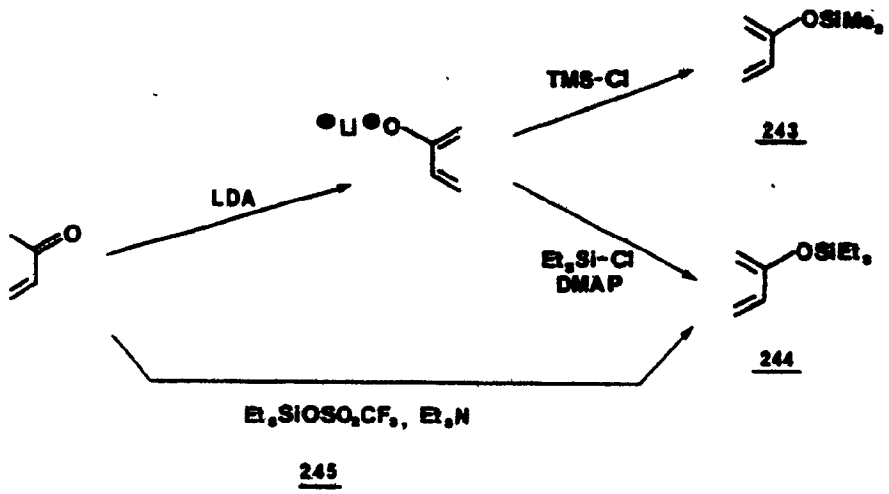
Diene (243) was easily prepared[605,608] by treating methyl vinyl ketone with LDA and trapping the enolate with chlorotrimethylsilane. Fractional distillation of the product readily afforded the desired pure diene as a light colorless oil. Its attempted reaction with xanthoquinone did not yield any adduct, a result which may be attributed to the susceptibility of the diene to hydrolysis in spite of all the necessary precautions that were taken (dry solvents and inert, dry atmosphere) in order to prevent such decomposition. In an effort to increase the hydrolytic stability of the silyloxy function we prepared the triethylsilyloxy analog 244. Trapping of the enolate of methyl vinyl ketone with triethylchlorosilane was a slow, inefficient process but which was accelerated by a catalytic amount of DMAP. However, the best results (yield essentially quantitative) were obtained by using triethylsilyl trifluoromethanesulfonate (245) as the silylating agent, itself prepared in 80% yield by reacting triethylchlorosilane and trifluoromethanesulfonic acid[609].




207 228 240a 240b

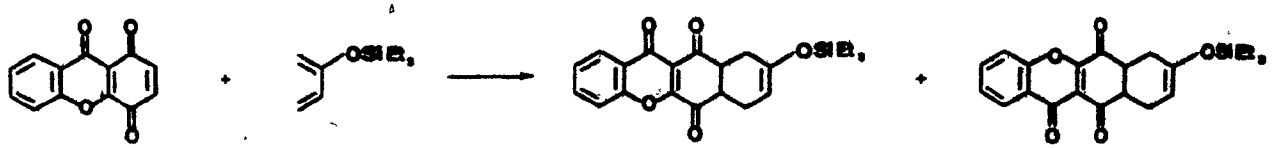



241a 241b 242a 242b




243 244 245

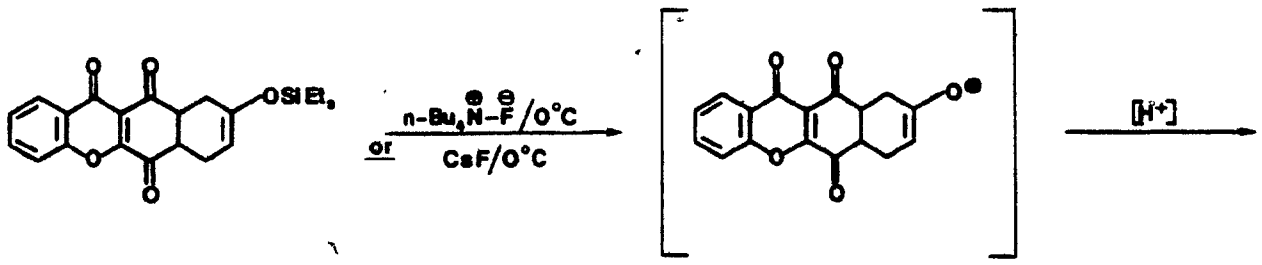
After four days at room temperature, the xanthoquinone reacted with diene 244 to give adduct 246 in about 50% yield which was accompanied by unreacted starting material. Purification by flash chromatography was only partially successful as the adduct was sensitive to the technique of



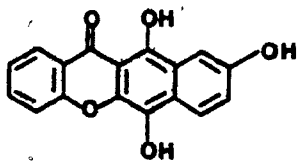
207 244 246a 246b

separation. While the pmr spectrum of the product showed unequivocally that the linear isomer was formed, it was not sufficiently informative to decide whether regioisomers were formed and in what ratio. Its mass spectrum showed a molecular ion of m/z 410 corresponding to that of adduct 246 and included a prominent $[M^{+} - C_2H_5]$ peak. Desilylation of 246 with tetra-

butylammonium fluoride or cesium fluoride in THF resulted in the formation of a highly insoluble compound which was identified as the fully aromatized compound 247. Presumably, enolate 248 is an intermediate in this transformation which is probably encouraged by fluoride ion (which can act as a base[610]) in a catalytic sequence involving tautomerization and aromatization.




246 248




247

No other attempts to desilylate 246 by different methods were made because our attention shifted to the use of

(E)-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (249)* (which had become commercially available), a reactant offering the possibility of forming an adduct carrying a functionality at position 7. Because diene 249 is more activated than analog 244, it was expected to provide better yields of cycloaddition product.

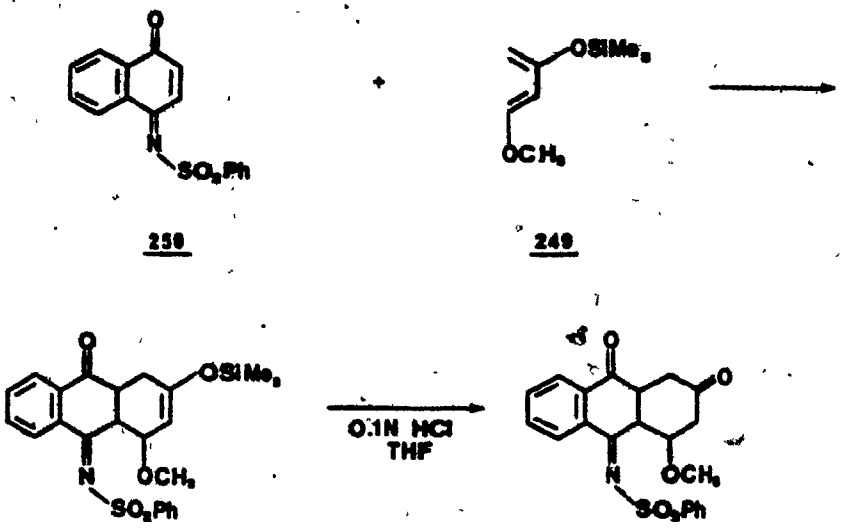
### 4.4.4 Cycloaddition with Danishefsky's Diene 249

The potential of diene 249 for the purpose of introducing functional groups at the 7- and 9-positions simultaneously was recognized by Kelly *et al.*[570] who in their study on the synthesis of adriamycin, reacted it with quinizarinquinone (213). Unfortunately, as only the useless internal adduct was obtained, no further elaboration was carried out thereby providing no information on the stability of the adduct to chemical transformations. (This interesting phenomenon regarding reaction of the internal double bond with electron-rich dienes has been rationalized using FMO theory[560,571])†. Later, it was reported[612] that reaction of 249 with 1,4-naphthoquinone monobenzenesulfonimide (250) followed by hydrolysis gave excellent yields of ketone 251.

---

*Commonly referred to as Danishefsky's diene[611].

†According to calculations[564], the LUMO of quinizarinquinone is heavily concentrated on the internal double bond. Coupled with the fact that the internal bond is more positive than the external one, electron-rich dienes will be directed to the internal bond. For less electron-rich dienes the difference between the interaction, of the diene with the external double bond, and the diene with the internal double bond is small, so that little selectivity can be expected.

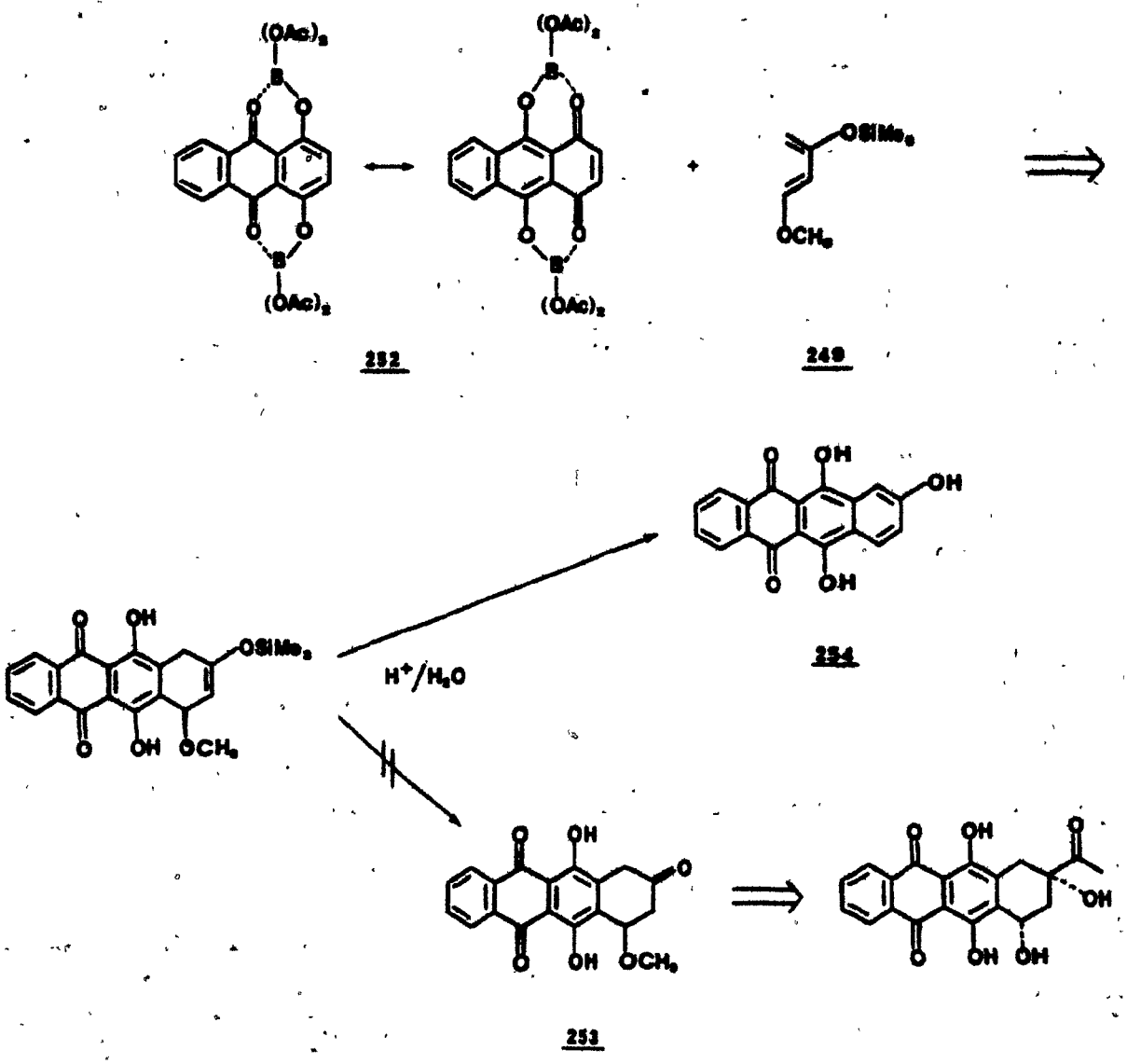



250 249

251

We were nonetheless alerted to the labile nature of adducts formed with 249 by a number of reports[600,613] in which β-elimination of methanol with subsequent tautomerization leading to aromatization was revealed as the predominating reaction. This was the case with quinizarin boroacetate 252[613] which upon hydrolysis did not give the expected ketone 253 but only the fully aromatized compound 254. Because of conflicting results when diene 249 was used, no reliable prediction regarding the outcome of its reaction with xanthoquinone could be made and accordingly, the appropriate experiments had to be carried out.

The reaction between xanthoquinone and a large excess of diene 249 was conducted at room temperature in the absence of light. Depending on the concentration, the reaction was sometimes complete within 18 h but because the solutions were



usually very dilute, the reaction was routinely stirred for at least 72 h and no attempt to optimize the reaction time was made. Removal of the solvent left an amorphous material which after trituration with pentane gave a pale orange crystalline compound in *ca.* 80% yield. This compound was identified as adduct 255 on the basis of its pmr spectrum

which showed a one-proton doublet at 5.20 ppm originating from the vinyl proton on C-8, coupled to H-7 itself appearing as a quartet at 4.26 ppm. A complex three-proton multiplet at 3.43 ppm could be assigned to the bridgehead H's at the C-6a and C-10a positions and to one of the H's on C-10*. The other H on C-10 appeared as a complex multiplet and was centered at 2.36 ppm. The D-ring H's exhibited the splitting pattern characteristic of the parent xanthone while the methoxy and trimethylsilyloxy singlets were positioned as expected. Although isomer 255a might be expected to be the predominating regioisomer, there was insufficient evidence to conclude that this was the case. The infrared spectrum showed a carbonyl band at 1710 and a double bond stretching mode at 1655 $cm^{-1}$. In the mass spectrum of the compound no molecular ion was observed but there was a prominent $[M^{+} - CH_3OH]$ peak providing good evidence that adduct 255 was indeed formed.

This adduct was extremely labile, suffering decomposition when heated slightly and requiring special precautions in order to avoid exposure to moisture as otherwise a highly insoluble tarry material, identified (by its pmr and mass spectra) as the fully aromatized compound 256, was formed. The pmr spectrum of the latter showed only signals in the aromatic region and its mass spectrum included a molecular ion of m/z 294 as expected for 256. In spite of our

*These assignements were made by analogy with the assignments made for the triethylsilyloxy adduct for which high field (400 MHz) spectra were measured.

apprehensions, we attempted the controlled hydrolysis of 255 to the corresponding methoxy ketone 257 (or tautomer 258). Not surprisingly, however, treatment with mildly acidic (THF - 0.1N aq HCl) or more strongly acidic (THF - 2N aq HCl) solutions*, led consistently to the fully aromatic compound 256.

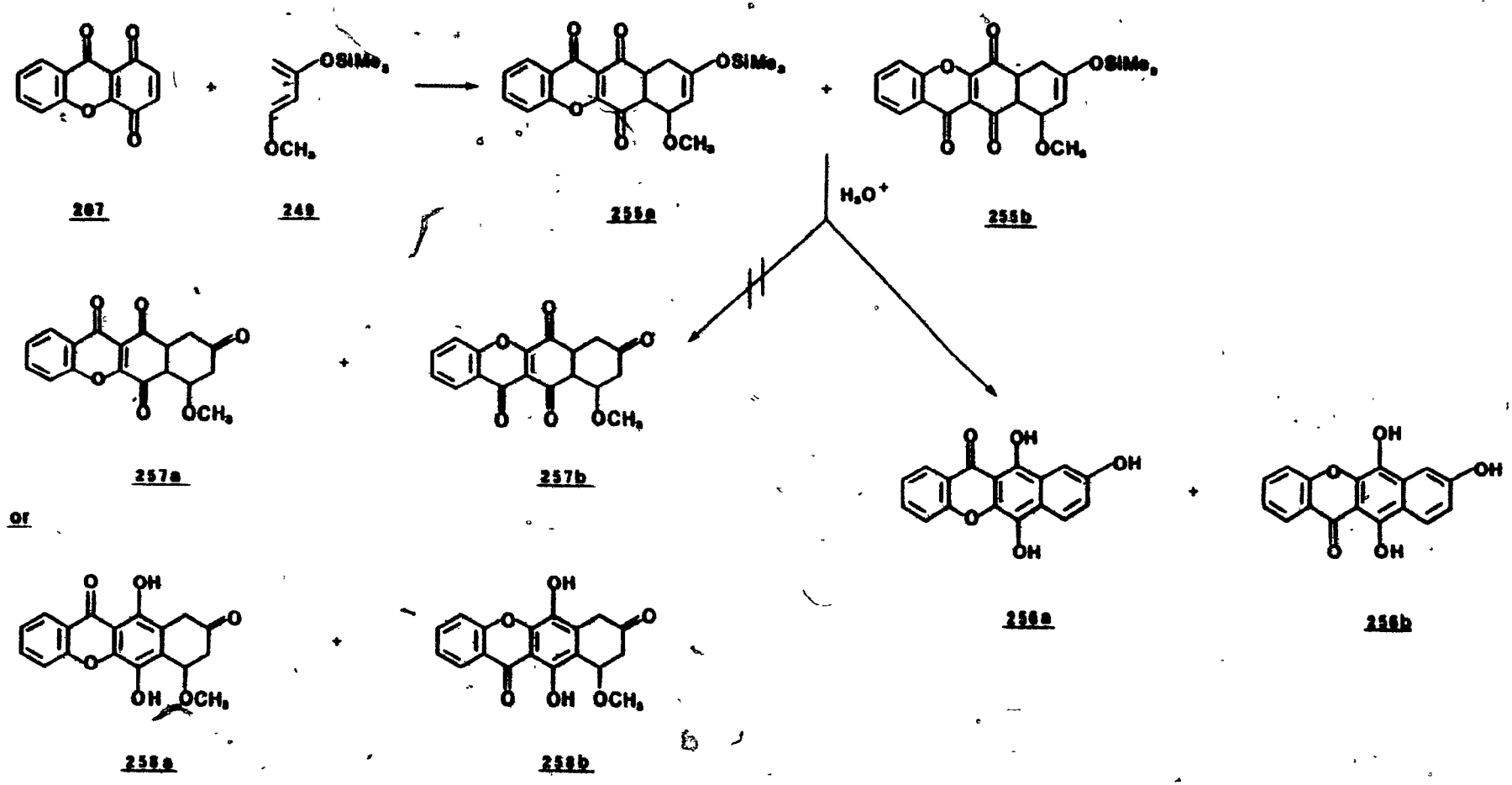
We attributed this marked lability of the adduct to the pronounced sensitivity of the silyl enol functionality. It was reasoned that if the stability of the enol ether could be increased, the adduct might then become usable. Since triethylsilyl enol ethers are substantially more stable towards hydrolysis,[4] the modified Danishefsky diene 1-methoxy-3-(triethylsilyloxy)-1,3-butadiene (259) was prepared.

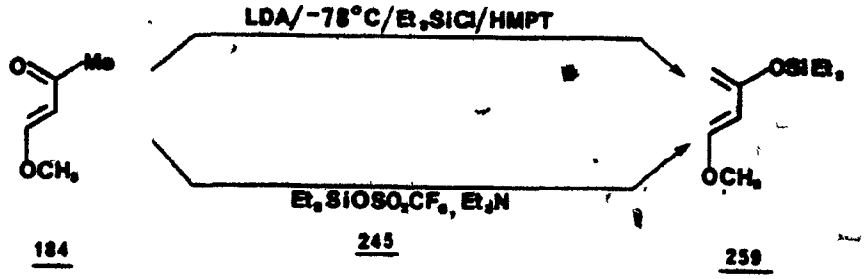
### 4.4.5 Cycloaddition Reactions with the *Modified* Danishefsky's Diene 259

#### Preparation of Diene 259

Diene 259 was easily prepared in *ca.* 73% yield by trapping the lithium enolate of 4-methoxy-3-buten-2-one (184) at low temperature with chlorotriethylsilane in the presence of HMPT[614]. However, an almost quantitative yield was obtained when the enone was reacted with triethylsilyl trifluoromethanesulfonate 245. The diene so obtained was a

*The more strongly acidic conditions were used because Danishefsky[600] observed that the hydrolysis of the silyl enol ether and the elimination of methanol became independent processes under more strongly acidic conditions. Clearly, it may not be valid to extrapolate this observation to include our substrate where the methoxy group is likely to (and probably does) become benzylic (as the B-ring tautomerizes) increasing the likelihood of elimination.


OSiMe3
OCH3
H3O+
OH
O




184 245 259

colorless, distillable oil and exhibited a simple pmr spectrum including a one-proton doublet (J = 12 Hz) centered at 6.9 ppm for the H-1 vinyl proton coupled to the H-2 vinyl one-proton doublet centered at 5.36 ppm. The broad two-proton singlet at 4.0 ppm was assigned to the C-4 protons. A sharp methoxy peak and a complex triethylsilyloxy signal appeared as expected. The infrared spectrum showed conjugate double bond bands at 1653 and 1586 $cm^{-1}$. The mass spectrum included a molecular ion corresponding to the expected mass of the diene but the base peak corresponded to the fragment $[M^{+} - C_2H_5]$.

4.4.5.1 Reaction with xanthoquinone

Reaction between the xanthoquinone and excess diene 259 (conducted under reaction conditions similar to those for diene 249) gave after evaporation and trituration with pentane an excellent yield (90%) of a pure light-orange crystalline material having a sharp melting point. It was stable enough to allow manipulation without the use of special precautions. Structure 260 for this product was confirmed

by routine pmr spectroscopy but high field (400 MHz) pmr measurements and decoupling experiments were performed in order to identify the protons.

Unfortunately, despite the use of high field nmr we were unable to determine (from either the $^{1}$H.m.r. or $^{13}$C.m.r. spectra shown in Figures 15 and 16 respectively) whether one or both regioisomers of 260 were formed. An attempt in which 260 was titrated with the shift reagent Eu(thd)$_3$ (*tris*[2,2,6,6-tetramethyl-3,5-heptanedionato] europium(III)), with the hope of measuring induced downfield chemical shifts in the resonance frequency of certain protons (*e.g.* H-6a, H-7), also failed as it gave ambiguous results. While the C-C connectivity experiment was considered as probably offering a good possibility of providing the answer the technical problems (large sample size and high concentration) associated with conducting such an experiment at this time did not permit it.

In spite of the more attractive properties of 260, we were no more successful with its controlled hydrolysis than with the trimethylsilyl analog 255. Under the same acidic conditions it gave, like analog 255, only the fully aromatic compound 256. Similarly, treatment with fluoride salts (KF, CsF, n-Bu$_4$NF) under a variety of mild aqueous buffered conditions gave only 256. Despite repeated attempts where the temperature, reaction time and acid concentration were varied, we were unable to obtain ketone 257 (or its

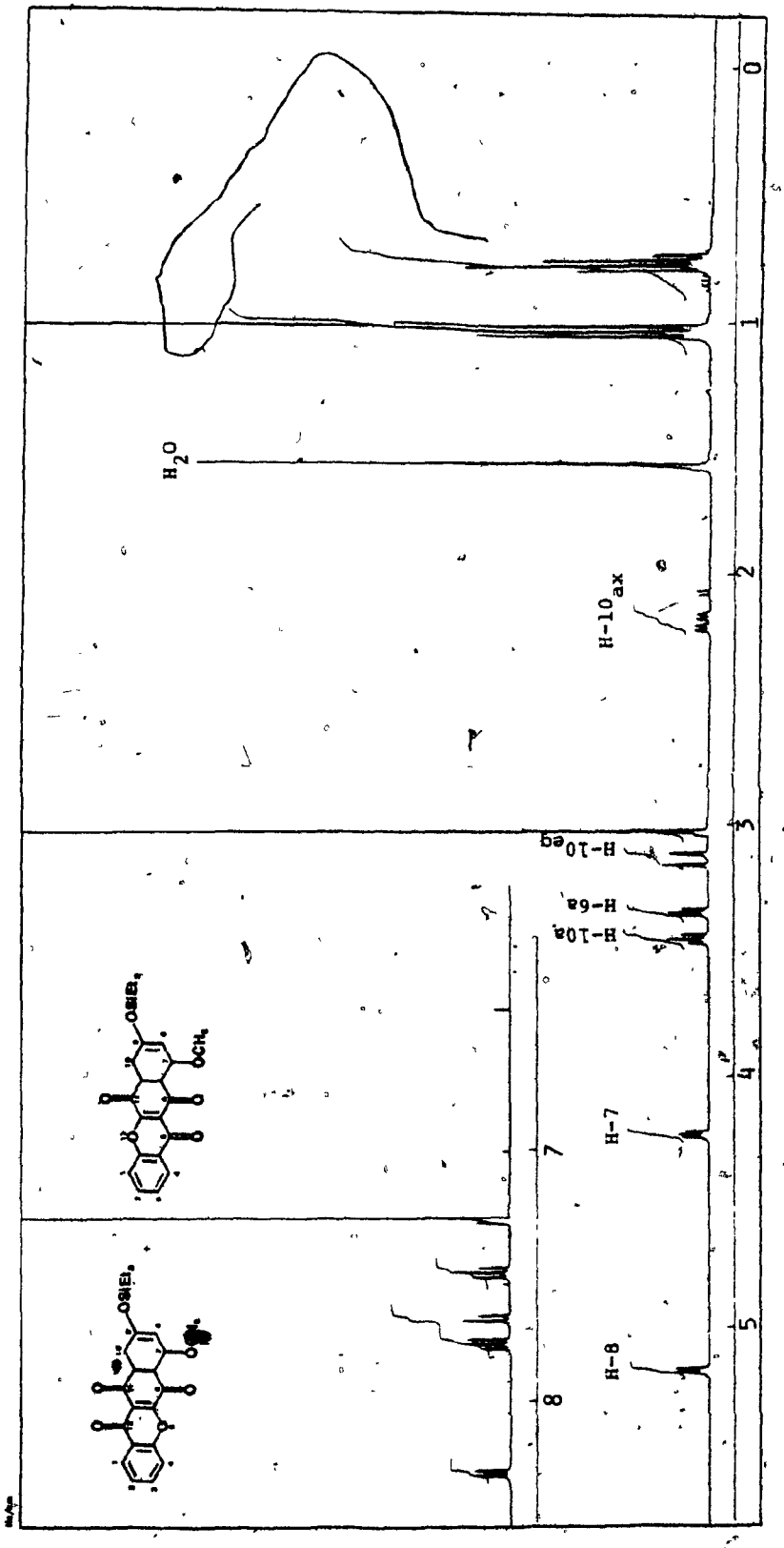



Figure 15: The 400 MHz $^1$H.m.r. Spectrum of Diels-Alder Adduct 260.

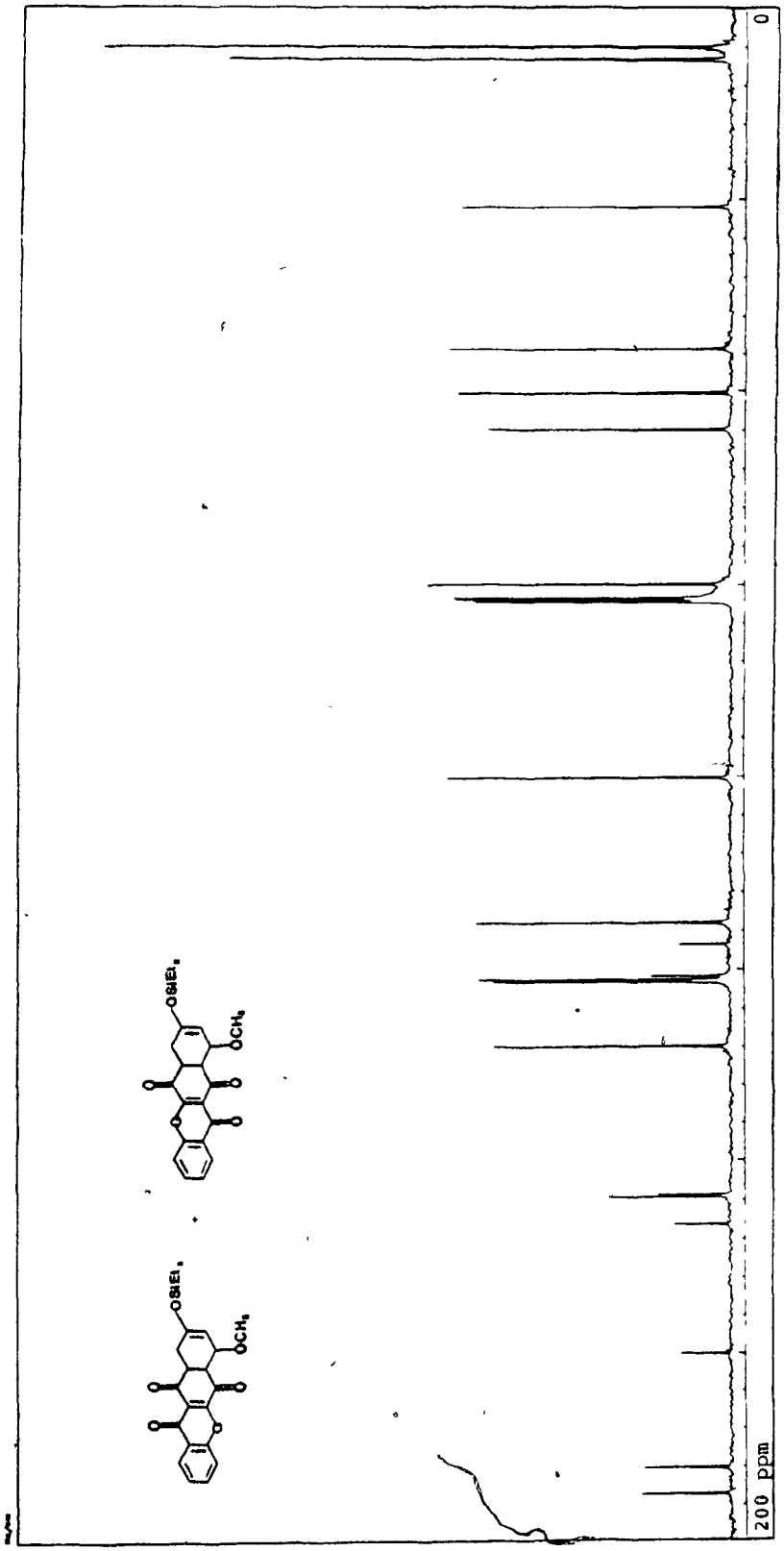


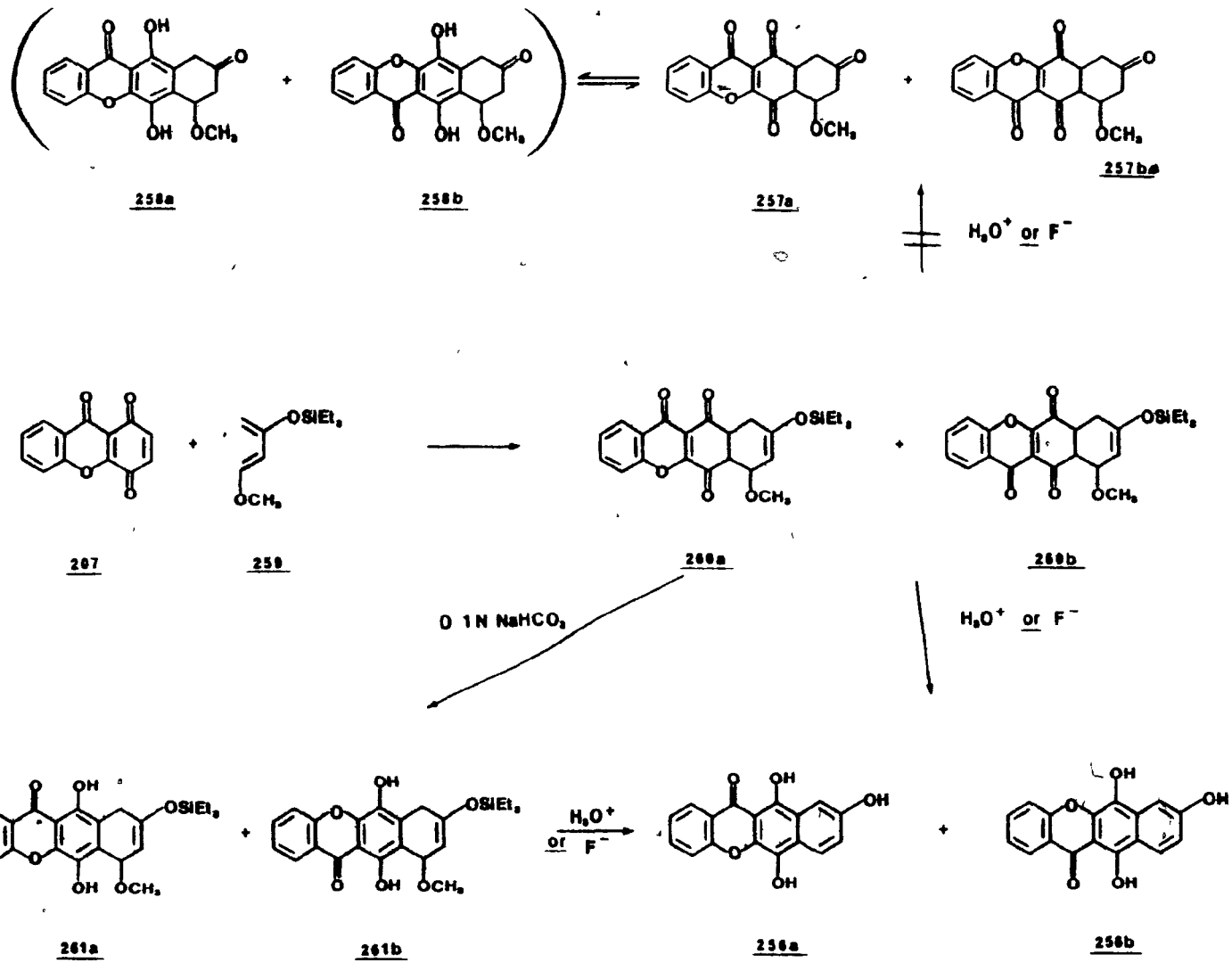

Figure 16: The 100.62 MHz $^{13}C$.m.r. Spectrum of Diels-Alder Adduct 260.

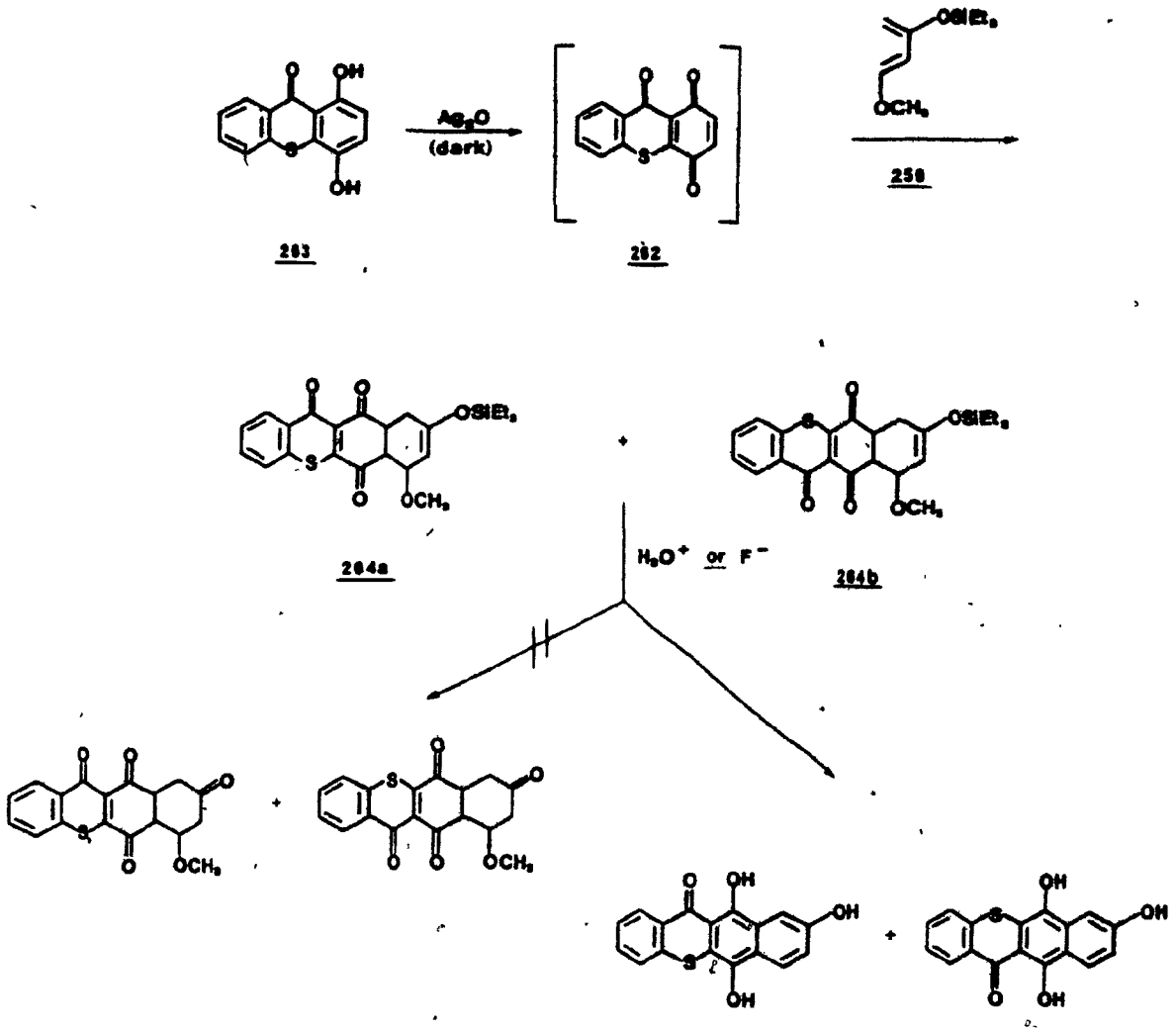
tautomer 258). Adduct 260 was quantitatively converted to its tautomer 261 by exposure to 0.1N aqueous sodium bicarbonate but upon subsequent treatment with acid or fluoride ion it again afforded only 256.

4.4.5.2 Reaction with thioxanthoquinone

The preparation of pure thioxanthoquinone (262) from 1,4-dihydroxythioxanthone (263) was reported as difficult and the quinone as refractory towards Diels-Alder reactions[439]. However, we found that oxidation of 263 with silver(I) oxide followed by *in situ* trapping of the quinone (a technique previously described but using isoprene) afforded a good yield (*ca.* 60%) of adduct 264 after only 24 h at room temperature. After this period, the reaction was stopped because oxidation of sulfur was feared. However, high field (200 MHz) pmr spectroscopy clearly indicated that no such oxidation had occurred as there was no significant downfield shift of the proton *ortho* to the carbonyl (at C-12 or C-5). It should thus be possible to optimize the reaction time. As expected the pmr spectrum of adduct 264 resembled that of 260, differing in minor details with no obvious indication as to whether only one or both regioisomers were formed.

This study of the thioxanthoquinone substrate was not pursued much beyond the formation of the Diels-Alder adduct 264, but preliminary studies aimed at transforming it


258a
258b
257a
257b
H3O+ or F−
207
259
260a
260b
0 1N NaHCO3
H3O+ or F−
261a
261b
H3O+ or F−
256a
256b

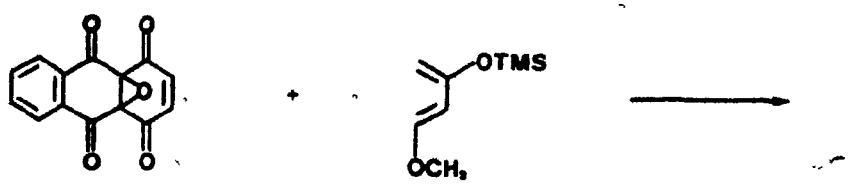



indicated that the same problem of ring A aromatization already encountered with the oxygen analog was also present.

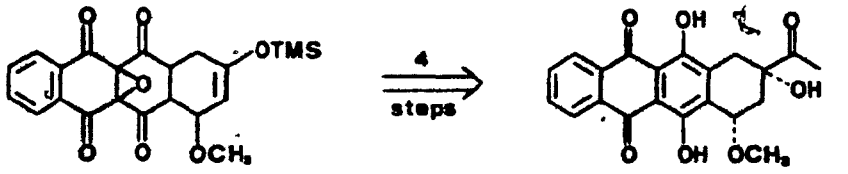
The difficulties experienced with the use of Danishefsky's diene were certainly disappointing but we were not altogether discouraged because the possibility of designing other *potentially* useful dienes still remained.

Subsequent to our work, there appeared other conflict-

ing reports regarding the use of Danishefsky's diene. Most prominent among the reports[615-617] (which made no mention of any significant problem of ring-A aromatization) was the one involving the synthesis of 4-demethoxy-7-O-methyldaunomycinone (29) from the protected quinizarinquinone 265[616]. On the



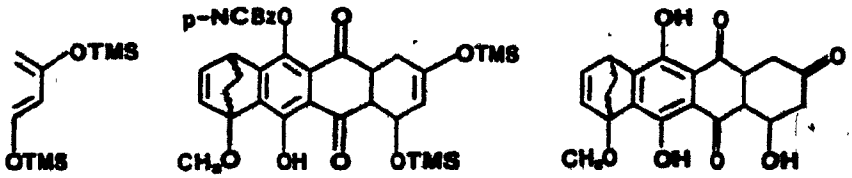

265 249




29

other hand, other reports[618-621] indicated that insurmountable difficulties arising from ring-A aromatization led to the adoption of different strategies[618,620] or to the development of different or modified dienes[619-621]. But not all of these new efforts have been successful either. Presumably the modified diene 1,3-*bis*(trimethylsilyloxy)-1,3-butadiene (266)[620-623] was prepared with the expectation that after hydrolysis the adduct would be less labile and thus less likely to aromatize because the hydroxyl group at the 7-position

is not as good a leaving group as a methoxy. However, though some success has been claimed[620,621], adducts 267 and 268




266 267 268

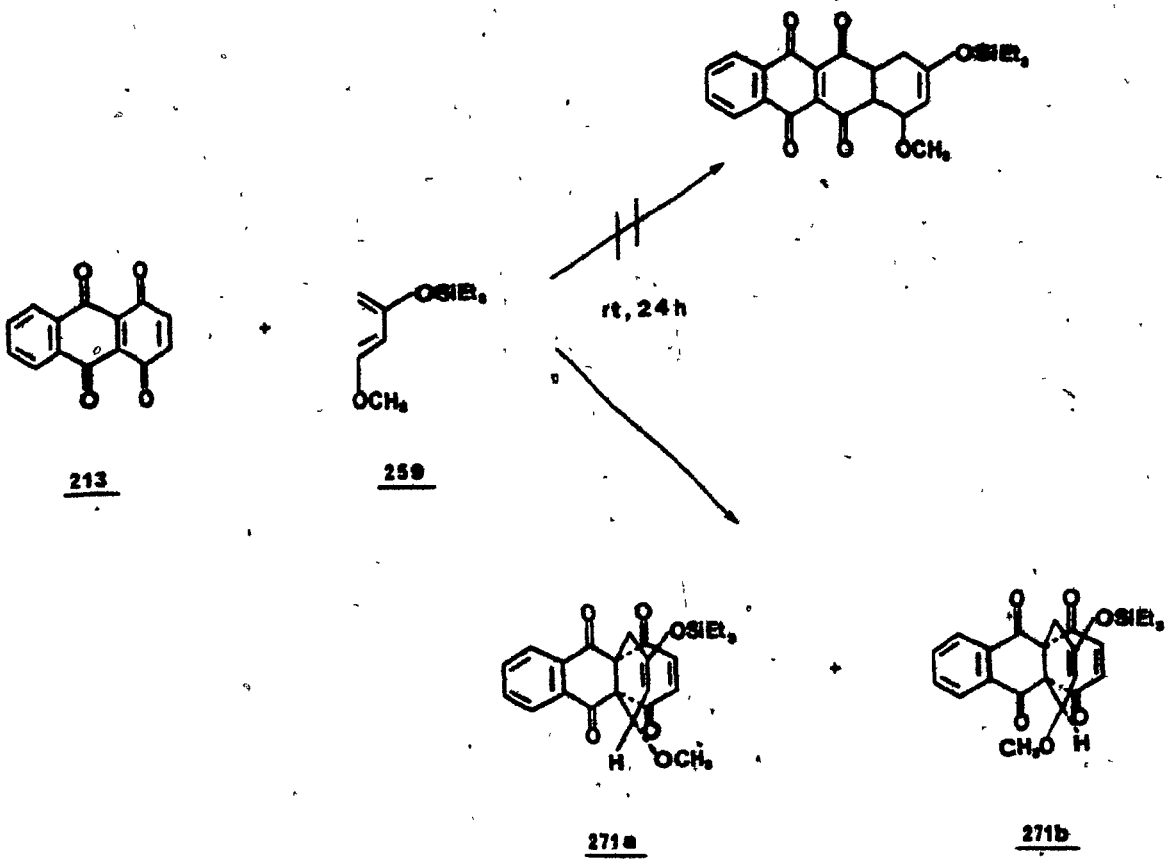
do have a *pronounced* tendency to suffer ring-A aromatization[621] and this result constituted the principal reason for the use of a trimethylsilyl group as a latent hydroxyl function[619]. The less than satisfactory results obtained with diene 266 as well as the fact that Kelly[621,624] was unable, after extensive investigation, to achieve a productive elaboration of the adduct resulting from a Diels-Alder reaction with diene 269, formed the basis of our abandoning further efforts along this line including our efforts directed at the synthesis of diene 270. (Work relating to the attempted synthesis of 270, based on the sugar 2-deoxyribose, is discussed in Appendix 4).


269 270

4.4.5.3 Reaction with quinizarinquinone

The use of an oxirane function as a protecting group for quinizarinquinone 265 is an example of a useful concept which has made it possible to employ the electron-rich diene 249 previously known to react with the internal double bond[560,570]. However, as it adds extra steps to the synthesis it would be advantageous to use the unprotected quinizarinquinone. The tendency of electron-rich dienes to add to the internal double bond of quinizarinquinone may be checked by steric hindrance[560]. Since diene 259 offers greater steric bulk than 249 we attempted the reaction with quinizarinquinone (213) as such in order to evaluate the steric hindrance effect.

The progress of the reaction at room temperature was not monitored but the reactants had completely reacted within 24 h. The pmr spectrum of the crystalline adduct obtained in quantitative yield, revealed that only the internal adduct had formed as evidenced by the olefinic quinone protons appearing as quartets. A mixture of the two stereoisomers 271a and 271b was formed in a ratio of 3:1. The structural assignment was based on the expectation that the methoxy group is more deshielded in isomer 271a and less so in isomer 271b. The mass spectrum of the adduct showed a molecular ion corresponding to the expected mass of the adduct, as well as a small but significant fragment corresponding to a *retro* Diels-Alder process. While the results are interesting by




themselves, the ratio of the stereoisomers being different from that reported[570] for diene 249 (stereoisomers are formed in equal amounts), they indicate that the use of diene 259 would still require an oxirane derivative of quinizarinquinone.

## 4.5 USE OF 4-SILYL-SUBSTITUTED DIENES AS LATENT PRECURSORS OF ADDUCTS WITH A FUNCTIONALIZED 7-POSITION

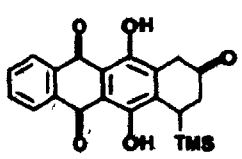
Garland *et al.*[619] made the important observation that benzyltrimethylsilane undergoes conversion into benzyl trifluoroacetate when treated with lead *tetrakis*trifluoroacetate[625]

or lead tetraacetate, and TFA, thus allowing the transformation of a carbon-silicon bond into an alcohol function. This process was a key in the successful use of diene 4-(trimethylsilyl)-2-acetoxy-1,3-butadiene (272) and constituted the only important difference in an otherwise familiar strategy for the synthesis of anthracyclines (see Scheme 4.1)*.

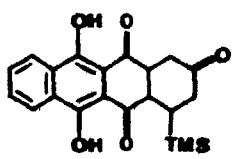
### 4.5.1 Attempted Synthesis of 4-(Trimethylsilyl)-2-ethoxycarbonyl-1,3-butadiene (274)

Since silylated dienes suitably substituted for our purposes are not readily available, we considered the use of the sulfone 3-ethoxycarbonyl-2,5-dihydrothiophene-1,1-dioxide (273) as a potential precursor of the diene 4-(trimethylsilyl)-2-ethoxycarbonyl-1,3-butadiene (274). However, successful silylation at C-5 was a requirement. A strategy involving direct silylation of the parent sulfone was not attempted because ring opening under basic conditions was previously observed[626,627]. As the carboethoxy group is expected to provide some stabilization of the negative

*It should be noted however that Garland *et al.* found it necessary to convert ketone i to the corresponding dihydro derivative ii in order to carry out the addition of ethynylmagnesium bromide. Compound ii is not described as being exceptionally prone to aromatization as is the similar compound 268 investigated by Kelly *et al.*[621].



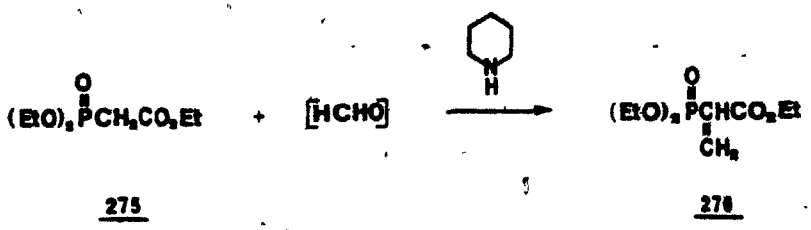

i



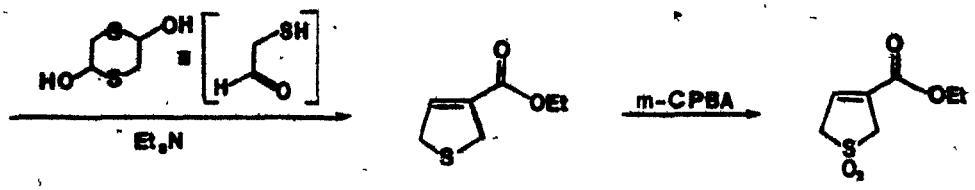

ii

charge*, it appeared possible to achieve the desired silylation.

The preparation of carboethoxy sulfone 273 was carried out according to the literature procedure[630,631] starting from the commercially available triethyl phosphonoacetate (275) which was boiled in the presence of *in situ* generated formaldehyde (through base treatment of paraformaldehyde) followed by condensation of the resulting phosphonate 276 with mercaptoacetaldehyde (added in the form of its dimer *p*-dithiane-2,5-diol) to give dihydrothiophene 277. Oxidation of the latter with *m*-CPBA gave sulfone 273.




275 276



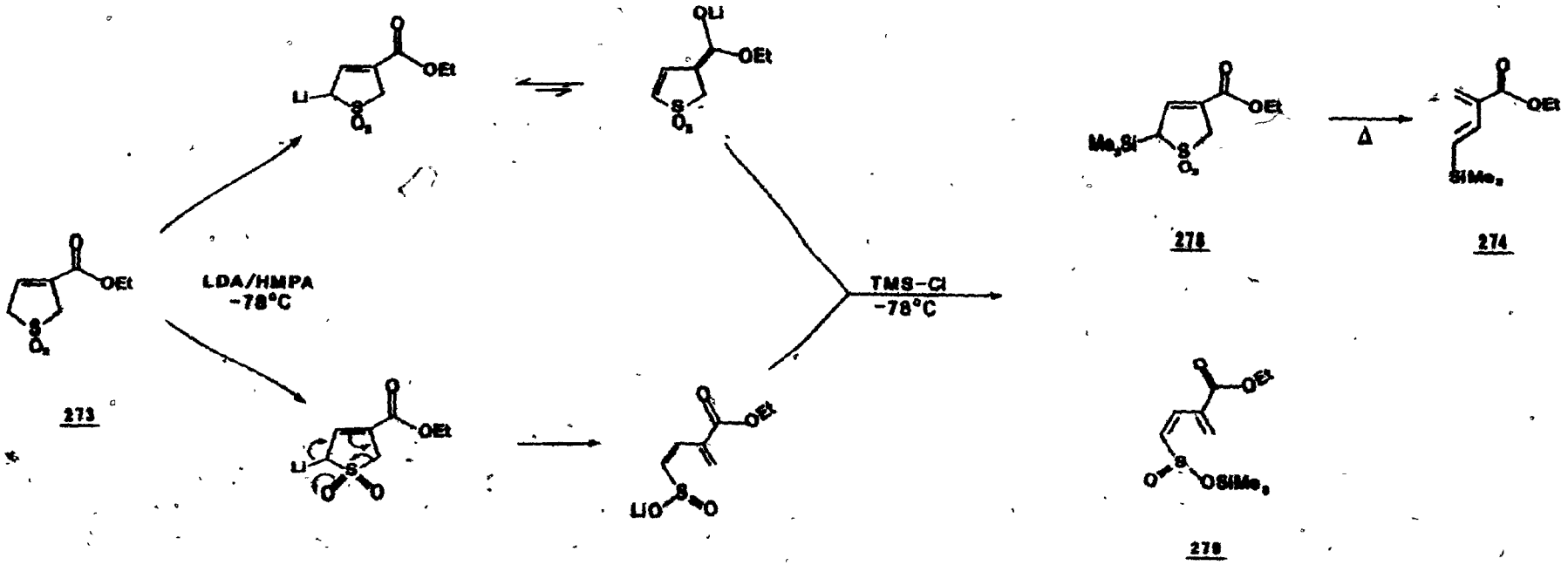

277 273

*It appears that this extra stabilization does not favor C-alkylation. As the negative charge is extensively delocalized, localization of the electron pair at the target carbon results in the loss of a significant amount of resonance energy[628]. On the other hand, C-silylated esters are thermodynamically more stable than O-silylated esters[629] so that a balancing effect may exist.

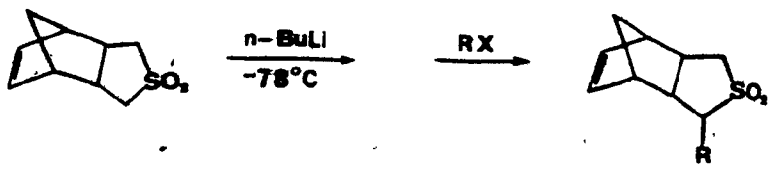
Treatment of this sulfone with LDA in the presence of HMPA at -78°C, (conditions known[632-634] to promote C-silylation over O-silylation), followed by quenching with TMS-Cl unfortunately did not yield the desired silylated sulfone 278. A dark oil was consistently obtained regardless of the conditions used (*viz.* lower temperature [-100°C] or shorter reaction time) and the products could not be identified by pmr or mass spectroscopy. There was no evidence that sulfinate 279 was formed.

It is noteworthy that Bloch reported[635] recently the use of sulfones as precursors of substituted dienes. However, in order to exploit this strategy successfully, the double bond had to be protected. For instance, compound 280 (prepared in 4 steps[635c]) readily underwent deprotonation at -78°C and subsequent alkylation without decomposition. The fact that such a low temperature had to be used suggested that the temperature applied by us may have been too high for the more acidic substrate 273 and that this may account for the observed decomposition reaction.

Lee[636] has also made use of the silyl group as a latent hydroxyl function in his synthetic study of modified anthracyclines. However, he used an allylsilane as a key intermediate for the purpose of introducing additional functional groups. In principle this methodology may be valuable for the purpose of generating heteroanthracyclines because it implies the use of a simple silylated diene.




273 278 274 279




288

4.5.2 Preparation of (E)-1-(Trimethylsilyl)-1,3-butadiene (281)

The synthesis of 281 has been described in varying degrees of detail by a number of groups[637-639]. However, there are no precise directives for its successful preparation. Our own efforts led to important modifications worth describing to the existing methods.

The dianion of propargyl alcohol generated by an excess of n-BuLi, was quenched with 2 eq of TMS-Cl. Mild acid hydrolysis of the silyl enol function gave, after distillation, a 75% yield of 3-(trimethylsilyl)-2-propyn-1-ol (282) as a clear, colorless oil. Reduction of 282 to *trans*-2-(trimethylsilyl)-2-propen-1-ol (283) was initially carried out using lithium aluminium hydride (LAH) in THF[640], but some (*ca.* 5%) *cis* isomer was invariably obtained along with the product of overreduction. The use of sodium *bis*-(2-methoxyethoxy)-aluminium hydride (Red-Al or Vitride)[641,642] on the other hand, gave only the *trans* reduction product as was clearly shown by pmr spectroscopy which revealed signals for the olefinic protons having a coupling constant J = 18 Hz. There

was no evidence that any product of overreduction was formed. Oxidation of 283 with pyridinium chlorochromate (PCC)[643] gave a 58% yield of the very volatile aldehyde 284 as a clear, colorless oil which darkened when stored over 0°C. Addition of 284 to the Wittig reagent methylenetriphenylphosphorane (prepared from methyltriphenylphosphonium bromide and n-BuLi)[644] gave the desired diene 281 in *ca.* 50% yield. The pmr spectrum of 281 consisted of the expected complex pattern of multiplets while the ir spectrum showed a stretching mode at 1565 $cm^{-1}$ for the conjugated olefin.

$$H\text{-}C{\equiv}C\text{-}CH_2OH \xrightarrow[THF]{n\text{-}BuLi\,(2eq)} LiC{\equiv}CCH_2OLi \xrightarrow{TMS\text{-}Cl\,(2eq)}$$

$$TMS\text{-}C{\equiv}CCH_2OTMS \xrightarrow[MeOH]{H^+/H_2O} TMS\text{-}C{\equiv}C\text{-}CH_2OH \xrightarrow[Et_2O]{NaAlH_2(OCH_2CH_2OCH_3)_2}$$

282

$$TMS\text{-}\underset{H}{\overset{H}{C}}{=}\underset{H}{\overset{H}{C}}\text{-}CH_2OH \xrightarrow[CH_2Cl_2]{PCC} TMS\text{-}\underset{H}{\overset{H}{C}}{=}\underset{H}{\overset{H}{C}}\text{-}\underset{O}{C}\text{-}H \xrightarrow[Et_2O]{Ph_3P{=}CH_2} TMS\text{-}\underset{H}{\overset{H}{C}}{=}\underset{H}{\overset{H}{C}}\text{-}C{=}CH_2$$

283 (100% *trans*) 284 281

## Reaction of diene 281 with xanthoquinone

Diene 281 has been used[637-639,645] in Diels-Alder reactions despite its apparently low reactivity. It has been

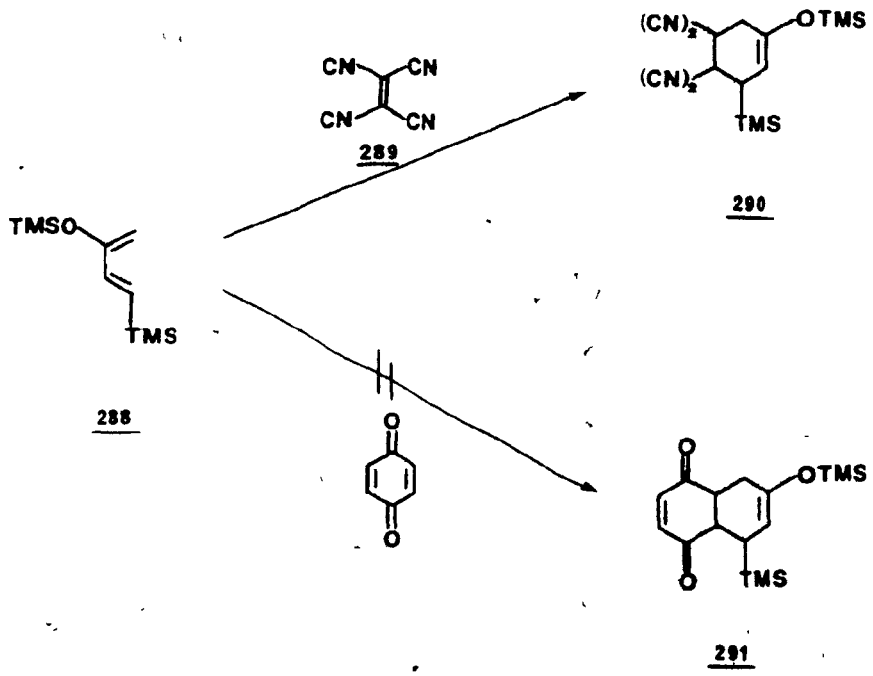
estimated[639,645] that its reactivity is from 10 to 1000 times poorer than that of butadiene, a conclusion contradicting estimates based on calculations[639] suggesting that the energy of the HOMO 281 is elevated relative to that of butadiene.

Not surprisingly then, diene 281 proved insufficiently reactive for condensation with xanthoquinone after 8 days at room temperature. The use of Lewis acid catalysts ($BF_3 \cdot Et_2O$, $SnCl_4$, anhydrous $ZnCl_2$) resulted only in decomposition. On the other hand, refluxing the reactants in 1,2-dichloroethane led to the rapid (*ca.* 5 h) disappearance of starting material. Analysis by tlc indicated the presence of no less than five products of which only two were present in large enough quantities to warrant investigation. The pmr, ir and mass spectral evidence obtained for the structures of these compounds were sufficiently informative to indicate that adduct 285 was not formed*. However, we could tentatively identify the compounds as the fully aromatized adducts, one carrying the expected silyl group intact as in 286 and the other lacking that group as in 287 (Scheme 4.2). The mass spectrum of each compound included a molecular ion corresponding to their respective molecular weights while their pmr spectra confirmed the presence in one case and absence in the other of a silyl group. As can be seen, the poor dienophilic character of this diene unfortunately precluded its use and the results

*Because the HOMO of diene 281 is only very slightly polarized, equal amounts of regioisomers might be expected whether the regioselectivity is controlled by primary or by secondary overlap[639].

made it necessary to search for a more reactive silylated diene.

Accordingly, attention was turned to diene (E)-1-trimethylsilyl-3-trimethylsilyloxybutadiene 288 which, as expected, shows greater reactivity than diene 281. However, harsh reaction conditions were still required in order to obtain adducts even with substrates recognized as being excellent dienophiles[639]. In our hands, diene 288 reacted with the very powerful dienophile tetracyanoethylene (TCNE) (289) at room temperature within one hour to give a quantitative yield of adduct 290 but with *p*-benzoquinone as the substrate under a variety of reaction conditions, none of the expected adduct 291 was obtained. (This latter result has recently



been observed by others[636]). In spite of this negative result, 288 represents a potentially useful diene which, in principle, could lead under special conditions to silylated adduct 292 (Scheme 4.2), an intermediate possessing attractive features*. We accordingly favored diene 288 over 272 because the silyloxy group should be more activating than an acetoxy group.

### 4.5.3 Synthesis of (E)-1-(Trimethylsilyl)-3-trimethylsilyloxybutadiene (288)

Fleming *et al.*[639] have prepared diene 288 *via* the addition of methylmagnesium iodide to aldehyde 284 followed by oxidation of the resulting alcohol. For tactical reasons we found it more convenient to use the process already applied to the preparation of diene 281 but starting with 3-butyn-2-ol (293) instead of propargyl alcohol.

Treatment of 293 with 2 eq of n-butyllithium in ether followed by quenching with 2 eq of TMS-Cl followed by treatment of the product with dilute acid gave, after distillation, a 90% yield of 4-(trimethylsilyl)-3-butyn-2-ol (294) as a clear, colorless oil. Reduction of the latter with

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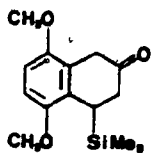
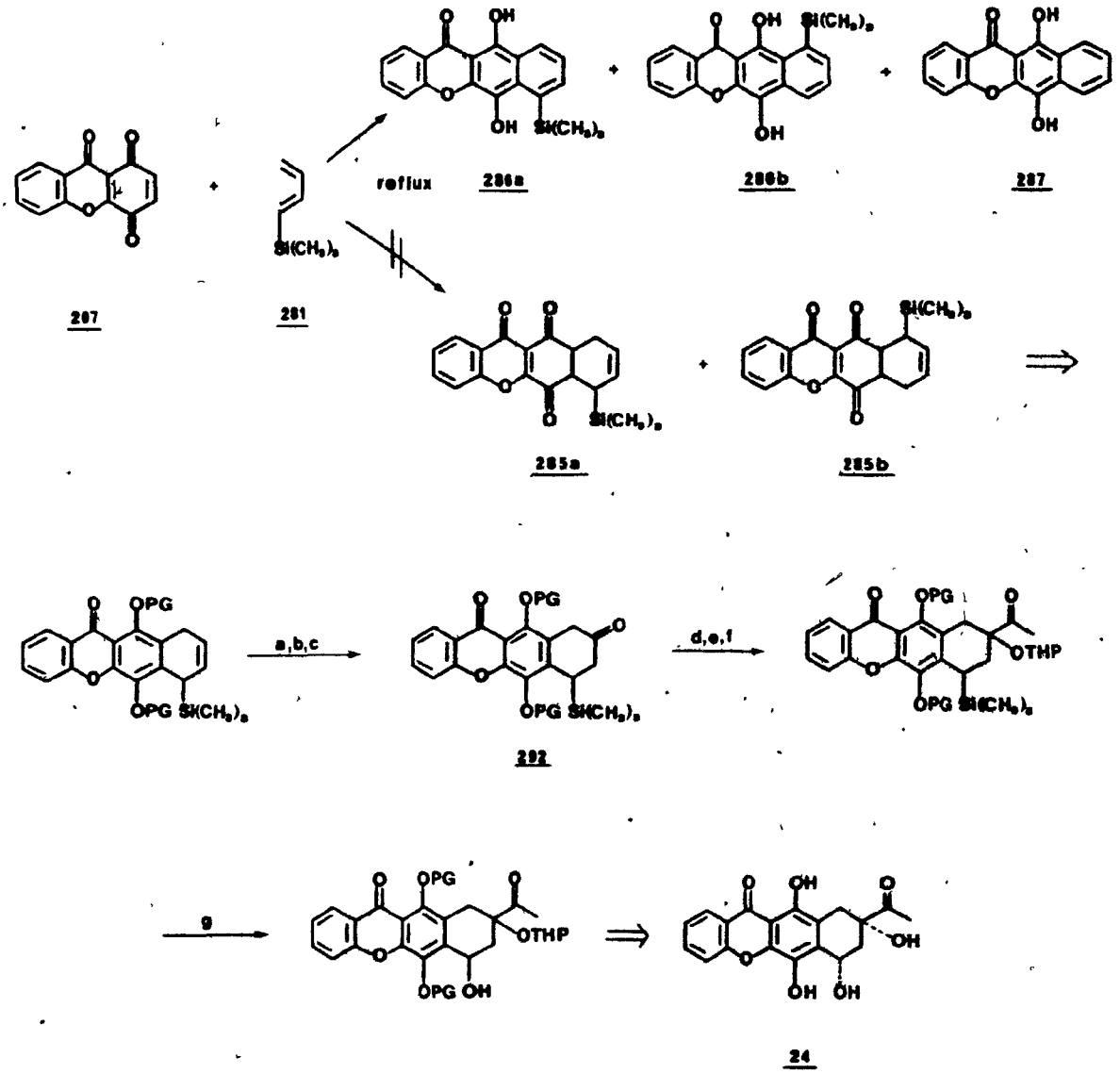
*Interestingly, Lee found that ethynylmagnesium bromide would not add to 1 because of the acidity of the benzylic protons. The problem was similar to that encountered by Garland *et al.*[619].




1

Scheme 4.2*

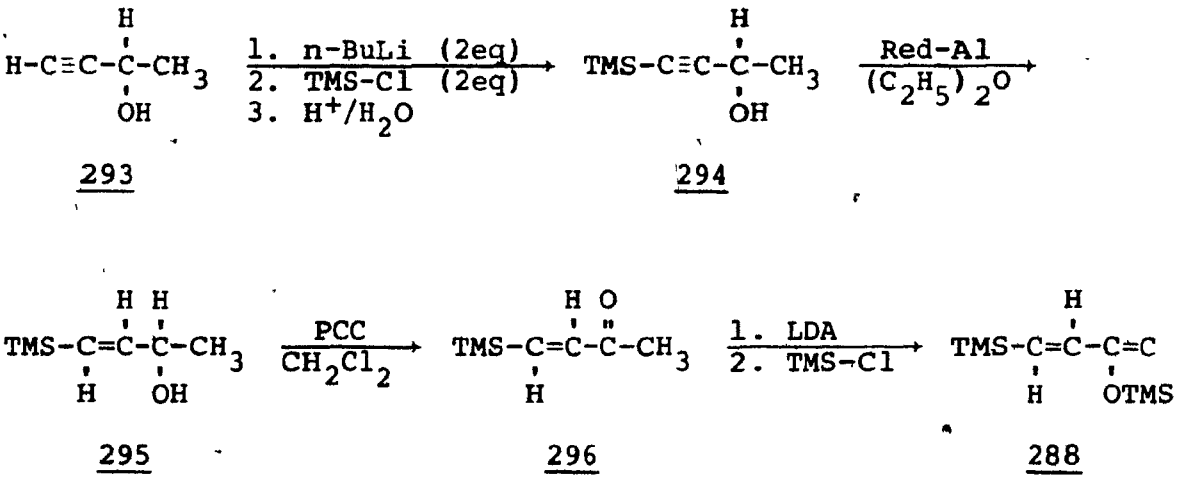



a) $B_2H_6$, THF; b) $Et_3NO$/MeOH; c) PCC; d) $Et_2AlCN$; e) Dihydropyran, $H^+$; f) $CH_3MgI$; g) $C_6H_5I(OCOCF_3)_2$.

*The sequence shown for one isomer only.

Red-Al in ether gave in high yield pure *trans*-4-(trimethylsilyl)-3-buten-2-ol (295) as evidenced by the coupling constant J = 18 Hz for the olefinic protons in the pmr spectrum. On the other hand, reduction with LAH in THF required refluxing temperatures and led to a mixture of 94:4 (%) *trans* to *cis*-alcohol 295 ($J_{cis}$ = 14 Hz) along with *ca.* 2% of the saturated alcohol, 4-trimethylsilyl-2-butanol. Oxidation of 295 with PCC gave after about 1.5 h at room temperature β-silylenone 296 in 80% yield. Treatment of the latter at -78°C with LDA and quenching of the enolate with excess TMS-Cl afforded after distillation the pure diene 288 in *ca.* 85% yield (Scheme 4.3).

Scheme 4.3

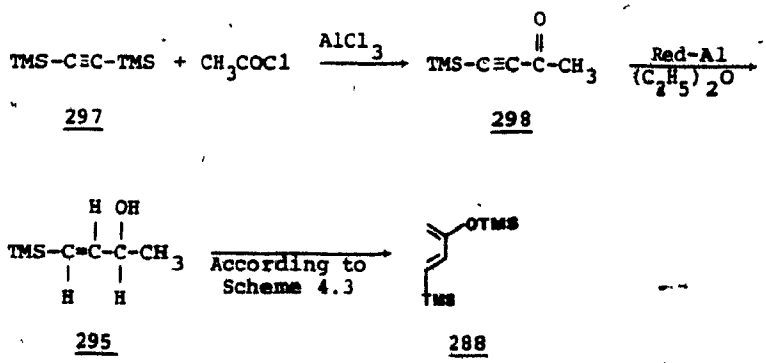



The pmr and ir spectra* of this product were consistent with the published data[639]. It was indefinitely stable when stored

*Fleming incorrectly assigned the frequency of the C-H bend of the *trans* CH=CH as 847 $cm^{-1}$. The correct value is 990 $cm^{-1}$.

under an inert atmosphere at 4°C and was stable for at least one week when stored in a stoppered flask at room temperature.

Although this process worked well, large quantities of n-BuLi were required in order to generate relatively small amounts of the desired diene which meant that the preparation had to be repeated several times because large scale operations with n-BuLi appeared unsafe in the absence of adequate equipment. Consequently, another process not requiring n-BuLi was adopted which allowed us to prepare alcohol 295 safely on a large scale. A Friedel-Crafts alkynylation[646-650] of acetyl chloride with *bis*-trimethylsilyl acetylene (297) in the presence of aluminium chloride gave β-silylynone 298 in 82% yield without need for further purification. Reduction of the latter with Red-Al in ether afforded in high yield (85%) the pure *trans* alcohol 299 while reduction with LAH in THF gave a 9:1 mixture of *trans* to *cis* isomers. Oxidation of alcohol 295 with pyridinium dichromate (PDC)[651] was considerably slower than with PCC and gave a product of inferior purity. The final step was the same as that shown above in Scheme 4.3,



In connection with another study we required a method for the preparation of *cis*-4-trimethylsilyl-3-buten-2-ol without having to resort to a hydrogenation step. The results of this study are summarized in a published paper[652], a copy of which can be found in Appendix 5.

4.5.3.1 Reaction with xanthoquinone

The reactants were left at room temperature and after 6 days the reaction mixture consisted mainly of unreacted material. After this time it was nevertheless worked-up and purified by flash chromatography which led to the isolation of a small amount of impure material whose mass spectrum indicated the presence of a compound with a molecular weight corresponding to that of the expected adduct 300. However, high field pmr spectroscopy did not provide any supporting evidence for adduct formation.

Reluctantly, we next attempted the same reaction but in the presence of Lewis acid catalysts such as $BF_3 \cdot Et_2O$ or anhydrous $ZnCl_2$* and as expected, decomposition of the diene was the only obvious result†. Attempted condensation with *in situ* generated xanthoquinone (from 1,4-dihydroxyxanthone and $Ag_2O$) and 288 did not produce any positive results either.

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*While it is true that Danishefsky has used anhydrous $ZnCl_2$ as a catalyst with diene 249, he stressed that the term cycloaddition has no mechanistic implication as no intermediate identifiable as products of cycloaddition have been detected[653-655].

†The use of the "non-destructive" Lewis acid catalyst, $B(OAc)_3$, has been used successfully with two *non-silylated* dienes[573,656,657].

We also attempted the use of an aminium cation-radical salt as the catalyst in view of recent reports on the powerful catalytic properties of such compounds in Diels-Alder cycloaddition reactions including those where Lewis acids are not effective[658,659]. Indeed, *tris*-(4-bromophenyl)aminium hexachloroantimonate (301) apparently enhances the dienophilicity of neutral or electron-rich dienophiles by converting them, *via* electron transfer, to highly reactive electron-deficient cation radicals[658-663]. Accordingly, we hoped that such a compound might promote the formation of a reactive electron-deficient double bond (at Δ 2,3) in the xanthoquinone. However, after long reaction times in the presence of such a catalyst (24 h) at room temperature, tlc analysis indicated that the reaction mixture consisted mainly of starting material and two other compounds but in quantities too small to warrant isolation and purification. Spectroscopic analysis of the crude mixture gave no evidence that adduct 300 was formed.

It may be that silicon plays a significant role in the stabilization of the cation-radical thereby facilitating the ionization of the more electron-rich diene 288 instead of the double bond of the xanthoquinone. As cycloaddition reactions are symmetry forbidden for the case of neutral dienophiles and ionized dienes[659,660], it may not be "too" surprising that our experience with 288 and the xanthoquinone turned out to be negative. However, ionization of the diene might be

expected to lead to the formation of dimeric or polymeric materials but this was not observed. Coupled with the observation by Kishi *et al.*[664] that cycloadditions under cation-radical catalysis could be achieved between a diene and 1,4-naphthoquinone, we speculate that it is most likely the heteroatom of the xanthoquinone substrate which suffers ready ionization, thus effectively preventing the catalyst from playing its assigned role.

Heating the same reactants over a period of 6 days at 50°C produced some interesting results although no adduct 300 was obtained. Analysis by tlc indicated that the starting material was completely consumed and that numerous compounds had formed. Isolation of pure fractions by flash chromatography proved difficult but spectral data (pmr and mass spectroscopy) of the main fraction unequivocally indicated it to be 1,4-dihydroxyxanthone (75). Mainly on the basis of mass spectral evidence, a component from an impure polar fraction was identified as the fully aromatized compound 256. These findings suggest that the Diels-Alder adduct 300 may actually form* but immediately undergoes disproportionation to give 75 and 256. (Disproportionation was already seen as an important reaction when the xanthoquinone was reacted with butadiene sulfone; see p. 180). We believe that the formation of 256 involves a mechanism in which the xanthoquinone would

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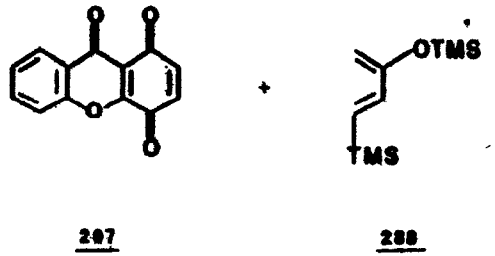
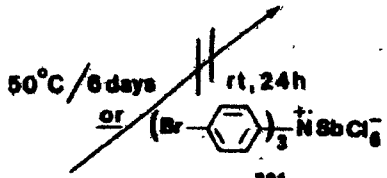
*Regioisomer 300a may be expected to dominate; the polarization of the diene being governed entirely by the silyloxy group[608,639,665].

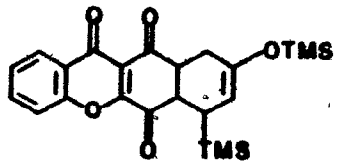



207 + 288

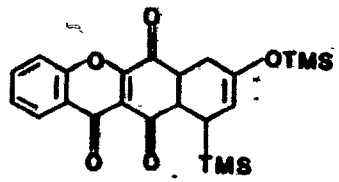



301

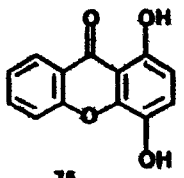
50°C
6 days



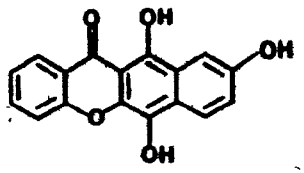

300a +



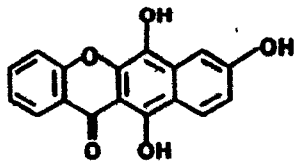

300b




79 +



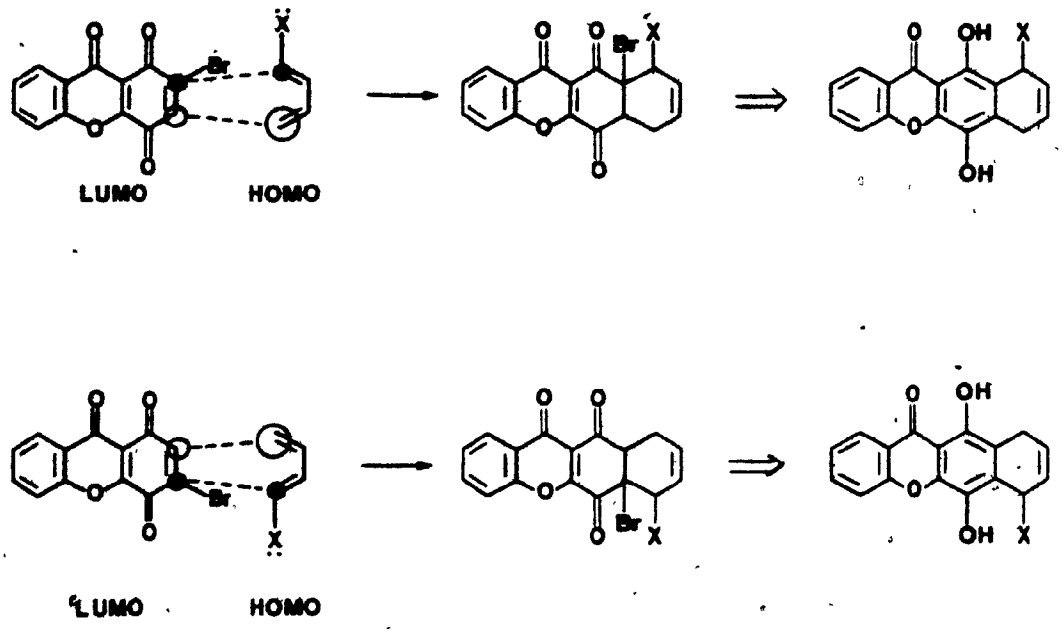

256a



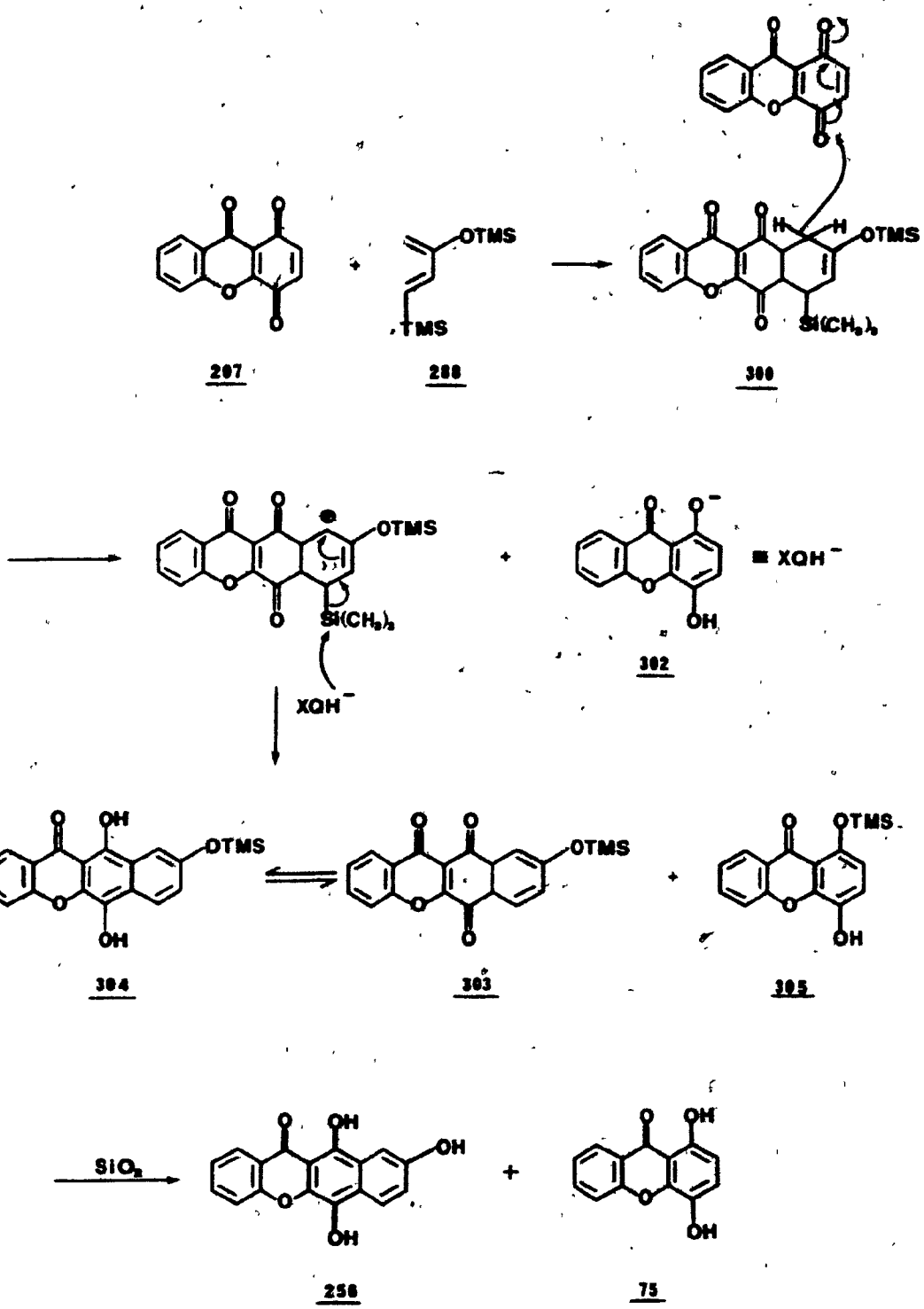

256b

behave as a dehydrogenating agent to give rise to the phenolate ion 302 which would then remove preferentially a silyl group rather than a proton[639] as shown in Scheme 4.4. Intermediate 303 is expected to readily tautomerize to the more stable aromatic system of 304 which like intermediate 305 would suffer loss of the labile O-silyl group during chromatography.

Because we had been unable to make use of Lewis acid catalysts with our dienes and also unable to promote their reactivity under mild reaction conditions, we then turned our attention to the modulation of the dienophile reactivity. A common way of increasing the dienophilicity (hence reactivity) of quinones involves the introduction of a halogen onto the olefin bond[666-673]. As an electronegative species, the halogen causes a lowering of both the HOMO and LUMO energies



Scheme 4.4*



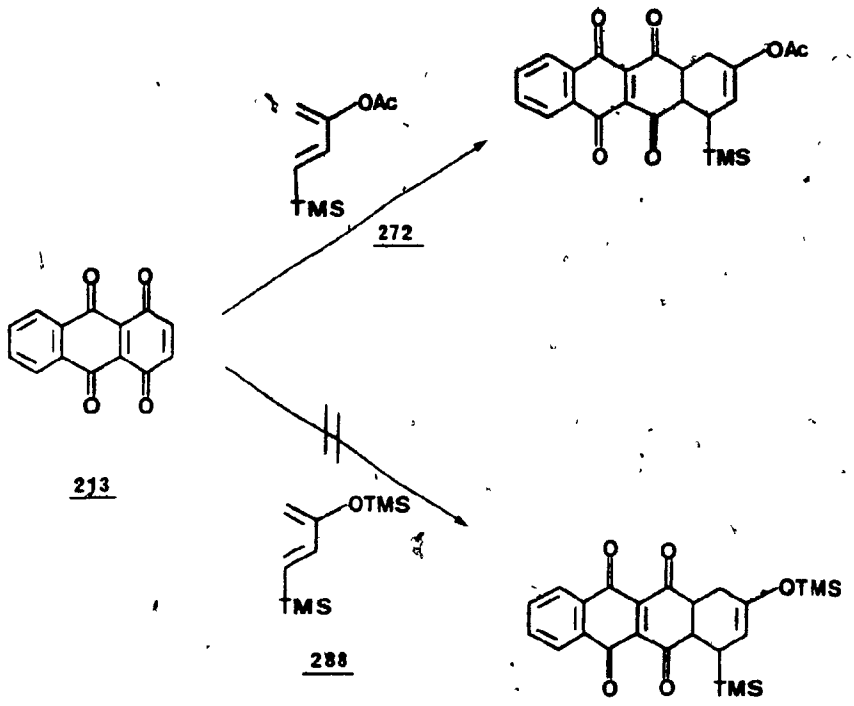

*Shown for one isomer only.

and being also a lone-pair donor, the HOMO energy is raised without affecting significantly the LUMO energy[602]. In addition the halogen can be expected[465,666-672] to orient the reactants and thus offer an excellent opportunity to exercise control over regioisomer formation. (The coefficients of the LUMO of the olefin will be polarized as though the substituent is electron-withdrawing[560,564,602,664,666-672], see Appendix 2). As bromoxanthoquinones 306 and 307 are easily accessible, this strategy for adduct formation appeared attractive. Unfortunately, the labile nature of the silyl dienes accessible to us was not expected[636] to be compatible with the reaction conditions (*e.g.* $Et_3N$, rt, 2 h)[668] normally required to remove the halogen atom after adduct formation. It comes as no surprise that this strategy (as described in the literature) was applied in fact to the synthesis of aromatic systems.

#### 4.5.3.2 Reaction with quinizarinquinone

As a result of the surprisingly poor results obtained with diene 288 we finally decided to compare its reactivity to that of 4-(trimethylsilyl)-2-acetoxy-1,3-butadiene (272)* under the same reaction conditions already used by Garland *et al.*[619] in their studies with quinizarinquinone (213). Thus,

*According to Houk's analysis[560] relating the site of reactivity of quinone 213 with the electronic character of the diene, 4-(trimethylsilyl)-2-acetoxy-1,3-butadiene (272) is not considered an electron-rich diene.



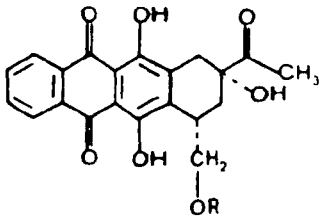

diene 288 and quinone 213 were stirred for four days at 50°C under an inert atmosphere but analysis of the reaction mixture showed that most of the starting material was still intact. Only mass spectral evidence could be obtained that any adduct had formed. It would appear from these results that the siloxy group is not as efficient an electron donor as would be expected and in fact it appears less efficient in this respect than an acetoxy group.

## 4.6 ATTEMPTS AT THE SYNTHESIS OF AN INTERMEDIATE CARRYING A CARBON SUBSTITUENT AT POSITION 7 OF RING A

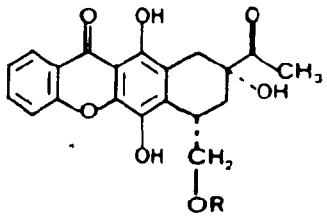
We have already seen the importance of having a

substituent at the C-7 position of an anthracycline analog which will not undergo elimination and thus generate a reactive alkylating intermediate in biological systems or favor aromatization reactions during attempted syntheses.

One of the most expedient ways of synthesizing the analogs 18-20 would involve a Diels-Alder reaction between the



18



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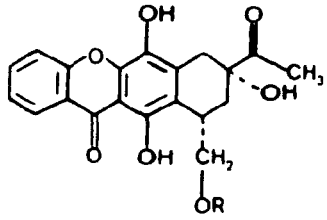

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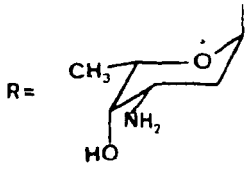
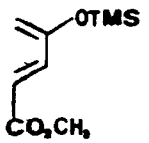
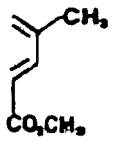


quinone-substrate and a diene such as 1-carbomethoxy-3-trimethylsilyloxy-1,3-butadiene (308). However, the latter may not be expected to display good reactivity. In fact, the carbomethoxy group is known to deactivate[465,674] such systems whereas the ability of the siloxy group to activate significantly by electron-donation is questionable in light of our previous experience with 2-siloxy dienes. Nevertheless, Kelly[570] reported that the diene methyl

4-methyl-2,4-pentadienoate (309) afforded a small amount (10%) of the desired adduct when reacted with quinizarinquinone at room temperature over an unreported period of time. In Woodward's reserpine synthesis[675], cycloaddition between benzoquinone and methyl vinylacrylate (methyl 2,4-pentadienoate) (310) was achieved (albeit in only 16% yield) by refluxing in benzene for 10 h. Thus, regardless of the possible activating or deactivating ability of the siloxy group, we were hopeful that provided 308 was thermally stable we might be able to apply higher reaction temperatures in order to compensate for the low reactivity of the diene.




308

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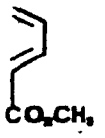



310

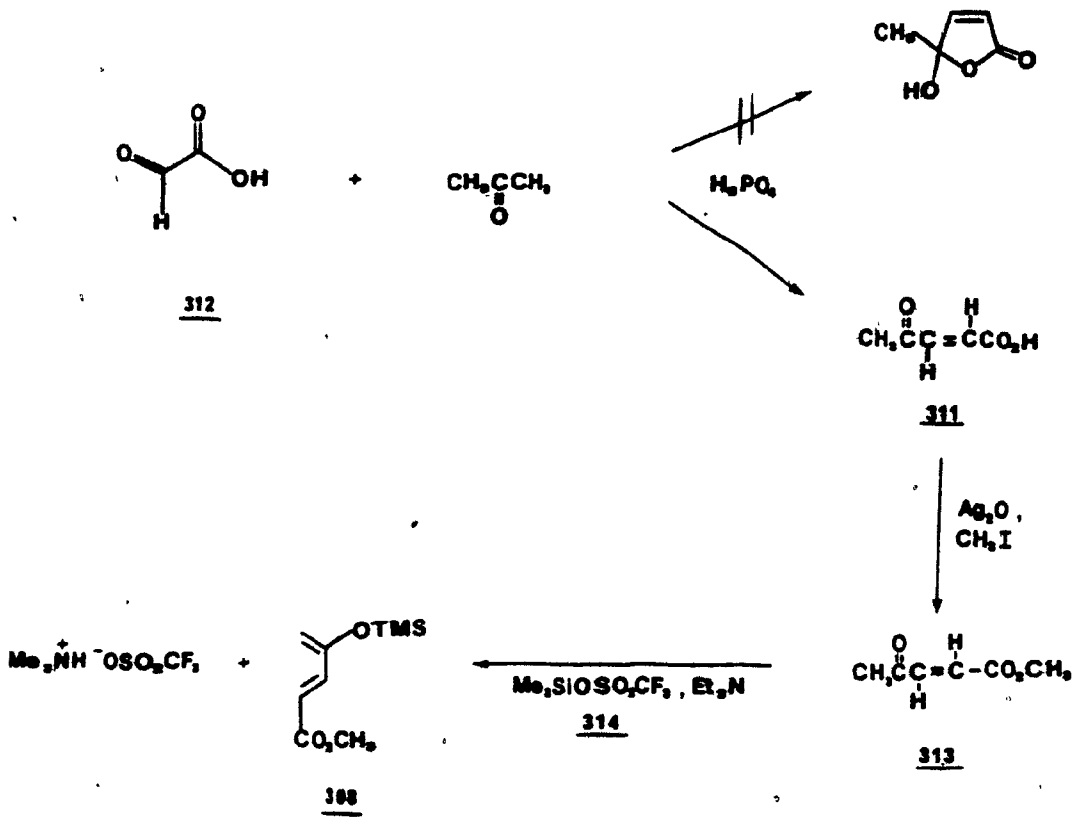
4.6.1 Preparation of 1-Carbomethoxy-3-trimethylsilyloxy-1,3-butadiene (308)

This intermediate was prepared starting from the β-keto acid 311 itself obtained by condensing glyoxylic acid (312) with acetone in the presence of orthophosphoric acid. Although not very efficient (*ca.* 45%) this method as reported[676-678] appeared to be the most convenient one for the preparation of β-acetylacrylic acid (*trans*-4-oxo-pentenoic

acid (311)[676]. It was obtained in a sufficiently pure form so that only one recrystallization was necessary to insure high purity. Its pmr spectrum showed olefinic protons with a coupling constant J = 16 Hz, whereas its infrared spectrum displayed a band at 1000 $cm^{-1}$ as expected for the *trans* isomer. A single methyl resonance at 2.4 ppm clearly indicated that the lactone was not formed.

The corresponding methyl ester of acid 311 was easily prepared in excellent yield (93%) by treatment with methyl iodide in the presence of silver(I) oxide in the dark[679-681]. Satisfactory results were also obtained when sodium bicarbonate powder in DMF and methyl iodide were used although a longer reaction time was required. The usual methods of esterification (TMS-Cl, $CH_3OH$; $CH_3OH$, $H^+$; $ClCOOCH_3$, $Et_3N$[682]) were clearly inferior, giving very low yields or none of the desired ester. This methyl ester 313 possesses the useful property of being readily sublimable (30°C at 20 mm Hg) to give a very pure, white crystalline mass.

Trimethylsilyl trifluoromethanesulfonate[609,683,684] (314) reacted in the presence of triethylamine with ester 313 to give essentially a quantitative yield of diene 308 which was freed of triethylammonium triflate (which precipitated as an oil) and used without further purification.



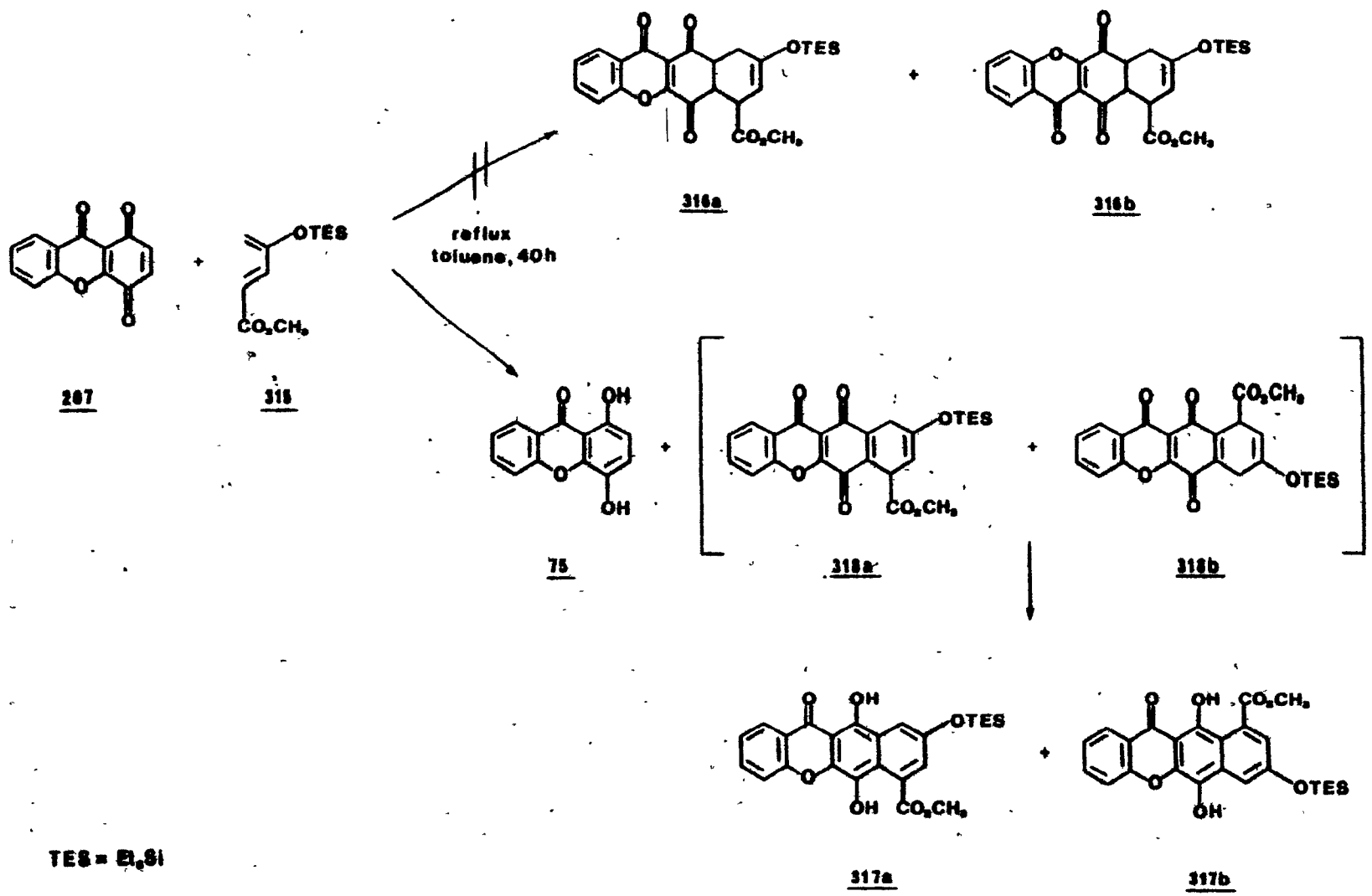
Reaction with Xanthoquinone

Reaction between diene 308 and xanthoquinone did not give any adduct under any of the conditions used. Pmr evidence clearly and consistently indicated the presence of xanthoquinone and keto-ester 313 in the reaction mixture. The presence of the latter led us to question the stability of diene 308. While indefinitely stable when stored at -20°C, it decomposed at room temperature over several hours, a phenomenon which escaped our attention because once generated, the diene was characterized by pmr spectroscopy immediately after isolation. Since reactions with the xanthoquinone were

carried out either at room temperature over a period of days or at elevated temperatures for hours, it is certain that the diene did not survive long enough for reaction with the substrate to occur. The cause of this instability was not thoroughly investigated but a likely possibility involves the fact that the diene was not rigorously purified so that some triethylammonium triflate may have remained as a contaminant and thus catalyze hydrolytic decomposition. Faced with this difficult problem of purification we decided to prepare instead the triethylsilyl analog of 308 since much improved stability is expectable on the basis of previous experience.

### 4.6.2 Preparation and Cycloaddition Reactions of Diene 315

Diene 315 was accordingly prepared in 94% yield from keto-ester 313 and triethylsilyl trifluoromethanesulfonate (245) and carefully freed of the generated triethylammonium salt. It is indefinitely stable at room temperature as well as to more vigorous thermal conditions such as boiling in benzene for 24 h. Some decomposition (*ca.* 10%) was observed however but only after refluxing in toluene for at least 48 h. Reaction with xanthoquinone at room temperature, not surprisingly gave no product even after 10 days regardless of whether the cation radical salt 301 was added or not. When the reactants were mixed in refluxing toluene for 40 h only mass spectral evidence could be obtained that adduct 316 had




287 315 316a 316b 75 318a 318b 317a 317b

TES = $Et_3Si$

formed. The pmr spectrum of the mixture showed that a small amount (< 10%) of dihydroxyxanthone 75 was formed indicating that disproportionation had again occurred - a result which is not surprising in light of the vigorous thermal conditions used. We made no attempt to isolate the fully aromatic adduct 317 (which would be expected to form readily from 318) and we have *only* mass spectral evidence that it was formed.

Apart from reacting readily with TCNE to give adduct 319, diene 315 showed very little reactivity. With benzoquinone for 23 h in refluxing benzene only a very low yield (< 5%) of an adduct was observed. Reaction with the more reactive naphthoquinone as the substrate in refluxing toluene for 21 h afforded some adduct but the use of anhydrous $ZnCl_2$ at room temperature served only to catalyze slow decomposition of the diene to the keto-ester. Similarly, attempted reaction with quinizarinquinone (213) afforded no adduct after refluxing for 24 h in toluene.

Recently, electron-poor dienes such as methyl 2,4-pentadienoate (310) and methyl 3-ethyl-2,4-pentadienoate have been induced to give good yields of adducts[685-687] by attempting the reaction under high pressure[688,689]. From the evidence in the literature there is no reason to believe that we could not achieve our goal, with any of our diene substrates (*e.g.* 281, 288, 315) by adopting this technique. While the pressures recommended* are technically difficult to achieve without

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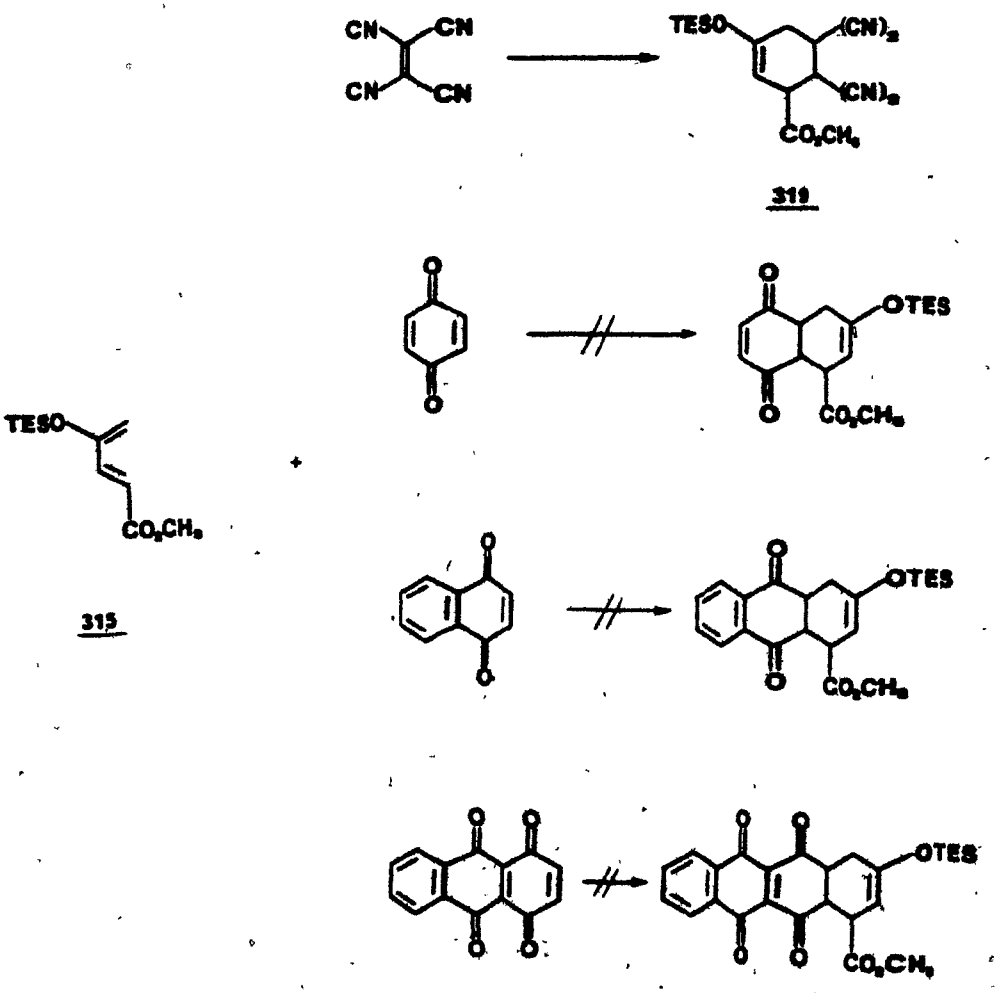
*Between 10-20 kbars (1 kbar = 986.9 atm).




specialized apparatus, it would be worthwhile investing in this approach as it would probably solve at least some of the problems encountered. Unfortunately, such a study was considered beyond present resources due to cost of equipment necessary.

## 4.7 CONCLUSION

The applicability of various Diels-Alder approaches

to the synthesis of heteroanthracyclines has been vigorously tested. Problems such as disproportionation, ring A aromatization restricting the use of certain potentially useful dienes and the lability of relevant dienes to Lewis acid catalysts have left the impression that the general strategy adopted cannot be used successfully. While the synthesis of adriamycin has been reported using a similar strategy, we must recognize that others have failed to reproduce the claimed exploits. We must also allow for the likelihood that the heteroanthracyclines possess a different intrinsic chemical reactivity manifested at important but sensitive positions (*e.g.* C-7). The use of high pressure techniques suggests very strongly that certain "unreactive" dienes may be induced to form valuable adducts and such anticipated success should serve to establish the Diels-Alder strategy as perhaps the most useful one for the purpose of synthesizing heteroanthracyclines.

# CHAPTER 5

# SYNTHESIS AND BIOLOGICAL EVALUATION OF AMINOXANTHONE

## 5.1 INTRODUCTION

There are numerous compounds with simpler structures than adriamycin that have antitumor properties[65]. Among some of these are the *bis*-(substituted aminoalkylamino) anthraquinones. They were designed[690] using as a basis the hypothesis that drug-DNA intercalation is the prime mode of action of the anthracyclines. In fact, these synthetic drugs incorporate those structural features (the anthraquinone chromophore and an aminosubstituted side chain) thought to be essential for binding to DNA. The idea that the amino sugar portion is responsible for the cardiotoxicity of the anthracyclines[691] led Zee-Cheng and Cheng[692] to synthesize compounds 320 and 321, where the amino sugar is replaced by an amino-containing side chain with the nitrogen atom at the proper spatial distance from the oxygen atoms of the aglycone portion of the molecule as required by the N-O-O triangulation theory*.

The biological activity profile of these compounds[692-695], especially 321, resembled that of adriamycin and daunomycin. Like adriamycin, 321 kills cells in all phases of their cycle

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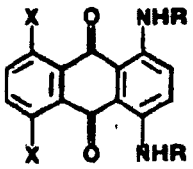
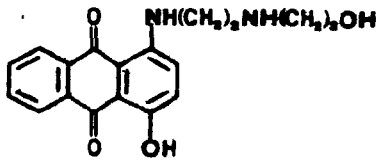
* This empirical and simple model suggests that there is a structural feature among some anticancer drugs consisting of a triangle composed of one nitrogen and two oxygen atoms with rather definite inter-atomic distances[693].

(a property important for the inhibition of slow growing tumors) and was somewhat less cardiotoxic. These remarkable results stimulated a broader study[696] in which hydroxyaminoanthraquinone 322 was included.




320 X = H or OH; R = aminoalkyl chains

321 X = OH; R = $(CH_2)_2NH(CH_2)_2OH$




322

Although considerably simpler, analog 322 showed activity comparable to 321 thus indicating that only one amino substituted side chain is sufficient for activity. However, there was no report dealing with its potential cardiotoxicity.

Since the absence of an amino sugar such as daunosamine resulted in only a slight reduction in cardiotoxicity, it remains to be seen whether the redox properties of the anthraquinone regarding its tendency to form a semiquinone is still an important factor in this regard*. Thus, on the basis of this argument and the structure-activity data provided above, it appeared reasonable to synthesize the xanthone analog (21) of 322 in order to alter the redox potential of the anthraquinone models.

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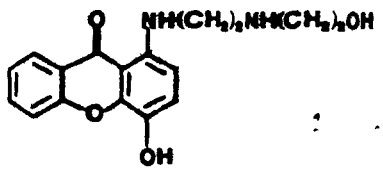
*Recently, it was suggested that the cytotoxicity of the aminoanthraquinones may depend more on their ability to form free radicals than their ability to intercalate with DNA[697].

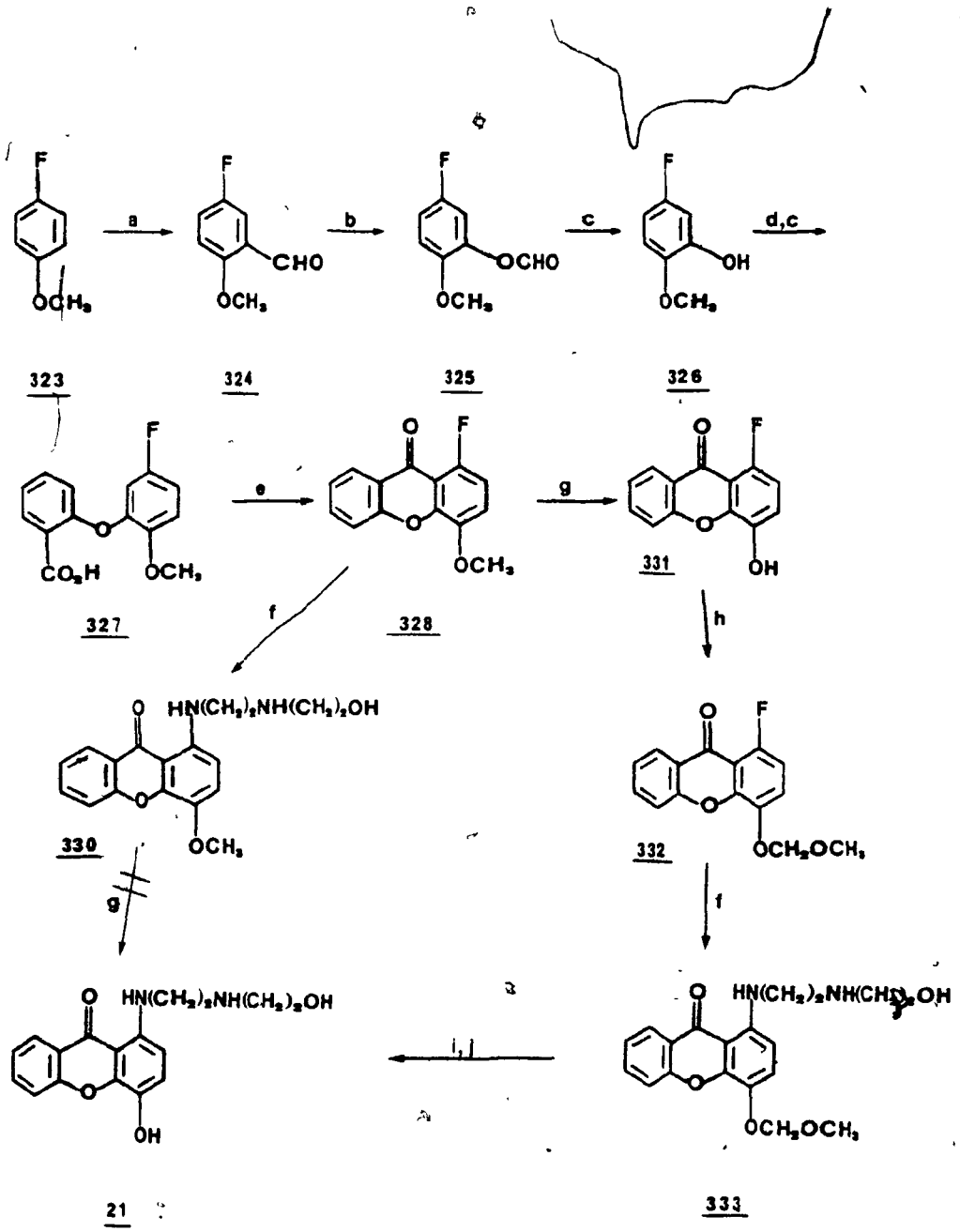



21

## 5.2 SYNTHESIS OF 4-HYDROXY-1-[[2-[(2-HYDROXYETHYL)AMINO]ETHYL]AMINO]XANTHONE (21)

Xanthone 21 was prepared in nine steps in 30% overall yield from commercially available *p*-fluoroanisole (323) using the now familiar strategy applied to the preparation of xanthones. Formylation of 323 using α,α'-dichloromethyl methyl ether and the catalyst titanium(IV) chloride, gave an excellent yield (92%) of 2-formyl-4-fluoroanisole (324). The ability of fluorine to couple (as judged by pmr spectroscopy) over a large number of bonds was evidenced with compound 324 in which coupling with the aldehydic proton was observed ($^5J \cong 3$ Hz). (The 200 MHz $^1$H.m.r. spectrum of the compound clearly showed two large couplings between the *ortho* H's and the F atom, thus unequivocally indicating the compound to be isomer 324 and not 3-formyl-4-fluoroanisole). Baeyer-Villiger oxidation with *m*-CPBA acid in the presence of the free-radical inhibitor 101 gave after refluxing in methylene chloride for 5 h an excellent yield of essentially pure formate 325 which was not isolated (characterized by pmr spectroscopy) but immediately hydrolyzed under basic conditions.

Phenol 326 and iodoester 97 in refluxing DMA in the presence of copper(I) oxide afforded an oil after 18 h which was immediately hydrolyzed to acid 327 and the latter cyclized without prior purification using a mixture of TFA-TFAA to give fluoroxanthone 328 in about 40% isolated yield as a white crystalline mass. This xanthone 328 was then combined with 2-(2-aminoethylamino)ethanol (329) and heated in refluxing pyridine for 5 days to afford a 65% yield of a bright orange amorphous material 330. The long reaction time was not only a reflection of the intrinsic sluggishness of the reaction (since it involves nucleophilic aromatic substitution) but also because high dilution of the reactants was a necessary condition. Demethylation of 330 using $BBr_3$ led only to degradation of the side chain as the main course of reaction. On the other hand, demethylation of xanthone 328 proceeded easily and in quantitative yield to hydroxyxanthone 331. Protection of the phenolic function as a methoxymethyl ether was readily accomplished by treatment with chloromethyl methyl ether and sodium hydride in THF which led to a quantitative yield of 332. Using a minimal amount of solvent, reaction between xanthone 332 and 329 was complete after 3 days of heating in refluxing pyridine, thereby affording 333. Hydrogen chloride removed easily and quantitatively the methoxymethyl protecting group within minutes at 0°C in the absence of side reactions. The dichloride salt of 21 was neutralized upon alkaline work-up and an excellent overall yield of 86% (from




a) $Cl_2CHOCH_3/TiCl_4$; b) *m*-CPBA, 101; c) $OH^-/H_2O$/MeOH; d) 97/$Cu_2O$/DMA; e) TFA-TFAA; f) $NH_2(CH_2)_2NH(CH_2)_2OH$, pyridine; g) $BBr_3$, -78°C; h) $ClCH_2OCH_3$/NaH; i) HCl; j) $^-OH/H_2O$.

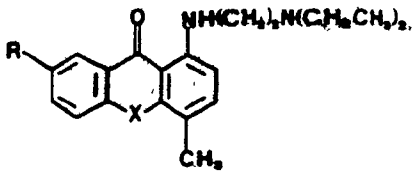
xanthone 328) of hydroxyaminoxanthone 21 was obtained as a red crystalline mass. The infrared spectrum of the product

confirmed the presence of a carbonyl group (H-bonded) while the mass spectrum included a molecular ion corresponding to the expected molecular weight of 21. The pmr spectrum of the substance where evidence of H to F coupling was absent, appeared simplified and clearly showed an AB-quartet for protons H-2 and H-3.

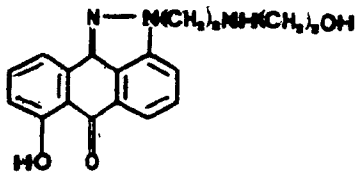
## 5.3 BIOLOGICAL RESULTS

Analogs 21, 328 and 330 (of which 21 was tested as the dihydrochloride salt) were tested at Bristol Laboratories (Syracuse, N.Y.) against the P388 mouse leukemia model* and were found to be *inactive*, a disappointing result in view of the known high effectiveness of anthraquinone 322. On the basis of the findings of Archer *et al.*[698] with xanthone analogs of lucanthone (334) (and related compounds), one would certainly expect xanthone 21 to intercalate with DNA. However, while intercalation may be a necessary condition for activity, it is obviously not sufficient for antitumor activity. Any explanation of the inactivity of compound 21 is complicated further by other recent results[699] indicating that the related cyclic analog 335 (patterned after the imino derivative described by Tong *et al.*[700] but expected to display an altered redox potential), shows activity comparable to that of

*The P388 leukemia system is used routinely for initial screening of crude natural products. It is generally considered to be a sensitive system capable of detecting low orders of activity and is more sensitive than the L1210 leukemia model to materials that show activity against both systems.



334 X = S; R = H
X = O; R = H



335

prototype 321.

As more such structure-activity relationship studies emerge thus increasing in principle our changes of achieving a better understanding of mechanisms of action, the more one realizes that there is as yet nothing simple about their interactions with biological systems. It becomes more and more apparent that an effort no less extensive than that which is currently expended in the field of the anthracyclines is sorely needed before significant progress in cancer chemotherapy can be made. We clearly do not know enough presently about their interaction mechanisms to make safe predictions.

## CONTRIBUTIONS TO KNOWLEDGE

1. This work comprises a study of the novel compounds, the heteroanthracyclines. Strategies to achieve the synthesis of the aglycone portion of these compounds were devised and investigated.

2. Useful syntheses of 1,4-dimethoxy substituted xanthones were developed.

3. Chloromethylation and bromination reactions of 1,4-dimethoxyxanthone as well as the formylation of 1,4-dimethoxyxanthene were shown to proceed regioselectively in high yield.

4. The chemistry of a hypothetical xanthone-derived *o*-quinodimethane was studied.

5. The potentially useful synthon of the α,β-dianion of acetaldehyde, (E)-N-vinylpyrrolidine-β-(2-lithio-1,3-dithian-2-yl) was synthesized and studied as an annulating reagent.

6. The synthesis and study of xanthoquinone and thioxanthoquinone as well as their chemistry, in particular, as dienophiles in Diels-Alder cycloaddition reactions is novel. Also, the potential usefulness of these compounds as dienophiles was demonstrated.

7. The novel synthesis of two dienes is reported.

8. Novel methodology to obtain *cis*-reduction of silylated-alkynes is reported as well as a useful modification of the *trans*-reduction of alkynes.

9. The study leading to the synthesis of analogs with carbon substituents at position 7 of the natural product or of the heterocyclic substrates, is novel.

10. The methodology to prepare 1-alkylaminoxanthones was developed and their biological significance reported.

## GENERAL EXPERIMENTAL

Azo*bis*isobutyronitrile (AIBN) was recrystallized from 95% ethanol to mp 103-104°C[701] (Lit.[702] mp 102-103°C) and stored at 4°C in the dark. Activated zinc (Zn*) was prepared from commercial grade zinc dust (99.99% pure, supplied by Fisher Scientific Ltd., Montreal) by the method described by Cava *et al.*[441a]. Silver(II) oxide (AgO) was prepared immediately before use according to the procedure of Hammer and Kleinberg[703]. Commercially available AgO (Aldrich Chemical Co., Milwaukee, Wisconsin) was activated by sonication for 1 h prior to use[566,704]. Potassium cyanide-18-crown-6 complex was prepared as described by Evans *et al.*[518]. N-Bromosuccinimide (NBS) was purified by recrystallization from water[705]. *tris*(Triphenylphosphine)rhodium(I) chloride $[(C_6H_5)_3P]_3RhCl$ was purchased from Alfa-Ventron Corp., Danvers, Massachusetts.

Ultrasound-promoted reactions were conducted using a laboratory ultrasound cleaner (150W, 50-55 kHz) manufactured by the Branson Co.

Analytical thin-layer chromatography (tlc) was carried out on aluminium-backed sheets pre-coated with silica gel $60F_{254}$, 0.2mm thick (Merck Co. Ltd., Darmstadt) and visualization was made by means of an ultraviolet light, iodine chamber, or by charring with sulfuric acid in ethanol (10%

v/v), or phosphomolybdic acid in isopropanol (3% w/v), or a solution consisting of ammonium molybdate(VI) (120 mmol), cerium(IV) sulfate (30 mmol) in 1ℓ aqueous sulfuric acid (10% v/v). Column chromatography (analytical and preparative scale) was performed by the "flash chromatography" technique as described by Still *et al.*[337a] on 32 to 63μ (400 to 230 mesh) silica gel (British Drug Houses, Toronto) or Woelm silica gel (32 to 63μ, ICN Nutritional Biochemicals, Cleveland, Ohio) using purified solvents. Analytical gas chromatography was conducted on a HP5750 Model instrument using a 3% OV-101 (3m x 2mm) column with dry helium as carrier gas.

Solutions were concentrated on a rotary evaporator at pressures of 15-20 mmHg and at temperatures of 20-30°C unless otherwise specified.

Melting points (mp) were determined in closed capillary tubes on a Büchi SMP-20 melting point apparatus and are uncorrected. Infrared (IR) spectra were measured on a Perkin-Elmer 297 spectrophotometer and absorptions are reported in wavenumbers ($cm^{-1}$). Mass spectra (ms) were recorded on either an LKB Model 9000 or HP Model 5984 mass spectrometers at 70 or 15 eV. Gas chromatography-mass spectrum (gc/ms) analyses were performed on the HP Model 5984 instrument only. All mass peak intensities are reported as % rel. int. Proton magnetic resonance ($^1$H.m.r.) spectra were measured on Varian T-60, T-60A, XL-200 or Bruker WH-400 spectrometers and carbon

magnetic resonance ($^{13}$C.m.r.) spectra were measured on Bruker WH-90 or Bruker WH-400 spectrometers. Chemical shifts are reported in δ units (parts per million, ppm) relative to tetramethylsilane (δ = 0.0 ppm) using deuterated solvents, 99.5 atom % D. Coupling constants are reported in hertz (Hz). All simple signals are described as singlets (s), doublets (d), triplets (t), or quartets (q) and assigned chemical shift values determined by the center of their resonance frequency signal while undefined multiplets (m) are described by the range of their resonance frequency signal.

Reactions requiring heating were carried out in paraffin oil baths for T < 125°C. For reactions requiring higher temperatures either a silicone oil bath, or a heating mantle connected to a variable transformer, were used. Reactions requiring low temperatures were performed in $CO_2$-diethyl ether (-100°C), -acetone (-78°C), -acetonitrile (-42°C), or -carbon tetrachloride (-22°C) baths and those requiring 0°C utilized ice baths.

The apparatus for anhydrous reactions was flame-dried in a stream of nitrogen. An argon atmosphere was used with organolithium reagents[706] while all other anhydrous reactions were carried out under an atmosphere of nitrogen. All additions wherever possible were made *via* syringe through a septum using techniques described by Brown[707] and Shriver[708].

Solutions of n-butyllithium (n-BuLi) in hexane,

*sec*-butyllithium (*sec*-BuLi) in cyclohexane and methyllithium (MeLi) in diethyl ether were titrated in tetrahydrofuran (THF) with diphenylacetic acid[709] prior to use. Solutions of lithium tri-*sec*butylborohydride (L-Selectride) in THF, sodium *bis*(2-methoxyethoxy)aluminium hydride (Red-Al or Vitride) in toluene and borane-THF complex in tetrahydrofuran were used without titration. Clear solutions of LAH in tetrahydrofuran were prepared as described by Krishnamurthy and Brown[710] except that the suspension was stirred for 20 h at room temperature (rt) in dry solvent prior to filtering through a 6-cm bed of tightly packed dry Celite under positive nitrogen pressure. The clear solutions were stored in a septum sealed flask under nitrogen at rt. The molarity of the solutions was determined by measuring the hydrogen evolved when the solution is injected into a glycerine-water-THF mixture (1:1:1). Lithium amide bases were generated *in situ* immediately before use from distilled amine bases and n-BuLi at -78°C.

Diisopropylamine, N,N,N',N'-tetramethylpiperidine (TMP), piperidine, pyrrolidine and 2,2,6,6-tetramethylethylenediamine (TMEDA) were allowed to stand over 20% w/v 3Å molecular sieves, decanted, stirred overnight with $CaH_2$, distilled and stored over 20% w/v 3Å molecular sieves[711]. Pyridine and triethylamine were stood over KOH for 24 h, decanted, fractionated and stored as above. Methylene chloride

was distilled from calcium chloride and stored over anhydrous sodium sulfate[712]. (Distillation from $P_2O_5$[713] requires filtering through neutral alumina, activity I to remove traces of polyphosphoric acid[714]). Anhydrous diethyl ether was obtained by distillation from lithium aluminium hydride (LAH) or purchased from Mallinckrodt Chemicals, Montreal. Absolute ethanol was obtained from Consolidated Alcohols, Toronto. Methanol was distilled from magnesium turnings immediately before use. Toluene, 1,2-dimethoxyethane (DME), dioxane and tetrahydrofuran (THF) were distilled from a purple solution of disodium benzophenone dianion[389c,701,715] (sodium/benzophenone) and hexane was distilled from a light blue solution of benzophenone ketyl (sodium/benzophenone)[716], under inert atmosphere immediately before use. Benzene was distilled from $CaH_2$ and stored over 4Å molecular sieves[717]. N,N-Dimethylformamide (DMF) and N,N-dimethylacetamide (DMA) were stood over 4Å molecular sieves overnight and distilled from $P_2O_5$ at reduced pressure, allowed to stand over anhydrous potassium carbonate (12h) and subsequently stored over 4Å molecular sieves[718]. Hexamethylphosphoramide (HMPA) was stirred over barium oxide overnight, filtered, distilled from calcium hydride at reduced pressure and stored over 20% w/v 4Å molecular sieves[718]. Other solvents were at least reagent grade and used as received.

# EXPERIMENTAL

## Chapter 1

### SYNTHESIS OF (±)-2-ACETYL-5,8-DIMETHOXY-1,2,3,4-TETRAHYDRO-2-NAPHTHOL

#### Knoevenagel Product 42

A solution of 2,5-dimethoxybenzaldehyde (83.1 g, 0.5 mol), dimethyl malonate (72.7 g, 0.55 mol), piperidine (1.23 g) and acetic acid (3.7 g) was refluxed with 350 mL of benzene in an apparatus equipped with a Dean-Stark water separator (containing 4Å molecular sieves) for 22 h. The product mixture was diluted with ether (300 mL) and washed successively with 100 mL portions of 5% HCl, 5% $NaHCO_3$, and saturated brine. The aqueous washes, which were not combined, were extracted once with ether. Evaporation of the solvent *in vacuo* gave 133 g (95%) of 42 as a yellow oil. An analytically pure sample of 42 as yellow plates, mp 65-66 °C was obtained by recrystallization ($CH_2Cl_2$/hexanes) after flash chromatography ($CH_2Cl_2$).

IR (KBr) $\nu_{max}$: 2840 ($CH_3$, $ArOCH_3$), 1710 (carbonyl, conjugated ester), 1615 (conjugated alkene), 1585 (ring C···C), 1303, 1250, 1175 (=C-O-C, $\nu_{as}$), 1065 (=C-O-C, $\nu_s$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 7.90 (s, 1H, vinyl), 6.76 (m, 3H, aryl-H), 3.86 (s, 9H, 2×$COOCH_3$, $OCH_3$), 3.76 (s, 3H, $OCH_3$).

Triester 43

To a solution of 42 (28 g, 0.1 mol) in 200 mL THF at -78°C was added, under inert atmosphere, L-Selectride (lithium tri-*sec*butylborohydride, 110 mL of a 1 M solution in THF, 0.11 mol). After complete addition, the flask was emersed in an ice-water (0°C) bath and stirred for 30 min. Following spectroscopic analysis of an aliquot that indicated hydride addition was complete, methyl bromoacetate (16.1 g, 0.105 mol) was added at once. The solution was refluxed for 3 h before the solvent was evaporated. The residue was neutralized with 5% HCl, extracted with $CH_2Cl_2$ (150 mL), washed with water (3 x 50 mL) and dried over anhydrous $Na_2SO_4$. After evaporation of the solvent, crude 43 was obtained which was purified by flash chromatography ($CH_2Cl_2$-EtOAc, 2:3) to afford 28.3 g (80%) of 43 as a yellow oil that although pure (by tlc) did not crystallize.

IR (film) $\nu_{max}$: 2840 ($CH_3$, $ArOCH_3$), 1745 (carbonyl - saturated ester), 1600 (ring C⋯C), 1249, 1180 (=C-O-C, $\nu_{as}$), 1058 (=C-O-C, $\nu_s$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 6.64 (s, 2H, aryl-H), 6.45 (s, 1H, aryl-H), 3.70-3.63 (m, 15H, 3×$COOCH_3$, 2×$OCH_3$), 3.36 (s, 2H, benzylic), 2.76 (s, 2H, -$CH_2$-$COOCH_3$).

Triacid 44

A mixture of triester 43 (7.1 g, 0.02 mol), 50 mL of ethanol, 80 mL of water and 16 g KOH was stirred at 75°C for 5 h and then overnight at room temperature. The solution was washed once with $CHCl_3$ (25 mL) and poured onto concentrated HCl (30 mL) and 30 g ice. The clear, acidic solution was cooled at 4°C for several days and 2.5 g (40%) of 44 was obtained as white needles, mp 189-190°C.

$^1$H.m.r. (60 MHz, $CF_3COOH$) δ: 7.0 (bs, 3H, aryl-H), 4.0 (s, 3H, $OCH_3$), 3.8 (s, 3H, $OCH_3$), 3.60 (s, 2H, benzylic), 3.43 (s, 2H, methylene).

Anhydride 45

A mixture of triacid 44 (2.27 g, 7.0 mmol) and 25 mL of acetic anhydride were refluxed for 20 min. Removal of the excess acetic anhydride *in vacuo* gave a 1.45 g (80%) anhydride 45 was a brown oil.

IR (film) $\nu_{max}$: 2842 ($CH_3$, $ArOCH_3$), 1860, 1780 (carbonyl - cyclic anhydride), 1248 (=C-O-C), 1222, 944 (C-O anhydride).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 7.26 (s, 1H, aryl-H), 6.73 (s, 2H, aryl-H), 3.3-2.3 (m, 5H).

3-Carboxy-5,8-dimethoxy-1-tetralone (46)

A solution of anhydride 45 (2 g, 8.0 mmol) in 15 mL TFA and 23 mL TFAA was stirred at room temperature for 12 h. Evaporation of the TFA-TFAA *in vacuo* left a residue which was dissolved in $CH_2Cl_2$, washed with water (5 x 10 mL) and dried over anhydrous $Na_2SO_4$. Removal of the solvent gave 1.8 g (90%) of tetralone 46 as a viscous oil.

IR (film) $\nu_{max}$: 3500-2700 (OH, carboxylic acid), 1690 (carbonyl, carboxylic acid), 1665 (carbonyl), 1600 (ring C···C), 1247 (=C-O-C, $\nu_{as}$), 1025 (=C-O-C, $\nu_s$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 10.2 (bs, 1H, exchangeable COOH), 6.73 (bs, 2H, aryl-H), 3.73 (s, 6H, 2×$OCH_3$), 3.2-2.4 (m, 5H).

5,8-Dimethoxy-2-carboxylic acid (47)

To a solution of tetralin 46 (1.8 g, 7.0 mmol) in 20 mL TFA was added triethylsilane (2.0 g, 17 mmol) and stirred at room temperature for 1 h. The TFA was removed by evaporation and the white gummy residue treated with excess 20% aqueous KOH, washed with ether (2 x 10 mL) to remove silicon by-products, and acidified with concentrated HCl. Acid 47 precipitated as an oil which was diluted with $CH_2Cl_2$, washed with water (3 x 10 mL) and dried over anhydrous $Na_2SO_4$. Evaporation *in vacuo* of the solvent gave 1.6 g (95%) of 47 as an oil.

IR (film) $\nu_{max}$: 3500-2700 (OH, carboxylic acid), 1690 (carbonyl, carboxylic acid), 1600 (ring C⋯C), 1248 (=C-O-C, $\nu_{as}$), 1020 (=C-O-C, $\nu_{s}$).

$^{1}$H.m.r. (60 MHz, $CDCl_3$) δ: 11.00 (bs, 1H, exchangeable COOH), 6.70 (s, 2H, aryl-H), 3.7 (s, 6H, 2x$OCH_3$), 3.2-1.9 (m, 7H).

2-Acetyl-5,8-dimethoxytetralin (48)

To a solution of acid 47 (1.2 g, 5.0 mmol) in 20 mL (1:1) THF-ether was added methyllithium (11 mL of a 1.4 M solution in ether, 15 mmol) dropwise under inert atmosphere at -20°C. The mixture was stirred for 8 h and then carefully hydrolyzed by adding the mixture *slowly*, dropwise, with vigorous stirring to a large solution of water-THF-HCl. The product was extracted with $CH_2Cl_2$, washed with 5% aqueous $NaHCO_3$ (3 x 10 mL), water (3 x 10 mL) and dried over anhydrous $Na_2CO_3$. Evaporation *in vacuo* of the solvent gave an amorphous mass which was recrystallized ($CH_3OH$) to afford 1.1 g (95%) of pure 48: mp 82-83°C (Lit.[292] 81-82°C).

IR (film) $\nu_{max}$: 2840 ($CH_3$, $ArOCH_3$), 1715 (carbonyl, acetyl), 1600 (ring C⋯C), 1249 (=C-O-C, $\nu_{as}$), 1020 (=C-O-C, $\nu_{s}$).

$^{1}$H.m.r. (60 MHz, $CDCl_3$) δ: 6.7 (s, 2H, aryl-H), 3.75 (s, 6H, 2x$OCH_3$), 2.28 (s, 3H, $COCH_3$), 2.78-1.62 (m, 7H).

M.s. (EI, 70eV, 45°C) m/z (%): 250 (55.7, $M^{+\cdot}$), 251 (15.8, $[M+1]^{+\cdot}$ isotope peak), 232 (56.2, $M^{+\cdot} - H_2O$), 207 (100, $M^{+\cdot} - CH_3CO$ or $M^{+\cdot} - CH_3\text{-}CO$), 189 (75.9, 207, $H_2O$), 43 (83.1, $CH_3CO^+$).

Synthesis of 6- and 7-(2-methoxybenzoyl)-2-acetyl-2-hydroxy-5,8-dimethoxytetralin (50) and (51)

A mixture of tetralin 30 (0.18 g, 0.72 mmol) and *o*-methoxybenzoic acid (0.55 g, 3.6 mmol) in 35 mL of (4:3) TFAA-TFA was refluxed for 24 h. Evaporation of the TFAA and TFA *in vacuo* gave a residue of a dark brown oil that consisted of a mixture (by tlc and pmr spectroscopy) of esters 52, 53 and 54. Hydrolysis with 30 mL 5% aqueous methanol (1:2) solution of KOH at 80°C for 3 h followed by purification by flash chromatography ($CH_2Cl_2$-EtOAc, 5:2) gave 100 mg (60%) tetralin 30 and 69 mg (25%) of desired compounds 50 and 51 as an oil.

IR (nujol) $\nu_{max}$: 3480 (br, OH), 2830 ($CH_3$, $ArOCH_3$), 1705 (carbonyl, acetyl), 1660 (carbonyl, diaryl), 1600 (ring C···C), 1250, (=C-O-C).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 7.56-6.93 (m, 4H, aryl-H), 6.86 (bs, 1H, aryl-H (7 or 6)), 3.8 (s, 3H, $OCH_3$), 3.73 (s, 3H, $OCH_3$), 3.5 (bs, 1H, exchangeable OH), 3.43 (s, 3H, $OCH_3$), 3.1-2.8 (m, 4H, benzylic), 2.3 (s, 3H, $COCH_3$), 2.0-1.8 (m, 2H, methylene).

2-Acetyl-5,8-methoxy-2-hydroxytetralin (30)

Oxygen was bubbled into a cooled mixture (-20°C) of t-BuOK (0.51 g, 4.5 mmol) in 15 mL t-butanol, excess trimethylphosphite (4 mL) and DMF (10 mL). Tetralin 48 (1 g, 4.3 mmol) was dissolved in 5 mL t-butanol and added to the oxygen-saturated solution. After complete addition, the cooling bath was removed and oxygen was bubbled into the mixture for an additional 5 min at room temperature. A stream of nitrogen was passed vigorously through the solution to expel the oxygen and the solution was acidified with acetic acid. After removal of as much of the solvent as possible by evaporation *in vacuo* (a favorable low boiling azeotrope is obtained between DMF and 1-propanol), the residue was dissolved in $CH_2Cl_2$, washed with water (3 x 10 mL), and dried over anhydrous $Na_2CO_3$. Evaporation *in vacuo* of the solvent gave crude tetralin 30 which was purified by recrystallization ($CH_3OH$/ether) to give 0.85 g (80%) of pure 30: mp 104-106°C (Lit.[292] 100-102°C).

IR (nujol) $\nu_{max}$: 3490 (OH, weak intramolecular H-bonding), 2840 ($CH_3$, $ArOCH_3$), 1700 (carbonyl), 1600 (ring C⋯C), 1250 (=C-O-C, $\nu_{as}$), 1030 (=C-O-C, $\nu_s$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 6.63 (s, 2H, aryl-H), 3.78 (s, 3H, $OCH_3$), 3.75 (s, 3H, $OCH_3$), 3.6 (bs, 1H, exchangeable OH), 3.0-2.7 (m, 4H, benzylic), 2.26 (s, 3H, $COCH_3$), 2.0-1.66 (m, 2H, methylene).

M.s. (EI, 70eV, 80°C) m/z (%): 384 (50, $M^{+\cdot}$), 385 (13, $[M+1]^{+\cdot}$ isotope peak), 366 (5, $M^{+\cdot} - H_2O$), 135 (100, $M^{+\cdot} - C_{14}H_{17}O_4$), 43 (10, $CH_3CO^+$).

Ester 52

A mixture of tetralin 30 (0.18 g, 0.72 mmol) and *o*-methoxybenzoic acid (0.12 g, 0.79 mmol) in 35 mL of (4:3) TFAA-TFA was refluxed for 16 h. After evaporation of TFAA and TFA *in vacuo*, the residue was dissolved in $CH_2Cl_2$ (30 mL), washed with dilute NaOH (3 x 10 mL), water (3 x 10 mL) and dried over anhydrous $Na_2SO_4$. Evaporation *in vacuo* of the solvent gave a crystalline material which was purified by recrystallization ($CH_3OH$/petroleum ether) as transparent prisms: mp 139-141°C.

IR (nujol) $\nu_{max}$: 2840 ($CH_3$, $ArOCH_3$), 1720 (carbonyl, acetyl and conjugated ester), 1600, 1580 (ring C⋯C), 1260 (=C-O-C, $\nu_{as}$), 1020 (=C-O-C, $\nu_s$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 8.1-6.6 (m, 4H, aryl-H), 6.58 (s, 2H, H-7), H-8), 3.76 (s, 3H, $OCH_3$), 3.73 (s, 3H, $OCH_3$), 3.7 (s, 3H, $OCH_3$), 3.1-2.8 (m, 4H, benzylic), 2.13 (s, 3H, $COCH_3$), 2.0-1.8 (m, 2H, methylene).

M.s. (EI, 70eV, 82°C) m/z (%): 384 (3.9, $M^{+\cdot}$), 385 (1.1, $[M+1]^{+\cdot}$), 232 (100, $M^{+\cdot} - C_8H_8O_3$), 135 (76.2, $[C_8H_7O_2]^{+\cdot}$), 43 (34, $CH_3CO^+$).

# EXPERIMENTAL

## Chapter 2

### SYNTHESIS OF 2-CARBOMETHOXY-1,4-BENZOQUINONE (87)

#### Preparation of methyl 2,5-dihydroxybenzoate (88)

To a stirred solution of 2,5-dihydroxybenzoic acid (6.2 g, 0.04 mol) in 50 mL spectrograde methanol was added a solution of boron trifluoride etherate (9.0 mL) under an inert atmosphere. The solution was refluxed overnight. The reaction was cooled (0°C) and 5% aqueous $NaHCO_3$ was added with vigorous stirring. The solution was concentrated *in vacuo* and ethyl acetate (80 mL) was added. The organic layer was separated, washed successively with 5% aqueous $NaHCO_3$ (3 x 40 mL), water (3 x 40 mL), saturated brine (3 x 40 mL) and dried over anhydrous $Na_2SO_4$. Evaporation of the solvent *in vacuo* gave a solid which was recrystallized (water) to yield 6.3 g (94%) of the pure ester 88 as long white needles: mp 79-80.5°C.

IR (KBr) $\nu_{max}$: 3200 (OH, intramolecular H-bonded), 1680 (C=O, H-bonded), 1610, 1500 (ring C···C), 1270 (=C-O-C, $\nu_{as}$), 1090 (=C-O-C, $\nu_s$), 800 (1,3,4 trisubstituted phenyl).

$^1$H.m.r. (60 MHz, $CD_3COCD_3$) δ: 10.2 (bs, 2H, exchangeable phenolic OH), 7.36-6.7 (m, 3H, aryl-H), 3.9 (s, 3H, $COOCH_3$).

Oxidation of methyl 2,5-dihydroxybenzoate (88)

To a solution of pure methyl 2,5-dihydroxybenzoate (0.72 g, 4.3 mmol) in 10 mL dry benzene was added silver(II) oxide (1.13 g, 9.0 mmol). The mixture, protected from light*, was heated for about 5 min at 60°C and stirred at room temperature for another 5 min before being filtered through a thin pad of Celite. Anhydrous $K_2CO_3$ was added to the filtrate and the mixture was vigorously stirred for 1 h. The mixture was filtered and evaporated *in vacuo* to give an amorphous material which was triturated with hot hexanes. Evaporation of the solvent *in vacuo* gave the quinone which was purified further by recrystallization (pentane). Pure quinone 87, 0.5 g (64%) was obtained as long light-orange needles: mp 53-53.5°C (Lit.[378] 53.5-54°C).

IR (melt) $\nu_{max}$: 2980 ($-CH_3$), 1728 (C=O, conjugated $COOCH_3$), 1660 (C=O, quinone), 1600 (C=C), 1270 (C-O-C, $\nu_{as}$), 1110 (C-O-C, $\nu_s$).

$^1$H.m.r. (60 MHz, $CDCl_3$) $\delta$: 7.1 (m, 1H, H-3), 6.8 (m, 2H, H-5, H-6), 3.9 (s, 3H, $COOCH_3$).

*The flask was conveniently wrapped in aluminium foil. Quinone 87 was protected from light throughout its manipulation as well as during its subsequent storage.

Synthesis of 4,4-dimethoxycyclohexa-2,5-dienone (91)

To an open 100-mL beaker was added 50 mL methanol, *p*-methoxyphenol (2 g, 16.1 mmol) and the inert electrolyte anhydrous lithium perchlorate (20 g, 188 mmol). The mixture was magnetically stirred and cooled (0°C) in an ice-water bath. The reaction, easily monitored by pmr, was complete after about 2.0 h when subjected to a current of about 1.0 A (Electrical Efficiency = 42%, Lit.[380] EE = 54%). The reaction mixture was concentrated *in vacuo* (< 25%), $CH_2Cl_2$ (50 mL) added, washed quickly with cold water (1 x 25 mL) and dried over anhydrous sodium sulfate. Evaporation of the solvent *in vacuo* gave a dark yellow oil which was purified by flash chromatography ($CH_2Cl_2$) affording 2.1 g (85%) of monoketal 91 as a light yellow oil: bp 109-111°/12mm (Lit.[380] bp 70-73°C/0.7mm). The silica gel used was washed with 5% aqueous ammonium hydroxide, distilled water and dried at 110°C overnight.

IR (film) $\nu_{max}$: 2825 ($CH_3$, $ArOCH_3$), 1695 (conjugated carbonyl), 1650 (C=C), 1145 (-C-O-C, $\nu_{as}$), 1080, 1045 (-C-O-C, $\nu_s$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 6.78 (d, J = 11 Hz, 2H, H-3, H-5 ), 6.15 (d, J = 11 Hz, 2H, H-2, H-6), 3.36 (s, 6H, $OCH_3$).

The undivided cell consisted of a platinum gauze and wire (anode) and a tungsten wire (cathode). The source of direct current was a 6-12 volt battery recharger (Canadian Tire Corporation, Model T1225), equipped with an internal ammeter. The battery recharger was connected to a variable voltage regulator (Variac), which in turn was connected to an alternating current supply.

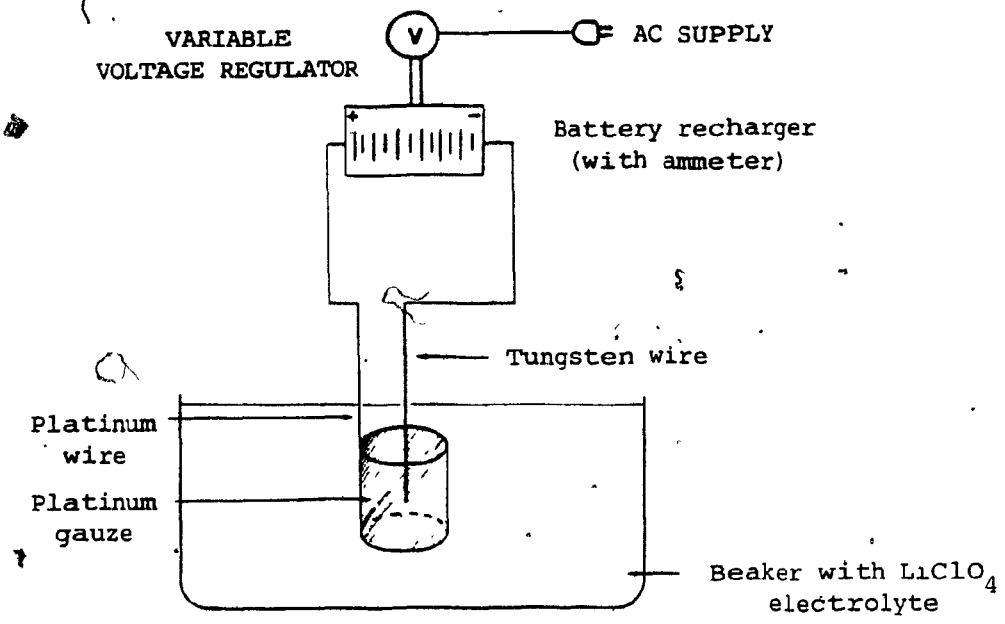



Figure 17: The schematic of the electrochemical apparatus.

Synthesis of 1-(*o*-methoxy)phenyl-1,3-dithiane (94)

To a stirred solution of 2-methoxybenzaldehyde (5 g, 0.037 mol) and 1,3-propanedithiol (4 g, 0.037 mol) in 50 mL $CH_2Cl_2$ was added chlorotrimethylsilane (6 g, 0.055 mol), over a period of 20 min with cooling at 0°C, under an inert atmosphere. After complete addition, the cooling bath was removed and the solution stirred at room temperature for 2 h. The solution was washed successively with 5% aqueous sodium carbonate (3 x 25 mL), water (3 x 25 mL), saturated brine (3 x 25 mL), and dried over anhydrous sodium sulfate. Evaporation of the solvent *in vacuo* gave a residue which was recrystallized (methylene chloride-hexane) to give 7.6 g (92%) of the white crystalline dithiane 94: mp 80-82°C.

IR (nujol) $\nu_{max}$: 2830 ($CH_3$, $ArOCH_3$), 1610, 1500 (ring C···C), 1420 (S-$CH_2$), 1250 (=C-O-C, $\nu_{as}$), 1020 (=C-O-C, $\nu_s$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 7.66-6.8 (m, 4H, aryl-H), 5.7 (s, 1H, methine), 3.83 (s, 3H, $OCH_3$), 3.16-2.8 (m, 4H, -S$\underline{CH_2}$$CH_2$$\underline{CH_2}$S-), 2.23-1.9 (m, 2H, -S$CH_2$$\underline{CH_2}$$CH_2$S-).

Preparation of 1-(*o*-methoxy)phenyl-1,3-dithianide (93)

To a solution of dithiane 94 (1 g, 4.42 mmol) in 20 mL THF-ether (1:1) was added n-butyllithium (1.8 mL of a 2.6 M solution in hexane, 4.68 mmol) at -22°C under inert atmosphere. After stirring 5 h, the reaction was quenched with an excess of deuterated methanol ($CH_3OD$). Evaporation of the solvent *in vacuo* gave a crude crystalline material which was purified by recrystallization (as for 94) to give essentially a quantitative yield of the deuterated compound. This established the conditions required for dithianide formation.

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 7.66-6.8 (m, 4H, aryl-H), 3.83 (s, 3H, $OCH_3$), 3.16-2.8 (m, 4H, $-SCH_2CH_2CH_2S-$), 2.23-1.9 (m, 2H, $-SCH_2CH_2CH_2S-$).

Esterification of *o*-iodobenzoic acid

Method A

To a solution of *o*-iodobenzoic acid (5 g, 20.3 mmol) in 50 mL anhydrous ether was added an ethereal solution of diazomethane (prepared from Diazald)[395] at room temperature until a yellow color persisted. The reaction mixture was stirred overnight at room temperature. Unreacted diazomethane was destroyed by the addition of 3 mL acetic acid. The reaction mixture was washed successively with 5% aqueous $NaHCO_3$ (3 x 25 mL), water (3 x 25 mL), saturated brine (3 x 25 mL) and dried over anhydrous $Na_2SO_4$. Evaporation *in vacuo* gave 5.25 g (quantitative yield) of the pure methyl ester 97 as a yellow free-flowing oil.

Method B

To a solution of *o*-iodobenzoic acid (248 g, 1.0 mol) in 500 mL $CH_2Cl_2$ was added methanol (96 g, 3 mmol) and 15 mL concentrated sulfuric acid. The reaction mixture was refluxed for 75 h. To the resulting cloudy solution was added water and the top layer was siphoned. The organic layer was treated as described in Method A. Evaporation of the solvent *in vacuo* gave 244 g (93%) of the pure ester 97.

Method C[397]

To a solution of *o*-iodobenzoic acid (20 g, 0.08 mol) in 150 mL dry methanol was added chlorotrimethylsilane (19.3 g, 0.18 mol) at room temperature under inert atmosphere. The mixture was refluxed for 18 h. Evaporation of the solvent and distillation of the crude oil gave 20 g (95%) of the pure ester 97: bp 80-82°/0.2mm (Lit.[394] bp 272-274°/760mm).

IR (neat) $\nu_{max}$: 1730 (C=O), 1590, 1565 (ring C⋯C), 1280 (=C-O-C, $\nu_{as}$), 1110 (=C-O-C, $\nu_{s}$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 8.0-7.0 (m, 4H, aryl-H), 3.8 (s, 3H, $OCH_3$).

Synthesis of 2,5-Dimethoxyphenol (98)

Preparation of the formate 99.

A solution of 2,5-dimethoxybenzaldehyde (113.5 g, 0.683 mol) and 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide (2 g, 5.5 mmol) in 450 mL dry $CH_2Cl_2$ under inert atmosphere was cooled to 0°C. *m*-Chloroperoxybenzoic acid (183 g, 1.05 mol) was added in small portions (highly exothermic reaction) over a period of 0.5 h, with vigorous stirring. After complete addition, the mixture (a suspension) was stirred for *ca.* 20 min at 0°C. The mixture (which became homogeneous when heated) was refluxed for 1 h. The solution was cooled to 0°C and 10% aqueous $Na_2SO_3$ was added and vigorously stirred for 10 min. The organic layer was tested for active peroxide with starch-iodide paper indicator and more aqueous $Na_2SO_3$ was added until a negative test resulted. The organic layer was washed successively with water (100 mL), 5% aqueous $NaHCO_3$ (3 x 100 mL), water (3 x 100 mL), saturated brine (3 x 100 mL) and dried over anhydrous $Na_2SO_4$. Evaporation *in vacuo* gave 122 g (98%) of a crude clear light-yellow oil. An analytically pure sample of formate 99 as clear transparent plates, mp 61-62°C, was obtained by recrystallization ($CH_2Cl_2$/hexane) after flash chromatography ($CH_2Cl_2$).

IR (film) $\nu_{max}$: 2840 ($CH_3$, $ArOCH_3$), 1735 (C=O, formate), 1610, 1590, 1500 (ring C···C), 1215 (=C-O-C, $\nu_{as}$), 1185 (-C-O-C, formate), 1040, 1020 (=C-O-C, $\nu_s$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 8.15 (s, 1H, O(C=O)-H), 6.80-6.60 (m, 3H, aryl-H), 3.66 (s, 3H, $OCH_3$), 3.63 (s, 3H, $OCH_3$).

$^1$H.m.r. (200 MHz, $CDCl_3$) δ: 6.93 (d, J = 8.6 Hz, 1H, H-6), 6.79 (d, J = 2.9 Hz, 1H, H-3), 6.72 (dd, J = 2.9 and 8.6 Hz, 1H, H-5), 3.66 (s, 3H, $OCH_3$), 3.63 (s, 3H, $OCH_3$).

Hydrolysis of the formate 99

The crude formate 99 (120 g, 0.659 mol) was dissolved in 100 mL methanol under inert atmosphere and an excess of 10% aqueous solution of NaOH (82 g, 2.05 mol) was added with cooling at 0°C. After a few minutes the cooling bath was removed and the reaction mixture was stirred at room temperature for 3.5 h. The solution was acidified with concentrated HCl which precipitated a red oil. The oil was separated and combined with the $CH_2Cl_2$ extracts (3 x 100 mL) of the aqueous layer. The organic solution was washed successively with water (100 mL), saturated brine (3 x 50 mL), dried over anhydrous $Na_2SO_4$ and evaporated *in vacuo*. The resultant oil (100 g) was purified by bulb to bulb distillation to give 97 g (94% overall) of the phenol 98 as a red viscous oil: bp 106-110°C/5mm (Lit.[398] 124-126°C/7mm).

IR (film) $\nu_{max}$: 3460 (OH), 2840 ($CH_3$, $ArOCH_3$), 1620, 1600, 1510 (ring C···C), 1340 (OH bend), 1240 (=C-O-C, $\nu_{as}$), 1200 (=C-O-H), 1045, 1020 (=C-O-C, $\nu_s$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 6.83-6.33 (m, 3H, aryl-H),

6.06 (bs, 1H, exchangeable OH), 3.73 (s, 3H, $OCH_3$), 3.66 (s, 3H, $OCH_3$).

$^1$H.m.r. (200 MHz, $CDCl_3$) δ: 6.79 (d, J = 8.8 Hz, 1H, H-6), 6.5 (d, J = 2.9 Hz, 1H, H-3), 6.37 (dd, J = 2.9, 8.8 Hz, 1H, H-5), 6.0 (bs, 1H, exchangeable OH), 3.73 (s, 3H, $OCH_3$), 3.66 (s, 3H, $OCH_3$).

Synthesis of 1,4-Dimethoxyxanthone (76)

A mixture of 2,5-dimethoxyphenol 98 (30.8 g, 0.2 mol), methyl *o*-iodobenzoate 97 (52.4 g, 0.2 mol) and copper(I) oxide (14.3 g, 0.1 mol) in 150 mL of dry DMA was refluxed with efficient stirring under a nitrogen atmosphere for 24 h. The reaction was cooled (0°C) and filtered. Most of the solvent was removed by distillation *in vacuo*. To the oily residue was added 6N HCl (300 mL) and extraced with ether (3 x 200 mL). The organic layer was washed successively with water (3 x 100 mL), 2N NaOH (2 x 100 mL) and again with water (2 x 100 mL). Evaporation *in vacuo* gave *ca.* 40 g (69%) of diaryl ether 102 as a crude red viscous oil.

To the crude compound 102 (40 g, *ca.* 0.14 mol) dissolved in 200 mL methanol, was added 3N NaOH (200 mL) and the mixture refluxed for 1 h. After cooling, the solution was acidified with 6N HCl and concentrated *in vacuo*. Methylene chloride (400 mL) was added to the oily residue, and the resulting solution washed successively with water (3 x 100 mL), saturated brine (3 x 100 mL)

and dried over anhydrous $Na_2SO_4$. The solution was concentrated *in vacuo* to about 300 mL and added over a period of 30 min to a vigorously stirred solution of 150 mL TFAA-TFA (2:1 v/v) at 0°C. The deep red solution was allowed to warm up to room temperature overnight. Evaporation of the solvent and most of the TFAA-TFA *in vacuo* gave a solid mass which was redissolved in $CH_2Cl_2$ (150 mL), washed successively with 5% aqueous $NaHCO_3$ (3 x 75 mL), water (3 x 75 mL) and dried over anhydrous $Na_2SO_4$. The crude mixture was purified by flash chromatography (EtOAc-$CH_2Cl_2$, 3:2) to give the main fraction, compound 76 and a more polar fraction, compound 104. Recrystallization, of the main fraction, from methanol gave 20 g (56% based on phenol) of pure 1,4-dimethoxyxanthone (76) as an off-white crystalline material: mp 164-165°C (Lit.[366] 168-169°C).

IR (KBr) $\nu_{max}$: 2840 ($CH_3$, $ArOCH_3$), 1670 (C=O, xanthone (γ-pyrone)), 1600, 1580, 1500 (ring C···C), 1260 (=C-O-C, $\nu_{as}$), 1030 (=C-O-C, $\nu_s$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 8.32 (dd, J = 2 and 8 Hz, 1H, H-8), 7.85-7.2 (m, 3H, H-5, H-6, H-7), 7.15 (d, J = 9 Hz, 1H, H-3), 6.66 (d, J = 9 Hz, 1H, H-2), 3.95 (s, 6H, 2×$OCH_3$).

$^1$H.m.r. (200 MHz, $CDCl_3$) δ: 8.31 (dd, $J_{H8-H7}$ = 8.0 Hz, $J_{H8-H6}$ = 1.8 Hz, 1H, H-8), 7.68 (m, $J_{H6-H5}$ = 8.5 Hz, $J_{H6-H7}$ = 6.9 Hz, $J_{H6-H8}$ = 1.8 Hz, 1H, H-6), 7.53 (dd, $J_{H5-H6}$ = 8.5 Hz, $J_{H5-H7}$ = 1.2 Hz, 1H, H-5), 7.35 (m, $J_{H7-H8}$ = 8.0 Hz, $J_{H7-H6}$ = 6.9 Hz, $J_{H7-H5}$ = 1.2 Hz, 1H, H-7), 7.18 (d, J = 8.9 Hz, 1H, H-3), 6.70 (d, J = 8.9 Hz, 1H, H-2), 3.98 (s, 6H, 2×$OCH_3$).

$^{13}$C.m.r.* (22.63 MHz, $CDCl_3$) δ: 176.4 (C=O), 154.9 (C-10a), 153.9 (C-1), 148.0 (C-4a), 142.3 (C-4), 134.2 (C-6), 126.7 (C-8), 124 (C-7), 122.9 (C-8a), 117.6 (C-5), 116.6 (C-3), 113.5 (C-9a), 104.5 (C-2), 56.9 ($OCH_3$), 56.5 ($OCH_3$).

M.s. (EI, 70eV, 23°C) m/z (%): 256 (100, $M^{+\cdot}$), 257 (17.0, $[M+1]^{+\cdot}$ isotope peak), 241 (56.5, $M^{+\cdot} - CH_3$), 227 (63.6, $M^{+\cdot}$ - CHO), 213 (36.5, $M^{+\cdot} - CH_3$-CO).

*Assignments were made using the method described in Appendix 6.

# EXPERIMENTAL

## Chapter 3

### Synthesis of 2-Chloromethyl-1,4-Dimethoxyxanthone (110)

#### Method A

To a heated (35°C) mixture of 1,4-dimethoxyxanthone (4 g, 1.56 mmol), 50 mL acetic acid, 25 mL concentrated hydrochloric acid (∿ 38%) and 25 mL formalin (∿ 37%) was bubbled hydrogen chloride at a vigorous rate for 1 h. The reaction was stirred for an additional 5 h, poured onto ice and the precipitated material was collected, dissolved in $CH_2Cl_2$ (100 mL), washed successively with cold 5% aqueous $NaHCO_3$ (3 x 40 mL), cold water (3 x 40 mL) and dried over anhydrous $Na_2SO_4$. Evaporation of the solvent *in vacuo* gave a residue which was purified by flash chromatography (EtOAc-$CH_2Cl_2$, 2:5) affording 280 mg (60%) of 110 as a light yellow crystalline compound. (Further elution gave 95 mg (20% of the more polar compound 111 which did not crystallize.).

#### Method B

To a solution of 1,4-dimethoxyxanthone (0.66 g, 2.57 mmol) in 30 mL spectrograde $CHCl_3$ was added a four-fold excess of chloromethyl methyl ether and 1 drop of concentrated $H_2SO_4$. After heating gently (< 35°C) for 4 h the solvent was evaporated *in vacuo* and the residue dissolved in $CH_2Cl_2$ (30 mL), washed

with water (3 x 10 mL) and dried over anhydrous $Na_2SO_4$. Purification by flash chromatography ($CH_2Cl_2$) gave 570 mg (73%) of crystalline compound 110: mp 178-179°C. (Further elution gave 67 mg (10%) of the diaryl compound 112.).

IR (KBr) $\nu_{max}$: 2840 ($CH_3$, $ArOCH_3$), 1668 (C=O, xanthone (γ-pyrone)), 1600, 1580, 1500 (ring C···C), 1270 (=C-O-C, $\nu_{as}$), 1020 (=C-O-C, $\nu_s$), 775 ($CH_2$-Cl).

$^1$H.m.r. (200 MHz, $CD_2Cl_2$) δ: 8.31 (dd, $J_{H8-H7}$ = 8.0 Hz, $J_{H8-H6}$ = 1.8 Hz, 1H, H-8), 7.77 (m, $J_{H6-H5}$ = 8.5 Hz, $J_{H6-H7}$ = 7.0 Hz, $J_{H6-H8}$ = 1.8 Hz, 1H, H-6), 7.57 (dd, $J_{H5-H6}$ = 8.5 Hz, $J_{H5-H7}$ = 1.2 Hz, 1H, H-5), 7.43 (m, $J_{H7-H8}$ = 8.0 Hz, $J_{H7-H6}$ = 7.0 Hz, $J_{H7-H5}$ = 1.2 Hz, 1H, H-7), 7.33 (s, 1H, H-3), 4.81 (s, 2H, $CH_2$-Cl), 4.03 (s, 3H, $OCH_3$), 3.97 (s, 3H, $OCH_3$).

M.s. (EI, 70eV, 81°C) m/z (%): 304 (35.4, $M^{\cdot+}$), 306 (12.2, $[M+2]^{\cdot+}$ isotope peak), 289 (62.2, $M^{\cdot+}$ - $CH_3$), 269 (38.5, $M^{\cdot+}$ - Cl), 240 (100, $M^{\cdot+}$ - Cl-CHO).

Preparation of 1,4-Dimethoxyxanthene (113)

To a solution of 1,4-dimethoxyxanthone (1.5 g, 5.86 mmol) in 40 mL THF (or dry $CH_2Cl_2$) was slowly added a five-fold excess of borane-THF complex (30 mL of a 1 M solution) at 0°C under inert atmosphere. After complete addition, the cooling bath was removed and the reaction was allowed to proceed at room temperature over a period of *ca.* 4 h. The reaction was quenched by the careful addition of methanol. Evaporation *in vacuo* of the solvent left an amorphous material which was purified by recrystallization from methanol-ether affording 1.4 g (quantitative yield) of off-white crystalline xanthene 113: mp 94-95.5°C.

IR ($CH_2Cl_2$) $\nu_{max}$: 2840 ($CH_3$, $ArOCH_3$), 1580, 1500 (ring C···C), 1230 (=C-O-C, $\nu_{as}$), 1040 (=C-O-C, $\nu_s$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 7.03 (bs, 4H, aryl-H), 6.66 (d, 1H, H-3), 6.35 (d, 1H, H-2), 3.9 (s, 2H, xanthene-H), 3.83 (s, 3H, $OCH_3$), 3.76 (s, 3H, $OCH_3$).

Preparation of 2-Chloromethyl-1,4-dimethoxyxanthene (114)

To a solution of 2-chloromethyl-1,4-dimethoxyxanthone (110) (1 g, 3.29 mmol) in 10 mL dry $CH_2Cl_2$ was added a three-fold excess of borane-THF complex (10 mL of a 1 M solution) at 0°C, allowed to reach room temperature slowly, stirred for an additional 8 h and finally quenched with water. (Methanol cannot be used because some methoxymethyl compound is also

obtained.). The organic layer was extracted and evaporation *in vacuo* gave a crude amorphous material which was purified by flash chromatography (EtOAc-$CH_2Cl_2$, 1:50) to give 0.86 g (90%) of the pure white crystalline chloromethylxanthene compound: mp 70-71°C.

IR ($CHCl_3$) $\nu_{max}$: 2860 ($CH_3$, $ArOCH_3$), 1580, 1500 (ring C···C), 1250 (=C-O-C, $\nu_{as}$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 7.10 (bs, 4H, aryl-H), 6.73 (s, 1H, H-4), 4.63 (s, 2H, $CH_2$-Cl), 4.0 (s, 2H, xanthene-H), 3.87 (s, 3H, $OCH_3$), 3.83 (s, 3H, $OCH_3$).

M.s. (EI, 70eV, 42°) m/z (%): 290 (59.2, $M^{\cdot+}$), 292 (20.4, $[M+2]^+$ isotope peak), 255 (100, $M^+$ - 35), 240 (24, $M^+$ - Cl-$CH_3$), 225 (59, $M^+$ - $CH_2O$-Cl).

Methoxymethyl compound

IR ($CHCl_3$) $\nu_{max}$: 1580, 1500 (ring C···C), 1250 (=C-O-C, $\nu_{as}$), 1125 (=C-O-C, $\nu_s$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 7.16 (bs, 4H, aryl-H), 6.86 (s, 1H, H-4), 4.48 (s, 2H, $-CH_2O-$), 4.03 (s, 2H, xanthene-H), 3.93 (s, 3H, $OCH_3$), 3.8 (s, 3H, $OCH_3$), 3.4 (s, 3H, aliphatic $OCH_3$).

M.s. (EI, 70eV, 38°C) m/z (%): 286 (100, $M^{\cdot+}$), 287 (19, $[M+1]^+$ isotope peak), 255 (88.1, $M^+$ - $OCH_3$), 240 (21.8, $M^+$ - $OCH_3$-$CH_3$), 225 (59, $M^+$ - $OCH_3$-$CH_2O$).

Preparation of Chloromethyl Chlorosulfonate (120)

To neat chlorosulfonic acid (300 mL) at 70°C was *very carefully* added paraformaldehyde (100 g) in small portions over a period of 1 h. The resulting viscous solution was stirred for an additional hour and then distilled affording *ca.* 24 mL of $CH_2Cl_2$. The remaining solution was distilled *in vacuo* to afford *ca.* 150 mL of a yellow viscous oil which was added to aqueous sodium bicarbonate to destroy any chlorosulfonic acid which had co-distilled. The oil was dried over anhydrous $Na_2SO_4$ and diluted with carbon tetrachloride which was used to wash down the sides of the flask. Distillation of the yellow residue afforded 120 g (7%) of a clear colorless oil which proved to be pure chloromethyl chlorosulfonate by GC/MS: bp 55-57°C/18mm (Lit.[427] 46-48°C/9mm).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 5.96 (s, $-CH_2-$).

GC/MS (6% OV101, 2m x6mm, 80°C + 16°C/min) retention time: 1.65 min/(EI, 70eV) m/z (%): 49 (100, $ClCH_2^+$), 129 (73, $M^+ - Cl$), 99 (31, $M^+ - CH_2Cl$), 65 (27, $ClCH_2O^+$).

Preparation of Guaiacyl-*o*-Methyl Chloride (126)

To a solution of *o*-methoxyphenol (guaiacol) (1.24 g, 10 mmol) in 25 mL THF was added sodium hydride (0.26 g, 10.5 mmol, prewashed with pentane) at 0°C. After a few minutes, the reaction mixture was warmed to room temperature and was transferred slowly dropwise *via* cannula to a dilute, vigorously stirred solution of a large excess of chloromethyl chlorosulfonate in $CH_2Cl_2$. A vigorous reaction occurred and the reaction was complete within a few minutes. The reaction was quenched with water and after extraction the organic phase was evaporated *in vacuo* to afford a crude oil which was submitted for gc/ms analysis without further purification. The pmr spectrum of the crude indicated that it consisted of several compounds but most prominent were those signals attributable to the desired compound 126. It was estimated (by both pmr and gc) that the mixture consisted of about 60% compound 126.

$^1$H.m.r. (60 MHz, $CCl_4$) δ: 7.3-6.6 (m, 4H, aryl-H), 5.8 (s, 2H, O-$CH_2$-Cl), 3.65 (s, 3H, $OCH_3$).

GC/MS (1% OV101, 2m x 6mm, 100°C +16°C/min) retention time: 0.9 min/(EI, 70eV) m/z (%): 172 (62.4, $M^+$), 174 (19.3, $[M+2]^+$ isotope peak), 123 (100, $M^+ - CH_2Cl$), 137 (25, $M^+ - Cl$), 95 (50, $C_6H_7O^+$), 77 (69.8, $C_6H_5^+$).

## SYNTHESIS OF 3,4-DIMETHYL-2,5-DIMETHOXYPHENOL (130)

### Preparation of Formate 132

To a solution of 2,3-dimethyl-4-methoxybenzaldehyde (10 g, 60 mmol) and 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide (0.2 g, 0.55 mmol) in 150 mL $CH_2Cl_2$ at 0°C was added *m*-chloroperoxybenzoic acid (16.0 g, 93 mmol) over a period of 5 min. After 45 min the reaction was essentially complete (*ca.* 90%) although it was stirred for an additional 30 min at room temperature. Excess peracid was destroyed by the addition of 5% aqueous $Na_2SO_3$ at 0°C followed by vigorous stirring for at least 10 min. The organic layer was tested for active peroxide and treated accordingly. The organic layer was washed successively with water (3 x 50 mL), 5% aqueous $NaHCO_3$ (3 x 50 mL), water (2 x 50 mL), saturated brine (3 x 50 mL) and dried over anhydrous $Na_2SO_4$. Evaporation *in vacuo* gave a crude formate which was distilled (bp 48-50°C/ 2mm) to afford 10.8 g (98%) of a clear colorless oil.

IR (film) $\nu_{max}$: 2940 ($CH_3$, =C-C-$CH_3$), 2830 ($CH_3$, Ar$OCH_3$), 1730 (C=O, formate), 1580, 1490 (ring C$\cdots$C), 1220 (=C-O-C, $\nu_{as}$), 1040 (=C-O-C, $\nu_s$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 8.23 (s, 1H, $O\overset{O}{\overset{\|}{C}}$-H), 6.85 (d, J = 9 Hz, 1H, H-6), 6.66 (d, J = 9 Hz, 1H, H-5), 3.8 (s, 3H, $OCH_3$), 2.15 (s, 3H, $CH_3$), 210 (s, 3H, $CH_3$).

## Hydrolysis of Formate 132

Formate 132 (9 g, 50 mmol) was treated in a fashion similar to formate 99 except that the reaction was stirred at room temperature for only 1 h. Evaporation of the solvent *in vacuo* gave 7.5 g (98%) of white crystalline phenol 133: mp 121-122°C.

IR (melt) $\nu_{max}$: 3400 (OH), 2940 ($CH_3$, $-C{=}C-CH_3$), 2830 ($CH_3$, $ArOCH_3$), 1600, 1500 (ring C···C), 1240 (=C-O-C, $\nu_{as}$), 1040, 1020 (=C-O-C, $\nu_s$).

$^1$H m.r. (60 MHz, $CDCl_3$) δ: 6.60 (s, 2H, aryl-H), 4.5 (bs, 1H, exchangeable OH), 3.76 (s, 3H, $OCH_3$), 2.16 (s, 6H, $2\times CH_3$).

## Methylation of Phenol 133

To a solution of 2,3-dimethyl-4-methoxyphenol (4.56 g, 29.9 mmol) in 50 mL acetone was added a large excess of dimethylsulfate (20 mL), 10 g anhydrous $K_2CO_3$ and refluxed overnight. The solvent was evaporated *in vacuo* and the residue was filtered, washed and recrystallized from pentane to afford 4.8 g (96%) of dimethoxy compound 134 as transparent plates: mp 78-79°C (Lit.[437] mp 78-79°C).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 6.56 (s, 2H, aryl-H), 3.73 (s, 6H, $2\times OCH_3$), 2.13 (s, 6H, $2\times CH_3$).

Formylation of Dimethoxy Derivative 134

To a solution of compound 134 (4.70 g, 28.3 mmol) in 25 mL $CH_2Cl_2$ and titanium(IV) chloride (5.2 mL, 51 mmol) cooled to 0°C was added dropwise α,α-dichloromethyl methyl ether (2.6 mL, 28.7 mmol) under inert atmosphere. The reaction mixture was allowed to warm up to room temperature over a period of *ca.* 2 h, poured onto an ice-water mixture and aqueous $NaHCO_3$ was cautiously added. The organic layer was extracted and washed successively with 5% aqueous $NaHCO_3$ (3 x 10 mL), water (3 x 10 mL), saturated brine (3 x 10 mL) and dried over $Na_2SO_4$. Evaporation of the solvent *in vacuo* afforded 5.4 g (98%) of the aldehyde 135 as off-white needles: mp 62-63°C.

$^1H$ n.m.r. (60 MHz, $CDCl_3$) δ: 10.3 (s, 1H, CHO), 7.0 (s, 1H, aryl-H), 3.76 (s, 6H, 2×$OCH_3$), 2.16 (s, 3H, $CH_3$), 2.13 (s, 3H, $CH_3$).

Baeyer-Villiger Oxidation of Aldehyde 135

To a mixture of 2,3-dimethyl-2,5-dimethoxybenzaldehyde (5.4 g, 28 mmol), 10 mg of 3-*tert*-butyl-4-hydroxy-5-methyl phenyl sulfide (10 mg, 0.027 mmol) in 50 mL $CH_2Cl_2$ was added *m*-chloroperoxybenzoic acid (8 g, 46.5 mmol) at 0°C under inert atmosphere. After *ca.* 1 h the reaction was quenched and the reaction was worked-up as for formate 132. The crude formate 136 was distilled affording 4.7 g (80%) of a light-yellow oil:

bp 63-65°C/2.1mm.

IR (film) $\nu_{max}$: 2940 ($CH_3$, =C-C-$CH_3$), 2830 ($CH_3$; Ar$OCH_3$), 1740 (C=O, formate), 1600, 1490 (ring C···C), 1230 (=C-O-C, $\nu_{as}$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 8.16 (s, 1H, O$\overset{O}{C}$H), 6.43 (s, 1H, aryl-H), 3.73 (s, 3H, $OCH_3$), 3.63 (s, 3H, $OCH_3$), 2.2 (s, 3H, $CH_3$), 2.1 (s, 3H, $CH_3$).

Phenol 130

Formate 136 (4.5 g, 21.4 mmol) was hydrolyzed using the same procedure used for formate 99. Evaporation of the solvent *in vacuo* gave a crude amorphous material which was recrystallized ($CH_2Cl_2$-pentane) to afford 3.23 g (83%) of phenol 130 as transparent needles: mp 72-73.5°C.

IR (melt) $\nu_{max}$: 3420 (OH), 2935 ($CH_3$, =C-C-$CH_3$), 2820 ($CH_3$, Ar$OCH_3$), 1600, 1500 (ring C···C), 1240 (=C-O-C, $\nu_{as}$), 1030 (=C-O-C, $\nu_s$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 6.4 (s, 1H, aryl-H), 6.0 (bs, 1H, exchangeable OH), 3.73 (s, 3H, $OCH_3$), 3.70 (s, 3H, $OCH_3$), 2.2 (s, 3H, $CH_3$), 2.06 (s, 3H, $CH_3$).

Synthesis of 2,3-Dimethyl-1,4-Dimethoxyxanthone (129)

A mixture of phenol 130 (3.0 g, 16.5 mmol), methyl *o*-iodobenzoate (4.32 g, 16.5 mmol) and copper(I) oxide (1.17 g, 8.3 mmol) in 40 mL of dry DMA was treated using the same procedure used for the preparation of 1,4-dimethoxyxanthone. The hydrolysis of the ester was carried out using 2 g NaOH and the cyclization achieved using 37 mL of TFAA-TFA (2:1 v/v) at 0°C. Recrystallization (methanol) of the crude material afforded 3.0 g (65%) of the xanthone as transparent needles: mp 157-158°C.

IR (nujol) $\nu_{max}$: 1670 (C=O, xanthone (γ-pyrone)), 1600, 1580, 1500 (ring C⋯⋯C), 1250 (=C-O-C, $\nu_{as}$), 1024 (=C-O-C, $\nu_{s}$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 8.26 (dd, J = 2 and 8 Hz, 1H, H-8), 7.76-7.1 (m, 3H, H-5, H-6, H-7), 3.93 (s, 3H, $OCH_3$), 3.86 (s, 3H, $OCH_3$), 2.33 (s, 3H, $CH_3$), 2.26 (s, 3H, $CH_3$).

M.s. (EI, 70eV, 149°C) m/z (%): 284 (61.4, $M^{+\cdot}$), 285 (16.8, $[M+1]^{+\cdot}$ isotope peak), 269 (100, $M^{+\cdot} - CH_3$), 255 (89, $M^{+\cdot}$ - CHO), 241 (62.3, $M^{+\cdot} - CH_3-CO$).

Preparation of 2,3-*bis*(bromomethyl)-1,4-dimethoxyxanthone (138)

A solution consisting of 2,3-dimethyl-1,4-dimethoxyxanthone (1.85 g, 6.5 mmol), azo*bis*isobutyronitrile (10 mg) and N-bromosuccinimide (2.32 g, 13.0 mmol) in 100 mL $CCl_4$ was refluxed for 26 h. The cooled reaction mixture was filtered and the filtrate was evaporated *in vacuo*. Recrystallization from $CCl_4$ afforded 2.3 g (80%) of white crystalline *bis*bromomethylated compound: mp 198-199°C.

IR (nujol) $\nu_{max}$: 2840 ($CH_3$, $ArOCH_3$), 1670 (C=O, xanthone (γ-pyrone)), 1600, 1580, 1500 (ring C⋯C), 1240 (=C-O-C, $\nu_{as}$), 1024 (=C-O-C, $\nu_s$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 8.26 (dd, J = 2 and 8 Hz, 1H, H-8), 7.76-7.1 (m, 3H, H-5, H-6, H-7), 4.83 (s, 4H, benzylic $CH_2$), 4.11 (s, 3H, $OCH_3$), 4.06 (s, 3H, $OCH_3$).

M.s. (EI, 70eV, 102°C) m/z (%): 440 (3.15, $M^{\cdot+}$), 442 (10.35, $[M+2]^{\cdot+}$ isotope peak), 444 (5.41, $[M+4]^{\cdot+}$ isotope peak), 363 (100, $[M+2]^{\cdot+}$ - Br), 361 (90, $M^{\cdot+}$ - Br), 282 (14, $M^{\cdot+}$ - $Br_2$), 267 (90, $M^{\cdot+}$ - $^{81}Br_2$ - $CH_3$).

Compound 137. $^1$H.m.r. (60 MHz, $CDCl_3$) δ: 8.26 (dd, J = 2 and 8 Hz, 1H, H-8), 7.76-7.1 (m, 3H, H-5, H-6, H-7), 4.7 (s, 2H, benzylic $CH_2$), 4.0 (s, 3H, $OCH_3$), 3.95 (s, 3H, $OCH_3$), 2.5 (s, 3H, $CH_3$).

Preparation of 3-(Triethylsilyl)oxy-3-buten-2-one (140)

To a solution of biacetyl (8.6 g, 0.1 mol), 4-dimethylaminopyridine (1.2 g, 0.01 mol) in 90 mL dry pentane was added triethylsilyl chloride (15 g, 0.1 mol) as a solution in pentane (10 mL). The flask was cooled (0°) and triethylamine (10.12 g, 0.1 mol) was added dropwise. The reaction mixture was allowed to reach room temperature slowly and stirred overnight. The solution was cooled, filtered and distilled (bp 73-75°C/15mm) to afford 15 g (75%) of olefin 140 as a colorless oil (turns yellow on standing at room temperature).

IR (film) $\nu_{max}$: 2940, 2880 ($CH_3$), 1690 (C=O, α,β-unsaturated), 1610 (C=C, α,β-unsaturated), 1240 ($Si-CH_3$), 1000 (Si-O), 860 (terminal $=CH_2$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 5.26 (d, J = 1.5 Hz, 1H, vinyl), 4.72 (d, J = 1.5 Hz, 1H, vinyl), 2.27 (s, 3H, $COCH_3$), 1.23-0.43 (m, 15H, $Si(CH_2CH_3)_3$).

Preparation of Cyclooctadiene 143

In a 10-mL round bottom flask was added dibromide 138 (100 mg, 0.23 mmol), activated zinc (300 mg) and 5 mL THF under an argon atmosphere. An aluminium foil seal was placed over the mouth of the flask and covered with a septum, (to prevent the solvent from coming into contact with the septum). The mixture was sonicated for 9 h in a water bath

kept at room temperature. An insoluble amorphous mass was obtained which was triturated with acetone. Evaporation of the solvent *in vacuo* gave a small amount of (10 mg) of grey-white cyclooctadiene 143.

M.s. (EI, 70eV, 308°C) m/z (%): 564 (5.5, $M^{\cdot+}$), 565 (2,0, $[M+1]^{\cdot+}$ isotope peak), 549 (64, $M^{\cdot+} - CH_3$), 536 (41, $M^{\cdot+} - CO$), 508 (50, $M^{\cdot+} - 2CO$).

Preparation of 3-Acetoxy-3-buten-2-one (144)

To a solution of biacetyl (17.22 g, 0.2 mol) triethylamine (20.2 g, 0.2 mol), 4-dimethylaminopyridine (0.5 g) in 200 mL dry $CH_2Cl_2$ at 0°C was added freshly distilled acetic anhydride (20.4 g, 0.2 mol) dropwise over a period of 15 min. The reaction mixture was allowed to warm up to room temperature and stirred overnight. The solvent was evaporated *in vacuo*, hexane was added and the precipitated salts filtered. The filtrate was concentrated and distilled (bp 44-46°C/1.9mm) to afford 16.6 g (65%) of olefin 144 as a clear colorless oil.

IR (film) $\nu_{max}$: 1765 (C=O, vinyl ester), 1715 (C=O, α,β-unsaturated), 1665 (C=C, α,β-unsaturated), 1240 (=C-O-C, $\nu_{as}$), 1020 (=C-O-C, $\nu_s$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 5.93 (d, J = 2 Hz, 1H, vinyl), 5.6 (d, J = 2 Hz, 1H, vinyl), 2.30 (s, 3H, $COCH_3$), 2.2 (s, 3H, OAc).

M.s. (EI, 70eV, 35°C) m/z (%): 128 (30, $M^{\cdot+}$), 129 (2.1,

$[M+1]^{+\cdot}$ isotope peak), 111 (80, $M^{+\cdot} - CH_3$), 85 (70, $M^{+\cdot} - COCH_3$), 43 (100, $COCH_3^+$).

Compound 145

Diacetoxy 145 was obtained as the unexpected major product when dibromide 138 was reacted with olefin 140 in the presence of sodium iodide in dry DMA: mp 176.5-178.5°C.

IR (nujol) $\nu_{max}$: 1735 (C=O, acetate), 1665 (C=O, xanthone (γ-pyrone)), 1600, 1580 (ring C···C), 1260 (=C-O-C, $\nu_{as}$), 1030 (=C-O-C, $\nu_s$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 8.31 (dd, J = 2 and 8 Hz, 1H, H-8), 7.85-7.2 (m, 3H, H-5, H-6, H-7), 5.5 (s, 2H, benzylic), 5.46 (s, 2H, benzylic), 4.06 (s, 3H, $OCH_3$), 3.96 (s, 3H, $OCH_3$), 2.1 (s, 6H, OAc).

M.s. (EI, 70eV, 180°C) m/z (%): 400 (19.7, $M^{+\cdot}$), 401 (5.5, $[M+1]^{+\cdot}$ isotope peak), 297 (56, $[C_{17}H_{13}O_5]^{+\cdot}$), 283 (100, $[C_{17}H_{15}O_4]^{+\cdot}$), 43 (53, $CH_3CO^+$).

Formation of 9-Acetyl-6,11-dimethoxyxantho[2,3-g]- and [3,2-g] Tetralins (148a) and (148b)

Method A

*bis*(Bromomethylxanthone) 138 (270 mg, 0.61 mmol) was added to a suspension of activated zinc (500 mg), hydroquinone (10 mg), and freshly distilled methyl vinyl ketone (0.21 g,

3.0 mmol) in 20 mL THF under an argon atmosphere. The mixture was sonicated for 6 h in a water bath maintained at room temperature. The mixture was filtered and the filtrate evaporated *in vacuo*. The residue was dissolved in $CH_2Cl_2$ (25 mL), acidified with acetic acid and stirred for 10 min. The solution was washed successively with water (3 x 15 mL), 5% aqueous $NaHCO_3$ (3 x 15 mL), water (2 x 10 mL), saturated brine (2 x 10 mL) and dried over anhydrous $Na_2SO_4$. Evaporation *in vacuo* afforded a gummy residue which was filtered through silica gel and finally processed by flash chromatography ($CH_2Cl_2$-EtOAc, 1:1). A slightly impure material (21 mg, 10%) was obtained which was identified as consisting of a mixture of compounds 148a and 148b.

IR (nujol) $\nu_{max}$: 1715 (C=O, acetyl), 1665 (C=O, xanthone (γ-pyrone)), 1600, 1580 (ring C⋯C), 1240 (=C-O-C, $\nu_{as}$), 1020 (=C-O-C, $\nu_s$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 8.31 (dd, J = 2 and 8 Hz, 1H, H-*ortho* CO), 7.85-7.2 (m, 3H, aryl-H), 3.86 (s, 3H, $OCH_3$), 3.82 (s, 3H, $OCH_3$), 2.6-3.3 (m, 5H, benzylic and methine), 1.8-2.3 (m, 5H, methylene and $COCH_3$).

M.s. (EI, 70eV, 150°C) m/z (%): 352 (11, $M^{+\cdot}$), 353 (2.4, $[M+1]^{+\cdot}$ isotope peak), 337 (50, $M^{+\cdot} - CH_3$), 309 (90, $M^{+\cdot} - COCH_3$), 254 (36.7, $M^{+\cdot} - [CH_2=CHCOCH_3]$), 43 (78, $CH_3CO^+$).

Method B

*bis*(Bromomethylxanthone) 138 (100 mg, 0.226 mmol), sodium iodide (1 g), freshly distilled methyl vinyl ketone (1 g,

14.2 mmol) in 5 mL anhydrous DMA was heated to 65°C for a period of 1 h. The solution was filtered and the precipitate washed with water, redissolved in $CH_2Cl_2$ (10 mL), washed successively with aqueous 5% sodium thiosulfate (2 x 5 mL), water (2 x 5 mL) and dried over anhydrous $Na_2SO_4$. Evaporation *in vacuo* gave an amorphous material which was purified as in Method A affording *ca.* 8 mg of a compound whose ir, nmr, and mass spectral properties were identical to those reported for the compounds 148a and 148b obtained by reaction with activated zinc.

Formation of Adduct 150

To a solution of dibromide 138 (61 mg, 0.138 mmol) in 5 mL anhydrous DMA was added N-phenylmaleimide (47 mg, 0.180 mmol) and sodium iodide (0.2 g). The mixture was heated to 70°C. After 5 h, the reaction was quenched with water and the precipitate filtered, washed, redissolved in $CH_2Cl_2$ (10 mL), washed with 5% aqueous sodium thiosulfate (2 x 5 mL), and dried over anhydrous $Na_2SO_4$. Evaporation of the solvent *in vacuo* gave about 13 mg (20%) of an amorphous material which was not purified.

IR (nujol) $\nu_{max}$: 1700 (CO, imide), 1670 (CO, xanthone), 1600, 1580, 1500 (ring C$\cdots$C), 1260 (=C-O-C, $\nu_{as}$).

$^1$H.m.r. (60 MHz, $CDCl_3$) $\delta$: 8.32 (dd, J = 2 and 8 Hz, 1H, H-*ortho* CO), 7.85-7.18 (m, 8H, aryl-H), 4.03 (s, 3H, $OCH_3$), 3.93

(s, 3H, $OCH_3$), 3.3-3.4 (m, 2H, CHCON), 3.2-3.9 (m, 4H, benzylic).

M.s. (EI, 70eV, 300°C) m/z (%): 455 (7.6, $M^{\cdot+}$), 456 (2.0, $[M+1]^{\cdot+}$ isotope peak), 440 (42.7, $M^+ - CH_3$), 416 (51.2, $M^+ - CHO$), 368 (19.1, $M^+ - C_6H_5$), 308 (48, $M^+ - PhN(CO)_2$), 77 (68, $C_6H_5^+$).

Synthesis of 2-Bromo-1,4-dimethoxyxanthone (165)

To a solution of 1,4-dimethoxyxanthone (200 mg, 0.78 mmol) in 15 mL methylene chloride was added bromine (0.80 mL, 0.80 mmol, as a 1 M acetic acid solution), and a small amount (10 mg) of unactivated iron filings. The mixture was stirred at room temperature for 3 h and quenched with 5% aqueous sodium bisulfite, washed with water (3 x 10 mL) and dried over anhydrous $Na_2SO_4$. Evaporation of the solvent *in vacuo* gave a crude amorphous material which was purified by flash chromatography ($CHCl_3$/petroleum ether/EtOAc, 4:1:0.25) and recrystallized ($CH_3OH$) to afford 0.24 g (90%) of 2-bromo-xanthone 165 as white crystalline needles: mp 182.5-183.5°C.

IR ($CHCl_3$) $\nu_{max}$: 1670 (CO, xanthone (γ-pyrone)), 1610, 1600, 1580 (ring C···C), 1260 (=C-O-C, $\nu_{as}$), 1060, 1020 (=C-O-C, $\nu_s$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 8.30 (dd, J = 2 and 8 Hz, 1H, H-8), 7.83-7.2 (m, 4H, H-5, H-6, H-7 and H-3), 4.0 (s, 3H, $OCH_3$), 3.96 (s, 3H, $OCH_3$).

$^1$H.m.r. (200 MHz, $CDCl_3$) δ: 8.32 (dd, J = 2 and 8 Hz, 1H, H-8), 7.73 (m, J = 8.5, 6.9 and 1.8 Hz, 1H, H-6), 7.57 (dd, J = 8.5 and 1.2 Hz, 1H, H-5), 7.39 (s, 1H, H-3), 7.37 (m, J = 8.0, 6.9 and 1.2 Hz, 1H, H-7), 4.0 (s, 3H, $OCH_3$), 3.96 (s, 3H, $OCH_3$).

$^{13}$C.m.r.* (22.63 MHz, $CDCl_3$) δ: 175.30 (C=O), 155.03 (C-10a), 149.54 (C-1), 146.87 (C-4a), 145.65 (C-4), 134.72 (C-6), 126.80 (C-8), 124.46 (C-7), 122.47 (C-8a), 119.22 (C-2), 117.86 (C-5), 111.83 (C-9a), 98.27 (C-3), 61.72 ($OCH_3$), 56.81 ($OCH_3$).

M.s. (EI, 70eV, 93°C) m/z (%): 334 (100, $M^{\cdot+}$), 336 (99.3, $[M+2]^{\cdot+}$ isotope peak), 319 (57.1, $M^+ - CH_3$), 321 (53.9, $[M+2]^+ - CH_3$), 305 (88.4, $M^+ - CHO$), 307 (86.4, $M^+ - CHO$), 306 (21, $M^+ - CO$), 308 (14.4, $[M+2]^+ - CO$), 255 (5, $M^+ - Br$).

Preparation of 2-Bromo-1,4-dimethoxyxanthene (166)

A large excess of $BH_3$-THF complex (5 mL of a 1 M solution) was added to a solution of 2-bromo-1,4-dimethoxyxanthone (1 g, 2.99 mmol) in 10 mL $CH_2Cl_2$ at 0°C under inert atmosphere and allowed to warm-up to room temperature. The reaction was quenched after 18 h with methanol. Evaporation of the solvent *in vacuo* afforded a yellowish crystalline material which was purified by recrystallization ($CH_3OH$) to afford 930 mg (97%) of the xanthone 166 as white needles: mp 121-122°C.

*Tentative assignment.

IR (nujol) $\nu_{max}$: 1580, 1500 (ring C···C), 1240 (=C-O-C, $\nu_{as}$), 1040 (=C-O-C, $\nu_s$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 7.2-6.9 (m, 5H, aryl-H and H-3), 4.0 (s, 2H, xanthene-H), 3.83 (s, 3H, $OCH_3$), 3.8 (s, 3H, $OCH_3$).

M.s. (EI, 70eV, 41°C) m/z (%): 320 (100, $M^{\cdot+}$), 322 (99.5, $[M+2]^{\cdot+}$ isotope peak), 306 (45.6, $M^{\cdot+} - CH_2$), 308 (43.5, $[M+2]^{\cdot+} - CH_2$), 305 (24.6, $M^{\cdot+} - CH_3$), 307 (21.5, $[M+2]^{\cdot+} - CH_3$), 291 (11.3, $M^{\cdot+}$ - CHO), 241 (2.0, $M^{\cdot+}$ - 79).

Formylation of 1,4-Dimethoxyxanthene

Xanthene 113 (2.25 g, 9.26 mmol) was dissolved in 40 mL dry $CH_2Cl_2$ and titanium(IV) chloride (1.7 mL, 14.8 mmol) was added at 0°C under inert atmosphere. Neat α,α-dichloromethyl methyl ether (1.1 g, 9.6 mmol) was added dropwise over a period of 3 min. The reaction was allowed to reach room temperature slowly and was stirred overnight. The reaction mixture was cautiously poured onto ice and diluted with more $CH_2Cl_2$ (50 mL). The organic layer was separated and washed successively with aqueous 5% $NaHCO_3$ (3 x 40 mL) and saturated brine (3 x 40 mL). A crystal of hydroquinone was added to the $CH_2Cl_2$ solution and dried over anhydrous $Na_2SO_4$. Evaporation of the solvent *in vacuo* gave a solid material which was purified by flash chromatography ($CH_2Cl_2$) to afford 2.3 g (92%) of aldehyde 172 as a white crystalline compound:

mp 177-178°C.

IR (nujol) $\nu_{max}$: 1700 (C=O, ArCHO), 1600, 1580 (ring C⋯⋯C), 1260 (=C-O-C, $\nu_{as}$), 1040, 1020 (=C-O-C, $\nu_s$).

$^1$H.m.r. (200 MHz, $CDCl_3$) δ: 10.23 (s, 1H, CHO), 7.26 (s, 1H, H-3), 7.13 (br, 4H, C-ring aryl-H), 4.02 (s, 2H, xanthene-H), 3.92 (s, 3H, $OCH_3$), 3.89 (s, 3H, $OCH_3$).

$^{13}$C.m.r. (22.63 MHz, $CDCl_3$) : 188.27 (C=O), 156.55, 150.78, 145.49, 129.15, 128.18, 124.24, 123.38, 118.95, 117.06, 115.82, 107.78, 84.58, 64.03, 56.37, 22.71.

## Preparation of Dimethyl Acetal 173

### Method A

To a solution of aldehyde 172 (1 g, 3.70 mmol) in 10 mL $CH_2Cl_2$ was added 15 mL methanol, a catalytic amount of *p*-TsOH·$H_2O$ and the mixture stirred at 25°C for 2 h. Removal of the solvent gave an oil which was diluted in $CH_2Cl_2$ (15 mL), washed with water (3 x 5 mL) and dried over anhydrous $Na_2SO_4$. Evaporation of the solvent *in vacuo* afforded the corresponding dimethyl acetal 173 as a yellow amorphous material which was purified by recrystallization ($CH_2Cl_2$-hexanes): mp 156-157°C (dec.).

### Method B

Alternatively, an excellent yield of dimethyl acetal 173 can also be obtained by dissolving aldehyde 172 in methanol, adding a trace of *p*-TsOH·$H_2O$, adding 4 Å molecular sieves and

stirring at 25°C for 15 h. The pasty solution is filtered, evaporated to dryness, redissolved in $CH_2Cl_2$, washed several times with water and dried to afford an almost quantitative yield of product.

Method C

Dimethyl acetal 173 can be prepared directly from 1,4-dimethoxyxanthone without the isolation of intermediate aldehyde provided the reaction is quenched with $CH_3OH$. (The presence of excess $TiCl_4$ is beneficial.).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 7.16 (bs, 4H, C-ring aryl-H), 7.0 (s, 1H, H-3), 5.6 (s, 1H, $CH(OCH_3)_2$), 4.06 (s, 2H, xanthene-H), 3.96 (s, 3H, $OCH_3$), 3.83 (s, 3H, $OCH_3$), 3.41 (s, 6H, 2×$OCH_3$ (acetal)).

M.s. (EI, 70eV, 150°C) m/z (%): 285 (6.1, $M^+ - OCH_3$), 284 (5.4, $M^+ - CH_3OH$), 269 (24.8, $M^+ - CH_3OH-CH_3$), 241 (10.3, $M^+ - CH(OCH_3)_2$).

Formation of Compound 174

Dimethyl acetal 173 (0.51 g, 1.6 mmol) was dissolved in 10 mL THF and treated with n-BuLi (0.95 mL of a 1.7 M solution in hexane, 1.61 mmol) at -78°C. After 15 min excess methyl iodide was added and the reaction allowed to warm up to room temperature. Evaporation of the solvent *in vacuo* gave a dark red material which was not purified.

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 7.16 (bs, 4H, C-ring aryl-H),

7.0 (s, 1H, H-3), 5.6 (s, 1H, $C\underline{H}(OCH_3)_2$), 3.94 (bs, 7H, $2\times OCH_3$ and xanthene-H), 3.41 (s, 6H, $2\times OCH_3$ (acetal)).

M.s. (EI, 70eV, 62°C) m/z (%): 330 (13.5, $M^{\cdot+}$), 331 (2.8, $[M+]^{\cdot+}$), 329 (29.1, $M^{\cdot+}$ - H), 315 (70.5, $M^{\cdot+}$ - $CH_3$), 229 (47.8, $M^{\cdot+}$ - $OCH_3$), 269 (100, $M^{\cdot+}$ - $OCH_3$-CO).

Preparation of 4-Methoxy-4-phenylthio-2-butanone

To a mixture of sodium ethoxide (35 mg, 0.5 mmol) in 15 mL THF under inert atmosphere was added 4-methoxy-3-buten-2-one (2.5 g, 25 mmol) and thiophenol (2.75 g, 25 mmol) at room temperature. After 19 h, the solvent was removed and the resulting viscous oil diluted with $CH_2Cl_2$ (25 mL), washed with water and dried over anhydrous $Na_2SO_4$. Evaporation of the solvent afforded 5.0 g (96%) of the compound as a yellow oil: bp 131-134°C/1.0mm (Lit.[520] bp 125-127°C/0.6mm).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 7.6-7.16 (m, 5H, aryl-H), 5.03 (t, J = 6 Hz, 1H, methine), 3.43 (s, 3H, $OCH_3$), 2.75 (d, J = 6 Hz, 2H, methylene), 2.07 (s, 3H, $COCH_3$).

Synthesis of 4-Phenylthio-3-buten-2-one (183)

To 5 mL absolute ethanol cooled to -15°C was added thiophenol (1.62 g, 14.7 mmol), 3-butyn-2-one (1 g, 14.68 mmol) and a catalytic amount of N-benzyltrimethylammonium hydroxide (Triton B). The reaction mixture was allowed to warm up to room temperature overnight. Ether (30 mL) was added and the

solution was washed successively with water (3 x 10 mL), saturated brine (3 x 10 mL) and dried over anhydrous $Na_2SO_4$. Evaporation of the solvent *in vacuo* gave a crude product mixture which was purified by flash chromatography ($CH_2Cl_2$). Three fractions were collected: 280 mg (7%) of the *bis*-addition product 186, 0.54 g (21%) of an oil which proved to be the Z-isomer and 1.89 g (72%) of a white crystalline material (mp 39-40°C) which was the E-isomer of compound 183.

Product 186.

IR (nujol) $\nu_{max}$: 1715 (C=O, ketone), 1602, 1586 (ring C···C).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 7.5-7.1 (m, 10 H, aryl-H), 4.9 (t, J = 7 Hz, 1H, H-C(SPh)$_2$), 2.85 (d, J = 7 Hz, 2H, $-CH_2$-C=O), 2.0 (s, 3H, $CH_3CO$).

Compound 183 (Z-isomer).

IR (film) $\nu_{max}$: 1665 (C=O, conjugated), 1600, 1580 (ring C···C), 1550 (C=C, thiovinyl).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 7.5-7.25 (m, 5H, aryl-H), 7.21 (d, J = 9 Hz, 1H, =CH(SPh)), 6.30 (d, J = 9 Hz, 1H, =CH($COCH_3$)), 2.27 (s, 3H, $COCH_3$).

Compound 183 (E-isomer).

IR (film) $\nu_{max}$: 1663 (C=O, conjugated), 1600, 1580 (ring C···C), 1553 (C=C, thiovinyl), 970 (CH bend, *trans* olefin).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 7.7 (d, J = 15 Hz, 1H, =CH(SPh), 7.43 (bs, 5H, aryl-H), 6.03 (d, J = 15 Hz, 1H, =CH($COCH_3$), 2.2 (s, 3H, $COCH_3$).

Phenylthiotriethylsilane (187)

To a mixture of thiophenol (5.50 g, 50 mmol), triethylsilane (5.8 g, 50 mmol) was added Wilkinson's catalyst [*tris*(triphenylphosphine)rhodium chloride] (250 mg, 0.5 mol%) under an inert atmosphere. The reaction mixture was heated to 50°C for about 1 h, cooled to room temperature, poured into hexanes and filtrered through Celite. The clear red solution was distilled to afford 10.6 g (95%) of 187 as a clear colorless oil: bp 105-106°C/1.4mm (Lit.[523] 77°C/0.25mm).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 7.5-7.0 (m, 5H, aryl-H), 1.2-0.4 (m, 15H, $(CH_3CH_2)_3Si$-).

Ethylthiosilylation of Thio-enone 183

To thio-enone 183 (1.02 g, 5.74 mmol) was added, under inert atmosphere, phenylthiotriethylsilane (1.35 g, 6.0 mmol) and 25 mg potassium cyanide-18-crown-6-complex. The reaction mixture was stirred at room temperature for 22 h and filtered through a pad of Celite affording 2.19 g (95%) of compound 188 as a clear yellow oil which proved to be sufficiently pure as not to require any purification for the next step.

IR (film) $\nu_{max}$: 1660 (C=C), 1600, 1580 (ring C···C), 1250 (Si-$CH_3$), 1050 (Si-O).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 7.6-7.2 (m, 10 H, aryl-H), 5.51 (d, J = 10 Hz, 1H, H-C=C-OSi), 4.5 (d, J = 10 Hz, 1H, C<u>H</u>$(SPh)_2$), 1.73 (s, 3H, $COCH_3$), 1.16-0.5 (m, 15H, -$Si(CH_2CH_3)_3$).

Keto-dithiane 195

To a cooled (0°C) solution of 4-methoxy-3-buten-2-one (4.4 g, 44.1 mmol) and 1,3-propanedithiol (4.78 g, 44.1 mmol) in 10 mL anhydrous ether was added a catalytic amount of boron trifluoride etherate. After stirring 30 min the reaction was quenched by the addition of 5% aqueous $NaHCO_3$. More ether was added (20 mL) and the organic layer was separated, washed successively with more 5% aqueous $NaHCO_3$ (3 x 10 mL), water (3 x 10 mL), saturated brine (3 x 10 mL) and dried over anhydrous $Na_2SO_4$. Evaporation of the solvent *in vacuo* afforded a yellow oil which slowly crystallized. Recrystallization (ether/pentane) afforded 7.0 g (96%) of transparent prisms: mp 69-70°C.

IR (nujol) $\nu_{max}$: 2910 ($CH_3$), 1720 (C=O, ketone), 1420 ($S-CH_2$).

$^1$H.m.r. (60 MHz, $CDCl_3$) $\delta$: 4.45 (t, J = 7 Hz, 1H, methine), 3.03-2.8 (m, 4H, $-SC\underline{H}_2CH_2C\underline{H}_2S-$), 2.85 (d, J = 7 Hz, 2H, methylene), 2.2 (s, 3H, $CH_3CO$), 2.16-1.8 (m, 2H, $-SCH_2C\underline{H}_2CH_2S-$):

M.s. (EI, 70eV, 74°C) m/z (%): 176 (5.4, $M^{+\cdot}$), 177 (0.6, $[M+1]^{+\cdot}$ isotope peak), 57 (17, $CH_3COCH_2^+$), 43 (100, $CH_3CO^+$).

SYNTHESIS OF ALDEHYDE 199

Alkylation of 1,3-Dithiane

Freshly recrystallized 1,3-dithiane (12.02 g, 0.10 mmol) was dissolved in 110 mL THF under an inert atmosphere. Tetramethylethylenediamine (TMEDA) (12.2 g, 0.105 mol) was added, the reaction mixture cooled to -78°C and n-BuLi (61.8 mL of 1.7 M solution in hexane, 0.105 mol) was added over a period of 25 min. After stirring 3.5 h, freshly distilled hexamethylphosphoramide (HMPA) (9.0 g, 0.05 mol) was added, stirred for 0.5 h and bromoacetaldehyde diethyl acetal (19.7 g, 0.10 mmol) was added. The reaction mixture was stirred for 4 h, brought to room temperature and quenched with water. The solvent was evaporated and the residue redissolved in pentane (150 mL) and washed with water (3 x 30 mL), 7% aqueous KOH (3 x 30 mL), water (3 x 30 mL), saturated brine (3 x 30 mL), dried over anhydrous $Na_2SO_4$ and evaporated to afford 23.0 g (97%) (bp 53-55°C/6mm) of acetal 202 as a yellow oil which was used without purification in the hydrolysis step.

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 4.8 (t, J = 6 Hz, 1H, $\underline{H}C-(OC_2H_5)_2$), 4.1 (t, J = 7 Hz, 1H, $\underline{H}-C-SR_2$), 3.9-3.36 (m, 4H, $-OC\underline{H}_2CH_3$), 3.0-2.83 (m, 4H, $-SC\underline{H}_2-CH_2-C\underline{H}_2-S-$), 2.20-2.0 (m, 4H, $CH_2$ and $-SCH_2C\underline{H}_2CH_2S-$), 1.23 (t, J = 9Hz, 6H, $-OCH_2C\underline{H}_3$).

Acetal Hydrolysis

Method A

To a solution of acetal 202 (5 g, 21.1 mmol) in 15 mL dry acetonitrile was added sodium iodide (6.64 g, 44.3 mmol) and chlorotrimethylsilane (4.8 g, 44.3 mmol) at room temperature. After 30 min the reaction was quenched with water. The solvent was evaporated and the residue redissolved in $CH_2Cl_2$ (20 mL), washed with water (2 x 10 mL), 2% aqueous thiosulfate (2 x 10 mL), water (2 x 10 mL), brine (2 x 10 mL) and dried over anhydrous $Na_2SO_4$. Evaporation *in vacuo* of the solvent afforded 3.1 g (90%) of aldehyde 199 as a light yellow oil which was stored at -22°C under inert atmosphere.

Method B

To a solution of acetal 202 (2.5 g, 10.55 mmol) in 20 mL THF-$H_2O$ (3:1) was added 20 mL of 10% aqueous trifluoroacetic acid and the solution heated to 45°C for 3 h. The solution was concentrated *in vacuo*, $CH_2Cl_2$ (40 mL) added, and the extracted organic layer was washed with water (3 x 10 mL), 5% aqueous $NaHCO_3$ (2 x 10 mL), saturated brine (3 x 10 mL), dried over anhydrous $Na_2SO_4$ and evaporated to afford 1.5 g (88%) of aldehyde 199.

IR (film) $\nu_{max}$: 2820, 2720 (CH, aldehyde), 1720 (C=O, aldehyde), 1420 ($S-CH_2$).

$^1$H.m.r. (60 MHz, $CDCl_3$) $\delta$: 9.76 (t, J = 1.5 Hz, 1H, -CHO), 4.56 (t, J = 7 Hz, 1H, $HC-SR_2$), 3.16-2.73 (m, 6H, $CH_2-\overset{O}{\overset{\|}{C}}-$ and $-SCH_2CH_2CH_2S-$), 2.2-1.9 (m, 2H, $-SCH_2CH_2CH_2S-$).

Enamine 198

Aldehyde 199 (1 g, 5.95 mmol) was dissolved in 10 mL dry benzene and pyrrolidine (0.465 g, 6.55 mmol) was added to the cooled (0°C) mixture. Titanium(IV) chloride (1.68 g, 2.98 mmol) was added dropwise under an inert atmosphere. The reaction was allowed to warm up to room temperature and then filtered through a dry pad of Celite. A clear solution was obtained which upon evaporation of the solvent afforded an orange amorphous material which was carefully recrystallized ($CH_2Cl_2$/hexane) to afford 1.2 g (86%) of enamine 198 as light-orange crystals: mp 50-51°C (dec.).

$^1$H.m.r. (200 MHz, $CDCl_3$) δ: 6.62 (d, J = 13.2 Hz, 1H, $=CH(NR_2)$, 4.66 (d, J = 9.3 Hz, 1H, $HC-(SR)_2$), 4.02 (dd, J = 13.2 and 9.3 Hz, $=C\underline{H}(CH(SR_2))$), 3.09-2.72 (m, 8H, $-SC\underline{H}_2CH_2C\underline{H}_2S-$ and $-N(C\underline{H}_2)_2-$), 2.1-1.75 (m, 6H, $-SCH_2C\underline{H}_2CH_2S-$ and $-N\begin{smallmatrix}CH_2-C\underline{H}_2\\CH_2-C\underline{H}_2\end{smallmatrix}$).

Adduct 204

To a solution of enamine 198 (1.31 g, 5.95 mmol) in 20 mL dry benzene and TMEDA (1 mL), cooled to -22°C was added n-BuLi (3.5 mL of 1.7 M solution in hexane) and stirred for 1.5 h. The lithium complex was transferred with a cannula to a dilute solution (-78°C) of *o*-xylene dibromide (1.56 g, 5.95 mmol) and HMPA (0.5 mL). The reaction mixture was allowed to warm up to room temperature slowly, refluxed for 1 h, cooled and evaporated *in vacuo*. A dark oil was obtained to which was added $CH_2Cl_2$ (40 mL) and washed with water (5 x 20 mL), saturated brine (3 x 20 mL), dried over anhydrous $Na_2SO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography to afford 250 mg (15%) adduct 204 as an amorphous (impure) material.

IR (nujol) $\nu_{max}$: 1720 (C=O, aldehyde), 1602, 1586 (ring C···C), 1424 (S-$CH_2$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 9.81 (s, J = 1.5 Hz, CHO), 7.2-7.0 (bs, 4H, aryl-H), 3.4-2.6 (m, 7H, 2 × benzylic, methine, -S$CH_2CH_2CH_2$S-), 2.2-1.95 (m, 2H, -SCH$_2$C$H_2$CH$_2$S-).

M.s. (EI, 70eV, 75°C) m/z (%): 264 (3.7, $M^+$), 265 (0.72, $[M+1]^+$), 263 (1.1, $M^+ - 1$), 250 (59, $M^+ - CH_2$), 104 (41.4, $C_8H_8^+$).

# EXPERIMENTAL

## Chapter 4

### Preparation of Xanthoquinone (207)

To a solution of 1,4-dimethoxyxanthone (0.490 g, 1.91 mmol) in 30 mL acetone was added freshly prepared silver(II) oxide (0.95 g, 7.65 mmol). The suspension was sonicated briefly and a catalytic amount (1.9 mL) of 6N $HNO_3$ was added at room temperature. After stirring for 6 min the reaction was quenched with 60 mL $CH_2Cl_2$-$H_2O$ (5:1) and the mixture filtered through a pad of Celite. The solvent was evaporated, the residue redissolved in $CH_2Cl_2$ (50 mL), washed with water (3 x 15 mL) and dried over anhydrous $Na_2SO_4$. Evaporation to dryness gave a reddish-orange compound which was purified by recrystallization ($CH_2Cl_2$/pentane) to afford 0.42 g (98%) of xanthoquinone as needles: mp 183.5-184.5°C (dec.).

IR ($CHCl_3$) $\nu_{max}$: 1693 (C=O, quinone and γ-pyrone), 1613 (C=C), 1570 (ring C$\cdots$C).

$^1$H.m.r. (200 MHz, $CDCl_3$) δ: 8.28 (dd, J = 2 and 8 Hz, 1H, H-8), 7.78 (m, J = 8.5, 6.9, 1.8 Hz, 1H, H-6), 7.66 (dd, J = 8.5, 1.2 Hz, 1H, H-5), 7.50 (m, J = 8.0, 6.9, 1.2 Hz, 1H, H-7), 7.08 (d, J = 10 Hz, 1H, H-3), 6.90 (d, J = 10 Hz, 1H, H-2).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 8.30 (dd, J = 2 and 8 Hz, 1H,

H-8), 7.8-7.4 (m, 3H, H-5, H-6, H-7), 6.9 (bs, 2H, H-2, H-3).

$^{13}$C.m.r.* (22.63 MHz, $CDCl_3$) δ: 182.90 (C=O), 180.20 (C=O), 174.03 (C-9), 155.77 (C-10a), 154.42 (C-4a), 138.50 (C-2 or C-3), 135.38 (C-3 or C-2), 134.09 (C-6), 126.98 (C-8), 126.67 (C-7), 126.36 (C-8a), 119.15 (C-5), 115.26 (C-9a).

M.s. (EI, 15eV, 57°C) m/z (%): 226 (100, $M^{+\cdot}$), 227 (14.9, $[M+1]^{+\cdot}$ isotope peak), 228 (36.7, $MH_2^{+\cdot}$), 104 (67, $C_7H_4O^+$).

Diels Alder Adduct 214

Method A

To a solution of xanthoquinone (100 mg, 0.442 mmol) in 10 mL $CH_2Cl_2$ was added isoprene (33 mg, 0.486 mmol) in a foil wrapped flask under an inert atmosphere and the mixture was stirred at room temperature for 72 h. Evaporation of the solvent afforded 128 mg (98%) of the adduct as a red crystalline compound: mp 255-259°C (dec.).

IR (KBr) $\nu_{max}$: 1695 (C=O), 1680 (olefin), 1640 (C=C, α,β-unsaturated), 1250 (=C-O-C, $\nu_{as}$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 8.20 (dd, J = 2 and 8 Hz, 1H, H *ortho*-CO), 7.83-7.2 (m, 3H, D-ring aryl-H), 5.4 (bs, 1H, H-8), 3.6-3.18 (m, 2H, H-6a, H-10a), 2.5-2.16 (m, 4H, H-7, H-10), 1.7 (bs, 3H, $CH_3$).

$^1$H.m.r. (200 MHz, $CDCl_3$) δ: 8.20 (dd, J = 2 and 8 Hz, 1H, H *ortho*-CO), 7.7 (m, J = 8.5, 6.9, 1.8 Hz, H-3 (or H-2

*Tentative assignment.

*iso*-isomer)), 7.67 (dd, J = 8.5, 1.2 Hz, 1H, H-4 (or H-1 isomer)), 7.48 (m, J = 8.0, 6.9, 1.2 Hz, 1H, H-2 (or H-3 isomer)), 5.41 (bs, 1H, H-8), 3.5-3.3 (m, 2H, H-6a, H-10a), 2.54-2.2 (m, 4H, 2×H-7, 2×H-10), 1.70 (bs, 3H, $CH_3$).

M.s. (EI, 70eV, 69°C) m/z (%): 294 (100, $M^{+\cdot}$), 295 (26, $[M+1]^{+\cdot}$ isotope peak), 279 (62.7, $M^{+\cdot} - CH_3$), 265 (23.7, $M^{+\cdot}$ - CHO), 251 (26, $M^{+\cdot} - CH_3CO$).

Method B

To a solution of 1,4-dihydroxyxanthone (0.133 g, 0.583 mmol) in 15 mL dry acetone, in a foil-wrapped flask cooled to 0°C, was added isoprene (43.7 mg, 0.641 mmol) and silver(I) oxide (0.27 g, 1.16 mmol). The mixture was sonicated briefly, stirred at 0°C, allowed to reach room temperature slowly and stirred for an additional 50 h. The reaction mixture was filtered through Celite, and evaporated to afford 160 mg (94%) of almost pure adduct 214 which had spectral properties identical to those described above.

1,4-Dihydroxyxanthone (75)

A solution of 1,4-dimethoxyxanthone (0.5 g, 1.95 mmol) in 50 mL dry $CH_2Cl_2$ was cooled to -78°C and a large excess of boron tribromide (4 mL) was added. The reaction mixture was allowed to warm up to room temperature overnight, quenched with $CH_3OH$ and evaporated to give a quantitative yield of crystalline material which was recrystallized ($CH_3OH$/hexane) to afford 0.40 g (91%) of dihydroxyxanthone as bright yellow needles: mp 239-240°C (dec.) (Lit.[365] mp 236-237°C).

IR (nujol) $\nu_{max}$: 3350 (OH), 1640 (C=O, hydrogen-bonded), 1610, 1585 (ring C$\cdots$C), 1230 (C-O phenol).

$^1$H.m.r. (60 MHz, DMSO-$d_6$) δ: 13.0 (bs, 1H, exchangeable OH(C-1)), 11.86 (bs, 1H, exchangeable OH (C-4)), 8.26 (dd, J = 2 and 8 Hz, 1H, H-8), 7.83-7.5 (m, 3H, H-5, H-6, H-7), 7.33 (d, J = 9 Hz, 1H, H-3), 6.65 (d, J = 9 Hz, 1H, H-2).

M.s. (EI, 70eV, 61°C) m/z (%): 228 (100, $M^{\cdot+}$), 229 (15.8, $[M+1]^{+}$), 227 (12.8, $M^{\cdot+}$ - 1), 200 (3.3, $M^{\cdot+}$ - CO), 199 (3.0, $M^{\cdot+}$ - CO-H).

## SYNTHESIS OF 2-(2-METHYL-1,3-DITHIAN-2-YL)-1,3-BUTADIENE (222)

### Formation of Thioketal 223

To a cooled (0°C) solution of biacetyl (9.8 g, 0.11 mol) in 25 mL dry $CH_2Cl_2$ and 1,3-propanedithiol (13.09 g, 0.121 mol) was added chlorotrimethylsilane (17 g, 0.16 mol) dropwise over a period of 30 min. After complete addition, the ice-water bath was removed and the mixture stirred at room temperature for 2 h. The mixture was poured into water, separated and the organic layer was washed successively with 5% aqueous $Na_2CO_3$ (3 x 15 mL), water (3 x 15 mL), saturated brine (3 x 15 mL) and dried over anhydrous $Na_2SO_4$. Evaporation *in vacuo* followed by distillation afforded 16.6 g (86%) of thioketal 223 as a light-yellow oil: bp 105-107°C/6mm.

IR (film) $\nu_{max}$: 2930, 2870 ($CH_3$), 1700 (C=O), 1440 ($-S-CH_2$), 1200 (CH bend).

$^1$H.m.r. (60 MHz, $CDCl_3$) $\delta$: 3.1-2.7 (m, 4H, $-SCH_2CH_2CH_2S-$), 2.45 (s, 3H, $CH_3CO$), 2.25-1.90 (m, 2H, $-SCH_2CH_2CH_2S-$), 1.80 (s, 3H, $CH_3-C(S)_2$).

### Alcohol 224

Vinylmagnesium bromide (19.1 mL of a 1.5 M solution, 29 mmol) was added dropwise, under an inert atmosphere, to a cooled (0°C) solution of thioketal 223 (4.9 g, 27.6 mmol) in 20 mL THF. The reaction was allowed to warm up to room

temperature over a period of 1 h then stirred for an additional 2 h at room temperature. The reaction was quenched with 20 mL of 1 M aqueous ethylenediamine tetracetic acid tetrasodium salt. Methylene chloride (75 mL) was added, the organic layer separated, washed with water until neutral and dried over anhydrous $Na_2SO_4$. Evaporation of the solvent *in vacuo* afforded 4.5 g (80%) of a yellow oil which decomposed when distilled.

IR (film) $\nu_{max}$: 3480 (OH), 2940, 2860 ($CH_3$), 1635 (C=C, terminal vinyl), 1440 (-S-$CH_2$), 1400, 995, 920 (CH, terminal vinyl).

$^1$H.m.r. (200 MHz, $CDCl_3$) δ: 6.2 (dd, J = 11 and 17 Hz, 1H, =C-(C)H), 5.48 (dd, J = 2 and 17 Hz, 1H, HHC=C(C)H), 5.26 (dd, J = 2 and 11 Hz, 1H, HHC=CH(C)), 3.0 (bs, 1H, exchangeable OH), 3.1-2.5 (m, 4H, -S$CH_2CH_2CH_2$S-), 2.2-1.8 (m, 2H, -S$CH_2CH_2CH_2$S-), 1.6 (s, 3H, $CH_3$), 1.4 (s, 3H, $CH_3$).

Diene 222

To a solution of alcohol 224 (5.1 g, 25 mmol) in 50 mL dry $CH_2Cl_2$ was added dropwise triethylamine (5 g, 49 mmol) under an inert atmosphere at 0°C. Mesyl chloride (3.15 g, 27.5 mmol) was added dropwise over a period of 10 min. After 30 min, the reaction mixture was added to ice-water, the organic layer separated, washed with water (3 x 20 mL) and dried over anhydrous $Na_2SO_4$. Evaporation of the solvent followed by distillation afforded 2.8 g (60%) of diene 222 as a yellow

viscous oil: bp 65-68°C/2mm.

IR (film) $\nu_{max}$: 2940, 2865 ($CH_3$), 1650, 1610 (C=C, diene), 1440 ($SCH_2$), 980 (CH, terminal vinyl, conjugated).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 6.16-5.1 (m, 5H, diene-H), 2.9-2.7 (m, 4H, $-SC\underline{H}_2CH_2C\underline{H}_2S-$), 2.1-2.0 (m, 2H, $-SCH_2C\underline{H}_2CH_2S-$), 1.63 (s, 3H, $CH_3$).

2-Acetoxy-1,3-butadiene (229)

n-BuLi (70 mL of a 1.5 M solution in hexane, 0.105 mmol) was added to a cooled (−78°C) solution of freshly distilled diisopropylamine (10.6 g, 0.105 mmol) in 25 mL THF under an inert atmosphere. Freshly distilled methyl vinyl ketone (7 g, 0.1 mol) was added dropwise over a period of 15 min followed by the addition of freshly distilled acetic anhydride (10.2 g, 0.1 mol). The reaction mixture was stirred for 5 h then allowed to reach room temperature slowly. The reaction was quenched with water, the solvent evaporated, the resultant oil diluted with pentane (50 mL), washed with water (3 x 20 mL), 5% aqueous $NaHCO_3$ (5 x 20 mL), dried over anhydrous $Na_2SO_4$, and distilled to afford 8.5 g (72%) of diene 229 as a colorless oil: bp 40-41°C/30mm (Lit.[603] bp 54°C/40mm).

IR (film) $\nu_{max}$: 2928 ($CH_3$), 1748 (C=O, vinyl ester), 1600 (C=C, diene), 1220 (=C-O-C, $\nu_{as}$), 1020 (=C-O-C, $\nu_s$), 878 ($=CH_2$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 6.26 (dd, J = 8 and 15 Hz, 1H, $H_2C=C(C)\underline{H}$), 5.5-4.8 (m, 4H, dienic-H), 2.16 (s, 3H, $OCOCH_3$).

GC/MS (6%, OV101, 2m x 6mm, 50° +10°C/min) retention time: 1.0 min/(EI, 70eV) m/z (%): 112 (30.8, $M^{+\cdot}$), 113 (1.3, [M+1]$^{+\cdot}$ isotope peak), 70 (100, $M^{+\cdot}$ - $CH_2=C=O$), 43 (98, $CH_3CO^+$).

2-Trimethylsilyloxy-1,3-butadiene (243)

To a solution of lithium diisopropylamine, freshly prepared from n-BuLi (15.8 mL of a 1.6 M solution in hexane, 25.25 mmol) and freshly distilled diisopropylamine (2.55 g, 25.25 mmol) in 25 mL THF at -78°C, was added under an inert atmosphere a solution of methyl vinyl ketone (1.75 g, 25 mmol) in 10 mL THF over a period of 10 min. HMPT (2.2 mL) was added, the reaction mixture stirred for an additional 10 min and quenched with chlorotrimethylsilane (2.7 g, 25 mmol) at -78°C and allowed to warm up to room temperature. The solvent was evaporated, the residue dissolved in pentane (50 mL), washed with water (5 x 20 mL), conc. aqueous $NH_4Cl$ (2 x 15 mL), water (3 x 15 mL) and dried over anhydrous $Na_2SO_4$. Distillation afforded 1.95 g (55% of diene 243 as a clear colorless oil: bp 30-33°C/30mm (Lit.[604,605,608] 52-53°C/50mm).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 6.35 (dd, J = 10 and 16 Hz, 1H, $H_2C{=}C(C)\underline{H}$), 5.5 (dd, J = 2 and 16 Hz, 1H, $\underline{H}HC{=}C(C)H$), 5.1 (m, 1H, $H\underline{H}C{=}C(C)H$), 4.4 (bs, 2H, $C\underline{H}_2{=}C(C)(O)$), 0.33 (s, 9H, $OSi(CH_3)_3$).

M.s. (EI, 70eV, 45°C) m/z (%): 142 (82, $M^{+\cdot}$), 143 (10.3, $[M+1]^{+\cdot}$ isotope peak), 127 (75, $M^{+\cdot} - CH_3$), 75 (100, $[(CH_3)_2SiOH]^+$).

2-Triethylsilyloxy-1,3-butadiene (244)

Method A

To a solution of lithium diisopropylamide (prepared as described for diene 243) (50.5 mmol) in 50 mL THF at -78°C, was added under inert atmosphere a solution of methyl vinyl ketone (3.50 g, 50 mmol) in 20 mL THF over a period of 10 min. HMPT (4.4 mL) was added, the reaction was stirred for an additional 20 min and the reaction quenched with triethylchlorosilane (7.54 g, 25 mmol). The reaction mixture was stirred for 5 h at -78°C followed by stirring 1¼ h at room temperature. The reaction was worked-up in the same fashion as described for diene 243. Distillation afforded 7.7 g (83%) of diene 244 as a colorless oil: bp 87-89°C/20mm.

IR (film) $\nu_{max}$: 2950 ($CH_3$), 1622 (C=C, diene), 1250 ($Si-C_2H_5$), 1060 (Si-O), 860 ($=CH_2$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 6.21 (dd, J = 10 and 16 Hz, 1H, $H_2C=C(C)\underline{H}$), 5.56 (dd, J = 2 and 16 Hz, 1H, $\underline{H}HC=C(C)H$), 5.13 (dd, J = 2 and 10 Hz, 1H, $H\underline{H}C=C(C)H$), 4.35 (bd, J = 2Hz, 2H, $\underline{H}_2C=C(C)(O)$), 1.2-0.5 (m, 15H, $Si(CH_2CH_3)_3$).

M.s. (EI, 70eV, 55°C) m/z (%): 184 (75, $M^{+\cdot}$), 185 (14.8, $[M+1]^{+\cdot}$ isotope peak), 155 (62.3, $M^{+\cdot} - C_2H_5$), 103 (89, $(C_2H_5)_2SiOH$).

Method B

To a solution of methyl vinyl ketone (1.75 g, 25 mmol) and triethylamine (2.52 g, 27.5 mmol) in 1,2-dichloroethane cooled to 0°C was added slowly triethylsilyl trifluoromethane-

sulfonate (6.93 g, 26.25 mmol). After several minutes the cooling bath was removed and the reaction stirred at room temperature for 2 h. The precipitated oil was removed, the solvent evaporated *in vacuo* with strict exclusion of moisture, diluted with ether (which precipitated more oil which was removed) and finally distillation afforded 4.4 g (95%) of colorless diene 244 which had spectral properties identical to those reported above.

Preparation of Triethylsilyl Trifluoromethanesulfonate (245)

Chlorotriethylsilane (55.2 g, 0.37 mol) was added slowly to neat trifluoromethanesulfonic acid (50 g, 0.33 mol) under an inert atmosphere. The mixture was heated for 6 h at 80°C and 70.4 g (80%) of pure product 245 was obtained as a clear colorless oil: bp 45-47°C/2mm (Lit.[609] 72°C/10mm).

Adduct 246

To a solution of xanthoquinone (100 mg, 0.44 mmol) in 20 mL $CH_2Cl_2$ was added (89 mg, 0.48 mmol) of 2-triethylsilyloxy-1,3-butadiene under an inert atmosphere in the dark. After stirring 4 days at room temperature, the solvent was evaporated and the residue triturated with pentane to afford a mixture consisting in roughly equal portions of adduct 246 and xanthoquinone. Purification by flash chromatography ($CH_2Cl_2$) was only partially successful because the adduct underwent decomposition on the column. As a result, *ca.* 63 mg (35%) of adduct 246 was obtained as a tan colored material which was not purified any further.

IR (nujol) $\nu_{max}$: 1695 (C=O), 1670 (C=C), 1640 (C=C, α,β-unsaturated), 1250 (Si-$C_2H_5$), 1060 (Si-O).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 8.20 (dd, J = 2 and 8 Hz, 1H, H *ortho*-CO), 7.83-7.2 (m, 3H, D-ring aryl-H), 5.06 (bs, 1H, H-8), 4.1-3.5 (m, 6H, H-6a, H-10a, 2×H-7, 2×H-10), 1.4-0.6 (m, 15H, $(SiC_2H_5)_3$).

M.s. (EI, 70eV, 73°C) m/z (%): 410 (100, $M^+$), 411 (31.2, $[M+1]^+$ isotope peak), 381 (20.7, $M^+ - C_2H_5$), 363 (49.6, $M^+ - C_2H_5$-CO), 103 (4.7, $Si(C_2H_5)_2OH^+$).

Adduct 255

Method A

To a stirred solution of xanthoquinone (121 mg, 0.535 mmol) in 40 mL dry $CH_2Cl_2$ was added a three-fold excess of 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (277 mg, 1.61 mmol) under inert atmosphere in the dark. After stirring 72 h at room temperature the solvent was evaporated *in vacuo* at low temperature and the residue triturated with pentane. A pale orange crystalline adduct 255 (0.17 g, 80%) was obtained which was extremely labile to moisture and heat.

IR ($CHCl_3$) $\nu_{max}$: 1710 (C=O), 1655 (C=C, α,β-unsaturated and C=C-O), 1610, 1570 (ring C⋯C), 1250 (Si-$CH_3$), 1070 (Si-O).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 8.23 (dd, J = 2 and 8 Hz, 1H, H *ortho*-CO), 7.8-7.3 (m, 3H, D-ring aryl-H), 5.21 (d, J = 6 Hz, 1H, H-8), 4.28 (dd, J = 4 and 6 Hz, 1H, H-7), 3.6-3.26 (m, 3H, H-6a, H-10a, H-10B), 3.08 (s, 3H, $OCH_3$), 2.36 (m, 1H, H-10A), 0.33 (s, 9H, $Si(CH_3)_3$).

M.s. (EI, 20eV, 106°C) m/z (%): 366 (6.1, $M^{+\cdot}$ - $CH_3OH$), 294 (100, $M^{+\cdot}$ - $Si(CH_3)_3$-$CH_3O$).

Method B

To a cooled (0°C) foil-wrapped flask containing a solution of 1,4-dihydroxyxanthone (114 mg, 0.5 mmol) in 30 mL dry acetone was added (232 mg, 1.0 mmol) silver(I) oxide and 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (260 mg, 1.5 mmol) under inert atmosphere. The reaction was allowed to warm up

to room temperature slowly and stirred for an additional 50 h. The reaction was worked-up in the same fashion as that described for Method A affording 149 mg (75%) of a pure adduct which had spectral properties identical to those reported above for adduct 255.

Adduct 256

The insoluble by-product obtained due to lability of adduct 255 was identified as the aromatized compound 256.

IR (nujol) $\nu_{max}$: 3340 (OH), 1645 (C=O, H-bonding), 1610, 1590, 1570 (ring C···C).

$^1$H.m.r. (60 MHz, DMSO-$d_6$) $\delta$: 13.5 (bs, 1H, exchangeable OH (*ortho*-CO)), 11.9 (bs, 2H, exchangeable OH), 8.27 (dd, J = 2 and 8 Hz, 1H, H *ortho*-CO), 7.9-7.38 (m, 6H, D-ring and A-ring aryl-H).

M.s. (EI, 70eV, 150°C) m/z (%): 294 (100, $M^{+\cdot}$), 295 (19.3, $[M+1]^{+\cdot}$ isotope peak), 293 (18, $M^{+} - 1$), 278 (10, $M^{+\cdot} - CO$).

Preparation of 1-Methoxy-3-(triethylsilyloxy)-1,3-butadiene (259)

Method A

To a cooled (-78°C) solution of freshly distilled diisopropylamine (11.1 g, 0.11 mol) in 60 mL THF was added n-BuLi (65.6 mL of a 1.6 M solution in hexane, 0.105 mol) under an inert atmosphere. A solution of 4-methoxy-3-buten-2-one (10 g, 0.10 mol) in 10 mL THF was added slowly over a period of 10 min. The mixture was stirred for 30 min at -78°C and *dry* HMPT (10 mL) was added followed, after a few minutes, by the addition of a solution of triethylchlorosilane (15.1 g, 0.10 mmol) in 10 mL THF over a period of 15 min. The mixture was stirred for 3 h at -78°C, allowed to warm up to room temperature slowly and finally stirred at room temperature overnight. Evaporation of the solvent *in vacuo* gave a dark brown oil which was diluted in pentane (100 mL), washed with water (5 x 40 mL), cold 1% aqueous HCl (3 x 20 mL), water (3 x 20 mL), saturated brine (3 x 20 mL) and dried over anhydrous $Na_2SO_4$. Distillation afforded 12 g (80%) of pure diene 259 as a colorless oil: bp 68-70°C/0.8mm.

IR (film) $\nu_{max}$: 2960 ($CH_3$), 1653, 1586 (C=C, conjugated), 1220 (Si-$C_2H_5$), 1030 (Si-O), 960 (CH, *trans* diene).

$^1$H.m.r. (60 MHz, $CDCl_3$), δ: 6.9 (d, J = 12 Hz, 1H, vinyl H(C-1)), 5.36 (d, J = 12 Hz, 1H, vinyl H(C-2)), 4.0 (s, 2H, vinyl H(C-4)), 3.53 (s, 3H, $OCH_3$), 1.2-0.33 (m, 15H, Si($C_2H_5$)$_3$).

M.s. (EI, 15eV, 100°C) m/z (%): 214 (24.0, $M^+$), 215

(3.7, $[M+1]^+$ isotope peak), 199 (60.4, $M^+ - CH_3$), 185 (100, $M^+ - C_2H_5$), 103 (27, $Si(C_2H_5)_2OH^+$).

Method B

Excellent yields (> 95%) of diene 259 were obtained when 4-methoxy-3-buten-2-one was reacted with triethylsilyl trifluoromethanesulfonate under conditions similar to those used for the preparation of diene 244. After removal of the precipitated triethylammonium triflate, distillation afforded pure diene 259.

Adduct 260

Method A

To a foil-wrapped flask containing a solution of xanthoquinone (178 mg, 0.787 mmol) in 50 mL $CH_2Cl_2$ was added 1-methoxy-3-(triethylsilyloxy)-1,3-butadiene (491 mg, 2.29 mmol) under an inert atmosphere. After stirring for 72 h at room temperature, the solvent was evaporated *in vacuo* without heat and the residue triturated with pentane to afford 311 mg (90%) of pure adduct 260 as a stable light-orange crystalline material: mp 192.5-194.5°C (dec.).

IR (nujol) $\nu_{max}$: 1710 C=O), 1645 (C=C, α,β-unsaturated and C=C-O), 1610, 1570 (ring C···C), 1240 (Si-$C_2H_5$), 1080 (Si-O).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 8.18 (d, J = 2 and 8 Hz, 1H, H *ortho*-CO), 7.73-7.16 (m, 3H, D-ring aryl-H), 5.13 (d, J = 6 Hz, 1H, H-8), 4.23 (dd, J = 4 and 6 Hz, 1H, H-7), 3.66-3.26 (m, 3H, H-6a, H-10a, H-10 eq), 3.03 (s, 3H, $OCH_3$), 2.16 (dd, J = 6 and 18 Hz, 1H, H-$10_{ax}$), 1.2-0.6 (m, 15H, $Si(CH_2CH_3)_3$).

$^1$H.m.r. (200 MHz, $CDCl_3$) δ: 8.21 (dd, J = 2 and 8 Hz, 1H, H *ortho*-CO), 7.71 (m, J = 8.5, 6.9, 2 Hz, 1H, H-3 (or H-2 isomer)), 7.61 (dd, J = 8.5 and 1.2 Hz, 1H, H-4 (or H-1 isomer)), 7.44 (m, J = 8.0, 6.9, 1.2 Hz, 1H, H-2 (or H-3 isomer)), 5.17 (d, J = 5.4 Hz, 1H, H-8), 4.23 (dd, J = 4.2, 5.4 Hz, 1H, H-7), 3.5 (m, 1H, H-10a), 3.36 (m, 1H, H-6a), 3.12 (d, J = 18 Hz, 1H, H-10 eq), 3.02 (s, 3H, $OCH_3$), 2.2 (dd, J = 8 and 18 Hz, 1H,

H-10$_{ax}$), 1.09-0.99 (t, J = 8 Hz, 9H, Si(CH$_2$C$\underline{H}_3$)$_3$), 0.82-0.70 (q, J = 8 and 6 Hz, Si(C$\underline{H}_2$CH$_3$)$_3$).

$^1$H.m.r. (400 MHz, CDCl$_3$) δ: 8.27 (dd, J = 1.7 and 7.9 Hz, 1H, H *ortho*-CO), 7.76 (m, J = 8.5, 7.0, 1.7 Hz, 1H, H-3 (or H-2 isomer)), 7.65 (dd, J = 8.5 and 1.4 Hz, 1H, H-4 (or H-1 isomer)), 7.47 (dt, J = 7.9, 7.0, 1.4 Hz, 1H, H-2 (or H-3 isomer)), 5.17 (dd, J = 5.6 and 1.5 Hz, 1H, H-8), 4.23 (dd, J = 5.6 and 4.2 Hz, 1H, H-7), 3.46 (ddd, J = 7.5, 6.0, 0.9 Hz, 1H, H-10a), 3.35 (dd, J = 6.0 and 4.2 Hz, 1H, H-6a), 3.13 (dd, J = 18.4 and 0.9 Hz, 1H, H-10 eq), 3.02 (s, 3H, OCH$_3$), 2.19 (ddd, J = 18.4, 7.5, 1.5 Hz, 1H, H-10$_{ax}$), 1.02 (t, J = 7.6 Hz, 9H, Si(CH$_2$C$\underline{H}_3$)$_3$), 0.77 (q, J = 7.6 Hz, 6H, Si(C$\underline{H}_2$CH$_3$)$_3$).

$^{13}$C.m.r. (100.62 Hz, CDCl$_3$) δ: 193.53 (C=O), 190.15 (C=O), 174.98 (C=O), 158.11, 154.66, 154.39, 134.95, 126.55, 126.26, 125.75, 121.71, 118.95, 100.19, 74.94, 54.98, 50.30, 44.37, 26.00, 6.59, 5.00.

M.s. (EI, 70eV, 105°C) m/z (%): 440 (1.1, M$^{\cdot+}$), 441 (0.4, [M+1]$^{\cdot+}$ isotope peak), 411 (28, M$^{\cdot+}$ - $C_2H_5$), 408 (100, M$^{\cdot+}$ - $CH_3OH$), 294 (14.2, M$^{\cdot+}$ - Si($C_2H_5$)$_3$-$OCH_3$).

Method B

A slightly inferior yield (80%) was obtained when the reaction was performed by trapping xanthoquinone *in situ* by the oxidation of 1,4-dihydroxyxanthone with silver(I) oxide. Nevertheless, a pure adduct was obtained which had spectral properties identical to those of adduct 260.

Compound 261

To a solution of adduct 260 (400 mg, 0.91 mmol) in 10 mL acetone was added sodium bicarbonate (168 mg, 2.0 mmol) in 2 mL water. The mixture was stirred at room temperature for 10 min and the solvent evaporated. $CH_2Cl_2$ (20 mL) was added, washed with water (3 x 5 mL), dried over anhydrous $Na_2SO_4$ and evaporated to afford 360 mg (90%) of the tautomer 261 as a pasty material.

IR (nujol) $\nu_{max}$: 3350 (OH), 1645 (C=O (H-bonding), C=C-O), 1240 (Si-$C_2H_5$), 1080 (Si-O).

$^1$H.m.r. (60 MHz, $CD_3COCD_3$) δ: 13.2 (bs, 1H, exchangeable, OH *ortho*-CO), 11.4 (bs, 1H, exchangeable OH), 7.98 (d, J = 2 and 8 Hz, 1H, H *ortho*-CO), 7.70-7.10 (m, 3H, D-ring aryl-H), 5.18 (d, J = 6 Hz, 1H, H-8), 4.45 (d, J = 6 Hz, 1H, H-7), 3.40 (bs, 2H, 2×H-10), 3.20 (s, 3H, $OCH_3$), 1.2-0.6 (m, 15H, $Si(CH_2CH_3)_3$).

Thio-Adduct 264

To a solution of 1,4-dihydroxythioxanthone (186 mg, 0.762 mmol) in 20 mL dry acetone was added silver(I) oxide (0.36 g, 1.55 mmol) and 1-methoxy-3-triethylsilyloxy-1,3-butadiene (0.25 g, 1.17 mmol) and the mixture was stirred in the dark at room temperature for 24 h. The reaction mixture was filtered through a pad of Celite, the filtrate evaporated to dryness and triturated with pentane to afford 220 mg (63%)

of pure adduct 264 as a light-orange crystalline material: mp 201-203°C (dec.).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 8.47 (dd, J = 1.5 and 8 Hz, 1H, H *ortho*-CO), 7.63-7.43 (m, 3H, D-ring aryl-H), 5.13 (d, J = 6 Hz, 1H, H-8), 4.21 (dd, J = 4 and 6 Hz, 1H, H-7), 3.73-3.26 (m, 3H, H-6a, H-10a, H-10B), 3.0 (s, 3H, $OCH_3$), 2.21 (dd, J = 6 and 18 Hz, 1H, H-10A), 1.3-0.6 (m, 15H, $Si(C_2H_5)_3$).

$^1$H.m.r. (200 MHz, $CDCl_3$) δ: 8.47 (dd, J = 1.2 and 7.9 Hz, 1H, H *ortho*-CO), 7.65 (d, J = 3.5 Hz, 1H, H-4 (or H-1 isomer)), 7.60-7.51 (m, 2H, H-2, H-3), 5.14 (d, J = 5.3 Hz, 1H, H-8), 4.23 (dd, J = 4.4 and 5.3 Hz, 1H, H-7), 3.52 (m, 1H, H-10a), 3.37 (m, 1H, H-6a), 3.09 (d, J = 18 Hz, 1H, H-10 eq), 2.17 (dd, J = 7.2 and 18 Hz, 1H, $H\text{-}10_{ax}$), 1.03 (t, J = 8 Hz, 9H, $Si(CH_2\underline{C}H_3)_3$), 0.78 (q, J = 8 Hz, 6H, $Si(\underline{C}H_2CH_3)_3$).

Preparation of Quinizarinquinone (213)

Quinizarin (10 g, 41.6 mmol) and lead tetraacetate (20 g, 45.1 mmol) were stirred in 100 mL glacial acetic acid at room temperature for 1 h. Glycerol (10 mL) was added to destroy excess $Pb(OAc)_4$, the reaction mixture was poured into water and extracted with $CH_2Cl_2$ (3 x 250 mL). The solution was concentrated, washed with 5% aqueous $NaHCO_3$ (3 x 25 mL), water (3 x 25 mL), saturated brine (3 x 25 mL), dried and evaporated *in vacuo*. Purification by flash chromatography ($CH_2Cl_2$) followed by recrystallization ($CHCl_3$/petroleum ether) afforded

7.9 (80%) of quionone (213) as yellow needles with a metallic luster: mp 210-211°C (Lit.[294] 212-213°C).

IR (nujol) $\nu_{max}$: 1675 (C=O, quinone), 1610, 1590 (ring C···C).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 8.2-7.67 (m, 4H, aryl-H), 6.90 (s, 2H, olefinic-H).

Adduct 271

To a solution of quinizarinquinone (104 mg, 0.437 mmol) in 10 mL $CH_2Cl_2$ was added 1-methoxy-3-triethylsilyloxy-1,3-butadiene (130 mg, 0.611 mmol) under an inert atmosphere and the solution stirred in the dark for 24 h. Evaporation of the solvent *in vacuo*, at low temperature, gave a tan colored amorphous material. Trituration with pentane afforded 193 mg (98%) of crystalline material which consisted of a 3:1 mixture of the two internal adducts 271a and 271b.

IR (nujol) $\nu_{max}$: 1710 (C=O), 1647 (C=C, conjugated and C=C-O), 1610, 1580 (ring C···C), 1240 (Si-$C_2H_5$), 1050 (Si-O).

Major isomer 271a

$^1$H.m.r. (200 MHz, $CDCl_3$) δ: 8.1-8.0 (m, 2H, aryl-H), 7.8-7.7 (m, 2H, aryl-H), 7.06 (d, J = 10.3 Hz, 1H, olefinic-H), 6.65 (d, J = 10.3 Hz, 1H, olefinic-H), 5.29 (d, J = 5.7 Hz, 1H, HC=C-OSi), 4.77 (d, J = 5.7 Hz, 1H, $(CH_3O)C\underline{H}$), 3.22 (d, J = 18.5 Hz, 1H, $>CH_1\underline{H}_2$), 3.15 (s, 3H, $OCH_3$), 2.06 (d, J = 18.5 Hz, 1H, $>CH_1\underline{H}_2$), 1.04-0.91 (t, J = 9 Hz, 9H, $Si(CH_2C\underline{H}_3)_3$),

0.78-0.61 (q, J = 9 Hz, 6H, $Si(C\underline{H}_2CH_3)_3$).

Minor isomer 271b

$^1$H.m.r. (200 MHz, $CDCl_3$) δ: 8.1-8.0 (m, 2H, aryl-H), 7.8-7.7 (m, 2H, aryl-H), 6.88 (d, J = 10.4 Hz, 1H, olefinic-H), 6.57 (d, J = 10.4 Hz, 1H, olefinic-H), 5.28 (d, J = 5.7 Hz, 1H, $\underline{H}C{=}C{-}OSi$), 4.65 (d, J = 5.7 Hz, 1H, $(CH_3O)C\underline{H}$), 3.32 (d, J = 16 Hz, 1H, $>C\underline{H}_1H_2$), 2.94 (s, 3H, $OCH_3$), 2.14 (d, J = 16 Hz, 1H, $>CH_1\underline{H}_2$), 1.04-0.91 (t, J = 9 Hz, 9H, $Si(CH_2C\underline{H}_3)_3$), 0.78-0.61 (q, J = 9 Hz, 6H, $Si(C\underline{H}_2CH_3)_3$).

M.s. (EI, 70eV, 240°C) m/z (%): 452 (28.6, $M^{+\cdot}$), 453 (10.1, $[M+1]^{+\cdot}$ isotope peak), 424 (38.9, $M^{+\cdot}$ - CO), 423 (10.7, $M^{+\cdot}$ - $C_2H_5$), 370 (100, $M^{+\cdot}$ - $C_4H_2O_2$), 238 (15.1, $M^{+\cdot}$ - $CH_2{=}C(OSiEt_3)$ - $CH{=}C(OCH_3)H$).

## SYNTHESIS OF 3-CARBOETHOXY SULFONE 273

### Phosphonate 276

Paraformaldehyde (6 g, 0.06 mol) was dissolved in 300 mL absolute ethanol containing 10 drops piperidine and refluxed for 0.5 h. Triethyl phosphonoacetate (19.95 g, 0.089 mol) was added all at once and the solution was refluxed for 36 h. Evaporation of the solvent *in vacuo* gave a yellow oil. The oil was dissolved in benzene (100 mL), a catalytic amount of *p*-toluenesulfonic acid was added and the mixture refluxed under a Dean-Stark water separator containing 4Å molecular sieves. After 29 h, removal of the solvent gave an oil which was distilled, bp 128-132°C/1mm to afford 12 g (90%) of phosphonate 276 as a clear colorless oil which turned yellow on standing.

IR (film) $\nu_{max}$: 2975 (CH), 1720 (C=O, α,β-unsaturated ester), 1610 ($C=CH_2$, conjugated), 1250, 1030 (C-O-C).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 6.98 (dd, J = 26 and 2 Hz, 1H, vinylic-H), 6.48 (dd, J = 4 and 2 Hz, 1H, vinylic-H), 4.13 (m, 6H, $CH_2$), 1.33 (t, J = 8 Hz, 9H, $CH_3$).

3-Carboethoxy-2,5-dihydrothiophene (277)

A suspension of 2,5-dihydroxy-1,4-dithiane (dimer of mercaptoacetaldehyde, 900 mg, 5.9 mmol) in 75 mL $CH_2Cl_2$ was heated with triethylamine (1.3 g, 13 mmol) under inert atmosphere. Phosphonate 276 (2.62 g, 11.8 mmol) was added as a solution in $CH_2Cl_2$ (10 mL) and the mixture refluxed for 4 h. The cooled solution was diluted with $CH_2Cl_2$ (100 mL), washed with 5% aqueous HCl (3 x 100 mL), water (3 x 100 mL), saturated brine (3 x 100 mL) and dried over anhydrous $Na_2SO_4$. Evaporation of the solvent *in vacuo* gave an oil which was purified by flash chromatography ($CH_2Cl_2$) to afford 1.6 g (86%) of thiophene 277 as a clear, colorless oil.

IR (film) $\nu_{max}$: 2975 (CH), 1720 (C=O, α,β-unsaturated ester), 1640 (C=C, conjugated), 1260, 1030 (C-O-C).

$^1$H.m.r. (60 MHz, $CDCl_3$), δ: 7.0 (bs, 1H, vinylic-H), 4.3 (q, J = 7 Hz, 2H, $COOCH_2$-), 4.0 (s, 4H, ring $CH_2$), 1.33 (t, J = 7 Hz, 3H, $CH_3$).

Sulfone 273

To a cooled (0°C) solution of thiophene 277 (451 mg, 2.85 mmol) in 20 mL $CH_2Cl_2$ was added *m*-chloroperoxybenzoic acid (1.2 g, 6.9 mmol). The mixture was stirred for 3 h and then allowed to warm up to room temperature slowly overnight. The reaction mixture was filtered, washed with saturated aqueous $Na_2CO_3$, dried over anhydrous $Na_2SO_4$ and evaporated *in vacuo* to afford an oil. Purification by flash chromatography ($CH_2Cl_2$-EtOAc, 4:1) afforded 0.50 g (92%) of sulfone 273 as a white crystalline compound: mp 59-60°C.

IR (nujol) $\nu_{max}$: 1720 (C=O, α,β-unsaturated ester), 1630 (C=C, conjugated), 1310, 1280 ($SO_2$), 1240 (C-O-C), 1140 ($SO_2$, $\nu_s$), 1010 (C-O-$\overline{C}$, $\nu_s$).

$^1$H.m.r. (200 MHz, $CDCl_3$) δ: 7.03 (bs, 1H, vinylic-H), 4.27 (q, J = 7 Hz, 2H, $COOCH_2$-), 4.0 (s, 4H, ring $CH_2$), 1.32 (t, J = 7 Hz, 3H, $CH_3$).

## SYNTHESIS OF (E)-1-(TRIMETHYLSILYL)-1,3-BUTADIENE (281)

### Preparation of 3-(Trimethylsilyl)-2-propyn-1-ol (282)

To a solution of n-BuLi (146.9 mL of a 1.7 M solution in hexane, 0.250 mol) in anhydrous ether cooled to -78°C was added freshly distilled propargyl alcohol (7 g, 0.125 mol). After about half of the propargyl alcohol was added, a gel formed and stirring became inefficient requiring that the flask be shaken manually. One hour after complete addition of the alcohol, chlorotrimethylsilane (27.4 g, 0.252 mol) was added at -78°C over a period of 20 min. The mixture was allowed to warm up *slowly* (the solid mass slowly disintegrated) and stirred for 2 h. The solvent was evaporated and the resultant oil dissolved in methanol (110 mL) to which was added 2N aqueous HCl, the mixture stirred overnight at room temperature and distilled to remove as much of the methanol as possible. Extraction with ether, followed by washing successively with water (3 x 20 mL), 5% aqueous $NaHCO_3$ (3 x 20 mL), saturated brine (2 x 20 mL), dried over anhydrous $Na_2SO_4$ and evaporation *in vacuo* of the solvent gave a light-yellow oil which was distilled to afford 11.7 g (73%) of alcohol 282: bp 50-51°C/0.5mm (Lit.[641] 56°C/0.7mm).

IR (film) $\nu_{max}$: 3340 (broad, OH), 2960 ($CH_2$), 2160 (C≡C), 1250 (Si-$CH_3$).

$^1$H.m.r. (60 MHz, $CDCl_3$ no internal standard) δ: 4.0 (d, J = 6 Hz, 2H, $CH_2$), 2.8 (bt, J = 6 Hz, 1H, exchangeable OH),

0.0 (s, 9H, C-Si$(CH_3)_3$).

Reduction of Alkyne 282

To a solution of sodium *bis*-(2-methoxyethoxy)aluminium hydride (92.4 mL of a 3.4 M solution in toluene, 0.314 mol) in 100 mL dry ether under inert atmosphere was added dropwise, with cooling at 0°C, alkyne 282 (11.5 g, 0.090 mol) in 20 mL ether over a period of 20 min. After stirring 10 min at 0°C, the cooling bath was removed and the reaction stirred at room temperature for 1 h. The reaction was quenched by the dropwise addition of 2N aqueous $H_2SO_4$. The organic layer was separated, washed with water (3 x 50 mL) and saturated brine (2 x 50 mL). The aqueous layer was extracted with ether (2 x 50 mL), combined with the other ether phase, dried over anhydrous $MgSO_4$ and the ether evaporated *in vacuo*. The residual oil was distilled affording 7.8 g (64%) of *trans*-alkene 283 as a clear colorless oil: bp 48-50°C/2.6mm (Lit.[641] 80-81°C/40mm).

IR (film) $\nu_{max}$: 3340 (broad, OH), 2945 ($CH_2$), 1615 (C=C), 1240 (Si-$CH_3$), 990 (C=C-H *trans*).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 6.0-5.8 (m, 2H, olefinic-H), 4.0 (bs, 2H, $CH_2$), 2.6 (bs, 1H, exchangeable OH), 0.03 (s, 9H, $Si(CH_3)_3$).

$^1$H.m.r. (200 MHz, $CDCl_3$) δ: 6.01 (dt, J = 19 and 3 Hz, 1H, C<u>H</u>=CHSiMe$_3$), 5.85 (d, J = 19 Hz, 1H, =C<u>H</u>SiMe$_3$), 4.04 (d,

J = 3 Hz, 2H, $CH_2$), 2.8 (bs, 1H, exchangeable OH), 0.03 (s, 9H, $Si(CH_3)_3$).

Oxidation of 283

To a solution of alcohol 283 (7 g, 53.8 mmol) in 40 mL $CH_2Cl_2$ was added, with cooling at 0°C, pyridinium chlorochromate (17.4 g, 80.7 mmol) in small portions over a period of 5 min. After complete addition, the reaction mixture was allowed to reach room temperature slowly and stirred for an additional 3 h at room temperature. The flask was cooled and the mixture filtered through a pad of dry Celite. The filtrate was concentrated *in vacuo*, anhydrous ether added and the mixture was again filtered through a fresh pad of Celite. Concentration *in vacuo* gave an oil which was then filtered through a small column of silica gel (ether) and finally distilled to afford 4.0 g (58%) of aldehyde 284 as a clear, colorless volatile oil: bp 50-52°C/26mm.

IR (film) $\nu_{max}$: 2960 ($CH_3$), 2780 (CH aldehyde), 1685 (C=O), α,β-unsaturated aldehyde), 1580 (C=C, conjugated), 1250 (Si-$CH_3$), 990 (C=C-H *trans*).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 9.4 (d, J = 7 Hz, 1H, CHO), 7.15 (d, J = 18 Hz, 1H, $(CH_3)_3SiC\underline{H}$=C), 6.4 (dd, J = 7 and 18 Hz, 1H, $\underline{H}C$=CHSi$(CH_3)_3$), 0.13 (s, 9H, $Si(CH_3)_3$).

Diene 281

To a solution of methyltriphenylphosphonium bromide (25.2 g, 70.5 mmol) in 300 mL dry ether, under inert atmosphere, was added n-BuLi (41.5 mL of a 1.7 M solution in hexane, 70.5 mmol) at room temperature. After stirring for 3 h, aldehyde 284 (9.02 g, 70.5 mmol) was added and the mixture refluxed overnight. The cooled mixture was filtered, the filtrate washed with water (5 x 100 mL), saturated brine (3 x 100 mL) and dried over anhydrous $MgSO_4$. Removal of the solvent and distillation afforded 4.4 g (50%) of diene 281 as a clear, colorless oil: bp 45-46°C/35mm (Lit.[638] 70-74°C/210mm).

IR (film) $\nu_{max}$: 2960 ($CH_3$), 1565 (diene), 1240 (Si-$CH_3$), 990 (C=CH *trans*).

$^1$H.m.r. (200 MHz, $CDCl_3$) δ: 6.4 (m, 2H, $H_2C{=}C\underline{H}{-}C\underline{H}{=}^{t}CHSiMe_3$), 5.88 (d, J = 20 Hz, 1H, $C{=}C\underline{H}SiMe_3$), 5.22 (dd, J = 2 and 16 Hz, 1H, $\underline{H}HC{=}CH-$), 5.12 (dd, J = 2 and 10 Hz, 1H, $H\underline{H}C{=}CH-$), 0.1 (s, 9H, $Si(CH_3)_3$).

Preparation of 3-Trimethylsilyl-1-trimethylsilyloxy-4,4,5,5-tetracyano Cyclohexene (290)

To a solution of tetracyanoethylene (0.113 g, 0.882 mmol) in 5 mL anhydrous benzene was added (E)-1-trimethylsilyl-3-trimethylsilyloxy-1,3-butadiene (0.195 g, 0.910 mmol) and the reaction mixture stirred for 1 h at room temperature. Evaporation *in vacuo* of the solvent gave 0.3 g (quantitative yield) of a white crystalline adduct which was not purified.

IR (nujol) $\nu_{max}$: 2240 (C≡N), 1660 (C=C), 1250 (Si-$CH_3$), 1080 (Si-O).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 4.80 (bs, 1H, =C-H), 2.66 (d, J = 12 Hz, 1H, $C\underline{H}_1H_2$), 2.46 (d, J = 12 Hz, 1H, $CH_1\underline{H}_2$), 1.23 (bs, 1H, $C\underline{H}SiMe_3$), 0.3 (s, 9H, $Si(CH_3)_3$).

## SYNTHESIS OF (E)-1-TRIMETHYLSILYL-3-TRIMETHYLSILOXY-1,3-BUTADIENE (288)

### Preparation of 4-Trimethylsilyl-3-butyn-2-ol (294)

To a solution of n-BuLi (117.7 mL of a 1.7 M solution in hexane, 0.2 mol) in 200 mL THF cooled to -78°C was added 3-butyn-2-ol (7.0 g, 0.1 mol) as a solution in 10 mL THF over a period of 15 min. Towards the end of the addition, the solution became a gel and stirring stopped. The mixture was kept at -78°C for 2 h and during this time the flask was shaken manually several times. Chlorotrimethylsilane (23.9 g, 0.22 mL) was added slowly over a period of 30 min and the gel slowly disintegrated. The reaction mixture was allowed to warm up to room temperature slowly overnight. The flask was cooled to 0°C and 2N aqueous HCl (50 mL) was added slowly. The mixture was stirred vigorously for 1 h. The THF layer was separated from the aqueous phase, the aqueous phase extracted with ether (5 x 50 mL) and the combined organic phase dried over anhydrous $MgSO_4$. Distillation (after the bulk of the solvent was removed by evaporation *in vacuo*) afforded 25.6 g (90%) of alcohol 294 as a colorless oil: bp 53-54°C/2mm (Lit.[619a] 49-50°C/0.2mm).

IR (film) $\nu_{max}$: 3340 (broad, OH), 2960 ($CH_3$), 2170 (C≡C), 1250 (Si-$CH_3$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 4.33 (q, J = 7 Hz, methine), 3.6 (bs, 1H, exchangeable OH), 1.28 (d, J = 7 Hz, 3H, $CH_3$),

0.0 (s, 9H, $Si(CH_3)_3$).

M.s. (EI, 70eV, 55°C) m/z (%): 142 (0.2, $M^{+\cdot}$), 127 (13.6, $M^{+\cdot} - CH_3$), 99 (100, $M^{+\cdot} - CH_3CO$), 75 (15.3, $[(CH_3)_2SiOH]^+$), 73 (16.1, $Si(CH_3)_3^+$).

*trans*-4-(trimethylsilyl-3-buten-2-ol (295)

Using LAH

To a slurry of lithium aluminium hydride (1.07 g, 0.282 mmol) in 10 mL THF under inert atmosphere was added slowly a solution of 294 (1 g, 7.04 mmol) in 5 mL THF. The mixture was refluxed gently for 2.5 g, cooled and quenched with $Na_2SO_4 \cdot 10H_2O$. The precipitate was filtered, the filtrate concentrated and distilled to afford 0.91 g (90%) of a 94:4 *trans* to *cis* mixture of 4-trimethylsilyl-3-buten-2-ol.

*trans*-Isomer of 295

IR (film) $\nu_{max}$: 3340 (broad, OH), 1620 (C=C), 1250 ($Si-CH_3$), 980 (=CH *trans*).

$^1$H.m.r. (200 MHz, $CDCl_3$) δ: 6.0 (dd, J = 4.9 and 19 Hz, 1H, SiCH=CH), 5.73 (d, J = 19 Hz, 1H, SiCH=CH), 4.14 (dq, J = 4 and 7 Hz, 1H, methine), 2.52 (bs, 1H, exchangeable OH), 1.15 (d, J = 7 Hz, 3H, $CH_3$), 0.0 (s, 9H, $Si(CH_3)_3$).

GC/MS (1% OV101, 2m x 6mm, 70° + 4°C/min) retention time: 4.5 min/(EI, 70eV) m/z (%): 144 (10, $M^{+\cdot}$), 129 (11.8, $M^{+\cdot} - CH_3$), 75 (100, $[(CH_3)_2SiOH]^+$), 73 (65.5, $Si(CH_3)_3$).

*cis*-Isomer of 295

IR (film) $\nu_{max}$: 3340 (broad, OH), 1615 (C=C), 1250

($Si-CH_3$), 760, 690 (=CH *cis*).

$^1$H.m.r. (200 MHz, $CDCl_3$) δ: 6.17 (dd, J = 14 and 8 Hz, 1H, SiCH=CH), 5.43 (d, J = 14 Hz, 1H, SiCH=CH), 4.33 (dq, J = 8 and 6 Hz, 1H, methine), 2.8 (bs, 1H, exchangeable OH), 1.12 (d, J = 6 Hz, 3H, $CH_3$), 0.0 (s, 9H, $Si(CH_3)_3$). (The 60 MHz $^1$H.m.r. spectrum is equally well resolved).

GC/MS (same conditions as for the *trans* isomer) retention time: 4.1 min/(EI, 70eV) m/z (%): 144 (5, $M^{+\cdot}$), 129 (6.6, $M^{+\cdot} - CH_3$), 75 (100, $[(CH_3)_2SiOH]^+$), 73 (45.9, $Si(CH_3)_3^+$).

Using RED-AL

To a solution of sodium *bis*-(2-methoxyethoxy)aluminium hydride (18.5 mL of a 3.4 M solution in toluene, 62.2 mmol) in 50 mL dry ether under inert atmosphere was added, with cooling at 0°C, alkyne 294 (2.56 g, 18 mmol) as a solution in 5 mL ether over a period of 30 min. After complete addition, the reaction mixture was allowed to warm up to room temperature and stirred for an additional hour. The reaction was quenched by the dropwise addition of 2N aqueous $H_2SO_4$. The organic layer was separated, washed with water (3 x 20 mL) and saturated brine (2 x 20 mL). The aqueous layer was extracted with ether (2 x 30 mL), and the combined ether phases dried over anhydrous $MgSO_4$. Concentration of the solution and distillation afforded 2.54 g (98%) of pure *trans*-4-trimethylsilyl-3-buten-2-ol (295).

Silylenone 296

To a solution of alcohol 295 (7.2 g, 50 mmol) in 20 mL $CH_2Cl_2$ cooled to 0°C was added portionwise pyridinium chlorochromate (16.1 g, 75 mmol) over a period of 10 min. After complete addition, the reaction mixture was stirred for 0.5 h at 0°C, followed by 1.5 h at room temperature. The mixture was cooled (0°C) and filtered through Celite. The filtrate was evaporated *in vacuo*, dry ether added and filtered through a fresh pad of Celite. Purification by flash chromatography ($CH_2Cl_2$) afforded 5.7 g (80%) of enone 296 as a clear, colorless oil.

IR (film) $\nu_{max}$: 2960 ($CH_3$), 1700, 1680 (C=O, α,β-unsaturated), 1590 (C=C, conjugated), 1250 ($Si-CH_3$), 995 (=CH *trans*).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 6.91 (d, J = 19 Hz, 1H, C<u>H</u>=CHCO), 6.27 (d, J = 19 Hz, 1H, CH=C<u>H</u>CO), 2.13 (s, 3H, $CH_3CO$), 0.03 (s, 9H, $Si(CH_3)_3$).

Diene 288

Lithium diisopropylamine (22 mmol) was prepared from freshly distilled diisopropylamine (2.24 g, 22 mol) and n-BuLi (14.4 mL of a 1.5 M solution in hexane, 22 mmol) as a solution in 10 mL THF at -78°C under inert atmosphere. β-Silylenone 296 (2.98 g, 21 mmol) was added slowly as a solution in 5 mL THF to LDA at -78°C and after stirring for 1 h the reaction was quenched with chlorotrimethylsilane (2.6 g, 24 mmol), stirred for 4 h and then allowed to warm up to room temperature slowly. The mixture was diluted with pentane (30 mL) and washed with cold 5% aqueous $Na_2CO_3$ (3 x 10 mL), dried over anhydrous $Na_2SO_4$, concentrated *in vacuo* and distilled to afford 3.6 g (80%) of diene 288 as a colorless oil: bp 47-50°C/1.2mm (Lit.[639] 82-84°C/19mm).

IR (film) $\nu_{max}$: 2960 ($CH_3$), 1620 (C=C), 1580 (C=C), 1250 (Si-$CH_3$), 1020 (Si-O), 980 (=CH *trans*).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 6.28 (d, J = 18 Hz, 1H, SiC<u>H</u>=CH), 5.93 (d, J = 18 Hz, 1H, SiCH=C<u>H</u>), 4.26 (s, 2H, $=CH_2$), 0.13 (s, 9H, $OSi(CH_3)_3$), 0.0 (s, 9H, $Si(CH_3)_3$).

M.s. (Ei, 70eV, 65°C) m/z (%): 214 (21, $M^{\cdot+}$), 199 (43, $M^{\cdot+} - CH_3$), 141 (100, $M^{\cdot+} - Si(CH_3)_3$), 75 (80, $(CH_3)_2SiOH^+$), 73 (75, $Si(CH_3)_3$).

## SYNTHESIS OF *trans*-4-(TRIMETHYLSILYL)-3-BUTEN-2-OL (295)

### Preparation of β-Silylynone 298

To a stirred solution of *bis*-trimethylsilylacetylene (2 g, 11.7 mmol) and acetyl chloride (0.912 g, 11.6 mmol) in 25 mL $CH_2Cl_2$ cooled at 0°C was added aluminium chloride (1.56 g, 11.7 mmol). After stirring a few minutes, the cooling bath was removed. The reaction mixture stirred at room temperature for 2 h, and quenched by pouring onto ice. The organic layer was separated, the aqueous layer was extracted with $CH_2Cl_2$ (3 x 10 mL) and the combined $CH_2Cl_2$ phases were washed with water (3 x 20 mL), 5% aqueous $NaHCO_3$ (3 x 20 mL), saturated brine (3 x 10 mL), and dried over anhydrous $Na_2SO_4$. Evaporation of the solvent *in vacuo* afforded 1.54 g (95%) of ynone 298 as a red oil which was sufficiently pure to be used without purification.

IR (film) $\nu_{max}$: 2960 ($CH_3$), 2160 (C≡C), 1680 (C=O, acetylenic ketone), 1250 (Si-$CH_3$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 2.1 (s, 3H, $CH_3CO$), 0.03 (s, 9H, $Si(CH_3)_3$).

Alcohol 295

To a solution of sodium *bis*-(2-methoxyethoxy)aluminium hydride (9.25 mL of a 3.4 M solution in toluene, 31.1 mmol) in 50 mL dry ether under inert atmosphere was added ynone 298 (1.08 g, 7.77 mmol) dropwise with cooling at 0°C. After addition of 298 was complete, the cooling bath was removed and the reaction mixture stirred at room temperature for 1 h. The reaction was quenched and worked-up as previously described. Distillation afforded 0.94 g (95%) of *trans*-alcohol 295 with spectral characteristics exactly as those previously described.

## SYNTHESIS OF 1-CARBOMETHOXY-3-TRIMETHYLSILYL-1,3-BUTADIENE (308)

### Preparation of *trans*-4-Oxo-pentenoic Acid (311)

A solution of glyoxylic acid (20 g, 0.22 mol) in 40 mL acetone and 30 mL 85% phosphoric acid was refluxed (80°C) for 5 h then stirred at room temperature overnight. The solution was concentrated *in vacuo* and extracted with $CH_2Cl_2$ (100 mL). The organic layer was washed with water (5 x 50 mL), saturated brine (3 x 30 mL) and dried over anhydrous $Na_2SO_4$. Evaporation *in vacuo* gave a light-brown crystalline material which was purified by recrystallization ($CH_2Cl_2$/pentane) affording 11.3 g (45%) of acid 311 as a white crystalline compound: mp 116.5-117.5°C (Lit.[676] 121-122°C).

IR (nujol) $\nu_{max}$: 3100-2500 (broad, COOH), 1690 (C=O, α,β-unsaturated acid), 1675 (C=O, α,β-unsaturated ketone), 1620 (C=C, conjugated), 1000 (=CH *trans*).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 9.7 (bs, 1H, exchangeable COOH), 7.1 (d, J = 16 Hz, 1H, $CH_3COC\underline{H}$=CH), 6.56 (d, J = 16 Hz, 1H, $CH_3COCH$=C$\underline{H}$COOH), 2.4 (s, 3H, $CH_3CO$).

### Esterification of 311

#### Method A

To a foil-wrapped flask was added a solution of acid 311 (3.65 g, 32.0 mmol) in 90 mL dry ether, silver(I) oxide (8.16 g, 35.2 mmol) and methyl iodide (9.1 g, 64 mmol). The

reaction mixture was stirred for 18 h at room temperature then filtered. Evaporation of the solvent *in vacuo*, at low temperature, gave a solid which sublimed readily at 30°C/20mm affording ester 313 as a white crystalline material: mp 59.6-60.5°C.

IR (nujol) $\nu_{max}$: 1720 (C=O, α,β-unsaturated ester), 1675 (C=O, α,β-unsaturated ketone), 1640 (C=C, conjugated), 1250 (C-O-C), 1020 (C-O-C, $\nu_s$), 990 (=CH *trans*).

$^1$H.m.r. (200 mHz, $CDCl_3$) δ: 7.0 (d, J = 16 Hz, 1H, $CH_3COCH{=}CH$), 6.61 (d, J = 16 Hz, 1H, $CH{=}CHCOOCH_3$), 3.8 (s, 3H, $COOCH_3$), 2.3 (s, 3H, $COCH_3$). The 60 MHz $^1$H.m.r. equally well resolved.

Method B

Acid 311 (7.37 g, 64 mmol) was dissolved in 50 mL dry DMF and sodium bicarbonate (10.7 g, 128 mmol) and methyl iodide (13.75 g, 96 mmol) were added. The mixture was stirred for 3 days at room temperature, filtered and excess $CH_3I$ evaporated. Cold water was added to the solution. The precipitate was filtered, redissolved in $CH_2Cl_2$ (50 mL), washed with water (3 x 20 mL), dried over anhydrous $Na_2SO_4$ and evaporated *in vacuo* to afford 6.8 g (83%) of a pure white crystalline compound which had spectral properties as those described for ester 313.

Diene 308

To a solution of ester 313 (4 g, 31.2 mmol) in 30 mL dry 1,2-dichloroethane under inert atmosphere was added triethylamine (4.5 g, 44.5 mmol) and trimethylsilyl triflate (7.08 g, 31.8 mmol) at 0°C. The reaction mixture was allowed to reach room temperature over *ca.* 1.5 h and dry ether was added. Removal of the precipitated triethylammonium triflate was achieved by using a pipet and the procedure of adding dry ether and removing the precipitate oil was repeated until no more oil was formed. The solvent was evaporated *in vacuo* to afford 6.1 g (98%) of diene 308 as a light-red oil which was pure enough to be used in the next reaction.

IR (film) $\nu_{max}$: 2960 ($CH_3$), 1720 (C=O, α,β-unsaturated ester), 1640, 1590 (C=C, diene), 1250 ($SiCH_3$), 1020 (Si-O), 970 (=CH *trans*).

$^1$H.m.r. (200 MHz, $CDCl_3$) δ: 7.1 (d, J = 16 Hz, 1H, COCH=CHC), 6.1 (d, J = 16 Hz, 1H, COCH=CHC), 4.67 (s, 2H, $=CH_2$), 3.73 (s, 3H, $COOCH_3$), 0.27 (s, 9H, $Si(CH_3)_3$).

Diene 315

To a solution of ester 313 (2.43 g, 19.0 mmol) in 5 mL dry 1,2-dichloroethane was added triethylamine (1.90 g, 18.8 mmol) and triethylsilyl triflate (4.98 g, 18.85 mmol) at 0°C under an inert atmosphere. The ice-bath was removed after a few minutes and the reaction was stirred at room temperature for 5 h. Evaporation of the solvent *in vacuo* followed by the addition of dry ether resulted in the precipitation of an oil which was removed by means of a pipet. Removal of ether afforded 4.3 g (94%) of diene 315 as a pale-yellow oil which was pure enough to be used without further purification.

IR (film) $\nu_{max}$: 2960 ($CH_3$), 1720 (C=O, α,β-unsaturated ester), 1640, 1592 (C=C, diene), 1250 (Si-$C_2H_5$), 1020 (Si-O), 970 (=CH *trans*).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 7.06 (d, J = 15 Hz, 1H, COCH=C<u>H</u>C), 6.13 (d, J = 15 Hz, 1H, COC<u>H</u>=CHC), 4.67 (s, 2H, $=CH_2$), 3.77 (s, 3H, $COOCH_3$), 1.2-0.4 (m, 15H, $Si(CH_2CH_3)_3$).

M.s. (EI, 70eV, 65°C) m/z (%): 242 (1.9, $M^{\cdot+}$), 243 (0.4, $[M+1]^{\cdot+}$ isotope peak), 213 (100, $M^{\cdot+}$ - $C_2H_5$), 211 (5.64, $M^{\cdot+}$ - $OCH_3$).

Adduct 3-Carbomethoxy-1-triethylsilyloxy-4,4,5,5-tetracyano-cyclohexene (319)

To a solution of tetracyanoethylene (316 mg, 2.47 mmol) in 5 mL dry benzene was added diene 315 (529 mg, 2.47 mmol) at room temperature under inert atmosphere. After 4 h, the solvent was evaporated *in vacuo* affording 0.84 g (quantitative yield) of a crystalline compound which had spectral properties attributable to the Diels-Alder adduct 319.

IR (nujol) $\nu_{max}$: 2240 (C≡N), 1735 (C=O, ester), 1670 (C=C-O), 1240 (Si-$C_2H_5$), 1010 (Si-O).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 4.96 (bs, 1H, =C-H), 3.36 (s, 3H, $COOCH_3$), 2.70 (bs, 1H, methine), 2.5 (d, 1H, J = 12 Hz, $C\underline{H}_1H_2$), 2.24 (d, 1H, J = 12 Hz, $CH_1\underline{H}_2$), 1.3-0.4 (m, 15H, $Si(C_2H_5)_3$).

# EXPERIMENTAL

## Chapter 5

## SYNTHESIS OF 3-FLUORO-6-METHOXYPHENOL

### Preparation of 3-Fluoro-6-methoxybenzaldehyde (324)

To a solution of *p*-fluoroanisole (3.34 g, 26.5 mmol) in 20 mL $CH_2Cl_2$ was added titanium(IV) chloride (8.37 g, 44.2 mmol) and α,α-dichloromethyl methyl ether (3.03 g, 26.4 mmol) at 0°C under inert atmosphere. The reaction was allowed to reach room temperature slowly and after stirring 8 h was cautiously poured onto an ice-water mixture and extracted with $CH_2Cl_2$ (50 mL). The organic layer was separated, washed with water (3 x 20 mL), saturated brine (3 x 20 mL) and dried over anhydrous $Na_2SO_4$. Evaporation *in vacuo* gave a solid which was recrystallized ($CH_2Cl_2$) to afford 3.78 g (92%) of white fluffy crystals of aldehyde 324: mp 46-47°C.

IR (nujol) $\nu_{max}$: 2950 (aromatic, aliphatic C-H), 2820, 2730 (C-H, CHO), 1690 (C=O, Ar-CHO), 1610, 1580, 1430 (ring C···C), 1260 (=C-O-C, $\nu_{as}$), 1030 (=C-O-C, $\nu_s$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 10.28 (d, J = 3 Hz, 1H, -CHO), 7.5-6.8 (m, 3H, aryl-H), 3.86 (s, 3H, $OCH_3$).

$^1$H.m.r. (200 MHz, $CDCl_3$) δ: 10.39 (d, J = 3 Hz, 1H, -CHO), 7.48 (dd, $J_{H-F}$ = 8, $J_{H2-H4}$ = 3 Hz, 1H, H-2), 7.24 (m, $J_{H4-F}$ = 10, $J_{H4-H5}$ = 9.1, $J_{H2-H4}$ = 3 Hz, 1H, H-4), 6.94 (dd, $J_{H5-F}$ = 3.8,

$J_{H4-H5}$ = 9.1 Hz, 1H, H-5), 3.8 (s, 3H, $OCH_3$).

Formate 325

To a cooled (0°C) solution of aldehyde 324 (3 g, 19.2 mmol) and 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide (100 mg) in 40 mL $CH_2Cl_2$ was added *m*-CPBA (4.63 g, 26.8 mmol) portionwise over a period of 5 min under an inert atmosphere. The mixture was refluxed for 5 h. The solution was cooled to 0°C, 10% aqueous $Na_2SO_3$ was added and the solution stirred vigorously for 10 min. After neutralizing the excess peroxide, the solution was washed with water (3 x 10 mL), 5% aqueous $NaHCO_3$ (3 x 10 mL), water (3 x 10 mL), saturated brine (3 x 10 mL) and dried over anhydrous $Na_2SO_4$. Evaporation of the solvent *in vacuo* afforded 3.15 g (96%) of formate 325 as a yellow oil (95% pure) which was used without purification in the next step.

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 8.2 (s, 1H, OCHO), 6.93 (s, 1H, H-2), 6.83 (bs, 2H, H-5, H-6), 3.76 (s, 3H, $OCH_3$).

3-Fluoro-6-methoxyphenol (326)

Formate 325 (3.0 g, 17.6 mmol) was dissolved in 50 mL ethanol-water (1:1) and sodium hydroxide (2.11 g, 52.9 mmol) was added at 0°C under an inert atmosphere. After 30 min the ice bath was removed and the reaction mixture stirred at room temperature for 3 h. Evaporation of the solvent *in vacuo* followed by neutralization with conc. HCl precipitated an oil which was extracted with $CH_2Cl_2$ (75 mL). The organic layer was washed with water (3 x 30 mL), saturated brine (3 x 30 mL) and dried over anhydrous $Na_2SO_4$. Evaporation of the solvent afforded 2.37 g (95%) of phenol 326 as a red oil which was at least 95% pure.

IR (film) $\nu_{max}$: 3440 (OH), 2840 ($CH_3$, $ArOCH_3$), 1610, 1600, 1510 (ring C⋯C), 1240 (=C-O-C, $\nu_{as}$), 1200 (=C-O-H), 1040 (=C-O-C, $\nu_s$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 6.8-6.32 (m, 3H; aryl-H), 5.8 (bs, 1H, exchangeable OH), 3.83 (s, 3H, $OCH_3$).

Synthesis of 1-Fluoro-4-methoxyxanthone (328)

A mixture of phenol 326 (2.7 g, 19 mmol), methyl *o*-iodobenzoate (5 g, 19 mmol) and copper(I) oxide (1.4 g, 9.5 mmol) in 40 mL dry DMA was refluxed for 18 h under an inert atmosphere. The reaction was cooled (0°C) and filtered. After removal of most of the solvent by distillation, 6N HCl (50 mL) was added to the oily residue and extracted with ether (3 x 50 mL). The organic layer was washed successively with water (3 x 25 mL), 2N NaOH (2 x 25 mL) and water (2 x 25 mL). Evaporation of the solvent *in vacuo* afforded *ca.* 5 g (95%) of crude diaryl 327 as a red oil.

To a solution of crude 327 (5 g, *ca.* 0.18 mmol) in 50 mL methanol was added 3 N NaOH (50 mL) and the mixture refluxed for 1 h. The cooled (0°C) solution was acidified with 6N HCl, evaporated *in vacuo* and extracted with $CH_2Cl_2$ (150 mL). The organic layer was washed with water (3 x 50 mL), saturated brine (3 x 50 mL) and dried over anhydrous $Na_2SO_4$. The solution was concentrated *in vacuo* to about 50 mL and added over a period of 15 min to a vigorously stirred solution of 90 mL TFAA-TFA (2:1 v/v) at 0°C. The red solution was allowed to warm up to room temperatue overnight. Evaporation of the solvent and of TFAA-TFA *in vacuo* gave an amorphous material which was redissolved in $CH_2Cl_2$ (50 mL), washed successively with 5% aqueous $NaHCO_3$ (3 x 25 mL), water (3 x 25 mL), saturated brine (3 x 25 mL) and dried over anhydrous $Na_2SO_4$.

Evaporation *in vacuo* gave a solid which was recrystallized ($CH_2Cl_2$/pentane) to afford 3.3 g (75%) of xanthone 328 as an off-white crystalline compound: mp 184-185°C.

IR (nujol) $\nu_{max}$: 1670 (C=O, xanthone (γ-pyrone)), 1610, 1600, 1580 (ring C⋯C), 1260 (=C-O-C, $\nu_{as}$), 1040 (=C-O-C, $\nu_s$).

$^1$H.m.r. (60 MHz, $CDCl_3$) δ: 8.26 (dd, J = 2.0 and 8 Hz, 1H, H-8), 7.8-6.65 (m, 5H, H-5, H-6, H-7 and H-2, H-3).

$^1$H.m.r. (200 MHz, $CDCl_3$) δ: 8.26 (dd, J = 2.0 and 8 Hz, 1H, H-8), 7.67 (m, J = 8.5, 6.9, 1.8 Hz, 1H, H-6), 7.53 (dd, J = 8.5, 1.2 Hz, 1H, H-5), 7.4 (m, J = 8.0, 6.9, 1.2 Hz, 1H, H-7), 7.12 (dd, J = 5 and 9 Hz, 1H, H-3), 6.91 (dd, J = 9 and 11 Hz, 1H, H-2), 3.96 (s, 3H, $OCH_3$).

1-[2-(2-Aminoethylamino)ethanol]-4-methoxyxanthone (330)

To a solution of xanthone 328 (0.60 g, 2.46 mmol) in 3 mL pyridine was added a large excess of 2-(2-aminoethylamino) ethanol (3 mL, 29.7 mmol). The solution was refluxed under an inert atmosphere for 5 days. The reaction mixture was poured onto an ice-water mixture, filtered, collected and redissolved in $CH_2Cl_2$ (10 mL). The organic solution was washed with water (2 x 4 mL), dried over anhydrous $Na_2SO_4$ and evaporated *in vacuo* to afford 0.52 g (65%) of aminoxanthone 330 as a bright orange amorphous compound (95% pure).

IR (nujol) $\nu_{max}$: 3280 (broad, NH, OH), 1630 (C=O, H-bonding), 1600, 1580 (ring C$\cdots$C), 1260 (=C-O-C, $\nu_{as}$).

$^1$H.m.r. (60 MHz, $CDCl_3$) $\delta$: 9.16 (bs, 1H, exchangeable N-H), 8.13 (dd, J = 2 and 8 Hz, 1H, H-8), 7.6-7.2 (m, 3H, H-5, H-6, H-7), 7.1 (d, J = 9 Hz, 1H, H-3), 6.21 (d, J = 9 Hz, 1H, H-2), 3.86 (s, 3H, $OCH_3$), 3.8-2.6 (m, 10 H, $NCH_2CH_2NHCH_2CH_2OH$).

1-Fluoro-4-hydroxyxanthone (331)

To a solution of xanthone 328 (1 g, 4.09 mmol) in 20 mL $CH_2Cl_2$ was added a large excess of $BBr_3$ (20 mL of a 1.07 M solution in $CH_2Cl_2$, 21.4 mmol) at -78°C. The reaction mixture was allowed to warm up to room temperature slowly overnight and quenched with methanol. Evaporation of the solvent with repeated addition and evaporation of methanol *in vacuo* gave an amorphous material which was recrystallized ($CH_3OH$) to afford 0.93 g (99%) of hydroxyxanthone 331 as a white crystalline compound: mp 253-255°C.

IR (nujol) $\nu_{max}$: 3280 (broad, OH), 1660 (C=O), 1600, 1580 (ring C$\overset{\cdots}{=}$C), 1245 (=C-O-C, $\nu_{as}$), 1040 (=C-O-C, $\nu_s$).

$^1$H.m.r. (60 MHz, $CDCl_3$ + $CD_3COCD_3$) $\delta$: 8.6 (bs, 1H, exchangeable OH), 8.21 (dd, J = 2 and 8 Hz, 1H, H-8), 7.8-6.6 (m, 5H, aryl-H).

1-Fluoro-4-methoxymethylxanthone (332)

To a solution of hydroxyxanthone 331 (120 mg, 0.52 mmol) in 10 mL THF was added sodium hydride (prewashed with pentane, 27.5 mg, 0.57 mmol) and chloromethyl methyl ether (100 mg, 1.24 mmol) at 0°C under an inert atmosphere. The reaction mixture was allowed to warm up to room temperature overnight, quenched with water and the solvent evaporated *in vacuo*. The residue was dissolved in $CH_2Cl_2$ (10 mL), washed with water (3 x 5 mL), saturated brine (3 x 5 mL) and dried over anhydrous $Na_2SO_4$. Evaporation of the solvent gave a solid material which was recrystallized ($CH_2Cl_2$/pentane) to afford 135 mg (95%) of white, crystalline methoxymethylxanthone (332): mp 118-120°C.

IR (nujol) $\nu_{max}$: 1665 (C=O), 1600, 1580 (ring C$\cdots$C), 1230 (=C-O-C, $\nu_{as}$), 1020 (=C-O-C, $\nu_s$).

$^1$H.m.r. (60 MHz, $CDCl_3$) $\delta$: 8.20 (dd, J = 2 and 8 Hz, 1H, H-8), 7.66-6.6 (m, 5H, aryl-H), 5.26 (s, 2H, $OCH_2$), 3.56 (s, 3H, $OCH_3$).

1-[2-(2-Aminoethylamino)ethanol]-4-methoxymethylxanthone (333)

To xanthone 332 (100 mg, 0.36 mmol), dissolved in a minimal amount of ethanol (0.5 mL), was added excess 2-(2-aminoethylamino)ethanol (4 g, 38 mmol) and 1.0 mL anhydrous pyridine. The reaction mixture was refluxed for 3 days. The solution was cooled (0°C) and added to ice-water. The suspension was filtered, collected, redissolved in $CH_2Cl_2$ (10 mL), washed with water (3 x 4 mL), and dried over anhydrous $Na_2SO_4$.[1] The solvent was evaporated *in vacuo* then dried under high vacuum to afford 120 mg (93%) of xanthone 333 (95% pure) as a bright yellow amorphous material.

IR ($CHCl_3$) $\nu_{max}$: 3480 (NH, Ar-NH-R), 3300 (OH), 1630 (C=O, H-bonding), 1580 (ring C⋯C), 1240 (=C-O-C, $\nu_{as}$).

$^1$H.m.r. (60 MHz, $CDCl_3$) $\delta$: 9.3 (bs, 1H, exchangeable NH), 8.2 (dd, J = 2 and 8 Hz, 1H, H-8), 7.6-7.4 (m, 3H, H-5, H-6, H-7), 7.13 (d, J = 9 Hz, 1H, H-3), 6.26 (d, J = 9 Hz, 1H, H-2), 5.15 (s, 2H, $OCH_2O$), 3.6 (s, 3H, $OCH_3$), 3.8-2.73 (m, 8H, $-N(CH_2)_2N(CH_2)_2O-$), 2.33 (bs, 2H, exchangeable C-NH, OH).

1-[2-(2-Aminoethylamino)ethanol]-4-hydroxyxanthone (21)

Xanthone 333 (100 mg, 0.279 mmol) was dissolved in methanol (10 mL) and hydrogen chloride was bubbled into the solution for 5 min at 0°C. The resultant suspension was filtered, collected and washed with ether. It was dissolved in a minimal amount of water, made alkaline with NaOH and then carefully neutralized with acetic acid affording 106 mg (94%) of aminohydroxyxanthone 21 as a red crystalline compound which was dried under high vacuum: mp 183-185°C.

IR (nujol) $\nu_{max}$: 3340 (broad, NH, OH), 1620, C=O, H-bonding), 1600, 1580 (ring C···C), 1260 (=C-O-C, $\nu_{as}$).

$^1$H.m.r. (200 MHz, $CH_3OD$) δ: 9.4 (bs, 1H, exchangeable Ar-O<u>H</u>), 8.23 (dd, J = 1.5 and 8 Hz, 1H, H-8), 7.8 (m, J = 8.5, 7.0, 1.5 Hz, 1H, H-6), 7.6 (dd, J = 8.5, 1 Hz, 1H, H-5), 7.46 (m, J = 8.0, 7.0, 1 Hz, 1H, H-7), 7.26 (d, J = 8.8 Hz, 1H, H-3), 6.75 (d, J = 8.8 Hz, 1H, H-2), 4.96 (bs, 3H, exchangeable 2×-N<u>H</u> and O<u>H</u>), 3.74-3.69 (m, 4H, Ar-NC<u>H</u>$_2$- and C<u>H</u>$_2$OH), 3.8-3.42 (m, 2H, Ar-NC-C<u>H</u>$_2$-N), 3.34-3.23 (m, 2H, -N-C<u>H</u>$_2$-C-O<u>H</u>).

M.s. (EI, 70eV, 86°C) m/z (%): 314 (10.2, $M^{+\cdot}$), 315 (2.5 $[M+1]^{+\cdot}$ isotope peak), 240 (100, $M^{+\cdot} - C_3H_8NO$), 241 (64.1, $M^{+\cdot} - C_3H_7NO$), 212 (10.2, $M^{+\cdot} - C_3H_8NO-CO$).

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